

ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

SUBSTANCE NAME(S): DIISOCYANATES

IUPAC NAME(S): n.a.

EC NUMBER(S): n.a.

CAS NUMBER(S): n.a.

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TABLE OF CONTENTS

B. Information on hazard and risk	13
B.1 Identity of the substance(s) and physical and chemical properties	13
B.1.1 Name and other identifiers of the substance(s)	13
B.1.2 Composition of the substance(s)	18
B.1.3 Physicochemical properties.....	18
B.1.4 Justification for grouping	20
B.2 Manufacture and uses	20
B.2.1 Manufacture, import and export of a substance.....	20
B.2.1.1 General information on manufacture	20
B.2.1.2 Information on supply chain	21
B.2.1.3 Import and export	22
B.2.2 Uses	22
B.2.2.1 Aromatic diisocyanates.....	24
B.2.2.2 MDI and TDI	24
B.2.2.3 Aliphatic diisocyanates	27
B.2.3 Uses advised against by the registrants	28
B.3 Classification and labelling	29
B.3.1 Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) and in the classification and labelling inventory/ Industry's self classification(s) and labelling.....	29
B.4 Environmental fate properties	33
B.5 Human health hazard assessment.....	33
B.5.1 Sources	33
B.5.2 Toxicokinetics (absorption, metabolism, distribution and elimination)	33
B.5.3 Acute toxicity.....	33
B.5.4 Irritation	34
B.5.5 Corrosivity	34
B.5.6 Sensitisation.....	34
B.5.6.1 Scope of the assessment	34
B.5.6.2 Hazard identification	34
B.5.6.3 Endpoints for diagnosis of respiratory hypersensitivity/respiratory allergy	45

B.5.6.4 Overview of animal data.....	47
B.5.6.5 Overview of human data	60
B.5.7 Repeated dose toxicity	81
B.5.8 Mutagenicity	81
B.5.9 Carcinogenicity	81
B.5.10 Toxicity for reproduction	82
B.5.11 Other effects.....	82
B.5.12 Derivation of DNEL(s)/DMEL(s)/Health-based exposure limits for diisocyanates with respect to sensitisation	82
B.5.12.1 Introductory thoughts	82
B.5.12.2 General considerations on determining DNELs/DMELs	84
B.5.12.3 Uncertainties in deriving a DNEL/DMEL.....	87
B.5.12.4 Summary of the assessment	90
B.6 Human health hazard assessment of physico-chemical properties	91
B.7 Environmental hazard assessment	91
B.8 PBT and vPvB assessment.....	91
B.9 Exposure assessment	92
B.9.1 General discussion on releases and exposure.....	92
B.9.1.1 Introduction.....	92
B.9.1.2 Summary of the existing legal requirements	96
B.9.1.3 Summary of the effectiveness of the implemented operational conditions and risk management measures	101
B.9.2 Manufacturing.....	103
B.9.2.1 Occupational exposure	103
B.9.3 Use in manufacture of polyurethanes and PU composite materials.....	103
B.9.3.1 General information	104
B.9.3.2 Exposure estimation	104
B.9.4 Use in manufacture of foam.....	116
B.9.4.1 General information	116
B.9.4.2 Exposure estimation	117
B.9.5 Use in spray foam applications.....	126
B.9.5.1 General information	126
B.9.5.2 Exposure estimation	127
B.9.6 Use in coatings	136

B.9.6.1 General information	136
B.9.6.2 Exposure estimation	137
B.9.7 Use in adhesives	148
B.9.7.1 General information	148
B.9.7.2 Exposure estimation	149
B.9.8 Other uses	153
B.9.9 Synopsis	153
B.10 Risk characterisation	158
B.10.1.1 Human health	158
C. Justification for action on a Union-wide basis	172
D. Baseline	173
E. Impact Assessment	176
E.1.1 Introduction	176
E.2 Risk Management Options	177
E.3 Alternatives	177
E.3.1 Identification of potential alternative substances and techniques	177
E.3.2 Assessment of alternatives	179
E.3.2.1 Availability of alternatives	179
E.3.2.2 Human health risks related to alternatives	180
E.3.2.3 Technical and economic feasibility of alternatives	181
E.4 Restriction scenario(s)	182
E.5 Economic impacts	182
E.5.1 Training Measures in Appendix "Training and measures": (valid for RMO1 and RMO2)	183
E.5.1.1 Estimation of costs units	184
E.5.1.2 Key parameters for estimation of costs units for RMO1 and RMO2	187
E.5.2 RMO1: Testing costs for identification of the exempted products ("Appendix Exemptions")	188
E.5.3 Economic impacts - Results	195
E.5.3.1 Other impacts, practicability and monitorability	195
E.6 Human health and environmental impacts	198
E.6.1 Humans Health impacts	198
E.6.1.1 Risk reduction capacity	199

E.6.1.2 Estimation on costs of Illness (CoI)	206
E.6.2 Human health impacts – results	218
E.7 Environmental impacts	220
E.8 Basic Data for modelling of costs and benefits	220
E.9 Proportionality (including comparison of options)	221
E.9.1 Cost-benefit analysis of the proposed restriction measure RMO1 – Appendix Trainings and Measures	222
E.9.1.1 Results on case example motor vehicle refinish (MVR)	222
E.9.1.2 Costs-benefit analysis results for overall affected sectors	228
E.9.1.3 Costs-benefit analysis: overview on results for sectors at high risks	233
E.9.1.4 Costs-effectiveness analysis	234
E.9.2 Cost-benefit analysis of the possible restriction measure RMO2	239
E.9.3 Comparison of impacts in RMO3	240
E.9.4 RMO1 and RMO2 – Comparison of the costs	241
E.10 Conclusion on risk management option analysis	242
F. Assumptions, uncertainties and sensitivities	246
G. Stakeholder information	249
G.1 Data on the number of exposed employees	249
G.2 Stakeholder information – Call for evidence	252
G.3 Further Comments from stakeholders	252
H. References	256
Appendix 1 Tabular Overview of Relevant Animal Data Available for the Diisocyanates	303
Appendix 2 Overview of available human case reports and case studies	329
Appendix 3 Overview of available epidemiological data	386
Appendix 4 Conversion factors	444
Appendix 5 Additional material regarding Appendix Exemptions and Appendix Trainings and Measures	445
Appendix 6 Information regarding alternatives.	454
Appendix 7 Appendix 12 to the future Annex XVII entry: Exempted substances and mixtures according to 2b) containing Isocyanates ≥ 0.1 % w/w	463
Appendix 8 Elements to be included into Appendix 13 Trainings and Measures to the future Annex XVII entry	465

TABLE OF TABLES

Table 1: Non-exhaustive list of diisocyanates covered by the restriction	14
Table 2: Physicochemical properties of the diisocyanates listed in Table 1 (data partially taken from the corresponding registration dossiers).....	18
Table 3: Imports and exports of isocyanates, EU-28 (in tons) (EUROSTAT 2016).....	22
Table 4: Diisocyanates registered under REACH relevant for this dossier	23
Table 5: Registered uses of MDI and TDI (ECHA, Sept. 2015)	25
Table 6: Uses advised against by the registrants	28
Table 7: Cross-reactivity of anti-TDI antibodies with other antigens	44
Table 8: Cross-reactivity of TDI-related antigens with other antibodies	44
Table 9: Overview of the number of available animal experiments per diisocyanate, species and "induction" route	54
Table 10: Exposure, BHR and asthma-like symptoms for the subsample.....	68
Table 11: Overview of the data sources for the occupational diseases due to isocyanates .	72
Table 12: Overview of the reported cases (stratified by member state, disease category and year) provided to the DS by 13 EU Member States	77
Table 13: Occupational exposure limit values (8 hours) for diisocyanates in various Member States of the EU. Values are given in ppb unless otherwise stated.	97
Table 14: Short-term occupational exposure limit values for diisocyanates in various Member States of the EU. Values are given in ppb unless otherwise stated.	99
Table 15: European and national regulations related to diisocyanates	100
Table 16: Long term inhalation exposure ranges (mg/m ³) for the exposure scenarios "Manufacturing" of MDI, TDI and HDI, taken from Registration Dossiers.....	103
Table 17: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)	106
Table 18: Overview of inhalation exposure levels to MDI in manufacture of PU and PU composite materials (in µg/m ³).....	108
Table 19: Overview of biological monitoring data for MDI in manufacture of PU and PU composite materials.....	112
Table 20: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)	113
Table 21: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013)	114
Table 22: Overview of inhalation exposure levels to TDI in manufacture of PU and composite materials (in µg/m ³).....	115
Table 23: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)	118
Table 24: Overview of inhalation exposure levels to MDI in manufacture of foam (in µg/m ³)	119
Table 25: Overview of the statistical evaluation from MEGA database for TDI, data period 2000- 2009 (IFA, 2010)	120

Table 26: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m ³)	121
Table 27: Overview of inhalation exposure levels to TDI in manufacture of foam (in µg/m ³)	124
Table 28: Overview of biological monitoring data for TDI in manufacture of foam	126
Table 29: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)	127
Table 30: Overview of inhalation exposure levels to MDI in spray foam applications (in µg/m ³).....	130
Table 31: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)	137
Table 32: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)	139
Table 33: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m ³)	140
Table 34: Overview of inhalation exposure levels to TDI in use in coatings (in µg/m ³)	141
Table 35: Overview of the statistical evaluation from MEGA database for HDI, data period 2000-2011 (IFA, 2012) (mg/m ³)	142
Table 36: Exposure levels to HDI species, measured by Pronk et al. (in µg/m ³)	145
Table 37: Overview of inhalation exposure levels to HDI and its oligomers in use in coatings (in µg/m ³).....	145
Table 38: Overview of dermal exposure levels to HDI and its oligomers in use in coatings	147
Table 39: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)	149
Table 40: Overview of inhalation exposure levels to MDI in use in adhesives (in µg/m ³)..	150
Table 41: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)	151
Table 42: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m ³)	151
Table 43: Overview of inhalation exposure levels to TDI in use in adhesives (in µg/m ³) ..	152
Table 44: Overview of inhalation exposure levels to HDI in use in adhesives (in µg/m ³) ..	153
Table 45: Inhalation exposure levels to HDI and its oligomers in use in coatings (in µg/m ³) (same as Table 37).....	154
Table 46: Inhalation exposure levels to MDI in spray foam applications (in µg/m ³) (same as Table 30).....	154
Table 47: Inhalation exposure levels to TDI in manufacture of foam (in µg/m ³) (same as Table 27).....	154
Table 48: Inhalation exposure levels to TDI in manufacture of PU and composite materials (in µg/m ³) (same as Table 22).....	155
Table 49: Inhalation exposure levels to TDI in use in adhesives (in µg/m ³) (same as Table 43)	155

Table 50: Inhalation exposure levels to MDI in use in adhesives (in $\mu\text{g}/\text{m}^3$) (same as Table 40)	155
Table 51: Inhalation exposure levels to TDI in use in coatings (in $\mu\text{g}/\text{m}^3$) (same as Table 34)	155
Table 52: Inhalation exposure levels to MDI in manufacture of PU and PU composite materials (in $\mu\text{g}/\text{m}^3$) (same as Table 18)	155
Table 53: Inhalation exposure levels to MDI in manufacture of foam (in $\mu\text{g}/\text{m}^3$) (same as Table 24).....	155
Table 54: Inhalation exposure levels to HDI in use in adhesives (in $\mu\text{g}/\text{m}^3$) (same as Table 44)	156
Table 55: Biological monitoring data for TDI in manufacture of foam (same as Table 28)	157
Table 56: Biological monitoring data for MDI in manufacture of PU and PU composite materials (same as Table 19)	157
Table 57: Most common causes of OA in different countries	159
Table 58: Number of cases in four EU Member States that provided numbers of exposed workers (for details see section B.5.6.5.3)	163
Table 59: National registry of work operations (KAPR) of the Czech Republic	164
Table 60: Exposed workers in Austria.....	164
Table 61: Number of isocyanate exposed workers by Finnish census occupation.....	165
Table 62: OA cases related to number of exposed workers in four Member States that provided data on numbers of exposed workers.....	165
Table 63: Annual incidence of TDI-induced occupational asthma (taken from Ott 2002) ..	167
Table 64: Incidence provided by a Canadian case-control study	167
Table 65: Proportion of occupational/work-related asthma cases with isocyanates as (suspected) causative agents	168
Table 66: Estimated incidences for spray painters	170
Table 67: Summary table of estimated occurrence of isocyanate OA in the EU (as number of new cases per year and as annual incidence)	171
Table 68: Overview on exposed workforce in sectors	173
Table 69: Overview on models for estimation of the annually occurring new asthma cases	174
Table 70: Discussion on estimation methods.....	174
Table 71: General situation of the PU value chain	176
Table 72: Estimated cost units and required personal time spendings (RMO1 and 2)	184
Table 73: Estimation of training fee in option c.....	185
Table 74: Calculation of annual direct costs for e-learning training.....	186
Table 75: Data basis for estimation of sector specific indirect costs for 10 working days (EUROSTAT)	186
Table 76: Costs parameter – all relevants sectors	187
Table 77: Costs parameters for example MVR sector – Appendix “Trainings and Measures”	187

Table 78: Estimation of costs units in construction sector	188
Table 79: Appendix Exemptions – estimated input variables (source own guess on basis of personal communication in expert group for Appendix Exemptions)	188
Table 80: Costs estimation of Appendix Exemptions.....	189
Table 81: Approach for estimation of total value loss based on concerned vehicle number	194
Table 82: Overview on results of costs estimation for each RMO.....	195
Table 83: Analysis of distributional effects on case sample of a MVR body shop*	197
Table 84 : Overview of reduction of accident rates in various industry sectors.....	200
Table 85: Forecast of the effectiveness of the proposed restriction measure	205
Table 86: Overview data sources for costs of illness components.....	206
Table 87: Comparison of medical cost per case	209
Table 88: Structure of Costs of Illness for a work-related asthma disease.....	212
Table 89: Overview on the DGUV’s study results with own derivation on the summarised likelihood for reduction in working disability of people suffering asthma.	217
Table 90: Overview on evidence from the literature search and own assumption	218
Table 91: Overview on results of human health impacts (based on 6500 cases of occupational asthma per year)	218
Table 92: Input parameter for calculation spray painters	219
Table 93: Overview on input parameter used for modelling of the costs for Appendix Trainings and Measures and Appendix Exemptions and benefit for human health.....	220
Table 94: Overview of training options in MVR sector	222
Table 95: MVR: Extrapolation method 3 – estimation of health benefits based on reported asthma cases.....	223
Table 96: MVR: Extrapolation method 3 covering the underreporting issue	225
Table 97: MVR: Extrapolation method 1 – calculation based on incidence rate epidemiological studies	226
Table 98: Overview on Training options in all relevant sectors.....	228
Table 99: All sectors – estimation of health benefits based on reported asthma cases (method 1)	228
Table 100: All sectors – estimation of health benefits based on reported asthma cases covering the underreporting issue (method 1).....	229
Table 101: All sectors - indirect approach by extrapolation method 3.....	231
Table 102: All sectors– random sample based incidence rate (method 2)	232
Table 103: Overview on results for costs-effectiveness analysis (after 20 years in €million/case avoided)	239
Table 104: Summary and overview on possible RMOs	240
Table 105: EUROSTAT data preparation for estimation of a daily fee [€] for a commissioned trainer.....	243
Table 106: Estimation of adjustment factors (source: ISOPA, EUROSTAT)	245

Table 107: NACE codes for sectors – potentially exposed workforce downstream.....	249
Table 1-1: Overview of available animal studies and results of tier 1 evaluation	305
Table 1-2: Tier 2 and tier 3 assessment of studies using the inhalation route for induction. The respective references can be identified in Table 1-1 above via the field "Report ID" ..	317
Table 1-3: Tier 2 and tier 3 assessment of studies using topical induction, in which a positive sensitisation result was obtained. The respective references can be identified in Table 1-1 above via the field "Report ID".....	323
Table 2-1: Isocyanate-related cases documented in the literature (non-comprehensive) .	329
Table 3-1: Reviews	387
Table 3-2: Data taken from (Ott, 2002) (Tables I and III)	394
Table 3-3: Longitudinal studies	395
Table 3-4: Case-control studies.....	420
Table 3-5: Cross-sectional studies with quantitative exposure-response estimates.....	422
Table 3-6: Further studies - cross-sectional studies	425
Table 4-1: Conversion factors used in the assessment of diisocyanates	444
Table 5-1: Measurement Methods for diisocyanates in the context of Appendix Exemptions	446
Table 5-2: Examples for applications and steps	448
Table 5-3: Biological limits.....	448
Table 5-4: Exposure stages (expert judgement)	450
Table 5-5: Generic uses and the corresponding "measures groups" – Industrial & professional	450
Table 6-1: Frequently used diisocyanates	456
Table 6-2: Distribution of services on craft sectors.....	458
Table 6-3: Uses of products containing diisocyanates in craft sector.....	460
Table 6-4: Summary of research results.....	461
Table 7-1 : Biological limits.....	464
Table 8-1: Generic uses and the corresponding "measures groups" – Industrial & professional	465

TABLE OF FIGURES

Figure 1: Chemical structure of diisocyanates	13
Figure 2: Value chain of the aliphatic diisocyanate industry (ALIPA 2006)	22
Figure 3: Simplified overview of the allergic cascade [from (Verstraelen et al., 2008)]; for a detailed description cf. also (Bloemen et al., 2007)]	39
Figure 4: Diseases documented for the 2312 reported cases in 13 EU countries (see Table 12)	80

Figure 5: Relationship between toxicological and exposure related aspects of isocyanates	158
Figure 6: Reaction with formation of urethane bonds without isocyanates	178
Figure 7: Moisture induced crosslinking of modified silanes	179
Figure 8: Expected risk reduction according to the proposed Appendix Exemptions	189
Figure 9: Forecast on costs incurring for identification of exempted products based on isocyanates	190
Figure 10: assumed scenario for distributional effects and assessment approach of proportionality of the incurred costs at firm's level	196
Figure 11: Structure of training costs for a worker in the vehicle refinish sector	197
Figure 12: Methodical approach for estimation of human health impacts	199
Figure 13: Forecast (low /high bound) for the relative development of the incidence rate after implementation of the proposed restriction measure.	206
Figure 14: Asthma – impacts on sufferer's welfare Source: DGUV http://publikationen.dguv.de/dguv/pdf/10002/reichenhallneu.pdf	213
Figure 15: Cause-and-effect chain for social costs caused by asthma	213
Figure 16: Likelihood tree for income loss due to work-related asthma source (Ayres et al., 2010)	216
Figure 17: Likelihood tree own "best guess" on incomeloss due to work related asthma	217
Figure 18: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma issue of 0.07 % per year	224
Figure 19: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma incidence issue of ≈ 0.3 % per year	226
Figure 20: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma incidence issue of 0.7 % per year	227
Figure 21: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 235 cases per year	229
Figure 22: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 2350 cases per year	230
Figure 23: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 6058 cases per year.	232
Figure 24: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming the incidence rate of 0.7 % per year	233
Figure 25: Overview on results for benefit-cost ratio after 20 years of training measure implementation – all considered scenarios (benefit in low bound)	235
Figure 26: Development of the cost units per avoided asthma case over time in MVR – estimation based on statistics of reported asthma cases covered by underreporting factor 10	236
Figure 27: Development of the cost units per avoided asthma case over 20 years in all sectors – estimation based on statistics of reported asthma cases covered by underreporting factor 4	237

Figure 28: Development of the cost units per avoided asthma case over 20 years in all sectors – estimation based on method 2.....238

Figure 29: Comparison of the costs over 20 years for Appendix Exemption and training ..241

B. Information on hazard and risk

B.1 Identity of the substance(s) and physical and chemical properties

B.1.1 Name and other identifiers of the substance(s)

Diisocyanates according to the following structure, whereby the group R is an aliphatic or aromatic hydrocarbon unit of unspecified length. R does not contain urethane, urea, uretdione, biuret or isocyanurate linkages (i.e. the diisocyanate entity is not the result of prepolymerisation of a parent diisocyanate):

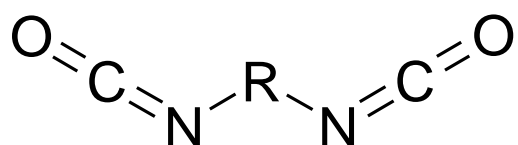


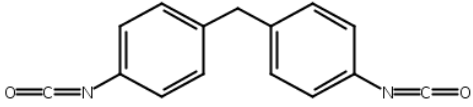
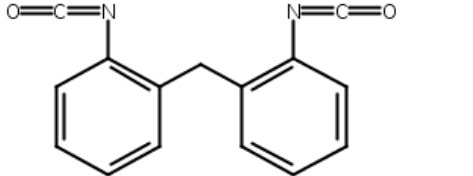
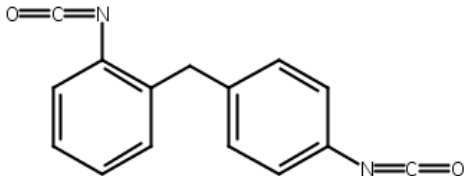
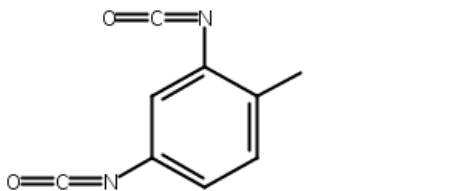
Figure 1: Chemical structure of diisocyanates

Detailed information and examples of diisocyanates covered by this restriction is given in Table 1 and Table 2.

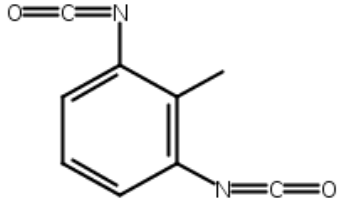
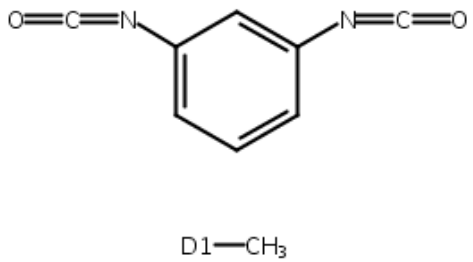
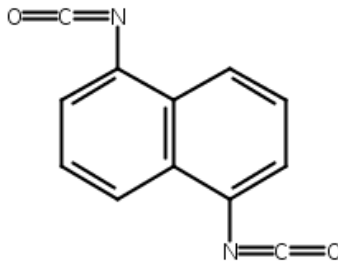
Please note that in the way the proposal for the scope of the restriction has been formulated in Section A.1.2.1, oligomers and prepolymers that contain >0.1 wt % of the diisocyanates that meet the above definition (of which a non-exhaustive list is shown below), would still be in scope of the restriction.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 1: Non-exhaustive list of diisocyanates covered by the restriction

EC Name	IUPAC Name	CAS Name	Trivial Name; Abbreviation	EC Number	CAS Number	Molecular formula	Structure
4,4'-methylenediphenyl diisocyanate	1,1'-methylenebis(4-isocyanatobenzene)	Benzene, 1,1'-methylenebis[4-isocyanato-	4,4'-MDI	202-966-0	101-68-8	C ₁₅ H ₁₀ N ₂ O ₂	
2,2'-methylenediphenyl diisocyanate	1,1'-methylenebis(2-isocyanatobenzene)	Benzene, 1,1'-methylenebis[2-isocyanato-	2,2'-MDI	219-799-4	2536-05-2	C ₁₅ H ₁₀ N ₂ O ₂	
o-(p-isocyanatobenzyl)phenyl isocyanate	1-isocyanato-2-(4-isocyanatobenzyl)benzene	Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-	2,4'-MDI	227-534-9	5873-54-1	C ₁₅ H ₁₀ N ₂ O ₂	
4-methyl-m-phenylene diisocyanate	2,4-diisocyanato-1-methylbenzene	Benzene, 2,4-diisocyanato-1-methyl-	p-Toluenediisocyanate (2,4-TDI)	209-544-5	584-84-9	C ₉ H ₆ N ₂ O ₂	

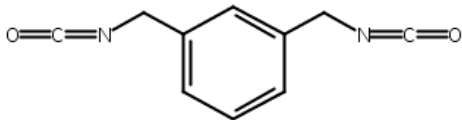
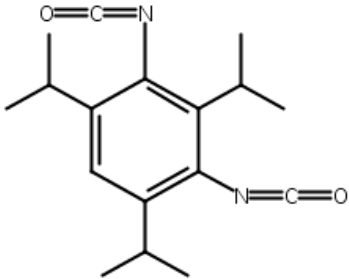
ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Name	IUPAC Name	CAS Name	Trivial Name; Abbreviation	EC Number	CAS Number	Molecular formula	Structure
2-methyl-m-phenylene diisocyanate	2,6-diisocyanato-1-methylbenzene	Benzene, 1,3-diisocyanato-2-methyl-	m-Toluenediisocyanate (2,6 - TDI)	202-039-0	91-08-7	C ₉ H ₆ N ₂ O ₂	
m-tolyldiene diisocyanate	1,3-diisocyanatomethylbenzene	Benzene, 1,3-diisocyanatomethyl-	T80 or T65; 80/20 TDI or 65/35 TDI	247-722-4	26471-62-5	C ₉ H ₆ N ₂ O ₂	
1,5-naphthylene diisocyanate	1,5-diisocyanatonaphthalene	Naphthalene, 1,5-diisocyanato-	NDI	221-641-4	3173-72-6	C ₁₂ H ₆ N ₂ O ₂	

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Name	IUPAC Name	CAS Name	Trivial Name; Abbreviation	EC Number	CAS Number	Molecular formula	Structure
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	4,4'-Diisocyanato-3,3'-dimethylbiphenyl	1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-	Tolidinediisocyanate (TODI)	202-112-7	91-97-4	C ₁₆ H ₁₂ N ₂ O ₂	
hexamethylene diisocyanate	1,6-diisocyanatohexane	Hexane, 1,6-diisocyanato-	HDI	212-485-8	822-06-0	C ₈ H ₁₂ N ₂ O ₂	
1,3-bis(1-isocyanato-1-methylethyl)benzene;	1,3-bis(1-isocyanato-1-methylethyl)benzene;	Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-	meta-Tetramethylxylylenediisocyanate (m-TMXDI)	220-474-4	2778-42-9	C ₁₄ H ₁₆ N ₂ O ₂	
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane	Cyclohexane, 5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-	Isophorondiisocyanate (IPDI)	223-861-6	4098-71-9	C ₁₂ H ₁₈ N ₂ O ₂	
4,4'-methylenedicyclohexyl diisocyanate	1-isocyanato-4-[(4-isocyanatocyclohexyl)methyl]cyclohexane	Cyclohexane, 1,1'-methylenebis[4-isocyanato-	Hydrogenated MDI (H12MDI)	225-863-2	5124-30-1	C ₁₅ H ₂₂ N ₂ O ₂	

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Name	IUPAC Name	CAS Name	Trivial Name; Abbreviation	EC Number	CAS Number	Molecular formula	Structure
1,3-bis(isocyanatomethyl)benzene	1,3-bis(isocyanatomethyl)benzene	Benzene, 1,3-bis(isocyanatomethyl)-	mXDI	222-852-4	3634-83-1	C ₁₀ H ₈ N ₂ O ₂	
2,4,6-triisopropylm-phenylene diisocyanate	2,4-diisocyanato-1,3,5-triisopropylbenzene	Benzene, 2,4-diisocyanato-1,3,5-tris(1-methylethyl)-	TRIDI	218-485-4	2162-73-4	C ₁₇ H ₂₂ N ₂ O ₂	

B.1.2 Composition of the substance(s)

In most cases, if measurements are reported (in reality mostly limited to TDI, MDI, HDI and some IPDI), these nearly always refer to the diisocyanates, although these are only a fraction of the formulations used and other isocyanate containing species may be present as well. In nearly all cases toxicological investigations exist only for these specific diisocyanates. Also OEL values exist only for specific diisocyanates fulfilling the definition in section B.1.1. Only more recently there is attention for the role of (pre-)polymers or oligomers containing isocyanate groups. This is reflected in the fact that both in the UK and in Germany a "total isocyanate" measurement is now being practised. See for example Table 13 in Section B9.1.2.3 and (AGS, 2009). It is generally accepted that the potency of sensitisation will decrease with increasing molecular weight. However, quantitative relationships in this respect are not available.

B.1.3 Physicochemical properties

Table 2: Physicochemical properties of the diisocyanates listed in Table 1 (data partially taken from the corresponding registration dossiers)

EC Name	CAS No.	EC No.	Physical State	Vapour pressure	Melting Point
4,4'-methylenediphenyl diisocyanate	101-68-8	202-966-0	Crystalline solid	0.00049 Pa, 20 °C (Gas saturation method (20-70 °C)) 0.0007 Pa, 20 °C (effusion method) < 0.002 Pa, 20°C (Watson method)	39 – 43 °C; EU Method A.1, capillary method
2,2'-methylenediphenyl diisocyanate	2536-05-2	219-799-4	Solid	0.0081 Pa, 20 °C 0.012 Pa, 25 °C (OECD 104) (Vapour Pressure Curve; Effusion method)	42.8 °C (1013 hPa) EU Method A.1, DSC
o-(p-isocyanatobenzyl)phenyl isocyanate	5873-54-1	227-534-9	Solid	0.0014 Pa, 20 °C (EU A.4, static method)	34 to 38 °C, EU A.1, capillary method,
4-methyl-m-phenylene diisocyanate	584-84-9	209-544-5	Solid	0.0014 Pa, 20 °C (EU A.4, gas saturation method) 0.0021 Pa, 20 °C 0,87 mbar (EU A.4, static method)	21 °C, (EU A.1, freezing temperature)
2-methyl-m-phenylene diisocyanate	91-08-7	202-039-0	Solid ((ICSC) 2012)	2.09X10 ⁻² mm Hg at 25 °C (Daubert, T.E., Danner	18.3 °C (CRC Handbook cited in HSDB Database)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Name	CAS No.	EC No.	Physical State	Vapour pressure	Melting Point
			cited in HSDB Database)	R.P. cited in HSDB Database)	
m-tolyldiene diisocyanate	26471-62-5	247-722-4	liquid	0.015hPa at 20 °C, calculated, 80/20 TDI* 0.014hPa at 20 °C, calculated, 65/35 TDI*	10 °C; (80/20 TDI ; EU A.1, freezing temperature)* 4 °C; (65/35 TDI; EU A.1, freezing temperature)*
1,5-naphthylene diisocyanate	3173-72-6	221-641-4	Crystalline solid	0.000008 hPa at 25 °C (OECD 104, gas saturation method)	127 °C (Handbook data)
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	91-97-4	202-112-7	solid	0.00295 Pa at 25 °C, calculated	>= 71.6 <= 72 °C at 1021.9 hPa, EU A.1, capillary method,
hexamethylene diisocyanate	822-06-0	212-485-8	liquid	0.007 hPa at 20 °C (Handbook data)	ca. -67 °C (NIOSH)
1,3-bis(1-isocyanato-1-methylethyl)benzene;	2778-42-9	220-474-4	liquid	0.0029 mm Hg (0.386 Pa) at 25 °C (OECD 104, effusion method)	4 °C; 1 atm (EU A.1, thermal analysis)
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	4098-71-9	223-861-6	liquid	0.000635 hPa at 20 °C (OECD 104, effusion method)	-59.9 °C (Knovel critical tables (2 nd edition))
4,4'-methylenedicyclohexyl diisocyanate	5124-30-1	225-863-2	liquid	0.0000122 hPa at 20 °C, 0.0000213 hPa at 25 °C, (OECD 104, effusion method)	(cis, cis-isomer: 14 %; cis, trans-isomer: 58 % and trans, trans-isomer: 20 %, 8 % 2,4-isomers) is 15 °C trans,trans-4,4'-diisocyanatodicyclohexylmethane is 83 °C (Ullmann's Encyclopedia)
1,3-bis(isocyanatomethyl)benzene	3634-83-1	222-852-4	liquid	0.0206 Pa at 20 °C, (OECD 104, gas saturation method)	-7°C (266 K) DSC EU A.1
2,4,6-triisopropyl-m-phenylene diisocyanate	2162-73-4	218-485-4	liquid	<= 0.19 Pa at 20 °C, Grain Watson estimation (EU A.4, dynamic method)	-56 °C EU A.1, DSC No melting of crystalline subcomponents has

EC Name	CAS No.	EC No.	Physical State	Vapour pressure	Melting Point
					been observed between -90 °C and 50 °C. Glass transition temperature (amorphous components) at -56 °C.

*The registrations for the EC# 247-722-4 list 2 of the 3 theoretically possible isomers of m-tolydine diisocyanates as main constituents: reaction mass of 4-methyl-m-phenylene diisocyanate and 2-methyl-m-phenylene diisocyanate (corresponding to 80/20 TDI and 65/35 TDI).

B.1.4 Justification for grouping

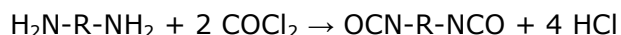
All diisocyanates are known as sensitisers and are classified as Resp. Sens. 1, either as a harmonised classification or as self-classification by the suppliers. The functional (di)isocyanate group is the important chemical group of these substances. Therefore, all diisocyanates are grouped together for the purpose of this restriction.

B.2 Manufacture and uses

B.2.1 Manufacture, import and export of a substance

B.2.1.1 General information on manufacture

The main process to produce diisocyanates is the phosgenation of corresponding diamines:



Because of the hazardous properties of phosgene (carbonyl chloride) the entire process operates in closed systems.

MDIs are produced firstly by a condensation reaction between aniline and formaldehyde to form MDA (and oligomers – PMDA). Reaction with phosgene and subsequent purification yields MDI. A more detailed description of the manufacturing processes of MDI and TDI is given in the EC Best Available Techniques Reference Document (BREF) in the Large Volume Organic Chemical Industry (European Commission, 2014).

TDIs are produced in three steps by the nitration of toluene to produce dinitrotoluenes, followed by hydrogenation yielding toluenediamines (TDA) and finally the phosgenation followed by purification (by distillation) to produce toluenediisocyanates (TDIs). A more detailed description can be found in the BREF document mentioned above (European Commission, 2014).

HDI is manufactured by the reaction of dexamethylenediamine (HDA) with phosgene and subsequent distillation.

IPDI is produced by the phosgenation of 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

H₁₂MDI is produced by the phosgenation of 4,4'-methylenebis(cyclohexylamine).

NDI is produced by the phosgenation of 1,5-naphthylenediamine (NDA).

TODI is manufactured outside the EU by phosgenation of the corresponding amine.

XDI is manufactured outside the EU by phosgenation of the corresponding amine.

m-TMXDI is produced outside the EU by phosgenation of the corresponding amine.

B.2.1.2 Information on supply chain

According to the European Diisocyanates and Polyol Producers Association (ISOPA) which represent the manufactures of the aromatic isocyanates MDI and TDI in Western Europe about 200 companies are directly involved in the production of polyurethane (PU) (ISOPA 2002). About 4600 companies are direct customers of these companies, and more than 18300 companies are producing polyurethane -based final articles. The highest number of companies involved as direct customers of polyurethane and producers of polyurethane-based products are found in Germany (850 and 3400 respectively) and Italy (650 and 2600) (ISOPA 2014). Aromatic diisocyanates and polyols are important ingredients for the production of rigid and flexible foams, rigid and flexible integral skin foams, elastomers, adhesives, coatings and sealants, and others.

Figure 2 shows the value chain for the aliphatic diisocyanate industry which is represented by the European Aliphatic Isocyanates Producers Association (ALIPA) founded by the 4 major European producers of aliphatic isocyanates and polyisocyanates. Aliphatic isocyanates (especially HDI) are important basic materials for protective and decorative coating systems, for modern adhesive systems and for specialties like elastomers.

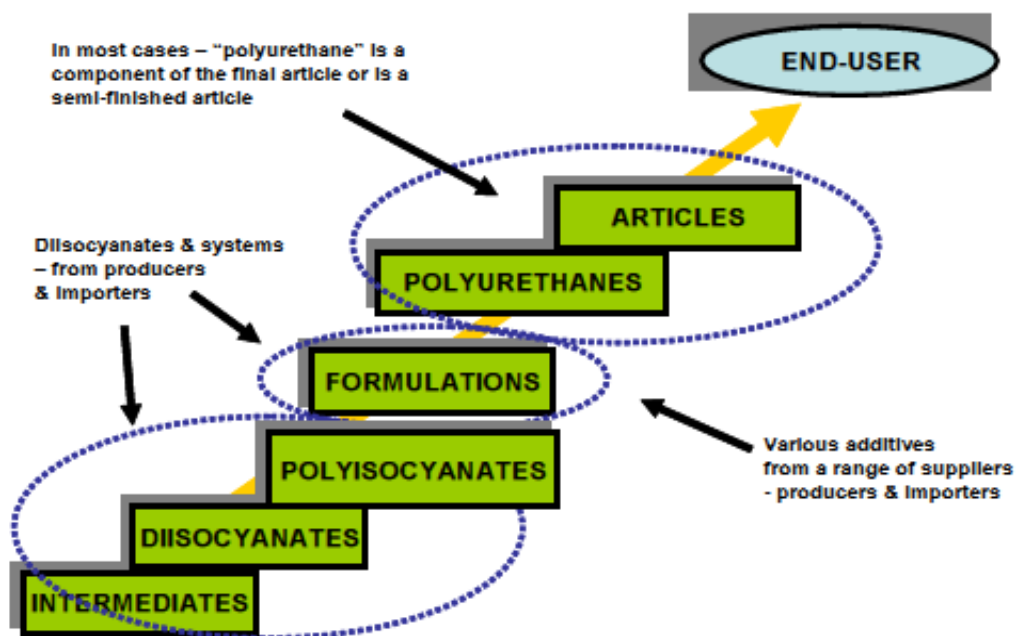


Figure 2: Value chain of the aliphatic diisocyanate industry (ALIPA 2006)

The aliphatic isocyanate raw material is supplied to about 1500 formulators, and further used by about 87000 companies to produce PU-based articles (coatings, adhesives, elastomers) (ALIPA 2006). ISOPA and ALIPA represent the major producers of isocyanates and cover about 80 % of the market (based on information of ISOPA / ALIPA).

B.2.1.3 Import and export

Table 3 shows the import and export of isocyanates between 2012 and 2014:

Table 3: Imports and exports of isocyanates, EU-28 (in tons) (EUROSTAT 2016)

	Import	Export
2012	27470.0	303917.3
2013	36823.8	288705.1
2014	40079.5	293839.1

As it can be seen, most of the substances are produced and consumed in the EU-market.

B.2.2 Uses

Isocyanates are highly reactive compounds defined by the isocyanate group, $R-N=C=O$, where R can be an aliphatic, cycloaliphatic or an aromatic group. Isocyanates undergo exothermic (and usually very fast) reactions with all kind of nucleophiles. Aromatic isocyanates are more reactive than aliphatic isocyanates. The most common type of isocyanates in workplaces are diisocyanates, which contain two isocyanate groups (NCO) and oligomers/polyisocyanates derived thereof. In the context of this exposure part of the dossier the term "isocyanates" refers to diisocyanate monomers (two NCO groups) and their related polyisocyanates as well as other species with NCO groups (e. g. break down products).

Diisocyanates act as cross-linking agents. The predominant use of isocyanates (>90 %) is in the direct manufacture of polyurethane plastic materials (PUs, also PURs), where diisocyanates are reacted with polyols and/or other nucleophiles like polyamines. In other uses diisocyanates are utilised in preparations, and the final reaction is intended to take place later. The properties of PUs are largely determined by the building blocks (both, the diisocyanates and polyols and, where applicable, other modifiers and additives), thus enabling a wide variety of PUs with a very broad range of characteristic features and fine tuning of material properties (Engels et al., 2013). Consequently diisocyanates are used in many workplaces and a broad spectrum of applications. Typical isocyanate based products include:

- flexible polyurethanes
- rigid polyurethanes
- polyurethane foams (rigid and flexible foam systems)
- assembly foams (e.g. insulation panels)
- foundry cores (casting)
- coating materials (paints, lacquers, varnishes)
- adhesives and glues
- elastomers

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

- sealants
- pre-polymers in chemical synthesis
- engineering plastics
- polyurethane fibres

A non-exhaustive list of diisocyanates currently registered with the European Chemicals Agency relevant for this dossier is shown in Table 4. However, it cannot be excluded that other, similar substances are also registered under REACH or may be registered under REACH in the future.

Table 4: Diisocyanates registered under REACH relevant for this dossier

EC Registration Name	Abbreviation [CAS No.]	Tons per year (ECHA)	Primary applications (according to ECHA's dissemination site)
4,4'-methylenediphenyl diisocyanate	4,4'-MDI [101-68-8]	100 000 – 1 000 000	Use as an Intermediate, Resins, Flexible Foams, Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres and other Polymers, Rigid Foams, Binders, Coatings, Adhesives and Sealants, Composite Materials, Foundry
2,2'-methylenediphenyl diisocyanate	2,2'-MDI [2536-05-2]	1000 - 10000	
o-(p-isocyanatobenzyl) phenyl isocyanate	2,4'-MDI [5873-54-1]	10000 – 100 000	
4-methyl-m-phenylene diisocyanate	2,4-TDI [584-84-9]	100 000 – 1 000 000	Use as an Intermediate, Flexible Foams, Coatings, Adhesives and Sealants, Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres, Composite Materials
m-tolylidene diisocyanate	T80 or T65 [26471-62-5]	100 000 – 1 000 000	
1,5-naphthylene diisocyanate	NDI [3173-72-6]	1000 - 10000	Use as an Intermediate, Pre-polymers, Elastomers and TPUs, Oil Additives (Additives in Lubricants)
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	TODI [91-97-4]	Conf.	Use as an Intermediate, Chemicals for Polymer Processing,
hexamethylene diisocyanate	HDI [822-06-0]	10000 – 100 000	Use as an Intermediate, Coatings, Adhesives, Elastomers
1,3-bis(1-isocyanato-1-methylethyl)benzene;	m-TMXDI [2778-42-9]	100 – 1000	Use as an Intermediate, Polyurethane Dispersions
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	IPDI [4098-71-9]	10000 – 100 000	Use as an Intermediate, Coatings, Polymer Production
4,4'-methylenedicyclohexyl diisocyanate	H12MDI [5124-30-1]	10000 – 100 000	Use as an Intermediate, Polyurethane Resins

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Registration Name	Abbreviation [CAS No.]	Tons per year (ECHA)	Primary applications (according to ECHA's dissemination site)
1,3-bis(isocyanato-methyl)benzene	mXDI [3634-83-1]	1000 - 10000	Use as an Intermediate, Coatings, Adhesives and Sealants, Optical Lenses
2,4,6-triisopropyl-m-phenylene diisocyanate	TRIDI [2162-73-4]	100 – 1000	Use as an Intermediate

Note: A list with more exact figures of the most important diisocyanates is contained in **Fehler! Verweisquelle konnte nicht gefunden werden.** (confidential information).

There are great variances between the different diisocyanates with respect to their uses (both, in volume and the patterns of use) and there are differences in their impact on workplace exposures. In the following exposure assessment emphasis will be on those diisocyanates and uses where significant occupational exposure can be expected, rather than a comprehensive evaluation of all of the diisocyanates registered under REACH. The most important (in terms of quantities used) and consequently most extensively monitored diisocyanates in workplaces are MDI, TDI and HDI, which together account for more than 95 % of the market volume for isocyanates. Also, the focus of the assessment is laid on the most relevant uses with respect to amount / volume and workplace exposure rather than a comprehensive list of all uses registered under REACH.

B.2.2.1 Aromatic diisocyanates

In aromatic diisocyanates the NCO group is directly attached to an aromatic ring and they are more reactive than their aliphatic counterparts. Airborne aromatic diisocyanates have a strong tendency for reacting at ambient conditions (with moisture and/or other isocyanates in the vapour phase) and tend to remain for shorter periods in workplace atmospheres than aliphatic diisocyanates (Dahlin et al., 2008).

They react extremely fast with polyols under catalysed conditions to polyurethanes. As mentioned above, depending on the chemical nature of the chemical building blocks (type of isocyanates and polyols), the reaction stoichiometry and the sequence of reaction an extremely wide range of PUs with tailored material properties can be realized (soft-elastic to hard).

B.2.2.2 MDI and TDI

Methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI) are aromatic diisocyanates of which several isomers exist.

There are three isomers of MDI, 2,2'-MDI, 2,4'-MDI and 4,4'-MDI namely. Under REACH all of the three isomers of MDI have been registered, whereas the MDI itself (as combination of the isomeric constituents [CAS-number: 26447-40-5]) has not been registered as such. The EU 2005 Risk Assessment Report on MDI refers to MDI with the CAS number 26477-40-5 with the understanding that this CAS number would cover all isomers and combinations of them. Currently the Estonian Health Board is carrying out a substance evaluation for a different substance containing mixed MDI isomers: the 'reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate' [EC-number n.a.; CAS-number n.a.].

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Of the isomers of TDI 2,4-TDI and 2,6-TDI are the most important ones. 2,4-TDI and the mixture of 2,4- and 2,6-TDI are registered under REACH, whereas the 2,6-TDI isomer is not, since it is difficult to isolate and the isomeric pure form is commercially not relevant.

In the following the term “MDI” (methylene diphenyl diisocyanate), if no further specification is given refers to commercially available products which may consist of a composition containing a combination of various isomers (4,4’-MDI, 2,4’-MDI, 2,2’-MDI) as well as “oligomeric MDI” or “polymeric MDI”. See also (ISOPA, 2013). Accordingly, “TDI” (unspecified) covers pure 2,4-TDI isomer and mixed isomers of 65-80 % 2,4-TDI and 20 – 35 % 2,6-TDI isomer.

Among all isocyanates, MDI and TDI are commodity chemicals with the highest tonnages on the market. Both together account for more than 90 % of the total isocyanate consumption (European Commission, 2014). The main application is in the manufacture of polyurethanes (PUs) and PU foams (flexible and rigid), but also in coatings, adhesives, sealants and elastomers (also known as C.A.S.E. applications) and binders (mostly MDI based) where there is potential for exposure to free diisocyanates.

Usually, flexible and rigid PUs, as well as elastomers are supplied in cured form/products and there is a low potential of exposure during their application. In coatings, adhesives, sealants and binders, on the other hand, the curing process itself is an integral part of their functionality and therefore exposure to isocyanates is more likely during and after their use.

B.2.2.2.1 Use of MDI and TDI as such

The following Table 5 shows the uses of MDI and TDI registered at ECHA (ECHA dissemination site, September 2015). For the purpose of the exposure assessment within this dossier only the highlighted uses will be discussed more in detail (but with some other grouping/naming of the uses).

Table 5: Registered uses of MDI and TDI (ECHA, Sept. 2015)

MDI	TDI
Industrial Uses	
Manufacturing	Manufacturing of TDI
Manufacturing of other substances	Manufacturing of other substances
Formulation (including Resin Manufacture), Repackaging and Distribution	Formulating, Repackaging and Distribution
Flexible Foam	Flexible Foam
Rigid Foam	
Coatings	Coatings
Adhesives and Sealants	Adhesives and Sealants
Other Composite Materials	Other Composite Material
Foundry Applications	
Composite Materials based on Wood/Man-made/Mineral/Natural Fibres	
Elastomers, TPU, Polyamide, Polyimide, Synthetic Fibres and Manufacturing of other Polymers	Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres
Professional Uses / Public Domain	
Rigid Foam	
Coatings	Coatings
Adhesives and Sealants	Adhesives and sealants

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

MDI	TDI
Other Composite Materials	Other Composite Materials
Composite Materials based on Wood/Man-made/Mineral/Natural Fibres	
Composite Material based on Man-made Fibres	
Consumer Uses / Private Households	
Consumer use - rigid foam	
Consumer use - coatings	
Consumer use - adhesives and sealants	
Uses advised against	
Consumer Spray applications	Consumer all uses of substance as such, in a mixture

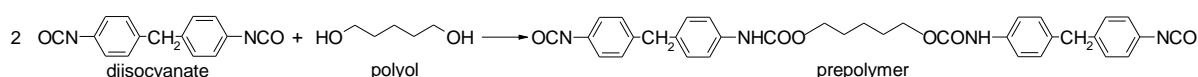
As mentioned previously the predominant use of MDI and TDI is in the manufacture of polyurethanes (PU). Usually the isocyanates (MDI/TDI) are reacted with polyols (and/or other polynucleophiles) and mixed with optional additives like catalysts, surfactants, stabilizers, flame retardants, pigments and the like. Immediately after mixing an exothermic reaction will start between the isocyanate and the nucleophile. Depending on the reaction quantities and conditions, the reaction may substantially increase the temperature of the reaction mixture. This process is usually largely completed within seconds up to 30 minutes. The final curing may take up to 72 h, where exposure to uncured isocyanates is still possible.

Foams (flexible and rigid) constitute a substantial part of the PU market, accounting for more than 60 % of the total production (Engels et al., 2013; IAL, 2014). Flexible foams, especially in case of TDI, can be produced by addition of a small amount of water to the reaction mixture. The reaction of water with isocyanates will produce the corresponding amine and carbon dioxide ($R-NCO + H_2O \rightarrow R-NH_2 + CO_2$). The carbon dioxide can act as an in-situ blowing agent in the process so that the final product is PU foam. Alternatively, foams can be produced by adding an external blowing agent. Both, flexible foam (e.g. cushioning for furniture, mattresses) as well as rigid foam (e.g. building insulation, refrigerators) are mostly produced in a one-shot-process. Further processing of foams (demoulding/removing from casts, cutting/sawing through bulk slab-stock) is typically carried out shortly (minutes) after production, when the PU usually is not fully cured and risk of exposure to remaining isocyanates is still present, e.g. when opening moulding forms, often at elevated temperatures.

B.2.2.2.2 Use as prepolymers/oligomers

PU prepolymers are formed when the polyol is reacted with an excess of diisocyanate. In that case the reactive polyol groups (OH) are completely converted to urethane bonds but the excess isocyanates remain as terminal functional groups of the prepolymer.

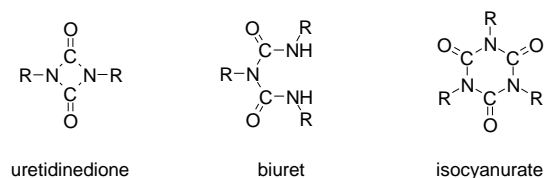
The reaction scheme below exemplarily shows the reaction of a simple polyol (a diol) with two 4,4'-MDI molecules. One of the isocyanate groups of the MDI reacts with one of the OH groups of the polyol, and the other end of the polyol reacts with another diisocyanate molecule.



ANNEX XV RESTRICTION REPORT – DIISOCYANATES

The resulting prepolymer has an isocyanate group (NCO) on both ends. The prepolymer reacts like a diisocyanate therefore, but has a greater molecular weight, lower isocyanate content by weight (% NCO), increased viscosity, and lower vapour pressure than the original diisocyanate. Instead of a diol, higher functional polyols can also be used for the polyol in the reaction. Depending on the stoichiometry, this will usually result in liquid urethane oligomers of medium to high molecular weight. Molar ratios of isocyanate (NCO) to polyol (OH) greater than two to one can also be applied, yielding so called quasi-prepolymers.

Oligomers are molecules of an intermediate molecular mass that are built by reaction of a limited number of monomeric molecules, and still capable of further polymerisation. A special case is when isocyanates react with themselves. These oligomers are of particular importance e.g. in the use of HDI based coatings as they usually constitute the major fraction of isocyanates in such formulations. In most cases the NCO groups undergo cyclo-addition reactions across the carbon-nitrogen bond. Reactions of this kind are the dimerization of NCOs to form uretidinediones and the trimerization to form biurets or isocyanurates, which are of particular commercial importance. The three typical self-condensation products of isocyanates are shown below.



The advantage of the use of prepolymers is that the mixing ratio and the viscosity of the components can be adjusted and more easily handled than in the case of pure diisocyanates. Moreover, the content of free diisocyanates is reduced. It may be assumed that the potential for exposure related to the handling of such substances is also reduced. However, it should be realized that because of the stoichiometry of the reaction, without further treatment, most prepolymer products contain significant concentrations of residual diisocyanate monomer which drive classification and labelling of polyisocyanate prepolymers.

B.2.2.3 Aliphatic diisocyanates

Aliphatic diisocyanates are isocyanates where the NCO group is not attached directly to an aromatic ring. Aliphatic isocyanates have a lower reactivity compared to their aromatic analogues. Aliphatic diisocyanates are generally considered to be speciality materials. They are used in considerably smaller quantities than MDI and TDI. In total, they represent less than 5 % of the overall diisocyanate consumption.

Aliphatic diisocyanates are used to produce highly resistant polyurethane materials. Aliphatic urethane bonds are more inert than aromatic ones.¹ Aliphatic based polyurethanes

¹ As aromatic urethanes constitute chromophores, they are generally prone to discolouring (becoming yellow to brown) and/or impairing of material properties due to exposure to light.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

display higher UV stability and durability as well as chemical and mechanical resistance compared to PUs based on aromatic diisocyanates. The primary use is in UV stable and durable coatings with a high degree of resistance to chemicals, abrasion and weather. They are also used to make adhesives, sealants and for polyurethane elastomers. Aliphatic diisocyanates are also used in specialty applications such as leather refinishing formulations, textile and fibre treatments, inks, thermoplastic polyurethane (TPU) sheets and others special applications to provide UV protection and enhance durability.

The most relevant aliphatic diisocyanates are HDI (1,6-hexamethylene diisocyanate), IPDI (isophorone diisocyanate) and HMDI (4,4'-dicyclohexylmethane diisocyanate). Due to the hazard profile and the high volatility of HDI most products do not use the monomers as such but polyisocyanates, typically made from HDI or IPDI. Such polyisocyanates usually still contain residual diisocyanate monomers with significant potential for exposure. The most common polyisocyanates are:

- HDI isocyanurate (trimer)
- HDI biuret (trimer)
- HDI uretdione (dimer)
- IPDI isocyanurate (trimer)

B.2.2.3.1 HDI

HDI is the most used aliphatic diisocyanate species. It is predominantly used to produce polyisocyanates (see above). The main applications of those are as hardeners for high quality surface coatings, where high performance is required, and as adhesives. (Often such PU systems utilize both, aliphatic and aromatic diisocyanates, in one product, to achieve an optimum on economic and material performance efficiency).

As mentioned above, typically, polyisocyanates are not completely monomer free but some residual HDI monomer (0.5 up to 3 %) is still present in the product and can pose a risk of exposure. Furthermore, HDI based coatings are often applied by spraying where significant exposure to aerosols can occur.

B.2.3 Uses advised against by the registrants

Table 6: Uses advised against by the registrants

EC Registration Name	EC Number	CAS Number	Used advised against
4,4'-methylenediphenyl diisocyanate	202-966-0	101-68-8	Consumer spray application
2,2'-methylenediphenyl diisocyanate	219-799-4	2536-05-02	Consumer spray application
o-(p-isocyanatobenzyl)phenyl isocyanate	227-534-9	5873-54-1	Consumer spray application
4-methyl-m-phenylene diisocyanate	209-544-5	584-84-9	Consumer use
2-methyl-m-phenylene diisocyanate	202-039-0	91-08-7	Not registered

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

EC Registration Name	EC Number	CAS Number	Used advised against
m-tolylidene diisocyanate	247-722-4	26471-62-5	Consumer use
1,5-naphthylene diisocyanate	221-641-4	3173-72-6	No entry found
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	202-112-7	91-97-4	Consumer use
hexamethylene diisocyanate	212-485-8	822-06-0	Do-it-yourself and consumer uses
1,3-bis(1-isocyanato-1-methylethyl)benzene;	220-474-4	2778-42-9	not advised for use in industrial or non-industrial spraying applications (PROC 7 and 11). Also, it is recommended to avoid hand mixing with intimate contact and only personal protection equipment (PROC 19).
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	223-861-6	4098-71-9	Do-it-yourself and consumer uses
4,4'-methylenedicyclohexyl diisocyanate	225-863-2	5124-30-1	Do-it-yourself and consumer uses
1,3-bis(isocyanatomethyl)benzene	222-852-4	3634-83-1	„none identified“
2,4,6-triisopropyl-m-phenylene diisocyanate	218-485-4	2162-73-4	“There are no uses advised against.”

B.3 Classification and labelling

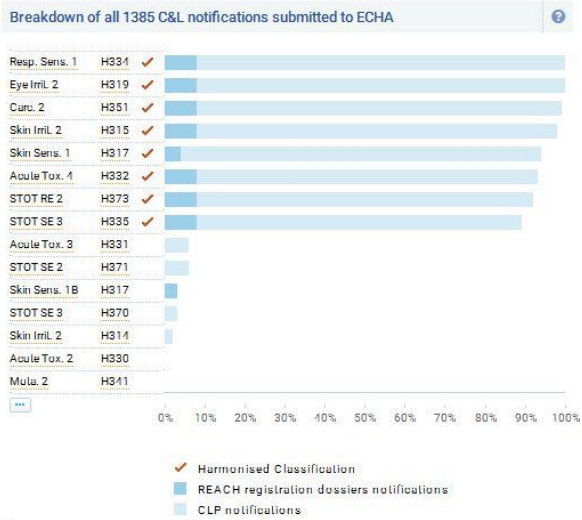
B.3.1 Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) and in the classification and labelling inventory/ Industry’s self classification(s) and labelling

The following is an overview of harmonised labelling and classification as well as further notifications to the C&L Inventory as available from the ECHA Website².

² Accessed on 2 September 2016

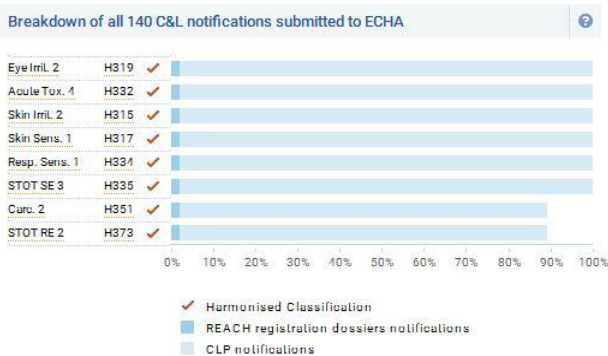
ANNEX XV RESTRICTION REPORT – DIISOCYANATES

4,4'-MDI (CAS: 101-68-8)

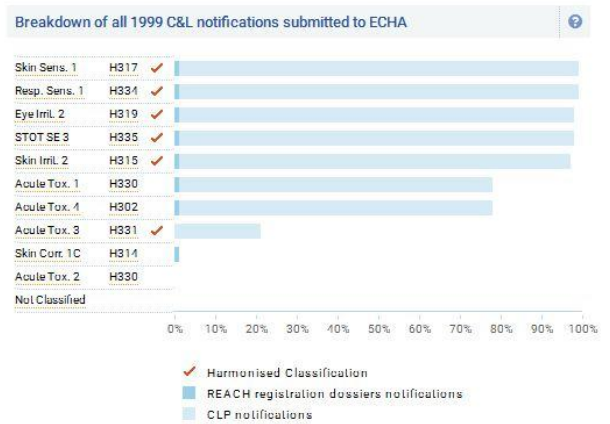


At least one notifier has indicated that an impurity or an additive present in the substance impacts the notified classification.

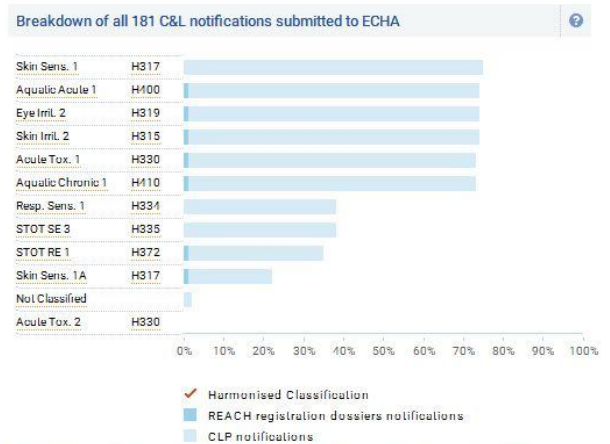
2,2'-MDI (CAS: 2536-05-2)



HDI (CAS 822-06-0)

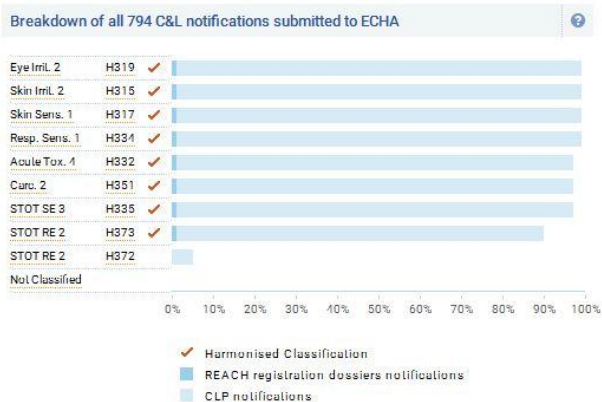


m-TMXDI (CAS: 2778-42-9)

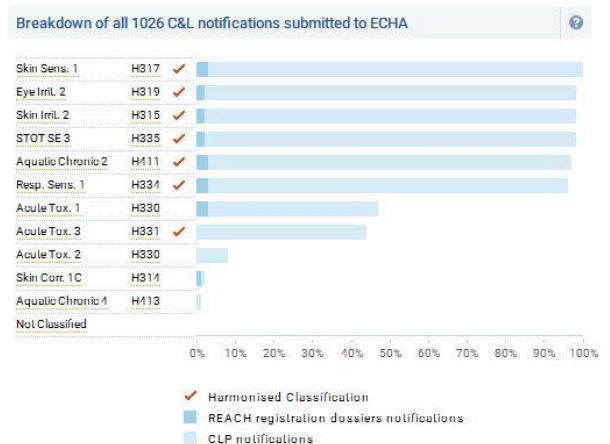


At least one notifier has indicated that an impurity or an additive present in the substance impacts the notified classification.

2,4'-MDI (CAS: 5873-54-1)

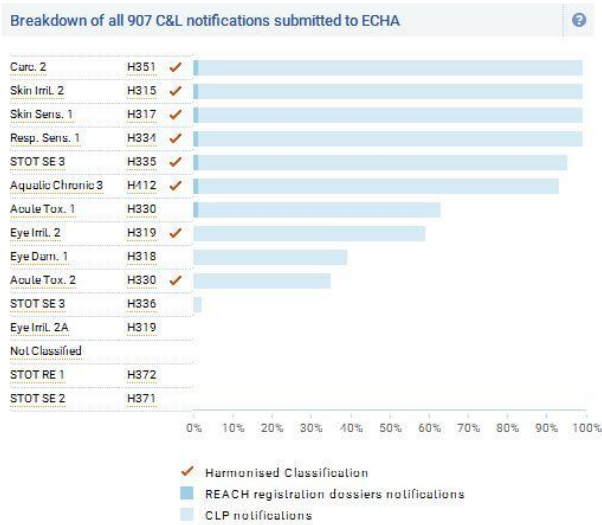


IPDI (CAS: 4098-71-9)



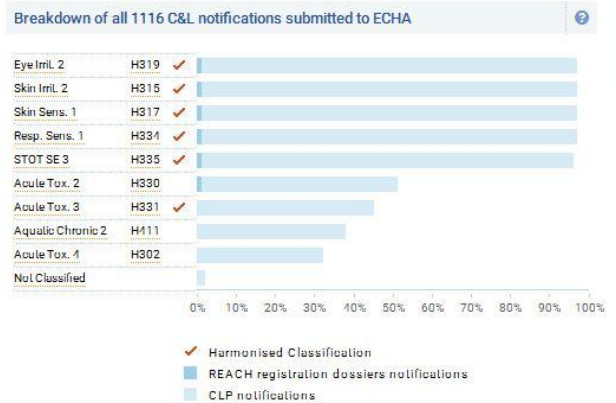
ANNEX XV RESTRICTION REPORT – DIISOCYANATES

2,4-TDI (CAS: 584-84-9)

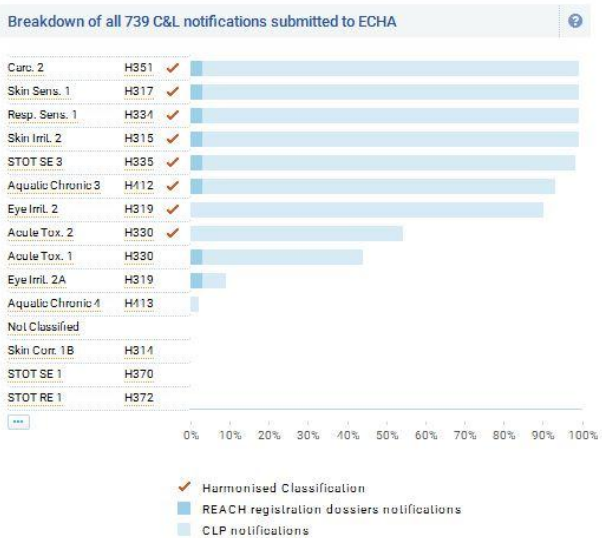


At least one notifier has indicated that an impurity or an additive present in the substance impacts the notified classification.

H12MDI (CAS: 5124-30-1)

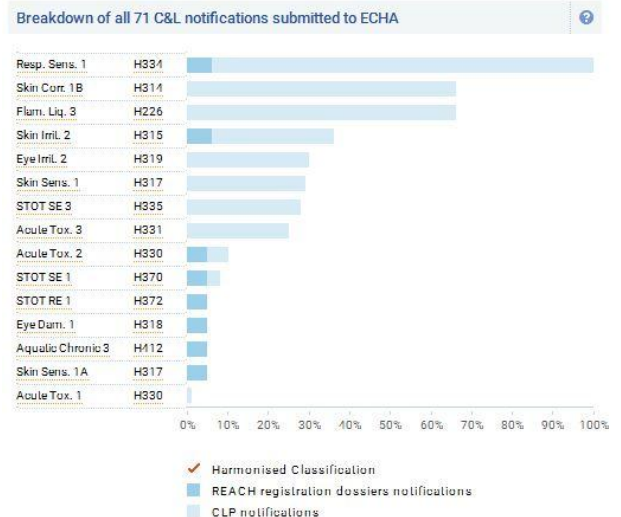


Reaction mass of 2,4-TDI and 2,6-TDI (CAS: 26471-62-5)



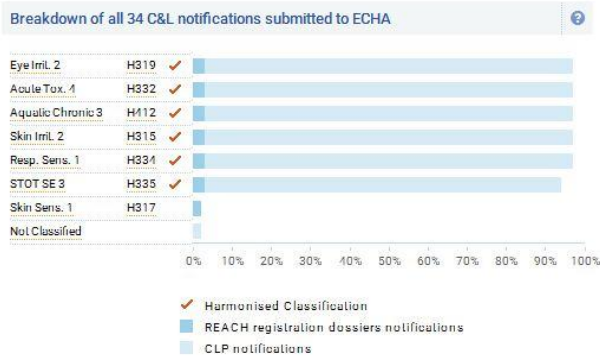
At least one notifier has indicated that an impurity or an additive present in the substance impacts the notified classification.

mXDI (CAS: 3634-83-1)

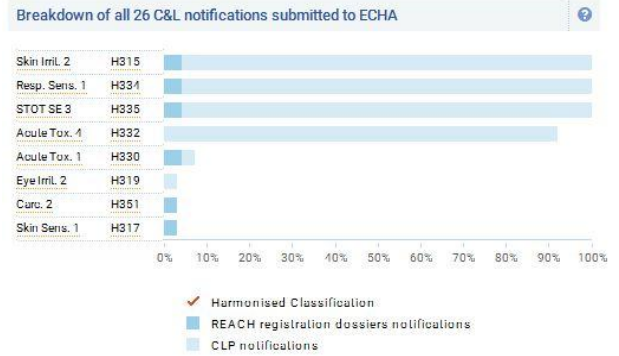


ANNEX XV RESTRICTION REPORT – DIISOCYANATES

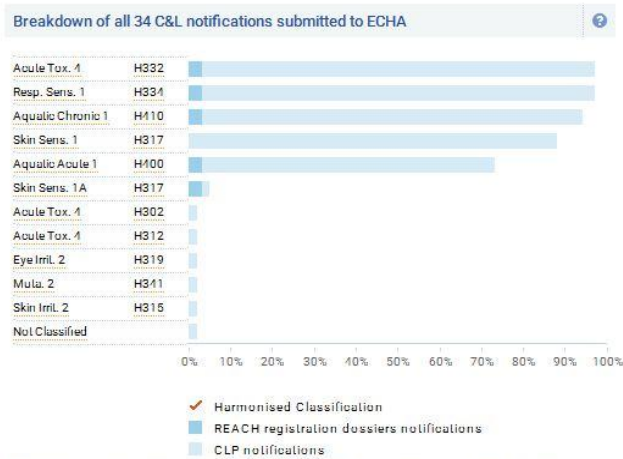
NDI (CAS: 3173-72-6)



TRIDI (CAS: 2162-73-4)



TODI (CAS: 91-97-4)



ⓘ At least one notifier has indicated that an impurity or an additive present in the substance impacts the notified classification.

B.4 Environmental fate properties

Not relevant for this dossier

B.5 Human health hazard assessment

B.5.1 Sources

The data presented herein were compiled from the results of a comprehensive search of the published literature as well as from the lead registration dossiers for HDI, HDI biuret, HDI isocyanurate HMDI, IPDI, IPDI isocyanurate, 2,2-MDI, 2,4-MDI, 4,4-MDI, NDI, 2,4-TDI, TDI isocyanurate, "TDImix" (80:20 mixture of 2,4- and 2,6-isomers), m-TMXDI, TODI, TRIDI, and m-XDI (last synchronisation: February 2016).

B.5.2 Toxicokinetics (absorption, metabolism, distribution and elimination)

In vivo ADME studies via the inhalation route are available e.g. for MDI (Centre Laboratoire d'Etudes, 1977; Gledhill et al., 2005; International Isocyanate Institute, 1998; Laboratoire d'Etude, 1976a; Laboratoire d'Etude, 1976b; Syngenta, 2003a; Syngenta, 2003b) and TDI (Brown et al., 1994; Dow, 1992; Kennedy, 1990; Kennedy et al., 1989; Kennedy et al., 1994; Laboratoire d'Etude, 1976b; Laboratoire d'Etude, 1977; MRI, 1987; NIEHS, 1985; Timchalk et al., 1994) and, in lesser number, for TODI (Nippon Soda, 2010), HDI (Bayer, 2009), and NDI (Bayer, 2010b).

The human health hazard assessment for this restriction proposal focuses on respiratory sensitisation. The Molecular Initiating Event (MIE) of sensitisation, i.e. binding of the low-molecular weight chemical hapten to protein to form a protein-hapten complex, may however occur already at the site of entry. Knowledge about the systemic distribution (and eventual elimination) is therefore not needed for deciding qualitatively on the sensitisation potential of the diisocyanates (whereas it may be of interest from the viewpoint of biomonitoring or when evaluating the relevance of potential genotoxic/carcinogenic aromatic amines as a result of the breakdown of aromatic diisocyanates).

Moreover, one of the major conclusions of the toxicology section is that neither animal nor human data available allow for a reliable quantitative risk assessment with respect to this endpoint. As a consequence it is currently not possible to derive a meaningful and reliable DNEL for respiratory sensitisation caused by any of the diisocyanates addressed in this dossier (otherwise ADME data might have been relevant for relative potency estimation).

In the subsequent assessment, therefore, the toxicokinetics of the diisocyanates have not been considered in detail.

B.5.3 Acute toxicity

Not considered for this report

B.5.4 Irritation

The focus of this dossier is on respiratory sensitisation. Diisocyanates have also been shown to cause respiratory irritation in animals and humans and, depending on the respective study setup, the delineation of sensitisation from irritation is often difficult. For this reason, all studies with respiratory effects are addressed together in section B.5.6.

B.5.5 Corrosivity

Not considered for this report

B.5.6 Sensitisation

B.5.6.1 Scope of the assessment

The primary health concern triggering this restriction proposal is posed by respiratory sensitisation. The regulatory importance of respiratory sensitisation is underscored by the fact that this endpoint is listed under Art. 36 of the CLP regulation for triggering harmonised classification and labelling (alongside CMR effects). Respiratory sensitisers are also highlighted as potential SVHCs under the SVHC roadmap (European Commission, 2013b).

Consequently, isocyanates, and diisocyanates in particular, have been included in priority lists for regulatory action, such as the Trade Union Priority List list of substances with occupational relevance which should be regulated under REACH (Santos et al., 2010).

Both animal experiments (mainly in guinea pigs, mice, rats) and human data give undisputable proof that diisocyanates can elicit respiratory sensitisation in a variety of species. All diisocyanates relevant under this restriction proposal are classified as Resp. Sens. 1 as well as Skin Sens. 1 according to CLP, either based on CLH or due to self-classification (cf. Annex B.3 on classification and labelling). It is therefore not necessary to specifically evaluate the available database with a view to the qualitative assertion of the potential of diisocyanates to cause respiratory sensitisation.

As a consequence, the toxicological assessment will predominantly be dedicated to the question of whether suitable starting points (Points of Departure, PoDs) for quantitative risk assessment can be derived from the database.

B.5.6.2 Hazard identification

B.5.6.2.1 Clinical picture

The basics of polyurethane (PU) chemistry were discovered in the late 1930s; large scale PU production only developed after World War II, during the 1950s. Very soon, cases of sensitisation following exposure to diisocyanates have been reported in the published literature.

The Merriam-Webster online medical dictionary³ defines allergy as follows:

"altered bodily reactivity (as hypersensitivity) to an antigen in response to a first exposure [...] exaggerated or pathological immunological reaction (as by sneezing, respiratory embarrassment, itching, or skin rashes) to substances, situations, or physical states that are without comparable effect on the average individual [...]".

In the frame of regulatory toxicity testing, the "first exposure" (in fact, depending on the exposure level, several might be required) to achieve the "altered bodily reactivity" mentioned in this definition is termed "induction", whereas triggering the allergic reaction by renewed exposure(s) is called "elicitation".

For the respiratory tract, one specific way of definition could be

"allergic reactions may range from reactions occurring in the nose (allergic rhinitis), in the bronchial airways (allergic bronchitis or asthma) or alveoli (e.g. hypersensitivity, pneumonitis)." ((Pauluhn, 2016))

Asthma

The pathophysiological and clinical characteristics of asthma have been summarised in the "Global Atlas on Asthma" edited by AACI, the European Academy of Allergy and Clinical Immunology in 2013:

"Pathophysiologically asthma is an inflammatory disorder of the lungs. It leads to widespread airflow limitation. The resulting signs and symptoms are dyspnea, discomfort, wheezing, anxiety and panic and occasionally fatal respiratory arrest. The pathogenesis of asthma is highly complex and as of today incompletely understood. [...] The majority of asthma occurs on an IgE-mediated background with sensitisations to inhaled allergens called allergic asthma. Asthma which occurs on a non-allergic background is termed intrinsic asthma. Asthma often results in chronic persistent airway inflammation unrelated to allergen contact and has features of autoimmunity. Long term chronic inflammation has been associated with airway remodelling with an increasingly fixed airflow limitation as a result of "scarring" of the airways.

Clinically signs and symptoms of asthma vary from patient to patient. Episodic shortness of breath, wheezing and the sensation that inspiration is no longer possible due to hyperinflation of the lungs are common. The pathophysiological equivalent in pulmonary function tests is a reduced FEV1 (Forced Expiratory Volume of the first second) and PEF (Peak Expiratory Flow). A circadian peak of symptoms in the early morning hours is typical. Bronchial hyperresponsiveness to non-specific airway irritants such as smoke, cold air, odours, etc. is characteristic and can be tested with bronchoprovocation test with histamine or methacholine. [...] None of

³ Source: Merriam-Webster online medical dictionary, [http://www.merriam-webster.com/medical/allergy_last accessed on](http://www.merriam-webster.com/medical/allergy_last_accessed_on) 2015/12/15

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

these signs or symptoms, however, is characteristic. Asthma therefore remains a clinical diagnosis.” (Virchow, 2013)

The nature of airway remodelling has been described by Pauluhn as:

“[...] structural changes in the airway walls and extracellular matrix remodelling, including abnormalities of bronchial smooth muscle, eosinophilic inflammation of the bronchial wall, hyperplasia and hypertrophy of mucus glands.” (Pauluhn, 2016)

Fuchs and Valade have likely been the first to give a thorough account of the development of asthmatic effects in 9 (out of a total of 12) workers from a factory, in which PU was produced from TDI:

“First, a normal period of work, without incident, a period of which the shortest duration was 8 days, the longest 2 months. The workers only complained about mild conjunctival irritation, slight lachrymation, and a laryngeal tingle. Then, progressively, signs of bronchial irritation appeared, in particular a dry cough which came about towards the end of the day, accompanied by dyspnoea and sometimes by a sensation of pressure on the chest and also anxiety. These troubles were often intensified during the night and did not cease until the morning when coughing produced limited amounts of viscous expectoration. During this period, persisting insomnia was always noted. In fact, maybe supported by cough and anxiety, this insomnia appeared to have been, in several cases, the earliest symptom. With progression, these troubles did not take long to intensify, forcing the worker to stop with his work. By then, almost all complained about weakness, of nausea and vomiting and of pain in the epigastric and subhepatic regions, symptoms which could have simply been linked to insomnia and provoked by the coughing efforts, but which we took as signals of a constant pattern. Some reported to us an attack of fever. This episode always appeared to have been fugacious and of little importance. After some days of rest and under the influence of simple symptomatic medication [...], the condition of the ill improved rapidly, but nightly cough and insomnia remained as the most persistent symptoms. However, on the same day resumption of work at the same factory was attempted, in the course of some hours, sometimes minutes, an acute crisis of intense [chest (?)] pressure with dolorous cough and thoracic constriction came about, forcing [the workers] to leave the factory and interrupt work. This acute crisis did not calm until the onset of viscous expectoration late at night (sometimes, but not constantly). Among 7 cases [...], this crisis of allergic and asthmatic character has appeared 6 times and has forced these workers to change employment. In the other two cases it has not been observed. One of these workers preferred to change his work after his first pause and did not return to the factory, the other took up his work again at the same workplace and did not have [further] incidents except for the cough which had motivated his first pause and persisted in a subacute manner for some weeks.” [(Fuchs and Valade, 1951), translated from French by the DS].

This description can be taken as typical of a progressively increasing (extreme) reaction of the respiratory system to inhalational exposure towards a diisocyanate, although the rapid deterioration of health reported in this example must likely be ascribed to extremely high exposure levels, as in the early days of isocyanate production, due to lack of knowledge about toxicity, only very limited protection measures, if any, were put in place.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

However, depending on the exposure pattern, also low-level exposure to diisocyanates over a long period of time may lead to chronic Occupational Asthma (OA), the severity of which may range from moderate impairment to permanent loss of lung function and to life-threatening crisis. Physical performance, also outside the workplace, may be affected significantly:

"Eye, nose and throat irritation are usually the first clinical manifestations. Dry cough with chest pain or tightness often follow. Because the cough or wheeze are characteristically worse in the evening or at night, the patient or doctor may not recognise its occupational aetiology. Rhonchi or coarse rales are frequently present. In some workers the characteristic pattern of bronchial asthma is the initial manifestation; in others it develops late. Chest radiographs taken during the acute stage are usually interpreted as normal, although increased markings and patchy infiltration are occasionally seen. The clinical picture can then approximate to acute or chronic bronchitis, bronchial asthma, or rarely, pneumonitis." (Wegman et al., 1977)

Individuals with chemically induced asthma upon each renewed contact with a respiratory sensitiser display hyperresponsiveness of the respiratory tract which is characterised by laboured breathing, wheezing, coughing, chest tightness and/or obstructive bronchospasms.

While asthma is a term mostly used to describe a medical condition in humans, the above symptoms are also found when experimental animals are subject to exposure against a sensitising chemical; however, in animals the term respiratory hypersensitivity appears to be more commonly used. Clinically, respiratory hypersensitivity associated with diisocyanate treatment, like asthma in humans, can be subdivided into two types⁴:

- Type I immediate (seconds to minutes) hypersensitivity: release of a variety of mediators (*inter alia* histamine, leukotrienes, and prostaglandins) from basophils and mast cells following interaction with IgE antibodies, and
- Type IV delayed (12-72 h) hypersensitivity: release of cytokines from specifically sensitised T lymphocytes upon renewed contact with a full antigen (hapten and carrier protein) which contribute to the activation or proliferation of macrophages and mononuclear cells and their migration to the site of antigen (infiltration and inflammatory response).

Both immediate and late-onset hypersensitivity reactions may be present in patients with diisocyanate-induced asthma, with the prevalence of late responses being as high as 70 % (Niimi et al., 1996). The importance of late-onset reactions for testing patients suspected of having acquired isocyanate-related occupational asthma has recently been discussed in (Hagemeyer et al., 2014).

In addition, patients often develop persistent bronchial hyperresponsiveness (BHR; often also the more general term "airway hyperresponsiveness/hyperreagibility (AHR)" is used interchangeably) to non-specific stressors including e.g. other chemicals such as

⁴ Source: Pschyrembel online clinical dictionary, <http://www.degruyter.com/tablewrapper/kw/4072171>, last accessed on 2015/12/15, translated from German

methacholine, cold, dust, or physical exercise that can last for years even in the absence of continued exposure, and complete recovery of lung function may never be achieved (Johnson et al., 2004a). The socio-economic impacts due to asthma are analysed in Section E.6.1.

B.5.6.2.2 Mechanistic considerations

Systematically, Type IV (late onset) reactions may be further subdivided depending on which type of T-helper cells (Th1 or Th2) is activated. However, in the case of diisocyanate-induced asthma, both Th1 and Th2 type patterns of mediator release have been described, as summarised e.g. by Fisseler-Eckhoff and co-workers:

"Elevated levels of induced immune cells, especially CD4 but also CD8 positive T cells and of different cytokines like IL-1 β , IL-4, IL-5, IL-6, IL-15 and TNF- α were demonstrated in biopsies, bronchoalveolar lavage (BAL), and sputum of patients with isocyanate-induced asthma (Boulet et al., 2007; Maestrelli et al., 1994b; Maestrelli et al., 1995; Maestrelli et al., 1997; Piirilä et al., 2008; Wisnewski et al., 2008). IFN- γ but no IL-5 or IL-13 expression was detected in human T-cell lines after exposure to HDI (Wisnewski et al., 2003). Other studies found a predominant activation of neutrophils (Fabbri et al., 1987; Lemièrè et al., 2002; Park et al., 1999) and an increase in myeloperoxidase and IL-8 after exposure to TDI supporting the neutrophil recruitment (Lee et al., 2003; Park et al., 1999). An increased MMP-9 level in TDI exposed patients was found (Park et al., 2003; Piirilä et al., 2010) associated with a decrease in MMP-7 expression and a regression of Th2 type inflammation (Piirilä et al., 2010). In late reaction after BAL Zocca et al. found increased levels of the chemotactic active leukotriene B4 in patients after exposure to TDI (Zocca et al., 1990). The role of neuropeptides in TDI induced hyperreactivity has been investigated so far in animal models (Mapp et al., 1998; Scheerens et al., 1996). Scheerens et al. demonstrated the role of sensory neuropeptides, especially tachykinins, in the development of airway hyperresponsiveness in a TDI induced mouse model (Scheerens et al., 1996) and Mapp et al. showed comparable effects in guinea pigs (Mapp et al., 1998). Taken together, these results show a heterogenic picture of a Th1 controlled inflammation process (TNF- α , IL-1, IL-8, INF- γ), but are also conform to a Th2 triggered allergic process (IL-4, IL-5, IL-6)." (Fisseler-Eckhoff et al., 2011)

If the inflammation process is prolonged, ultimately airway remodelling will be the result (cf. Figure 3).

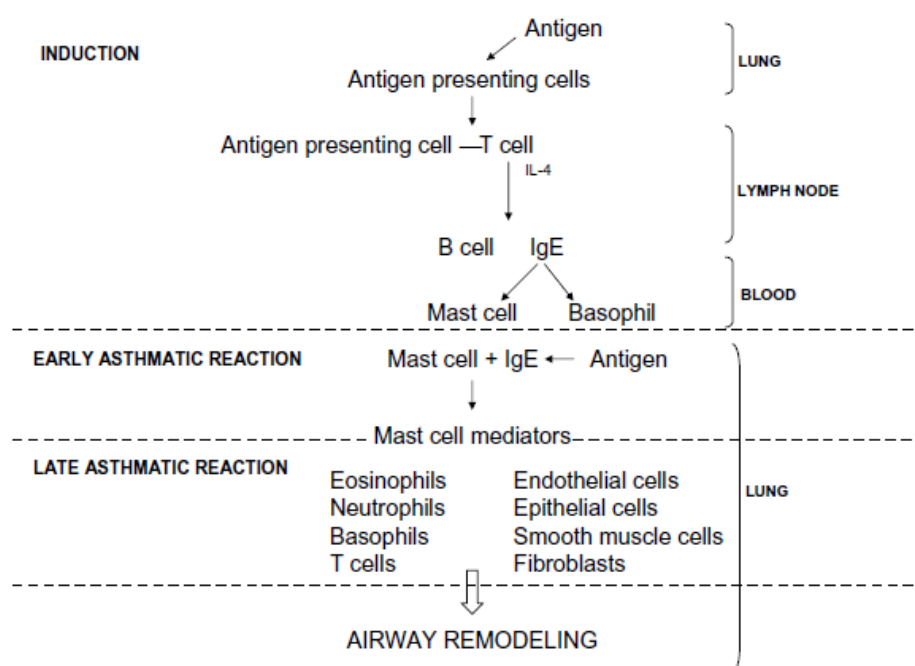


Figure 3: Simplified overview of the allergic cascade [from (Verstraelen et al., 2008)]; for a detailed description cf. also (Bloemen et al., 2007)]

To a varying extent, these cell types and cytokines also play a role in non-allergic inflammation processes. It has already been mentioned above that, as a consequence, it is often difficult to discern respiratory irritation from sensitisation effects. Recently Pauluhn noted:

"A separation of endpoints differentiating unequivocally the 'irritant' from the 'allergic' airway inflammation is experimentally complex, if possible at all. In this context, it should be recalled that lung macrophages are a type of antigen presenting cells (APC), including PMN, that infiltrate inflamed tissues and release prodigious quantities of reactive oxygen/nitrogen species (ROS/RNS) and inflammatory cytokines/chemokines. These orchestrate not only the inflammatory response, but also contribute to antioxidant depletion with further enhancement of inflammation and glutathione (GSH) depletion. Evidence suggests that depletion of GSH from APCs in vivo results in lowered Th1 and higher Th2 activity. Thus, macrophages with mostly oxidized GSH are effectively type 2 and could polarize Th2. Thus, it seems immune activity can have Th1 or Th2 character depending on the redox-status of the cell and the diverse biological activity they develop in response to pro-inflammatory mediators they encounter in their immediate microenvironment (Kidd, 2003; Laskin et al., 2011). In this context, it is important to recall that many reactive low molecular weight chemicals may undergo direct electrophilic reactions with GSH (Pauluhn, 2011), and hence are biased to polarize Th2 by an entirely different mechanism. Once initiated, APC and Th2 cells may undergo a self-reinforcing 'autocrine' loop with amplification. Hence, despite the fact that the terminal phenotypic appearance speaks for an immunological sequence of events, it becomes increasingly demanding and complex to link

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

'respiratory sensitization' unequivocally to any specific immunological so-called 'master or fingerprint cytokines' or non-immunological process." (Pauluhn, 2015)

A review of cell types involved in allergic asthma is given by Verstraelen and co-workers (Verstraelen et al., 2008). A comprehensive review of the role of endogenous mediators in the generation and progression of asthma within the airway epithelium has been provided by Lambrecht and Hammad (Lambrecht and Hammad, 2012).

The recent update of the IR&CSA guidance R.7a on sensitisation notes:

"For substances that sensitise via the respiratory tract, there is still uncertainty regarding the exact mechanisms leading to respiratory sensitisation. [...] The current hypothesis is that the mechanism favours Th2-type immune responses (skin sensitisation favours Th1-type response), which is characterised by the production of cytokines, such as IL-4 and IL-5, and IgE antibodies. [...] Recently, it has been hypothesised that Th17 cells would also play a crucial role in respiratory sensitisation via secretion of IL-17 [...]. The role of IgE may be the greatest reason for uncertainty, as there are patients who display serum IgE antibodies of the appropriate specificity, whereas in other instances (and particularly with respect to the diisocyanates) there are symptomatic subjects in whom it is not possible to detect these IgE antibodies. It has been hypothesised that either there may be mechanisms leading to respiratory sensitisation that is IgE-independent, or this is linked to technical difficulties in the accurate measurements of hapten-specific IgE-antibodies [...]". (ECHA, 2016)

Hofmaier and co-workers have recently reviewed the role of IgG antibodies in IgE-mediated allergy (Hofmaier et al., 2014).

Extrinsic allergic alveolitis

Symptoms of acute forms of hypersensitivity pneumonitis include fever, malaise, non-productive cough, leukocytosis, and elevated immunoglobulin levels (Karol and Dean, 1986). The transient symptoms develop several hours following exposure.

Other respiratory diseases

Isocyanate exposure may be responsible also for non-allergic forms of asthma and chronic obstructive lung diseases based on irritant-induced mechanisms, cf. e.g. (Baur et al., 2012).

B.5.6.2.3 Delay of effect

It has already been noted above that respiratory hypersensitivity to diisocyanates includes delayed reactions such as bronchoconstriction, thoracic pressure, and anxiety peaking several hours after exposure, e.g. at night following a working day. Notably also another form of delay is involved with respect to the (often considerable) time it takes to develop isocyanate asthma (i.e. delay of first occurrence of the effect):

"Diisocyanate OA is often characterized by a variable latent period, consisting of months to years of exposure before the development of symptoms in workers [...]" (Johnson et al., 2004b).

In a study by Pisati and co-workers, the average time between uptake of work and onset of asthmatic symptoms was almost 9 (8.8 ± 7 , mean \pm SD) years of work and at the time the

study was performed, workers had continued working under isocyanate exposure with asthmatic symptoms present for an average of 3 (2.9 ± 2.9) years (Pisati et al., 2007).

The results reported by Lim and co-workers in 2007 even raise the question whether delay of effects might also cross generation borders. In this study sensitisation of female mice to TDI increased the susceptibility of their offspring to develop diisocyanate-related asthma (Lim et al., 2007).

B.5.6.2.4 Reversibility

A recurring issue in discussions between authorities and industry on sensitising chemicals is the question of the reversibility of sensitisation. Interpretations of the term "reversibility" appear to be variable. Thus, below, a short explanation of the interpretation of "reversibility" by the DS in the context of this dossier is given.

The Merriam-Webster Online Medical Dictionary⁵ defines the term 'reversible' as "*capable of being corrected or undone: not permanent or irrevocable*".

According to the Pschyrembel Clinical Online Dictionary⁶, "reversible" in the medical context means "*healable*".

Terms like "irrevocable", "undone", or "healable" support the notion that "reversibility", in the medical sense of the word, could best be translated into "full restitution to the health status which could be expected if exposure had never occurred".

In the context of respiratory sensitisation and in line with the WHO definition of "health"⁷, the direct improvement of the clinical symptoms in a patient upon removal from exposure is therefore not sufficient to render the effect reversible. Sensitised people may at any time upon re-exposure suffer from respiratory impairment again (which they would not do, had they not been sensitised).

WHO/IPCS and OECD in their definition of "key generic terms used in hazard/risk assessment" note that the term "adverse effect" also includes physiological changes that result in "an increase in susceptibility to other influences." (IPCS, 2004)

Therefore, in the view of the DS, the acquisition of sensitisation in itself represents an adverse effect, and for true reversibility, also hypersensitivity itself must have been "healed". In other words: OA caused by diisocyanates would only be considered reversible if

⁵ Source: Merriam-Webster online medical dictionary: <http://www.merriam-webster.com/medical/reversible>, last accessed on 2016/06/30

⁶ Source: Pschyrembel online database: <http://www.degruyter.com/view/hunnius/5056418>, last accessed on 2016/06/30, translated from German

⁷ 'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.' (Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948, cf. <http://www.who.int/about/definition/en/print.html>, last accessed on 2016/06/30).

the affected individual(s) would not react to a later re-challenge in any other way than non-sensitised persons.

In contrast, workers with asthma symptoms from isocyanate exposure often continue to have symptoms even months or years after exposure has been terminated, cf. e.g. (Akimoto et al., 1992; Banks et al., 1990; Fabbri and Mapp, 1991; Lemièrè et al., 1996; Padoan et al., 2003; Paggiaro et al., 1990; Park et al., 2002; Park and Nahm, 1997; Piirilä et al., 2008; Piirilä et al., 2000; Pisati et al., 2007; Rachiotis et al., 2007; Rüegger et al., 2014; Saetta et al., 1992; Valentino and Rapisarda, 2002).

"The symptoms recede quite rapidly when the exposure is discontinued, only to return in many cases in the form of an acute attack on renewed, even very short and slight, exposure" (Swensson et al., 1955).

Karol reported that the serum of one person with TDI hypersensitivity kept containing TDI-sensitive antibodies until 18 months following the last symptomatic exposure (Karol, 1981).

In 1987, Lozewicz and co-workers reported a follow-up of 50 cases of occupational, TDI-related asthma, all of whom had avoided exposure for at least 4 years. Patients came from a variety of different professions, such as printing/laminating of flexible packaging, polyurethane foam production, paint manufacture or use etc. Details on the extent and duration of previous diisocyanate exposure are not given. At follow-up, 82 % continued to have respiratory symptoms and approximately half of these required treatment at least once per week. According to the authors,

"[...] these results indicate that a significant proportion of those with isocyanate-induced asthma are likely to have persisting symptoms for at least several years after exposure is avoided". (Lozewicz et al., 1987)

Over the last decades, diisocyanate exposure levels at the workplace have been reduced by successive lowering of and more general adherence to Occupational Exposure Limits (OELs). Thus, it may be assumed that the above reports refer to considerably higher exposure than would be expected today. However, data from follow-up studies are also available from more recent years. Padoan and co-workers conclude that:

"Results indicate that respiratory symptoms and airway hyperresponsiveness to methacholine persist in subjects removed from exposure to TDI for > 10 yrs. A more favourable prognosis was associated with a better lung function and a lower degree of airway hyperresponsiveness to methacholine at [first] diagnosis." (Padoan et al., 2003)

Pisati et al. report that:

"25 non-atopic spray painters originally diagnosed with OA due to TDI were re-examined 46-73 months after removal from exposure. This included non-specific hyperreactivity as well as a re-challenge with TDI, to which 7 reacted positively. All persistent reactors had still asthma and their symptom score, medication score, FEV1, PD20 [i.e. dose resulting in a 20 % fall of the FEV1] and serum IgE were unchanged between assessments. In the 18 subjects no longer responsive to TDI, 8 had still features of asthma: their symptom and medication score had improved significantly, but FEV1, PD20, and serum IgE had not significantly changed; the other ten patients no longer reacting to TDI were also asymptomatic and their PD20

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

had become normal. The duration of symptomatic exposure to TDI served well to distinguish between these groups (TDI-responders: 4 ± 1.6 yr, asthmatic non-responders: 2.1 ± 0.8 yr; non-asthmatics: 0.6 ± 0.3 yr; $p < 0.001$).” (Pisati et al., 2007)

Birdi and Beach state that

“There is considerable variability in outcomes from occupational asthma, and so for a given individual complete recovery is not guaranteed even with complete removal from further exposure.” (Birdi and Beach, 2013)

Symptoms of acute respiratory impairment may diminish or even completely vanish in a proportion of the population (but not in all of its members), as long as no renewed exposure occurs. On the other hand, even a long time after removal, a certain percentage of affected individuals will still show hypersensitivity to diisocyanates. Of those not reactive to the diisocyanates anymore, a certain percentage will maintain asthmatic symptoms (i.e. in the form of AHR) for at least several years, possibly life-long.

In individuals, in whom chronic asthma-related inflammation already has resulted in airway remodelling, these changes are not only irreversible by themselves, they also strongly impair physical performance at and outside the workplace.

It is noted that cases of complete remission have been reported, however, for a considerable number of patients, lifetime impairment (of varying degree) will result, once isocyanate asthma has been acquired.

Thus, while removal of affected workers will in most cases alleviate acute symptoms of respiratory distress, in the view of the DS, respiratory hypersensitivity and asthma caused by exposure to diisocyanates have to be considered as a generally irreversible, chronic disease, with life-long negative consequences for the individuals concerned.

B.5.6.2.5 Interindividual variability

Development of OA is not only dependent on the exposure pattern experienced in the workplace. There are also aspects of individual predisposition (e.g. existing diseases of the respiratory tract or the cardiovascular system, immune status). Also genetic (Yucesoy et al., 2014; Yucesoy et al., 2012) and epigenetic factors might play a role, cf. e.g. (Ho, 2010; Moggs et al., 2012; Vercelli, 2016; Yang and Schwartz, 2012). The influence of atopy on the susceptibility for sensitisation has been discussed. Based on dermal prick testing, Baur and Barbinova found that the fraction of atopics in employees sensitive to isocyanates was lower than in the control population [(Baur and Barbinova, 2013); for workers sensitized to latex, the opposite was found]. Pronk and co-workers reported similar findings in spray painters (Pronk et al., 2007). However, it remained unclear whether this apparent suppression really represented a protective effect or whether it was explainable by negative selection, i.e. as atopics could in fact be more susceptible and therefore might have needed to leave their work (whereupon they would also have left – or never entered - the respective study). Arguably, the definition of atopy is also not rigid enough to allow firm conclusions in this matter.

Put simply, the immune system can be understood as a dynamic tool for discerning “things that belong in the body” from those which do not, and for protection of the body against the latter. Moreover, in order to be successful in changing environments, this system is

equipped with constantly active mechanisms of learning and re-programming. From there it becomes clear that any individual's susceptibility to an adverse immune reaction will to a large part be driven by that person's previous "immune history", i.e. the individual traits of the innate immune system as well as the development of the adaptive immune system based on the individual "exposome" (Miller and Jones, 2014) of that person. As a consequence, in any given human collective, significant interindividual variability in terms of sensitivity towards sensitisation against diisocyanates can be expected, which pertains both to the dose/concentration needed to elicit certain symptoms and to the nature and severity of these symptoms.

B.5.6.2.6 Cross-reactivity

Cross-reactivity between different (di)isocyanates (most prominently TDI and MDI) and also polyisocyanate resins has been demonstrated both in animals and humans, cf. e.g. (Baur, 1983; Innocenti et al., 1988; Karol, 1983; Karol and Hauth, 1982; Karol et al., 1981; Karol and Magreni, 1982; Malo et al., 1983; Pauluhn and Mohr, 1998; Pollaris et al., 2015; Svensson-Elfsmark et al., 2009; Tanaka, 1980; Tanaka et al., 1987; Thorne et al., 1987; Vanoirbeek et al., 2009; Wass and Belin, 1989). Below, examples of cross-reactivity of anti-TDI antibodies with other antigens (Table 7) as well as cross-reactivity of TDI-related antigens with other isocyanate-specific antibodies (Table 8) are shown.

Table 7: Cross-reactivity of anti-TDI antibodies with other antigens

Species	Antigen	Reaction rel. to corresponding TDI-protein-hapten conjugate (%)	Reference
Guinea pig	HDI-HSA	3	(Karol et al., 1981)
	HMDI-HSA		
	MDI-HSA	8-13	(Karol, 1983)
	MIC-GPSA	0-100	
	HDI-GPSA	1-3	

Table 8: Cross-reactivity of TDI-related antigens with other antibodies

Species	Antigen	Antibody	Reaction rel. to anti-TDI (%)	Reference
Rat	MIC-HSA	Anti-MIC	> 100	(Svensson-Elfsmark et al., 2009)
Guinea pig	TDI-HSA	Anti-HDI	3	(Karol et al., 1981)
		Anti-MDI	14	
		Anti-HMDI	0	
	DI-GPSA	Anti-Polyisocyanate-Resin	Not referable to Anti-TDI due to different induction concentrations; but quantitatively comparable with reaction towards Resin-GPSA	(Pauluhn and Mohr, 1998)

B.5.6.2.7 Aggregate (multi-route) exposure

Respiratory sensitisation to diisocyanates appears to be closely linked to skin sensitisation. According to Dearman and co-workers,

"[...] the majority of the respiratory allergens tested were found to elicit positive responses in one or more standard tests used for the identification of skin-sensitizing potential (guinea pig maximization test, the Buehler test and/or the local lymph node assay)". (Dearman et al., 2013)

Moreover, for diisocyanates, respiratory symptoms or antibody production have been observed after epidermal [e.g. (Haag et al., 2002; Karol, 1981; Scheerens et al., 1999; Vanoirbeek et al., 2004)], subcutaneous (Sarlo and Clark, 1992) and intradermal induction (Blaikie et al., 1995; Mapp et al., 1996; Pauluhn, 1994; Pauluhn, 1997; Pauluhn, 2013).

Also the opposite phenomenon (epidermal or dermal hypersensitivity following inhalative induction with diisocyanates) has been reported (e.g. (Ebino et al., 2001; Karol, 1983)). In fact, some authors, e.g. (Pauluhn, 2013), have noted that dermal induction (followed by an inhalation challenge) may be the route of choice for respiratory hypersensitivity testing of irritants, as *inter alia* an irritant effect on the airway epithelium already at the induction stage can be excluded.

B.5.6.3 Endpoints for diagnosis of respiratory hypersensitivity/respiratory allergy

B.5.6.3.1 Non-human data

Physical endpoints of respiratory impairment in animals have been measured after reaction with diisocyanates themselves, with diisocyanate-serum albumin conjugates (*inter alia* to circumvent the irritant properties of the respective diisocyanate), but also as unspecific hypersensitivity following provocation tests with serotonin [5-hydroxytryptamine or 5HT, (Scheerens et al., 1996; Scheerens et al., 1999)], acetylcholine (Pauluhn, 1997; Pauluhn and Mohr, 1998), or metacholine (Lee et al., 2002; Matheson et al., 2005b; Matheson et al., 2001; Matheson et al., 2002; Vanoirbeek et al., 2004).

Clinical symptoms of diisocyanate-related respiratory hypersensitivity in animals include changes in breathing frequency and volume. Aside from measurements of increased respiration rate [RR, (Aoyama et al., 1994; Huang et al., 1993; Karol, 1983; Sarlo and Clark, 1992)] or tidal volume [TV, (Blaikie et al., 1995)], several authors have used composite, dimensionless, flow-derived measures of respiratory function [e.g. (Matheson et al., 2005b; Matheson et al., 2001; Pauluhn, 1997; Pauluhn, 2013)].

At lower doses, moderate changes in endpoints of respiratory impairment, e.g. RR, 'Penh'⁸ or "FDP"⁹, are noted. With increasing dose, laboured/'exertional' breathing is observed

⁸ Penh: enhanced end-expiratory pause, an indirect indicator of airway obstruction and lung resistance; $Penh = [(ET-RT)/RT] \times (PEF/PIF)$, where ET = expiration time, RT = relaxation time, PEF = Peak expiratory flow, and PIF = Peak inspiratory flow, as obtained from full body plethysmograph measurements (Matheson et al., 2005b)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

(Tanaka et al., 1983; Yamada et al., 1995; Zheng et al., 2001). At high challenge concentrations of 1 to 5 %, even anaphylaxis and mortality have occurred (Karol, 1983; Tanaka et al., 1983).

Aside from evaluation of respiratory impairment itself, typical endpoints assessed in the studies performed with diisocyanates in animals include a histological or cytometrical assessment of the influx of inflammatory cells, measurement of total and specific IgE and IgG antibodies, and levels of cytokines and chemokines associated with Th1 and Th2 type release patterns.¹⁰

Immunochemically, diisocyanates increase levels of specific as well as total IgE and specific IgG antibodies in animals (Aoyama et al., 1994; Blaikie et al., 1995; Botham et al., 1988; Huang et al., 1993; Karol, 1981; Karol, 1983; Mapp et al., 1996; Matheson et al., 2001; Pauluhn, 1997; Sarlo and Clark, 1992; Scheerens et al., 1999).

At the biochemical level, histamine (Huang et al., 1993), substance P (Kalubi et al., 1992), IL-1 β , IL-4, IL-5, and IL-6 (Fukuyama et al., 2010; Johnson et al., 2004b; Lee et al., 2003; Matheson et al., 2005b; Matheson et al., 2001; Zheng et al., 1998; Zheng et al., 2001), IFN- γ (Matheson et al., 2005b; Matheson et al., 2001; Zheng et al., 1998), TNF- α (Fukuyama et al., 2010; Lee et al., 2003; Matheson et al., 2001; Matheson et al., 2002), vascular endothelial growth factor [VEGF, (Lee et al., 2002)], matrix metalloproteinase 9 (MMP-9), intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion molecule 1 [VCAM-1, (Lee et al., 2003)] levels have all been determined as a result of diisocyanate exposure. Plitnick and co-workers published an overview of the influence of diisocyanates (after dermal application) on diverse cytokine mRNA levels (Plitnick et al., 2005).

Histologically, an increased influx of inflammatory cells, e.g. eosinophilic and neutrophilic granulocytes and macrophages (Mapp et al., 1996; Matheson et al., 2001; Pauluhn, 1997; Scheerens et al., 1996; Scheerens et al., 1999; Yamada et al., 1995; Zheng et al., 2001), B, and T lymphocytes [CD4+, CD8+, NK, e.g. (Svensson-Elfsmark et al., 2009)] in bronchoalveolar lavage fluid (BALF), lung and upper airway tissues and, ultimately, epithelial damage [e.g. (Matheson et al., 2001)] have been observed following treatment of animals with diisocyanates.

Pauluhn and Mohr have proposed that, in order to classify a low-molecular-weight substance as respiratory sensitiser, a triad of responses should be considered: (1) positive respiratory response upon challenge with the substance of concern, and if negative, also challenge with a protein conjugate of the substance, (2) an influx of eosinophilic granulocytes, and (3) increased specific IgG₁ response (Pauluhn and Mohr, 1998).

⁹ FDP ('Flow-derived Dimensionless Parameter') = $PEF \times [(ET+IT)/TV]$, where TV = Tidal Volume (Pauluhn, 1994; Pauluhn, 1997)

¹⁰ The above mediators are also involved in chemically induced irritation. Care must be taken to use experimental designs which are capable of delineating immediate-onset reactions from respiratory irritancy, another aspect of the toxicological profile of diisocyanates, from immediate hypersensitivity responses.

None of the available animal experiments included a long-term follow-up of sensitised animals; therefore these tests cannot elucidate the question of a potential reversibility of hypersensitivity after a sufficiently long period of abstinence.

B.5.6.3.2 Human data

Diagnosis of occupational asthma is primarily based on anamnesis. Work-related obstructive complaints could be objectified by serial spirometry or self-monitoring by means of portable spirometers.

Validated skin tests for verification of sensitisation against isocyanates do not exist (Nowak, 2010). Testing for specific serum IgE antibody reveals as negative in many patients with symptomatic isocyanate asthma. This may be due to methodological problems and the short half-life of unbound IgE (Kimber et al., 2014). In case of positive results, isocyanate specific IgE is a strong indicator for isocyanate asthma in symptomatic patients (Fisseler-Eckhoff et al., 2011; Wisnewski, 2007).

Non-specific tests for bronchial hyperresponsiveness should be performed at the end of the working week after two weeks of work with relevant exposure. There are cases of negative testing in patients with isocyanate asthma. In these cases specific inhalation challenge tests are indicated. Even small concentrations can elicit severe asthmatic reactions (Nowak, 2010). Therefore this test needs special equipment and trained personal (Fisseler-Eckhoff et al., 2011).

Positive testing of IgG antibodies is an essential part of diagnosis for extrinsic allergic alveolitis, but is not specific for the disease. Changes in chest radiographs may be observed. Diagnostic challenge tests or re-exposure combined with clinical observation could be necessary to confirm the diagnosis (Sennekamp et al., 2007).

Endpoints used regularly for the diagnosis of OA in the human case reports, case studies, and epidemiological studies described in detail below, are:

- clinical symptoms: wheezing, dry cough, intermittent shortness of breath, particularly in connection with physical activity,
- lung function testing following unspecific or specific bronchial provocation: Forced Expiratory Volume in one second (FEV1), Peak Expiratory Flow (PEF),
- presence of diisocyanate-specific IgE and IgG antibodies.

B.5.6.4 Overview of animal data

B.5.6.4.1 Endpoint selection

The most recent version of the IR&CSA guidance 7a, section 7.3, defines respiratory sensitisation as follows:

"Respiratory sensitisation (or hypersensitivity) is a term that is used to describe asthma and other related respiratory conditions, irrespective of the mechanism (immunological or non-immunological) by which they are caused." (ECHA, 2016)

The Guidance on the Application of the CLP Criteria adds that:

„Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.“ (ECHA, 2015)

For this reason, in this dossier, the toxicological database for the diisocyanates was evaluated for two types of effect:

- Respiratory effects: In line with the above definitions, the primary focus of the dossier is on respiratory effects: asthma, rhinitis, airway pathology. As it is difficult to separate irritation and sensitisation with regard to the latter two points, also studies assessing irritant/inflammatory processes of the airways without specifically investigating immunological endpoints have been included, as from a regulatory viewpoint such effects are undesired as well.
- Effects indicative of the sensitised state: Most of the studies in animals and humans cover only a limited fraction of the lifespan or working life. For this reason, the DS already regards the sensitised state as such as an unwanted and adverse effect, since this state persists and exacerbation of the symptoms of respiratory allergy may occur over time.

In summary, this evaluation will focus on all adverse effects on the respiratory system, and all effects indicative of sensitisation, namely:

- respiratory function (e.g. clinical signs, respiration rate (RR), or dimensionless flow parameters),
- inflammation markers in the respiratory tract (e.g. histopathology, cytokines, clinical signs of irritation etc.),
- antibody titres (e.g. total IgE, specific IgE, specific IgG), and
- dermal contact hypersensitivity (positive results in skin sensitisation tests).

Such effects will be evaluated both after uptake via the skin or by inhalation. However, since the focus is on respiratory effects, positive results in skin sensitisation tests will not be considered for their own sake, but rather for providing evidence of the sensitised state.

B.5.6.4.2 Dose-response relationships (DRRs)

A multitude of factors govern the quantitative outcome of an animal experiment (with respect to sensitisation) under a given exposure regimen. To name just a few:

- Test species: In the literature the preferability of one animal species over the other in terms of under- or overprediction in humans has been discussed, but there is no consensus about which species should be the “gold standard”. Considerable physiological differences e.g. regarding organisation of immune response have been noted and systematic knowledge on intraspecies variability regarding toxicokinetic and –dynamic factors (with respect to diisocyanates) is lacking. With respect to skin sensitisation, historical test designs mostly used guinea pigs or rabbits, a paradigm which over time shifted towards mice (with the introduction of the LLNA). The development of respiratory

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

sensitisation testing started in rabbits and guinea pigs, whereas more recent models use mice or rats;

- Group size (statistical resolution);
- Exposure scheme: Induction route (epidermal, subcutaneous, intradermal, intranasal, inhalation as vapour or as aerosol), induction concentration and vehicle, number of repetitions of induction exposure, time between induction exposures, time between last induction and first challenge, and between challenges, challenge route (intranasal, intratracheal, inhalational), challenge concentration, number of repetitions of challenge exposure;
- Often experimental designs are optimised for obtaining a yes/no decision on sensitisation potential, e.g. for classification and labelling rather than for obtaining a DRR (or threshold) in animals.
- Nature of the agent used for challenge (diisocyanate, diisocyanates serum albumin conjugate, provocant of unspecific hyperreactivity);
- Laboratory methodology used for assessing the endpoint (e.g. method of antigen or antibody preparation).

Associations between some of these parameters have been identified in a qualitative way, e.g.:

- The way in which allergic inflammation is mediated is species-dependent, e.g. predominantly via IgE mediation in the Brown Norway rat vs. via IgG in guinea pigs (Pauluhn, 2013).
- The doses required for elicitation of a hypersensitivity reaction in sensitised animals seem to be lower than those required for sensitisation [e.g. (Aoyama et al., 1994; Arts et al., 2006)].
- Elicitation of hypersensitivity seems to depend on the administered C x t (concentration multiplied with exposure duration) product, but the same C x t administered in small repeated doses induces higher antibody titres than in one single higher dose (Karol, 1983). Such data seem to suggest that lower doses are required to induce sensitisation upon prolonged repeated exposure as compared to a single or only a few successive exposures. In conjunction with the observation that in the workplace humans sometimes develop allergic reactions only weeks or months after the onset of exposure, a plausible hypothesis explaining this finding would be that upon continuous low-level exposure the immune memory gradually builds up until a critical level for triggering the allergic reaction is reached. Alternative explanations for the observation in humans could be found in unreliable exposure measurements and/or unnoticed peak exposures. However, it is not clear how the latter should explain findings in experimental animals that were tested in a controlled exposure setting.

When comparing the outcome of elicitation thresholds of animals sensitised by different routes, it appears to be of paramount importance to take into account the differences between dosages used for sensitisation and challenge because the threshold of elicitation is not an inherent property of the allergen (hapten) alone, but is also a consequence of the severity of the induction regimen (Hostynek and Maibach, 2004) This is *inter alia* further illustrated by the following findings:

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

- For dermal contact hypersensitivity in humans, an inverse correlation exists between the sensitising dose per unit area and the elicitation dose to which an individual will show an allergic response (Friedmann, 2007). This statement was also found valid for animal models of respiratory sensitisation (Pauluhn, 2013).
- Under otherwise identical experimental conditions, antibody titres vary with the preparation method of (the identical) antigen (Botham et al., 1988).
- With intradermal induction, challenges with diisocyanate-guinea pig serum albumin conjugate (GPSA) were more sensitive than with the diisocyanates itself, whereas with inhalation induction, the opposite was observed (Pauluhn, 1994).

Overall, the above factors appear to be interrelated in a highly complex way (Vanoirbeek et al., 2004) which seems virtually impossible to predict.

A large number of different test designs have been employed for investigating respiratory sensitisation caused by diisocyanates in experimental animals (cf. Table 1-1 in Appendix 1) and there is still no agreed, independently validated test protocol with regulatory acceptance even for establishing respiratory sensitisation qualitatively:

"The challenges that chemical respiratory allergy pose for toxicologists are substantial. No validated methods are available yet for hazard identification and characterization, and this is due in large part to the fact that there remains considerable uncertainty and debate about the mechanisms through which sensitization and hypersensitivity of the respiratory tract is acquired and aggravated." (Pauluhn, 2015)

Moreover, the available studies often do not cover all of the potentially relevant endpoints (cf. previous section), perhaps because this would require expertise in many different areas of experimental (immuno)toxicology.

Even bigger challenges are encountered when trying to derive DRRs from animal studies with a view to perform quantitative interspecies extrapolation to humans. Moreover, even if agreement on a suitable protocol was reached, systematic verification/validation of DRRs obtained in animals would be generally difficult due to lack of suitable data on the human side (with *de novo* generation of such data not possible for obvious reasons). It follows that due to numerous knowledge gaps it is currently not possible to extrapolate DRRs from animal experiments to humans with sufficient certainty.

The IR&CSA guidance R.8 clearly states that:

"Since there are currently no available methods to determine the thresholds and to establish DNEL for respiratory hypersensitivity, only qualitative risk assessment for this endpoint can be performed. There is evidence from both human and animal studies which indicate that effective sensitisation of the respiratory tract can result from dermal contact with a chemical respiratory allergen." (ECHA, 2012)

Notably the above statement refers to respiratory hypersensitivity regardless of the induction route¹¹. This position has also been confirmed in the recent update of the endpoint-specific IR&CSA guidance on sensitisation (ECHA, 2016).

In summary, the DS finds that based on animal experiments currently no reliable exact quantitative relationship between exposure pattern (in terms of C x t, intervals between exposures etc.) and outcome in terms of respiratory sensitisation in humans can be established.

Arts and co-workers expressed a similar view in their review from 2006:

"Notwithstanding the observation of dose-response relationships and no-effect levels, due to a number of uncertainties, no definite conclusions can be drawn about absolute threshold values for allergens with respect to sensitization of and elicitation reactions in the skin and respiratory tract" (Arts et al., 2006).

It is noted that more recent reviews (Cochrane et al., 2015; Dotson et al., 2015) still arrive at essentially the same conclusion.

B.5.6.4.3 Potency

The above considerations also preclude derivation of relative potencies of diisocyanates (with respect to respiratory sensitisation) in humans. Notably, „potency“ has both a toxicokinetic and a toxicodynamic aspect. Toxicokinetic differences (bioavailability, metabolism etc.) between the different diisocyanates are still poorly understood. This is further complicated by a lack of understanding of how e.g. diisocyanate vapours or aerosols behave in ambient air (e.g. reaction with humidity, oligomerisation) and by technical challenges regarding the analytical methodology available at the workplace. For the toxicodynamic part, it seems prudent to assume that sensitisation potency will depend on the amount of free isocyanate (NCO) groups. At least for the monomeric congeners, reactivity differences caused e.g. by steric hindrance might appear less relevant, although again, knowledge is insufficient. Thus, in subsequent sections, dose metrics will be based on NCO rather than the amount of respective substance itself.

B.5.6.4.4 No Observed Adverse Effect Concentrations (NOAECs)

Another consequence of the reasoning presented in the previous paragraphs is that No Observed Adverse Effect Concentrations (NOAECs) from animal experiments currently cannot be used to extrapolate to NOAECs in humans.

¹¹ Some authors consider the situation to be different with regard to skin sensitisation (as a result of dermal exposure). However, such studies usually do not cover respiratory effects as well, so there is not enough knowledge to conclude how dermal dose-response relationships for skin sensitisation in animals might be related to dermal dose-response relationships for respiratory sensitisation in humans.

B.5.6.4.5 Lowest Observed Adverse Effect Concentrations (LOECs)

Again based on the considerations presented in the previous sections and in order to assist qualitative risk characterisation, the DS decided to at least characterise the available database with respect to the Lowest Observed Effect Concentrations (LOECs) in experimental animals. The expression "LOEC" (and not "LOAEC", for Lowest Adverse Effect Concentration) has been chosen deliberately. Due to the sheer amount of available studies in animals it was not possible in the time-frame available for the preparation of this dossier to assess each experimental observation in every study with respect to its adversity. However, the DS notes that

- in many, if not most of the studies, clearly adverse effects were obvious,
- it is not the purpose of the following analysis to provide a definitive PoD for risk assessment, and
- many studies use an acute and short-term exposure regime while relevant human exposure might continue for months or years, and effects associated with inflammation and/or allergy, even if observed at sub-adverse levels in these studies, might aggravate over time.

Therefore, as presented in more detail below, first the available data - after elimination of irrelevant and/or inadequate studies - have been screened for LOECs. Then a closer look is taken at those studies/experiments with the lowest LOEC values and the effects observed in these studies are discussed, *inter alia* with a view to adversity.

The REACH IR&CSA guidance, section R.8 notes that "*elicitation thresholds seem to correlate poorly with induction potency*" (ECHA, 2012). This is in line with the above considerations on the various and poorly understood factors influencing whether in a given exposure setting, an allergic reaction will be observed.

As a consequence of all these uncertainties, the assessment reported below concentrates on LOECs for induction. However, it should be borne in mind that elicitation LO(A)ECs may be assumed to be even lower than the ones obtained for induction.

B.5.6.4.6 Evaluation strategy

Spanning a time range from 1965 to today, around 400 reports were identified containing data obtained with diisocyanates in experimental animals (all toxicological endpoints). One of the major tasks of the toxicological work package for this dossier was to break down this vast amount of available data into manageable portions.

After narrowing down the scope of the assessment to respiratory effects and sensitisation (cf. above) and subsequent elimination of obviously irrelevant studies, a total of 163 published papers and unpublished reports of animal experiments were selected for further evaluation. In a considerable number of these documents, more than one study was reported. In a first step, these studies were characterised in terms of their general design (species and strain used, induction route and agent, and, where applicable, elicitation route and agent). A total of 264 different potentially relevant studies were identified in that way. For these, also the broader endpoint categories covered (cf. above, i.e. detection of antibodies, respiratory function, inflammation markers, skin sensitisation) were recorded. A tabular overview of all studies is given in Appendix 1, Table 1-1.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

From there it was decided to follow a tiered approach:

- Tier 1: Deselect all studies with induction routes not representative of the real-life exposure situation in the scope of this restriction proposal.
- Tier 2: Separate the remaining studies according to induction route (inhalation, topical) and deselect those studies not matching pre-defined acceptance criteria.
- Tier 3: For the remaining studies record more detailed experimental parameters and LOECs to provide an overview (separately for the dermal and inhalation routes) of the lowest dose levels at which relevant effects were seen.

B.5.6.4.7 Tier 1: Pre-selection step

The aim of this assessment tier was to dismiss all studies with designs not representative of the exposure situation in humans in the scope of this restriction proposal or otherwise unsuitable to derive LOECs.

To that end, first studies were discarded which used an induction route not representative of the exposure route in humans. For the dermal route, only studies with topical induction were accepted, while studies using intradermal or subcutaneous exposure, or e.g. toepad inoculation, were dismissed. Likewise, for the inhalation route, only true inhalation studies were accepted, while those using intranasal exposure, intratracheal instillation, or oropharyngeal administration were not considered any further. Also studies with intraperitoneal application were discarded.

Studies lacking basic information on experimental animals (strain and/or sex) were likewise removed.

In addition, since the assessment goal was to provide an overview of LOECs, only studies reporting the presence of one or more relevant effects were selected for further processing. Where several experiments were reported from one study, only those with effects were processed further.

Finally, studies which used agents other than diisocyanate monomers or prepolymers, e.g. monoisocyanates, isocyanate breakdown products or a diisocyanate hapten-protein conjugate for induction were dismissed.

Application of these filters resulted in 123 experiments with induction exposure via inhalation and 64 studies with topical induction exposure, which were then taken to further evaluation under tier 2.

B.5.6.4.8 Tier 2: Evaluation of studies with inhalation exposure

In a first data recording round the following basic study parameters were captured :

- physical state (aerosol or vapour)
- inhalation type (whole-body or nose-only)
- presence of negative control
- number of animals per dose group

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

If any of these data had been missing, studies/experiments would have been excluded from further processing. However, no further experiment was dismissed on this basis (for details cf. Table 1-2 in Appendix 1) still leaving 123 experiments for further processing under tier 3 (cf. below).

B.5.6.4.9 Tier 2: Evaluation of studies with dermal exposure

In a first data recording round the the following basic study parameters were captured:

- number of animals per group;
- body weight (this was not needed for the inhalation studies since there the relevant dose metric was mg/m³ air, i.e. an external atmospheric concentration, while the dose in the dermal studies needed to be provided on a per-body-weight basis (cf. below, tier 3);
- vehicle;
- mode of application (open/occlusive);
- negative control present (y/n);

If any of these data were missing, studies/experiments were excluded from further processing. Application of these criteria resulted in an exclusion of 24 experiments (for details cf. Table 1-3 in Appendix 1), leaving 40 for further processing under tier 3.

B.5.6.4.10 Overview of the data base following tier 2

For the different diisocyanates, Table 9 below gives an overview of the number of available experiments per species and "induction"¹² route.

Table 9: Overview of the number of available animal experiments per diisocyanate, species and "induction" route

Diisocyanate	Inhalation „induction“			Topical „induction“			Total
	Guinea pigs	Mice	Rats	Guinea pigs	Mice	Rats	
HDI	-	11	4	1	1	1	18
HMDI	1	2	1	7	2	-	13
IPDI	-	8	1	2	1	-	12
MDI	3	2	7	2	2	-	16
NDI	-	-	1	-	-	-	1
TDI	22	16	7	3	9	-	57
m-TMXDI	1	2	2	1	-	-	6
PMDI	1	-	21	-	-	4	26
PHDI ¹³	-	-	8	2	-	-	10
PIPDI ¹⁴	-	-	1	-	-	-	1

¹² Note that from here on often quotation marks are used in order to highlight that the term „induction“ route is understood in this assessment more broadly in the sense of „route of first contact“. Since – as stated earlier – delineation of irritation from sensitisation is often not clearly possible, „induction“ could also refer to „induction of irritation“.

¹³ HDI prepolymer, including HDI biuret and HDI isocyanurate

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Diisocyanate	Inhalation „induction“			Topical „induction“			Total
	Guinea pigs	Mice	Rats	Guinea pigs	Mice	Rats	
PTDI¹⁵	-	-	-	2	-	-	2
Mixed prepolymers	-	-	1	-	-	-	1
Total	28	41	54	20	15	5	163

B.5.6.4.11 Tier 3: Evaluation of studies with inhalation exposure

Evaluation strategy

For studies acceptable for tier 3, further experimental design parameters were captured:

- number of exposures
- hours per exposure
- total study duration (d; including days without exposure)
- critical effect category (antibodies/AB, inflammation markers/IF, respiratory function or clinical signs/RF, skin sensitisation/SS).

Then “induction” LOECs were recorded and converted to the following exposure metrics, if necessary: a) actual concentrations per exposure (mg NCO/m³) and b) total dose [(mg NCO/m³) x h].

Results

Tier 3 results can be found in Table 1-2 in Appendix 1. Numerous designs in terms of the exposure pattern were encountered in the database.

The following evaluation is separated according to single and multiple exposures. To indicate the uncertainties associated with the animal tests reported, dose levels have been rounded to the first significant figure, unless that figure was 1, in which case one figure more was included (e.g. 5.25 was rounded to 5, but 1.25 was rounded to 1.3).

Single exposure

For this part of the evaluation, only experiments with single exposure lasting up to 24 h were considered. A total of 43 experiments (8 in guinea pigs, 10 in mice, and 25 in rats) from 22 study reports matched this criterion. Exposure durations ranged from 10 min to 6 h, LOECs from ca. 0.2 to 800 mg NCO/m³ air, and total doses received (at the LOEC) from 0.4 to 800 (mg NCO/m³ air) x h.

Hardly any of the available experiments were designed for detecting effects specifically linked to sensitisation. Most studies instead were directed at detecting (sensory) irritation

¹⁴ IPDI-prepolymer, including IPDI isocyanurate

¹⁵ TDI prepolymer, including TDI isocyanurate

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

comparatively shortly after the end of exposure. For instance, sensory irritation was reported at air levels greater than or equal to ca. 0.4 mg NCO/m³ [LOEC reported in (Sangha and Alarie, 1979)]. Increased levels of total protein (and, at higher dose levels, further inflammation markers) in BAL fluid were demonstrated at a LOEC of ca. 0.5 mg NCO/m³ in rats by (Ma-Hock et al., 2007) 1 d after single 6 h exposure to vapours of a mixed TDI/HDI-based polyisocyanate (equivalent to ca. 0.4 mg NCO/m³ x 8 h when converted using modified Haber's law, cf. (ECHA, 2012)) as well as by a number of other authors at higher dose or total dose levels.

The lowest LOEC (in this case: a clear LOAEC) for sensitisation-related effects after single exposure was reported by Matheson and co-workers from NIOSH, the US National Institute for Occupational Safety and Health. Mice were sensitised by single 2-h inhalation exposure to ca. 4 mg TDI/m³ [ca. 1.7 mg NCO/m³ x 2 h or 0.4 mg NCO/m³ x 8 h]. Fourteen days later, animals were challenged by administration of 20 ppb TDI (0.14 mg TDI/m³ or 0.07 mg NCO/m³) via the same route for 1 h. Exposed animals showed a clear increase in airway hyperreactivity (AHR) to a methacholine challenge (expressed in the form of the dimensionless respiratory flow parameter Penh) both compared to sham-exposed controls and to animals that only received the induction or the challenge dose. Moreover, total IgG as well as TDI-specific IgG₁ and IgG_{2a} levels were statistically significantly increased (vs. non-detects in controls). Markers of inflammation in the exposed group included histopathological findings in lungs and nares and an 8-fold increase in leukocytes in BAL fluid vs. controls. Sensitisation was further demonstrated by increased AHR (as Penh, the level of increase amounted to a little more than 50 % compared to that observed in sensitised and challenged animals) in naïve mice challenged 24 h after receiving unfractionated lymphocytes from sensitised animals. The study did however not aim at (and therefore did not succeed in) establishing a NOEC (Matheson et al., 2005b).

Ebino and co-workers demonstrated dermal contact hypersensitivity in guinea pigs exposed to ca. 9 mg TDI/m³ via a single 4 h nose-only exposure (ca. 4 mg NCO/m³ x 4 h or ca. 2 mg NCO/m³ x 8 h) when challenged in a patch test 15 or 29 d post-induction. Again the study did not demonstrate a NOEC (Ebino et al., 2001).

Gagnaire et al. reported increased AHR measured as increased airway resistance as a consequence of acetylcholine challenge one hour or one day after a single 1-h whole-body exposure of guinea pigs to 22 mg TDI/m³ (ca. 10 mg NCO/m³ x 1 h or 1.3 mg NCO/m³ x 8 h) (Gagnaire et al., 1997).

Cibulas and co-workers reported increased bronchial hyperreactivity (measured as specific airway conductance, sGaw) in guinea-pigs intravenously administered acetylcholine 2-h after having been exposed to ca. 20 mg TDI/m³ (ca. 12 mg NCO/m³ x 0.17 h or 0.2 mg NCO/m³ x 8 h) for 10 min via nose-only inhalation (Cibulas et al., 1988).

In summary, several studies demonstrated effects related to sensitisation in animals following a single exposure to diisocyanates by inhalation. The lowest reported LOECs were in the order of 0.2-2 mg NCO/m³ x 8 h. It is important to stress again that these LOECs are a consequence of dose level selection which might have been influenced by both technical (capability of reliably generating/analysing test atmospheres) or experimental considerations (doses were selected such that the study authors expected an effect to occur). Therefore they do not allow any conclusion on putative NOECs.

Repeated exposure

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

In the database, a total of 77 experiments (15 in guinea pigs, 28 in mice, and 34 in rats) including standard subchronic and chronic inhalation tests as well as reproductive toxicity studies with more than one exposure to diisocyanates by inhalation were identified. The number of exposures ranged from 5 to more than 500, while the time per exposure was varied from 10 minutes to 24 hours. The LOECs reported, when converted to daily 8-h exposure using modified Haber's law as proposed by the IR&CSA guidance, section R.8 (ECHA, 2012)) ranged from 0.01 to 6 mg NCO/m³ x 8 h). Again a large fraction of these studies did not investigate effects with specific relevance to sensitisation.

In many experiments with repeated exposure to diisocyanates by inhalation, signs of chronic inflammation were demonstrated, e.g. already at a LOEC of 0.03 mg HDI/m³ (ca. 0.02 mg NCO/m³ x 6 h/d equivalent to 0.013 mg NCO/m³ x 8 h/d) in a 2-year chronic inhalation and oncogenicity study (Mobay, 1989), similar effects were seen in a 90-d study with the same diisocyanate in (Mobay, 1988) at about a two-fold dose level]. It is therefore impossible to tell whether these effects represent sensitisation acquired over time and/or rather non-immunological chronic respiratory irritation.

Below only those of the studies specifically dedicated to investigate sensitisation-related endpoints (i.e. either investigating immunological parameters or using an induction-elicitation scheme to demonstrate effects on respiratory function or inflammation markers in sensitised vs. non-sensitised animals) are summarised. Furthermore, experiments applying whole-body inhalation were excluded, since an unknown amount of diisocyanate might have been absorbed via the skin or taken up orally upon grooming.

Since the total number of exposures is varying widely between experiments, the question arises how to extrapolate the obtained LOECs to chronic exposure. It needs to be stressed that the REACH default extrapolation factors have been developed based on historical experience with endpoints not related to sensitisation, while the understanding of the combined dose-time-dependency of effect doses regarding both induction and elicitation of sensitisation is extremely limited. Nevertheless, short of anything better, the REACH default factors below are applied for illustration purposes, keeping in mind that the resulting figures are indicative at most.

Finally, since the task of this overview was to gain insight into the lowest LOECs reported, only the three studies resulting in the lowest extrapolated chronic LOECs (given as daily doses in mg NCO/m³ x 8 h) are summarised here.

Matheson and co-workers from the US National Institute for Occupational Safety and Health (NIOSH) exposed mice via head-only inhalation to 0.02 ppm TDI aerosol-free vapour for 4 h/d, 5 d/wk, over a period of six weeks (dose per exposure ca. 0.07 mg NCO/m³ x 4 h, equivalent to ca. 0.03 mg NCO/m³ x 8 h, total exposure 8.4 mg NCO/m³ x h). A single inhalational challenge with the same concentration was performed 14 days later. At this dose level statistically significant changes in the whole spectrum of endpoints typical of respiratory hypersensitivity testing in animals (i.e. AHR expressed as Penh, cytokine and antibody levels, influx of inflammatory cells) was present. Since the duration of this study was 1.5-fold that of a subacute (28 d) study, the REACH default subacute to chronic extrapolation factor of 6 might be reduced to 4, resulting in a chronic LOEC estimate (at 8 h exposure/d) of ca. 9 µg NCO/m³. A NOAEC was not established. (Matheson et al., 2005a; Matheson et al., 2005b).

Karol demonstrated dermal contact hypersensitivity in guinea pigs when epicutaneously

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

challenged at the end of a 5 d period of 3 h/d head-only inhalation exposure to ca. 0.9 mg TDI/m³ (ca. 0.4 mg NCO/m³ x 3 h or 0.16 mg NCO/m³ x 8 h). Extrapolating to chronic exposure by again using an extrapolation factor of 10 would result in a chronic LOEC estimate in the order of 16 µg NCO/m³ x 8 h (Karol, 1983).

Stadler and Karol exposed guinea pigs via head-only inhalation to ca. 3 mg HMDI/m³ (ca. 1.0 mg NCO/m³ x 2 h or ca. 0.2 mg NCO/m³ x 8 h) for 2 h/d on 3 consecutive days. Upon topical challenge 4 days later, contact hypersensitivity was demonstrated. Using an extrapolation factor of 10, the corresponding chronic LOAEC might be estimated to lie in the order of a daily dose of 20 µg NCO/m³ x 8 h (Stadler and Karol, 1984).

Arts et al. performed a „respiratory Local Lymph Node Assay“ in mice. When challenged 2 days after the end of 45 min/d exposures to ca. 8 mg IPDI/m³ (ca. 3 mg NCO/m³ x 45 min or ca. 0.3 mg NCO/m³ x 8 h) on 3 consecutive days, statistically significant proliferation of mandibular and auricular lymph nodes and changes in cytokine profiles were seen. For TDI, similar results were obtained at a dose level of ca. 4 mg NCO/m³ x 45 min (equivalent to ca. 0.3 mg NCO/m³ x 8 h). Using again an extrapolation factor of 10 would result in a chronic LOEC estimate in the order of 30 µg NCO/m³ x 8 h in both cases (Arts et al., 2008; de Jong et al., 2009).

In summary, sensitisation to diisocyanates has been demonstrated in a number of animal experiments after subacute to subchronic exposure via head-/nose-only inhalation. When extrapolated to chronic 8 h/d exposure (using extrapolation factors that are associated with high uncertainty), the LOECs obtained in these experiments correspond to chronic LOECs in the order of a few µg NCO/m³. For estimating chronic NOECs in humans, these LOECs would need to be further corrected with Assessment Factors for LOEC-to-NOEC extrapolation, inter- and intraspecies variability, and a factor accounting for the huge uncertainties about the dose-time-response relationships behind respiratory sensitisation.

B.5.6.4.12 Tier 3: evaluation of studies with dermal exposure

Evaluation strategy

For studies acceptable for Tier 3, further experimental design parameters were recorded:

- number of applications
- concentration of test item (in g NCO/L)
- applied volume
- application area

Then, as far as possible, LOECs were recorded and converted to the following dose metrics, if necessary: a) dose per exposure [mg NCO/kg bw] and b) total dose [(mg NCO)/kg bw]. Arguably area dose per exposure [mg NCO/cm²] or total area dose [(mg NCO x h)/cm²] would have been the most meaningful dose metric (and where given, they were recorded), as the rate of uptake into the skin is governed by the concentration gradient (the same volume and concentration of test item spread on a smaller area will generate a steeper

gradient). However, in the end the application area was only reported in 3 out of 40 experiments and therefore the database was too small for a meaningful evaluation.¹⁶

Results

Tier 3 results can be found in Table 1-3 in Appendix 1. In almost none of the available studies with topical induction the size of the exposed area is reported. Thus, the most relevant dose metric, i.e. mg NCO/cm² x h is not accessible. Furthermore, reliable data on the relationship between applied external and effective internal dose of diisocyanates after topical administration are absent. Finally, reliable quantitative measurement of dermal worker exposure is not possible at the workplace.

As a consequence of all these drawbacks of the data base, the DS considers that further quantitative discussions would not have any merit here. Therefore below only the lowest topical induction doses for which sensitisation was reported are given on the basis of the total dose received (in mg NCO/kg bw).

Single exposure

In total, 21 experiments (18 in guinea pigs, 3 in mice) with single exposure were available for this evaluation. The lowest doses reported as causing sensitisation in experimental animals were ca. 0.09 mg NCO/kg bw in both guinea pigs and mice exposed to HMDI (Stadler and Karol, 1985), ca. 1.5 mg NCO/kg bw in guinea pigs exposed to IPDI, and ca. 1.8 mg NCO/kg bw in guinea pigs exposed to m-TMXDI, both of the latter reported in (BRC, 1981). In all of these cases, sensitisation was demonstrated as contact hypersensitivity.

Multiple exposures

For the assessment of multiple exposures, a total of 15 experiments were available (2 in guinea pigs, 9 in mice, and 4 in rats). When topically exposed to HMDI once a week for 6 h in three consecutive weeks (total dose: ca. 0.5 mg NCO/kg bw), guinea pigs displayed contact hypersensitivity in a repeated-insult patch test under occlusive conditions (Bio-Dynamics, 1984).

Woolhiser and co-workers obtained positive LLNA test results in mice exposed to a total dose of TDI (corresponding to about 5 mg NCO/kg bw) over 4 consecutive days (Woolhiser et al., 1998). Further positive LLNA test results in mice were reported for TDI at total doses of ca. 7 mg NCO/kg bw received over 2 consecutive days (de Vooght et al., 2013; Liang et al., 2015; Tarkowski et al., 2007; Vanoirbeek et al., 2009).

Respiratory sensitisation following topical induction was shown after two epicutaneous exposures of rats to a total dose of HDI corresponding to ca. 9 mg NCO/kg bw (Pauluhn, 2015) and after 3 exposures of mice to a total dose of TDI equivalent to 11 mg NCO/kg bw (Vanoirbeek et al., 2004).

¹⁶ Due to insufficient knowledge on dermal absorption behaviour, it is not meaningful to report (or compare) assumed internal doses (e.g. in mg/kg bw).

B.5.6.5 Overview of human data

The production of diisocyanates on a commercial scale began during the late 1930s in Europe and expanded to the U.S. in the 1950s (Ott et al., 2003). Since these early years of the industry, human health effects due to diisocyanates have been described in the literature, with more systematic investigations since the 1970s. Thus a huge amount of studies is available today. In the following chapters and for discussion of the given results the data are divided in case studies and epidemiological studies.

B.5.6.5.1 Case reports and case studies

About 100 human case reports or case studies have been identified in the literature. An overview is given in Table 2-1 in Appendix 2. These reports primarily provide overwhelming proof that humans exposed to diisocyanates may suffer from a broad spectrum of respiratory effects including asthma and pathological remodelling of the airways. Also a number of fatal cases have been reported, albeit not in recent years. On the other hand none of these studies include reliable exposure (let alone dose-response) information, they feature only a small number of patients, and in most cases only a limited spectrum of diagnostic endpoints is covered. For all of these reasons, these reports are therefore principally unsuited for use in quantitative risk assessment.

B.5.6.5.2 Epidemiological studies

An overview of epidemiological studies on diisocyanates and respiratory effects conducted until today with short study descriptions and results is given in Appendix 3. The focus is on studies that may provide quantitative information on exposure and exposure-response relationships.

According to the hypothesis that the NCO group of the isocyanates plays the relevant role for the toxicological effect and allows for assessing different isocyanates, including oligomers and mixtures (Bello et al., 2004), studies on several different diisocyanates (and sometimes also their oligomers) are presented together here. In case an eligible study for dose-response assessment would be found, transfer of this to the whole group of diisocyanates could be considered. The tables in Appendix 3 comprise three reviews on TDI from the early 2000s (Diller, 2002; Ott, 2002; Ott et al., 2003), two case-control studies on asthma due to TDI, MDI or HDI (Meredith et al., 2000; Tarlo et al., 1997) and many longitudinal as well as cross-sectional studies. The longitudinal studies are of different length, ranging from 1 year to 19 years (Cassidy et al., 2010). Most of the studies were performed with workers exposed to TDI.

Prevalence and incidence of diisocyanate asthma in epidemiological studies

Prevalence estimates for isocyanate-induced asthma in exposed working populations are likely to vary depending on the use of (and therefore exposure to) diisocyanates as well as the health and safety management at the workplace and thus show a wide range. Although workplace exposures and disease prevalence have decreased during the last decades, it may still be true that prevalence is higher in end-users than in production facilities as found in (Ott, 2002).

In the early 2000s, three reviews on respiratory effects due to TDI were published. Diller (2002) reviewed studies on occupational asthma (OA) due to TDI to calculate prevalence

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

and incidence of TDI-induced asthma (Diller, 2002). The author states that the reviewed studies are heterogeneous (regarding population, validity of diagnosis of TDI asthma, industry, exposure levels), of limited validity, and difficult to interpret.

The prevalence of asthma due to TDI was estimated from ten cross-sectional studies conducted in TDI manufacturing, foam production, applications of varnish or paint, and other uses. The studies included 788 individuals and covered the 38-year period from 1954 to 1992. The reported prevalence of OA varied widely (from 0 to 85 %) and ranged from 0 to 10 % since the late 1980s at workplaces with mean TDI exposure levels < 15 ppb and was higher in workplaces with higher exposures (Diller, 2002). Similarly, prevalence of work-related allergic respiratory disorders due to TDI was estimated to be 1-10 % and prevalence due to MDI 13-27 % by the Health Council of the Netherlands [(Gezondheidsraad, 2008), p.147]. In a study by Pronk et al. prevalence of bronchial hyperreactivity was as high as 20 % in spray painters, who were mainly exposed to HDI oligomers (Pronk et al., 2009).

It should be noted that cross-sectional studies are likely to look at survivor populations and therefore disease frequency may be underestimated.

Incidence of OA due to TDI was estimated by Diller et al. (2002) from nine longitudinal studies conducted in TDI manufacturing, research and development, and flexible foam production. The studies included 2751 workers under risk and cover the 38-year period from 1954 to 1992. Annual incidence of TDI asthma has been up to more than 5 % before 1980 and was reported to be between 0 and 0.7 % thereafter. The downward trend is attributed to a downward trend in TDI exposure. The review reports sparse and mostly qualitative information on the exposure levels and the incidence of TDI-induced asthma is not discussed with regard to particular exposure levels.

The reviews of Ott (2002) and Ott et al. (2003) however focus on exposure-response relationships (Ott, 2002; Ott et al., 2003). Table 3-2 in Appendix 3 gives an overview of the exposure levels and the incidence of OA in the studies reviewed by Ott (2002). It shows that annual OA incidence rates were reported as 5-6 % in earlier times (1950s-1970s) both in TDI manufacture and in TDI using industries and that incidence declined to < 1 % with reduction of TDI concentrations to < 5 ppb (8 h personal samples). The second review by Ott et al. (2003) also reports annual asthma incidences between 0.7 to 1.1 % from four newer studies (1970s to 1990s) with TWA concentrations mostly < 5 ppb. However, short-term TDI concentrations were > 20 ppb and occasionally > 80 ppb. The author of the two reviews assumes that the majority of asthma cases may arise from TDI short-term concentrations > 20 ppb. For example, in one of the longest studies in a TDI manufacturing facility, 7 of 19 cases had reported previous incidents of exposure to TDI, 2 of them related to rashes that had developed while handling TDI or waste products containing TDI (Ott et al., 2000). Likewise, in a cross-sectional study in a urethane mould plant designed to minimise exposure to MDI and where continuous monitoring of MDI area levels showed concentrations below 5 ppb, asthma cases were considered to be due to intermittent higher than normal exposures to MDI during non-routine working activities (Bernstein et al., 1993). However, when trying to establish a threshold or exposure-response relationship for sensitisation, one has to keep in mind that very high exposure concentrations, for example during accidental spills, might also lead to irritant induced asthma (Reactive Airways Dysfunction Syndrome, RADS).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

The two case-control studies also indicate a dose-response relationship for OA. Meredith et al. (2000) conducted a case-control study on asthma in two companies (Meredith et al., 2000). For company A, 27 OA cases were matched to 51 controls by sex and work area. In company B seven cases were identified and all non-cases (n = 12) served as controls, because matching was not possible (moving between work areas, few workers). Data from the two sites were analysed separately.

In company A, 24 cases were attributed to TDI (n = 22 in the manufacture of moulded and block flexible PU foam, n = 2 in factories involved in flame bonding and surface coating of fabrics) and three cases were attributed to MDI (batch moulding of rigid PU components (vehicle roof liners) at 200 °C). Personal exposure measurements by job category, which were performed for a separate study (1979-1986), as well as data collected after 1986 by occupational hygiene consultants were used to estimate the 8-h TWA and peak exposure for each subject based on job title and date. Peak exposures were between 1 - 50 ppb, and in 31 subjects peak exposure was > 20 ppb. There was no difference between cases and controls. Mean 8-h TWA was 1.5 ppb for cases and 1.2 ppb for controls. With a conditional logistic regression analysis an odds ratio (OR) for exposure above the median of the control group of 3.2 (95 % CI 0.96 - 10.6; p = 0.06) was calculated. The OR for 0.1 ppb increase in 8-h TWA was 1.07 (95 % CI 0.99 - 1.16; adjusted for smoking and atopic diseases). The adjusted OR was higher for smoking (2.4) as well as for history of atopic disease (3.4), but not statistically significant.

Cases of company B (n = 7) were attributed to MDI from a chemical plant in which MDI and polymeric MDI mixtures were processed and poured into drums. Some processes involved heating the mixtures. Personal monitoring results from 1988 were available (Marcali method to the middle of 1990 (Marcali, 1957), HPLC thereafter). For each subject, the proportion of measurements \geq LOD of the Marcali method (2 ppb) and > 5 ppb were calculated. Measurements < 2 ppb were treated as being zero. Ninety percent of the 269 TWA samples were < 2 ppb. For the two groups this meant that 169/185 TWA samples for controls and 74/84 for cases were < 2 ppb. Mean and median exposures were < LOD for cases and controls. Median of the highest concentration recorded for each subject was 3 ppb for both groups. The proportion of measurements \geq 2 ppb was 0.09 for controls and 0.18 for cases. The proportion of measurements > 5 ppb was 0.004 for controls and 0.09 for cases. 3/7 cases and 1/11 controls had at least one 8 h TWA exposure measurement > 5 ppb (OR 7.5; p = 0.09). The authors conclude: "*Asthma can occur at low concentrations of isocyanates, but even at low concentrations, the higher the exposure the greater the risk.*"

Tarlo et al. (1997) used a case-control study design, treating 20 companies with compensated isocyanate asthma claims as cases and 203 companies without claims as controls, to investigate the association between isocyanate exposure level and asthma claims (Tarlo et al., 1997). OA cases with identified isocyanate exposure during the 4-year period from mid-1984 to mid-1988 were identified in the Ontario Workers' Compensation Board. Exposure data were taken from a database of the Ontario Ministry of Labour (MOL): air samples collected during the same 4-year period during which the OA claims arose. For the study, exposure in the companies was determined as a binary variable on the basis of the highest level identified (always < 5 ppb vs. ever \geq 5 ppb). The estimated incidence of OA in the 4-year study period was 2.7 % for high exposure companies with claims, 2.2 % for low exposure companies with claims and 0.9 % overall in the total 223 companies surveyed (56 out of 6 308 workers). Combined across isocyanate types, 10/20 (50 %) companies with claims were in the high exposure category and 50/203 (25 %) companies

without claims were in the high exposure category (OR = 3.1; 95 %; CI: 1.1–8.5; p = 0.03).

The most recent study on health effects due to TDI was published in 2014 by Gui et al. and indicates that even keeping 8-h TWA below 5 ppb and peak exposures below 20 ppb may not prevent sensitisation, and dermal exposure may contribute to the induction of the effect (Gui et al., 2014). This inception cohort study was conducted in a newly built factory in Eastern Europe, which is reported to apply TDI-based state-of-the-art polyurethane foam production technology. Newly hired workers (n = 49) were evaluated pre-employment, after 6 months and after 12 months. Over the first year of employment, 7 workers (14 %) had findings that could indicate TDI-related health effects (new asthma symptoms: n = 3, TDI-specific IgG: n = 1, new airflow obstruction: n = 1, decline in FEV₁ ≥ 15 %: n = 3). Twelve workers (25 %) were lost to follow-up. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up. Exposure to TDI measured by continuous fixed-point air sampling was below the LOD (0.1 ppb) in 90 % of the samples. The maximum recorded was 10.0 ppb. No air sampling period exceeded an 8-h TWA of 5 ppb and peak exposures recorded were below 20 ppb. However, fixed area samples may underestimate personal exposures, especially those near the source when fulfilling cleaning or maintenance tasks. Personal sampling performed on seven workers showed TDI levels < LOD. Skin exposure probably has occurred, because TDI was detected on surfaces such as handrails and tables, which workers touch without gloves. In addition, 28 % of the workers reported potential skin contact and during site visits unprotected hand contact with uncured or just cured foam was noted.

These studies indicate that asthma incidence decreases when exposure levels decrease. However, despite modern standards and air levels below current OELs, risks for workers may exist and no minimum level of exposure to TDI for humans is known, below which sensitisation and asthma will not occur in susceptible individuals.

Beside the above limitations regarding a minimum exposure level for humans to TDI, all tabulated studies (Appendix 3) also show limitations that hamper the derivation of an exposure-response relationship (ERR) for diisocyanates regarding sensitisation.

Challenges in assessing an exposure-response relationship

First of all, when describing an ERR, the relevant outcome has to be defined. The endpoint of interest here is respiratory sensitisation, which finally leads to the clinical picture of allergic asthma in humans.

OA can be defined as “a disease characterised by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to exposure to a particular occupational environment and not to stimuli encountered outside the workplace.” Allergic or immunological OA includes both OA caused by agents with an allergic IgE-mediated mechanism as well as OA induced by specific occupational agents in which the responsible allergic or immune mechanisms have not yet been identified or fully characterised ((Bernstein et al., 2013), p.3).

A critical event in the development of occupational allergic asthma is the induction of sensitisation. If sensitisation is prevented, elicitation of asthma will also be prevented. There seems to be high variability in individual susceptibility in already sensitised subjects,

and it will be difficult to estimate a “safe” exposure level for this group. Therefore, sensitisation of naïve individuals rather than elicitation in already sensitised persons is suggested to be a more suitable endpoint to serve as the basis for an OEL/DNEL (Dotson et al., 2015). A possible marker for the induction of sensitisation in IgE mediated allergy is the IgE specific for the antigen. However, in the case of diisocyanates, the diisocyanate-specific IgE have been shown to be too insensitive markers of disease (Kimber et al., 2014). As no reliable marker of induction is known that could be used as a basis for derivation of a DNEL or risk-based values from epidemiological studies, instead, markers of the elicitation phase of the sensitisation need to be considered. Adverse effects of diisocyanates on the respiratory tract investigated in epidemiological studies include respiratory symptoms, accelerated lung function decline and bronchial hyperresponsiveness (Appendix 3).

Respiratory symptoms are often assessed by self-reporting and therefore do not constitute an objective measure. In addition, respiratory symptoms do not have to be specific for asthma, but may also include for example COPD-like symptoms.

Accelerated lung function decline as another outcome was examined in longitudinal epidemiological studies in diisocyanate exposed workers and reviewed by Ott and co-workers (Ott, 2002; Ott et al., 2003). In these reviews, the effect of TDI on accelerated lung function decline was investigated. Eleven longitudinal studies (five in TDI production units and six in sites using TDI) as well as three cross-sectional studies in units using TDI were included. Decline in FEV₁ was seen in earlier studies and in follow-up studies of workers who continued to work after their diagnosis of OA. However, no consistent evidence of accelerated loss in FEV₁ was found in more recent longitudinal studies with 8-h TWA exposure mostly < 5 ppb and even with short-term TDI concentrations > 20 ppb. Accelerated lung function decline is not seen as a sensitive predictive marker of asthma, as asthma is characterised by variable airflow limitation, and lung function may not be decreased permanently. The time of day at spirometry may therefore have a large impact on lung function. There is a diurnal variation, which also may be influenced by shift work. Before to after shift changes in lung function can have high specificity, but have low sensitivity for the validation of occupational asthma (Nicholson et al., 2010). They are not reliable for separating subjects with and without OA (Vandenplas et al., 2013). Further, there is a large intrinsic variability. Thus, the DS concludes that accelerated lung function decline does not serve as a suitable predictive marker for asthma.

In the view of the DS the most relevant marker for asthma examined in the available studies is non-specific bronchial hyperresponsiveness, assessed by a methacholine challenge. In such a test, lung function (FEV₁) of the subjects is measured before the challenge and after inhalation of increasing doses of methacholine. After a certain fall in FEV₁ (for example 15 or 20 %) or when the maximum cumulative dose is reached, the test is stopped. A subject is defined as being hyperresponsive if a certain cumulative dose of methacholine leads to a certain fall in FEV₁ (Pronk et al., 2007). A stricter definition of asthma proposed for epidemiology is the concurrent presence of bronchial hyperresponsiveness (BHR) and wheezing (Toelle et al., 1992). Specific inhalation challenge tests (with the diisocyanate suspected as the cause of sensitisation) are regarded as the reference standard against which other tests for the diagnosis of asthma are validated. The specific challenge test is time consuming, expensive, and needs special facility and expertise (Vandenplas et al., 2013). These probably are some of the main reasons why these tests are not performed in larger groups in epidemiological studies.

Beside these aspects regarding the outcome, a further problem in selecting studies for dose-response assessment is related to exposure assessment. To assign a quantitative exposure value to a specific effect requires reliable quantitative measurements. However, measurement of airborne isocyanates is still a challenge today (see Sections A.2.1.2 and B.9). In addition, the methods for measurement/analysis of inhalation exposure have changed over time and therefore different methods were used in the epidemiological studies (sometimes within the same study) and results may not be comparable. For example, in the older studies the Marcali method (Marcali, 1957) was used for analysis, which is reported to underestimate exposure to a large part (Ott et al., 2003). Besides the method also the site of measurement is of importance, as discrepancies between simultaneously measured area and personal exposure levels are reported (Butcher et al., 1977).

There are also questions concerning the dosimetry and temporal exposure patterns relevant for the effect (see animal experiments). A great issue is the fact that peak exposures are thought to be relevant in inducing sensitisation (see above). The risk of sensitisation may therefore be better reflected by an index that quantifies the occurrence of short intense peaks of exposure than by average or cumulative exposure measures (Checkoway et al., 2004) p. 310). However, Pronk et al. found in their study in Dutch spray painters an association between the cumulative exposure and hyperresponsiveness (Pronk et al., 2009; Pronk et al., 2007).

In addition to all these issues concerning inhalation exposure, dermal exposure as an important route of entry may contribute to induction of sensitisation and subsequently lead to respiratory effects. This was shown in animal models and is thought to be relevant for humans as well (Bello et al., 2007). Dermal exposure is difficult to measure and to quantify (see Sections A.2.1.2 and B.9) and is often not reported and never quantified in epidemiological studies.

Last but not least, the quality of exposure assessment in epidemiological studies also depends on the level at which exposure is described. In some studies, exposure levels are given on factory or area level only. For example, longitudinal studies on TDI asthma often report mean exposure levels for a group of workers and the respective incidence of disease (cf. Table 3-2 in Appendix 3). Some studies investigate exposure groups using ranks (low/medium/high) without assigned quantitative exposure levels. Only few studies provide quantitative exposure estimates on an individual worker level. These also differ regarding their quality, because they may be based on personal sampling of the individual worker or may be task-based.

A further uncertainty in exposure assessment relates to the use of personal protective equipment. Many studies do not report on it. Other studies try to account for the use. For example, in a retrospective study, the sampling record was not considered if it indicated that respiratory protection was used (Cassidy et al., 2010). Respiratory protection was taken into account by subtracting 50 % of calculated exposure values for exposed jobs in a longitudinal study (Clark et al., 2003). Another longitudinal study considered exposure only when not wearing respiratory protection (Hathaway et al., 1999). This introduces error in the exposure assessment, may bias the results, and makes it harder to compare results from different studies. In addition, the use of personal protective equipment may be associated with the exposure level, as is indicated by the report of Gui and co-workers (Gui et al., 2014). Here, self-reported glove use differed significantly between the exposure risk groups (25 % of the workers in the low, 32 % in the medium, 100 % in high exposure risk group).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Co-exposures to other isocyanates or to other substances, such as irritants, are likely to be present at several of the workplaces studied, and they may influence the observed effect of the studied diisocyanate. Some reports do not even mention potential co-exposures, other report co-exposures, but do not quantify them (for example (Cassidy et al., 2010; Omae, 1984)).

Limitations due to the study design for example include the lack of an (unexposed) control group (Gui et al., 2014; Hathaway et al., 2014), a small number of subjects and selection bias. The latter includes different issues. Susceptible individuals will not be hired based on entry examinations. Self-selection of workers is likely, as individuals with allergy or respiratory problems will not apply for work at a chemical plant (Hathaway et al., 2014). The studied workers therefore mostly are selective populations that are "healthier" in terms of respiratory diseases. The selective loss of exposed symptomatic individuals is especially important in cross-sectional studies on diisocyanate related health effects. These studies are likely to underestimate the risk for workers, because workers with symptoms may already have left their job and are not available for the study. Cross-sectional occupational studies therefore are prone to both "healthy worker hire bias" and "healthy worker survivor bias" (Le Moual et al., 2008). The potential for this kind of bias may be reduced in prospective longitudinal studies, but they also miss workers with health problems who have left before the start of the study as well as those who are lost to follow-up. The most meaningful estimate of the incidence of health effects could be achieved by an inception cohort study (which includes newly hired workers) with further investigations also of those workers who left their job.

The inception cohort study of polyurethane foam production workers in Eastern Europe illustrates the healthy worker survivor effect. It describes a loss to follow-up of 25 % (12 out of 49 exposed workers) after the first year of employment (Gui et al., 2014). Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up.

Likewise, a study of health effects of HDI in painters and auto body repair workers found significant differences between the workers who left the auto body shops and those who stayed. This 1-year follow-up subsequent to a cross-sectional study investigated whether or not a healthy worker effect may exist in the auto body industry (Redlich et al., 2002). Forty-eight workers from seven shops were contacted, 13 of these (27 %) had left their original shop and three (6 %) were lost to follow-up. Those who left were less experienced in the industry and more likely to have a history of asthma and bronchial hyperresponsiveness. The authors conclude: "*The differences in workers who stayed at their shop compared to those who left, combined with the low asthma prevalence and high job turnover rate, all suggest that a healthy worker effect may exist in the auto body industry, and may in part account for the low prevalence of asthma noted in SPRAY and other cross-sectional studies of diisocyanate workers.*"

In conclusion, the available studies have limitations and are not considered eligible for assessing dose response relationships if using strict criteria.

However, one study comes close to meeting the criteria, as it included > 200 exposed workers, quantified the cumulative exposure on an individual level (expressed as total NCO and therefore including monomers and oligomers), conducted methacholine tests for assessing BHR and combined it with the information on wheezing from a questionnaire, provided a quantitative analysis of the exposure and response data using regression

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

analysis and showed a statistically significant dose-response relationship (Pronk et al., 2009; Pronk et al., 2007; Pronk et al., 2006). The study was conducted in the Dutch spray painting industry in the mid-2000s. Although it is cross-sectional in design, in the opinion of the DS it is the only study that provides quantitative exposure-response data in principle allowing the derivation of risk-based values and may be of interest for further considerations.

Exposure-response relationship for isocyanates and asthma, data of Pronk et al.

Pronk et al. conducted a cross-sectional study on exposure-response relationships of respiratory symptoms and sensitisation due to isocyanates in various spray-painting industries in the Netherlands. The included companies were mainly car body repair shops, but also furniture paint shops and industrial paint shops. In total, 581 workers from 128 companies took part in the study, including 50 office workers (no tasks outside the office), 241 spray painters (workers involved in spray painting) and 290 others (mostly mechanics and metal workers; (Pronk et al., 2007)). In a subsample of 229 workers, the association between isocyanate exposure and bronchial hyperresponsiveness (BHR) as a hallmark of asthma was studied (Pronk et al., 2009).

Individual cumulative exposure estimates were obtained by combining personal task-based inhalational measurements for 23 isocyanate compounds (monomers and oligomers) and time-activity information.

$$\text{Exposure} = \sum_{n=1}^6 (\text{Time})_n \times (\% > \text{LOD})_n \times (\text{MedianNCOConcentration})_n$$

The personal exposure is expressed in $\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$.

n describes the task (spray painting, mixing, cleaning paint equipment, assisting a spray painter, sanding, welding).

$(\text{Time})_n$ is the time task n was performed expressed in hours per month. On average, 82 h [SD, 89] out of a 161 h [SD, 26] working month were spent on exposed tasks.

$(\% > \text{LOD})_n$ is the percentage of samples above the limit of detection (LOD) for task n .

$(\text{Median NCO concentration})_n$ is the median inhalational isocyanate concentration during task n expressed in $\mu\text{g NCO}/\text{m}^3$.

Respiratory symptoms were assessed by a questionnaire. Blood samples were taken to investigate HDI-specific IgE and IgG antibodies. In the subsample of 229 workers, associations between isocyanate exposure and more objective respiratory effect measures (BHR, baseline spirometry, exhaled nitric oxide (eNO)) were assessed. BHR was assessed by methacholine challenge. It was defined as a provocative cumulative dose of methacholine of 2.5 mg ($\sim 10 \mu\text{mol}$) or less required to cause a 20 % fall in forced expiratory volume in one second (FEV_1) and is therefore referred to as BHR20.

For BHR, symptoms and serology, the prevalence ratios (PR) with 95 % confidence intervals (CI) were calculated using log-binomial regression. Log-transformed exposure data were used and PRs were expressed per interquartile range (IQR) increase in exposure (for the subsample: $0.3\text{-}2799 \mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$; factor 9330). This means that the calculated PR compares the prevalence of symptoms at the 75th percentile of exposure

(2799 $\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$) and the prevalence of symptoms at 25th percentile of exposure (0.3 $\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$).

Table 10: Exposure, BHR and asthma-like symptoms for the subsample

	Office workers n = 20	Spray painters n = 91	Others n = 118
Exposure [$\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$]			
Total isocyanate	0	4530 (15.4 - 66464)	5.6 (0 - 3785)
HDI	0	36.2 (1.3 - 472)	0.7 (0 - 354)
BHR20 [%] (n = 214)	0	20.0	14.7
Asthma-like symptoms [%]	26.3	35.6	29.1

Asthma-like symptoms were more often reported in workers with higher exposure, but the association was not statistically significant: adjusted PR per IQR increase in exposure was 1.3 (95 % CI 0.9 - 1.7). Hyperresponsiveness was found in 33 subjects and it was clearly associated with exposure: PR of BHR20, adjusted for smoking, age, sex and atopy, was 2.0 (1.1 - 3.8). BHR combined with asthma-like symptoms was present in 19 subjects and the adjusted PR was 2.7 (1.0 - 6.8). This means that workers with an exposure of 2799 $\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$ are twice as likely to be hyperresponsive and are 2.7 times as likely to be both hyperresponsive and have asthma-like symptoms than workers with an exposure of 0.3 $\mu\text{g NCO}/\text{m}^3 \times \text{hours}/\text{month}$.

The study shares several of the limitations that have been discussed previously. Concerning selection bias, a healthy worker effect is likely due to the cross-sectional design and has been shown for the spray painting industry (Redlich et al., 2002). Pronk and co-workers interpret the fact that atopy was less common in workers with high exposure in their study as indicative of a healthy worker effect (Pronk et al., 2009). In addition, they discuss selection bias on the company level: although control measures are similar among Dutch car body repair shops, it cannot be ruled out that more compliant companies were more likely to participate (Pronk et al., 2007).

Regarding exposure assessment it has to be noted that only exposure outside the respirators has been measured (Pronk et al., 2006). Therefore, the actual exposure of the workers will be lower and may vary between the individual workers depending on their working practices. It is questionable if the control group has been actually unexposed, as 25 % of the office workers had "COPD-like symptoms", 16 % had "asthma-like symptoms", 55 % were atopic and at least 40 % had specific anti-HDI IgG (Pronk et al., 2009). In every company included in the study all workers were working in the same building (Pronk et al., 2007). Accordingly, stationary samples showed detectable exposure levels in offices in 64 % of the car body repair shops and 100 % of the industrial painting companies (Pronk et al., 2006). Leng et al. (2013) also found evidence for exposure in office workers in an HDI-producing plant. Here, 25 % of production and control room workers, but also 19 % of office workers displayed urinary HDA levels above 20 $\mu\text{g}/\text{L}$ (Leng et al., 2013). Taken together, overestimation of the exposure of the exposed workers and underestimation of the exposure of the controls will lead to an underestimation of the risk associated with a specific exposure level.

Further uncertainties in the exposure assessment include the algorithm used for exposure estimation (see above) and the considerable exposure ranges per event (Pronk et al.,

2006). In the algorithm, median concentrations of the task-based measurements were used, which is not a worst case approach (for which the lower confidence limit of the exposure might have been considered). On the other hand, exposure at or below LOD is not counted in this algorithm (which is a worst case approach).

Dermal exposure occurred during tasks that involve direct handling of paint (Pronk et al., 2006), but was not included in the analysis of the ERR (Pronk et al., 2009). Therefore, the contribution of dermal exposure to the health effects stays unclear and the quantitative inhalation exposure level gets less meaningful.

In summary, although this study provides evidence of a dose-response relationship of total NCO and asthma, the DS finally finds the uncertainties concerning the effective quantitative inhalation exposure too high for using the study as a basis for derivation of a risk value.

Conclusions

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.

Nevertheless, the epidemiological studies on diisocyanate exposed workers conducted in the last decades show that the annual incidence of OA has decreased with decreasing exposure levels over time. However, more recent studies still show a risk of respiratory sensitisation for workers under current working conditions. As a consequence, every year a number of new cases of occupational disease are reported in the EU.

B.5.6.5.3 Occupational Diseases

Diseases caused by isocyanates are on the European schedule of occupational diseases (European Commission, 2003). This schedule is in Annex I of the "Commission Recommendation of 19 September 2003 concerning the European schedule of occupational diseases", which says that the Member States should "introduce as soon as possible into their national laws, regulations or administrative provisions concerning scientifically recognised occupational diseases liable for compensation and subject to preventive measures, the European schedule in Annex I".

The WHO defines the terms "occupational disease" and "work-related disease" as follows:

"An 'occupational disease' is any disease contracted primarily as a result of an exposure to risk factors arising from work activity. "Work-related diseases" have multiple causes, where factors in the work environment may play a role, together with other risk factors, in the development of such diseases." (WHO, 2016)

In the EU context, however, "A case of occupational disease is defined as a case recognised by the national authorities responsible for recognition of occupational diseases." By contrast, "A case of work-related health problem and illness does not necessarily refer to recognition by an authority" (European Parliament and Council, 2008b).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

In the following, the term „occupational disease” is used in a broader sense to encompass the diseases reported to the different recording and compensation systems of the Member States.

Recording systems

Two types of systems for reporting occupational diseases can be distinguished: those based on claims for recognition and compensation administered by the national social security systems and those based on an independent system (European Commission, 2013a). Nearly all Member States have a list of occupational diseases (OD) (26 countries), which are established for the purposes of recognition and compensation. These national lists vary in the degree of exhaustiveness and in content depending on the country. However, in many countries the national list is similar to Annex I of the European list. Twenty-three countries have a specific compensation system. There is great heterogeneity among these systems, for example concerning the management methods of the insurance organisations, the extent of the insurance coverage, the extent of the range of benefits and the nature and level of benefits. The European commission therefore concludes that any classification of the national systems is difficult (European Commission, 2013a).

Several countries have OD surveillance systems in place that have been established to address issues independent of compensation (Carder et al., 2015). In the context of “Modernet” (Monitoring trends in occupational diseases and tracing new and emerging risks in a network) 14 countries provided information for 33 OD systems and the authors acknowledge that there may be further systems for which information was not received.

Underreporting of occupational diseases

It may be possible that some cases that are reported as being related to isocyanates may actually not be caused by isocyanates. For example, in countries where the reporting system is not connected to a compensation system, usually no verification of the actual exposures will take place. This may apply to registries that record cases voluntarily reported by physicians, such as the THOR schemes in the UK. Sometimes more than one agent is named as the probable cause of the disease. Another issue that may lead to higher numbers of cases in the registries is that the documentation of cases in countries with compensation systems is mainly done for administrative purposes rather than for scientific purposes. Therefore, the coding may not always be correct and some cases assigned to isocyanates may actually be caused by other substances at the workplace. This may apply to jobs where workers are exposed to a lot of different substances, like construction.

The issue of overreporting is evaluated as of minor importance for the following reasons:

- There may be some cases that are attributed to, but not actually caused by isocyanates, but there may also be cases that are attributed to other substances, but actually are caused by isocyanates. Therefore, the reporting of an isocyanate case that actually is caused by another substance may be seen as a random error and may not lead to overestimation of cases.
- Underreporting is estimated to be much higher (see in the following).

“With the exception of Bulgaria, all the countries recognise (BE, CY, CZ, DK, EE, FI, FR, GR, HU, IS, IT, LV, LT, MT, NO, RO, SI, SK, ES, SE, CH, UK) or do not rule out (AT, DE, IE, PL, PT) a problem of under-reporting of occupational diseases.” (European Commission, 2013a)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

The mentioned causes for underreporting include:

- lack of knowledge, information and motivation among doctors (especially general practitioners)
- reporter fatigue in voluntary reporting schemes
- the bureaucracy of the system
- the scale of benefit
- pressure from employers causing a lack of independence of occupational physicians
- the worker's fear of the consequences of a report for their job
- the scale of undeclared work in any country has a major influence on the applicability and use of the reporting system
- under-recognition (individual and/or physician not associating the condition with work)
- individual may be unaware of the availability of compensation or may not meet the eligibility criteria of the compensation based system
- specific sectors of the workforce may not be covered
 - only the private, not the public sector covered
 - often the self-employed are not covered, a sector which accounts for ~15 % of the EU working population
 - access to an occupational physician within the UK is biased towards the public sector and larger industries (has influence on the cases reported to the OPRA surveillance system) (Carder et al., 2015; European Commission, 2013a; Walters et al., 2015).

The extent of underreporting is not known and is dependent on different factors. For example, the level of physician participation is decisive. *"This will vary amongst the different systems (and also over time), in part depending on the nature of reporting (i.e. voluntary or mandatory), but other factors, for example physician workload, level of training in and affinity with occupational health or area of specialism will also play a role."* (Carder et al., 2015)

It is for example estimated that underreporting is *"50-90 % in Hungary, 50 % in Latvia, almost 100 % in Slovenia, and is considered significant in Sweden and Iceland. Only an estimated 3 % of occupational disorders are reported in Norway, and in the United Kingdom the Trades Union Congress believe that only 1/8th of victims eligible for the compensation system have reported their disease or taken legal action to obtain reparation."* (European Commission, 2013a). For the THOR schemes it has been estimated that during the period of 2005 to 2007, 62 % of skin cases and 60 % of respiratory cases were likely to have been captured (Carder et al., 2011). The Health and Safety Executive of the UK (HSE) estimates that the total number of new cases of work-related asthma (asthma caused or made worse by work) each year could be more than 10 times higher than that reported by chest physicians to the reporting scheme THOR-SWORD. This is suggested by other data sources like the Labour force survey and the reporting scheme for general practitioners THOR-GP (HSE, 2015). The participants of the MODERNET project also generally acknowledged that occupational diseases were underreported, but the scale was unknown or only partly known (Carder et al., 2015).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

From the data request for this dossier for most of the Member States no information on the scale of underreporting was available. BG noted that the diseased person has to be insured for “occupational diseases” to be recorded as a case. SE estimated underreporting to be about 50 % for occupational accidents and to be higher than this for occupational diseases. HU is “*aware that there is severe under-reporting concerning every occupational disease.*”

Estimation of cases of occupational disease due to isocyanates in the EU

In autumn 2015 the DS carried out an EU-wide data request, addressing institutions that were known from former data requests to hold data on occupational diseases, and additionally the CAs.

Table 11 gives an overview of the data suppliers. For twelve Member States there are no data available. Three Member States stated that no cases due to isocyanates had been reported (BG, CY, HR). One Member State did not provide any data in 2015, but had already provided data in an earlier request in 2013 (FR). For further two Member States data of the previous request in 2013 were used and were supplemented with newer data provided in the recent request (BE, ES). In total, data on cases from 13 Member States could be used. The data differ considerably in the extent and form of the information.

Table 11: Overview of the data sources for the occupational diseases due to isocyanates

Country	Data source	Is the reporting system linked to a compensation system?	Is reporting mandatory?	Remarks
DK	No data			Documentation of causative substance not specific enough.
EL				
EE				
IT				
LT				
LU				
LV				
MT				
NL				
PT				
RO				
SI				
BG	National Social Security Institute (NSSI), General Labour Inspectorate Executive Agency	Yes	Yes	No cases known “Cases of occupational diseases connected with diisocyanates exposure are not reported (there are no data for certain cases by isocyanates and by disease).”

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Country	Data source	Is the reporting system linked to a compensation system?	Is reporting mandatory?	Remarks
CY	Department of Labour Inspection, Ministry of Labour, Welfare and Social Insurance	No (although compensation for ODs possible, diisocyanate-derived diseases cannot be compensated as ODs)	Yes	No cases known "No occupational diseases have been reported in the related industries."
HR	Croatian Institute for Health Protection and Safety at Work	No information available	No information available	No cases known "There are no recognized occupational diseases caused by isocyanates in Croatia."
BE	Fund for Occupational Diseases (FMP)	Yes	Yes, but in practice not all physicians report their cases.	Data from the data request 2013 were used for this report (years 2000-2012) and supplemented by additional data provided in 2016 (years 2013 - 2014).
CZ	National Institute of Public Health, Centre of Occupational Health.	No answer	No answer	
DE	German Social Accident Insurance (DGUV)	Yes	Yes	
IE	The Health and Occupation Reporting network in the Republic of Ireland (THOR ROI)	Yes (administered by the Department of Social Protection)	No	
ES	National Institute of Occupational Safety and Health (INSHT)	Yes	Yes	Data from the data request 2013 were used for this report (years 2007, 2008, 2012) and supplemented by additional data provided in 2016 (year 2014).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Country	Data source	Is the reporting system linked to a compensation system?	Is reporting mandatory?	Remarks
FR	National Network for Monitoring and Prevention of Occupational Diseases (rnv3p), ANSES	No	Yes, but only for all 32 French occupational disease clinics.	In 2015 no data were provided, but data from the data request 2013 could be used for this report.
HU	Occupational Health Department, Office of the Chief Medical Officer (OTH-MFF)	Yes	No (in practice, as there is no proper legal definition or sanctioning)	
AT	Allgemeine Unfallversicherungsanstalt - the Austrian Workers' Compensation Board (AUVA)	Yes (cases have to be reported and recognised, at least 20 % impairment of earning capacity)	Yes	
PL	Polish Central Register of Occupational Diseases, Nofer Institute of Occupational Medicine	No answer	No answer	
SK	National Health Information Centre (NHIC)	No	Yes	
FI	Finnish Register of Occupational Diseases	Yes	Yes	
SE	Swedish Work Environment Authority	Yes (administered by the Swedish social insurance system Försäkringskassan)	Yes	
UK	The Health and Occupation Research Network (THOR), Centre for Occupational and Environmental Health (COEH), University of Manchester	No	No	

The estimation of the annual number of diseases due to isocyanates in the EU was done in three steps:

- The first step was to collect the cases of the different countries per year from 2000 to 2014 and to calculate the mean per year (Table 12).
- The second step was the extrapolation of the numbers to the whole EU, based on the estimated cases of those countries that had provided data and on the working population.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

- The last step was to estimate the “true” number of cases based on the cases recorded in the registries and taking underreporting into account.

Mean number of cases per year for the data-providing countries

For some countries, it had to be decided which kind of the provided cases should be included. In Germany three possible case statuses for isocyanate related diseases are recorded: reported cases (notifications of suspected cases), confirmed cases (occupational causation confirmed) and recognised cases (subgroup of confirmed cases with absence of additionally required insurance characteristics). Finland provided “reported” and “confirmed” cases. For both countries, the “confirmed” cases were used.

As mentioned before it has to be acknowledged that the cases shown in Table 12 vary in terms of their ascertainment across the countries. Whereas some are reported voluntarily to reporting schemes by physicians, others are confirmed by a national authority. But also within the same kind of system great differences may exist (see above).

In case information on the diagnosis was available, the cases were grouped into respiratory diseases, skin diseases and other diseases. The remaining cases were put into the category “unspecified disease”.

The mean number of cases per year (and disease group) was calculated for every country and summed up to derive the mean number of cases per year for the 13 countries. For the period from 2000 to 2014, a mean of 193 cases per year was calculated on the basis of the total number of 2312 cases. The mean number of respiratory disease cases per year for the 13 data-providing countries is 139. Accordingly, the percentage of respiratory cases is 87 % of total cases without unspecified diseases (139/159).

For three Member States (BE, ES, FR) also data requested and provided in 2013 were used. As the earlier data request was focussed on occupational asthma, FR searched for “asthma” in their RNV3P-database. In this way, other respiratory diseases as well as skin diseases in FR may be underreported in the current data compilation. The ratio of the mean annual number of respiratory diseases to the mean annual number of skin diseases in countries that provide this differentiation between the diseases is used as a rough indication for the “missing” cases in FR. The ratio is about 1 (FI) to about 11 (SE). A ratio of 5 (which for example is also found in DE) is chosen here. This results in an additional number of $33.7/5 = 6.7$ cases. BE and ES did not distinguish between respiratory and skin diseases and provided a total number of cases encompassing all isocyanate diseases. Therefore the kind of underreporting assumed for FR does not apply to BE and ES. The mean annual number of cases is therefore adjusted to 200.

As an alternative approach one could use only the more recent data, for example only the cases documented in the last ten years (2005-2014) or in the last 5 years (2010 to 2014). This would lead to a mean number of cases of 178 cases per year (173 + 4.8 for FR) or 157 cases per year (155 + 2.3 for FR). There are many factors influencing reporting over time, for example changes in the data protection act, changing numbers of physicians reporting, reporter fatigue (Carder et al., 2015; Walters et al., 2015). Time trends in occupational disease incidence cannot be assessed without taking into account time trends in reporting in the different countries. It is therefore not possible in the scope of this dossier to assess time trends in occupational diseases due to isocyanates. In addition, not only the absolute number of cases, but also the number of exposed workers in the different countries and in the different years would be needed for a sound interpretation of potential changes over

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

time. Of course, underlying time trends may also be different in the countries. In some countries incidence may be increasing whereas in others it may decrease in the same period of time. A period of 5 years seems to be too short to reflect a substantiated mean value, because numbers vary from year to year and for some countries data for less than 5 years are available in this period. As the difference between the mean values for the 15-year period and the 10-year period is not too big, the greater data basis (15-year period) is used here and accordingly, the derived mean annual number of cases is 200.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 12: Overview of the reported cases (stratified by member state, disease category and year) provided to the DS by 13 EU Member States

		Year															Total cases [n]	Reporting years [n]	Mean per year [n]
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014			
Country	Disease Group	Cases [n]																	
AT	Respiratory disease	6	6	5				1	1		3	13	6	5	7	6	59	15	3.9
	Total	6	6	5				1	1		3	13	6	5	7	6	59	15	3.9
BE	Unspecified				1	11	11	5	7	3	3	5	3	4	5	1	59	13	4.5
	Total				1	11	11	5	7	3	3	5	3	4	5	1	59	13	4.5
CZ	Unspecified	1		1	2	1	1										6	15	0.4
	Respiratory disease	1	4	4	1	3	2	4	3	1	7	14	25	27	19	18	133	15	8.9
	Skin disease	1	1	1		2	1	2			1	1	2			1	13	15	0.9
	Total	3	5	6	3	6	4	6	3	1	8	15	27	27	19	19	152	15	10.1
DE	Respiratory disease	59	60	50	54	45	44	35	40	35	33	43	34	63	50	35	680	15	45.3
	Skin disease	4	14	17	12	8	8	5	9	6	8	6	6	11	11	9	134	15	8.9
	Total	63	74	67	66	53	52	40	49	41	41	49	40	74	61	44	814	15	54.3
ES	Unspecified								27	42						30	113	4	28.3
	Total								27	42						30	113	4	28.3
FI	Unspecified						1										1	14	0.1
	Respiratory disease						3	2	4	6	9	3		2	2		31	14	2.2
	Skin disease						1	2	4	4	5	4	2	2	2		26	14	1.9
	Total						5	4	8	10	14	7	2	4	4		58	14	4.1
FR	Respiratory disease		60	48	52	43	40	43	21	22	19	12	11				371	11	33.7
	Total		60	48	52	43	40	43	21	22	19	12	11				371	11	33.7
HU	Respiratory disease	4	1					2			1						8	15	0.5
	Skin disease			1										1			2	15	0.1
	Total	4	1	1				2			1			1			10	15	0.7
IE	Respiratory disease						1			2	2	1					6	10	0.6
	Total						1			2	2	1					6	10	0.6
PL	Respiratory disease	4	5	2		2		2		1		1		1	1	1	20	15	1.3
	Skin disease	1		1		1	1	1									5	15	0.3

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

		Year														Total cases [n]	Reporting years [n]	Mean per year [n]	
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013				2014
Country	Disease Group	Cases [n]																	
	Other disease	3			1												4	15	0.3
	Total	8	5	3	1	3	1	3		1		1		1	1	1	29	15	1.9
SE	Unspecified					4	2			1							7	11	0.6
	Respiratory disease					37	39	17	20	23	11	19	11	12	18	6	213	11	19.4
	Skin disease					3	2	2		4	2	2	2	1	1	1	20	11	1.8
	Other disease					8	4	1	1	1		1	1	2		1	20	11	1.8
	Total					52	47	20	21	29	13	22	14	15	19	8	260	11	23.6
SK	Unspecified				2						1	4					7	12	0.6
	Total				2						1	4					7	12	0.6
UK EPIDERM ¹	Skin disease	4	4	4	4	1	5	4	1	1			1	1	2	2	34	15	2.3
	Total	4	4	4	4	1	5	4	1	1			1	1	2	2	34	15	2.3
UK OPRA ²	Respiratory disease	6	2	7	7	4	8	1	1	2							38	10	3.8
	Skin disease	2	2	1	1	1	1				2						10	10	1.0
	Total	8	4	8	8	5	9	1	1	2	2						48	10	4.8
UK SWORD ³	Respiratory disease	32	26	28	32	20	14	20	19	20	17	20	9	11	15	5	288	15	19.2
	Total	32	26	28	32	20	14	20	19	20	17	20	9	11	15	5	288	15	19.2
UK THOR-GP ⁴	Respiratory disease								2							1	3	8	0.4
	Skin disease														1		1	8	0.1
	Total								2						1	1	4	8	0.5
Sum of cases of 13 countries	Unspecified	1	0	1	5	16	15	5	34	46	4	9	3	18	5	31	193		34
	Respiratory disease	112	164	144	146	154	151	127	111	112	102	126	96	121	112	72	1850		139
	Skin disease	12	21	25	17	16	19	16	14	15	18	13	13	16	17	13	245		17
	Other disease	3	0	0	1	8	4	1	1	1	0	1	1	2	0	1	24		2
	Total	128	185	170	169	194	189	149	160	174	124	149	113	157	134	117	2312		193

Grey fields: no data available; UK schemes: reported to by ¹ dermatologists; ² occupational physicians; ³ chest physicians; ⁴ general practitioners

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

The second step in the estimation of the annual number of diseases due to isocyanates in the EU is the extrapolation from the estimated cases of those countries that had provided data to the whole EU. To extrapolate the number of cases, the working population of the Member States is used as a basis. Of course, extrapolating implicitly assumes that the countries that provided data are representative of all EU countries with respect to isocyanate industry, number of exposed workers and the exposure conditions/safety levels. The 16 countries (which provided cases or stated that there are none) have 74 % of the EU working population (EUROSTAT). Therefore, the estimated number of cases per year in the 16 countries is extrapolated to a number of 270 cases per year in the EU. For the 13 data-providing countries, the percentage of respiratory cases is 87 % of total cases without unspecified diseases. Assuming that this proportion holds also true for the cases with unspecified disease, the yearly number of respiratory disease cases is estimated to be 235.

As this number only covers the cases that have appeared in some kind of registry, they have to be considered as the "tip of the iceberg". To come closer to the "true" number of cases, a factor for underreporting has to be applied as the last step of the estimation. By definition the scale of underreporting is unknown. Thus it has to be estimated. There are some estimations of underreporting for single countries or registries; however, for most of the countries no information is available. These estimations for single countries or registries are not used here, to prevent pretended accuracy. Instead, an overall factor for the whole EU is applied to account for the underreporting. This factor is intended to cover the different percentages of underreporting in the different countries and registries as well as the cases in countries with no recorded cases. (Note that for the three countries that reported that they have no cases, underreporting actually cannot be taken into account by a factor, but rather an absolute number would have to be assumed.)

From the data cited above it is plausible to assume for this task an underreporting of cases in the EU of at least 50 %. However, for some countries estimates for underreporting are even as high as 90 to 100 %. To cover this, a factor of 10 seems plausible as well (corresponding to an overall percentage of uncovered cases by this request of 90 %). Therefore, the mean number of cases per year should be multiplied by two at least and probably even by ten, resulting in an estimated number of cases of 540 to 2700.

In conclusion, the estimation of the annual number of new cases in the EU is hampered by the uncertainties concerning the recording systems, the underreporting and the differences in isocyanate use between the countries. However, it is obvious that every year isocyanates lead to a significant number of new disease cases in the EU. On the basis of reported disease cases the rounded number is estimated to be at least 540 and probably 2700 new cases per year, including about 470 or 2350 respiratory diseases, respectively.

Information on diagnosis

Ten countries provided data that specified disease group (respiratory or skin disease) or even provided a more specific diagnosis. All cases were assigned to one of four disease groups (respiratory/skin/other/unspecified). Cases of respiratory disease were further subdivided into four disease categories (asthma/chronic obstructive lung disease (COPD)/extrinsic allergic alveolitis (EAA)/other or unspecified respiratory diseases). Cases of skin disease were further subdivided into two disease categories (allergic dermatitis/other or unspecified skin diseases).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

For 9 % of all cases, the disease was unspecified. As stated above, 87 % of the cases for which at least disease group was specified (respiratory/skin; n = 2119) were respiratory diseases. Skin diseases made up 12 % of the cases with information on disease. The respiratory diseases were mainly unspecified or other (52 %), followed by asthma (48 %). Among the skin diseases 19 % were reported as allergic contact dermatitis.

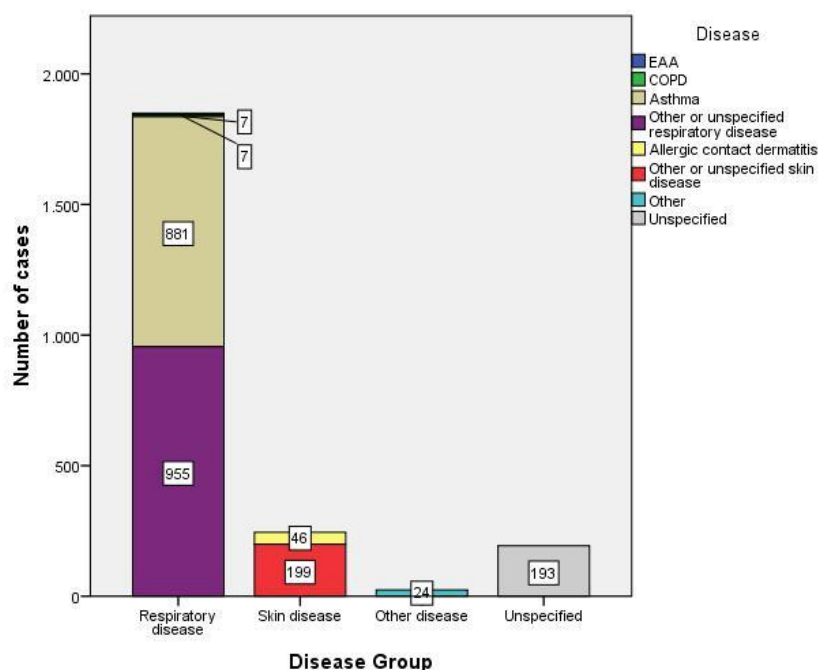


Figure 4: Diseases documented for the 2312 reported cases in 13 EU countries (see Table 12)

Information on causative agents

Eight of the 13 countries (AT, CZ, FI, HU, IE, PL, SE, UK) provided some information on the isocyanate type(s) that were recorded as causative agents, because the recording system in principle allows to differentiate. However, even in these countries, for most of the recorded cases the causative isocyanate is not documented. Overall, a specific agent is not given for 87 % of all cases (2019 out of 2312 cases in 13 countries) and for 71 % of the cases in the eight countries (range 17-97 %). For the small part of cases with information on the specific isocyanate, MDI, TDI and HDI are reported in 97 % of the cases (95-100 % depending on the country). Overall, 65 % of the cases are attributed to MDI in the first place, 18 % to TDI and 14 % to HDI. By country, the percentage ranges from 20 to 93 % for MDI, from 0 to 80 % for TDI and from 0 to 36 % for HDI. Note that for some countries, case numbers with information on causative agents are very small (n < 10) and percentages may not be informative. In conclusion, the reported isocyanates are not in contradiction to the tonnages and uses. However, as for most of the cases (87 %) the isocyanate is not known, it is not possible to conclude on the relative importance of single isocyanates concerning occupational diseases.

B.5.7 Repeated dose toxicity

Apart from effects on the respiratory tract, repeated dose toxicity has not been considered explicitly for this report. However, in many of the animal studies evaluated in the section on sensitisation, test substances have been administered repeatedly and some of these have investigated inflammatory processes in the airways as a result of repeated diisocyanate exposure.

B.5.8 Mutagenicity

Not considered for this report. However, none of the diisocyanates considered in this report are classified for mutagenicity. Aromatic diisocyanates may be hydrolysed and/or metabolised to mutagenic primary aromatic amines but this aspect has not been further considered for this report for the following reasons:

- At this point in time there is no specific concern for genotoxic carcinogenicity from the available diisocyanate genotoxicity or carcinogenicity test database in animals or from human case reports.
- There are open questions with respect to competing degradation reactions and suitable analytical methodology with a view to demonstrating the potential systemic bioavailability of the amines.
- The restriction proposal does not aim at enforcing a specific threshold for respiratory sensitisation. Rather it is assumed that the proposed measures will achieve a considerable reduction in exposure of workers, professionals, and bystanders, thereby reducing the established risk of respiratory sensitisation as well as any other potential health risks.

B.5.9 Carcinogenicity

Not considered for this report. However, none of the diisocyanates considered in this report are classified for carcinogenicity. Aromatic diisocyanates may be hydrolysed and/or metabolised to carcinogenic primary aromatic amines but this aspect has not been further considered for this report for the following reasons:

- At this point in time there is no specific concern for genotoxic carcinogenicity from the available diisocyanate genotoxicity or carcinogenicity test database in animals or from human case reports.
- There are open questions with respect to competing degradation reactions and suitable analytical methodology with a view to demonstrating the potential systemic bioavailability of the amines.
- The restriction proposal does not aim at enforcing a specific threshold for respiratory sensitisation. Rather it is assumed that the proposed measures will achieve a considerable reduction in exposure of workers, professionals, and bystanders, thereby reducing the established risk of respiratory sensitisation as well as any other potential health risks.

B.5.10 Toxicity for reproduction

Not considered for this report. However, none of the diisocyanates considered in this report are classified for reproductive toxicity.

B.5.11 Other effects

Not considered for this report

B.5.12 Derivation of DNEL(s)/DMEL(s)/Health-based exposure limits for diisocyanates with respect to sensitisation

B.5.12.1 Introductory thoughts

In the context of the risk assessment of respiratory sensitisers often the question is posed whether a „threshold for sensitisation“ can be derived. In most of these cases, however, no clear explanation is given what this should mean exactly. For the purpose of this dossier, it is assumed that under REACH such statements refer to the possibility to derive a DNEL to protect against sensitisation.

The formal mechanistic concept of chemical-induced allergy¹⁷ involves two steps: first the adaptive immune system must be primed to the allergen for later recognition (induction step). Only after this induction step which renders the affected individual “sensitised” can an allergic reaction be triggered (elicitation step) upon renewed contact with the sensitising substance. While this concept has been established primarily for skin sensitisation it is generally believed that it also holds for respiratory sensitisation (Dotson et al., 2015; ECHA, 2015; Kimber and Basketter, 2014).

For a given exposure scenario as characterised by route, duration, pattern and level of exposure, it is plausible to assume that a level of exposure exists, below which in a well-defined, previously unexposed human population no single case of sensitisation will occur [cf. also (Pauluhn, 2013): “A *certain antigen dose is required to overcome endogenous homeostasis*”].

Equally, for such a well-defined exposure scenario, there will be an exposure level, below which in a well-defined population of already sensitised people no elicitation of an allergic reaction will be observed. Observations in animals and humans suggest that for chemical sensitisers of low molecular weight (i.e. haptens requiring the formation of a protein-hapten complex for triggering sensitisation), elicitation thresholds can generally be assumed to be lower than induction thresholds. Notably some authors have claimed that the opposite might hold for sensitisers of higher molecular weight, such as enzymes (Kimber and Basketter, 2014).

¹⁷ Cf. for instance the OECD Adverse Outcome Pathway (AOP) for skin sensitisation by covalent binding to proteins (OECD, 2012a).

The REACH guidance IR&CSA, section R.8 notes, however, that *"elicitation thresholds seem to correlate poorly with induction potency"*. According to the same guidance, for respiratory sensitisation *"currently available methods do not allow determination of threshold and establishment of a DNEL. Therefore for substances classified as respiratory sensitizers only qualitative assessment [...] can be performed"* (ECHA, 2012).

While this statement relates to respiratory sensitisation following inhalation exposure, it also holds for respiratory sensitisation as a consequence of dermal contact. The available data on diisocyanates (cf. previous sections) indicate that both steps (induction and elicitation) may be triggered by the dermal or inhalation routes. In other words: respiratory tract symptoms may be observed upon inhalation challenge following dermal induction. It has been claimed that topical or intradermal exposure may be even more effective than inhalation exposure in inducing respiratory sensitisation (Rattray et al., 1994). In addition, *vice versa*, topical contact hypersensitivity was observed upon dermal challenge after previous induction by inhalation [e.g. (Ebino et al., 2001; Stadler and Karol, 1984)].

With many industrial and professional uses, humans are exposed via both routes. Even if in such cases exposure was kept below the induction/elicitation threshold for each route individually, the combined exposure level via both routes could be high enough to cause induction/elicitation.

Currently, beyond the difficulties in establishing DNELs for the individual routes, there is also a lack of understanding of the quantitative interaction of the different routes in inducing sensitisation or eliciting an allergic response, so a "combined DNEL" (i.e. a combination of dermal and inhalation DNELs which, when adhered to at the same time, would protect from sensitisation/elicitation) cannot be set. Pauluhn notes that: *"Any holistic threshold of sensitization appears to be more complex to define due to exposure route-specific differences in immune response"* (Pauluhn, 2015). In addition, beyond the technical problems of such an approach (the quantitative interrelationships between local and systemic toxicokinetic and toxicodynamic processes are not even understood for each route alone, and are basically unknown for combined exposure over several routes), the value of such a combined exposure level in regulatory terms might be questioned as it would be difficult or even impossible to control and/or enforce. Cf. the following statement by Pauluhn from 2013 (translated from German by the DS):

"If isocyanate asthma should develop progressively as a combination of dermal induction(s) and inhalational (re-)exposures with sufficiently high C x t doses, only the pulmonary process is accessible to a systematic risk management." (Pauluhn, 2013)

As a result of these considerations, for uses with combined exposure via dermal contact and inhalation only qualitative risk characterisation can be performed.

In contrast, where significant dermal or inhalation exposure can be ruled out for a specific use, only one route of exposure would have to be considered. Here the IR&CSA guidance R.8 notes (with respect to skin sensitisation) that at least in principle there might be *"cases where good data (i.e., dose descriptors) are available, which has to be evaluated on a case-by-case basis, allowing setting DNELs for these endpoints"*. Such DNELs would then primarily be used to aid in qualitative assessment (*"could be used to judge the remaining/residual likelihood of risks"* (ECHA, 2012)).

However, it is noted that this statement refers to skin sensitisation, i.e. dermal contact hypersensitivity, and not to the induction of respiratory allergy via the dermal route. Nevertheless, in conjunction with the above overview of the available experimental data base, the subsequent subsections will analyse for respiratory sensitisation both via the dermal and the inhalation route whether the available data and knowledge on diisocyanates are sufficient to derive sufficiently reliable DNELs. Also the question whether a DMEL can be derived will be addressed¹⁸.

First some general considerations on setting DNELs will be presented, followed by a step-by-step analysis of the various aspects of hazard characterisation (HC) in order to identify relevant uncertainties and/or gaps in knowledge. The general difficulties in deriving DNELs for (respiratory) sensitisation have also been the subject of a number of reviews, most recently by members of the chemical industry's European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Task Force on Thresholds in Respiratory Sensitisation (Cochrane et al., 2015) and by authors from the United States National Institute for Occupational Safety and Health [NIOSH; (Dotson et al., 2015)]. A number of issues raised in these papers will also be addressed here.

B.5.12.2 General considerations on determining DNELs/DMELs

Contemporary strategies for the regulation of potential risks of chemicals foresee a separation between risk assessment and risk management. While such an – often even institutional - separation is intended to keep risk characterisation purely scientific and to protect it from inappropriate political or economical influences, nevertheless the two processes are closely interlinked:

Risk managers need to provide risk assessors with a sufficiently precise problem formulation. The WHO/IPCS "Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization" [(IPCS, 2014); this document will be referenced as "IPCS guidance" subsequently] states that:

"Problem formulation is a critical phase of the risk assessment process and provides the context for risk characterization. [...] problem formulation includes the risk management scope and goals in relation to relevant exposure scenarios, the level of uncertainty that is acceptable as well as the urgency of the assessment".

Hence, aside from delivering numerical products such as DNELs/DMELs or RCRs (Risk Characterisation Ratios), risk assessment needs to inform risk management about the extent to which these values fulfil the protection goals and about the amount of uncertainty associated with them.

¹⁸ It is important to understand that the term „DMEL“ is used here in the sense of an exposure level corresponding to a *quantifiable* minimum risk that could be tolerated from a regulatory perspective. In other words: the "minimum" risk needs to be specified in quantitative terms, which is different from reference exposure levels that refer to a "minimum achievable" risk (e.g. taking into account quantification limits of analytical methodology or socioeconomic considerations).

In the following subsections the protection goals and the acceptable level of uncertainty in the scope of this dossier are discussed (in more simple words: “who is to be protected from what and how much confidence is required for the statement that this is the case?”).

A formal procedure to be taken for this purpose has been suggested in the above IPCS guidance (IPCS, 2014). In the next subsection, some of the concepts from that guidance will be applied in order to specify more precisely the protection goals and the level of confidence that is needed. In subsequent subsections – again along the lines of the IPCS guidance – the available data for diisocyanates will be analysed in terms of whether they are sufficiently reliable to achieve these goals.

B.5.12.2.1 Formulation of protection goals

First it is necessary to define more precisely the boundary conditions of the DNEL/DMEL to be established. In risk communication, exposure levels up to a DNEL are frequently declared “safe”. However, it is a simple fact of life that 100 % safety cannot be found in any area of risk assessment (or life in general, for that matter). Given both the uncertainties and variability associated with observations of real-life phenomena and the principal limitations of human knowledge, it is therefore practically impossible to establish an exposure level, at which - with 100 % confidence - 100 % of a given population can be protected from even the slightest manifestation of a given unwanted health effect.

Therefore, first the desired protection goals need to be defined more precisely: which percentile (designated I , for incidence, in the IPCS guidance) of the target population needs to be protected from which effect level (M , for magnitude)?

Then the task of DNEL/DMEL derivation may be expressed as the attempt to determine the so-called “ HD_M^I ”, i.e. the human dose corresponding to the protection goals I and M , for the exposure scenario under question. However, the HD_M^I as such represents the theoretical “true” human dose which – due to uncertainty and variability – can only be estimated with some probability of error (in this case in the form of a DNEL or DMEL). As a consequence, another important boundary condition which should be specified when deriving a DNEL/DMEL is the level of confidence that this value is not less protective than the “true” HD_M^I (another way to put this: the percentage of cases in which the DNEL can be expected to achieve the desired protection goals formulated with the HD_M^I ; in the WHO concept this is expressed as percent “coverage”).

The following sections will address how protection goals might be defined and which confidence level might be desirable. For that purpose, specific choices, e.g. with regard to certain percentiles of the population or to a confidence level, need to be made.

It is important to understand that these choices are somewhat arbitrary at this stage and their sole purpose is to illustrate the challenges associated with defining and transparently reporting protection goals. Specifically, they do not represent a harmonised and agreed choice of the DS with regard to the restriction proposal for diisocyanates.

In the end it will be shown that problems do not so much arise from the choice of specific numbers (in fact, within the IPCS approach it is even possible to evaluate the impact of different choices on the HD_M^I) but rather from establishing that these numbers are met by risk management in the end.

B.5.12.2.2 Definition of target population

The target population of this restriction proposal encompasses adult workers and professionals of both sexes who may be exposed to diisocyanates at their respective workplaces. In certain cases also bystanders (i.e. third parties exposed to diisocyanates through industrial or professional uses) might be affected, e.g. office staff in a factory, third parties working at, or residents living near to a construction site. In the latter case, the target population would also comprise children and elderly people which might have an impact regarding necessary assumptions on human interindividual variability.

B.5.12.2.3 Magnitude of effect and incidence

One of the fundamental principles in the IPCS guidance is given by the notion that *"for all types of end-points, the magnitude of effect M can be regarded as changing gradually"*. Another principle is that *"individual-level effects (magnitude) and population-level effects (incidence) are conceptually distinct"* (IPCS, 2014).

On an individual level it is obvious that the extent or intensity of being sensitised will increase continuously with increasing dose [cf. (Friedmann, 2007)]. For example, the Stimulation Index (SI), i.e. the increase in lymphocyte proliferation vs. control, is measured in the Local Lymph Node Assay (LLNA) at different concentrations and will increase gradually with increasing dose. Different sensitised individuals may respond to a sensitizer with a varying degree of severity of the allergic reaction. Of course this could be due to interindividual variability in the elicitation mechanisms alone, but it appears acceptable to assume induction of sensitisation to be an effect the intensity of which may vary gradually between individuals¹⁹.

At the same time, on the population level, within a given percentile of the population, the fraction of sensitised individuals (incidence) will increase gradually, too.

For practical reasons, however, sensitisation is mostly treated as a quantal effect. In other words: an individual (experimental animal or human) subjected to a sensitizer under a specific test design will either be considered sensitised (if an arbitrary cut-off, such as an SI of 3 in the LLNA is exceeded), or not. Under CLP, a further distinction between moderate and strong sensitizers is possible, provided the available data allow for it. For the present dossier this is not relevant, as workers/professionals/bystanders etc. shall be protected from sensitisation as such.

The desired level of protection is basically a political/risk management decision. The REACH guidance does not contain a harmonised view on this issue.

¹⁹ Note that the concept of being sensitised more or less strongly (instead of being sensitised or not) also forms the basis for hyposensitisation therapy aiming at creating tolerance to the respective allergen by decreasing IgE production. In fact in the context of this dossier, tolerance phenomena are yet another uncertainty issue with respect to the experimental designs used in animal and human studies.

As demonstrated above (sections B.5.6.4 and B.5.6.5), reliable PoDs for quantitative risk characterisation are not available for the diisocyanates. As a consequence, qualitative risk characterisation needs to be based on a different approach.

In abstract terms, the present restriction proposal is based on the assumption that in Europe each year a certain percentage of the working population exposed to diisocyanates will suffer from occupational asthma (and that this population-based incidence is not acceptable from a regulatory point of view).

Unfortunately, reliable information on exposure patterns (and levels) in this population is missing. Likewise there is insufficient knowledge about the average time for which the population under question had been exposed prior to falling ill and about the average time workers would maintain their respective jobs. Any attempt to translate the observed population incidence into an individual added or extra risk to become sensitised as a consequence of occupational diisocyanate exposure would therefore be associated with very high uncertainties.

Consequently, the regulatory protection goal can only refer to the observed population incidence itself (e.g. the regulatory target could be to lower that incidence to, say, 50 % of the current level within a given period of time).

B.5.12.2.4 Desired "coverage" of the DNEL/DMEL

Again the required confidence in the statement "the derived DNEL is not less protective than the 'true' HD_M^I " is a political/risk assessment decision. Confidence levels frequently aspired in regulatory toxicology, e.g. in the context of statistical significance testing are 95 or 99 %. If the desired coverage was set to 99 %, this would mean that the likelihood that the DNEL/DMEL indeed was less protective, would not be greater than 1 %.

Summary of protection goals

The DNEL/DMEL to be derived would have to be an estimate of the human dose in a pre-defined time-frame of exposure/exposure scenario (e.g. 8 h/d, 40 working years, for workers) associated with protecting a defined percentage (e.g. 95 or 99 %) of the population (for most scenarios: healthy workers/professionals of both sexes, but potentially including children or elderly persons for some scenarios with bystander involvement) from a predefined added sensitisation risk (e.g. of 1 % or more) when exposed to diisocyanates in the workplace. The DNEL should meet these protection goals with predefined confidence (e.g. 95 or 99 %).

B.5.12.3 Uncertainties in deriving a DNEL/DMEL

The IPCS guidance (IPCS, 2014) states that:

"Hazard characterization involves making inferences about the human population of interest for risk assessment (the "target population") based on information obtained from a scientific study (the "study population"). [...] Specifically, making inferences between the "study" and "target" populations involves the following:

- making adjustments due to characteristics of the study population or study design that differ from the target population or target conditions;

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

- accounting for variability due to heterogeneity in the human population;
- and accounting for uncertainty associated with the two previous bullets due to incomplete data or knowledge.”

In the following subsections, these issues are addressed for each relevant aspect of hazard characterisation, i.e.:

- identification of a suitable “Point of Departure” (PoD) for risk assessment,
- where relevant and needed: adjustment for differences between the experimental setting under which the PoD was generated and the exposure scenario to be assessed,
- in case animal data are used: extrapolation from the “typical”²⁰ experimental animal to the „typical” human individual (adjustment for interspecies variability),
- extrapolation from the „typical” to a „sensitive” human individual (intraspecies variability), and
- potentially, other aspects, e.g. considering poor data quality or steep dose-response.

B.5.12.3.1 Selection of PoD

Animal data

It has been shown above that only a subset of the available animal studies qualify at all for being used as a starting point for LOEC identification. In addition, in some of the most sensitive experiments, the lowest dose tested already lead to relevant effects and estimation of a NOAEC or BMC is either not possible or would be associated with huge uncertainties.

Regarding the choice of endpoint, there is also a general problem directly relating some of the endpoints in these studies (e.g. presence of antibodies or biomarkers of inflammation) to the outcome of respiratory allergy in humans. While this may be overcome by choosing a conservative approach (accept any endpoint that could be related to respiratory sensitisation), the magnitude of effect statistically resolvable in an animal test with a few animals per group generally exceeds the maximum magnitude of effect desired here. NOAELs/BMDs from such studies are therefore associated with a high degree of uncertainty. Alternatively one could proceed by starting from a dose with a higher magnitude of effect (e.g. an ED₂₅ or a BMDL₁₀) and performing low-dose extrapolation in analogy to the DMEL methodology provided in the IR&CSA guidance R.8 (ECHA, 2012). This approach, however, would in turn be associated with huge uncertainties.

Essentially, these views have been shared in recent reviews from industry (Cochrane et al., 2015) and government (Dotson et al., 2015) institutions.

²⁰ (represented by the median of the test population from which the PoD was generated)

Human data

Available data in humans have been discussed, also with a focus on dose-response assessment above, in section B.5.6.5. The practical problems associated with case reports/studies and epidemiological studies have already been addressed. In brief, while case reports/studies generally do not allow for the establishment of a dose-response relationship, the size of the test populations subject to epidemiological studies is generally limited and exposure is difficult to assess. This is due to the fact that workers on study are not always naïve, i.e. previous exposure before the onset of the study is difficult to establish, co-exposure may exist at the workplace, and/or dermal and peak exposures are not quantifiable. Furthermore, the studies are prone to selection bias and appropriate control groups are difficult to identify.

In addition and in analogy to the animal experiments, choice of the most critical endpoint, limitations of the available measurement methodology etc. further limits the ability to reliably identify NOAELs or BMDs in such studies.

B.5.12.3.2 Adjustment for differences in test design

As a standard procedure in line with the IR&CSA guidance R.8 (ECHA, 2012), the PoD needs to be corrected for any differences in the daily or weekly exposure pattern. For risk assessment of inhalation exposure of workers, an increased respiratory volume under light activity has to be considered by an additional factor of 10/6.7.

As already discussed above with respect to animal data, the quantitative impact of different exposure designs (exposure duration, intermittent vs. continuous exposure) on the sensitisation outcome is poorly understood, making any adjustment highly uncertain.

The IR&CSA guidance *inter alia* uses default AF for extrapolation from subacute to subchronic (AF=3) and subchronic to chronic (AF=2) duration extrapolation. Most of these approaches are based on Haber's law or modified versions thereof, all developed from data on endpoints different than sensitisation. As for sensitisation the relevant exposure metric (dose- or concentration-dependency) is poorly understood, it is completely unclear whether these laws really can be applied to sensitisation, too.

B.5.12.3.3 Interspecies extrapolation

Under REACH the interspecies AF is subdivided into an allometric scaling factor (not relevant if external air or skin concentrations are compared) and a factor of 2.5 for "residual uncertainty". Unfortunately the latter contains elements of both adjustment and uncertainty for both toxicokinetics and toxicodynamics. Some authors have addressed interspecies differences with respect to sensitisation [e.g. (Collins, 2012; Pauluhn, 2016)], but overall there is insufficient quantitative knowledge in this regard rendering any extrapolation highly uncertain.

B.5.12.3.4 Intraspecies extrapolation

Genetic, e.g. (Yucesoy et al., 2014; Yucesoy et al., 2012), epigenetic, e.g. (Ho, 2010; Miller and Ho, 2008; Moggs et al., 2012) and environmental, e.g. (Miller and Jones, 2014) factors will determine whether or not an individual will be sensitised by a given dose of a chemical. However, both the exact nature of these factors and their quantitative influence are as yet poorly understood.

No reliable data were found regarding the human interindividual variability regarding the induction of sensitisation via the skin or the respiratory tract. It has been proposed to use a default factor of 10 for skin sensitisers (Griem et al., 2003) but this conclusion was drawn from a small set of human experimental data for only one chemical, aside from the fact that the adequacy of the underlying experimental data might be questioned. Again any quantitative extrapolation would be highly uncertain.

B.5.12.3.5 Potency and combined exposure

Finally, the available data do not suffice to derive relative potencies for the different diisocyanates in the scope of this restriction proposal (see also the description of the available database above). In addition, it should be noted that the database for some of the diisocyanates under this restriction proposal is fairly thin and this should be taken into account when considering an extra AF for gaps in knowledge.

B.5.12.3.6 Overall data quality

As portrayed above (sections B.5.6.4 and B.5.6.5), the available data base suffers from many deficits, inter alia with respect to relevance of test design, incomplete coverage of relevant endpoints, and lack of understanding regarding the quantitative relationship between exposure and risk.

B.5.12.4 Summary of the assessment

The above assessment has shown that almost every aspect of quantitative hazard characterisation is associated with a high amount of uncertainty.

Overall the DS concludes that for principal reasons, a combined DNEL/DMEL reflecting exposure scenarios with both dermal and inhalational exposure cannot be set.

For scenarios in which one of these routes may be considered virtually negligible, currently the overall uncertainties are unacceptably high when trying to establish a DNEL/DMEL for sensitisation by diisocyanates.

Generally speaking, there are three ways to deal with unacceptably high uncertainty in risk assessment:

- refinement of the assessment,
- generation of additional data (if the leeway for refinement is exhausted), or
- a regulatory decision is made despite/in view of this intolerable uncertainty²¹.

²¹ For example, if a reliable DNEL cannot be derived, the regulatory decision might be based on other principles, e.g. on qualitative risk characterisation or the pragmatic approach to keep exposure “As Low As Reasonably Achievable” (ALARA principle).

B.5.12.4.1 Refinement of the assessment

It is not expected that a more refined analysis would lead to a significant reduction of the uncertainties portrayed above.

B.5.12.4.2 Generation of additional data

While experiments in humans are not acceptable for ethical reasons, agreed testing protocols for respiratory sensitisation in animals are still lacking. As a consequence, it is currently not possible to develop a meaningful testing strategy to improve the existing data base in animals. With respect to human data, the need for better designed epidemiological studies has become obvious (however, it is acknowledged that many technical difficulties would have to be overcome, most notably the challenges in establishing reliable exposure measurements). Industry is called upon to generate longitudinal data that allow the evaluation of risks at current workplaces as well as its change that is expected to be achieved by this restriction.

B.5.12.4.3 Regulatory decision in view of the uncertainties

In the end the DS concludes that meaningful quantitative risk assessment cannot be performed and a DNEL or DMEL of sufficient reliability (with respect to the aspired protection goals) cannot be derived. For this reason, the DS has chosen a qualitative risk characterisation approach based on the assumption that in Europe each year a certain percentage of the working population exposed to diisocyanates will suffer from occupational asthma (and that this population-based incidence is not acceptable from a regulatory point of view). It is stressed again that for respiratory sensitisers also the REACH guidance recommends a qualitative approach to risk characterisation.

An alternative approach would use the most sensitive animal study and compensate the huge uncertainties with correspondingly high additional Assessment Factors. In the process of preparing this dossier the DS has performed an exemplary cursory analysis (not shown in this report), using the study by Matheson and co-workers (Matheson et al., 2005b) and applying an Approximate Probabilistic Analysis [APROBA, cf. (IPCS, 2014)] approach of uncertainty analysis. Very soon, however, it became evident that if appropriate AF/distributions were chosen to account for all uncertainties, the resulting overall uncertainty would become so large that any DNEL derived on that basis would become scientifically meaningless. As a consequence, this approach was not pursued any further.

B.6 Human health hazard assessment of physico-chemical properties

Not relevant for this dossier

B.7 Environmental hazard assessment

Not relevant for this dossier

B.8 PBT and vPvB assessment

Not relevant for this dossier

B.9 Exposure assessment

B.9.1 General discussion on releases and exposure

B.9.1.1 Introduction

The most likely routes of occupational exposure to isocyanates are via inhalation and the dermal route. Isocyanates can become airborne particularly in hot processes as fumes and vapours (e. g. hot melt adhesives and sealants) or as aerosols (e. g. spray painting, blow foaming) but can also be released by thermal degradation of polyurethanes.

The potential for occupational exposure to isocyanates is determined by several factors:

Volatility: One factor is the volatility of the compounds. Diisocyanates with a low molecular weight have significant vapour pressures already at room temperature. In particular toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) are common diisocyanates which can vaporise easily at ambient temperature thus leading to significant concentrations in the workplace air.

Hot processes: Higher temperatures increase the vapour pressure and thus the tendency of isocyanates to become airborne. Monomers of diisocyanates do not tend to thermally decompose. But some polyurethane material can decompose at temperatures as low as 150-200 °C (Delebecq et al., 2013; Simon et al., 1988; Wang et al., 2013). Thermal degradation can give rise to release of the original monomeric diisocyanate but also other low molecular isocyanates or fragments as part of thermal decomposition processes. Therefore hot work activities and processes can lead to significant exposure to isocyanates. Such work may include (but is not limited to):

- welding
- brazing
- soldering
- grinding
- treatment with a heat gun
- cutting with torches or hot wire
- heating of diisocyanate based glues
- flame laminating and bonding
- heating of polyurethane containing materials

Aerosols: Isocyanate based paints and varnishes are often used for spray painting. Especially in vehicle body repair HDI based spray paints are ubiquitously used and lead to significant occupational exposures. Spray foaming, especially when applied to greater surfaces (e. g. insulation of ceilings/walls) can also lead to high aerosol release (Christensen et al., 2014). Inhalation can also occur with dust arising from handling of solid diisocyanate-containing products or articles.

Dermal exposure: Skin contact with products containing isocyanates (e. g. uncured PU foams, paint or glue splashes) is a significant route of exposure (Austin, 2007).

Occupational exposure to diisocyanates is in particular possible during:

- production of polyurethanes (e.g. slab-stock foam)
- handling of partly uncured PU products (e.g. cutting, demoulding, spray-application of foam)
- when isocyanates/PUs are heated (e.g. hot lamination, foundry applications/casting forms)
- C.A.S.E. applications (Coatings, Adhesives, Sealants, Elastomers)

B.9.1.1.1 Inhalation exposure

Airborne diisocyanates can exist as vapour or aerosols, the latter with a wide range of particle sizes. Also, the formation of airborne isocyanates species can be a highly dynamic process. There is a strong tendency for aromatic diisocyanates in the gas phase to condense to aerosols (particles < 1µm), while monoisocyanates and aliphatic diisocyanates in the gas phase were not found to form particles in a similar way (Dahlin et al., 2008).

Usually, inhalation exposure data are collected in form of air monitoring of workplace for compliance reasons. Consequently, most of the available exposure measurement data is on those diisocyanates with the highest volumes and relevance for workplaces, namely TDI, MDI, HDI and, to a lesser degree, IPDI.

Accurate measurement of airborne isocyanates is a complex and difficult matter for several reasons:

Isocyanates are highly reactive, and therefore unstable. Even in the same air sample several different chemical species may be present (Streicher et al., 2000). Especially when applications involve higher mechanical energy, for example in spray foaming, aerosols are the primary form of airborne diisocyanates (Roberge et al., 2009).

Spray foam aerosols are droplets of fast curing and highly reactive mixtures of isocyanates with polyols, which makes sampling particular challenging (Puscasu et al., 2015).

It is also highlighted in literature that there is no existing sampling and analytical method that fully satisfies all of the requirements for monitoring limit values. Choice of the most appropriate measurement method is critical for the design and conduct of the sampling and analysis, especially as very low limits of detection and limits of quantification are essential (Brandt et al., 2013).²²

²² Most of the sampling methods use either impregnated filter with a derivatisation reagent or impingers, where the derivatisation reagent is dissolved in an organic solvent and the analyte air is bubbled through (or a combination of both). While impingers provide better results for measurement of fast curing systems, they are often difficult to use for personal sampling (and may pose a risk of leakage, evaporation of volatile organic solvents etc.) (Lockey et al., 2015; Puscasu et al., 2015).

Finally, most of the sampling and analytical standards address only few diisocyanate monomers and quantification of polyisocyanates is much more complex (Bello et al., 2004). This is an additional difficulty as there is a trend in industry to minimize the content of free monomers in formulations, where monomers of diisocyanates often constitute only a minor fraction (< 1 %) of the isocyanate species (Streicher et al., 2002).

For these reasons, even if air monitoring / measurement data are below the limit of detection or below the limit of quantification, such findings do not necessarily support the assumption that the exposure actually is adequately controlled for all such cases. Especially when complemented with biomonitoring data there is often clear evidence for occupational exposure to isocyanates of workers, even in cases where air monitoring suggests that the exposure situation might be well controlled. For example, Kaaria et al. assessed worker exposure to MDI at three factories in Finland during moulding of rigid PU foam. While MDI concentrations were below the limit of detection in 64 % of the breathing zone air samples they found MDA (as a MDI metabolite) in 97 % of the urine samples of the workers (Kääriä et al., 2001). These findings are especially important since there is an increasing body of literature highlighting the relevance of the dermal route for causing occupational asthma by isocyanate.

B.9.1.1.2 Dermal exposure

The contribution of the dermal route is of particular relevance when assessing the overall exposure to isocyanates for there is a growing body of literature on the role of skin exposure to isocyanates for development of respiratory sensitization and occupational asthma (Fent et al., 2009b). Cowie et al conducted a comprehensive study on where isocyanates were used in the UK and found that the airborne isocyanate exposure were minimal in almost all of the investigated workplaces, but “there was nearly always potential for skin contact” (Cowie et al., 2005). This aspect is of particular importance since it was demonstrated that isocyanates (e.g. from uncured resins) can deposit on and penetrate into the skin (Liljelind et al., 2010).

While airborne exposures could in principle be reduced by changing to less volatile isocyanates (like MDI or/and prepolymers) for many uses, such substitutions do not necessarily reduce dermal exposure and there are ample opportunities for skin contact in workplaces. The significance of dermal exposure may depend on factors like the form (and volatility) of the diisocyanates as well as on the processes involved (Cocker, 2011). For example, uncured or not fully cured polyurethane products pose a source of skin exposure to isocyanates (Bello et al., 2007). Furthermore, assessment of dermal exposure in workplaces is often complicated by the irregular and random occurrence of skin exposure, such as spills, contact with contaminated surfaces or during clean-up (Bello et al., 2007; Heederik et al., 2012).

Quantification of dermal exposure on the other hand is particularly difficult. Measurement of dermal exposure, in general, is less established than air monitoring and data on dermal exposure to isocyanates in workplaces are scarce (Liu et al., 2007). There are no standardized methods available for measuring dermal isocyanate exposure (Lockey et al., 2015). Sampling of dermal exposure to isocyanates is challenging as the analytical methods are adaptations of the methods for airborne isocyanates and rely on presence of unreacted NCO groups. Because NCOs (and especially mixtures of isocyanates with polyols or amines) are highly reactive and they also react with moisture on or proteins of the skin, timing of the sampling is particularly critical (Redlich, 2010).

For these reasons, dermal exposure to isocyanates often is assessed indirectly by comparison of personal air samples with corresponding biomonitoring data (see below).

B.9.1.1.3 Biological monitoring

Biological monitoring (or biomonitoring) allows the assessment of the total body burden of workers irrespectively of the exposure pathway and exposure source and is increasingly used for assessment of exposure to isocyanates. Biological monitoring of diisocyanates is based on the analysis of isocyanate-adducts with haemoglobin or albumin in the blood or the determination of corresponding diamines in urine or in plasma (Cocker, 2011; Swierczynska-Machura et al., 2015). Diamines (MDA in case of MDI exposure, TDA for TDI, HDA for HDI) are formed by the hydrolysis of the diisocyanate adducts. However, as isocyanates as well as their corresponding amine analogues (e.g. MDA and MDI) react with proteins directly the amines formed after hydrolysis in urine or plasma are not specific markers for isocyanates and it is therefore not possible to distinguish between exposure to the isocyanate or the corresponding amine (Gries and Leng 2013). When assessing the exposure to diisocyanates exposure to the corresponding diamines (e.g. in case of biological monitoring of MDI exposure to MDA) has to be ruled out since the results can be biased otherwise. In addition to assessment of exposure levels, biological monitoring can also be used to assess the influence of behavioural aspects regarding the effectiveness of risk management measures like proper use of PPE and efficacy of training interventions (Jones et al., 2013). When done by analysis of metabolites in urine, biological monitoring is also a relatively simple and less expensive way of exposure assessment to isocyanates.

One limitation of biological monitoring is that it may only reflect average daily exposures while peak exposures are not accessible by these methods since urine metabolites have a poor correlation to short-term peak exposures (Chappelle et al., 2001).

B.9.1.1.4 Peak exposure and non-routine operating conditions

Typically, peak exposures that occur during incidents and other non-routine handling are not measured. But even if short-term peak exposure occurs on a more regular and foreseeable basis measurement of such peak exposures is challenging (Jankowski et al., 2014). Especially during hot-work processes the applied or generated heat is often variable, thus release of isocyanates will occur as short peak exposures. Incidents such as spills may cause peak exposures and should be avoided. If such incidents occur, safe procedures, which should be decided on in advance should be applied. But, deviation from normal operating conditions like flaws in the equipment, incidents etc. are by definition not planned situations and therefore not foreseeable when they do occur. Furthermore, such situations often require immediate interventions to minimize potential damage or restore normal operating conditions. It is crucial to act with proper caution and in compliance with the safety obligations to keep the exposure controlled in such situations.

The use of personal protective equipment (PPE) is the least preferred method of controlling exposure. They should not be used as the primary control for routine operations, but PPE may be unavoidable during non-routine situations such as emergencies or some maintenance procedures, e.g. when closed equipment has to be opened and the existing engineering controls do not offer adequate exposure reduction. Proper use of protective clothing and equipment such as chemical resistant gloves and eye protection is also necessary when handling uncured material such as freshly produced polyurethane or reactive resins. However, the effectiveness of PPE largely depends on the proper use and

good worker education is vital to ensure that PPE is used correctly and in compliance with the required safety procedures. For example, if a supplied air respirator with a full face shield is used correctly during spray painting operations an adequate reduction of exposure can be assumed. But when the air-fed visor is lifted immediately after spraying e.g. for quality checking of the spray coating, this period of working with a lifted visor can be treated a period of non-wear of RPE (Clayton and Baxter, 2015).

While quantification of peak exposures and exposures due to unintended events like incidents is particularly difficult, it is also necessary to consider these types of exposure for a comprehensive assessment. To control such exposures the use of personal protective equipment is often unavoidable. But effectiveness of PPE is highly dependent on its correct use and therefore particular attention has to be paid that it is applied consistently. For this reason, without regular (and targeted) training the assumed effectiveness of PPE in the context of exposure reduction often appears to be overoptimistic.

B.9.1.1.5 Focus of the exposure assessment for this dossier

In the following assessment emphasis is placed on the most relevant uses of diisocyanates with respect to amount / volume and workplace exposure rather than a comprehensive list of all uses registered under REACH. Descriptions of workplace exposures will be based on data from Chemical Safety Reports (CSRs) of the Registration Dossiers (which were prepared by the Netherlands Organisation for Applied Scientific Research (TNO)), selected literature as well as measurement data published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) and the UK Health and Safety Executive (HSE). The exposure assessment is limited to some selected types of diisocyanates with the most relevance for workplaces, namely MDI, TDI and HDI. The literature discussed was selected according to timeliness (since 2000) and relevance for the EU. Some of the data and literature from North America are deemed similarly representative for the situation in European workplaces and are also considered.

2,4-TDI has been subject to a substance evaluation under REACH carried out by the Polish Competent Authority (Polish CA, 2013). Occupational exposure has been assessed by evaluation of the exposure scenarios of the CSR. The Polish CA concluded in the SEV report that the measured data as the basis for exposure assessment in the CSR are well documented and plausible and that the exposure estimates for inhalation exposure are appropriate.

B.9.1.2 Summary of the existing legal requirements

B.9.1.2.1 Introduction

The fact that the use of low molecular weight diisocyanates may lead to occupational health problems has been known for a long time.

As a reaction to this situation, many EU-countries have introduced occupational exposure limits for the use of such compounds. A harmonised EU-wide exposure limit does not exist. In some cases additional measures and actions have been introduced to support employers and workers in preventing adverse effects from handling isocyanates and to increase the knowledge of such effects and disseminate the use of good practices. This has been done in the framework of national OSH regulations or as support actions of national occupational

health authorities. Unfortunately, within Europe these actions have never been synchronized, so that it is rather difficult to compare use conditions in the various EU-MS.

Apart from the EU, a lot of investigation and regulations is available in the USA. Because the proposal focuses on the European situation, these will not be discussed in detail. However, relevant literature on this aspect is referred to, or data added where this helps to interpret European data

B.9.1.2.2 Occupational Exposure Limits

The available OELs of various countries are listed in Table 13. In the interpretation of the numbers it has to be realized that there are various ways to report exposure to isocyanates.

- As vapour in air on a volume basis, usually expressed in ppb
- As weight of substance /(air volume), usually expressed as mg/m³ or as µg/m³
- As weight of NCO groups/(air volume) basis, usually expressed as mg/m³ or as µg/m³.

These different ways of expressing exposure can be converted into each other. The necessary conversion facts are listed in Appendix 4 at the end of the dossier

The first option is obviously only suited for vapours of isocyanates, where the second and third may also include liquid or solid aerosols. The advantage of the third way of representing isocyanate exposure is that it concentrates on the functional groups (which are considered to be the critical entity) only and allows an addition over various substances of different functionalities and molecular weights which may simultaneously be present in an application of isocyanates, where the material starts reaction directly after mixing or application. Special adapted analytical methods (AGS, 2009) are available to determine the total "NCO content" Over the last few years, this latter way of expressing exposure has been used in an increasing number of countries.

The available background information to the different OELs in the different MS does not always allow to judge if this value was derived from toxicological studies, epidemiological considerations, or represents a concentration that was deemed to be a reasonable technical achievable value.

B.9.1.2.3 Additional regulatory measures in the EU and by some MS

In addition to the implementation of OELs, either in the EU as a whole or in some MS additional measures were introduced in order to improve working standards during use or improve the risk control. A summary of known regulations is shown in Table 15.

Table 13: Occupational exposure limit values (8 hours) for diisocyanates in various Member States of the EU. Values are given in ppb unless otherwise stated.

	A T	BE	D K	F R	DE	HU	IE [#]	IT	LV	PL	E S	S E	UK
TDI	5	5	5	10	5		0.001 mg/m ³	20	0.05 mg/m ³	0.007 mg/m ³	5	2	
MDI	5	5	5	10	0,05 mg/m ³	0,05 mg/m ³	0.02 mg/m ³			0.03 mg/m ³	5	2	

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

	A T	BE	D K	F R	DE	HU	IE [#]	IT	LV	PL	E S	S E	UK
HDI	5	5	5	10	5	0.035 mg/m ₃	5	1 mg/m ₃	0.05 mg/m ₃	0.04 mg/m ₃	5	2	
IPDI	10	5	5	10	5		5			0.04 mg/m ₃	5	2	
NDI	10		5	10	0,05 mg/m ₃	0,09 mg/m ₃					5	2	
TMXDI	5	0.05 mg/m ₃	5									2	
HMDI	5	5	5								5		
NBDI					5								
„Poly-meric MDI“[§]					0,05 mg/m ₃								
Diisocyanate s							0.02 mg/m ₃					2	
Isocyanates, all (as –NCO)													0.02 mg/m ³ _§

Data are taken from the database "GESTIS - International limit values for chemical agents (Occupational exposure limits, OELs)", which is maintained by the German Social Accident Insurance (DGUV). URL: <http://limitvalue.ifa.dguv.de/>, last update April 2015, accessed May 2015.
[#] as NCO

[§] calculated as MDI (TRGS 900, Issued: January 2006. BArBI Heft 1/2006 S. 41-55. last time changed and extended : GMBI 2015 S. 139-140 v. 2.3.2015 [Nr. 7])

[§] Except methyl isocyanate (HSE 2013, available at <http://www.hse.gov.uk/pubns/priced/eh40.pdf>, accessed May 2015)

B.9.1.2.4 Other additional measures or initiatives

Apart from these formal regulations, additional actions were taken in some Member States to address specific problem situations or to try to improve general standards.

1. In the UK HSE put a considerable effort in investigating the use of diisocyanates in spray painting for car repairs and came up with valuable instruction material to improve awareness and handling standards of workers (HSE, 2014).
2. In the Netherlands problems reported during the insulation of house crawlcellars using MDI based polyurethane spray foams got wide spread attention (Nuon, 2013). Occasionally, inhabitants of the houses being treated reported respiratory problems after reoccupation. Up to now it remains unclear if these problems were caused by the Isocyanates or by other substances used in the formulation and/or errors during application. However, following these problems a country-wide voluntary certification system was introduced for companies applying such spray foams that improved protective measures and work quality.
3. Similar problems, discussions and measures are reported from the USA. <https://www.buildinggreen.com/blog/epa-raises-health-concerns-spray-foam-insulation> ; (California EPA, 2014), resulting in a strict working code <http://www.sprayfoam.org/>

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 14: Short-term occupational exposure limit values for diisocyanates in various Member States of the EU. Values are given in ppb unless otherwise stated.

	AT	BE	DK	FR	FI	DE	HU	IE #	IT	PL	ES	SE*	UK
TDI	20	20	10	20		5 [#] 20*	0.035 mg/m ³	0.003 mg/m ³	0.01 mg/m ³	0.021 mg/m ³	20	5	0.01 mg/m ³
MDI	10		10	20		0,05 mg/m ³ [#] 0,1 mg/m ³ * [*]	0.05 mg/m ³	0.07 mg/m ³		0.09 mg/m ³		5	
HDI	5		10	20		5 [#] 10*	0.035 mg/m ³			0.08 mg/m ³		5	
IPDI	20		10	20		5 [#] 10*							
NDI	20		10	20		0,05 mg/m ³ [#] 0,1 mg/m ³ * [*]	0.09 mg/m ³					5	
TMXDI	10		10									5	
HMDI	5		10								50	5	
„Polymeric MDI“ §						0,05 mg/m ³ [#] 0,1 mg/m ³ * [*]							
HDI, prepolymer				1 mg/m ³									
Diisocyanates								0.07 mg/m ³				5	
Isocyanates, all (as -NCO)					0.035 mg/m ³								0.07 mg/m ³ §

15 Min

* ceiling limit value

§ § calculated as MDI (TRGS 900, Issued: January 2006. BArBI Heft 1/2006 S. 41-55. last time changed and extended : GMBI 2015 S. 139-140 v. 2.3.2015 [Nr. 7])

§ Except methyl isocyanate (HSE 2013, available at <http://www.hse.gov.uk/pubns/priced/eh40.pdf>, accessed May 2015)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 15: European and national regulations related to diisocyanates

Regulation	EU/ National	Substance concerned	Description (short)
Annex XVII of REGULATION 1907/2006	EU	2,2'-MDI, 2,4'-MDI, 4,4'- MDI and mixes of MDI isomers (CAS-number 2536- 05-2, 5873-54-1, 101-68-8 and 26447-40-5).	Protective gloves mandatory for supply to the general public. Not for hot melt adhesives
COMMISSION RECOM- MENDATION 2008/98/EC of 6 December 2007 on risk reduction measures for a number of substances, including MDI	EU	MDI (CAS-number 26447- 40-5), which in the underlying risk assessment is assumed to address all MDI isomers.	Employers using MDI for uses identified as a concern in the EU risk assessment (2005) should take note of any sector specific guidance developed at national level based on the practical non- binding guidance, to be published by and available from the Commission as foreseen under Article 12(2) of Council Directive 98/24/EC (3)
COMMISSION REGULA- TION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food	EU	CAS-number: 91-08- 7 (2,6- TDI), CAS- number: 584- 84-9 (2,4-TDI) , CAS- number: 101-68-8 (4,4'- MDI) and CAS- number: 5873-54-1 (4,4'-MDI) TDI dimers and other isocyanates are listed as well Primary aromatic amines formed by hydrolysis of isocya- nates (MDI and TDI can form primary aromatic di-amines)	It is required that isocyanate migration from plastic packaging should not be analytically detectable in the food, and that the content of isocyanates in the food plastic material must not exceed 1 mg/kg in the final product expressed as isocyanate moiety
REGULATION (EC) No 1223/2009 OF THE EURO- PEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products	EU	2,4-TDI, 2,6-TDI and mixes thereof (CAS-numbers: 584- 84-9, 91-08-7 and 26471- 62-5)	Included in Annex II (LIST OF SUBSTANCES PROHIBITED IN COSMETIC PRODUCTS)
COMMISSION RECOM- MENDATION of 19 September 2003 concerning the European schedule of occupational diseases	EU	Isocyanates	Recommends Member States to implement provisions for scientifically recognised occupational diseases liable for compensation and subject to preventive measures with reference to Annex I. Annex I, item 1 (Diseases caused by chemical agents) lists "Isocyanates".
Executive order on occupational health educations (Bekendtgørelse om	DK	Isocyanates	Specifies that work with isocyanates requires certificate from specific training. It is specified which skills must be

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Regulation	EU/ National	Substance concerned	Description (short)
arbejdsmiljøfaglige uddannelser, BEK nr. 1088 af 28/11/2011)			obtained via this education and who can provide the training.
Chemical hazards in the working environment AFS 2014:43	SE	Isocyanates	In the framework of provisions for working with chemicals, describes specific duties for isocyanates (a.o. training certificate)
Work Environment Authority on thermosets and general advice on the application of Regulations AFS 2005:18	SE	Thermoset resins, including isocyanates	Rules for working with thermoset resins, including isocyanates

Note: Many specific Danish regulations in (Møller Christensen et al., 2015)

B.9.1.3 Summary of the effectiveness of the implemented operational conditions and risk management measures

When assessing the exposure estimations given in the CSRs there are some principal concerns to be raised. It is the registrants obligation²³ to describe in the exposure scenarios how the manufacturer (or importer) controls, or recommends downstream users to control exposures of workers.

The exposure estimates in the registration dossiers for MDI, TDI and HDI are mostly based on large sets of data which are deemed to be of good quality and also representative for situations with good industrial hygiene and good practise (Polish CA, 2013). However, as the role of exposure assessments in the CSRs is to demonstrate how substances can be used safely, by definition, exposure assessments within CSRs are limited to situations with good occupational hygiene and technical standards. In addition, the respective risk management measures taken into account often include and rely on correct use of personal protective equipment (PPE). This is completely fine for the sake of the registration dossiers, where it has to be demonstrated how substances can be used safely. But it is a well-known fact that effectiveness of PPE highly depends on that it is used correctly. Also, use of PPE often constitutes an additional burden for the wearer or can pose risks on its own. Therefore, reliability of PPE is highly prone to failure and variation in effectiveness by factors such as deliberate or negligent wrong (or non-)use.

While exposure assessments in the CSRs reflect situations with good occupational hygiene standards, they do not cover some maybe more realistic workplace practises, where effectiveness of PPE is often questionable. For this reason some of the assumptions and estimates in the CSRs are deemed to be overoptimistic in terms of that they do not (as they

²³ Regulation (EC) No 1907/2006; Annex I, 0.7.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

do not have to) represent all of the actual workplace situations, where isocyanates are handled often in a less than ideal way.

Assessing the effectiveness of implemented operational conditions and RMM is usually done by comparison of exposure data before and after a specific measure was applied. Unfortunately these kinds of data are rarely available. However a limited number of studies followed this approach are described in the following paragraphs.

Tinnerberg et al. for example assessed the exposure to isocyanates in 13 Swedish industry plants in 2000. Particularly high exposure levels were measured in a foaming plant with a median value of 62.9 µg/m³ of total TDI in the personal air samples (Tinnerberg and Mattsson, 2008). However, the measurements were repeated in 2005 after technical improvements were made to reduce the exposure at that plant. The measures included replacement of a semi-enclosed foaming tunnel by an enclosed one and a more airtight system with increased ventilation but also a reduction of amine in the mixture to slow down the reaction. The results from the measurements in 2005 were around 80 % lower compared to the exposure levels in 2000, with a median value of 12.5 µg/m³ in 2005. The study also included biological monitoring of biomarkers in the plasma of the workers (P-2,4-TDA and P-2,6-TDA). The effects of the implemented exposure reduction measures were even more pronounced when comparing the median values of the biomarker concentrations in plasma of workers from 2000 with those from 2005, the latter being around 90 % less of the previous median values. The median plasma concentrations of P-2,4-TDA were 7.0 mg/mL in 2000 compared to 1.0 ng/mL in 2005 and the corresponding median plasma concentrations of P-2,6-TDA were 30.8 ng/mL in 2000 and 4.0 ng/mL in 2005. Although the study has some limitations mostly due to the limited sample size it can serve as an example to illustrate the potential for exposure reduction when facilities are at a technical level at or near to the state of the art.

Another study found highly relevant with respect to effectiveness of worker training in controlling exposure was published by Jones, Cocker and Piney (Jones et al., 2013). The authors compared exposure measurement data based on biological monitoring from the motor vehicle repair industry in the UK before and after spray painters participated in trainings. These trainings were so called Safety and Health Awareness Days (SHADs) with the aim to improve the understanding and to increase the awareness of the hazards and risks associated with isocyanates and to give advice on controlling exposure especially during spray painting. The SHADs were organised as half-day events and the key messages were repeated in a variety of different ways by combining diverse media such as showing explanatory videos, working model demonstrations, oral presentations as well as performing drama by professional actors. For example, it was found that lifting up the visor of the respiratory protective equipment (RPE) immediately after spraying is a common workplace practice of sprayers to check the quality of the paint finish (Clayton and Baxter, 2015). While spray mist is still present in the workplace environment these periods of visor lift lead to decrease of the reduction efficiencies of the RPE dramatically and can be effectively seen as periods of non-wear. After the SHADs the participants were offered to take a biological monitoring sampling kit free of charge and were instructed to provide the urine samples within an hour of the end of the spraying activities. Overall 995 urine samples from spray painters were received after taking part at a SHAD and analysed for the levels of HDA as the metabolite of HDI in urine. The results were statistically evaluated and compared to results of biological monitoring measurements prior to the SHADs. The overall levels of HAD were significantly lower in spray painters following SHADs than from the previous HSE samples. These lower levels were also maintained over the following years. The

90th percentile value of urinary HDA concentrations was 1.34 µmol/mol creatinine for the pre-SHAD data and 0.68 µmol/mol creatinine for the post-SHAD averaged over the following four years indicating an effective reduction of exposure by around 50 %. The 90th percentile value of the measurements directly after the SHADs was 0.60 µmol/mol creatinine. The authors concluded that the weight of evidence suggests that trainings (SHADs) were influential.

The same conclusion was drawn in a subsequent study by Stocks et al. (Stocks et al., 2015). The authors compared the trends in incidence of work related asthma and in urinary HDA levels in motor vehicle repair workers in UK and found that the number of samples with detectable levels of HDA in urine declined significantly from 2006 to 2014 and was lower in the samples submitted through the SHADs. However, they also reported an increase between 2013 and 2014 in the number of samples with HDA detected and those with HDA levels over the guidance limit. In the opinion of the authors the implication is that the impact of the SHADs might be fading and that refresher training could be valuable.

B.9.2 Manufacturing

A description of the general processes involved is given in section B.2.1.1 of the dossier.

B.9.2.1 Occupational exposure

As the manufacture of diisocyanates involves the conversion of diamines with phosgene (and owing to the dangerous properties of isocyanates themselves) the production processes are carried out in high integrity closed systems. Occupational exposure to diisocyanates is generally considered to be low at this stage as long as the manufacturing processes run under normal operating conditions. This appraisal is corroborated by occupational exposure data in the exposure scenarios for MDI and TDI published by ISOPA (ISOPA, 2012; ISOPA, 2014).

Table 16 presents the ranges of the exposure estimates for MDI, TDI and HDI taken from the CSRs. The ranges cover the exposure estimates of the contributing scenarios within the scenarios "Manufacturing" of the respective diisocyanate. All of the exposure estimates are based on data from occupational hygiene measurements and represent the 90th percentiles of the respective datasets.

Table 16: Long term inhalation exposure ranges (mg/m³) for the exposure scenarios "Manufacturing" of MDI, TDI and HDI, taken from Registration Dossiers

MDI	TDI	HDI
0.0056 – 0.029	0.005 – 0.032	0.003 – 0.0235

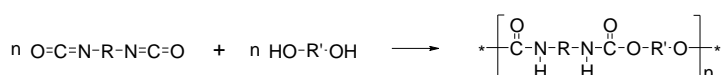
B.9.3 Use in manufacture of polyurethanes and PU composite materials

This is the use with the highest volume. Occupational exposure often takes place on a regular basis and can be expected to be frequent while also exposure control measures by technical engineering are often applied and exposure levels can be expected to be moderate.

B.9.3.1 General information

As mentioned before manufacture of polyurethanes is the by far predominant use of diisocyanates and in a certain sense almost all of the other uses can be subsumed as special uses / applications of polyurethanes (such as polyurethanes in foam applications, coatings, adhesives etc.). Nevertheless, for the exposure assessment a differentiation in some selected scenarios / applications linked to potentially high exposure is considered appropriate. Manufacture of block foam in continuous slabs will be discussed separately. However, as foam moulding is considered to take place in more closed systems (moulds) this use is also considered as part of the manufacture of polyurethanes and the respective exposure data will be presented within this use.

To produce polyurethanes the diisocyanates are reacted with macropolyols and/or other polynucleophiles and usually optional additives like catalysts, surfactants, stabilizers, flame retardants and the like. The polyaddition of isocyanates with the nucleophiles is a highly exothermic reaction. Depending on the reaction quantities and conditions, the temperature can increase considerably during the process. The chemical equation below exemplifies the general mechanism the reaction (based on a simple single phase PU, which is just one species of diisocyanate and polyol are reacted):



Usually the reaction is largely completed within seconds up to 30 minutes, whereby the isocyanate groups form urethane bonds with the polyol in the polymer backbone. However, the final curing and post-curing of polyurethanes, where exposure to unreacted isocyanates is still possible may take up to 72 h.

As mentioned above, the reaction of isocyanates with polyols or amines is a highly exothermic process. Therefore, especially when high volumes of diisocyanates are reacted to produce polyurethanes, a significant increase in temperature of the reaction mass can be assumed. This also affects the potential for exposure since the vapour pressure may rise significantly.

B.9.3.2 Exposure estimation

B.9.3.2.1 Workers exposure

MDI

MDI is the diisocyanate with the highest market volume and also the diisocyanate with the highest volume in the manufacture of PU and PU materials.

Inhalation exposure

Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)

The data published by ISOPA in the document "MDI: Final Exposure Scenarios in the e-SDS format" were clustered at request of the consortia by TNO following the life cycle tree of MDI (ISOPA, 2012). The overall eight clustered exposure scenarios are based on the respective CSRs for MDIs. From this ISOPA document following exposure scenarios are taken into account for the use of MDI in manufacture of polyurethanes and PU composite materials in manufacture of polyurethanes and composite materials. Both, industrial uses [SU 3] and professional uses [SU 22] are considered:

- Exposure scenario cluster 2: Use of MDI for Manufacturing of other Substances and Formulation (including Resin Manufacture), Repackaging and Distribution
- Exposure scenario cluster 3 B): Industrial use of MDI in Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres and Manufacturing of other Polymers
- Exposure Scenario cluster 5: Industrial use of MDI for Composite Material Based on Wood/Man-made/Mineral/Natural Fibres
- Exposure Scenario cluster 6: B) Industrial use of MDI in Other Composite Material
- Exposure Scenario cluster 7: Professional end uses of MDI
 - D) Composite material based on wood/manmade/mineral/natural fibres, professional use
 - E) Other composite material, professional use

The exposure estimates in the exposure scenarios are based on occupational hygiene measurement data. The exposure levels were assigned to the different PROCs according to the use descriptor system. According to the CSRs the 90th percentile values of the exposure distributions were used. Where no data could be found, that seemed to fit the purpose for a specific PROC, the value of another PROC was taken instead, that was considered to be similar but also more conservative. Due to the general approach of the statistical analysis the same values were assigned to the respective PROCs in all of the exposure scenarios and for the different MDI isomers. For the long term inhalation exposure they range from 0.002 mg/m³ to 0.029 mg/m³ for ES 2, 3 B, 6, 7 D and E and up to 0.038 mg/m³ for ES 5. In case of the short term inhalation exposure the values range from 0.003 mg/m³ to 0.058 mg/m³ and 0.076 mg/m³, respectively. The highest exposure estimate values (0.029 mg/m³ for long term and 0.058 mg/m³ for short term inhalation exposure) are allocated to PROC 8a and 8b (transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities and at dedicated facilities), and also to PROC 5 (mixing or blending in batch process) for most of the contributing scenarios within the exposure scenarios relevant for this use. In exposure scenario 5 the highest exposure value of 0.038 mg/m³ is allocated to PROC 2.

Occupational exposure data from the German Social Accident Insurance (IFA)

Measured workplace exposure data from Germany have been evaluated in a study by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2010). The data have been gathered from 2000 to 2009 and were documented in accordance to the measurement system of the German Social Accident Insurance

Institutions for exposure assessment (MGU) (Gabriel et al., 2010). Overall, a total of 6294 measurement data for MDI (4484 for 4,4'-MDI and 1810 for 2,4'-MDI) have been evaluated according to industry groups as well as work area groups. Since this assignment of measurement data to industry groups and area groups does not follow the use classifications in the registration dossiers, a simple one-to-one translation / allocation of the MEGA data to the registered uses (see Table 5) is not possible. However, Table 17 provides an extract of the statistical evaluations of the measurement values for MDI for those work area groups thought to fit to the use description "manufacture of polyurethanes and PU composite materials" based on expert judgement of the DS. The data are representative for more than six hours of time of exposure.

Occupational exposure data from the Health and Safety Executive of the United Kingdom (HSE UK)

In the course of the dossier preparation the DS asked the other MSCAs for data regarding the exposure to isocyanates. From the UK HSE some air monitoring data as well as biological monitoring data from HSE's National Exposure Database (NEDB) were provided.

However, due to the confidential nature of the data provided, the following statement has to be included to this section:

'The data is not representative of any industry partly due to bias in selection of the sites where data has been collected and is determined by HSE interest in specific substance or process. Most of the data was collected between 1986 and 1993 after which the rate of data collection reduced significantly. It should be noted that NEDB itself has an inherent bias, in that HSE Specialist Occupational Hygiene Inspectors as part of their enforcement duties obtained approximately 90 % of the samples. Consequently, a tendency towards high levels of exposure would be expected, as companies with no perceived problems were generally not sampled. Even so, NEDB still contains many samples indicating low exposure (<25 % of the appropriate occupational exposure limit), so the actual bias is not as large as would be expected. Whether or not NEDB should be considered as containing worst case data is debatable, but it cannot be regarded as being truly representative of occupational exposure in Great Britain given that it does not come from a random selection of workplaces and circumstances.'

Out of the air monitoring data (with overall 450 measurement entries) 26 measurements were attributable to exposure to MDI in manufacture of polyurethane (13 of which were long term personal and 13 long term static (background) samples). The MDI concentrations of the personal measurements were in a range from 0.09 to 32.8 µg/m³ while the static samples ranged from 0.07 to 5.64 µg/m³.

Table 17: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th per-centile (mg/m ³)	90 th per-centile (mg/m ³)	95 th per-centile (mg/m ³)
Moulding 4,4'-MDI	Yes	22	0.00482	0.00988	0.002	0.018	0.0229
	No	11	0.00364	0.0059	LOQ	0.0127	0.0154
Moulding 2,4'-MDI	Yes	13	0.00131	0.000855	LOQ	0.002	0.0027

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Foaming moulds 4,4'-MDI	Yes	141	0.00162	0.00264	LOQ	LOQ	0.005
	No	56	0.00107	0.000322	LOQ	LOQ	0.002
Foaming moulds 2,4'-MDI	Yes	52	0.00107	0.000384	LOQ	LOQ	0.002
	No	14	0.001		LOQ	LOQ	LOQ
Casting 4,4'-MDI	Yes	82	0.00293	0.00529	0.002	0.005	0.0108
	No	54	0.00105	0.000176	LOQ	LOQ	LOQ
Casting 2,4'-MDI	Yes	39	0.00106	0.000366	LOQ	LOQ	LOQ
	No	26	0.0011	0.000246	LOQ	LOQ	LOQ
Pressing, extrusion 4,4'-MDI	Yes	38	0.00716	0.00126	0.006	0.0174	0.028
	No	11	0.00145	0.00151	LOQ	LOQ	0.00325

Abbreviations:

LOQ limit of quantification
 LEV local exhaust ventilation
 Arithm. Mean arithmetic mean
 SD arithmetic standard deviation

Data from literature

Kääriä et al. conducted a comparative air and biological monitoring study at three Finnish factories where MDI was used in moulding rigid PU foam as parts for insulation of refrigerators (Kääriä et al., 2001). The moulding process was done by injecting the MDI and polyol components through a mixing head directly into moulds. Hence the foaming process completely did take place inside the moulds and exposure to MDI was most likely limited to either the MDI resin of the final PU panels. For this reason, the study is discussed in this section (use in manufacture of PU) instead of the following chapter (use in manufacture of foam). Exposure to MDI was measured for 57 workers by overall 205 personal air measurements and 70 stationary samples. 131 of the personal (64 %) and 49 of the stationary (70 %) air samples were below the limit of detection of 0.03 µg/m³. The overall measured levels of airborne MDI were low, ranging, as far as quantifiable, from 0.3 to 3.3 µg/m³. No further analysis of the stationary air samples was presented in the study, besides that the measured stationary concentrations were less than 0.5 % of the Finnish OEL of 35 µg/m³ for isocyanates (expressed as NCO groups). The results of the biological monitoring will be discussed later in the respective section of this chapter.

Sennbro et al. surveyed airborne isocyanate exposure in Swedish PU industries at 13 plants handling diisocyanates / polyurethanes (Sennbro et al., 2004). Out of the presented data in this study only one plant seems to fit the use of MDI in manufacture of polyurethane and PU materials (plant M1). The measured 8 h TWA levels of MDI in this plant ranged between 0.042 µg/m³ to 7.8 µg/m³ (median 3.74 µg/m³).

Creely et al. assessed worker inhalation and biological exposure to isocyanates in polyurethane industry sectors in the UK (Creely et al., 2006). The study included 22 companies using isocyanates for moulding PU products, insulation material as well as industrial painting. The companies were selected by being judged to be only using good working practices. 70 personal air samples and corresponding urine samples were taken and analysed during the study. The results of the air monitoring were generally low, with only

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

20 samples showing concentrations above the limit of quantification (LOQ) of 0.001 mg/m³. Out of the selected companies 14 used MDI in the manufacture of PU materials. The exposure levels for these companies range between below the LOQ up to 0.0072 mg/m³ of total NCO content. Results of the biological monitoring will be discussed later.

Brzeźnicki and Bonczarowska conducted a study on air concentrations of selected isocyanates in Polish industry (Brzeznicki and Bonczarowska, 2015). Measurements of 4,4'-MDI, HDI, 2,4-TDI and 2,6-TDI exposure were carried out in 21 manufacturing plants, which were differentiated according to the isocyanates used, the types of production and the activities of workers. It seems plausible to subsume five of the 21 manufacturing plants to the group of "use of MDI in manufacture of polyurethanes and PU composite materials" (namely plant A, O, R, T, and, with reservation, E; as coded in the original article). Without consideration of spraying activities, which will be discussed separately, the measured concentrations of MDI range between below the limit of detection (0.60 µg/m³) to 3.3 µg/m³. The authors pointed out that while the concentrations of analysed MDI in the study were low, possibility of additional adsorption through the skin cannot be excluded but remained outside the scope of this study.

Table 18 provides an overview of the inhalation exposure levels to MDI according to the sources above. (The data from IFA do not provide values for the total isocyanate concentrations but only for the respective isomers, i.e. 4,4'-MDI and 2,4'-MDI were evaluated separately).

Table 18: Overview of inhalation exposure levels to MDI in manufacture of PU and PU composite materials (in µg/m³)

CSRs	(IFA, 2010) 90 th percent tile	HSE UK	(Kääriä et al., 2001)	(Sennbro et al., 2004)	(Creely et al., 2006)	(Brzeznicki and Bonczarowska, 2015)
2.0-29.0	LOD-18.0	0.07-32.8	0.3-3.3	0.04-7.8	LOQ-7.2	LOD-3.3

Dermal exposure

Data from the Registration Dossiers

Potential for dermal exposure to MDI is almost always given when liquid or uncured materials are handled. Assessment of the dermal exposure in the CSRs for MDI were either done qualitatively or based on the estimates reported in the EU RAR (Belgian CA, 2005) which were calculated with the EASE model. In case of the qualitative assessment the likelihood and frequency of dermal exposure were assessed in four categories: very low, low, medium and high. The assessment was carried out taking account of the use of personal protective equipment (PPE) like suitable chemical resistant gloves, eye protection and coveralls. For this assessment it was assumed that dermal exposure due to formation of aerosols or splashing could only occur for PROCs 7, 10, 11 and 24 and suitable skin and specific eye protection is recommended always for these PROCs. For all other PROCs the registrant concluded that aerosol formation or splashing is generally unlikely. Assuming that personal protective equipment is used properly, there are only allocations of PROCs to "very low likelihood/frequency of actual skin exposure" (for PROCs 1, 2, 3, 8b, 9, 14, 15, 21, and 24) and "low likelihood/frequency of actual skin exposure" (for PROCs 4, 5, 7, 8a, 10, 11,

13) in the qualitative assessment of dermal exposure in the CSR. The estimated intensities of exposures (according to the CSRs where quantitative estimates were made) are 0.73 mg/cm² for PROC4, 0.42 mg/cm² for PROCs 5, 7, 8a, 10, and 13 and 0.17 mg/cm² for PROC 11.

As mentioned above, the role of the exposure assessments in the CSRs is to demonstrate the safe use of substances and how a situation is controlled when all risk management measures are applied correctly. Therefore, they are deemed to be only representative for workplaces with good work practise and high level of occupational hygiene. Assuming that such standards are met by all workers dealing with isocyanates is highly questionable at the least. Therefore, the dossier submitting CA considers following PROCs associated with a high likelihood of dermal exposure: PROC 6, 7, 8a, 10, 11, 13, 17, 19, 23 and 24 and PROC 4 with a medium likelihood of dermal exposure. Specifically, the qualitative assessment for likelihood of dermal exposure is different from the CSRs for PROCs 4, 7, 8a, 10, 11, 13 and 24.

Data from literature

Petsonk et al. surveyed the respiratory health in a case study of 214 workers (out of 276) at a newly built MDI plant (Petsonk et al., 2000). Despite that the plant was designed with the goal of minimizing airborne concentrations of MDI a high proportion of the workers reported development of new asthma-like symptoms. To evaluate the prevalence of cases, firstly the potential for exposure to MDI for the workers was assessed by questionnaires. Based on the answers from the workers given, work areas were assigned to low exposure potential when less than 20 % of workers reported potential exposure to liquid MDI resin for these areas (namely office and outside). Intermediate exposure potential was assigned to work areas, where 20-50 % of workers reported exposure (handling with products) and high exposure potential, where more than 50 % of workers reported exposure to liquid MDI resin. It was found that skin staining with MDI highly correlated with development of new asthma-like symptoms, as 11 of 21 workers (57 %) who reported MDI skin stains also reported asthma-like symptoms at follow-up. In areas with the highest potential for exposure to MDI resin asthma-like symptoms developed in 15 out of 56 affected workers (27 %), while no new asthma symptoms were reported for the areas with the lowest potential exposure (out of 43 workers). Air measurement data was not available from the period of the study, but seven months after the last health survey six personal breathing zone measurements and one wipe sample of a workers glove were performed. While all of the air samples were below the detection limit the glove sample had a measurable quantity of MDI. The authors concluded that dermal exposure to MDI (e.g. during cleaning of the MDI blender or cleaning up spills) was associated with new-onset asthma-like symptoms and that the skin is a potential site for sensitization and development of respiratory symptoms.

Henriks-Eckerman et al. measured dermal exposure to and dermal uptake of MDI among workers manually handling MDI-urethanes in Finland (Henriks-Eckerman et al., 2015). The dermal exposure measurements were carried out by three consecutive tape-strip samples at four sites of the dominant hand and arm of the workers (skin area 10 cm²) and subsequent analysis. The measured amounts of MDI on the workers hands ranged from below 0.1 to 17 µg/10 cm² but were below 2 µg/10 cm² for nearly all workers despite great variations in glove usage and working methods. Mean concentrations were below 1 µg/10 cm² for all workers for all skin sites except the palm and were below 0.1 µg/10cm² when chemical protective gloves were worn. The highest median concentrations were measured on skin of workers without gloves, which was seen as a proof for the efficiency of chemical protective

gloves in reducing dermal exposure by the authors. The outstandingly high exposures of 8.15 and 17 $\mu\text{g}/10\text{ cm}^2$ were attributed to accidental situations where no protective gloves were used and there was direct contact to the chemical. Inhalation exposure was also determined and ranged from 0.08 to 0.8 $\mu\text{g}/\text{m}^3$ when workers did not use respiratory protection. Dermal uptake of MDI was evaluated in the group of workers with the highest exposure with biological monitoring by comparison of the MDA excretions in urine of those workers who were working with respiratory protection equipment and those without. The MDA concentrations in urine were in the range of 0.1 to 0.2 $\mu\text{mol}/\text{mol}$ creatinine during the work period and were below 0.1 $\mu\text{mol}/\text{mol}$ creatinine during the days off. However, the authors pointed out that the studied group was too small to allow statistically significant findings in mean concentrations that could be linked to the different exposure routes.

Biological monitoring

Data from literature

As already discussed in the context of inhalation exposure, Kääriä et al. conducted a comparative study of MDI inhalation exposure and urinary biomarkers (MDA) among 57 workers in Finland who were manufacturing rigid PU foam parts by moulding (Kääriä et al., 2001). Despite that the measured levels of MDI in the air were generally very low and below the detection limit for 64 % of the personal samples, MDA was detected in 97 % of the urinary samples, ranging from 0.015 to 1.38 nmol/mmol creatinine. The mean concentrations ranged between 0.12 to 0.20 nmol/mmol creatinine and the median concentrations between 0.04 to 0.12 nmol/mmol creatinine. The highest concentrations were found in the post-shift samples. For control, the urinary MDA levels of eleven non-exposed workers were also measured and ranged from 0.012 to 0.022 nmol/mmol creatinine.

The biological monitoring part of the study by Creely suggested similar findings (Creely et al., 2006). Despite that the measured levels of airborne exposure for most of the PU tasks (not involved spraying) were very low (50 out of 70 personal samples were below the LOD) and although the companies were selected by having good working practise, urinary isocyanate metabolites were detected in the majority of the samples (37 out of 70), ranging between the LOD and 12.64 $\mu\text{mol}/\text{mol}$ creatinine (mean total isocyanate level for all samples was 0.29 $\mu\text{mol}/\text{mol}$ creatinine). 23 of the samples were above the agreed biological monitoring guidance value for isocyanate metabolites in urine in the UK, set at 1.0 μmol urinary diamines per mol creatinine. The highest biological monitoring results were found at the task "mixing and casting" (12.64 $\mu\text{mol}/\text{mol}$ creatinine; median 5.24 $\mu\text{mol}/\text{mol}$ creatinine), "semiautomatic moulding" (4.80 $\mu\text{mol}/\text{mol}$ creatinine; median 1.85 $\mu\text{mol}/\text{mol}$ creatinine), "resin application" (3.91 $\mu\text{mol}/\text{mol}$ creatinine; one sample) and "glazing" (1.09 $\mu\text{mol}/\text{mol}$ creatinine; median 0.91 $\mu\text{mol}/\text{mol}$ creatinine). The authors highlighted the finding that urinary metabolite levels for workers with observable dermal contamination were over two times that of workers that did not have evident skin exposure. Isocyanate metabolites were also present in several samples of workers using control measures (RPE, ventilated work areas and gloves). In particular the effectiveness of protective gloves in providing adequate protection was found to be questionable since many companies used unsuited gloves that were a compromise between chemical protection and minimal limitation of dexterity and where dermal exposure was evident.

Robert et al. conducted a biological monitoring study among workers exposed to MDI in 19 French PU industries, ranging from medium sized enterprises to large factories (Robert et al., 2007). The study covers various industrial processes and uses of MDI like moulding, but also spraying and continuous foaming.²⁴ All of the workers investigated were classified according to the potential for exposure into three categories (high (I), medium (II) and low (III)) by assessment via questionnaires. The types of processes run in the workplaces were also classified into enclosed, open and speciality processes. Urinary levels of MDA were measured for 169 exposed workers as well as for 120 not exposed workers as a control group. Detectable levels of MDA were found in 73 % of all of the post shift samples, ranging from <0.10 µg/L (LOD) to 23.60 µg/L, while the levels of MDA in the control group ranges from below the detection limit to 0.08 µg/L. Some further findings according to the authors of the study were:

- The type of process is a key determinant when assessing the exposure: the highest levels of urinary MDA were linked to spraying operations and hot processes.
- The degree of automation had a major influence on the urinary MDA levels of the workers. It was significantly lower in factories with automatic operations than for those with manual.
- Surprisingly, data for enclosed processes were higher than those of open processes. The authors explained this result by the fact that the sensation of safe workplace design leads to lower / lacking precaution for skin contamination.
- Neither the quantity of the MDI containing product handled nor the concentration of MDI in the products were found to have big impact on the urinary MDA levels of exposed workers.
- Skin exposure (both, to MDI monomer or to PU resin during curing) was always linked to significantly higher levels of urinary MDA. The authors recommended that freshly made PU should therefore be handled with care.
- Use of PPE appeared to be based on personal choice and large variation among workers was found even in the same facilities.

Gries and Leng developed an analytical method to determine a specific MDI marker (ABP-Val-Hyd) in human blood at very low concentrations (Gries and Leng, 2013). The method was tested by measuring blood samples of 25 workers exposed to MDI in a MDI plant and 40 non-exposed workers as a control group. The samples were also tested for MDA in blood. In addition the workers' MDA levels in urine were determined. It was found that the ABP-Val-Hyd marker could be detected in 22 of the 25 samples from exposed workers, ranging from below the LOD up to 16.2 pmol/g. MDA in blood was found in just eight of the samples and the ratio of ABP-Val-Hyd adducts to MDA was calculated where possible, with a mean ratio of 16.9 (± 4.8) of ABP-Val-Hyd to MDA in blood. MDA in urine was detected in 14 out

²⁴ Since the evaluation of workers exposure was carried out over all industries and uses of MDI according to the generic potential for exposure (as high, medium or low levels of exposure) it is not possible to further differentiate the results of the study according to the scheme of uses as presented in the context of this dossier.

of 22 samples of exposed workers. The urinary MDA levels were ranging from below the LOD to 125 nmol/g creatinine.

Tinnerberg et al. investigated the utility of urinary samples after two days of non-exposure (Monday morning urine) as long-term measure of exposure at three plants in Sweden (Tinnerberg et al., 2014). One of the plants manufactured rigid PU products by manual mixing and moulding of MDI, TDI and NDI. Of the 16 workers employed at this plant twelve were measured for personal airborne exposures and the detected levels were between 0.04 and 9.7 µg/m³ for 4,4'-MDI. Corresponding biomarkers (MDA) in urine and in plasma were measured for nine workers. MDA levels in urine were in the range from 0.5 to 8.4 ng/mL with a median concentration of 0.7 ng/mL and MDA levels in hydrolysed plasma ranged from 0.4 to 19.4 ng/mL (median 0.7 ng/mL). The high correlation found between adduct levels in plasma and the urinary levels of MDA showed in the authors' opinion that urine samples collected after two days of non-exposure (Monday morning urine) could be used as long term biomarker.

The data from literature on ranges of biomarkers of MDI exposure are summarized in Table 19.

Table 19: Overview of biological monitoring data for MDI in manufacture of PU and PU composite materials

(Kääriä et al., 2001)	(Creely et al., 2006)	(Robert et al., 2007)	(Gries and Leng, 2013)	(Tinnerberg et al., 2014)
0.015 - 1.38 nmol/mmol creatinine (± 0.015 - 1.38 µmol/mol creatinine; MDA in urine)	LOD - 12.64 µmol/mol creatinine (MDA in urine)	LOD - 23.60 µg/L (MDA in urine)	LOD - 16.2 pmol/g (ABP-Val-Hyd in blood) LOD - 125 nmol/g creatinine (± LOD - 14.14 µmol/mol creatinine; MDA in urine)	0.5 - 8.4 ng/mL (MDA in urine) 0.4 - 19.4 ng/mL (MDA in plasma)

TDI

Inhalation exposure

Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)

The data in the document "TDI: Final Exposure Scenarios in the e-SDS format" published by ISOPA were clustered at request of the consortia by TNO following the life cycle tree of TDI (ISOPA, 2014). The overall four clustered exposure scenarios are based on the respective CSRs for TDIs. Out of these the exposure scenarios "Elastomers, TPU, Polyamide, Polyimide & Synthetic Fibres" and "Other Composite Material" from the exposure scenario cluster 3 "End uses – industrial" and the exposure scenario "Other Composite Material" from the exposure scenario cluster 4 "End uses professional" are considered relevant for this use (Use of TDI in manufacture of polyurethanes and PU composite materials).

The exposure estimates in the exposure scenarios are based on measurement data as far as available. The exposure levels were assigned to the different PROCs according to the use descriptor system. According to the CSRs the 90th percentile values of the exposure distributions were used for the estimates of exposure levels assigned to the respective PROCs. Where data were found to be insufficient for a contributing scenario, a worst case approach was applied and the value of another PROC was taken instead, that was considered to be similar but also more conservative. As the data base for the statistical analysis is the same for 2,4-TDI and mixed TDI the values assigned to the respective PROCs are also the same for both TDI species in all relevant exposure scenarios. For the long term inhalation exposure the exposure values range from 0.001 mg/m³ (for PROC 5 with RMM applied) to 0.032 mg/m³ (for PROC 4). In case of the short term inhalation exposure the values range from 0.001 to 0.064 mg/m³ (for PROC 5, with RMM applied, and PROC 4, respectively). The highest exposure estimate values (0.032 mg/m³ for long term and 0.064 mg/m³ for short term inhalation exposure) are allocated to PROC 4 as part of the contributing scenarios within the exposure scenarios relevant for this use.

Occupational exposure data from German Social Accident Insurance (IFA)

The Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) also provided workplace exposure data from Germany which has been evaluated for both of the TDI isomers (IFA, 2010). A total of 4247 measurement data for TDI (2113 for 2,6-TDI and 2134 for 2,4-TDI) were statistically evaluated. Table 20 presents an overview of those data for work area groups which are thought to fit to the use description "manufacture of polyurethanes and PU composite materials" (based on expert judgement of the DS in analogy to the data for MDI). The data are representative for more than six hours of time of exposure. As the measurement data do differentiate between the respective TDI isomers they do not reflect the total concentration of TDI (both isomers) at the workplaces. It seems plausible to assume that both concentration values were linked according to the ratio of the TDI mixture used, i.e. that the presented data are underestimating the total exposures.

IFA also prepared a more recent and more detailed evaluation of the MEGA database for TDI (2,4-TDI and 2,6-TDI) covering a period of data from 2000 to 2011 (IFA, 2013). Table 21 gives an excerpt of the data, representative for more than six hours of time of exposure, for those work area groups that are thought to fit to the use description "manufacture of polyurethanes and PU composite materials" (translated from German by the DS).

Table 20: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile	90 th percentile	95 th percentile
Processing, subsequent treatment 2,6-TDI	Yes	29	0.0153	0.0453	0.002	0.0221	0.0961
	No	12	0.00113	0.000311	LOQ	LOQ	LOQ
Processing subsequent treatment 2,4-TDI	Yes	30	0.00347	0.00645	LOQ	0.008	0.017
	No	12	0.00113	0.000311	LOQ	LOQ	LOQ
Casting	Yes	29	0.00362	0.00658	LOQ	0.0078	0.0177

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile	90 th percentile	95 th percentile
2,6-TDI	No	13	0.00108	0.000277	LOQ	LOQ	LOQ
Casting 2,4-TDI	Yes	29	0.00517	0.0102	LOQ	0.015	0.0255
	No	13	0.00108	0.000277	LOQ	LOQ	LOQ
Foaming moulds 2,6-TDI	Yes	24	0.00164	0.00266	LOQ	0.002	0.0026
	No	13	0.001		LOQ	LOQ	LOQ
Foaming moulds 2,4-TDI	Yes	29	0.00245	0.00415	LOQ	0.0044	0.0102
	No	13	0.001		LOQ	LOQ	LOQ

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. Mean arithmetic mean

SD arithmetic standard deviation

Table 21: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013)

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
Processing, subsequent treatment 2,4-TDI	45	LOQ	0.0075	0.018
Processing subsequent treatment 2,6-TDI	45	LOQ	0.021	0.0755
Casting 2,4-TDI	57	LOQ	0.012	0.0158
Casting 2,6-TDI	55	LOQ	0.0056	0.0163
Pressing, extrusion 2,4-TDI	14	LOQ	0.041	0.0477
Pressing, extrusion 2,6-TDI	14	LOQ	0.0673	0.0728
Foaming, plastic articles, manufacture 2,4-TDI	32	LOQ	0.006	0.0268
Foaming, plastic articles, manufacture 2,6-TDI	31	LOQ	0.004	0.01

LOQ: 1.2 µg/m³ for 2,4-TDI and 1.3 µg/m³ for 2,6-TDI for 210 l of probe air volume

Data from literature

In the study by Sennbro et al. (already mentioned above in the context of MDI exposure) one of the 13 polyurethane plants in Sweden manufactured rigid PU based on TDI by moulding (plant M3) (Sennbro et al., 2004). The personal 8 h TWA TDI levels measured in this plant ranged between 1.30 µg/m³ to 6.67 µg/m³ (median 3.14 µg/m³) in case of 2,4-

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

TDI and between 0.038 µg/m³ to 3.53 µg/m³ (median 1.76 µg/m³) for 2,6-TDI. The total isocyanate exposure in this plant was in the range between 1.69 µg/m³ to 9.97 µg/m³ (median 4.91 µg/m³). Four of the other plants (M4 – M7) manufactured TDI based PU components by foam moulding. The respective exposure levels measured in these plants ranged from 0.23 µg/m³ to 4.75 µg/m³ for 2,4-TDI and from 0.15 µg/m³ to 3.91 µg/m³ for 2,6-TDI. (The median concentrations for the plants were in case of 2,4-TDI between 0.61 µg/m³ and 2.99 µg/m³ and for 2,6-TDI between 0.69 µg/m³ and 2.53 µg/m³). The corresponding total isocyanate exposures ranged from 0.08 µg/m³ to 14.60 µg/m³ (median 1.23-3.91 µg/m³).

The inhalation exposure levels to TDI in manufacture of polyurethane and PU composite materials from the sources above are shown in Table 22. (The data from IFA do not provide values for the total isocyanate concentrations but only for the respective isomers, i.e. 2,4-TDI and 2,6-TDI were evaluated separately).

Table 22: Overview of inhalation exposure levels to TDI in manufacture of PU and composite materials (in µg/m³)

CSRs	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile	(Sennbro et al., 2004)
1-32	LOQ-22.1	4-67.3	0.08-14.6

Dermal exposure

Data from the Registration Dossiers

Assessment of the dermal exposure in the CSRs for TDI was either done quantitatively when DNELs could be derived for the hazard endpoints by modelling using ECETOC TRA v2. Or hazards without a DNEL like sensitization were assessed qualitatively. For the qualitative approach first an assessment of the likelihood and/or frequency of exposure was carried out and, where exposure was considered to be likely, a further assessment of the intensity / quantity of exposure was done. The assessment was carried out taking account of the use of personal protective equipment (PPE) like suitable chemical resistant gloves, eye protection and coveralls. Based on these assumptions all tasks / PROCs were identified as either “very low” or “low likelihood/frequency of exposure”. Very low likelihood for dermal exposure was allocated to PROCs 1, 2, 3, 8b, 9, 14, 15 and 21, low likelihood for skin exposure to all other PROCs, namely PROC 4 and 5 as part of exposure scenario 7 (Elastomers, TPU, Polyamide, Polyimide & Synthetic Fibres – Industrial Use) and PROC 13 as part of exposure scenario 8 (Other Composite Material – Industrial Use) and PROC 8a for the professional use in Other Composite Material (exposure scenario 8 – professional). In the second step of the exposure assessment the dermal exposures for those PROCs (4, 5, 8a and 13) were estimated assuming a reduction of 90 % by stringent use of protective gloves. The estimates are: PROC 4: 0.100 mg/cm², PROC 5: 0.200 mg/cm², PROC 8a: 0.040 mg/cm², PROC 13: 0.080 mg/cm².

Data from literature

Relevant data on dermal and biological exposure to TDI are available mostly for the use in manufacture of foam and will be discussed in the following chapter.

HDI

The use of HDI in the manufacture of PU and PU materials is mostly limited to speciality applications. Due to the very limited data available this use will not be considered further here.

B.9.4 Use in manufacture of foam

Manufacture of foam is often linked to high exposures to isocyanates; foams are also the largest market for polyurethanes, with flexible foams being the larger part.

B.9.4.1 General information

PU foams are generally divided by their elasticity into flexible, semi-flexible and rigid foams. Both, MDI and TDI are used as the isocyanate component. High molecular polyols with a functionality of two to six yield flexible foams. When combined with low molecular polyols and/or amines, semi-flexible foams can be realized, while rigid foams are made of highly branched polyols with a relatively low molecular mass (Adam et al., 2005). As very different manufacturing processes may be applied for different foams, generally a distinction is made between slab-stock foaming processes, foam moulding and spray foaming. Due to the different exposure profiles of these processes, the focus in the context of this use is laid on slab-stock foaming. Spray foaming will be discussed separately in the following chapter (B.9.5). Mould foaming was allocated to the use in manufacture of polyurethanes (B.9.3) as the foaming processes takes place in more or less closed systems (moulds) where lower likelihood of direct contact to the foam is assumed.

Flexible foams have an open-cell structure and are permeable e.g. to air. Flexible foams are mostly produced in a continuous process to give slabs of any length. Typical dimensions of slabs are of around 220 cm width and 120 cm height. Before the start of the reaction the isocyanate and polyol components are adjusted to the right temperature. Both are then passed through a mixing head in strictly controlled ratios onto the conveyor of the processing line. The polyol component of the reaction mixture may contain an adjusted amount of water. In this case the reaction between the isocyanate and water is the basic step for the foam process. First, the isocyanate reacts with water and decomposes into an amine and carbon dioxide ($R-NCO + H_2O \rightarrow R-NH_2 + CO_2$). The thus formed amine reacts with additional isocyanates to a urea while the CO_2 serves as the blowing agent. Alternatively, additional blowing agents (often also carbon dioxide) can be incorporated in the isocyanate-polyol reaction mixture. Immediately after passing the mixing head of the process line the polyurethane mixture starts to expand. The conveyor belt underneath the mixing unit of the line is usually covered with a sheet (made out of paper or plastic film). Additional side layers and a top cover are often applied as well to the rising foam as it passes along the production line. The foam is usually moved through a series of panels and skids that control the shape and dimension of the slab, which otherwise expands dome shaped. As the reaction of isocyanates with polyols is highly exothermic the temperature of the foam may go up to 165 °C. The foaming process is usually completed within three minutes but the final curing may take up to 72 hours (Adam et al., 2005).

B.9.4.2 Exposure estimation

B.9.4.2.1 Workers exposure

MDI

Inhalation exposure

Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)

The exposure estimates in the CSRs for MDIs are based on data published by ISOPA in the document "MDI: Final Exposure Scenarios in the e-SDS format" (ISOPA, 2012). From the exposure scenario cluster 3 (Industrial use of MDI for Flexible Foam and Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres and Manufacturing of other Polymers) in this document the exposure scenarios A) Use in Flexible Foam and from the exposure scenario cluster 4 (Industrial use of MDI for Rigid Foam, Coatings and Adhesives and Sealants) also the exposure scenario A) Use for Rigid Foam are taken into account. The exposure scenario Use in Flexible Foam comprises PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 14, 15 and 21. Exposure scenario Use in Rigid Foam includes PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 10, 15 and 21.

The exposure estimates in the exposure scenarios are based on occupational hygiene measurement data, which have been allocated according to the REACH use descriptor system to the respective PROCs. According to the CSRs the 90th percentile values of the specific exposure distributions thought to fit to a PROC were used. Where no data could be found for a specific PROC, the value of another PROC was taken instead following a worst case approach. I.e. a PROC was chosen instead, that was considered to be similar but also more conservative. The dataset used for the statistical analysis is the same for all exposure scenarios and isomers of MDI. Consequently, the exposure estimates to the specific PROCs are the same within most of the exposure scenarios covered. They range between 0.006 mg/m³ (for PROCs 10, 14, 15 and 21) to 0.029 mg/m³ (PROCs 5, 8a and 8b) for the long term inhalation exposure and between 0.012 mg/m³ to 0.058 mg/m³ for the short term inhalation exposure.

Occupational exposure data from German Social Accident Insurance (IFA)

The Institute for Occupational Safety and Health of the German Social Accident Insurance evaluated workplace exposure data from Germany for MDI (IFA, 2010). The data have been gathered from 2000 to 2009 and were documented in accordance with the measurement system of the German Social Accident Insurance Institutions for exposure assessment (MGU) (Gabriel et al., 2010). 6294 measurement data for MDI (4484 for 4,4'-MDI and 1810 for 2,4'-MDI) have been evaluated in this study according to industry groups as well as work area groups of use. As mentioned before, the translation / allocation of the industry and work area groups to the registered uses (see Table 5) is often not simple or unambiguous. Specifically the data for all work areas (Foaming, all WA) are somewhat biased because the work area Foaming moulds is also represented in the collective, while the foam moulding process was discussed in the context of the use of MDI in manufacture of polyurethanes and PU composite materials (B.9.3). However, Table 23 provides an extract from the IFA evaluation of the data for the work area groups related to foaming. These data are representative for more than six hours of time of exposure.

Table 23: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Foaming, all WA 4,4'-MDI	Yes	250	0.00143	0.00209	LOQ	LOQ	0.003
	No	180	0.00258	0.00702	LOQ	0.002	0.008
Foaming, all WA 2,4'-MDI	Yes	93	0.00106	0.000323	LOQ	LOQ	LOQ
	No	63	0.00138	0.00156	LOQ	LOQ	0.00285
Foaming blocks 4,4'-MDI	Yes	73	0.00182	0.00234	LOQ	0.005	0.007
	No	43	0.00107	0.000338	LOQ	LOQ	LOQ
Foaming blocks 2,4'-MDI	Yes	25	0.00112	0.000506	LOQ	0.0015	0.002
Foaming, expanding and insulating foam 4,4'-MDI	Yes	11	0.00173	0.00241	LOQ	LOQ	0.0046
	No	22	0.00207	0.00447	LOQ	LOQ	0.00285
Foaming (other) 4,4'-MDI	Yes	82	0.00115	0.000723	LOQ	LOQ	LOQ
	No	98	0.00363	0.00917	LOQ	0.0042	0.0182
Foaming (other) 2,4'-MDI	Yes	32	0.00108	0.000257	LOQ	LOQ	LOQ
	No	41	0.00159	0.00191	LOQ	LOQ	0.00585

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Occupational exposure data from the Health and Safety Executive of the United Kingdom (HSE UK)

In the following some air monitoring data from HSE's National Exposure Database (NEDB) provided by HSE UK will be presented. As already stated above, due to the confidential nature of the data provided, the following statement needs to be mentioned here:

'The data is not representative of any industry partly due to bias in selection of the sites where data has been collected and is determined by HSE interest in specific substance or process. Most of the data was collected between 1986 and 1993 after which the rate of data collection reduced significantly. It should be noted that NEDB itself has an inherent bias, in that HSE Specialist Occupational Hygiene Inspectors as part of their enforcement duties obtained approximately 90 % of the samples. Consequently, a tendency towards high levels of exposure would be expected, as companies with no perceived problems were generally not sampled. Even so, NEDB still contains many samples indicating low exposure (<25 % of the appropriate occupational exposure limit), so the actual bias is not as large as would be expected. Whether or not NEDB should be considered as containing worst case data is debatable, but it cannot be regarded as being truly representative of occupational exposure in Great Britain given that it does not come from a random selection of workplaces and circumstances.'

Out of the air monitoring data (with overall 450 measurement entries) only three measurements were attributable to exposure to MDI in manufacture of foam. The measured

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

concentrations of these long term personal samples were in a range from 0.03 to 0.170 µg/m³.

Data from literature

The study conducted by Brezeńnicki and Bonczarowska on isocyanate exposures in Polish industry also included two plants (F and N), both of which used TDI and MDI in the manufacture of continuous block foams (Brzeznicki and Bonczarowska, 2015). All measurements of MDI in these facilities yielded results below the LOQ of 0.6 µg/m³.

Similarly, in another study on exposure to MDI and TDI in a Polish PU block foam plant, all measurement data for MDI were below the detection limit of the applied method of 0.6 µg/m³ (Swierczynska-Machura et al., 2015).

The ranges of inhalation exposure to MDI in manufacture of foam according to the sources discussed above are presented in Table 24. (The data from IFA do not provide values for the total isocyanate concentrations but only for the respective isomers, i.e. 4,4'-MDI and 2,4'-MDI were evaluated separately).

Table 24: Overview of inhalation exposure levels to MDI in manufacture of foam (in µg/m³)

CSRs	(IFA, 2010) 90 th percentile	HSE UK	(Brzeznicki and Bonczarowska, 2015).
6-29	LOQ-4.2	0.03-0.17	<LOQ

Dermal exposure

Data from the Registration Dossiers

The assessment of the dermal exposure in the CSRs for the use of MDI in manufacture of foam is based on the same approach and assumptions as described before (see B.9.3). For the hazard of sensitization a qualitative exposure assessment has been carried out. Analogous to the assessment for the use of MDI in manufacture of polyurethanes and PU composite materials (B.9.3.2.1) the likelihood / frequency of skin exposure has been either assessed as very low (for PROCs 1, 2, 3, 8b, 14, 15 and 21) or low (for PROCs 4, 5, 7, 8a and 10) provided that PPE is used properly (chemical resistant gloves and eye protection). The estimated intensities of exposures (according to the CSRs where quantitative estimates were made) are 0.73 mg/cm² for PROC4, 0.42 mg/cm² for PROCs 5, 7, 8a, and 10 and 0.17 mg/cm² for PROC 11.

As for the assessment of dermal exposure in the use of MDI in manufacture of PU and PU composite materials, the dossier submitting CA does not subscribe to all of the assumptions made by the registrants, as the role of the CSRs is to describe how a substance can be used safely, i.e. good practise, and not how a substance is used actually. Assuming a less than ideal work practise, a high likelihood of dermal exposure is given for PROCs 7, 8a, 10, and a medium likelihood for PROC 4.

Biological monitoring

No data available for this use.

TDIInhalation exposure**Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)**

As for the exposure data for MDI the exposure estimates in the CSRs are based on measurement data as published by ISOPA in the document "TDI: Final Exposure Scenarios in the e-SDS format" (ISOPA, 2014). Out of this document the relevant exposure scenario for the use of TDI in manufacture of foam is exposure Scenario 3 A (Industrial use for Flexible Foam), which comprises PROCs 1, 2, 3, 4, 5, 8b, 14, 15 and 21. The corresponding exposure estimates are based on 90th percentile values of the exposure measurement data assigned to the respective PROCs. In case of insufficient data the value of another PROC was taken instead, that was considered to be similar but also more conservative. The same data base was used for the assessment of the exposure levels for 2,4-TDI as well as mixed TDI for the respective PROCs. Consequently they have the same exposure values.

For the relevant exposure scenario (Flexible Foam Industrial Use) the long term inhalation exposure values range from 0.001 mg/m³ (for PROC 5 with RMM applied) to 0.032 mg/m³ (for PROC 4). In case of the short term inhalation exposure the values range from mg/m³ 0.001 to 0.064 mg/m³ (for PROC 5, with RMM applied, and PROC 4, respectively). The highest exposure values were allocated to PROC 4 (0.032 mg/m³ for long term and 0.064 mg/m³ for short term inhalation exposure).

Occupational exposure data from German Social Accident Insurance (IFA)

As for the before discussed use of TDI (B.9.3.2.1), both of the evaluation studies provided by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2010; IFA, 2013) were analysed and interpreted with regard to the use of TDI in manufacture of foams (without moulding, for the same reasons as above). Table 25 shows the data from the first IFA study (IFA, 2010) of the work area groups related to foaming, representative for more than six hours of time of exposure for 2,4-TDI and 2,6-TDI.

Table 25: Overview of the statistical evaluation from MEGA database for TDI, data period 2000- 2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Foaming, all WA 2,4-TDI	Yes	64	0.00684	0.000668	0.005	0.0212	0.0342
	No	44	0.00122	0.00375	LOQ	0.002	0.002
Foaming, all WA 2,6-TDI	Yes	63	0.0105	0.00034	0.00425	0.0217	0.0355
	No	44	0.00108	0.000302	LOQ	LOQ	LOQ
Foaming blocks 2,4-TDI	Yes	11	0.00264	0.00375	LOQ	0.0073	0.0098
	No	13	0.001		LOQ	LOQ	LOQ
Foaming blocks 2,6-TDI	Yes	11	0.00109	0.000302	LOQ	LOQ	0.002
	No	13	0.001		LOQ	LOQ	LOQ

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Foaming (other) 2,4-TDI	Yes	14	0.0085	0.0164	0.0055	0.0246	0.0424
	No	28	0.00132	0.00819	LOQ	0.002	0.0032
Foaming (other) 2,6-TDI	Yes	14	0.00457	0.00947	0.0035	0.0052	0.0153
	No	28	0.00111	0.000416	LOQ	LOQ	0.002

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

The data from the more recent evaluation (Pauluhn, 2005) for 2,4-TDI and 2,6-TDI are shown in Table 26. The data are representative for more than six hours of time of exposure.

Table 26: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m³)

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
Foaming 2,4-TDI	39	LOQ	0.00215	0.004
Foaming 2,6-TDI	39	LOQ	LOQ	0.00302
Foaming blocks 2,4-TDI	16	0.005	0.0326	0.0412
Foaming blocks 2,6-TDI	16	0.015	0.0728	0.119

LOQ: 1.2 µg/m³ for 2,4-TDI and 1.3 µg/m³ for 2,6-TDI for 210 l of probe air volume

Occupational exposure data from the Health and Safety Executive of the United Kingdom (HSE UK)

In the following some air monitoring data from HSE's National Exposure Database (NEDB) provided by HSE UK will be presented. As already stated above, due to the confidential nature of the data provided, the following statement needs to be mentioned here:

'The data is not representative of any industry partly due to bias in selection of the sites where data has been collected and is determined by HSE interest in specific substance or process. Most of the data was collected between 1986 and 1993 after which the rate of data collection reduced significantly. It should be noted that NEDB itself has an inherent bias, in that HSE Specialist Occupational Hygiene Inspectors as part of their enforcement duties obtained approximately 90 % of the samples. Consequently, a tendency towards high levels of exposure would be expected, as companies with no perceived problems were generally not sampled. Even so, NEDB still contains many samples indicating low exposure (<25 % of the appropriate occupational exposure limit), so the actual bias is not as large as would be expected. Whether or not NEDB should be considered as containing worst case data is debatable, but it cannot be regarded as being truly representative of occupational exposure

in Great Britain given that it does not come from a random selection of workplaces and circumstances.'

Out of the overall 450 air monitoring data 44 measurements were attributable to exposure to unspecified isocyanates in manufacture of foam. Being aware that these data are not clearly linked to exposures to TDI they are nevertheless presented in this section as manufacture of foam is the most important use of TDI (in terms of quantity). Out of 14 long term personal samples the concentrations of isocyanates were in the range from 0.06 to 9.0 $\mu\text{g}/\text{m}^3$ while the concentrations of long term static samples (N = 8) ranged from 0.05 to 11.85 $\mu\text{g}/\text{m}^3$. The total of 13 short term personal samples were in the range from 1.37 to 45.0 $\mu\text{g}/\text{m}^3$ and another ten short term static samples were in the range from 1.0 to 19.0 $\mu\text{g}/\text{m}^3$.

Data from literature

Kääriä et al. also conducted a comparative air and biological monitoring study on the exposure to TDI during production of flexible slab foam at two plants in Finland (Kääriä et al., 2001). In plant 1 the personal air measurements of total TDI were in a range between below the LOD ($<0.2 \mu\text{g}/\text{m}^3$) to 203 $\mu\text{g}/\text{m}^3$. The measured concentrations in plant 2 ranged from below LOD ($<0.2 \mu\text{g}/\text{m}^3$) to 41 $\mu\text{g}/\text{m}^3$. The corresponding biological monitoring data of urinary TDA levels will be discussed later.

Out of the 13 Swedish plants assessed in the study by Sennbro et al. two plants (CF1 and CF2) manufactured TDI-based continuous block foams (Sennbro et al. 2004). The personal 8 h TWA TDI levels measured in these plants were in the range between below the LOQ (of 20 ng/sample) to 16.1 $\mu\text{g}/\text{m}^3$ (median 0.77-9.97 $\mu\text{g}/\text{m}^3$) for 2,4-TDI. The respective values for 2,6-TDI were in the range between 0.61 to 26.1 $\mu\text{g}/\text{m}^3$ (median 4.06-20.7 $\mu\text{g}/\text{m}^3$). The total isocyanate exposure in the two plants ranged between 0.61 to 39.9 $\mu\text{g}/\text{m}^3$ (median 4.83-31.4 $\mu\text{g}/\text{m}^3$). Four of the other plants (M4-M7) manufactured TDI based PU components by foam moulding. The respective exposure levels measured in these plants ranged between 0.23 to 4.75 $\mu\text{g}/\text{m}^3$ for 2,4-TDI and between 0.15 to 3.91 $\mu\text{g}/\text{m}^3$ for 2,6-TDI. (The median concentrations for the plants were in case of 2,4-TDI between 0.61 to 2.99 $\mu\text{g}/\text{m}^3$ and for 2,6-TDI between 0.69 to 2.53 $\mu\text{g}/\text{m}^3$). The corresponding total isocyanate exposures ranged between 0.08 to 14.60 $\mu\text{g}/\text{m}^3$ (median 1.23-3.91 $\mu\text{g}/\text{m}^3$).

Tinnerberg and Mattsson investigated the effect of several risk management measures implemented at one of the TDI plants in Sweden, that was also investigated in the study by Sennbro et al. (see above) (Tinnerberg and Mattsson, 2008). In the initial study (in 2000) high levels of exposure were measured at this plant, ranging from 46.5 to 73.6 $\mu\text{g}/\text{m}^3$ total TDI during two hours foaming and a median value of 62.9 $\mu\text{g}/\text{m}^3$ for the personal air samples. Thereafter the foaming machine was modernized and several technical measures were implemented to reduce exposure. In 2005, after implementation of these improvements the measured levels of total airborne TDI in the plant were in the range between 5.0 to 86.5 $\mu\text{g}/\text{m}^3$, with a median value of 12.5 $\mu\text{g}/\text{m}^3$. Compared with the data from 2000 the median exposure in 2005 went down by 80 %. The authors also conducted a biological monitoring study among the workers which will be discussed in the respective section later.

Austin investigated TDI concentrations and complementary biomarker levels of workers with and without direct skin contact to uncured block foam in a TDI plant in UK (Austin, 2007).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

For both groups the personal exposure levels were essentially the same, ranging from < 3.5 (LOD) to 8.4 µg/m³.

Geens et al. compared the external exposure to TDI by personal air measurements of nine workers in a Belgian foam producing plant with the corresponding internal exposure by urinary pre- and post-shift biological monitoring of TDA (Geens et al., 2012). The TDI concentration of the air samples ranged from 4.20 to 141.90 µg/m³. The corresponding biological monitoring part of the study will be discussed later.

Gui et al. conducted a comprehensive medical surveillance study in a newly build TDI foam factory in Romania (Gui et al., 2014). As the focus here is laid solely on inhalation exposure data, the findings of the medical surveillance will be presented under the section biological monitoring. The airborne TDI levels in this new plant were overall low, with more than 90 % of the samples below the LOD of 0.1 ppb (corresponding to 0.71 µg/m³ at 25 °C and 1.013 bar). All personal air samples were below the LOD. The static exposure measurements also showed non-detectable exposures during periods where no production took place and peak exposures during peak production times (between 10 AM and 2 PM). The maximum exposures were 10.0 ppb (76.7 µg/m³) measured in the foaming hall and 5.4 ppb (41.4 µg/m³) in the cutting area.

In the study by Breżeńnicki and Bonczarowska the levels of exposure to TDI were also measured in the two continuous block foam plants in Poland (plants F and N, same as discussed for MDI) (Brzeznicki and Bonczarowska, 2015). The concentrations of total TDI ranged from 7.0 to 12.7 µg/m³ with a median concentration of 9.8 µg/m³ at plant F and between 0.2 to 58.8 µg/m³ (median 4.0 µg/m³) at plant N.

Świerczyńska-Machura et al. investigated the health effects of exposure to diisocyanates among 30 (male) workers in a TDI flexible block foam plant in Poland (Swierczynska-Machura et al., 2015). The clinical-medical part of the study, including biological monitoring will be discussed later. In the course of the study 20 personal air measurements were collected in the breathing zone of the workers during representative times of their work shifts. The total TDI concentrations measured were in a range from 0.2 to 58.9 µg/m³. Further differentiation according to the work place/task leads to the following results: foaming head operators (N = 10 measurements): 0.6 to 11.3 µg/m³ (arithmetic mean (AM) 3.7 µg/m³); cutting machine operators (N = 3): 0-2 to 6.5 µg/m³ (AM 3.6 µg/m³); maintenance workers (N = 2): 9.9 to 41.5 µg/m³ (AM 25.7 µg/m³) and in the folding paper area: 0.3 to 58.7 µg/m³ (AM 26.3 µg/m³).

An overview of the respective inhalation exposure levels to TDI during production of foam from the sources above is given in Table 27 (The data from IFA do not provide values for the total isocyanate concentrations but only for the respective isomers, i.e. 2,4-TDI and 2,6-TDI were evaluated separately).

Table 27: Overview of inhalation exposure levels to TDI in manufacture of foam (in µg/m³)

CSRs	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile	HSE UK	(Kääriä et al., 2001)	(Sennbro et al., 2004)	(Tinnerberg and Mattsson, 2008)	(Austin, 2007)	(Geens et al., 2012)	(Brzezicki and Bonczarowska, 2015)	(Swierczynska-Machura et al., 2015)
1-32	LOQ-24.6	LOQ-72.8	0.06-45	LOD-203	LOQ-39.9	46.5-73.6, (med. 62.9)* 5.0-86.5, (med. 12.5)**	<3.5-8.4	4.2-141.9	0.2-58.8	0.2-58.9

* before RMM improvements

** after RMM improvements

Dermal exposure

Data from the Registration Dossiers

As for all uses in the CSRs for TDI also the dermal exposures to TDI were assessed qualitatively in terms of likelihood and frequency of skin contact. According to the CSRs the likelihood/frequency of dermal exposure in the use of TDI in flexible foam was considered to be negligible for PROCs 1 and 14, very low for the PROCs 2, 3, 8b, 15 and 21 and low for PROCs 4 and 5. This qualitative assessment was complemented by a quantitative exposure assessment for PROCs 4 and 5, with calculated dermal exposures of 0.100 mg/cm² for PROC 4 and 0.200 mg/cm² for PROC 5.

Data from literature

The role of the dermal route to total exposure to TDI is mostly discussed in the context of biological monitoring data, e.g. by comparing biomarker levels of handlers and non-handlers from the same work place. These findings will be presented in the section dealing with biological monitoring accordingly.

The only actual dermal exposure measurements known to us that were carried out during the manufacture of TDI block foams were done qualitatively using SWYPE™ sampling by Gui et al. at the before mentioned newly build TDI foam factory in Eastern Europe (Gui et al., 2014). Altogether eleven SWYPE samples were taken, out of which three were positive. Two of the positive samples were taken from the paper lining peeled from the foam shortly after the curing oven and just before cutting. The other positive sample was from the hands of a worker who had just cleaned the foaming head.

Biological monitoring

Kääriä et al. compared the personal TDI measurements of 17 workers in two foam plants with urine samples collected before, in the middle and at the end of the shift, as well as twelve urine samples from a non-exposed control group (Kääriä et al., 2001). In the group

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

of the exposed workers the total TDA levels (2,4-TDA and 2,4-TDA) in urine ranged from <0.05 to 39 nmol/mmol creatinine. The TDA concentrations of the non-exposed control group were in the range from 0.02 to 0.1 nmol/mmol creatinine. The authors found a good correlation between the airborne TDI concentrations and the TDA levels in urine of the exposed workers with correlation coefficients of 0.91 for plant 1 and 0.86 for plant 2.

Austin conducted a biological monitoring study with complementary personal air measurements (see above) in a block foam plant in UK with the aim to assess whether dermal adsorption makes a significant contribution to the total body burden (Austin, 2007). Out of the 26 workers included in the study, 13 had direct skin contact with uncured PU, while 13 employees worked in the same work area but had no direct contact with the PU foam. (Uncured foam was defined as foam within 24 hours after production.) Between both groups (direct handlers and non-handlers of uncured foam) no significant difference in the personal air concentrations was found (range <3.5 to 8.4 µg/m³). The urinary levels of total urinary TDA (2,4- and 2,6-TDA) in pre-shift samples were also comparable, ranging from <0.05 to 1.6 µmol/mol creatinine (detectable levels were found only in 4 out of 13 of the samples in the group of the handlers, and none in the group of the non-handlers). Post-shift urinary concentrations however differed significantly between both groups. TDA was detected in ten out of 13 urine samples of the handlers, ranging from 0.30 to 1.6 µmol/mol creatinine (mean concentration 2.21 µmol/mol creatinine). In the group of the non-handlers only two samples had TDA concentrations above the LOD (mean concentration 0.11 µmol/mol creatinine). The author concluded that manual handling of uncured PU foam had a major contribution to the total exposure to TDA as a 20-fold difference in urinary TDA levels was observed between the handler and non-handler groups.

As already described above, in the study by Tinnerberg and Mattsson focus was on the effects of technical improvements (modernization of the machinery) in addition with implemented risk management measures on the worker exposure in a TDI foaming plant in Sweden (Tinnerberg and Mattsson, 2008). As written, the airborne levels of total TDI after implementation of the improvements decreased to 20 % of the initial level. In addition to the air monitoring, the levels of biomarkers in urine and in plasma among the workers were assessed before and after the technical improvements in the plant. In 2000 the biomarker levels in plasma ranged from 2.9 to 27.2 ng/mL (median 7.0 ng/mL) for 2,4-TDA. The 2,6-TDA levels in plasma ranged from 8.2 to 62.1 ng/mL, with a median concentration of 30.8 ng/mL. In 2005 the corresponding biomarker levels were in the ranges from 0.5 to 2.0 ng/mL (median 1.0) for 2,4-TDA in plasma and between 2.0 to 11.8 ng/mL with a median concentration of 4.0 ng/mL for 2,6-TDA. This was 14 % for the median level of 2,4-TDA and 13 % for the median 2,6-TDA plasma level in 2005 compared to the levels in 2000.

Gui et al. conducted a study among 49 workers without any previous occupational contact to TDI in a newly build foam factory in Eastern Europe (Gui et al., 2014). The facility was described as a state-of-the-art with a health-clinic on site. The study included medical surveillance by questionnaires, spirometry testing and blood sampling for TDI-specific antibodies (IgG and IgE). Airborne exposure levels were low and in none of the personal samples detectable levels of TDI were found (see above). Despite the very low levels of airborne TDI and despite the intensive industrial hygiene efforts made at the facility seven out of the 49 workers (14.2 %) had findings after 12 month that were indicative for development of new asthma or TDI-related health effects (new asthma symptoms, new airflow obstruction, decline in FEV1 ≥ 15 % and/or TDI-specific IgG). 12 of the 49 workers participating at the beginning of the study were lost to follow up over the first year. The

prevalence of asthma like symptoms was 25 % in the workers who were not available for follow up compared to 2.7 % among those who completed the follow up.

Świerczyńska-Machura et al. carried out a comprehensive study including biological monitoring, physical examinations, blood sampling for TDI-specific antibodies (IgE), skin prick test and pulmonary function tests among 30 workers in a TDI block foam factory in Poland (Swierczynska-Machura et al., 2015). Work-related allergic symptoms were reported for 13 of the 30 workers (43.3 %). A mild degree of bronchial obstruction was observed in five workers. In no sample were TDI specific antibodies (IgE) detected. The urinary total TDA levels (2,4- and 2,6-TDA) of the pre shift samples were in a range from <LOD to 1.75 µg/L and from <LOD to 8.85 µg/L in the post shift samples. Creatinine adjusted concentrations were in the range from <LOD to 3.9 µmol/mol creatinine (but some of the samples exceeded the accepted rang of 0.3-3 µg/L and therefore the data were presented also in µg/L). The highest levels of TDA were found in the samples of maintenance workers (range 1.7 - 3.9 µmol/mol creatinine; mean 3.0 µmol/mol creatinine) and cutting machine operators (range 0.6 -2.1 µmol/mol creatinine; mean 1.1 µmol/mol creatinine).

Table 28 provides a summary of the biological monitoring data for TDI in the manufacture of foam.

Table 28: Overview of biological monitoring data for TDI in manufacture of foam

(Kääriä et al., 2001)	(Austin 2007)	(Tinnerberg and Mattsson 2008)	(Swierczynska-Machura et al. 2015)
0.05 - 39 nmol/mmol creatinine (total TDA in urine)	<0.05 - 1.6 µmol/mol creatinine (total TDA in urine)	2.9 - 27.2 ng/mL (2,4-TDA in plasma) 8.2 - 62.1 ng/mL (2,6-TDA in plasma)	<LOD - 3.9 µmol/mol creatinine (total TDA in urine)

HDI

HDI is not considered relevant for this use.

B.9.5 Use in spray foam applications

This is a use with potentially high exposure. Polyurethane foams are also a large part of the PU market (> 60 %).

B.9.5.1 General information

Spray foams are typically rigid foams made of two components that are applied by spraying. One component is the isocyanate containing hardener which is usually MDI based and the other component is a polyol formulation with catalysts, the blowing agent and other additives like flame retardants, and surfactants. For application the two components are pumped from separate containers through a proportioning and heating unit into a spray gun which also serves as the mixing unit. The reactivity of spray foam systems is usually very high so that the finished foam forms within seconds after spraying (Adam et al., 2005). Spray foams are mainly used for insulation of buildings or industrial installations but can also serve as a speciality packing material for fragile items. Depending on the formulation, open and closed cell foams can be realized. Open cell foams have a sponge like structure

and a lower density than closed cell foams. As open cell foams are permeable to air and moisture they are not suggested for outdoor applications or contact with water. Closed cell foams are more rigid and usually water resistant and can be well used for outdoor applications (including roofing). Spray foams can be applied with low pressure (injection), usually between existing drywalls or as high pressure foams to any surface suitable. As they are often applied to residential buildings there is particular potential for bystander exposure.

B.9.5.2 Exposure estimation

B.9.5.2.1 Workers exposure

MDI

Inhalation exposure

Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)

As for the uses before the exposure estimates in the CSRs for MDIs are based on data published by ISOPA (ISOPA, 2012). From the exposure scenario cluster 4 (Industrial use of MDI for Rigid Foam, Coatings and Adhesives and Sealants) and the cluster 7 (Professional end uses of MDI) the respective exposure scenarios A) (Use for Rigid Foam and Rigid Foam, professional use) do also cover the uses of MDI in spray foam applications. The exposure scenario for the industrial Use for Rigid Foam comprises PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 10, 15 and 21. The exposure scenario Rigid Foam, professional use includes PROCs 3, 4, 5, 8a, 8b, 10, and 11.

As described before, the exposure estimates in the exposure scenarios are based on occupational hygiene measurement data, with the same dataset used for all exposure scenarios and isomers of MDI. The estimates for the long term inhalation exposure range between 0.006 mg/m³ (for PROCs 15 and 21) to 0.029 mg/m³ (for PROCs 5, 8a and 8b) and between 0.011 mg/m³ to 0.058 mg/m³ for the respective short term inhalation exposures.

Occupational exposure data from German Social Accident Insurance (IFA)

The evaluation for MDI by the Institute for Occupational Safety and Health of the German Social Accident Insurance already described earlier also includes some data on the exposure to 4,4'-MDI during foaming of expanding and insulating foam (IFA, 2010). Table 29 gives an excerpt from the IFA evaluation of the data for the work area group foaming, expanding and insulating foam. These data are representative for more than six hours of time of exposure.

Table 29: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Foaming, expanding and insulating foam 4,4'-MDI	Yes	11	0.00173	0.00241	LOQ	LOQ	0.0046
	No	22	0.00207	0.00447	LOQ	LOQ	0.00285

LOQ limit of quantification – not further specified in the report

Occupational exposure data from the Health and Safety Executive of the United Kingdom (HSE UK)

In the following some air monitoring data from HSE's National Exposure Database (NEDB) provided by HSE UK will be presented. As already stated above, due to the confidential nature of the data provided, the following statement has to be included to this section:

'The data is not representative of any industry partly due to bias in selection of the sites where data has been collected and is determined by HSE interest in specific substance or process. Most of the data was collected between 1986 and 1993 after which the rate of data collection reduced significantly. It should be noted that NEDB itself has an inherent bias, in that HSE Specialist Occupational Hygiene Inspectors as part of their enforcement duties obtained approximately 90 % of the samples. Consequently, a tendency towards high levels of exposure would be expected, as companies with no perceived problems were generally not sampled. Even so, NEDB still contains many samples indicating low exposure (<25 % of the appropriate occupational exposure limit), so the actual bias is not as large as would be expected. Whether or not NEDB should be considered as containing worst case data is debatable, but it cannot be regarded as being truly representative of occupational exposure in Great Britain given that it does not come from a random selection of workplaces and circumstances.'

Out of the overall 450 air monitoring data eight measurements are attributable to exposure to MDI in application of spray foam (insulation work and floor and wall coverings). All samples were long term personal samples and the measured concentrations of MDI were in the range from 0.03 to 200.0 µg/m³.

Data from literature

Crespo and Galán surveyed the personal inhalation exposure to MDI of spray gun operators and helpers during indoor and outdoor spray foaming at 17 construction sites in Spain (Crespo and Galan, 1999). The measured exposure of the individual samples ranged from 0.010 to 0.570 mg/m³ for the sprayers and from 0.001 to 0.408 mg/m³ for the helpers. Indoor concentrations were found to be higher than those measured during outdoor spraying.

Lesage et al. investigated the time and distance dependencies of airborne MDI concentrations during and after spray foaming (Lesage et al., 2007). Personal samples of the sprayers and the assistants were complemented by static samples collected at various times and distances relative to the spraying. The static samples were 1.5-2 m above floor level at ranges from 1) 1-3 m, 2) 3-6 m, and 3) 6-12 m from the spray foam applicator. Exposure levels of the 13 personal samples ranged from 0.07 to 2.05 mg/m³ for monomeric MDI and from 0.01 to 0.87 mg/m³ for oligomers of MDI. The MDI concentrations for the static sampling at a distance of 1-3 m were in the range from 0.147 to 1.55 mg/m³ with an average concentration of 0.603 mg/m³ for the monomers and 0.02-0.830 mg/m³ (average 0.285 mg/m³) for the oligomers. At a distance of 3-6 m the measured concentrations of monomeric MDI ranged from 0.005 to 1.12 mg/m³ (average 0.344 mg/m³) and from 0.004 to 0.678 mg/m³ (average 0.182 mg/m³) for the oligomers. At a distance of 6-12 m the concentrations measured were in a range from 0.024 to 0.822 mg/m³ (average 0.166 mg/m³) for the monomers and 0.020-0.498 mg/m³ (average 0.122 mg/m³) for the oligomers. Time dependent samples were also taken with the sampling devices nearest to the foamed walls (2 m or less) after 15 or 30 min. apart for up to 90 min. Most of the

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

samples taken after spraying were below the LOQ of 0.036 µg per sample (equivalent to 0.0012 mg/m³ when 30 L of air are sampled). The highest concentrations found after 15 min. were 0.019 mg/m³ of monomeric MDI and 0.014 mg/m³ of oligomers. Concentrations above the LOQ after 45 min. were measured in only one sample with monomer and oligomer results of 0.003 and 0.004 mg/m³, respectively. All measurements sampled after 24 hours after spraying were below the LOQ. 20 surfaces swiping samples were taken at several times after foaming. Each of the samples taken at freshly applied foam was tested positive. After 15 min. all of the tested surfaces yielded negative results. Additionally, the aerosol particle sizes of the foam spray were measured for three of the five surveys and it was found that around two-thirds of the total mass of the particles was > 3.5 µm diameter.

Roberge et al. performed field studies during polyurethane foam spraying activities in commercial and residential construction (Roberge et al., 2009). Sampling was performed in the spraying zone and in the assistant's zone. In the spraying zone (94 samples), average MDI concentrations ranged from 11 to 591 µg/m³ and MDI oligomer concentrations from 3 to 330 µg/m³. In the assistant's zone (24 samples, usually 3 meters behind the sprayer) MDI concentrations ranged from < 1 to 170 µg/m³ and MDI oligomer concentrations from < 1 to 99 µg/m³.

RPS Advies determined the sum of MDI concentrations during polyurethane spraying activities in crawlspaces of residential buildings (RPS, 2014). According to the authors, the results should be regarded as indicative as they are from static sampling and not from personal sampling. In two objects, where the sampler was positioned along the sprayer's position, the determined sum of MDI concentrations was 525 µg/m³ and 770 µg/m³, and the authors point out that these results would more accurately reflect potential worker exposure. In the other five objects, where the sampler was positioned near the crawlspace access, the sum of MDI concentrations ranged between < LOQ and 210 µg/m³.

In the United States of America, the Center for the Polyurethane Industry (CPI) Ventilation Research Task Force performed experiments on chemical emissions during and following polyurethane spray foam applications (Wood, 2013; Wood, 2014). Air monitoring was conducted under controlled environmental conditions in a ventilated area during application of the generic formulations. Ventilation rates were 10.4 air changes per hour (ACH) for all formulations, 233 ACH for the low and medium density formulations and 598 ACH for the medium density formulation. Samples were taken in various sessions about 15 minutes after begin of spraying and 30 minutes after application. Personal sampling was performed for the applicator and additional stationary sampling in the area. The highest concentration detected during spraying was 550 µg/m³ for pMDI (Medium Density High Pressure Formulation – 233 ACH).

Puscasu et al. conducted a comparative field study on MDI aerosols with an optimized CIP 10M device and an impinger technique as a reference (Puscasu et al., 2015). For the tests MDI based insulation foam was sprayed on two plywood panels (1.2 x 2.4 m) in a small test room (3.1 x 4.0 X 2.3 m) over three different days. The measured concentrations of monomeric MDI were in the range from 0.03 to 0.09 mg/m³ and ranged from 0.03 to 0.075 mg/m³ for MDI oligomers. The results provided by the CIP 10M were about 14 % lower than those of the impinger.

The same working group also compared another sampling device (ASSET EZ4 NCO) with the impinger method as the reference in namely the same test setting as described above

(spraying of MDI based foam on two plywood panels of 1.2 x 2.4 m size, using same procedures as in a normal working day) (Puscasu et al., 2015). The concentrations measured with the impinger method were in the range from 0.02 to 0.08 mg/m³ for MDI monomers and ranged from 0.02 to 0.04 mg/m³ for the oligomers. The ASSET EZ4 NCO device was found to significantly underestimate the MDI levels.

Table 30 gives an overview of the levels of inhalation exposure during spray foam applications as described above.

Table 30: Overview of inhalation exposure levels to MDI in spray foam applications (in µg/m³)

CSRs	(IFA, 2010) 90 th percentile	HSE UK	(Crespo and Galan, 1999)	(Lesage et al., 2007)	(Roberge et al., 2009)	(Puscasu et al., 2015)	(Puscasu et al., 2015)
6-29	LOQ	0.03- 200	10-570 (sprayer) 1-408 (helper)	7-2050 (personal, monomers) 10-870 (personal, oligomers)	11-591 (MDI) 3-330 (MDI oligomers)	30-90	20-80

Dermal exposure

Data from the Registration Dossiers

The assessment of the dermal exposure in the CSRs for the use of MDI in Rigid Foam is based on the same approach and assumptions as described before (see B.9.3). In analogy to the assessment for the use of MDI in manufacture of polyurethanes and PU composite materials (B.9.3.2.1) the likelihood / frequency of skin exposure has been either assessed as low for the relevant PROCs describing spray applications, i.e. PROCs 5 (Mixing or blending in batch processes) and 11 (Non industrial spraying), but also for PROCs 7 (Industrial spraying), and 8a (Transfer of substance at non-dedicated facilities) under the assumption that PPE is used properly (skin protection measures and eye protection). The estimated intensities of exposures (according to the CSRs where quantitative estimates were made) are 0.42 mg/cm² for PROCs 5, 7, and 8a and 0.17 mg/cm² for PROC 11.

As for the assessment of dermal exposure in the use of MDI in manufacture of PU and PU composite materials, the dossier submitting CA does not subscribe to all of the assumptions made by the registrants, as the role of the CSRs is to describe how a substance can be used safely, i.e. good practise, and not how a substance is used actually. Assuming a less than ideal work practise, a high likelihood of dermal exposure is given for all of the PROCs considered (PROCs 5, 7, 8a, and 11).

Biological monitoring

As far as known no relevant data are available on biological monitoring for spray foaming.

B.9.5.2.2 Bystander exposure during and after polyurethane foam spraying activities

This section is not part of the assessment of workers exposure but an additional chapter on exposure of bystanders and potentially inhabitants of objects where spray foam applications were performed.

Monitoring results on bystander exposure to diisocyanates from polyurethane foam spraying

In order to monitor exposure of workers from other trades during polyurethane spraying activities, Roberge et al. took 29 additional samples in the centre of the floor where the spraying work was performed. The average monomer MDI vapour and aerosol concentrations determined in these samples with the IRSST High Sensitivity Method ranged from < 1 to 11 µg/m³. In the first two hours after completion of the spraying works, 30 additional samples (22 on the floor where spraying had been done, and 8 on another floor) were taken. MDI vapour and aerosol concentrations determined in these samples with the IRSST High Sensitivity Method ranged from < 0.01 to 2.4 µg/m³. However, according to the authors, a pre-treated glass fibre filter according to IRSST's laboratory specifications is not suitable for aerosols in which polymerization takes place rapidly and an impinger method should be preferred (Roberge et al., 2009).

Lesage et al. used filter and impinger samples to determine MDI concentrations as a function of time after polyurethane foam spraying. They found detectable concentrations in 3 out of 5 surveys 15 minutes after spraying had ceased (up to 19 µg/m³ MDI monomers and up to 14 µg/m³ MDI oligomers), and in 1 out of 5 surveys after 45 minutes (up to 3 µg/m³ MDI monomers and 4 µg/m³ MDI oligomers). Results were below the LOQs of 0.036 µg MDI monomer/sample and 0.041 µg MDI oligomer/sample after 30, 60, 75, 90 minutes, and on the next day. Nevertheless, the authors point out that due to different spray foam formulations and the wide range of application conditions, caution should be exercised when using these data to establish operational or administrative guidelines (Lesage et al., 2007).

In the United States of America, the CPI Ventilation Research Task Force performed experiments on chemical emissions during and following polyurethane spray foam applications (see above). Air monitoring was conducted under controlled experimental conditions in a ventilated area during application of the three generic formulations. Ventilation rates were 10.4 air changes per hour (ACH) for all formulations, 233 ACH for the low and medium density formulations and 598 ACH for the medium density formulation. All post spraying MDI concentrations of 2,2-MDI, 2,4-MDI, and pMDI were below the analytical detection limits. It should however, be noted that for pMDI these detection limits ranged from 1.4 µg/m³ to 460 µg/m³ (high pressure medium density formulation, 233 ACH) (Wood, 2013).

In a further study by the CPI Ventilation Task Force, the decay rates of the chemical emissions were evaluated for the above mentioned three generic formulations under experimentally controlled conditions with 10.4 ACH, which was lowered to 1 ACH after 3 hours. Samples were taken 1, 2, 4, 8, 12 hours after the spray foam application. 2,4-MDI and 4,4 MDI were sampled with glass fibre filters treated with 1-(2-pyridyl) piperazine and analysed with a modified OSHA 47 HPLC and UV detection. Only MDI vapours and no MDI aerosols were analysed. The isocyanate component that dominated the emissions of these formulations in the previous study, pMDI, was not analysed. Both analysed MDIs were below the detection limits of 0.00014 to 0.00016 ppm 1, 2 and 4 hours after application.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Several other components of the mixtures were detected in all samples. The amine catalyst Bis(2-Dimethylaminoethyl)ether (BDMAEE) from the generic low density high pressure formulation was detected in concentrations above the Occupational Exposure Limit of 0.05 ppm up to 12 hours after the application (Wood, 2014).

TNO determined MDI concentrations in 14 residential buildings. The crawlspaces of these buildings had been isolated with polyurethane spray foam weeks to months before. MDI concentrations above the detection limit were only found in two living areas with a maximum concentration of 0.0031 µg/m³ (TNO, 2013b).

In another study by TNO, MDI concentrations were determined in three houses during and after spray foam isolation of crawlspaces. The maximum concentration determined in the living area during polyurethane spraying was 0.251 µg/m³. Samples were taken up to 144 hours after the spraying activity, and detectable concentrations were occasionally found up to 72 hours after the activity. The maximum MDI concentration determined after the spraying activity was 0.025 µg/m³ (TNO, 2013a).

In the above mentioned study by RPS, samples were taken in the living areas of seven buildings during and after polyurethane spray foam isolation of crawlspaces. Only in two buildings MDI concentrations above the LOQ were found in the living areas during spraying, the maximum was 0.5 µg/m³. 44 samples were taken from ten minutes up to three days after spraying, and 7 were above the LOQ. The maximum MDI concentration of 15.4 µg/m³ was found in the time interval of 60 to 120 minutes after spraying. The longest time interval with detectable traces of 0.32 µg/m³ was three days after spraying. MDI concentrations within the same object seem to vary significantly over time. Interestingly, a concentration of 4.77 µg/m³ was determined in one object before the spraying had started (RPS, 2014).

These monitoring results should be interpreted with caution because the full procedures of sampling and analysis were not disclosed in the published TNO and RPS reports. Moreover, it is not clear whether MDI oligomers were determined and included into the sum of MDI or not. If MDI oligomers were not determined by TNO and RPS, this would result in an underestimation of the total NCO concentrations in air. Also, it is not clear whether the cited monitoring results represent the common practice of spray foam applications in Europe.

Case reports:

Tsuang and Huang reported the case of a couple that suffered from persistent cough and dyspnea upon exertion and showed a positive methacholine challenge test. Symptoms had begun after the installation of a two component polyurethane spray foam in the attic of their home. The patients had evacuated the home for 4 hours as recommended. When returning, they noted a strong noxious odor and almost immediately developed cough, dyspnea, dizziness, nausea, headache and watery eyes. The odor could not be abated by several attempts of venting and eventually removing the spray foam. After 3 months the family vacated the home. No measured data from samples obtained in the house were reported. The A component of the SPF foam used in the house contained pMDI, 2,4'-MDI and 4,4'-MDI. Both patients were diagnosed with asthma or reactive airway dysfunction syndrome induced by exposure to isocyanates (Tsuang and Huang, 2012).

Verschoor and Verschoor reported on eleven persons from seven households with health complaints after installation of spray polyurethane foam insulation in their homes. Symptoms included cough, sore throat, irritated eyes, dyspnea, nausea, headache and also

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

intestinal symptoms in some cases. Measured data from samples obtained in the homes were not reported. Symptoms were decreased by moving out of the home and increased when returning to the home to pick up things (Verschoor and Verschoor, 2013; Verschoor and Verschoor, 2014).

Redlich and Wilson reported on four families that presented with upper airway, mucosal and CNS symptoms and distinct odours associated with exposure to spray polyurethane foam in their homes. No case of new onset asthma or sensitization to MDI was found. Air samples were obtained from each house and from the chamber head space above foam samples from the homes. Air samples were analysed for total VOCs, aldehydes, amines, MDI, and other airborne contaminants using standard thermal desorption GC/MS and HPLC-UV methods. Airborne MDI was not detected. However, total VOCs measured 2 to 20 months after application of the polyurethane spray foam were evaluated as high and above recommended levels. Specific chemicals identified in the air and chamber samples were consistent with the known components of the PU foam. Three of the four families were unable to return to their homes. The authors concluded that polyurethane spray foam can off-gas VOCs, amines and related chemicals for months after home application, and can be associated with distinct odours and persistent symptoms in home inhabitants (Redlich and Wilson, 2013).

Huang and Tsuang summarised adverse health effects after spray polyurethane foam insulation activities in thirteen adults from ten households. Six subjects were present during spraying, two moved into the homes four hours after spraying, two one day after spraying and three several months after spraying. In some cases, proper ventilation was not used or a wrong mixing ratio of sides A and B was applied. All subjects reported unpleasant odours during spraying or when they returned to their homes and all developed acute irritation symptoms like watery and burning eyes, burning nose, sinus congestion, throat irritation, cough, dyspnea and chest tightness. Twelve subjects reported acute neuropsychiatric symptoms, including headache, dizziness, forgetfulness, difficulty in concentrating and insomnia. Three subjects had nausea, vomiting and abdominal cramps and three developed skin rash. The symptoms persisted for a long time after the end of the spraying activities, subsided after the subjects left their homes, but recurred upon returning. All subjects eventually vacated their homes. The methacholine challenge test was positive for one of 7 patients with a known history of asthma. This patient had to change her therapy from occasional albuterol to steroids after the spray polyurethane foam installation. The authors reported on volatile organic compounds in indoor air samples from several homes and in headspace gas from foam samples. These analyses had been performed by different laboratories and with different methods. No specific analyses on isocyanates had been performed. The authors concluded that faulty application of spray polyurethane foam was associated with acute and persistent pulmonary and extra-pulmonary symptoms which may be associated with spray foam-derived compounds as well as increased concentrations of indoor VOCs (Huang and Tsuang, 2014).

Conditions affecting polyurethane spray foam emissions, re-entry times and re-occupancy times

Faulty or non-standard application conditions have also been reported from crawlspace insulation works in the Netherlands: Verschoor commented the report by RPS Advies listing a variety of conditions found in practice of polyurethane spraying in crawlspaces, that may contribute to worst case scenarios not covered by the RPS study. These conditions included blocked nozzles, pollution by old polyurethane, spraying layers of 15 – 25 cm polyurethane,

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

lack of forced ventilation, water in the crawlspace, very high humidity, a heating system in the crawlspace turned on during polyurethane spraying, low outside temperatures, open connections to the living area via an open access, via cracks and holes in the floor of the house or via the crawlspace cupboard, or occupants present during spraying (Verschoor, 2014).

This is in line with internet information from spray foam distributors on causes of spray foam odours in residential buildings:

"Spraying CC SPF in thicker passes will generate more heat in the cells of the foam and can result in lighter density foam with more open cells and create more amines than would be created with a proper 2" pass. We all know that off ratio (resin rich) foam can cause odours. While dirty filter screens, transfer pump and/or proportional issues can cause off ratio foam there can be other causes. Poorly mixed foam from spraying at too low a temperature and/or too low a pressure can cause an off ratio situation. Moisture present on the substrate can react with some of the iso in the foam. If and when this happens then there is not enough iso to react off all of the resin resulting in resin rich foam. In additions to these concerns, proper ventilation is also needed during the spray foam install. Care should be taken to establish a negative pressure in the work area. Plenty of air flow will help get the odours out of the building before they have time to penetrate the porous wood, fibrous insulations, or anything else in the spray area that can possibly absorb odor." (Spray Foam Distributors of New England, 2015)

While training programs for spray foam contractors are meant to avoid such "off ratio" conditions, it is not known how often they still may be found in Europe at present.

Even for spray foams that are applied under best-practice-conditions, there are several factors that may affect emissions and curing times. In the case of crawlspace insulation with spray polyurethane foam, RPS commented that

"the results of the emission measurements will mainly depend on the number, position of the natural ventilation points, the climatic conditions outside, the position, presence and power of the forced ventilator and the presence and/or air tightness of the access lid used during spraying." (RPS, 2014)

The CPI Ventilation Task Force (Wood, 2013) gave a summary of ventilation experiments according to which it may be concluded that ventilation rate does impact chemical emissions of the spray polyurethane foams. However, according to the data presented in the report, such an effect cannot be clearly demonstrated for MDI and pMDI concentrations. The authors concluded,

"that there are factors beyond ventilation rate that impact emissions. Such factors include: chemical characteristics of the formulation (e.g.: reactive vs. non-reactive catalyst), the quantity of individual chemicals in the formulation, temperature of the formulation as it is applied, the temperature created during reaction, the density of the formulation, the cell structure, and the air distribution of the ventilation. These application factors coupled with many environmental variables related to a residential or commercial site being sprayed make it difficult for workers directly involved in SPF application to be protected strictly through engineering controls. CPI continues to recommend SPF applicators and personnel

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

working in the proximity of the applicator be properly equipped with personal protective equipment (PPE) including respiratory protection, gloves, and protective clothing.”

Another study by the CPI Ventilation Task Force on emission decay rates after polyurethane spray application (Wood, 2014) was performed in order

“to estimate the time required to restrict unprotected workers, such as plumbers, electricians, dry wall installers, etc. from the work area to minimize their exposure.”

Due to high non-isocyanate emissions found in this study, the authors concluded as follows:

“Based on the results of this study it is apparent that emissions of SPF chemicals will vary depending on the type of foam (open cell vs. closed cell) and the specific chemicals comprising the B-side of the formulation. It is therefore essential that emissions from commercial SPF formulations, in particular open cell formulations, be controlled through the use of mechanical ventilation during application and for 12 hours or more following application. Control effectiveness should be evaluated through industrial hygiene air monitoring. The use of respiratory protection must then be used to supplement ventilation where worker exposure to SPF chemicals cannot be controlled. In those instances where SPF Producers desire reduced re-entry times for commercial products, those formulations should be evaluated in the laboratory using similar ventilation rates used in this study. Laboratory studies should then be validated in the field with contractor-provided mechanical ventilation.” (Wood, 2014)

In order to enable such laboratory studies, the CPI is supporting the development of ASTM standards for environmental chamber emissions testing at the ASTM Subcommittee D22.05 on Indoor Air). The underlying idea is to determine emission rates for the diverse components, to use them for modelling of indoor air concentrations at different times, and to use these modelled concentrations to define the re-entry time / the re-occupancy time, at which these indoor air concentrations will be lower than occupational exposure limits/threshold limit values for protection of the general population. ASTM D 7859-13 covers spraying, sampling, packaging and test specimen preparation of spray polyurethane foam. A standard practice for estimating chemical emissions from spray polyurethane foam using Micro-Scale Environmental Test Chambers is being developed under Work Item 40293 and a standard test method for measuring chemical emissions from spray polyurethane foam in environmental test chambers with thermal desorption and gas chromatography/mass spectroscopy under Work Item 40292. However, the latter method has been found to be inadequate for measuring of MDI and pMDI, and at present, there is no standardized method for the determination of these components in emission chamber experiments (Sebroski, 2013).

Thus, from a scientific point of view, the question of safe re-entry times for unprotected workers of other trades and safe reoccupancy time for the general population after spray polyurethane foam applications still remains unsolved. The US EPA as well as the American Chemistry Council give the advice to contact the spray foam suppliers for specific guidance on ventilation time and reoccupancy (ACC, 2016; US EPA, 2015).

Until a spray polyurethane foam product is fully cured and the building has been thoroughly ventilated and cleaned, the access to the application area should be restricted to trained workers with personal protection.

TDI

Not relevant for this use.

HDI

Not relevant for this use.

B.9.6 Use in coatings

This is a use with potentially high exposure.

B.9.6.1 General information

Polyurethane coatings can be one-component (one-pack) systems or two-component (one-pack) systems. One-pack paints containing free isocyanates are usually high molecular prepolymers of polyols with excess isocyanate groups that undergo a cross link reaction with formation of urea groups under atmospheric moisture.

The by far most important are two-component systems that comprise the “conventional” PU coatings and paints (Adam et al., 2005). The principal curing constituents of two-component PU coatings are polyisocyanates which are based on TDI, HDI, IPDI, MDI or HMDI. Solvent borne curing agent solutions have an isocyanate content of 5-16 % w/w, while solvent free may have up to 30 % w/w isocyanate (Stoye et al., 2000). The other component of the paint contains polyols and/or polyamines as well as additives like pigments, catalysts and solvents. Both components have to be kept separate until immediately before application. Mixing of both components (preferably in an equimolar ratio) therefore is always part of the use. These coatings can be applied by all conventional coating techniques apart from dipping but often spraying is the most preferred method of application, where exposure to aerosols and vapour is particularly high. Curing of the applied coatings takes place at ambient temperatures but can also be accelerated by heat.

Due to their outstanding properties (especially high mechanical resistance, chemical resistance and light and weather resistance) polyurethane coatings are the systems of choice for protecting coatings like vehicle finishes and refinishes and in the building sector (floor coatings, anti-corrosion coatings etc.).

B.9.6.2 Exposure estimationB.9.6.2.1 Workers exposureMDIInhalation exposure**Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)**

As for the exposure data presented before the exposure estimates in the CSRs for MDIs are based on data published by ISOPA (ISOPA, 2012). The use of MDIs for coatings is included in the exposure scenario cluster 4 (Industrial use of MDI for Rigid Foam, Coatings and Adhesives and Sealants) and exposure scenario cluster 7 (Professional end uses of MDI) in the respective exposure scenarios B) (Use for Coatings). The exposure scenario for the industrial use for Coatings comprises PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 9, 10, 13, and 15. The exposure scenario coatings, professional use includes PROCs 5, 8a, 10, 11, and 13.

As already written the exposure estimates in the exposure scenarios are based on occupational hygiene measurement data, with the same dataset used for all exposure scenarios and isomers of MDI. The estimates for the long term inhalation exposure of the use of MDI in coatings range between 0.006 mg/m³ (for PROC 15) to 0.029 mg/m³ (for PROCs 5, 8a and 8b) and between 0.011 mg/m³ to 0.058 mg/m³ for the respective short term inhalation exposures.

Occupational exposure data from German Social Accident Insurance (IFA)

The evaluation for MDI by the Institute for Occupational Safety and Health of the German Social Accident Insurance already described earlier also covers measurement data for exposure to 2,4'-MDI and 4,4'-MDI in the work area groups of brushing, rolling, painting and different types of spraying (IFA, 2010). Table 31 gives an excerpt from the IFA evaluation of the data for the work area group surface coating processes and spraying. These data are representative for more than six hours of time of exposure.

Table 31: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Surface coating processes, miscellaneous 4,4'-MDI	Yes	64	0.0063	0.0115	0.004	0.0188	0.037
	No	21	0.00157	0.00263	LOQ	LOQ	LOQ
Surface coating processes, miscellaneous 2,4'-MDI	Yes	29	0.00128	0.00064	LOQ	0.002	0.002
Spraying (all work areas) 4,4'-MDI	Yes	210	0.00216	0.00935	LOQ	LOQ	0.0025
	No	21	0.00355	0.00881	LOQ	0.00555	0.00885

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Spraying (all work areas) 2,4'-MDI	Yes	81	0.0023	0.00959	LOQ	LOQ	LOQ
Spraying (Airless) 4,4'-MDI	Yes	51	0.00143	0.00187	LOQ	LOQ	0.002
Spraying (Airless) 2,4'-MDI	Yes	15	0.001		LOQ	LOQ	LOQ
Spraying (Airmix) 4,4'-MDI	Yes	14	0.00175	0.00267	LOQ	LOQ	0.00435
Spraying (pressurised air) 4,4'-MDI	Yes No	119 15	0.00266 0.00153	0.0123 0.00207	LOQ LOQ	LOQ LOQ	0.00205 0.003
Spraying (pressurised air) 2,4'-MDI	Yes	45	0.00328	0.0128	LOQ	LOQ	0.0035

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Dermal exposure

Data from the Registration Dossiers

The assessment of the dermal exposure in the CSRs for the use of MDI in coatings is based on the same approach and assumptions as described before (see B.9.3). For the hazard of sensitization the likelihood / frequency of skin exposure has been assessed qualitatively. The likelihood/frequency of exposure has been considered to be very low (for PROCs 1, 2, 3, 8b, 9, and 15) or low (for PROCs 4, 5, 7, 8a, 10, 11, and 13) under the provision that PPE is used properly (chemical resistant gloves and eye protection). However, potential exposure to the skin has been identified to be high for batch processes, open mixing, industrial and professional spraying, rolling and brushing, transfer using non-dedicated equipment or dipping, if no suitable gloves and protection as prescribed by the RMM is used. The estimated intensities of exposures (according to the CSRs where quantitative estimates were made) are 0.73 mg/cm² for PROC4, 0.42 mg/cm² for PROCs 5, 7, 8a, 10, and 13 and 0.17 mg/cm² for PROC 11.

TDIInhalation exposure**Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)**

The exposure estimates in the CSRs are based on measurement data that were also published by ISOPA in the document "TDI: Final Exposure Scenarios in the e-SDS format" (ISOPA, 2014). Two exposure scenarios in this document are covering the use of TDIs in coatings: exposure Scenario 3 B (Industrial use for Coatings), which comprises PROCs 1, 2, 3, 4, 5, 8b, 9, 10, 13, and 15. The Professional use for Coatings (exposure scenario is 4 A) is covered by the PROCs 5, 8a, and 10. The exposure values of the respective PROCs are based on measurement data (90th percentile values) as already described above.

For the industrial use of TDI in coatings the long term inhalation exposure values range from 0.001 mg/m³ (for PROC 5 with RMM applied) to 0.035 mg/m³ (for PROC 10 – large scale > 10 m²). In case of the short term inhalation exposure the values range from 0.001 mg/m³ to 0.0698 mg/m³ (for PROC 5, with RMM applied, and PROC 10 - large scale, respectively). The corresponding long term inhalation exposure ranges for professional use of TDI in coatings are from 0.001 mg/m³ (PROC 5, RMM applied) to 0.035 mg/m³ (PROC 10 – large scale) ; the respective short term inhalation exposure levels are ranging from 0.001 mg/m³ (PROC 5, RMM applied) to 0.070 mg/m³ (PROC 10 - large scale).

Occupational exposure data from German Social Accident Insurance (IFA)

Both of the evaluation studies on occupational exposure measurements for TDI prepared by IFA (IFA, 2010; IFA, 2013) are summed up with respect to the use of TDI in coatings.

Table 32 shows the data from the first IFA study (IFA, 2010) for 2,4-TDI and 2,6-TDI in work area groups related to the use in coatings, representative for more than six hours of time of exposure.

Table 32: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Surface coating processes, miscellaneous 2,6-TDI	Yes	43	0.00227	0.00468	LOQ	0.004	0.00585
	No	17	0.00106	0.00024	LOQ	LOQ	LOQ
Surface coating processes, miscellaneous 2,4-TDI	Yes	45	0.00266	0.00635	LOQ	0.0045	0.00575
	No	18	0.00106	0.00024	LOQ	LOQ	LOQ
Spraying (all work areas) 2,6-TDI	Yes	201	0.00122	0.00091	LOQ	LOQ	LOQ
	No	20	0.00108	0.00025	LOQ	LOQ	LOQ

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Spraying (all work areas) 2,4-TDI	Yes	212	0.00118	0.00065	LOQ	LOQ	0.002
	No	21	0.00107	0.00024	LOQ	LOQ	LOQ
Spraying (Airless) 2,6-TDI	Yes	45	0.00107	0.00023	LOQ	LOQ	LOQ
Spraying (Airless) 2,4-TDI	Yes	43	0.00107	0.00023	LOQ	LOQ	LOQ
Spraying (Airmix) 2,6-TDI	Yes	16	0.00125	0.001	LOQ	LOQ	0.002
Spraying (Airmix) 2,4-TDI	Yes	17	0.00118	0.00073	LOQ	LOQ	0.002
Spraying (pressurised air) 2,6-TDI	Yes	118	0.00128	0.00105	LOQ	LOQ	0.003
	No	17	0.00106	0.00024	LOQ	LOQ	LOQ
Spraying (pressurised air) 2,4-TDI	Yes	130	0.0012	0.00071	LOQ	LOQ	0.00225
	No	18	0.00106	0.00024	LOQ	LOQ	LOQ

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Table 33 shows the data representative for more than six hours of time of exposure to 2,6-TDI and 2,4-TDI from the 2013 IFA evaluation (IFA, 2013).

Table 33: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m³)

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
Surface coating processes, miscellaneous 2,4-TDI	49	LOQ	0.006	0.00732
Surface coating processes, miscellaneous 2,6-TDI	49	LOQ	0.00605	0.008
Surface coating processes, manually, painting, rolling, brushing, dipping, flooding 2,4-TDI	19	LOQ	LOQ	LOQ
Surface coating	15	LOQ	LOQ	LOQ

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
processes, manually, painting, rolling, brushing, dipping, flooding 2,6-TDI				
Surface coating processes, by machine 2,4-TDI	56	LOQ	LOQ	0.0022
Surface coating processes, by machine 2,6-TDI	56	LOQ	LOQ	0.0022
Spraying (pressurised air) 2,4-TDI	185	LOQ	LOQ	LOQ
Spraying (pressurised air) 2,6-TDI	173	LOQ	LOQ	0.003
Spraying, painting 2,4-TDI	24	LOQ	LOQ	0.002
Spraying, painting 2,6-TDI	24	LOQ	LOQ	LOQ
Spraying (air-mix, airless) 2,4-TDI	79	LOQ	LOQ	0.00252
Spraying (air-mix, airless) 2,6-TDI	80	LOQ	LOQ	LOQ

Abbreviations:

LOQ limit of quantification (1.2 µg/m³ for 2,4-TDI and 1.3 µg/m³ for 2,6-TDI for 210 l of probe air volume)

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Table 34 gives an overview of the inhalation exposure levels to TDI according to the data from ISOPA/CSRs and the evaluations by IFA.

Table 34: Overview of inhalation exposure levels to TDI in use in coatings (in µg/m³)

CSRs long-term inhalation	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile
1 – 35	LOQ - 4.5	LOQ - 6.05

Abbreviations:

LOQ limit of quantification

Dermal exposure

Data from the Registration Dossiers

Dermal exposure was assessed qualitatively in the CSRs by the likelihood/frequency of skin contact. The likelihood for dermal contact and was considered to be practically negligible for PROC 1 and likelihood/frequency of dermal exposure was assessed to be very low for PROCs 2, 3, 8b, 9, and 15. A low potential for exposure was attributed to PROCs 4, 5, 7, 8a, 10, and 13 and quantitative estimates were made for these PROCs, ranging from 0.04 mg/cm² (PROC 8a) to 0.20 mg/cm² (PROC 5). The estimates are based on that protective gloves are used stringently and a reduction factor of 90 % was assigned to the efficiency of PPE.

As written before, it is the DS's point of view that stringent use of PPE like gloves highly depends on behavioural aspects and attitudes of the workers performing the task and it cannot be assumed that an efficiency of 90 % protection is reliably achievable without corresponding control measures (like training and monitoring).

HDI

Inhalation exposure

Occupational exposure data from the Registration Dossiers

In the CSR for HDI (monomer) only the uses in manufacture, in formulation and the industrial use of HDI as an intermediate / monomer are covered. The industrial and professional end uses (which include the application in coatings) are covered by the CSRs for the oligomers of HDI, i.e. HDI isocyanurate and HDI biuret (both are trimers of HDI). For both oligomers the worker exposures have been estimated by modelling using the ECETOC TRA model (version 3 in case of the HDI isocyanurate (n=3); and version 2 for the estimates for HDI biuret). Some of the relevant PROCs were also modelled with the Advanced REACH Tool (ART) v 1.0 as no safe use could be demonstrated based on the ECETOC estimates. These PROCs with refined estimates with ART were PROC 7 (industrial spraying) and PROC 10 (roller application or brushing) for the industrial end use of HDI isocyanurate and PROC 11 (professional spraying). The exposure estimates were in the range from 0.11 mg/m³ (PROC 10 - industrial use) to 0.43 mg/m³ (PROC 7).

Occupational exposure data from the German Social Accident Insurance (IFA)

Measured workplace exposure data from Germany have been also been evaluated by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2012). The data have been gathered from 2000 to 2011 and were documented in accordance with the measurement system of the German Social Accident Insurance Institutions for exposure assessment (MGU) (Gabriel et al., 2010). Overall, a total of 3034 measurement data for HDI have been evaluated according to industry groups as well as work area groups. Table 35 provides an extract of the statistical evaluations of the measurement values for HDI for those work area groups found relevant for the use in coatings.

Table 35: Overview of the statistical evaluation from MEGA database for HDI, data period 2000-2011 (IFA, 2012) (mg/m³)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
Painting, rolling time of exposure ≥ 6h	59	LOQ	LOQ	LOQ
Painting, rolling time of exposure < 6h	46	LOQ	0.00786	0.0132
Spraying, painting time of exposure ≥ 6h	924	LOQ	0.0045	0.008
Spraying, painting time of exposure < 6h	192	LOQ	0.012	0.0186

Abbreviation:

LOQ: limit of quantification (2.3 µg/m³ for 210 l of probe air volume)

Occupational exposure data from the Health and Safety Executive of the United Kingdom (HSE UK)

In the following some air monitoring data from HSE's National Exposure Database (NEDB) provided by HSE UK will be presented. As already stated above, due to the confidential nature of the data provided, the following statement needs to be mentioned here:

'The data is not representative of any industry partly due to bias in selection of the sites where data has been collected and is determined by HSE interest in specific substance or process. Most of the data was collected between 1986 and 1993 after which the rate of data collection reduced significantly. It should be noted that NEDB itself has an inherent bias, in that HSE Specialist Occupational Hygiene Inspectors as part of their enforcement duties obtained approximately 90 % of the samples. Consequently, a tendency towards high levels of exposure would be expected, as companies with no perceived problems were generally not sampled. Even so, NEDB still contains many samples indicating low exposure (<25 % of the appropriate occupational exposure limit), so the actual bias is not as large as would be expected. Whether or not NEDB should be considered as containing worst case data is debatable, but it cannot be regarded as being truly representative of occupational exposure in Great Britain given that it does not come from a random selection of workplaces and circumstances.'

Out of the overall 450 air monitoring data 161 measurements were attributable to exposure to HDI or not further specified isocyanates in spray paint applications. Being aware that the data for the unspecified isocyanates are not clearly linked to exposures to HDI they are nevertheless presented in this section as HDI and its derivatives are the most common isocyanate species present in spray paints. Out of the 15 long term personal samples the concentrations of isocyanates were in the range from 0.35 to 208.0 µg/m³ while the concentrations out of a total of 57 long term static samples ranged from 0.04 to 85800.0 µg/m³. The range of the concentrations out of the 47 short term personal samples was in the range from 0.82 to 245000.0 µg/m³. The corresponding short term static samples (N=42) were in the range from 0.06 to 62000.0 µg/m³. The corresponding 90th percentile values for these data are: 126,4 µg/m³ for the long term personal sample data, 1008.6 µg/m³ for the long term static sample data, 1094.0 for the short term personal sample data and 5566.3 µg/m³ for the short term static sample data.

Data from literature

Sparer et al. conducted a study among vehicle sprayers in 37 auto body shops in New Haven, Conn. (Sparer et al., 2004). All of the various layers applied in the repair tasks evaluated in the study (primer, sealer and clear-coat) were containing isocyanates. The exposure levels of personal samples measured during the spray painting tasks outside of the respiratory protective equipment were statistically evaluated for the spraying of primer, sealer and clear-coat. The median exposure values of the total NCO air concentrations were 66.5 µg/m³ for primer, 134 µg/m³ for sealer and 358 µg/m³ for clear-coat. The respective 75th-percentiles were 165 µg/m³ (primer), 296 µg/m³ (sealer) and 855 µg/m³ (clear-coat).

Pronk et al. assessed the exposure levels to isocyanates in spray-painting environments in the Netherlands by 566 personal air samples collected from 24 car body repair shops and five industrial companies (Pronk et al., 2006). The samples were analysed for 23 isocyanate compounds. HDI and its oligomers were the most abundant species in frequency and concentration found and consequently the most important source and major contributor of isocyanate exposure. The measured concentrations of monomeric HDI were (as far as above the LOD) in the range from 0.002 to 15.5 µg/m³ (median 0.44 µg/m³) in the car body repair shops and from 0.01 to 28.8 µg/m³ (median 0.11 µg/m³) for industrial spray painters. For HDI uretdione (dimer) the measured concentrations (> LOD) ranged from 0.12-47.5 µg/m³ (median 1.29 µg/m³) in the car body repair shops and from 0.07 to 61.9 µg/m³ (median 3.2 µg/m³) in the industrial settings. The corresponding measurements for HDI isocyanurate (trimer) were in the range from 0.02 to 892 µg/m³ (median 13.29 µg/m³) in the professional shops and from 0.11 to 522 µg/m³ (median 5.31) for the industrial workers. HDI diisocyanurate levels ranged from 0.84 to 149 µg/m³ (median 24.27 µg/m³) for professional workers and for the industrial workers from 0.65 to 577 µg/m³ (median 4.21 µg/m³). The concentrations of HDI biuret (trimer) were in the range from 0.06 to 306 µg/m³ (median 8.11 µg/m³) for the car body repair shop workers and from 0.11 to 522 µg/m³ (median 2.78 µg/m³) for the industrial spray painters.

In another study published by Pronk et al. inhalation and dermal exposures to HDI and its oligomers as well as urine samples taken from car body repair shop workers and industrial spray painters were assessed (Pronk et al., 2006). Overall 95 personal task based inhalation samples were collected from six car body repair shops and five industrial sites. The samples were taken separately for the different tasks involved in the work. In the car body repair shops exposure during following tasks were measured: mixing of coating, spraying, cleaning of spray guns, and welding. The tasks identified at the industrial sites were: mixing of PU lacquer, spraying of lacquer, rolling/brushing of PU lacquer, and assisting a spray painter. Exposure levels to HDI and its oligomers were strongly correlated to tasks that involved aerosol formation and ranged (as far as above the LOD) from 0.2 to 6.5 µg/m³ (median 2.1 µg/m³) for monomeric HDI and from 2.5 to 728.4 µg/m³ (median 116.3 µg/m³) for the oligomers in the car body repair shops. At the industrial sites the inhalation exposure levels (> LOD) were in the range from 0.03 to 28.8 µg/m³ (median 3.7 µg/m³) for monomeric HDI and from 6.4 to 2613.8 µg/m³ (median 199.6 µg/m³) for the oligomers.

Fent et al. conducted exposure measurements of HDI and HDI oligomers during spray painting on 47 sprayers in North Carolina and Washington State as one part of a broader series of studies (also addressing dermal exposure and biological monitoring of exposed workers) (Fent et al., 2009a). The breathing zone concentrations of monomeric HDI measured during spray painting were in the range from 0.003 to 179 µg/m³. The concentrations of the corresponding oligomers were in the case of uretdione (dimer) in the

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

range from 0.002 to 1430 µg/m³ and for biuret (trimer) from 0.01 to 7720 µg/m³. The levels of isocyanurate (trimer) were higher than for all other analytes, ranging from 0.09 to 18700 µg/m³. **Table 36** shows the levels of exposure to the different HDI species as published by Pronk et al. in the two studies above. The first line in the table fields are the values for the measured data in the car body repair shops as the range of the values above the LOQ and the median value in brackets followed by the data for the industrial spray painters.

Table 36: Exposure levels to HDI species, measured by Pronk et al. (in µg/m³)

	HDI monomer	HDI Uretdione	HDI Isocyanurate	Diisocyanurate	HDI Biuret
(Pronk, Tielemans, et al. 2006)	0.002 - 15.5 (0.44) 0.01 - 28.8 (0.11)	0.12 - 47.5 (1.29) 0.07 - 61.9 (3.2)	0.02 - 892 (13.29) 0.11 - 522 (5.31)	0.84 - 149 (24.27) 0.65 - 577 (4.21)	0.06 - 306 (8.11) 0.11 - 522 (2.78)
(Pronk, Yu, et al. 2006)	0.2 - 6.5 (2.1) 0.03 - 28.8 (3.7)	2.5 - 728.4 (116.3); all oligomers 6.4 - 2613.8 (119.6); all oligomers			

Table 37 provides an overview of the inhalation exposure levels to HDI and its oligomers as available in the CSRs (ALIPA), the MEGA evaluation by IFA and the literature above.

Table 37: Overview of inhalation exposure levels to HDI and its oligomers in use in coatings (in µg/m³)

CSR (HDI isocyanurate)	(IFA, 2012) 90 th percentile	HSE UK 90 th percentiles (range)	(Sparer et al., 2004) 75 th percentile	(Pronk et al., 2006)	(Pronk et al., 2006)	(Fent et al., 2009a)
110 - 430	LOQ - 120	126.4 1008.6 1094.0 5566.3 (0.06 - 245000)	165 - 855	0.01 - 28.8 (monomer) 0.07 - 61.9 (uretdione) 0.06 - 577 (biuret) 0.02 - 892 (isocyanurate)	0.03 - 28.8 (monomer) 2.5 - 2613.8 (oligomers)	0.003 - 179 (monomer) 0.002 - 1430 (uretdione) 0.01 - 7720 (biuret) 0.09 - 18700 (isocyanurate)

Dermal exposure

Data from the Registration Dossiers

As stated above the CSR for HDI (monomer) does not cover the industrial or professional end uses such as in coatings. The industrial and professional end uses (also covering the use in coatings) are in the CSRs for HDI isocyanurate and HDI biuret. No quantitative dermal exposure estimates are given in the CSR for HDI isocyanurate. In the CSR for HDI biuret on the other hand the dermal exposure was assessed using the ECETOC TRA model (version 2009). For processes where dermal exposure is possible (i.e. any other than

PROC 1, 2, and 3), the use of gloves is recommended to control the risk and in these cases an exposure reduction of 90 % is assumed. It is highlighted in the CSR that dermal exposure of workers is likely to occur at spraying, roller, (dis)charging and sampling steps. The outcomes of the ECETOC TRA estimates for dermal exposures for the relevant PROCs (for use in coatings) are 1.37 mg/kg/day for PROC 5 (mixing or blending) and 8a (transfer at non-dedicated facilities), 2.7 mg/kg/day for PROC 10 (roller application of brushing), 4.3 mg/kg/day for PROC 7 (industrial spraying) and 10.7 mg/kg/day for PROC 11 (non-industrial spraying).

Data from literature

Pronk et al. also assessed the dermal exposure resulting from spray painting tasks at car body repair shops as well as industrial painting companies in the Netherlands (Pronk et al., 2006). As described before, the tasks identified as relevant were mixing of lacquer, spraying, cleaning of spray guns, and welding in case of the car body repair shops and for the industrial companies the relevant tasks were spraying, rolling/brushing, mixing, and assisting the spray painter. For assessment of the dermal exposure nitrile rubber gloves were worn during the tasks and immediately after finishing prepared for extraction of HDI (and its oligomers). By this approach a total mass of HDI and its oligomers on two gloves was quantified per sample. The exposure levels ranged (as far as above the LOD) from 0.3 to 20.1 µg NCO (per two gloves) for monomeric HDI at the samples taken at car body repair shops. At industrial sites only one sample yielded a quantifiable level of monomeric HDI on two gloves, which was 0.5 µg NCO. The levels of HDI oligomers were (> LOD) in the range from 6.5 to 2848.5 µg NCO for the samples taken at the car body repair shops and ranging from 0.7 to 209.8 µg NCO (per two gloves) for the samples taken at industrial painting companies.

As part of the assessment of exposures to HDI and its oligomers among spray painters in North Carolina (NC) and Washington State (WA) Fent et al. also measured the dermal exposure in addition to the inhalation exposure assessment described before (Fent et al., 2009b). The assessment was done by consecutive tape-strip sampling with three successive samples from each site of the skin. To estimate the total dermal exposure the mass collected from each body part was multiplied with the regional surface area estimates of the respective body parts. The thus calculated whole-body dermal concentrations of monomeric and polymeric HDI measured were in the range from 0.00003 to 121 ng/mm³ for monomeric HDI. The measured whole-body dermal concentrations of HDI uretdione were in the range from 0.0001 to 55.9 ng/mm³. Biuret concentrations were ranging from 0.0001 to 2830 ng/mm³. Isocyanurate was found to be the predominant species and was measured in 95 % of the samples, while the other polyisocyanates were detected in less than 23 % of the samples. The whole-body dermal concentrations of HDI isocyanurate were ranging from 0.01 to 7880 ng/mm³. Significant higher whole-body dermal concentrations were measured when the workers did not use proactive clothing (gloves and coveralls) with geometric mean concentrations of 0.02 and 0.21 ng/mm³ for HDI monomers when coveralls and gloves were worn or not. Similarly the geometric mean concentrations measured when protective clothing was worn were 0.06 and 0.52 ng/mm³ in case of HDI uretdione, 0.08 and 1.15 ng/mm³ for biuret, and 12.9 vs. 276 ng/mm³ for isocyanurate, suggesting roughly a ten- to twenty-fold reduction of dermal exposure by wearing of coveralls and protective gloves.

As can be seen the two methods for measuring the dermal exposure differ considerably both in the sampling strategy and the results. While Pronk et al. did measure the total

amount on two nitrile gloves by extraction Fent et al. applied a tape-strip sampling method direct to the skin where the total mass of dermal exposure was calculated by multiplying the point measurements (ng/cm²) and the regional surface area estimates. To calculate the whole-body exposure the calculated mass of exposure to each body part was summed and divided by the total body surface area and, because the strip samples were considered to remove a layer of approx. 1 µm thickness of skin, the dermal exposures were reported as concentrations (ng/mm³).

Table 38 shows the levels of dermal exposure to HDI and its oligomers measured in the use of coatings.

Table 38: Overview of dermal exposure levels to HDI and its oligomers in use in coatings

(Pronk, Yu, et al. 2006)		(Fent, Trelles Gaines, et al. 2009)	
HDI monomer:	0.3 - 20.1 µg/two gloves	HDI monomer:	0.00003 - 121 ng/m ³
HDI oligomer:	0.72848.5 µg/two gloves	HDI biuret:	0.0001 - 2830 ng/m ³
		HDI uretdione:	0.0001 - 55.9 ng/m ³
		HDI isocyanurate:	0.01 - 7880 ng/m ³

Biological monitoring

Data from literature

In the afore mentioned study conducted by Pronk et al. also urinary HDA levels of workers exposed to HDI during spray painting tasks in car body repair shops and industrial painting companies in the Netherlands were assessed (Pronk et al., 2006). Out of urine samples collected from the car body repair shops HDA could be detected in 36 % of the workers (with 21 % of all samples being tested positive on HDA). HDA was also detected in a large proportion of the workers that did not handle any paint or reported any bystander exposure in the car body repair shops. In the industrial painting companies urinary HDA was detectable in 10 % of the workers (and 8 % of all samples). Information on the use of PPE collected through questionnaires showed that RPE was widespread during spraying but protective gloves were used by 40 % of the workers in the car body repair shop and 75 % of the industrial spray painters. The detected levels of urinary HDA ranged from 1.9 to 150.2 µg HDA/g creatinine. Median concentrations were calculated for different time intervals of the sampling time and were around 20 µg HDA/g creatinine, ranging from 7.3 to 21.5 µg HDA/g creatinine.

In a complementary study to the survey for inhalation and dermal exposure to HDI in automotive spray painters in North Carolina and Washington State published by Fent et al. (see above), Gaines et al. investigated the quantitative time-dependent relationship between dermal and inhalation exposure to HDI and the urinary HDA levels (Gaines et al., 2010). Samples were collected throughout the workday and varied from non-detectable to 65.9 µg/L with an arithmetic mean concentration of 0.54 µg/L. HDA levels normalised with creatinine concentrations were in the range from <LOD to 21.6 µg/g creatinine (arithmetic mean 0.003 µg/g creatinine). The authors observed that both dermal and inhalation exposure correlated significantly with urinary HDA concentrations.

Jones, Cocker and Piney used biological monitoring to assess the changes in control of exposure to HDI based paints in vehicle spraying after participating in a so called "Safety

and Health Awareness Day” (SHAD) to increase the awareness of risks related to isocyanate based paints (Jones et al., 2013). Free biological monitoring sampling kits together with a brief work task form (asking for consent and some information on the work and PPE used) were offered to approx. 4000 attendees of the SHAD events. 995 urine samples were returned, out of which 81 % also included the filled task form. When the urinary HDA level was above the LOQ the sprayers were asked to send another sample after reviewing and improving the exposure control measures. These repeat samples had significantly lower results than those before. The urinary HDA levels of the SHAD data ranged from <LOQ in 83 % of the samples up to 20 µmol HDA/mol creatinine. When comparing the data from the SHAD events and subsequent years following the events with HSE’s pre-SHAD data no significant difference was found between the SHAD and the post-SHAD data sets both being significantly lower than the pre-SHAD data. The 90th percentile value of the pre-SHAD data was 1.34 µmol HDA/mol creatinine compared to 0.60 µmol HDA/mol creatinine for the 90th percentile of the SHAD data set. The 90th percentile values of the post-SHAD data sets from 2008 to 2011 were in the range from 0.55 to 0.76 µmol HDA/mol creatinine.

Stocks et al. statistically evaluated the data on urinary HDA levels from the UK HSE and compared the trends in these data with trends in incidences of occupational asthma attributed to isocyanates or spray painting in the UK Surveillance of Work-related and Occupational Respiratory Disease scheme (SWORD) (Stocks et al., 2015). The finding was that there was a significant decline in the number of urine samples with detectable levels of HDA in the period from 2006 to 2014 as well as in the number of reported asthma cases attributed to isocyanates or spray painting. This decline was attributed to training interventions (SHADs) carried out by the UK HSE from 2006 onwards (see B.9.1.2). No significant differences in urinary HDA levels were found between motor vehicle repair workers and workers employed in other sectors like coachworks, boat, trailer or aircraft repair.

B.9.7 Use in adhesives

This use is linked to potentially high exposure and widespread use.

B.9.7.1 General information

Due to the wide variety of compositions of the building blocks the properties of PU adhesives can be tailored to a wide range of requirements and purposes. Consequently PU adhesives are used in a broad scope of applications and products ranging from rigid to elastic bonds. As for the reactivity of the NCO groups they offer very good adhesion to porous or closed polar surfaces (ability to form hydrogen bonds; e.g. wood, glass, metals, rubbers, leather, tile, concrete etc.) but less to non-polar surfaces like polypropylene or polyethylene plastics, silicone etc. PU adhesives can be two-component or one-component systems which can be solvent-based, water-borne (aqueous dispersions) or solvent free (granulates, dry powders). They can be processed and/or curing at ambient temperatures or at elevated temperatures (from 50-80 °C to 180-200 °C). With respect to potential exposure it was shown that both the content of isocyanate monomers and the processing temperature have a significant impact on emissions (Cuno et al., 2015).

B.9.7.2 Exposure estimationB.9.7.2.1 B.9.7.2.1 Workers exposureMDIInhalation exposure**Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)**

As for the exposure data discussed before, the exposure estimates in the CSRs for MDIs are based on the data published by ISOPA (ISOPA, 2012). The use of MDIs for adhesives and sealants is included in the exposure scenario cluster 4 (Industrial use of MDI for Rigid Foam, Coatings and Adhesives and Sealants) and exposure scenario cluster 7 (Professional end uses of MDI) in the respective exposure scenarios C) (Use for Adhesives and Sealants). The exposure scenario for the industrial Use for Adhesives and Sealants comprises PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 9, 10, 13, 14, and 15. The exposure scenario Adhesives and Sealants, professional use includes PROCs 4, 5, 8a, 8b, 10, 11, and 13.

As already written the exposure estimates in the exposure scenarios are based on occupational hygiene measurement data, with the same dataset used for all exposure scenarios and isomers of MDI. The estimates for the long term inhalation exposure of the use of MDI in coatings range between 0.005 mg/m³ (for PROC 9) to 0.043 mg/m³ (for PROC 11-outdoor) and between 0.009 mg/m³ to 0.087 mg/m³ for the respective short term inhalation exposures.

Occupational exposure data from German Social Accident Insurance (IFA)

The evaluation for MDI by the Institute for Occupational Safety and Health of the German Social Accident Insurance already described earlier also covers measurement data for exposure to 2,4'-MDI and 4,4'-MDI in the work area group gluing (IFA, 2010). The IFA evaluation data representative for more than six hours of time of exposure for this work area group are shown in Table 39.

Table 39: Overview of the statistical evaluation from MEGA database for MDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Gluing 4,4'-MDI	Yes	165	0.006	0.0319	LOQ	0.0065	0.0138
	No	196	0.00265	0.0123	LOQ	0.003	0.006
Gluing 2,4'-MDI	Yes	60	0.00112	0.00098	LOQ	LOQ	LOQ
	No	112	0.00147	0.00115	LOQ	LOQ	LOQ

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Data from literature

In the already cited study by Breżeński and Bonczarowska on isocyanate exposures in Polish industries are included several plants where MDI is used for gluing, mainly of layers of construction boards (Brzeznicki and Bonczarowska, 2015). The MDI concentrations of the personal samples ranged from below the LOQ of 0.6 µg/m³ to 5.2 µg/m³ in one plant. However, in four out of the six plants the measured exposures were below the LOQ.

Table 40 gives an overview of the inhalation exposure levels to MDI in the use of adhesives according to the sources described above. (The IFA data do not provide values for the total isocyanate concentrations but only for the respective isomers, i.e. 4,4'-MDI and 2,4'-MDI were evaluated separately).

Table 40: Overview of inhalation exposure levels to MDI in use in adhesives (in µg/m³).

CSRs	(IFA, 2010) 90 th percentile	(Brzeznicki and Bonczarowska, 2015).
5 - 43	LOQ - 6.5	LOQ - 5.2

Dermal exposure

Data from the Registration Dossiers

The assessment of the dermal exposure in the CSRs for the use of MDI in adhesives is based on the same approach and assumptions as described before (see B.9.3). For the hazard of sensitization a qualitative exposure assessment has been carried out. Analogous to the assessment for the use of MDI in manufacture of polyurethanes and PU composite materials (B.9.3.2.1) the likelihood / frequency of skin exposure has been either assessed as very low (for PROCs 1, 2, 3, 8b, 9, 14, and 15) or low (for PROCs 4, 5, 7, 8a, 10, 11, and 13) provided that PPE is used properly (chemical resistant gloves and eye protection). The estimated intensities of exposures (according to CSR) are 0.73 mg/cm² for PROC 4, 0.42 mg/cm² for PROCs 5, 7, 8a, and 10 and 0.17 mg/cm² for PROC 11.

As for the assessment of dermal exposure in the use of MDI in manufacture of PU and PU composite materials, the dossier submitting CA does not subscribe to all of the assumptions made by the registrants, as the role of the CSRs is to describe how a substance can be used safely, i.e. good practise, and not how a substance is used actually. Assuming a less than ideal work practise, a high likelihood of dermal exposure is given for PROCs 7, 8a, 10, and a medium likelihood for PROC 4. No further data on dermal exposure to MDI based adhesives could be found.

TDI

Inhalation exposure

Occupational exposure data from the European Diisocyanate and Polyol Producers Association (ISOPA)

The exposure estimates in the CSRs are based on measurement data also published by ISOPA in the document "TDI: Final Exposure Scenarios in the e-SDS format" (ISOPA, 2014). Two exposure scenarios in this document do cover the use of TDIs in adhesives: exposure

Scenario 3 C (Industrial use for Adhesives and Sealants) covering PROCs 1, 2, 3, 4, 5, 7, 8b, 9, 10, 13, 14, and 15. Exposure scenario 4 B covers the Professional use for Adhesives and Sealants and includes the PROCs 4, 5, 8a, and 10. The exposure values of the respective PROCs are based on measurement data (90th percentile values) as already described above.

For the industrial use of TDI in adhesives the long term inhalation exposure values range from 0.001 mg/m³ (for PROC 5 with RMM applied) to 0.035 mg/m³ (for PROC 10-large scale > 10 m²). In case of the short term inhalation exposure the values range from 0.001 mg/m³ to 0.0698 mg/m³ (for PROC 5, with RMM applied, and PROC 10-large scale, respectively). The corresponding long term inhalation exposure for professional use of TDI for adhesives ranges from 0.001 mg/m³ (for PROC 5 with RMM applied) to 0.035 mg/m³ (PROC 10-large scale); the respective short term inhalation exposure levels are ranging from 0.001 mg/m³ (PROC 5, RMM applied) to 0.070 mg/m³ (PROC 10-large scale).

Occupational exposure data from German Social Accident Insurance (IFA)

Both MEGA evaluation studies on occupational exposure measurements for TDI prepared by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2010; IFA, 2013) are presented with respect to the use of TDI in adhesives. Table 41 gives an overview of the data from the first IFA study (IFA, 2010) for 2,4-TDI and 2,6-TDI in work area group gluing, representative for more than six hours of time of exposure.

Table 41: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2009 (IFA, 2010)

Work area group	LEV	No. of measured data	Arithm. mean (mg/m ³)	SD	75 th percentile (mg/m ³)	90 th percentile (mg/m ³)	95 th percentile (mg/m ³)
Gluing 2,6-TDI	Yes	77	0.00231	0.00659	LOQ	0.0023	0.005
	No	85	0.00136	0.00193	LOQ	LOQ	0.002
Gluing 2,4-TDI	Yes	74	0.00163	0.00311	LOQ	0.0018	0.002
	No	83	0.00143	0.00282	LOQ	LOQ	LOQ

Abbreviations:

LOQ limit of quantification – not further specified in the report

LEV local exhaust ventilation

Arithm. mean arithmetic mean

SD arithmetic standard deviation

Table 42 provides an overview of the exposure data to 2,6-TDI and 2,4-TDI (representative for more than six hours of time of exposure if not stated otherwise) from the 2013 IFA evaluation report (IFA, 2013).

Table 42: Overview of the statistical evaluation from MEGA database for TDI, data period 2000-2011 (IFA, 2013) (mg/m³)

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
Gluing in the textile industry 2,4-TDI	12	0.0039	0.033	0.0402
Gluing in the textile industry 2,6-TDI	12	0.006	0.0482	0.13
Gluing, adhesives, contact	39	LOQ	LOQ	LOQ

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Work area group	No. of measured data	50 th percentile	90 th percentile	95 th percentile
adhesives 2,4-TDI				
Gluing, adhesives, contact adhesives 2,6-TDI	41	LOQ	LOQ	LOQ
Gluing, plastic products manufacturing 2,4-TDI	16	LOQ	0.0046	0.0108
Gluing, plastic products manufacturing 2,6-TDI	17	LOQ	0.0039	0.0078
Gluing, reactive adhesives 2,4-TDI	53	LOQ	0.0012	0.00168
Gluing, reactive adhesives 2,6-TDI	54	LOQ	0.0012	0.00165
Gluing, melt adhesives 2,4-TDI	11	LOQ	LOQ	LOQ
Gluing, melt adhesives 2,6-TDI	24	LOQ	LOQ	LOQ
Gluing, other proceedings 2,4-TDI (time of exposure < 6h)	15	LOQ	0.0035	0.00875
Gluing, other proceedings 2,6-TDI (time of exposure < 6h)	14	LOQ	0.00532	0.00794

LOQ limit of quantification (1.2 µg/m³ for 2,4-TDI and 1.3 µg/m³ for 2,6-TDI for 210 l of probe air volume)

Table 43 provides an overview of the inhalation exposure levels to TDI according to the data from ISOPA/CSRs and the MEGA evaluations by IFA.

Table 43: Overview of inhalation exposure levels to TDI in use in adhesives (in µg/m³)

CSRs long-term inhalation	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile
1 - 35	LOQ - 2.3	LOQ - 48.2

Dermal exposure

Data from the Registration Dossiers

Dermal exposure was assessed qualitatively in the CSRs in terms of the likelihood/frequency of skin contact. The likelihood for dermal contact was considered to be practically negligible for PROC 1 and likelihood/frequency of dermal exposure was assessed to be very low for PROCs 2, 3, 8b, 9, and 15. A low potential for exposure was attributed to PROCs 4, 5, 7, 8a, 10 and 13 and quantitative estimates were made for these PROCs, ranging from 0.04 mg/cm² (PROC 8a) to 0.20 mg/cm² (PROC 5). The estimates are based on that protective gloves are used stringently and a reduction factor of 90 % was assigned to the efficiency of PPE.

As written before, it is the DS's point of view that stringent use of PPE like gloves highly depends on behavioural aspects and attitudes of the workers performing the task and it cannot be assumed that the assumed efficiency of 90 % protection is achievable without corresponding control measures (like training and monitoring).

HDIInhalation exposure**Data from the Registration Dossiers**

The use of HDI in adhesives is not covered by or described in the CSRs for monomeric HDI nor for HDI oligomers (isocyanurate and biuret).

Data on inhalation exposure to HDI for the use of adhesives at German workplaces was evaluated by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2012). However, the exposure levels were below the LOQ of 2.3 µg/m³ for all percentiles given in the evaluation report (50th, 90th, and 95th percentile out of 294 measurement data).

Data from literature

The study by Brezeńnicki and Bonczarowska on isocyanate exposures in Polish industries also lists two plants where HDI is used for gluing, namely plant H (gluing in the manufacture of car interiors) and plant J (gluing of bulb elements) (Brzeńnicki and Bonczarowska, 2015). The concentrations personal samples were below the LOQ in the first plant and ranged from below the LOQ (of 0.8 µg/m³) to 1.0 µg/m³ in the other.

Table 44: Overview of inhalation exposure levels to HDI in use in adhesives (in µg/m³)

CSR	(IFA, 2012) 95 th percentiles	(Brzeńnicki and Bonczarowska, 2015)
No data	< LOQ	LOQ - 1.0

Where the respective parts on exposures or biological monitoring are not filled in the sections above there no data was found for any of the isocyanate species or specific uses.

B.9.8 Other uses

Isocyanates are used in a wide range of sectors and products out of which not all uses are covered in great detail in this dossier (the registered uses of MDI, as reported in Table 5, being the most comprehensive). As stated above, rather than a comprehensive listing of all registered uses the emphasis of this exposure assessment is placed on those uses that were found to be most relevant with respect to the amount/volume and/or workplace exposure. The dossier submitting DS is aware that other isocyanate species like NDI, IPDI can also have an impact on the workplace exposure (e.g. see (Tinnerberg et al., 2014).) And potentially high exposures can also pose risks in other uses than those described above, e.g. in foundry applications (Liljelind et al., 2010). However, information on those isocyanates and/or uses was found to be too limited to allow a meaningful assessment of the exposure situations and of little extra value to this rather extensive part of the dossier.

B.9.9 Synopsis

The following overview shows the inhalation exposure to the respective isocyanates and uses from the tables presented before summarized in ranking order.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 45: Inhalation exposure levels to HDI and its oligomers in use in coatings (in µg/m³) (same as Table 37)

CSR (HDI isocyanurate)	(IFA, 2012) 90 th percentile	HSE UK	(Sparer et al., 2004) 75 th percentile	(Pronk et al., 2006)	(Pronk et al., 2006)	(Fent et al., 2009a)
110 - 430	LOQ - 120	0.06 - 245000	165 - 855	0.01 - 28.8 (monomer) 0.07 - 61.9 (uretdione) 0.06 - 577 (biuret) 0.02 - 892 (isocyanurate)	0.03 - 28.8 (monomer) 2.5 - 2613.8 (oligomers)	0.003 - 179 (monomer) 0.002 - 1430 (uretdione) 0.01 - 7720 (biuret) 0.09 - 18700 (isocyanurate)

Table 46: Inhalation exposure levels to MDI in spray foam applications (in µg/m³) (same as Table 30)

CSRs	(IFA, 2010) 90 th percentile	HSE UK	(Crespo and Galan, 1999)	(Lesage et al., 2007)	(Puscasu et al., 2015)	(Puscasu et al., 2015)
6 - 29	LOQ	0.03 - 200	10 - 570 (sprayer) 1 - 408 (helper)	7 - 2050 (personal, monomers) 10 - 870 (personal, oligomers)	30 - 90	20 - 80

Table 47: Inhalation exposure levels to TDI in manufacture of foam (in µg/m³) (same as Table 27)

CSRs	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile	HSE UK	(Kääriä et al., 2001)	(Sennbro et al., 2004)	(Tinnerberg and Mattsson, 2008)	(Austin, 2007)	(Geens et al., 2012)	(Brzezniak and Bonczarska, 2015)	(Swierczyńska-Machura et al., 2015)
1-32	LOQ - 24.6	LOQ - 72.8	0.06 - 45	LOD - 203	LOQ - 39.9	46.5 - 73.6, (med. 62.9)* 5.0 - 86.5, (med. 12.5)* *	<3.5 - 8.4	4.2 - 141.9	0.2 - 58.8	0.2 - 58.9

* before RMM improvements

** after RMM improvements

Table 48: Inhalation exposure levels to TDI in manufacture of PU and composite materials (in µg/m³) (same as Table 22)

CSRs	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile	(Sennbro et al., 2004)
1 - 32	LOQ - 22.1	4 - 67.3	0.08 - 14.6

Table 49: Inhalation exposure levels to TDI in use in adhesives (in µg/m³) (same as Table 43)

CSRs long-term inhalation	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile
1 - 35	LOQ - 2.3	LOQ - 48.2

Table 50: Inhalation exposure levels to MDI in use in adhesives (in µg/m³) (same as Table 40)

CSRs	(IFA, 2010) 90 th percentile	(Brzezniccki and Bonczarowska, 2015).
5 - 43	LOQ - 6.5	LOQ - 5.2

Table 51: Inhalation exposure levels to TDI in use in coatings (in µg/m³) (same as Table 34)

CSRs long-term inhalation	(IFA, 2010) 90 th percentile	(IFA, 2013) 90 th percentile
1 - 35	LOQ - 4.5	LOQ - 6.05

Table 52: Inhalation exposure levels to MDI in manufacture of PU and PU composite materials (in µg/m³) (same as Table 18)

CSRs	(IFA, 2010) 90 th percentile	HSE UK	(Kääriä et al., 2001)	(Sennbro et al., 2004)	(Creely et al., 2006)	(Brzezniccki and Bonczarowska, 2015)
2.0 - 29.0	LOD - 18.0	0.07 - 32.8	0.3 - 3.3	0.04 - 7.8	LOQ - 7.2	LOD - 3.3

Table 53: Inhalation exposure levels to MDI in manufacture of foam (in µg/m³) (same as Table 24)

CSRs	(IFA, 2010) 90 th percentile	HSE UK	(Brzezniccki and Bonczarowska, 2015).
6 - 29	LOQ - 4.2	0.03 - 0.17	<LOQ

Table 54: Inhalation exposure levels to HDI in use in adhesives (in $\mu\text{g}/\text{m}^3$) (same as Table 44)

CSR	(IFA, 2012) 95 th percentiles	(Brzezicki and Bonczarowska, 2015)
No data	< LOQ	LOQ - 1.0

Abbreviation:

LOQ limit of quantification

As mentioned before (B.9.1.1.2 – Dermal Exposure) there is almost always potential for skin contact when handling isocyanate containing formulations or reactions products thereof which are not fully cured (Cowie et al., 2005). The dermal exposure levels might differ from the inhalation exposure pattern of the uses described above. However, due to the more limited data on dermal exposure available and the large variance of the different measurement methods applied such data are mostly not commensurable. A ranking of the described uses based on dermal exposure data is therefore not practicably meaningful. Hence emphasis is placed on inhalation data. However, it has to be kept in mind that the dermal route can also contribute significantly to the total body burden to isocyanates and is always likely to occur when isocyanates are used at workplaces.

The uses with the highest inhalation exposure levels are HDI and its oligomers in coatings and MDI in spray foam applications. In both of these uses the isocyanates are applied by spraying. This confirms that high exposures are to be expected when isocyanate containing mixtures are sprayed or applied in high energy processes.

Relatively high inhalation exposure levels are also found for some uses of TDI such as in the manufacture of foam as well as in the manufacture of polyurethanes and PU composite materials and, in parts, for the use in adhesives. The exposure levels of MDI on the other hand are significantly lower for all of these uses. These findings are in line with the expectation that use of low volatile diisocyanates leads to lower inhalation exposure levels.

In general for most of the uses the majority of the measured data are quite low (near or below the LOQ). However, some relatively high exposure levels occur also in uses that appear to be well controlled at first sight (e.g. TDI in adhesives). Such relatively high levels of inhalation exposure seem to occur in an unpredictable manner in all sectors and uses. For example, when looking into the statistical evaluation data prepared by IFA for TDI more in detail in the work area groups for gluing there are 212 personal measured data for 2,6-TDI representative for more than six hours of exposure duration. Most of these measurement data (98.6 %) are well below the German limit value of $35 \mu\text{g}/\text{m}^3$ or even below the limit of quantification (83.5 %) (IFA, 2013). However, out of these data for the use of 2,6-TDI in glues quite high exposure levels were measured for gluing in the textile industry, where 25 % of the measured data were found to be above the limit value, with a 90th percentile value of $48.2 \mu\text{g}/\text{m}^3$ and a 95th percentile value of even $130 \mu\text{g}/\text{m}^3$.

Another example for relatively high exposure levels with no clear picture can be found in the IFA evaluation for HDI (IFA, 2012). Again, the majority of the measurement data are below the LOQ (92.9 %) and 99.5 % of the measured values are below the German limit value of $35 \mu\text{g}/\text{m}^3$. But for no apparent cause a conspicuous accumulation of measurements exceeding the limit value can be seen in the industry group glass; 9.3 % of the measured values (N = 54) were above $35 \mu\text{g}/\text{m}^3$ with a 90th percentile value of $26 \mu\text{g}/\text{m}^3$ and a 95th percentile value of $73.6 \mu\text{g}/\text{m}^3$.

It should also be kept in mind that measurement of airborne isocyanates is also particularly challenging and therefore some of the measurement data might be less accurate with respect to the sensitivity, hence resulting in some underestimation of the actual exposure levels at workplaces. This might be particularly true when it comes to assessing / detecting peak exposures to isocyanates. Especially when exposure peaks can be expected to occur on a regular basis (such as when opening machinery parts / starting or ending production etc.) this might lead to some systematic underestimation of the exposure situation and risk when no additional risk management precautions are taken.

This assessment is supported by the findings when considering the biological monitoring data as shown in the following tables. (Where possible the data were also expressed in same units to make comparability easier)

Table 55: Biological monitoring data for TDI in manufacture of foam (same as Table 28)

(Kääriä et al., 2001)	(Austin 2007)	(Tinnerberg and Mattsson 2008)	(Swierczynska-Machura et al. 2015)
0.05 - 39 nmol/mmol creatinine (total TDA in urine; \pm 0.05 - 39 μ mol/mol creatinine)	<0.05 - 1.6 μ mol/mol creatinine (total TDA in urine)	2.9 - 27.2 ng/mL (2,4-TDA in plasma) 8.2 - 62.1 ng/mL (2,6-TDA in plasma)	<LOD - 3.9 μ mol/mol creatinine (total TDA in urine)

Table 56: Biological monitoring data for MDI in manufacture of PU and PU composite materials (same as Table 19)

(Kääriä et al., 2001)	(Creely et al., 2006)	(Robert et al., 2007)	(Gries and Leng, 2013)	(Tinnerberg et al., 2014)
0.015 - 1.38 nmol/mmol creatinine (\pm 0.015 - 1.38 μ mol/mol creatinine; MDA in urine)	LOD - 12.64 μ mol/mol creatinine (MDA in urine)	LOD - 23.60 μ g/L (MDA in urine)	LOD - 16.2 pmol/g (ABP-Val-Hyd in blood) LOD - 125 nmol/g creatinine (\pm LOD - 14.14 μ mol/mol creatinine; MDA in urine)	0.5 - 8.4 ng/mL (MDA in urine) 0.4 - 19.4 ng/mL (MDA in plasma)

As discussed above, isocyanate metabolites can often be detected in biological monitoring samples even if the corresponding air monitoring measurements were below the limit of detection (see for example (Creely et al., 2006)) and by this also underlining the limited explanatory power of air measurements of isocyanates. The study by Creely et al. also confirmed that urinary levels of isocyanate metabolites of workers with observable dermal exposure were over two times that of workers who did not have evident skin contact, highlighting the significance of the dermal route when assessing the total body burden to isocyanates (Creely et al., 2006). Unfortunately, data on dermal exposure to isocyanates are scarce and there is no established standard for measuring skin exposure. Therefore, even if some measurement data are available comparison of the results is usually not directly possible.

B.10 Risk characterisation

B.10.1.1 Human health

B.10.1.1.1 Workers

According to the previous sections B.5 and B.9 several questions regarding quantitative hazard and exposure assessment cannot be sufficiently answered. On the one hand, there is no agreement on which sensitive predictive markers for diisocyanate related sensitisation to use as starting point for quantitative risk characterisation. This is one reason, why it is not possible to derive a threshold for respiratory sensitisation. On the other hand, uncertainties exist regarding the quantitative assessment of exposure. Although various measurement data exist for inhalation exposure, these measurement data only assess a part of the actual exposure that is relevant for respiratory sensitisation. Dermal exposure as well as inhalation peak exposure in most cases is not quantitatively assessable. The different exposure components can contribute alone or in combination to respiratory sensitisation. Therefore, Figure 5 shows all components as parts (partly with undefined size) of one column. The existing OELs do not cover this combined actual exposure.

Therefore, an approach comparing a DNEL or DMEL with inhalation and dermal exposure to derive risk characterisation ratios (RCRs) is not considered an expedient option for the endpoint of Resp. Sens. of isocyanates in this dossier (see also section B.5).

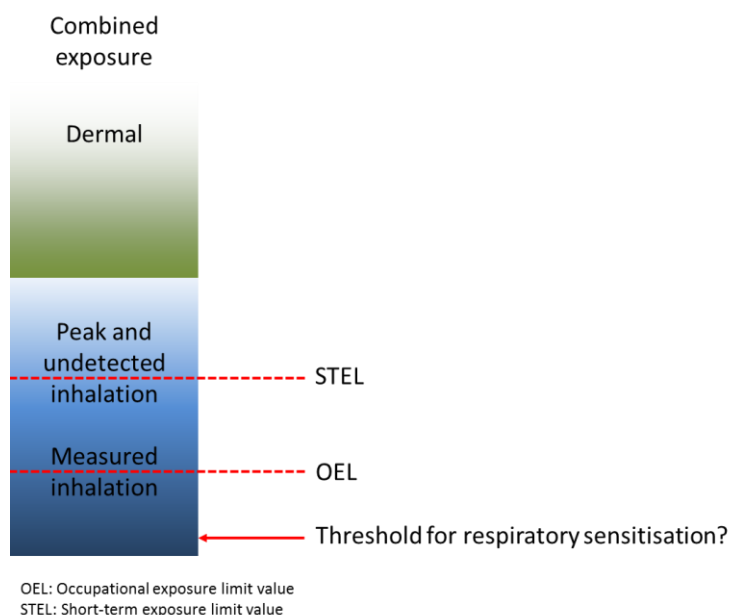


Figure 5: Relationship between toxicological and exposure related aspects of isocyanates

However, occupational asthma (OA) due to isocyanates is a problem identified worldwide and isocyanates are one of the commonest causes of occupational asthma in the EU (see Table 57). Therefore, in the following, the risk characterisation makes directly use of the occurrence of OA due to isocyanates in humans (workers in the EU). This approach is more straightforward than the usual RCR derivation, which is done for substances where human cases cannot be assessed directly or cannot be ascribed to the specific substance.

Table 57: Most common causes of OA in different countries

Country, data source	Causative agents of OA (proportion)	Reference
DE, German Federation of Institutions for Statutory Accident Insurance and Prevention	Year 2004 (n = 711 confirmed cases; n = 487 men) Men: flour/flour products (41.1 %), food/animal feed (9.2 %), isocyanates (7.8 %) Women: flour/flour products (17.9 %), hair dyes (11.6 %) hair fixing (11.2 %) Both sexes: flour/flour products (33.8 %), food/animal feed (7.5 %), isocyanates (6.8 %)	(Latza et al., 2007)
DE, German Federation of Institutions for Statutory Accident Insurance and Prevention	Year 2003, n = 835 confirmed cases Flour, flour constituents/products (35.9 %), food and feed dust (9.0 %), isocyanates (6.5 %), natural rubber latex (5.9 %)	(Latza and Baur, 2005)
FI, FROD	Years 1989-1995 (n = 2602 cases): animal epithelia, hairs or secretions (37.7 %), flours, grains, fodders (22.3 %), mites (5.3 %), di-isocyanates (4.8 %)	(Karjalainen et al., 2000)
FR, French Observatory of occupational asthma (ONAP)	The most common reported causative agents were flour (18.7% of cases) and isocyanates (12.7%).	(Société de Pneumologie de Langue Française, 2005)
FR, ONAP	Years 1996-1999 (n = 2178 cases): flour (20.3 %), isocyanates (14.1 %), latex (7.2 %), aldehyde (5.9 %), persulphate salts (5.8 %), wood dusts (3.7%)	(Ameille et al., 2003)
FR, RNV3P	Years 2001-2009: isocyanates (3.4-13.1 %), flour (12.1-19.3 %), hairdressing products (5.6 -12 %)	(Paris et al., 2012)
UK, THOR schemes	"For the period 2012-2014 and the previous two 3-year periods, 'vehicle paint technicians' and 'bakers and flour confectioners' were the occupations with the highest rates of new cases per year (THOR-SWORD). The most common causes of occupational asthma continue to be isocyanates, and flour/grain (THOR-SWORD)."	(HSE, 2015).
UK, SHIELD (West Midlands)	Isocyanates were the most frequently reported causative agents of occupational asthma between 1991 and 2011 (383 notifications; 23 % of total). For comparison, flour and amylase were reported as causative agent in 83 OA cases (5 %). Isocyanates were also the most common causative agents in every single year in the last years (2006-2012).	(Walters et al., 2015) (Midland Thoracic Society)

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Country, data source	Causative agents of OA (proportion)	Reference
UK, SWORD	Years 1998-2014: isocyanates (13.8 %), flour (8.6 %), wood dusts (4.3 %), solder/colophony (4.3%) Years 2012-2014: isocyanates (12.7 %), flour (10.8 %), cleaning products (9.0 %), wood dusts (7.2 %)	(HSE, 2016)
UK, Labour Force Survey	"The role of isocyanates and flour/grain in occupational asthma is further supported by more detailed questioning about the causes of work related illness included in the 2009/10/ 2010/11, and 2011/12 Labour Force Survey (LFS). Based on data from these surveys, of those with breathing and lung problems, approximately 13 % thought that "Airborne materials from spray painting or manufacturing foam product" had contributed to their ill health with a further 7 % citing "Dusts from flour or grain/cereal, animal feed or bedding (straw)"."	(HSE, 2015)
ES, Catalonia	Year 2002 (n = 174 cases): isocyanates (15.5 %), persulphates (12.1 %), cleaning products (8.6 %), wood dust (8.0 %), flour (7.5 %) latex (6.9 %)	(Orriols et al., 2006)
Canada	Year 2007: Isocyanates (17 %), wood dust (17 %), seafood (13 %)	(Roberge et al., 2009)

Quantitative assessment of OA induced by isocyanates

The request for occupational diseases due to isocyanates conducted by the DS is described in section B.5.6.5.3 Estimation of the number of cases by this approach is hampered by the uncertainties concerning the recording systems, the significant underreporting and the differences in isocyanate use between the countries. Therefore, in the following two further approaches are applied using different data sources.

These three different approaches to assess the occurrence of isocyanate OA in the isocyanate exposed workers in the EU can be assigned to two general categories:

A. Assessment of the occurrence of isocyanate OA per se

- Occurrence of isocyanate OA based on an EU-wide request for OA statistics (Approach 1)
- Occurrence of isocyanate OA observed in occupational epidemiological studies (Approach 2)

B. Assessment of adult-onset asthma in the population and quantifying the fraction that is due to occupational exposure to isocyanates (Approach 3)

Although uncertainties are inherent in such estimations, which have to be based on several assumptions, they are required here to estimate the magnitude of the problem.

Whereas approaches 1 and 2 are based on identifying individuals with diagnosed OA in a specific population, approach 3 estimates the occurrence of OA at the population level, but does not identify individuals with OA (Jaakkola and Jaakkola, 2012).

In each of these approaches the estimations are given as

- the absolute number of new OA cases due to isocyanates in the EU every year
- the annual incidence of OA due to isocyanates in the exposed workers

For this report the incidence (new cases within a certain time period) of asthma due to isocyanates is more interesting than the prevalence (existing cases at a particular time point). Therefore, "occurrence" of OA means incidence of OA here. For the estimation of incidence of OA two estimates are needed:

- the numerator representing the cases of OA
- the denominator representing the population at risk in which the cases develop (in person-years)

In addition, the estimated incidence is interpreted as measure of excess risk here. It is the incidence that additionally occurs in an exposed population due to isocyanate exposure.

One possibility is to use the data of occupational disease statistics (as nominator) and relate them to the number of exposed workers (denominator), which is realised in approach 1. This gives an estimate of the incidence rate if interpreting the denominator as person-years. This estimated incidence of isocyanate OA is an estimate combined for all industries and workplaces, irrespective of the exposure duration and the exposure level. It provides a mean incidence that covers the higher incidence in highly exposed jobs as well as the lower incidence in lower exposed jobs. Ideally, the number of person-years should be known (years of exposure for every individual). However when using data from registries or estimations of exposed workers, this often is not available.

Another source of information for disease incidences are longitudinal epidemiological studies. In these studies the new cases as well as the exposed person-years can be assessed directly in a defined study population. They may provide an estimate for the incidence at workplaces that were investigated in the study, but may be less meaningful for the whole working population (see below under approach 2).

In this report, incidence estimates are expressed as "annual incidence in %", meaning new cases per 100 persons per year.

Exposed workers (denominator)

The number of exposed workers in the EU is needed as a denominator to estimate incidence in approaches 1 and 3 and to estimate the absolute number of cases in approach 2. Table 68 in chapter D gives an estimation of the number of isocyanate exposed workers in the EU based on estimations by ISOPA. This gives a value of 1.6 million higher exposed workers. It is reported that between 0 to 30 % of isocyanate exposed workers have asthma (see section B.5.6.5.2). Therefore, it is assumed here, that about 10 % of exposed workers have already become diseased and therefore are not part of the population at risk that generates the new cases. After subtracting prevalent asthma cases 1.45 mio workers are supposed to

be exposed to a higher level of isocyanates and to be at risk. In the following this group will be designated as “high risk”.

As neither the DS nor ISOPA do have valid information on the change of exposed workers over the years, it is assumed for the calculations, that this number is constant and can be interpreted as person-years. Just like the number of cases is assumed to provide an estimate of the mean number in the EU per year, the number of exposed workers is assumed to be a mean number per year.

Approach 1: Number of OA cases related to the exposed population

The cases of OA due to diisocyanates (nominator) have already been estimated in section B.5.6.5.3. Based on 13 countries that provided data on occupational disease cases, the annual number of cases was extrapolated to the EU. This resulted in an average annual number of 270 cases (among these an estimated number of 235 respiratory disease cases). As it is known that occupational disease statistics are prone to underreporting (European Commission, 2013a), different assumptions (factor of 2 and a factor of 10) for underreporting were made. This gives a range of occupational diseases due to isocyanates in the EU between 540 and 2700 cases per year including about 470 to 2350 respiratory diseases, respectively.

Reasons for underreporting include for example poor recognition by physicians and workers or the worker’s fear of the consequences of a report for their job.

As a considerable underreporting of isocyanate induced OA has to be assumed (and this is also supported by the other approaches below), the annual incidence estimated here is based on the higher estimate for underreporting:

2350 new cases per year/1.45 million workers = 0.0016 new cases per year/worker = annual incidence of 0.16 %

This means, that **every year**, 16 out of 10000 isocyanate exposed workers of the high risk group become an asthma case due to isocyanate exposure.

This estimated incidence of isocyanate induced OA is an estimate combined for several industries and workplaces, irrespective of the exposure duration and the exposure level. It provides a mean incidence of the high risk group.

Approach 1 for four EU Member States that provided numbers of exposed workers

As a reply to the data request for this dossier, some countries provided data on the number of workers exposed to isocyanates in their country. Using the transmitted data in combination with the data on occupational diseases from the same country an incidence for this country can be roughly estimated. In the following estimations from four Member States (Belgium, Czech Republic, Austria, and Finland) are given, which presented the corresponding data.

Table 58 summarises the occupational disease cases for the four countries, which are presented in Table 12 in section B.5.6.5.3. For consistence with other estimations, only the respiratory diseases are counted here. Skin diseases were not considered. A percentage of 87 % of unspecified cases was considered to be respiratory diseases (for details see section B.5.6.5.3).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

In the following paragraphs country-specific information on the number of exposed workers that were provided to the DS by Belgium, Czech Republic, Austria and Finland are presented. They will be used as denominator in Table 62.

Belgium

For Belgium, the number of workers exposed to isocyanates can be estimated on the basis of the data reported by the “external services for prevention and protection at work” (ESPP). The ESPP register data concerning exposure at the workplace and by law. They have to send an annual report to the Federal Public Service Employment, Labour and Social Dialogue. For 2013, the reported number of workers exposed to “Isocyanaten - Diisocyanaten (methyilisocyanaat, toluendiisocyanaat, TDI, difenylmethaandiisocyanaat, MDI, hexamethyleendiisocyanaat, isoforondiisocyanaat)” extrapolated to the total number of Belgian employees was 17 600. This estimation was provided to the DS by the Belgian Federal Public Service Employment, Labour and Social Dialogue (November 2015), and it was noted that the quality of the data may be very poor and the obtained number not accurate. However, data provided by ISOPA provide a similar number of 13600 employees in the Belgium PU sector.

Table 58: Number of cases in four EU Member States that provided numbers of exposed workers (for details see section B.5.6.5.3)

Country	Data reported by countries				Own calculations	
	Reporting period (number of years)	Total cases [n]	Respiratory disease cases [n]	Unspecified disease cases [n]	Respiratory disease cases among the unspecified diseases*	Sum of respiratory diseases cases per year (column 3 + column 5)
BE	2002-2014 (13)	59	-	59	51	51
CZ	2000-2014 (15)	152	133	6	5	138
AT	2000-2014 (15)	59	59	-		59
FI	2000-2013 (14)	58	31	1	1	32

*assuming 87 % of unspecified cases being respiratory disease cases, rounded

Czech Republic

Data about occupational exposure to (di)isocyanates is available from the national registry of work operations (KAPR). In this registry, all workers potentially or actually exposed to harmful factors in the workplace are assigned one of four work categories. Recently only exposures to 2,4-TDI, 2,6-TDI, MDI and HDI are registered. In the past, several other diisocyanates were also registered in the KAPR system. The number of workers exposed to several diisocyanates is shown in the following table (status on 30.9.2015):

Table 59: National registry of work operations (KAPR) of the Czech Republic

Diisocyanate	Number of exposed workers
2,4-TDI	412
2,6-TDI	32
4,4'-MDI	1689
1,6-HDI	179
Sum	2312

Data provided to the DS by the Czech Ministry of Health, November 2015

Austria

In Austria, workers exposed to isocyanates must only be employed if a fitness test and follow-up examinations are carried out. Exposed workers are examined once a year. In the case of an abnormality the examinations are carried out in a shorter interval. This provides the possibility to estimate the number of exposed workers in Austria. According to Table 60 an average number of about 5268 persons per year are exposed to isocyanates, about 955 of them are exposed to MDI per year.

Table 60: Exposed workers in Austria

Year	Number of Examinations	Number of examinations in a shorter interval because of abnormality
2013	5356 + 791 (MDI) = 6147	1005 + 187 (MDI) = 1192
2014	4510 + 564 (MDI) = 5074	777 + 100 (MDI) = 877
Half 2015	2067 + 225 (MDI) = 2292	354 + 45 (MDI) = 399
Sum of 2015	4134 + 450 (MDI) = 4584	
Sum (numbers of 2015 were multiplied with 2)	14000 + 1805 (MDI) = 15805	2490 + 377 (MDI) = 2867
Mean per year	4666.7 + 601.7 = 5268.3	830 + 125.7 (MDI) = 955.7

Data provided to the DS by the Austrian Federal Ministry of Labour, Social Affairs and Consumer Protection, December 2015

Finland

Information on exposed workers in Finland is provided in Table 61. To calculate the person-years for the period of 2000-2013, the number of exposed workers given for the year 2001-2003 ($n = 1108$) was also assumed for the year 2000 and the number given for 2010-2012 ($n = 1474$) was also assumed for the year 2013. The sum of person-years for the years 2000-2013 then is: $1\ 108\ \text{persons} * 4\ \text{years} + 1213\ \text{persons} * 3\ \text{years} + 1170\ \text{persons} * 3\ \text{years} + 1474\ \text{persons} * 4\ \text{years} = 17477$.

The estimations in Table 62 are expressed as the number of new cases per 10000 person-years (py) and as annual incidence in %. The sum of cases in a specific period of time was divided by the sum of py for the same period of time. However, the single presented estimations must be interpreted with caution, because they are based on more or less uncertain numbers both for the cases and the exposed workers and have a different basis. Percentage of cases and exposed workers covered by the registry may vary considerably between the countries. So the differences in incidence cannot be attributed to true

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

differences in incidence between the countries, but are also to a great part determined by their reporting systems. Therefore, these estimations are only intended for giving an impression of the magnitude of the incidence in the EU.

Table 61: Number of isocyanate exposed workers by Finnish census occupation

Occupation	Number of exposed workers			
	Period	Men	Women	Total
Lasters and sole fitters etc.	2001-03	33	9	42
	2004-06	26	7	33
	2007-09	29	8	37
	2010-12	7	20	27
Foundry Workers	2001-03	101	11	112
	2004-06	113	12	125
	2007-09	89	10	99
	2010-12	68	5	73
Painters, lacquerers and floor layers	2001-03	885	69	954
	2004-06	979	76	1055
	2007-09	960	74	1034
	2010-12	1194	180	1374
Total	2001-03	1019	89	1108
	2004-06	1118	95	1213
	2007-09	1078	92	1170
	2010-12	1269	205	1474

Data provided to the DS by the Finnish Ministry of Social Affairs and Health (October 2015)

Remark attached to the data: "Data have not been entered for all agents and periods and therefore a missing value does not necessary indicate lack of exposure. The figures are usually based on calculations and require rounding to the precision of one or two integers when reported. The gender-specific figures are based on an assumption that exposure (prevalence and level) among men and women is similar within the same occupation."

Table 62: OA cases related to number of exposed workers in four Member States that provided data on numbers of exposed workers

MS	Data source for number of exposed workers	Sum of respiratory cases (period) ¹	Calculation of person-years ²	Estimated new cases/10 000 person-years	Estimated annual incidence in %
BE	ESPP register ("external services for prevention and protection at work")	51 (2002-2014)	17600 persons * 13 years = 228 800 py	2.2	0.02
	ISOPA, Excel Table (Jobs without Non-PU Sectors)		13600 persons * 13 years = 176 800 py	2.9	0.03

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

CZ	National registry of work operations (KAPR)	138 (2000-2014)	Number of workers exposed to several diisocyanates (status on 30.9.2015): 2312 2312 persons * 15 years = 34680 py	39.8	0.40
AT	Austrian Federal Ministry of Labour, Social Affairs and Consumer Protection (Number of examinations of workers exposed to isocyanates)	59 (2000-2014)	Mean per year: 5268 workers 5 268 persons * 15 years = 79020 py	7.5	0.07
		30 cases due to MDI ³ (estimated; 2000-2014)	602 workers exposed to MDI * 15 years = 9030 py	33.2	0.33
FI	Ministry of Social Affairs and Health	32 (2000-2013)	17477 person-years (2000-2013)	18.3	0.18

¹ see Table 58

² for details see text above

³ Of the cases in AT for which an isocyanate is specified, 50 % are due to MDI (n = 7). Assuming that also among the unspecified cases (n = 45) 50 % are due to MDI, it can be assumed that 22.5+7=29.5 ≈ 30 cases are due to MDI in Austria (2000-2014).

The estimations range from 0.02 to 0.40 % new cases per year. Considering that differences in both reporting of OD cases (nominator) as well as in the assessment of exposed workers (denominator) exist between the countries, this variation seems plausible. The estimation of 0.16 % for the whole EU presented above falls into this range. However, it has to be considered that (in contrast to the EU-wide estimate and to simplify the descriptions here) both underreporting of OD cases and accounting for prevalent cases has not been considered in Table 62, which results in lower estimates. These country-specific data might indicate that the EU-wide estimate based on OD statistics could be still a low estimate, even if using an underreporting factor of 10.

Approach 2: Occurrence of OA in epidemiological studies

Based on two reviews on respiratory effects due to TDI (Ott, 2002; Ott et al., 2003), longitudinal studies were selected that may be nearest to the present exposure situation: The 8h-TWA were < 5 ppb and therefore below most of the present OEL values in the EU and the DNEL for TDI and MDI provided by the registrants. However, short-term TDI concentrations were > 20 ppb (the present short-term exposure limit value e. g. in Germany and the acute DNEL). Undetected peak exposures are likely to be still present in recent workplaces (see sections A.2.1.2 and B.9). These studies were conducted in TDI production and foam production. Table 63 gives an overview of the studies. An overview of the studies reviewed by Ott et al. (2002) is given in Appendix 3, Table 3-2.

Table 63: Annual incidence of TDI-induced occupational asthma (taken from Ott 2002)

Study	Time period (facility)	Annual incidence of TDI-induced occupational asthma [%] (case identification)	TDI concentration [ppb], assessed by personal sampling
(Ott et al., 2000)	1980 - 1996 (TDI production unit)	0.7 (Assessment by physician)	0.3 - 2.7 (TWA; range by job) (STC > 20: 0.5 - 0.9 times/shift in moderate to high-exposure jobs)
(Bugler et al., 1991)	1981 - 1986 (PU foam production facility)	0.8 (Self-reporting)	0.9 - 2.6 (TWA; range by job) 22 % of 8-hr samples with short-term conc. > 20 and 10 % > 40
(Jones et al., 1992)	1982 - 1986 (PU foam production facility)	0.7 (Assessment by physician)	1.4 - 4.5 (TWA; range by job) (STC > 20: 3 % time in production and 0.1 % of time in finishing jobs)

STC: short-term concentration (9-12 minutes)

TWA: time-weighted average

In a Canadian case-control study based on compensation claims for OA due to diisocyanates (TDI, MDI, HDI) and covering 223 companies, an incidence of 0.9 % in 4 years (1984-1988) has been calculated (56 workers with claims accepted for OA out of 6308 workers), see Table 64 (Tarlo et al., 1997). This corresponds to an annual incidence of 0.2 %. For those companies that had claims, the incidence was 2.7 % in 4 years (= 0.675 % per year) in the high exposure companies (ever \geq 5ppb) and 2.2 % in 4 years (= 0.55 % per year) in the low exposure companies (always < 5 ppb).

Table 64: Incidence provided by a Canadian case-control study

	Incidence	
	As provided in the study (% in 4 years, 1984-1988)	Annual incidence in %
Overall (223 companies)	0.9	0.2
High exposure companies (ever \geq 5ppb) with claims	2.7	0.7
Low exposure companies with claims (always < 5 ppb)	2.2	0.6

The above cited studies indicate, that in companies keeping 8h-TWA below 5 ppb still asthma cases develop. This may be due to both the 5 ppb being not protective enough as well as peak exposures, undetected inhalation exposures and dermal contact.

The recent study by Gui et al. (2014) even indicates that keeping 8h-TWA below 5 ppb and peak exposures below 20 ppb may not prevent from sensitisation, and dermal exposure may contribute to the induction of the effect (Gui et al., 2014). Newly hired workers (n = 49) were evaluated pre-employment, after 6 months and after 12 months. Recorded 8h-TWA exposure to TDI was not higher than 5 ppb and peak exposures were below

20 ppb. After the first year of employment, 7 workers (14 %) had findings that could indicate TDI-related health effects (new asthma symptoms, TDI-specific IgG, new airflow obstruction, decline in FEV₁ ≥ 15 %). Twelve workers (25 %) were lost to follow-up. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up. Although this study is not suitable to derive an estimate for TDI-induced OA incidence, it shows that under current conditions in the EU, incidence of sensitisation might be much higher than indicated by epidemiological studies prone to healthy worker effect and indicated by occupational disease statistics.

In conclusion, according to this approach an incidence in the range from 0.2 - 0.7 % per year may be assumed. Applying this to the 1.45 million exposed workers in the EU gives **2900 to 10150** new isocyanate asthma cases in the EU per year in the high risk group.

Approach 3: Assessment of adult-onset asthma in the population and quantifying the fraction that is due to occupational exposure to isocyanates

In an international prospective population-based study the overall incidence of adult-onset asthma was estimated to be 2.2 per 1000 person-years (= 0.22 % per year; based on new asthma symptoms) or 0.99 per 1000 person-years (= 0.099 % per year; based on new asthma symptoms and bronchial hyperreactivity) (Kogevinas et al., 2007). The population attributable fraction for adult asthma due to occupational exposures was estimated to be in the range of 10 % to 25 % (Kogevinas et al., 2007; Toren and Blanc, 2009) and was also expressed as 250 – 300 cases per million people per year by Kogevinas et al. 2007. The working population in the EU is about 242.3 million people (Eurostat, 2015). With this, the new asthma cases due to occupational exposure each year can be estimated:

250 cases per million people * 242.3 million people = 60575.

Assuming that about 10 % of OA is due to isocyanates (see Table 65), the estimated number of OA cases due to isocyanates each year would be **6058**. Calculating with 300 cases per million people would result in **7269** cases, respectively. Applying these numbers of cases to 1.45 million workers gives an estimate of the annual incidence of 0.42 % or 0.50 %, respectively.

Table 65: Proportion of occupational/work-related asthma cases with isocyanates as (suspected) causative agents

Proportion (%)	Refers to	Reference
10-20	EU compensation statistics "Ten to twenty percent of asthma cases recorded in EU compensation statistics are due to isocyanates; this proportion has changed little over 20 years. It is not unreasonable to expect regulation of isocyanate use to improve through the introduction of REACH."	(Pickvance, Karnon et al. 2005)
23	1991 – 2011, SHIELD surveillance scheme for OA, West Midlands, UK	(Walters et al., 2015)
23	2012, SHIELD	(Midland Thoracic Society)
17	2007, Canada	(Roberge, Gravel et al. 2009).

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Proportion (%)	Refers to	Reference
15.5	2002, Catalonia, Spain	(Orriols, Costa et al. 2006).
14.1	1996-1999, Observatoire National des Asthmes Professionnels (ONAP), France	(Ameille et al., 2003)
13.8	1998-2014, SWORD, UK	(HSE, 2016)
3.4 - 13.1	2001 – 2009, French national network of occupational health surveillance and prevention (RNV3P), France	(Paris, Ngatchou-Wandji et al. 2012)
12.7	French Observatory of occupational asthma	(Société de Pneumologie de Langue Française, 2005).
12.7	2012-2014, SWORD, UK	(HSE, 2016)
7.8	2004, Germany, men	(Latza et al., 2007)
6.8	2004, Germany, both sexes	(Latza et al., 2007)
6.5	2003, Germany	(Latza and Baur, 2005)
4.8	1989-1995, Finnish Registry of Occupational Diseases (FROD)	(Karjalainen et al., 2000)

Strengths and limitations of the estimations

It seems plausible that the three approaches lead to different results (absolute number of cases per year and annual incidence) as all of them have different uncertainties.

Strength of approach 1 is that the actual cases that are reported to registries can be counted directly. However, numbers are heavily influenced by the national reporting systems (as well health care and workers' compensation systems), which is also shown by the four available country-specific estimates. In addition, a considerable underreporting has to be assumed adding uncertainty to the estimates.

In approach 2 cases are also observed directly (in epidemiological studies in factories) and here the risk of missing cases may be lower than in approach 1. However, due to healthy worker effects it is also plausible that the true incidence may be higher. Further uncertainties concern the fact that the exposure situation in the selected studies may not reflect the actual exposure of the exposed workers to which the incidence estimate is assigned to calculate the absolute number of cases.

In approach 3 isocyanate asthma cases are not counted directly, but are estimated as a fraction of all OA asthma cases. Underreporting therefore may have a minor influence on the estimate, as this concerns all OA cases and not only isocyanate asthma cases. However, the fraction may vary between the countries and is for example influenced by the frequency of other causative agents (such as flour).

Further disease cases not quantified in this section include the dermal occupational disease cases (see section B.5.6.5.3) as well as cases in the general population. A number of publications have shown that bystanders such as residents in buildings, where spray-foaming with diisocyanates has been performed, may suffer from sometimes severe health effects when protection measures are inadequate (see section B.9).

Subgroup spray painters

Table 66 shows estimates of asthma incidence in spray painters: Based on UK occupational disease statistics (SWORD) for 2005-2014, an incidence of occupational asthma in vehicle paint technicians of 66 new cases per 100 000 workers per year was calculated (HSE, 2016). For the period of 2009 to 2011, the calculated incidence also was 67 new cases per 100 000 workers per year. This is equal to an annual incidence of 6.6 new cases per 10 000 workers. Accounting for underreporting leads to higher numbers (66 per 10 000 workers per year if underreporting is assumed to be 90 %).

Table 66: Estimated incidences for spray painters

Occupational group	Data source	Annual incidence in %		Reference
			underreporting factor 10	
Vehicle paint technicians	SWORD, UK (2005-2014)	0.066	0.66	(HSE, 2016)
Spray painters	population-based study among adults in Northern Europe	0.85		(Lillienberg et al., 2013)

In a population-based study in Northern Europe the incidence of adult-onset asthma in men was estimated to be 1.3 cases/1000 py and a significant higher risk for adult-onset asthma was reported for spray painters (Hazard ratio (95 % CI): 7.5 (2.4-24.1)) (Lillienberg et al., 2013). Using the hazard ratio to calculate the incidence in spray painters leads to:

$$7.5 * 1.3 \text{ cases}/1000 \text{ py} = 9.75 \text{ cases}/1000 \text{ py}$$

The risk difference (excess risk) of asthma in spray painters compared to the general adult population then is:

$$9.75/1000 \text{ py} - 1.3/1000 \text{ py} = 8.45/1000 \text{ py}$$

This can be interpreted as meaning that in spray painters, there are 8.45 new asthma cases due to the spray painting job in 1000 py (0.845 % of the workforce per year). It has to be kept in mind that other substances than isocyanates that are also present at spray painting jobs may contribute to this asthma incidence.

Table 67: Summary table of estimated occurrence of isocyanate OA in the EU (as number of new cases per year and as annual incidence)

	Approach of OA assessment				
	Assessment of OA per se			3 Assessment of asthma in the population and quantifying the fraction due to isocyanates	
	1 OD statistics	2 Epidemiological studies			
New isocyanate asthma cases in the EU per year (n)	235 ¹	2350 ¹	2900 – 10150		6058 ² 7269 ²
Exposed workers in the EU (n) ³	1.45 mio				
Annual incidence in the EU (%)		0.16	0.2 – 0.7 ⁴		0.42 0.50

¹ Estimated number is based on the reported cases per year in the 13 countries that provided data on disease cases. After extrapolation to the EU a value of 270 cases (includes respiratory as well as skin diseases) is estimated. Based on the available information the percentage of respiratory cases is estimated as 87 % of total cases, the yearly number of respiratory disease cases is estimated to be 235. Due to a significant amount of underreporting this number does not reflect the real amount of OA cases in the opinion of the DS and is therefore coloured light grey. Using an overall factor for underreporting of 10 leads to the estimate of 2350 new respiratory disease (OA) cases per year.

² Depending on the estimate of the incidence of adult-onset asthma

³ Without low exposed workers and 10 % prevalent asthma cases

⁴ In studies where TWA exposure was mostly < 5 ppb, but peak exposures existed. This may be similar to the actual exposure scenarios at the workplace today. Recent studies indicate that due to healthy worker effects true incidence may actually be higher than observed in studies (Gui et al., 2014).

Conclusion on risk characterisation

Although the incidence of isocyanate asthma has decreased over the last decades, there is still a significant number of new cases of isocyanate induced OA every year throughout the EU. Depending on the assumptions which are made in the different approaches, it is estimated that the absolute number of new cases lies in the range between **2350 and 10150**.

The annual incidence (excess risk) of asthma due to isocyanates in workers corresponding to this absolute number of new cases exposed to isocyanates (excluding low exposed workers) is estimated to range between 0.16 % and 0.7 %. This means, that **every year**, 16 to 70 out of 10000 higher exposed workers (and even more in special occupations such as spray painters), become new asthma patients due to isocyanate exposure. The Dossier Submitter considers this as unacceptably high.

C. Justification for action on a Union-wide basis

This has been discussed in Section A.2.2.

D. Baseline

Exposed working population

According to data collection performed by ISOPA there are around 4.34 million potentially exposed workers in several industrial and professional sectors (see chapter G). According to ISOPA, this figure covers approximately 80 % of the market. That means that \approx 5.2 million workers have contact with isocyanates or isocyanate based products. It should be emphasised that depending on the use sector the exposure to workers is not on an equal level and risk for workers varies. The following differentiation on risks groups between the sectors is presumed for the socio-economic analysis in Table 68. The more or less reliable quantification of risk is solely available for the use sectors at relatively high risk.

Table 68: Overview on exposed workforce in sectors

Sector	Workforce	Healthy workers*	Risk for healthy workers
Construction chemicals	1 800 000	1 620 000	Low
Automotive repair (excl. motor vehicle refinish (MVR))	1 800 000	1 620 000	Low
Other sectors (e.g. metal treatment, insulating panels etc.)	1 608 306	1 447 475	High**
All sectors	5 208 306	4 687 475	

Source: ISOPA, data modified (see chapter G)

*Free of asthma. Corrected for asthma prevalence of 10 % in exposed population. See Section B.5.6.5.2 for more details

**0.2 – 0.7 %/yr

An exact number of new asthma cases per year is not available. Estimations of the annual occurring asthma cases in the baseline scenario can be performed by the methods explained in Section A.2.1.3, Table 3. As explained in that section, in this approach it is distinguished between healthy workers in activities of relatively high risk (about 1.45 million) and those that are less exposed (either by using products with lower potential risk for exposure and/or because they use diisocyanate products only during short irregular periods (about 3.6 million). Calculations regarding new asthma cases are only based on the high potential risk group due to lack of data for the incidence rate for lower exposure group.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

In Table 69 the outcome is summarised:

Table 69: Overview on models for estimation of the annually occurring new asthma cases

Method	OA Assessment Method 1 with reported numbers	OA Assessment 1 with under-reporting factor 10	OA Assessment Method 2	OA Assessment Method 3
Incidence rate (%/yr) relating to healthy workers	0.02	0.2	0.70	0.42
New OA cases/ yr	235	2 350	10 150	6 058
Cumulative number of cases after 20 years	4 700	47 000	203 000	121 160

Source: Estimation based on methods presented in Section A.2.1.3, Table 3

All three estimation methods are appropriate for the forecast modelling of number of asthma cases in the baseline and restriction scenario. However, it should be emphasised that the forecast certainty of the used methods varies. In the following the aspects of certainty regarding forecast on occurring number of diseases in the next 20 years is discussed.

Table 70: Discussion on estimation methods

Method	Advantage	Drawback
Empirical based risk / reported statistics on OA (method 1)	Certain quantitative evidence for occurring asthma caused by isocyanates.	Underreporting; Represents solely the minimum level of occurring asthma/skin diseases. Underestimation in forecast modelling is possible.
Empirical based risk / study sample (method 2)	Extrapolation of annual number of cases is possible; Enables the anticipation of the high bound for asthma cases number.	Uncertainties regarding to representativeness and generalisation to all companies. Overestimation is possible.
Indirect, top-down approach (method 3)	Covers all sectors, empirical representative. The risk on overestimation is low.	The fraction of causative agent is not exact identifiable. Some data are study-based. Direct anticipation is not possible.

The results of the method 1 cover only the reported or registered occupational asthma and skin diseases induced by isocyanates. As some underreporting is assumed, these figures on

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

the risk of isocyanates may pose only the minimum level of possible asthma cases induced by isocyanates. In the previous section B.10 "risk characterisation" and according to (Nicholson et al., 2010) the issue on underreporting of the occupational diseases is highlighted. The adjustment of the annual registered cases with an underreporting factor would support to perform an estimation of the real magnitude of the asthma cases. Furthermore the application of the incidence/sensitisation rate method provides an estimation of the highest level of asthma cases, which can potentially occur. The extrapolation method 2 is an indirect method supporting the verification of other used extrapolation methods, which supports the estimation of a magnitude of occurred asthma cases caused by isocyanates.

If no further action is taken, it is likely that the number of occupational asthma cases (either being estimated from official statistics or estimated via epidemiological investigations) in the population at risk will remain of similar magnitude in the years to come. This will lead to an accumulation of health related costs caused by new cases on top of the already existing burden of cases that occurred in previous years. The calculation on basis of 0.7 % provides a high number of cases. This bears a risk of overestimation. On the other side, the modelling of asthma cases on basis of the low bound for incidence rate would run the realistic risk of underestimation. In Section A3 a value of 6500 cases was chosen as being the best representation of the real burden of yearly new asthma diseases.

Due to existing uncertainties regarding the quantitative estimation of the incidence rate for all relevant industrial sectors, the proportionality of the socio-economic impacts is also demonstrated for the case example of the European motor vehicle refinish sector (MVR). Recently, this sector has been researched intensively and relatively robust data (SWORD) based on the registered asthma cases for the estimation of the incidence rate for asthma cases are available.(HSE, 2015) However, underreporting cannot be excluded in this case too. In addition, the studies on the behavioural-based training effectiveness for the spray painters were performed in the motor vehicle refinish sector and the results will be used to forecast the development of the health benefits. Nevertheless, the estimation of the occurring asthma cases will also be performed for all relevant industrial and professional sectors, which are indicated in chapter G.

E. Impact Assessment

E.1.1 Introduction

This chapter gives an overview on methodical approach applied in the impact assessment of three options for a restriction proposal.

The modelling approaches, input factors and the results on economic as well as on human health impacts are presented in the chapters below. The possible distribution impacts are estimated on basis of an assumed model. The mainly social impacts are included in estimation of human health impacts.

In principle in the scope for estimation of the socio-economic impacts are the following two scenarios:

- Baseline scenario – “business as usual” – i.e. without additional measures
- Restriction scenario (RMO1, RMO2, RMO3).

The socio-economic impacts result from the delta of the baseline and the restriction scenario. The impact assessment (forecast modelling of costs and benefits) is limited to the EU-28 and a time period of 20 years. Environmental impacts are not in the scope of the socio-economic analysis. All estimations for benefit and costs will be presented as net present values (PV). Based on the analysis of alternatives for diisocyanates and the feedback from the stakeholders, a major shift towards the use of isocyanate free products is not foreseen anytime soon. Therefore such effects are not taken into account.

Table 71: General situation of the PU value chain

Use Sector	Number of companies	Number of employees	Economic value added (million Euro) 2013	Direct economic Impact (RMO3)
PU Chemicals Producers	200	10160	3900	<input checked="" type="checkbox"/>
SUPPLIERS/SUBCONTRACTORS	800	47410	2800*	<input checked="" type="checkbox"/>
Direct PU Customers	4600	68850	17600	<input checked="" type="checkbox"/>
Downstream Users	no data available	5 139 456**	no data available	<input checked="" type="checkbox"/>
Final Producers of PU-based finished goods	18400	184 000	31400	-

Source: ISOPA

*lack on data for value added, refining of market value with the share of (50 %) for value added, derived from PU Chemicals Producers.

**derived from ISOPA's data.

E.2 Risk Management Options

The following risk management options are identified and analysed:

- RMO1: implementation of restrictive conditions of use described in the proposed Appendix on **“Trainings and Measures”** (mostly affected are workers at high risk) and in the Appendix on **“Exemptions”** (mostly affected are workers at low risk).
- RMO2: only implementation of restrictive conditions of use according to proposed Appendix on **“Trainings and Measures”** Note that in this case all workers need to be trained, without an option for exemption.
- RMO3: complete ban of the use of diisocyanates and diisocyanates based products
Note: This is an extreme option that will only be analysed semi-quantitatively

The socio-economic impacts result from the delta of the baseline and the restriction scenario. The impact assessment (forecast modelling of costs and benefits) is limited to EU-28 and a time period of 20 years. Environmental impacts are not in the scope of the socio-economic analysis. All estimations for benefit and costs will be presented as present values (PV). Based on the analysis of alternatives for diisocyanates and the feedback from the stakeholders, a major shift towards the use of isocyanate free products is not foreseen anytime soon. Therefore such effects have not been taken into account. The different restriction options were assessed according to their criteria regarding effectiveness, practicality and monitorability. As a result of this assessment, the restriction option RMO1 is proposed. As a further option authorisation was considered but not further assessed mainly because substitution is considered to be not really feasible (either no alternatives at all, or alternatives which will also have health risks).

E.3 Alternatives

E.3.1 Identification of potential alternative substances and techniques

In line with the hierarchy of control measures, the very first Risk Management Measure (RMM) that should be considered is the option to look for substitutes for isocyanate products. Despite the fact that the Human Health (HH) issues related to the use of isocyanates have been known for decades, the reality is that PU products based on diisocyanates have found an increasing number of applications, as is indicated by the continuous growth of the volume of the substances, at a rate at or above the growth of the general economy (Avar, 2008). This suggests that substitution, if any, has not progressed very far. This is also borne out by replies to a “Call for Evidence” (See chapter G) where nearly all comments about alternatives indicate that “these do not exist”. In some cases comments were made that isocyanate based products had been introduced as substitutes for products with more hazardous characteristics, like formaldehyde resins. Similar remarks were made by experts from the German building industry, stating that in their area the increasing use of isocyanate based products was welcomed because they replaced traditional solvent based products (e.g. adhesives), that had a history of recurring severe accidents because of flammability of the solvent and/or post-application emissions. Although isocyanate based products require high attention for RMMs during application, in the end they are considered to present less risks compared to the traditional solvent based products.

The use of polyurethanes (PU) based on diisocyanates in so many applications makes it nearly impossible to identify one or more alternatives that cover all these uses. The attractive properties that have led to the growing number of uses of PU plastics based on

the use of low molecular weight isocyanates (fast reaction, properties adjustable in a wide range, reduced necessity for the use of volatile solvents, no emission after full cure, etc.) are not easily matched by other substances. However, upon closer inspection, it appears that in some areas alternatives are available and in some cases in commercial use. This is especially true in the area of building products (e.g. sealants). The situation around alternatives in the building industry is described in more detail in Appendix 6, based on a research project from an external consultant. Also the recent review from the Danish Ministry of Environment and Food (Møller Christensen et al., 2015) shows a similar picture. Although this report focuses on consumer uses of MDI, most of the products discussed may also find use in the professional sector.

A number of potential alternatives deserve special mentioning because they are regularly mentioned in this respect:

(1) Epoxy resins

These are polymers resulting from the reaction of multifunctional Epoxy Resins (based on bisphenol A or bisphenol F) and multifunctional primary or secondary amines ("epoxies"). Also in this case a polymer is formed by reaction of low molecular weight substances under moderate reaction conditions and over a wide range of application temperatures.

(2) Hybrid Non-Isocyanate Polyurethanes (HNIPU); (Hybrid) Non-Isocyanate Polyurethanes (NIPU, resp. HNIPU)

These polymers contain urethane bonds that are not formed in the reaction of isocyanates and polyols, but by the reaction of cyclic carbonates and primary amines. See Figure 6

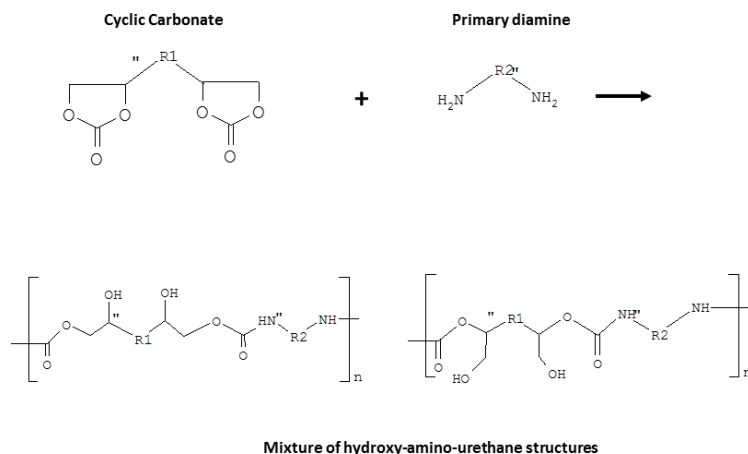


Figure 6: Reaction with formation of urethane bonds without isocyanates

Although the structure of the polymer contains different side groups compared to traditional polyurethanes, there is some similarity and at least some of the properties

may be comparable. In principle this opens the possibility to obtain polyurethanes without the risk of sensitisation by the use of low molecular weight diisocyanates.

(3) Modified Silanes

Silanes can be used to produce polymers in the way shown as a basic representation in Figure 7.

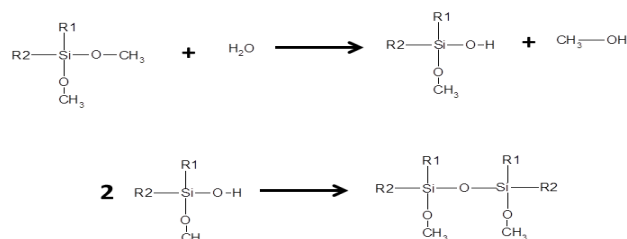


Figure 7: Moisture induced crosslinking of modified silanes

In this figure the Group "R2" may also be an oligomeric backbone derived from PU chemistry (i.e. containing urethane bonds). Reaction of the silane with moisture or with a prepolymer with hydroxyl groups may liberate methanol. Also in this case a "hybrid structure" between silane and PU may be obtained avoiding the use of diisocyanates, although these are still needed to prepare the PU part of the backbone.

(4) Monomer reduced Isocyanates

During normal preparation of prepolymers (see section B.2), the final product consists of isocyanate terminated polyurethane prepolymers of varying chain lengths and a still significant amount of residual free diisocyanate monomer. However, it is possible to adjust the molecular weight of the prepolymer in such a way that higher molecular weight species are dominant. In addition, the residual monomer can be stripped off by suitable post-treatment. This results in a (usually high viscous) polymer with still some terminal isocyanate groups, but of a composition that does not require labelling as RS1.

E.3.2 Assessment of alternatives

E.3.2.1 Availability of alternatives

E.3.2.1.1 Epoxy resins

These resins are widely available on the market from a large number of suppliers.

E.3.2.1.2 Hybrid Non-Isocyanate Polyurethanes

Although this type of chemistry has already been discussed for more than forty years, (Figovsky et al., 2012) it still has not made any significant inroads into the market. The reasons for this disappointing development have been listed in a recent review of this technology (Figovsky et al., 2012): The necessary building blocks (cyclic carbonates based on the reaction of diols or epoxy resins with carbon dioxide) are not generally available. Apart from some carbonate solvents, none of the cyclic carbonates from diols or epoxy resins that are needed for this technology seem to have been registered under REACH so far.

E.3.2.1.3 Modified silanes

This is a technology that is well established for sealants in the building industry (see Appendix 6). Products using this chemistry are widely available. It remains unclear what the release of methanol in confined spaces will mean for risk to HH. For a discussion of the properties of such polymers it is referred to Appendix 6 or (Møller Christensen et al., 2015). Still, sealant foams based on this technology seem to present one of the few cases where an alternative comes at least close to comparable PU products.

E.3.2.1.4 Monomer reduced Isocyanates

Because of the necessary post-treatment these products are more expensive in the market. Experts cited in Appendix 6 also indicate that their availability in the market is limited

E.3.2.2 Human health risks related to alternatives

E.3.2.2.1 Epoxy resins

In the aspect of safe handling, a major drawback of low molecular weight epoxies is the fact that dermal contact with the uncured product may induce skin sensitisation as an occupational disease. In fact, especially within the building industry, this disease appears to be more wide spread than the respiratory sensitisation because of the use of Isocyanates (Ziegler and Kersting, 2012). In practice, this means that there may be applications where use of both PU and epoxies is feasible, but the risk of skin sensitisation means that epoxies cannot be considered as a general low risk alternative for polyurethanes.

E.3.2.2.2 Hybrid Non-Isocyanate Polyurethanes

In view of the fact that the basic building blocks for this chemistry have not been registered under REACH, this means that their toxicology profile is largely unknown. In the scarce available product literature (Nanotech, 2008) it appears that the few products in the USA that seem to be commercially available, and which claim to use this technology, are in fact two component epoxy/amine systems where the amine hardener contains some of the amine terminated NIPU that has been synthesised separately. The final use of the system is then similar to the normal epoxy/ amine systems. Effectively this results in polymers that are part epoxy/amine, part NIPU (therefore the term Hybrid NIPU (HNIPU) is used). Unfortunately, this means the use of such products may suffer from some of the HH problems of the epoxy chemistry (skin sensitisation). In addition, apart from the sensitisation issues of the epoxy resin itself, many of the primary amines

mentioned as potential curing agents are strongly corrosive or skin or respiratory sensitisers by themselves.

E.3.2.2.3 Modified silanes

It remains unclear what the release of methanol in confined spaces will mean in terms of risk to HH.

E.3.2.2.4 Monomer reduced Isocyanates

In view of the very low content of free diisocyanate, these products are to be considered as having a lower potential for sensitisation. However, they still need to be labelled with EUH 204 – “Contains isocyanates. May produce an allergic reaction”

E.3.2.3 Technical and economic feasibility of alternatives

E.3.2.3.1 Epoxy resins

Epoxies have very good anticorrosive properties and are widely used in coatings for metal, as well as in many other areas (e.g. electronics, composites, etc.). Because of their strong bonding to substrates and low shrinkage, they also have uses as binders, adhesives, sealants and fillers in the construction and building industry. However, their versatility and the possibility to fine tune the properties by the selection of suitable building blocks is more limited than for polyurethanes. And although the temperature resistance of epoxies is better than that of PU, in most cases they are more brittle (Zhang and Evans, 2003). Resistance to UV light is much less than that of aliphatic diisocyanates (Mailhot et al., 2005). This means that their use in coatings is limited to primers and intermediate layers. Where exposition to UV light is to be expected, a weather resistant topcoat (in many cases again based on aliphatic isocyanate) needs to be applied. Both epoxies and PU have found their own niches of application where the properties they achieve are specifically desired.

E.3.2.3.2 Hybrid Non-Isocyanate Polyurethanes

Despite the ongoing R&D work on this chemistry, currently it cannot be considered as a feasible alternative as too little is known about its performance in various applications. As far as epoxy resins are used as a major component, it may be expected that these products will also suffer from the rather poor weatherability of such resins and the reaction between these carbonates and the second compound (a primary amine) is much slower than that of Isocyanate/polyol. A few practical applications of such products have been described in the USA (Nanotech, 2016) but it remains unclear how they perform against “true” diisocyanate based PU.

E.3.2.3.3 Modified silanes

For a discussion of the properties of such polymers it is referred to Appendix 6 or to (Møller Christensen et al., 2015). Even if these products do not seem to be a full alternative to foams based on diisocyanates, sealant foams based on this technology seem to present one of the few cases where an alternative comes at least close to comparable PU products.

E.3.2.3.4 Monomer reduced Isocyanates

See Appendix 6.

E.3.2.3.5 Other information on alternatives

See Appendix 6 and the report mentioned there.

E.4 Restriction scenario(s)

The proposed restriction concerns all uses of diisocyanates as monomer and as component in formulations. According to the Appendix "Exemptions" and "Trainings and measures" for workers which are directly exposed to diisocyanates it will be mandatory to attend a specific training (in average 8 hours). Target of the trainings is increased compliance to safe use of diisocyanates. In the restriction scenario according to RMO1 adjustments regarding the conditions for placing on the market of diisocyanates are expected. Manufacturers and importers as well as trade associations of relevant downstream users have already indicated their commitment to such an approach and have started internal consultations in developing such training materials²⁵. Thus a risk reduction for workers is to be expected. The "exemption" procedure has the aim to identify the diisocyanates based products with very low potential on risks. The behavioural stakeholders' response is considered under economic impacts. There are already indications that some industrial sectors are considering to develop formulations that have monomer content < 0.1 wt%.

E.5 Economic impacts²⁶

Economic impacts in RMO1 and 2 result predominantly from the additional costs for the training measures. In addition, costs may incur for testing of the products potentially eligible for an exemption according to the proposed Appendix Exemptions. The investments in planning, installation and maintenance of the technical equipment are not in the scope of the economic impact analysis, because these do not imply additional efforts under this risk management option beyond what is already required for companies in the established Directives 89/391 EEC and 98/24/EC. In addition to such technical requirements, which create the basis for workers' protection, the proposed RMO1 and RMO2 support these by the explicit training obligation. This should lead to an improvement in handling standards of diisocyanates, with less potential for unrecognised situations of high risks. Organisational measures will support this further.

The following factors have been identified as cost drivers for the estimation of additional costs of the considered restriction measures:

²⁵ First drafts are available on request.

²⁶ Where in the following discussion "EUROSTAT data" are mentioned, this refers to the online data bases of EUROSTAT (<http://ec.europa.eu/Eurostat/web/structural-business-statistics/data/database>). From the complex structure of this database the specific data referred to (e.g. per NACE code, etc.) can be extracted. Excel sheets containing only the specific data indicated can be provided upon request.

E.5.1 Training Measures in Appendix “Training and measures”: (valid for RMO1 and RMO2)

Different options exist to attend and complete the trainings. A specific company may choose for one or the other form, depending on its circumstances. This will result in different costs.

The following training options were identified and analysed as part of the economic impact assessment:

- a) Courses at an established education centre / competence academy etc.
- b) Integration of the training part into the product presentation/ supplier’s technical customer support
- c) Training course external (off-site) incl. training material and certificate
- d) Training on-site (in-house course with a commissioned trainer), in addition to the usual mandatory EHS training. Because this consumes additional time, this will generate extra costs compared to standard EHS trainings.
- e) E-learning
- f) Train the trainer principle including in-house instruction of the workers

On company level the following factors have been identified as cost drivers for the additional costs depending on the training measure chosen:

- Direct costs: training fee or trainer’s daily fee in price level of each member state
- Indirect costs: time spendings for training/instruction and sector specific figures on gross value added per employee (productivity loss values indicated in Table 72)
- Company size or number of workers per firm /course
- The number of suppliers for isocyanate containing products (in option b)
- Frequency (validity period of training) (according to Appendix “Training” every four years)
- E-learning: one-off costs for software creation and annual running costs for system maintenance, further efforts are additional program adjustments e.g. after 10 years of implementation.

The total training costs of the proposed restriction measure are calculated by use of an estimate for the number of companies and exposed workers concerned in the EU-28.

To avoid double counting, it is assumed that further efforts e.g. for creation of training materials are already included in calculated various training fees.

Costs will be incurred each year at the same level. For our analysis we will consider cumulative cost effects over a period of 20 years. – leading to a increase over time, with the slope determined by the yearly costs of the various options considered.

E.5.1.1 Estimation of costs units

The quantitative estimation of the input parameter is performed on the basis of empirical data obtained by literature screening or by expert judgement. In most of the calculations secondary data sources were used. These were generated by adjustment factors which are based on statistical and market data, specific study findings and experts' indications.

Table 72: Estimated cost units and required personal time spendings (RMO1 and 2)

Option	Concept	Direct costs (fee for a commissioned trainer [€/group] or course fee [€/participant])*	Indirect costs: Investment of personal time [personnel h]
A	Course at established education center / competence academy etc.	<u>870</u>	8
B	Integration of the training part into the product presentation/ supplier's technical customer support	425 or <u>870</u> for trainer	8 for "trainer" 4 for "worker" 4 for "supplier"
C	Training course extern incl. training material and certificate	425	8
D	Training at work (in-house course with a commissioned trainer)	<u>870</u>	3
E	E-learning	Annual fixed costs for all: 22 000	4
F	train the trainer principle including in-house instruction of the workers	425	8 for "trainer" 4 for "worker"

* Underlined: costs per group of 20 persons. Not underlined: per person
Data source: Table 73, Table 74, Table 105, Table 106, own estimation

An important factor in the options a, d and f is the number of participants in one course session with a commissioned trainer. Due to economies of scale, the higher the number of participants at the training course, the lower is the total cost for each single option. A supposedly near-optimum for acosts/benefit ratio can be achieved by grouping 20 participants in one course.

The estimation of the daily fee for a commissioned trainer is carried out on the basis of EUROSTAT statistics on the indicator "Turnover per person employed" in the relevant sectors identified by NACE codes. It is understood that the most employees of such firms are trainers. For this purpose certain assumptions are made and documented. The following economic sectors were analysed.

- Professional, scientific and technical activities (NACE Code M)
- Management consultancy activities (NACE Code M70.2)
- Engineering activities and related technical consultancy (NACE Code M72)
- Other professional, scientific and technical activities (NACE Code M74)
- Other professional, scientific and technical activities NACE Code M74.9.0)

- Even on inquiry at EUROSTAT, data Educational support activities (NACE Code 85.60) are not available

Assumption made: 50 per cent of the working time (230 working days) are training days/ days of active consulting, or account days. The number of account days does not differ from MS to MS. The data preparation is embedded in Table 105. The distribution of the isocyanates' use or market share within the EU-28 is taken into account, because no data on the distribution of workers within the EU-28 are available. This information is needed to calculate the representative training costs in the EU-28. However, it is supposed that the number of exposed workers correlates with the isocyanates volume in use by each Member State. The data on market segments for 10 Member States was obtained from ISOPA and weighted according to the market share with the price level in each member state respectively. The isocyanate market share of others Member States is weighted according to the averaged price level of these Member States (Table 106).

Estimation on fee for training course (option c):

The estimation of the fee for training course in accredited institutions is performed on the basis of an analysis of the offers and prices for comparable trainings on the German and British market, e. g. TÜV, Haus der Technik, HSL (HSL, 2016).

Table 73: Estimation of training fee in option c

Option c	Fee for training course extern incl. training material and certificate	Ø course fee € per person per day incl. learning material	Weighted and on the EU price level adjusted fee
	Germany	450	426
	UK	540	424
	Average		425

The costs of training in vehicle repair /refinish sector (MVR) are only calculated for options a, b, c, d and f. Activities carried out in this sector are professional. These are mostly spaying applications which surely would require the proposed measures of the group 2 or even 3. According Appendix Trainings and Measures, e-learning is not suggested as a training measure for these risk groups. Therefore the training measure by e-learning is excluded in the costs calculation from the case sample "vehicle refinish sector".

Estimation of costs components for e-learning (option e)**Table 74: Calculation of annual direct costs for e-learning training**

Option e	Cost components e-learning	Total costs €	Annual costs* €
	Concept and software creation	250 000	1 533
	Update / program maintenance	400 000	20 000
	Additional costs, program adjustments 10 years after implementation	62500	642
	Total annual costs in € 0-10 years		21533
	Total annual costs in € 10-20 years		22175

*assumptions: 20 years investment, 4 % interest rate

Table 75: Data basis for estimation of sector specific indirect costs for 10 working days (EUROSTAT)

Class (NACE Rev. 2)	Description	Value added per employee* [€]	Personnel cost per employee* [€]
C16.21	Manufacture of veneer sheets and woodbased panels	2008	1399
C20.30	Manufacture of paints, varnishes and similar coatings, printing ink and mastics	2722	1808
C20.52	Adhesive production	2896	1723
C22.21	Manufacture of plastic plates, sheets, tubes and profiles	2320	1560
C22.90	Manufacture of Plastic Products	2098	1392
C25.61	Treatment and coating of metals	1874	1298
C31.03	Manufacture of mattresses	1494	1087
C31	Manufacture of furniture	1650	1230
C33.15	Repair and maintenance of ships and boats	2276	1548
G45.20	Maintenance and repair of motor vehicle	1442	988

Class (NACE Rev. 2)	Description	Value added per employee* [€]	Personnel cost per employee* [€]
All relevant sectors in average (excluded construction and automotive repair)	Random sample \approx 50 % coverage of compiled sectors	1762	1380

*230 working days per year are assumed.

Data source: EUROSTAT statistics on annual detailed enterprise statistics for industry

E.5.1.2 Key parameters for estimation of costs units for RMO1 and RMO2

Table 76: Costs parameter – all relevant sectors

Total number of exposed workers	5 208 306	Remark on assumptions for calculation of costs and benefits
Construction chemicals	1 800 000	In scope of Appendix "exemptions"
Automotive repair (excl. vehicle refinish)	1 800 000	In scope of Appendix "exemptions"
Other sectors	1 608 306	To train according to Appendix "trainings"
Productivity loss* all sectors (excluded construction and automotive repair)		22** €/h
Productivity loss in construction and automotive repair		23*** €/h

*EU-28 wide incl. Norway, weighted with the factor for isocyanates market share within the MS and sector specific number of workers, see Table 106.

**based on data provided in Table 75 and Table 76

*** based on data provided in Table 75 and Table 78, assuming 8 working hours/day

The construction sector represents 50 % of the impacts considered in scenario RMO2 with regard to e-learning. It is assumed that the data from the construction sector are valid for both sectors.

Table 77: Costs parameters for example MVR sector – Appendix "Trainings and Measures"

Input parameter motor vehicle repair /refinish sector	
Number of exposed workers	150 000
Number of body shops (own estimate*)	40000
Productivity loss**	18 €/ person h

*based on (OECD, 2011)

**based on data provided in Table 75.

Table 78: Estimation of costs units in construction sector

Class (Nace Rev. 2)	Description	Value added per employee* (€)
F41.20	Construction of residential and non-residential buildings	1 769
F43.22	Plumbing, heat and air-conditioning installation	1 785
F43.32	Joinery installation	2 015
F43.33	Floor and wall covering	1 881
F43.34	Painting and glazing	2 082
F43.91	Roofing activities	1 798
Weighted average	All sectors	1 837

*230 working days per year are assumed.

Data source: EUROSTAT statistics on annual detailed enterprise statistics for industry. To receive EU-28 values the country specific values are weighted according to market shares of isocyanate consumption in the respective country (see Table 106) (Adjustment factors).

From the economic perspective the annual costs of training are identified as operating costs. Therefore this type of costs is not considered as investment costs. The total costs of each option are shared amongst four years. For the adequate comparison with benefits the present values of costs are calculated with the discount rate of 4 % for the period of 20 years.

E.5.2 RMO1: Testing costs for identification of the exempted products ("Appendix Exemptions")

The following factors are essential for the estimation of additional costs:

- Initial number of product groups to be tested, or candidates for exemption
- One-off costs: testing the frame formulations and accordingly the conditions of use
- Annual running costs: additional efforts for data preparation and communication due to launching the new products and/ or information update

Table 79: Appendix Exemptions – estimated input variables (source own guess on basis of personal communication in expert group for Appendix Exemptions)

Number of product groups	Initial testing costs [€/product group]	Annual running costs [€/a]
80-120	50000 - 100 000	500 000 - 1 000 000

The anticipation of figures is underpinned by consideration on examples from the construction chemicals sector (e.g. GISBAU data base) and the expert discussion group on exemptions.

Table 80: Costs estimation of Appendix Exemptions

Cost category	Total investment [€] million	Annual costs [€] million	Assumption
one-off costs	5-10	0.4-0.74	Interest rate 4 %; 20 years investment period
running costs		0.25-1	Annually 500-1000 products a 500-1000 € per product
Total annual costs for product exemptions according to Appendix Exemptions		0.625-1.74	Assumed average of total costs round € 1.2* million/yr

*not PV

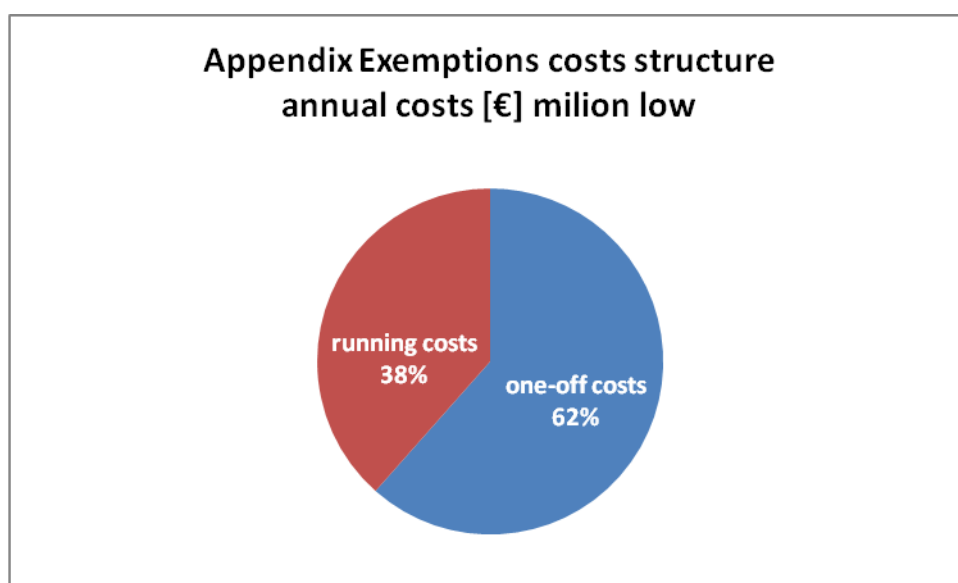


Figure 8: Expected risk reduction according to the proposed Appendix Exemptions

Costs modelling for implementation of the proposed Appendix Exemptions

The total additional costs will incur in a range between €9 and €24 million for a time perspective of 20 years. This means that in average as PV €0.825 million will annually incur (estimation in Table 80).

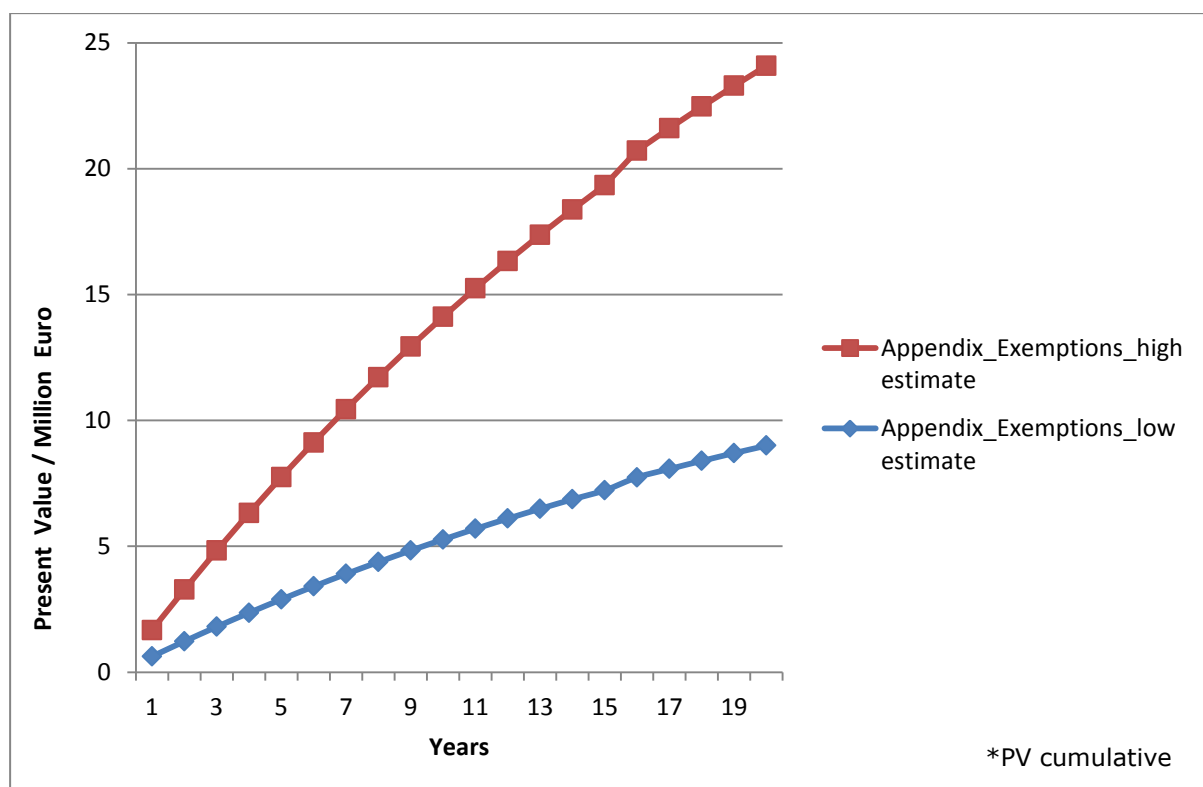


Figure 9: Forecast on costs incurring for identification of exempted products based on isocyanates.

Additionally around €1.2 million will incur annually for identification of exempted products. It should be noted that most expenditures will be made for the initial procedure for already existing products on the market. Over time the invested costs would be less worth due to inflation.

RM03: Elimination in the supply chain (complete ban)

PU-products made from isocyanates (i.e. foam mattress, adhesives, furniture coatings and vanishes / coatings, construction foam, textiles etc.) contribute to a very high living standard in modern society and have become an essential factor in the daily lives. The consequences of this theoretically possible option would therefore be a partial shift to alternative products which are mainly based on epoxides and acrylates. As described above in the section "Alternatives" these chemicals have hazardous properties themselves. The study on alternatives shows that, as far as feasible alternatives are available, they are not without the risks themselves and in some cases several present risks similar to isocyanates. Consequently, in most cases no significant improvements for human health and thus positive benefits for the workers can be expected after the implementation of RM03. As described above, in the construction sector there is an alternative product for foam insulating or construction which is based on a silane terminated polyurethane. However, the risks arising from possible methanol emissions are not clarified until now. On the other side, in the cases where no suitable alternatives are available, a relocation of manufacturing PU-based articles outside the EU-28 states seems to be most likely market's reaction on the ban of the diisocyanates in use in EU-28. For instance, within the stakeholder consultation (cf. section G.3) the Europur Association has reported that in Turkey, Russia and Ukraine the production capacities for PU based products are already available. This fact underpins the assumption regarding a

probable replacement of the manufacturing location of PU-based products. Thus, the socio-economic consequences are obvious. A complete ban would relocate the risks arising from diisocyanates use to the non-European countries, probably with lower worker protection standards. On the other hand, the EU-28 would lose the innovative PU-market and correspondently the value creation within the union. Another issue could arise from increasing import dependency. The PU-products do not contain diisocyanates anymore and could be imported into the EU-28. The possible consequences are highlighted in detail in the section "Stakeholder consultation".

However, several products such as sealants for the application in the construction sector could not be reimported, because of their diisocyanate content being more than 0.1 % [w/w]. They have recently become more important, because of the continuing construction growth particularly in middle/Eastern Europe. Furthermore, due to a complete ban, the use of modern PU-adhesives which contain isocyanates would also not be possible within the EU. Such products replaced the traditional welding and are being used in modern joining technology by robots e.g. in the aerospace sector.

Wider economic and health impacts

In case of a complete ban of isocyanates from the EU market an extreme disturbance of the smooth-running processes within the supply chain where 240 000 (ISOPA, 2014) companies are involved is to be expected. Particular the direct producers, suppliers/subcontractors, direct isocyanate users e.g. foam, textile/PU-plastics producers are directly negatively affected because their business model is ultimately based on direct use of isocyanates. For instance, the non-use costs of isocyanates could be characterised on the basis of investments made in production plants which should be then modified for other production or sunk costs due to non-utilisation. Theoretically the customer for PU primary products could import them into the EU. The efforts for a complete shift of the supply chain processes including suppliers certification/qualification in non-EU countries are associated with additional overhead / administration costs / time and resource consumption e.g. for transport of PU-based goods to the European market. According to the trade balance of €95.1 billion (ACEA, 2016), the European Automotive sector is one important PU consumption sector, which is in direct competition with the global market players. The additional costs of reimport of PU-based goods would negatively affect the competitiveness of the European automotive industry. On the other hand, the EU-28 would lose the innovative PU-market and correspondently the value creation within. The direct manufacturing and use of isocyanates in the EU market contribute annually to value added creation of round €24.3 billion in the EU-28. Another issue can arise from increasing import dependency. For the reasons discussed above PU products could be imported into the EU-28. The possible consequences in detail are highlighted in section "Stakeholder consultation".

Social and economic benefits of the manufacturing and use of PU-based products in Europe

In addition, the European PU industry contributes to the diversification of the European market (Avar G. 2008). This ability enables strengthening the economic climate in the EU, particularly in economic crisis periods, but also strengthens the EU's competitiveness in the global market. Recently, PU-systems have provided impulses for innovation inter alia of technologies beside exclusively the polyurethane production. The demand for specific / individual solutions of high quality on the market led to product specification and diversification of the PU-based products but also to increased know-how and R&D activities e.g. development of complex multi-layers textiles or insulating materials (Avar G. 2008). Enterprises improved the efficiency of the manufacturing technology, because

of a demand for high scale production plants for PU feedstock and PU materials and cost pressure. For instance, the new gas phase phosgenation for producing toluene diisocyanate requires 80 per cent less solvent and consumes 60 per cent less energy as conventional production plant. The manufacturing technology of flexible foam has been recently improved. Energy consumption is down by 25 per cent and VOC content has been reduced. Depending on the information source, the market share of PUR mattresses is 40 per cent (2007) – 60 per cent (Stiftung Warentest, 2007). Due to high resilience their social benefit is obvious and replacement of the product is not possible at the moment. Further development to improve the features of mattresses requires R&D activities, which are concentrated in Europe creating social and economic benefits. Generally, PU-based products do not make only a notable contribution to creation of value added on the European market, but also enable the efficient use of resources in Europe. Thus, in order to reduce the weight of vehicles and correspondently the energy consumption and CO₂ emissions, several components based on polyurethanes are being used. For instance, roof module concepts for cars enable a weight reduction of 25 per cent compared to the conventional steel sheet for roofing and lightweight yet resilient trunk compartment floors. The weight could be reduced up to 80 per cent using the PUR-sandwich-construction of trunk floors, spare wheel covers and sunroofs. The vehicle body parts are being produced from PU-based materials as light-weight alternative for steel or Sheet-Mold-Compound even for use in utility vehicles. A further advantage results from costs-efficient processing of the parts in vehicle production, thereby realising parts of high geometric complexity. A further benefit results from using the PU-based insulating materials in engine compartment for reduction of the noise level. Insulating materials based on rigid foam are more efficient due to lower thermal conductivity than other products on the market. Thus, their use provides benefits for space savings in refrigerators, buildings, pipelines etc. The use of polyurethanes in a track superstructure system cuts noise pollution and maintenance costs. Due to technical features of PUR-based elastomers, their use enables for instance the production of durable wheels and rollers which are used in the transport sector.

In the manufacturing of upholstered furniture PUR-based materials coated with elastomers make the use of PVC based shell including softening superfluous agents. The manufacturing process is thereby even more efficient.

In summary, polyurethanes are a versatile material group which provide incentives for engineering innovation and/or optimisation of their use technology (processes/ engineering/ plant). PU-based products contribute to sparing use of resources due to their mechanical robustness, protection features, lightweight, cost-efficient processing flexible treatment, etc.

Complete ban of diisocyanates use – rough estimation of costs

The overall costs resulting from a complete ban of diisocyanates are too complex to estimate because diisocyanates are in wide dispersive use. Therefore, the economic impacts of a complete ban are quantitatively indicated on basis of statistics for economic value added, which is being directly created by diisocyanates use as monomer for goods production in the EU-28. Additional indicators such as value of lost jobs or the share of investment costs and extra costs for supply chain reorganisation may be used to quantify the economic impacts. In the DS's opinion the largest economic impact in the EU-28 results from value added loss. For modelling of the costs over 20 years in RMO3 on average 1 per cent for annual growth of the value added is assumed. This premise is underpinned by the information provided by ISOPA and market forecasts. Although the forecasts provide a higher growth rate in the short term, market saturation is expected in the long term.

Partial costs of RMO3 (example of vehicle refinish)

The overall costs and benefits for human health resulting from a complete ban of isocyanates are too complex to estimate because isocyanates are in wide dispersive use. Furthermore, firm specific data on investments made and additional costs due to a shift to import of PU-based products are not available. Nevertheless a partial or a use specific costs-benefit analysis of RMO3 is possible.

As described in the section “alternatives” the PU-based coating replaced the traditional high VOC systems, whose emission characteristics and content are already regulated in in the EU market (VOC Directive 2004/42/EC). Further possible alternatives are acrylates, epoxides, and amine resins. However, very often these coating systems are being applied in combination with isocyanates (See Appendix 6). For instance, in the case of a complete ban of isocyanates based repair coatings, a further consequence would be premature obsolescence of motor vehicles in the EU-28. According to various sources (CEPE personal communication), the repair of a car body always requires the use of diisocyanate based coatings:

Quote:

“(…)The final layer is a two component clear coat, which will provide the strength and the durability of the repaired coating. The hardeners used for the clearcoats are isocyanate based. There are no isocyanate free technologies available. In a few cases, the basecoat / clearcoat combination can be replaced by a two component solid colour coating, but this technology from the 80's and 90's is hardly used anymore. It will not work with metallic or pearlescent coatings. Especially in the last layer of the coating (the topcoat), isocyanate based hardeners are inevitable for a durable invisible repair. Today there are no alternatives in the market. Research on isocyanate free systems carried out by several companies, never resulted in a successful product. It is unlikely that a ban on isocyanates would lead to alternative technologies in the coming 10 years, with the same durability, technical performance and low VOC emissions. This option would require a massive investment from the industry and new technologies with new chemicals and drying techniques (UV-curing). Such new inventions may not necessarily be less hazardous than the currently used isocyanates. In addition most end-users will require training is using new technologies. One component products (air drying one component) have been used in the past, but due to the poor durability on the one hand and the impossibility to repair an effect coating (metallic or pearlescent) and their high content of VOC's, making them non-compliant, these products have disappeared almost completely from the EU market. Also it should be noted that what was common practice 40 years ago (weekly manual car wash and subsequent waxing and polishing), may not be embraced by the car owners today. For this option the cost would increase (lengthier repair process), the quality would go down, reducing the economic life of cars and waste would increase (more VOC emissions, re-repair and polishing). These coatings use the same isocyanate hardeners. The average lifecycle of cars will reduce drastically since damaged cars can no longer be repaired, so they start rusting, etc.” (CEPE within the stakeholder consultation)

Taking into account the received information on the possibility to replace the isocyanate based coating the following two assumptions on consequences can be considered in the so called “**non-use scenario**” of coating in the vehicle refinish sector:

- No use of isocyanate based coating and no repair of damaged vehicle, means a premature obsolescence (around 5 years per vehicle, estimated on basis of ACEA statistics on car age).
- Shift to alternatives with a significant lower performance (poor durability) and similar risks.

The second consequence does not seem to provide a risks reduction potential. Therefore solely the impacts of the first consequence are considered. According to statistics (ACEA, 2016) there is a trend of increasing service life time of cars. It is estimated that a one year of car service time lost results in a value loss of about 2 100-2 800 Euro. This estimation is based on the information that currently "Cars in the European Union are on average 9.65 years old" (ACEA, 2016). Further assumptions are: average price of about € 20 000 – 26 000 for a new car, a residual value of € 2 000-3 000 for an accident damaged car at interest rate of 4 % and on average €1 000 body repair investment for next 5 years. Assuming normal Gaussian distributions for age of damaged vehicles (excluded the cars with an age over 10 years) and the traffic incidence rate of 4.68 per cent from Germany, a requirement of 50 per cent for car body repair, the economic consequences of a ban for isocyanates based coating based would then result in costs about €5.3 billion per year. A conservative scenario with assumed 3 per cent of the traffic and 50 per cent of the need for car body repair provides a value for costs of about €5.3 billion per annum. This is only a rough estimate. The costs might be higher, because conservative assumptions have been made.

Input parameter for costs calculation and estimation of the restriction costs according to RMO3

Table 81: Approach for estimation of total value loss based on concerned vehicle number

Input parameter	Low bound	High bound	Remark/data source
Traffic incidence rate [%]	3	4.68	4.68 example from Germany(Statistisches Bundesamt, 2016) ≈ 45 mm vehicle in use (ACEA(ACEA, 2016) 2.1 million annual number of damaged vehicles (2014); 3 %: best guess for low bound
Number of vehicle in use within the EU-28 in relevant age [million]	172.26	none	287.1 millions in use, deducted 40 % in age above 10 years
Expected number of damaged vehicles per year [mm]	5.2	8.1	Extrapolation of input parameter
Fraction of vehicle required for body refinish [%]	50	75	Own guess
Vehicle value per year[€]	2100	2800	Excluded residual value of €2000 and 3000 and repair investment of €500 or €1000; rough values
Estimated annual costs per damaged vehicle [€ billion]	5.5	17	Extrapolation of input parameter

E.5.3 Economic impacts - Results

It should be stressed that depending on the training option the share of indirect costs due to loss of productivity (i.e. the time spent on training instead of productive work) varies between 20 % and 90 %. Using the basic data in Table 72 and Table 76 the following results are obtained:

Table 82: Overview on results of costs estimation for each RMO

	RMO1*	RMO2*	RMO3
Additional costs (PV, million € in average per year)	25.6 – 165.4	79 – 218	18 126
Remark	For training (high risk group)* and exemption procedure (low risk group)	Only training, but for a larger collective (high and low risk groups)	At least. For overall EU market

*Range refers to the various training options listed in A.3.1.3.1

The proposed Appendix “Exemptions” would predominantly affect the sectors applying construction chemicals and automotive repair (≈3.6 million workers, excluded MVR sector). According to the screened literature and the expert group on the Appendix Exemptions, the risks arising from the use of products based on isocyanates in both sectors are supposed to be very low. According to the information of experts from Germany, there is no high concern for occupational asthma in uses relevant for isocyanates in the building sector. However, to create more certainty on products risk or to identify the products with lower risks for use in these sectors such an exemption procedure as proposed is needed. Furthermore it can be supposed that the incentive to use the exempted products with lower risk will increase. If no exempted products are identified, each downstream user will be obliged to attend the training. In such case e-learning may be an appropriate model for training.

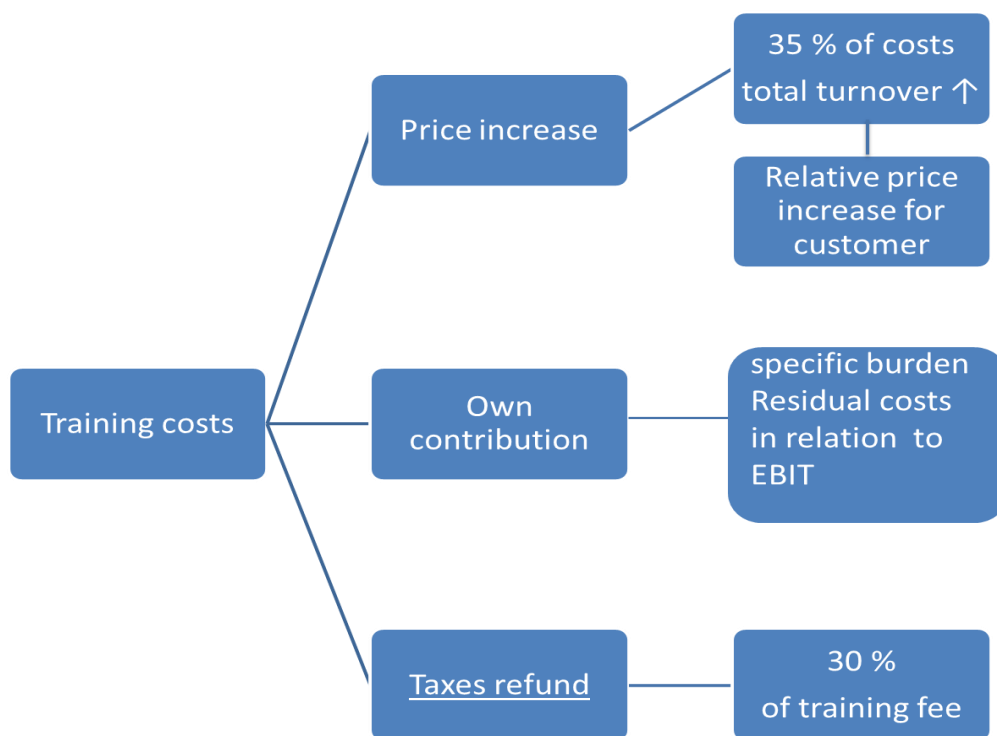
In case of RMO2 the additional costs due to training are calculated for the e-learning option.

E.5.3.1 Other impacts, practicability and monitorability

A.5.3.1.1 Distributional impacts

Distributional effects and proportionality of the costs at firm’s level

The following distribution model is assumed for analysis of the distributional effects and proportionality of the additional costs due to proposed training obligation according to the Appendix Trainings and Measures. According to the model 35 per cent of total costs will be passed on to customers with the consequence of unit price increase e.g. for service. On the other side, the relative costs increase for a customer is to be analysed.



EBIT = Earnings before interest and taxes

Figure 10: assumed scenario for distributional effects and assessment approach of proportionality of the incurred costs at firm's level

The analysis of distributional effects for additional costs due to the proposed Appendix Exemptions is carried out using another approach. It will be analysed how the costs units of each product will increase. For this purpose, the total annual costs are to be set in relation to the overall number of relevant products sold or manufactured per year. It is assumed that at least 100 million products are being annually placed on the European market.

Taxes refund in some Member States

In Germany and Austria (and probably also in other countries) the expenditures for trainings are partly being refunded by taxes, because they will be accepted as business expenses.

RMO1: Analysis of distributional effects and proportionality of the training costs at firm's level

The distributional effects are demonstrated for body shops in the MVR sector. The EUROSTAT statistics on turnover and gross operating surplus (\approx EBIT) are used to calculate the relative economic burden for customer as well as body shop. It is assumed that not all costs can be passed on to the customer. This is a conservative assumption. It might be possible that more costs could be allocated within the supply chain. The distribution model postulated in Figure 10 is applied to calculate single values representing distributional effects. Under the condition that only 35 % of the costs

(excluded taxes refunds) could be passed on to customers, the share of own costs in relation to EBIT provides an indication to what extent the additional costs would impair the profit of the body shop. Even the most expensive training option c would cause a price increase with up to 62 Eurocent per service. Assuming 100 per cent of residual costs would be charged to unit prices, the customer has to pay €1.76 more for an automotive repair/refinish service. The specific costs burden for a body shop as well as for customer is very marginal. The analysis in depth of distributional costs effects demonstrates that the costs are proportional to the affected firms.

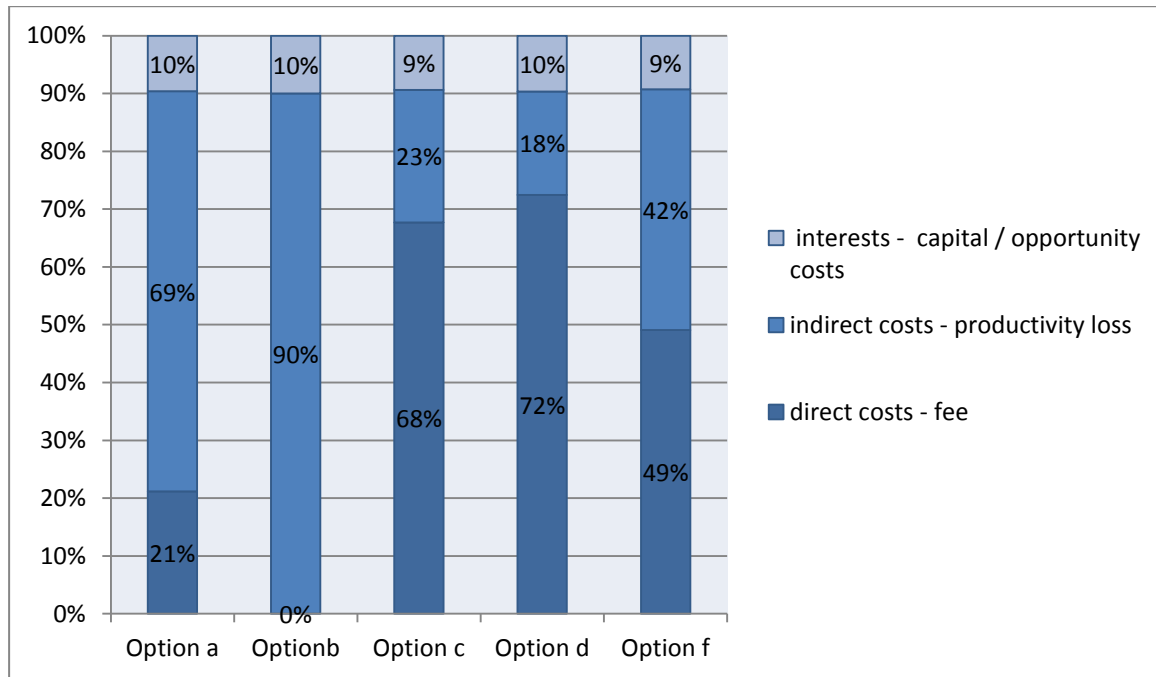


Figure 11: Structure of training costs for a worker in the vehicle refinish sector

Table 83: Analysis of distributional effects on case sample of a MVR body shop*

Impact / Training Option	Total costs for a training per body shop incl. 4 % interests	30 % tax refund of the training fee/ duty trainer	Required relative increase of annual turnover	Price increase ¹⁾	Share of own costs in relation to EBIT
a: Course at established competence academy etc. (e.g. education centre)	€880	€50	0.06 %	€0.23 ²⁾	0.1 %
b: Integration of the training part into the product presentation/ supplier's technical	€337	none →no direct costs for a body shop	0.02 %	€0.09	0.4 %

Impact Training Option	Total costs for a training per body shop incl. 4 % interests	30 % tax refund of the training fee/ duty trainer	Required relative increase of annual turnover	Price increase¹⁾	Share of own costs in relation to EBIT
customer support					
c: Training course extern incl. training material and certificate	€2 737	€500	0.15 %	€0.62	2.7 %
d: Training at work (in-house course with a commissioned trainer)	€1 270	€240	0.7 %	€0.28²⁾	1.2 %
f: train the trainer principle including in-house instruction of the workers	€750	€120	0.04 %	€0.17²⁾	0.75 %

*assuming: on average 4 workers per body shop shall be trained

1) 35 % of residual training costs allocate on turnover in next 4 years

according to EUROSTAT 127 000 turnover and 13670 gross operating surplus (EBIT) for nace code G45.20

2) customers expenditures per automotive service €400 (Gibson et al., 2014), therefore it is assumed that 318 services are performed per year. Relative and absolute increase of expenditures per service

E.6 Human health and environmental impacts

E.6.1 Humans Health impacts

The methodological approach for the estimation of the monetary value of health effects (according to the model presented in Figure 12) enables the comparison of the benefits which result from the cost savings in the restriction scenario. It is constituted of certain influencing factors presented in the figure.

It must be explicitly noted that this model for estimation of the number of asthma cases is not based on an exposure-risk-relationship. The factor "risk" is derived from empirical data such as statistics and studies on reported asthma cases (See section "risk characterisation").

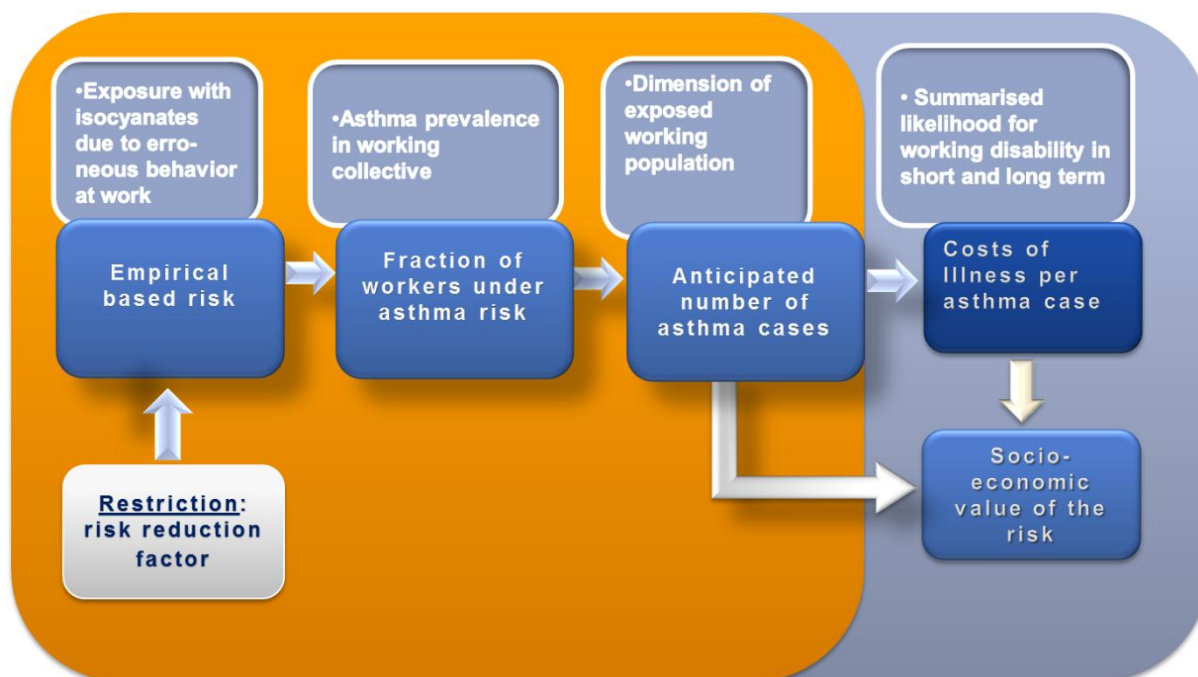


Figure 12: Methodical approach for estimation of human health impacts

E.6.1.1 Risk reduction capacity

Effectiveness of the measures expresses the potential to avoid a certain fraction of asthma cases in the future relative to the baseline.

The estimated number of asthma cases in both scenarios (business as usual and restriction), which are induced by the contact with diisocyanates at the workplace, is the crucial input parameter for the calculation of the avoided socio-economic costs by the restriction measure. Thereby it should be emphasised, that the annually occurring asthma cases accumulate in a “pool” of asthma sufferers in the baseline and restriction scenario.

Because the restriction concept focusses on specific mandatory training measures, it is important to discuss insights on effectiveness of such measures in general and in particular how these insights can be transferred to the current restriction proposal.

Effectiveness of training measures in general

Various studies on the effectiveness of training are available. In general, a conceptual model of OSH training may comprise a stepwise process of acquisition of new knowledge on hazards and safe behaviour, modification of attitudes/beliefs, and behavioural change. A successful training measure reduces unsafe behaviour and accident risks or exposure to hazardous substances resulting in a lower accident rate or lower rate of occupational diseases.

In systematic reviews undertaken by NIOSH (USA) and IWH (CA) the effectiveness of trainings and education of workers for reduction of occupational accidents and diseases were analysed (Cohen and Colligan, 1998; Robson et al., 2010) and a recent meta-

analysis covering 28 evaluation studies published between 2007 and 2014 (Ricci et al., 2016). The included studies cover a broad range of educations, skills and occupations, for example construction workers, carpenters, health care workers, clerical workers/computer users, hairdresser. The trainings most often combine class room lessons with different forms of active teaching including feedback and advice to learners. Safety and prevention trainings e.g. for construction workers and nurses mostly also included practical exercises and supervised training sessions.

All interventions showed positive, statistically significant results regarding the effect of the trainings on the knowledge level. The results regarding attitudes were rather mixed showing positive and negative results both with small and large effects. A positive effect on behavioural change (though with a varying level of significance) could be confirmed by most of the studies.

Regarding training methods, those inducing a larger engagement of the trainee (e.g. by including hands-on exercises, structured group discussions and feedback to the trainee) have an up to three times greater impact on learning success and finally on effectiveness of trainings (Burke et al., 2006; Vignoli et al., 2014).

Further important variables that were proven to have a positive influence on behavioural change were a.o. presence of an expert trainer, a longer length of the training session and a relatively small training group (less than 25 participants).

Evaluation results for the direct health impacts of trainings are not always easy to determine. However, evaluation studies that have been published generally show considerable impacts. In an overview of the effects of behaviour based safety methods in a wide range of industries (Sulzer-Azaroff and Austin, 2000) accident and incident rates were reportedly reduced by <10 - 85 % (see Table 1 in this reference).

In a study from HSE (Fleming and Lardner, 2002) 33 studies were reviewed that focussed on a reduction of accident numbers. In widely varying industry sectors (wholesale bakeries, machinery production, packaging production), behaviourally based safety approaches (also including the Antecedent, Behaviour, Consequences (ABC) model), were found to result in a reduction of accidents of up to 85%. Apart from obtaining management support to the programs as an essential element that was critical for the outcome, other factors that were common to successful approaches are listed in Table 84 below (table taken from the reference indicated above):

Table 84 : Overview of reduction of accident rates in various industry sectors

Case study	Risk reduction	Techniques/Approach
US Wholesale Bakery	<ul style="list-style-type: none"> - the injury frequency rate dropped from 53.8 to 10 per million man-hours worked - at least 80% reduction 	<ul style="list-style-type: none"> - Behavioural analysis - behavioural observation - checklist describing safe and unsafe behaviours - Independent, trained observers measured baseline levels of safe behaviour - Groups of employees took part in a thirty-minute training session, - Slides demonstrating safe/unsafe behaviour, focusing on behaviours with the lowest baseline level. - Feedback at work from supervisor - Employees' responsibility for observing and providing feedback

Case study	Risk reduction	Techniques/Approach
US Sugar-Cane Machinery Manufacturing Plant	<ul style="list-style-type: none"> - Average behavioural safety performance improved from 62 to 95% - decrease in accident rates - cost-benefit ratio (1:8) 	<ul style="list-style-type: none"> - Observations of employee behaviour were conducted by independent external observers and a company safety supervisor - Training was provided in which the checklist, observation method and safe/unsafe behaviours were explained - Regular feedback on safety performance was displayed
UK cellophane manufacturing	<ul style="list-style-type: none"> - 74% reduction in those accidents directly linked to the safe behaviours 	<ul style="list-style-type: none"> - At-risk behaviours were pinpointed by analysing the previous two years' accident records: type of accident, place of injury on the body and time - Identified: behavioural causes of accidents (e.g. not wearing eye protection) - Verification of the at-risk behaviours (from accidents analysis) by Interviews with a sample of the workforce - Identification by interview of additional at-risk behaviours not evident from accident records - Employee observers were recruited from the site, and each was provided with two days of theoretical and practical training (trained observer) - Goal-setting: with trained observers in meetings to establish and agree target levels of safe behaviour

Two evaluation studies on the reduction capacity of training measures with regard to cases of occupational asthma and dermatitis were considered as of specific relevance for the training measure considered in this restriction. These are pre-/ post-evaluation studies, where evidence for the effectiveness was considered as sufficient.

a) Effectiveness of a nationwide interdisciplinary preventive programme for latex allergy (Latza et al., 2005)

An interdisciplinary awareness campaign (duration: 2 years) with nationwide activities on several levels was set up aiming at replacement of powdered natural latex gloves with powder-free gloves with a low latex allergen content. Target group of the campaign were healthcare workers only in the non-public healthcare sector. For the campaign an information brochure for workers and informational material for lecturers was developed, including a video-tape for nursing schools. In addition, the effectiveness of the program was increased by practical advice and counselling regarding glove management for the target group of health care workers. Furthermore, the messages and the material were distributed by trade fairs, and regional events at 12 medical centres. The general public was informed by the media (popular press), and co-operations with academic institution and legislative authorities within occupational safety and health was set-up.

The program evaluation covered the change in glove-wearing behaviour and the number of occupational diseases (recognized and accepted for compensation), based on compensation claims for occupational diseases. During the campaign the use of powder-free and low-protein latex gloves increased. Two years after the campaign, the number of occupational skin and airway diseases in the groups being targeted had dropped by an amount of 25 %. A reduction of 46 and 60 % was reached after three, resp. four years.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Groups not included in the campaign did not show this reduction. Use of the concepts used in this project was recommended for transfer to areas of other occupational diseases, specifically mentioning occupational asthma caused by diisocyanates.

b) Reducing isocyanate exposure and asthma risk in motor vehicle repair (Piney et al., 2015; Stocks et al., 2015)

HSE has run a hazard awareness project for the Motor Vehicle Refinish (MVR) spray painters (in SMEs and micro enterprises) to reduce the incidence of occupational asthma by improving control to isocyanate exposure. The core of the project consisted of a so called "Safety and Health Awareness Days" (SHADs) information event (duration: half a day), reaching a limited number of carbody painting shops. As communication media at the SHADs presentations lectures showing risks and control of exposure, a video showing an interview with an asthma sufferer and a working scale model demonstrating of the clearing time of paint mist in a spray booth were used. For the target group of workers addressed the communication tools and working model were considered as suitable and effective measures for increasing hazard awareness. Free analysis of urinary hexamethylenediamine (UHDA: a biomarker for exposure to HDI) was offered to SHADs attendees. The HSE inspectors were instructed to deliver the key messages of the project to the body shops and to distribute the information material. Furthermore, the key messages were distributed by third parties like booth and paint suppliers, trainers, trade associations etc. (See box below for more information.)

(HSL, 2010):

"The issue: HSE identified that asthma was a major cause of ill-health in the motor vehicle repair (MVR) industry. Two-pack paints are used extensively in primers and lacquers and although the paints are ideal for vehicles, the isocyanates in them present risks to operators, especially during application when spray mist and vapours containing isocyanates may cause asthma or worsen an existing condition. To address the lack of awareness of the potential risks among employers and sprayers, HSE inspectors worked with us and trade associations to develop simple and clear guidance. This was delivered through a series of multi-media presentations at Safety and Health Awareness Days (SHADs), 28 of which were held across the country in a sustained campaign between 2004 and 2007.

A range of experts provided information at these events about the hazards and risks associated with spraying isocyanates and how to control exposure to prevent ill-health. A video of an interview with an asthma sufferer brought home the life-changing consequences of the condition. Scale models developed by our ventilation specialists used a smoke generator to show how ventilation systems in spray enclosures work and how long it takes for paint mist to clear after spraying. Industry speakers gave presentations on paints and equipment, and an HSE Inspector gave a clear message about legal requirements. Scientists from our biological monitoring team distributed sampling kits, enabling sprayers to collect a urine sample after spraying for analysis of isocyanate metabolites using an analytical method developed by HSL. This provided a simple check on whether the exposure controls were

working properly

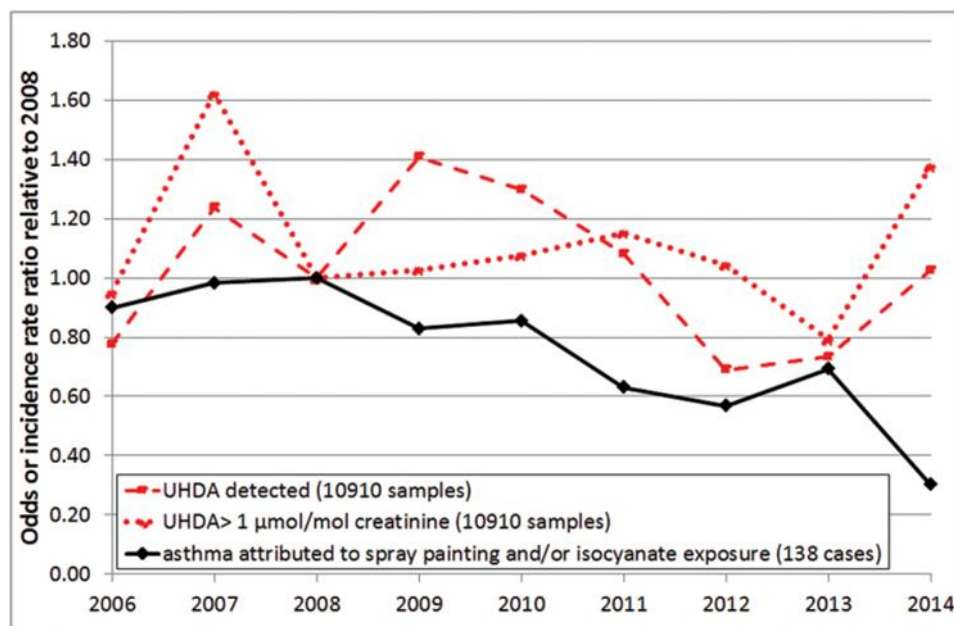
Outcome/Benefits

Overall the SHAD campaign was highly successful – post-event questionnaires by our work psychologists show improved awareness, with well over 90 % of attendees pledging to make improvements. Quantitative data from urine samples show that exposure levels were lower in workers who had attended the SHAD events than those who had not. Where levels of isocyanate metabolites in urine were above the Biological Monitoring Guidance Value, the sprayer was advised to look again at control measures, make improvements and repeat the test. These follow-up samples revealed lower levels of metabolites and a reduction in exposure. A further significant demonstration of the effectiveness of the campaign has come from recent HSE statistics, showing **that incidence of occupational asthma** in vehicle spray painters, along with associated costs in 2004 - 2006 was approximately **half the rate** of 2001 - 2003.

(Stocks et al., 2015):

From 2004 to 2008, the Health & Safety Executive, in collaboration with industry and other stakeholders, ran a national body shop project which aimed to reduce exposure to isocyanates in MVR. Safety and Health Awareness Days (SHADs) provided information about asthma and advice about clearance times before entering the spray painting booth without personal protective equipment. Free UHDA analysis was offered to SHADs attendees. Those employers declining to participate were more likely to be inspected during the lifetime of the project. In addition, new guidance was written in association with, and supported by, the spray booth and paint manufacturers and SHAD material was supplied free of charge to training colleges and trade associations.

Another finding in the study was that the continuing vigilance by the industry is needed and that the declining trend in exposure may not be sustainable without further intervention.”



Comparison of annual changes in the number of workers with UHDA detected or over the guidance threshold (two-level logistic regression model OR relative to 2008) with changes in the incidence of asthma reported to SWORD

Source: (Jones et al., 2013; Stocks et al., 2015)

The short and medium term evaluation of the HSE project showed that the key messages about isocyanates health hazards and the importance of clearing times in spray booths could be recalled by most of the SHADs attendees at least one year after the events.

The analysed quantitative data from urine samples showed that exposure levels were lower in workers who had attended the SHAD events than those who had not.

For outcome evaluation the trends in the number of workers employed in MVR with detectable UHDA levels or levels over the guidance limit were compared with trends in incidence of asthma in MVR workers which were reported to the UK-based occupational respiratory disease surveillance network (SWORD). The trend in incidence rates more or less has followed the trends of detectable UHDA levels. After an initial increase, compared to 2008 over a 6 year period the incidence rate of occupational asthma in vehicle spray painters was reduced between 50 % and 70 %. An increase in UHDA level in 2014 HDA may indicate that sustainability of the gains should not be taken for granted.

Transfer to the current restriction concept

An exact quantitative prediction of the expected reduction rate of cases of occupational asthma is scientifically not possible. Taking into account the learnings from the studies cited above, the training methods expected to be most effective in the case of this restriction proposal content are mentioned Appendix 5. The outline of the training structure (listed by topic) for industrial and professional uses is described in Annex 13 ("Trainings and Measures"). The approach focusses on inducing behavioural changes in the trainees, which should then lead to a reduction in risk-prone behaviour and eventually to the indicated reduction in new cases of occupational diseases.

It was decided to base a quantitative prediction estimate for the reduction of the incidence rate after implementation of the proposed restriction measure on the reported effectiveness of past studies cited above and in particular on the Motor Vehicle Refinish study by HSE because this specifically addresses one of the groups also covered in the current restriction concept. Of course the DS is aware that differences exist between the approach in the HSE project and the current restriction proposal. For example, apart from improving hazard awareness, the HSE project also included follow-up visits of labour inspectorates in body-shops. On the other hand, our approach plans a staged approach (depending on the expected level of potential risk level), and is also supported by some practical exercises for the second and third stage. Moreover, our concept foresees all exposed workers to be obliged to participate in a training (with subsequent examination), and a four year repetition cycle to improve sustainability.

Therefore, as a "best guess" on the effectiveness of the proposed training measures a range between 50% (as a lower limit, hereafter called "low bound") and 70% (as maximum result that may be imagined if all factors would fit, hereafter called "high bound") reached within a transition period of 4 years was assumed. In the approach of the restriction, each year 1/4th of the exposed workforce would attend the training.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

On the basis of this assumption a future development of the effectiveness rate has been derived and modelled. It is expected that the effectiveness of the training will develop with a constant rate within the first four year training cycle. This is justified by the consideration that either not all workers can be trained at the same time or that it takes some time for changing the workers' behaviour or to implement the behavioural aspects in the process flow systems in the firms. After the first cycle only minor improvements may be expected. Graphically this is shown in Figure 4 showing values for a main expectation of effectiveness for both the "low bound" and the "high bound" scenario.

The forecast on the reduction of asthma cases will then be based on the input factors according to Table 85.

According to the identified results by the literature research the assumed range for the effectiveness of the training is in the range of about 50 % overall in a time period of four years. Furthermore it is assumed that from the third period on some slight synergy effects on the effectiveness would be realised due to iteration of the training. As of the third training cycle after implementation of the proposed restriction, further slight improvements in reduction of new asthma cases are expected because of a gradual further improvement on the basic improved behaviour. In the model the estimated annual effectiveness would further increase by 3 resp. 4 %.

In our calculations, the costs for e-learning for the workers at high risk were calculated and compared with the benefits achievable at 50-70 % of risk reduction. However, it may be supposed that effectiveness of e-learning for workers in high risk group would be less compared to a face-to-face training. Therefore, e-learning will only be proposed as an option foreseen for "stage 1" (basic module) of the trainings. See Annex 13 „Trainings and Measures“.

Table 85: Forecast of the effectiveness of the proposed restriction measure

Year/period	Training cycle	Low bound annual effectiveness	High bound annual effectiveness
0	1	--	--
1		12.5 %	17.5 %
2		25.0 %	35.0 %
3		37.5 %	52.5 %
4	2	50.0 %	70.0 %
5		50.0 %	70.0 %
6		50.0 %	70.0 %
7		50.0 %	70.0 %
8	3/4	50.0 %	70.0 %
9		53.0 %	74.0 %
10...20		53.0 %	74.0 %

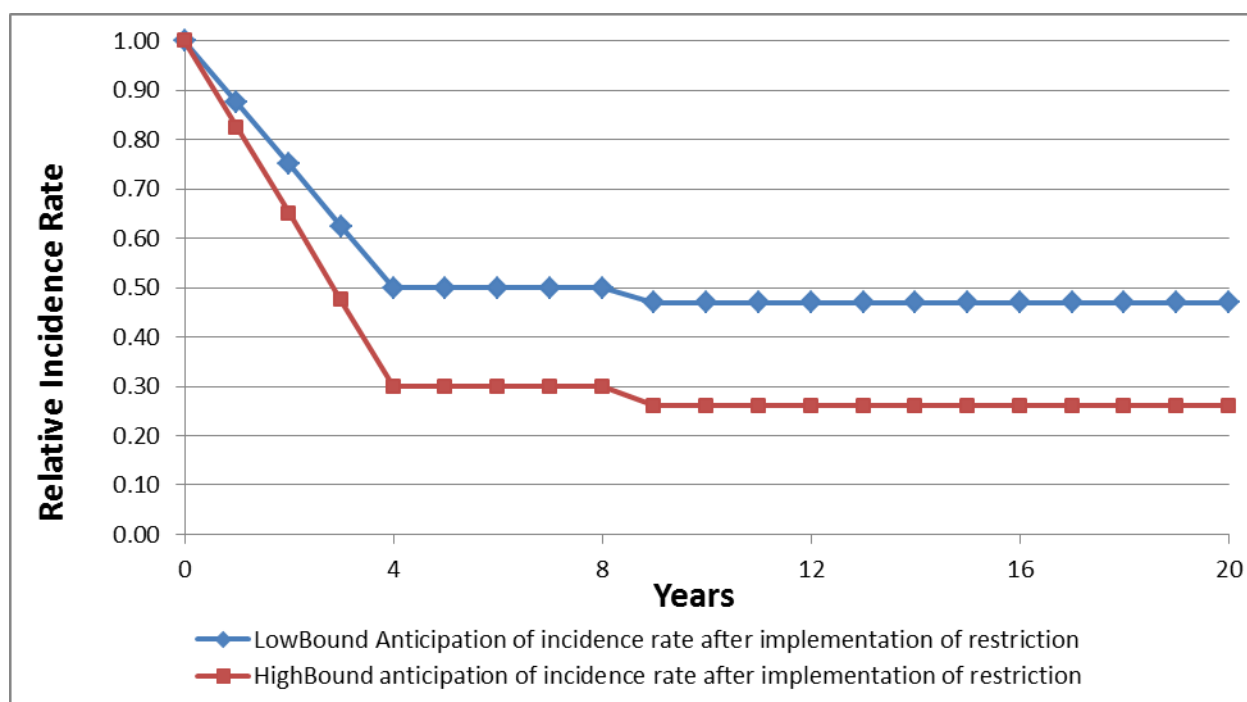


Figure 13: Forecast (low /high bound) for the relative development of the incidence rate after implementation of the proposed restriction measure.

The monetary evaluation of health impacts in both scenarios is based on material and immaterial so called intangible factors for cost components. The aggregation comprises also the losses of life quality caused by asthma. The following components and sources are used for the monetary valuation:

Table 86: Overview data sources for costs of illness components

Cost component	Valuation factor	Source
Direct (resource use)	Medical costs	Claims data analysis of German Social Accident Insurance
Indirect (resource loss)	Productivity loss	Number of days of incapacity to work: Federal Health Monitoring, Germany Added value / Personal cost per employee: EUROSTAT
Loss of life quality	Welfare loss	Stated preference study, ECHA 2015

The focus of indirect costs of illness covered under the heading “Human Health Impacts” is on work disability caused by isocyanates. Long-term impacts of the disease resulting in job changes or job losses are analysed under the heading “Social impacts”.

E.6.1.2 Estimation on costs of Illness (CoI)

A study was done to estimate costs of illness resulting from specific occupational lung and skin diseases caused by isocyanates. First, a comprehensive systematic literature search was conducted in selected databases to identify articles dealing with costs of illness of occupational lung and skin diseases. Second, analysis of costs of illness was

conducted from the perspective of Germany on the basis of highly aggregated data obtained from the German Social Accident Insurance (DGUV) for the years 2004-2013.

For impact assessment only the results of cost of illness of occupational lung diseases were used. Costs of illness of skin diseases were not included because data on occupational skin diseases are only available in a few Member States and large uncertainties by extrapolating to the EU-28 were expected. Because the share of dermatitis in the total number of cases of diseases is rather low, it is considered justified to delete this from the calculations, in order to reduce complexity. As a consequence, the estimated health impacts of the restriction proposal may be underestimated.

E.6.1.2.1 Direct costs of illness

Claims data analysis

To derive the medical costs of occupational asthma (OA) due to isocyanates and contact dermatitis (CD) a claims data analysis of the German Social Accident Insurance (DGUV) was done. In case an employee becomes sick as a result of his work or work circumstances, this impairment can be confirmed and recognised as an occupational disease. In this case, according to articles 26 and 27 of the Social Security Code VII, the DGUV is exclusively responsible for paying the medical services. By comparison, as other social insurance agencies, e.g. the statutory health insurance (GKV), are not obliged to pay medical services in the case of recognised occupational diseases they do not provide information about costs of occupational diseases. Thus in general, GKV claims data can be used to estimate costs of illness of specific diseases based on ICD-Codes or medications (e.g. respiratory diseases) but do not allow a link to the cause of illness (e.g. isocyanates). Thus by use of claims data of the Social Accident Insurance a more accurate estimate of medical costs attributable to isocyanates compared to more general public health insurance data can be reached.

Occupational asthma

Between 2003 and 2013 5 043 insured persons are entitled to services of the DGUV because of a recognized occupational disease (OD) caused by isocyanates affecting the respiratory tract. The analysis of claims data focuses with regard to the annual costs from 2004-2013 on insured persons which suffer from the occupational diseases listed in Annex 1 of the German Occupational Disease Ordinance (Aumann and Kreis, 2017): Asthma, COPD, and alveolitis (mainly OD number 1315), as well as contact dermatitis (OD number 5101). OD 1315 is specific for ODs caused by isocyanates affecting the respiratory tract and the lungs. OD-1315 covers the following diagnosed diseases: Allergic asthma bronchial (ICD-10, J45.0), Non-Allergic asthma bronchial (ICD-10, J45.1), COPD (Chronic obstructive pulmonary disease, ICD-10, J44.8) and Allergic alveolitis covered under the coding "Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours" (ICD-10, J68.4). Based on the analysis of claims data average annual direct costs of **€ 2433** (price level 2013) per case of occupational allergic asthma recognized by the German Social Accident Insurance arise per year (price level 2013)

For extrapolation to the EU-28 a non-modelling approach of benefit transfer is used. The study results are transferred to the other EU-countries based on health or medical specific Purchasing Power Parities (PPP) using the prices of a basket of health related goods and services, and then a simple population-based average is calculated. For the EU-28 direct costs are estimated to be € 1760 (rounded).

Occupational contact dermatitis

The total number of patients with newly confirmed occupational contact dermatitis (OD number 5101) by definition making use of at least one healthcare service, decreased over the years from 25 insured persons in 2004 to 17 insured persons in 2013. Between 2003 and 2013 209 insured persons are entitled to services of the DGUV because of a recognized occupational contact dermatitis. Unfortunately, the OD for contact dermatitis does not further differentiate between the chemical substances causing the skin disease, on contrary chemical substances in general are covered. Thus these claims data cannot be considered as a reliable data base for the estimation of costs of contact dermatitis caused by isocyanates.

Based on the analysis of claims data average annual direct costs of **€ 3186** (price level 2013) per case of occupational contact dermatitis recognized by the German Social Accident Insurance arise per year (price level 2013) (Aumann et al. 2017).

Systematic literature review

Complementary to the analysis of claims data a comprehensive systematic literature search in selected data-bases from the German Institute for Medical Documentation and Information (DIMDI) was performed in order to identify articles dealing with costs of illness as well as indicators of severity / duration of occupational lung and skin diseases. The quality of included studies was evaluated. The selected search strategy includes different terms for "isocyanates" and search terms for isocyanate-induced airway and skin diseases. By use of these terms about 15000 hits resulted. The search was restricted further to studies with an occupational or working focus.

Titles and abstracts were screened and a total of 3 046 matches were excluded after the first investigation since they are e.g. guidelines, do not have a direct connection to one of the selected diseases, address only therapies, medication, management of the disease, have an other languages than English or German, etc.

Main inclusion criteria of the literature search were:

- Studies with a focus on occupational asthma, occupational COPD or occupational contact dermatitis
- Cost of illness studies
- Studies who calculated economic consequences due to the diseases
- Studies about the severity or duration of the diseases.

Overall, 281 publications have been obtained in full texts. Of these publications, 82 titles have been removed since these publications were general cost studies, studies on productivity loss and general guidelines to the selected respiratory and skin diseases without references to occupational or work related diseases. A total of 32 records were identified as eligible.

Occupational asthma

The systematic literature review has identified two studies of high relevance for direct costs of occupational asthma considered as useful for the estimation of direct medical costs due to isocyanates and for validation of German claims data:

Ayres et al. 2010 estimated social costs of OA based on different exposures in the UK (Ayres et al., 2010). They calculated direct and indirect costs for six hypothetical patient groups which are exposed to isocyanates, latex, biocides (e.g. glutaraldehyde) or flour in the UK. The calculation of direct costs included resource consumption for general practice, medications, hospital admission, outpatient services and payments by the department of Work and Pensions (taxpayer). Additionally, the costs for an individual person like for example prescription charges, commuting or additional transport costs were included. Total direct resource costs amount to about **€ 1049** (adapted to € and price level 2013). It has to be mentioned that the costs of treating occupational asthma were assumed to be the same as for non-occupational asthma.

Another cost of illness study was conducted by (Garcia Gomez et al., 2012) in Spain. The authors estimated the number of asthma cases attributable to occupational activities. The estimation of the costs for specialized care, like inpatient care and specialized outpatient care was based on statistical data of the National Health Service (NHS) in Spain. The cost for primary care and pharmaceuticals were taken from secondary data sources. The costs for the specialised care are calculated for all men and women with asthma attributed to occupational exposures. Costs per patient were not specified and had to be calculated. Total direct resource costs amount to about **€ 1764** (adapted to price level 2013).

Because of variances in the healthcare systems in the EU-28, comparison and transfer of healthcare costs to other countries in the EU-28 is difficult. The transfer of results from the cost of illness study to other countries has certain challenges. Healthcare systems often differ from each other with regards to the attributes of financing, insurance coverage, care structures, and degree of co-payments by the patients, as well as quality of care. These different characteristics can cause limitations concerning transferability. The table shows a comparison of the German claims data after adaption of the studies done in UK and Spain to Germany by use of the Medical Health PPP (OECD, 2012b):

Table 87: Comparison of medical cost per case

Source	DGUV 2013 (Germany)	Ayres et al 2010 (UK)	Gomez et al 2010 (Spain)
Original value	€ 2433	BP 535 – 717	€ 1554
Adapted to € and price level 2013		€ 1049	€ 1764
Adapted to German price level by use of Medical Health PPP		€ 1563	€ 2934

The table shows that the primary cost data derived for Germany are located between the values for UK and Spain. Because the derived German claims data are considered as robust and comparable to other European primary healthcare data after adaption to the EU-28 they are used here to value medical costs per case.

Occupational contact dermatitis

The systematic literature review has identified three studies of high relevance for direct costs of occupational skin diseases to be used for the estimation of direct costs:

To investigate the effects of CD on labour market affiliation and societal costs **Saetterstrom et al.** linked data from a clinical database to patient, healthcare service and drug registries. In Denmark all cases in which work is a causal or contributory factor are defined as occupational and reported to the Board of Occupational Health. This registry includes 21 441 patients patch tested either in hospital departments or at

dermatological clinics in the period between 2004 and 2009. The registry includes all patients with CD (covering also those with no current or minor symptoms). By use of a case-control design (propensity score matching) yearly attributable costs were estimated from four years prior to patch testing (date of recognition) until one year after patch testing. The healthcare costs include costs of drugs, primary care, outpatient care, inpatient care. Healthcare costs are analysed over a period of 5 years showing a tendency to increase. Occupational CD health care costs rise up from € 49 (year 1) to **€ 415.75** (year 5) after patch testing and recognition of CD (Sætterstrøm et al., 2014).

In 2008 (Diepgen et al., 2013a) conducted two surveys including 310 patients of chronic hand eczema (either occupational or unrelated to work): one at 24 dermatology practices and clinics across Germany including patients insured by the Social Health Insurance (SHI), and one in two specialized centers including only patients insured by the German Social Accident Insurance (DGUV). Four groups depending on the impact of chronic hand eczema on their work were defined by differentiating between non-working, work-unaffected, work-impaired and work-diseased patients. Analyses of 310 patients showed that annual direct costs of work-impaired (SHI) and work-diseased (DGUV) patients were approximately twice as high as costs of non-working and work-unaffected (SHI) patients. The estimated direct annual costs (healthcare costs) for work diseased patients amount to **€ 3164**, and for work-impaired patients to **€ 3309**.

In a further study (Diepgen et al., 2013b) estimated annual societal costs of 151 patients with occupational hand eczema in Germany 12 months prior to entering a special rehabilitation program. To this end, they used information from medical records covering medical history, diagnostic / therapeutic procedures as well as 1-hour structured interviews. Due to un-availability of some data, some calculations were based on assumptions. Moreover, analyses were stratified by two severity groups, that is group A (no signs / mild) and group B (moderate to severe). While there was no significant difference in annual direct costs per patient between group A and B, the analyses revealed a trend towards higher indirect costs for patients suffering from moderate to severe severity occupational hand eczema (group B). Per patient annual medical care costs of **€ 2464** were estimated based on data for all patients, € 2705 for no signs / mild, and € 2610 for patients with severe symptoms.

E.6.1.2.2 Intangible cost

Individual welfare losses (intangible costs) may arise if the quality of life is impaired due to pain and suffering caused by occupational allergic asthma. In 2012 an academic consortium commissioned by the European Chemicals Agency (ECHA) started a two-year, four-country research study to estimate the willingness to pay for avoiding diseases including respiratory and skin sensitization. The study appears to be by far the largest survey to date of individual willingness to pay for diseases associated with respiratory and skin sensitisation.

Occupational asthma

The FP6 project HEIMTSA provides the analysis of willingness to pay for avoiding asthma discomfort using data from stated preference studies. The original HEIMTSA FP6 project is based on main wave data comprising Czech Republic, France, Germany, Greece, Norway, United Kingdom. The study done on behalf of ECHA includes also data from additional wave conducted in 2012 in the Czech Republic, Slovakia and the United Kingdom (Máca and Scasný, 2014). Sample sizes were approximately N=1900 per country with exception of N=1000 for the Czech Republic in the first wave. The response rates ranged between 83 % (Czech Republic) and 18 % (Greece).

Given the size of the sample and the sample strategy the survey can be considered as representative for the countries included. In addition, the survey covers large countries from central Europe (France, Germany, UK), includes new Member States in Eastern Europe (Czech Republic, Slovakia), and with Greece also one state from Southern Europe is included. Thus the sample can be considered as providing a central EU-wide value of willingness to pay for avoidance of asthma discomfort per asthma attack of **€ 50**. The survey also includes a set of questions on frequency of asthma attacks in the past 3 months ranging between 3.9 (Slovakia) and 14.1 (Germany). **9** attacks are considered as the mean number. Combining both values and extrapolating to one year gives an average value of asthma discomfort of **€ 1800** per year (own calculation).

Only a few of stated-preferences studies are available for avoidance of asthma attacks/episodes. One comparable study is (Blomquist et al., 2011). In the study adults were asked about their willingness to pay for improved asthma control (N=317), and parents for improved asthma control of their children (N=192). Willingness to pay for adults ranging in the age between 35 and 45 is considered as of special relevance here. Annual willingness to pay for adults of age 35 are 2,382 USD (~ € 1804, 2007) (= € 1603; after adaption of GDP per capita and price level 2015), and for adults of age 45 are 1960 USD (~ € 1484, 2007) (= € 1319, after adaption of GDP per capita and price level 2015) (Blomquist et al. 2011; own calculations). The results of Blomquist et al. 2011 are similar to willingness to pay derived by the ECHA 2015 study which is used here for the valuation of intangible costs.

E.6.1.2.3 Indirect cost of illness

Specific data on duration of work disability per case caused isocyanates are not available. But the Institutions of the German Public Health Insurance collect data on the average number of sick leave days per case of Asthma bronchiale (ICD-10, J45). An average value of about 10 days is reported by the German Federal Ministry of Health based on the reporting of the Institutions of the Health Insurance (Federal Ministry of Health, 2013). This value is used for the estimation of the productivity loss per case of asthma bronchiale per year caused by disability at work.

The indirect costs may vary. They are sector specific and should be measured using sector specific statistical figures on gross value added per employee.

In the following table an overview of productivity losses for different relevant industrial sectors is given. The productivity loss is measured by gross value added in the relevant sectors (NACE codes provided by ISOPA, Table 75, Table 78 and (EUROSTAT 2016)).

Referring to personal costs per employee and assuming 230 working days per year the average value for annual loss in income in **all sectors** results in **€ 31740**.

For the costs-benefit analysis data on averaged added value and personal costs per employee has also been prepared, which would be representative for overall affected sectors. The impact of sector specific shares on the comprehensive cost units has also been considered. Accordantly, the weighted average on figures was estimated.

Table 88: Structure of Costs of Illness for a work-related asthma disease

Cost category	Costs driver	Annual value [€]
Direct costs	Therapy/ medicine	1764*
Indirect costs (including social costs)	Disability [10 disability days of 230 working days x sector specific gross value added]	0.04 x Value added
	Reduction in earning and value creation capacity [32 %** of the sector specific personnel costs]	0.32 x Personnel costs
Intangible costs	Pain & Suffering/ Welfare loss	1800

Source: (Máca and Scasný, 2014) and own estimations shown in Table 87 and in Table 89.

*adapted to EU-28 by use of Medical Health PPP (OECD, 2012b)

** weighted average

Note: for calculation of total CoI in high risk sectors the data in Table 76 are needed.

Social impacts of work disability and individual costs for employee in the long-term

The indirect costs of illness are measured by the productivity loss caused by short-term work disability. But in the long-term the employees may be driven to leave the job because of the risk of exposure to isocyanates. The concerned employee may change job internally in the company, change the company and the job as a whole or is becoming unemployed at least temporarily. In case of total work disability, the employee can ultimately be forced to leave the labour market and retire. An overview on constellations how the job market participation of an employee may evolve in case of occupational disease or work-related illness is shown in Figure 15. If an employee is forced to leave the job because of asthma caused by isocyanates he/she may not be able to apply work specific capabilities/skills and experiences any longer. At least temporarily, an income loss may result. Degradation of work qualification level or job experiences and corresponding work capabilities or skills in the following are considered as social costs due to occupational/ work-related asthma. These social costs per employee are valued by the income (indication with personal costs according to EUROSTAT) in the respective industrial sector. In addition the loss in income negatively impacts the individual welfare (e.g. according Figure 15).

Depending on the level of unemployment in the industrial sector, partial and full work disability may transfer into permanent productivity loss if a job position remains vacant also in the long-term. In this case valuation of the social impacts of work disability by use of the valuation factor "added value" would be more appropriate. Figure 15 below demonstrates possible constellations of impacts on working ability. But because forecasting unemployment levels for different industrial sectors is difficult, the social impacts are conservatively valued by income loss which is measured by personal costs according to EUROSTAT statistics. Thus, the individual welfare loss due to loss in income of asthma sufferers is being taken into account.

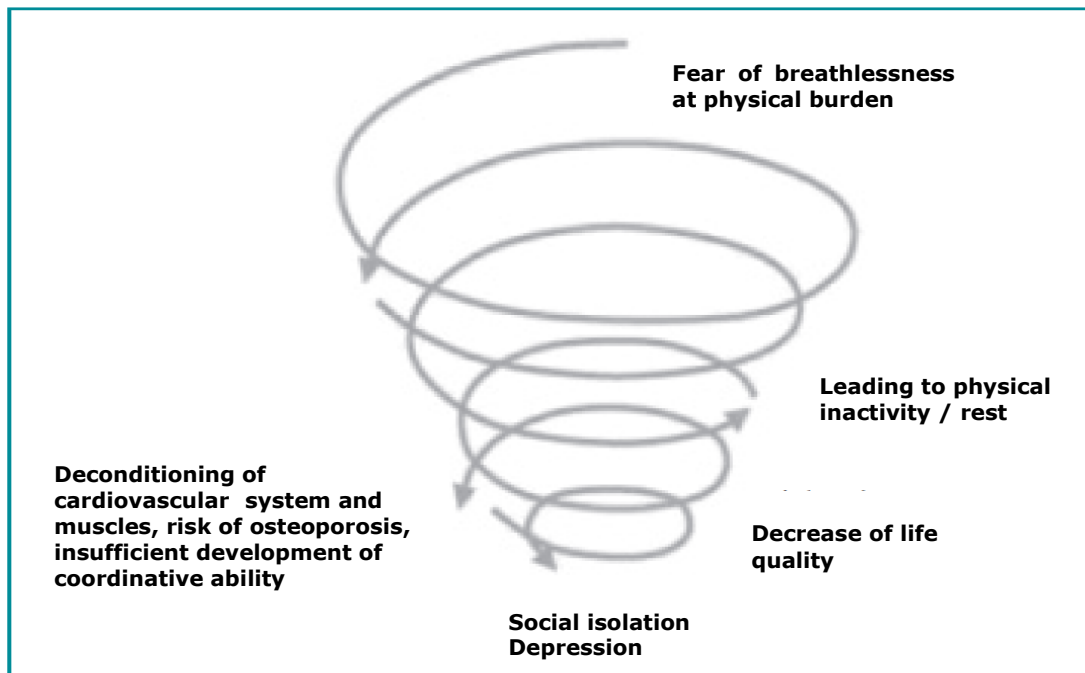


Figure 14: Asthma – impacts on sufferer’s welfare Source: DGUV <http://publikationen.dguv.de/dguv/pdf/10002/reichenhallneu.pdf>

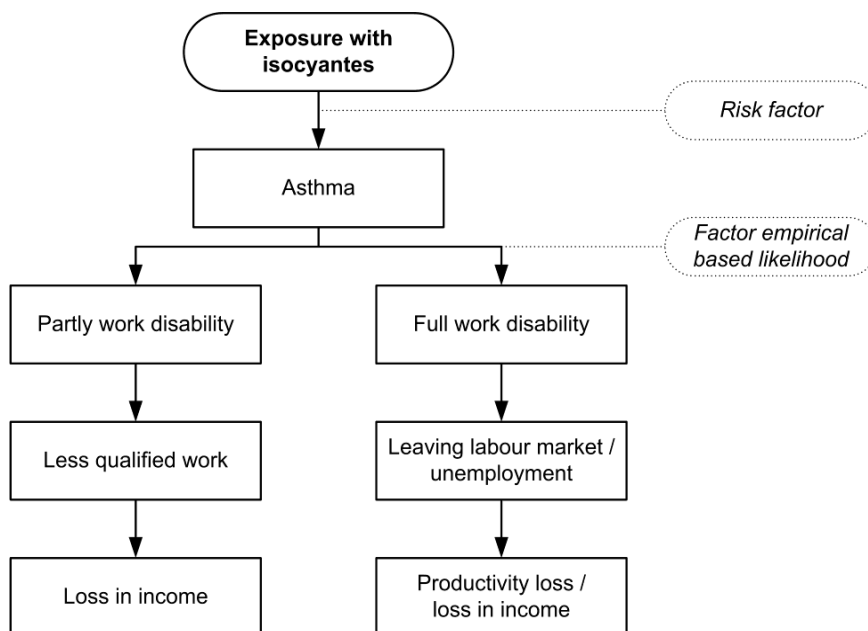


Figure 15: Cause-and-effect chain for social costs caused by asthma

Empirical evidence for job change and for frequency and degree of income losses is given in several empirical studies which were analysed by a literature screening to get input parameters for the estimation of the social effects due to work-related asthma. In the following, firstly, empirical results on **income loss** linked with job change (same or a

different employer) caused by disability are presented. Secondly, income losses linked to unemployment are reported:

Job change and income loss

The analysis of **Ameille et al.** is based on a follow-up study with 257 patients with a diagnosis of OA in France/Paris. One year after a medical based diagnosis, patients were interviewed via telephone or questionnaire by post. 46 % of patients reported a reduction of income (**84 %** of those who had left their employer including intermediate unemployment, and **19 %** of those who are still employed in the same company ($p < 0.001$)). Mean loss of annual income were significantly higher in subjects who left their employer than in those who remained in the same company. In case of employer change or intermediate unemployment (41 %) the study results show that 84 % suffer an income reduction of **50 %**. Of those who stayed in the same company (56 %) 19 % suffer a reduction of annual income of **19 %** (Ameille et al., 2003).

Moscato et al. evaluated the socioeconomic consequences of patients with OA in Italy. In a longitudinal study 25 patients were questioned who underwent follow-up visits (1, 3, 6 and 12 months) after their diagnosis. The monthly and annual income at the time of the diagnosis and after 12 months for Group A (patients who ceased exposure because of employer change or unemployment) and Group B (patients who continued the exposure) was calculated. A significant loss of income of about **27 %** was reported for patients of group A (12 months after diagnosis), whereas no significant change was seen for patients in group B (Moscato et al., 1999).

In a follow-up study by **Larbanois et al.** based on structured telephone interviews of 157 patients of OA in France on average 43 months after diagnosis, patients were asked about employment status, income changes, and asthma-related work disability. The analysis was done for a group of patients with documented OA and for a group of patients who failed to develop a positive response to specific inhalation challenge (SIC) with occupational agents. Regarding socioeconomic consequences both groups showed similar responses. 62 % of the respondents with documented OA reported a reduction in income of about **22 %** (Larbanois et al., 2002).

Gannon et al. in a cross sectional study (112 workers included) collected information about respiratory symptoms, employment state, and current financial situation (including compensation) one year after diagnosis by the use of a self-administrated questionnaire . Diagnostic data, respiratory function, and causative agent were obtained from the workers' case records. **74 %** of those who had changed job (51 %) reported that they had a reduced income as opposed to **14 %** (44 %) that remained exposed. Median perceived loss as a percentage of annual income was **54 %** in case of employer change (unexposed), and **35 %** for those who stayed at the same employer (exposed) (Gannon et al., 1993).

Leira et al. studied the employment and financial situation of workers with OA in UK and Norway with a cross sectional study design. 723 patients with different forms of physician diagnosed OA were asked questions about working status, symptoms, relationship of symptoms to work, smoking, and socioeconomic consequences of the disease (study period 1995-1999). **55 %** reported a reduction in annual income, and 5 % a temporary income reduction (Leira et al., 2005).

In the five studies mentioned before **frequency of income loss** of those who have changed employer or job ranges between **54 %** and **74 %** (**84 %** if unemployment is included). **Income loss** is reported to be in the range of **27 %** and **50 %** in case of

employer change. The income loss for those who remained at the **same employer** is lower and in the range between **19 %** and **35 %**.

Unemployment and income loss

Loss in income: According to (Nicholson et al., 2010) et al "Generally, occupational asthma has a poor prognosis, with about 1/3 of workers achieving symptomatic recovery and about 3/4 having persistent none-specific bronchial hyper-responsiveness. Early diagnosis and early avoidance of further exposure offer the best chance of complete recovery. Workers who remain in the same job and continue to be exposed to the same agent after diagnosis are unlikely to improve and may worsen. Once sensitised, a worker's symptoms may be incited by exposure to extremely low concentrations of a respiratory sensitiser. Respiratory protective equipment is effective only insofar as it is worn when appropriate, that there is a good fit on the face and proper procedures are followed for removal, storage and maintenance. There is consistent evidence that about 1/3 of workers with occupational asthma are unemployed after diagnosis and that loss of employment following a diagnosis of occupational asthma is associated with loss of income."(Nicholson et al., 2010)

In four of the five studies mentioned above also information about the unemployment rate after diagnosis were included. In Larbanois et al. (2002) **22 %** of the patients with documented OA about 40 months after diagnosis, and in Ameille et al. (1997) about 3 years after diagnosis **25 %** are unemployed. In contrary to these quite high rates Leira et al. (2005) reported a figure of **3 %** based on a socioeconomic survey of registered OA cases in different industries of Norway. But data on the time between diagnosis and survey response was not provided in this study.

There is consistent evidence derived from clinical and workforce case series in a limited number of countries that about one third of workers with occupational asthma are unemployed after diagnosis. The risk may (Axon 1995, Goe 2004) or may not (Cannone 1995, Labarnois 2002) be higher than among other adult asthmatics although this has been examined in only three studies. The risk of unemployment may fall with increasing time after diagnosis (Ross 1998). There is consistent evidence that loss of employment following a diagnosis of occupational asthma is associated with loss of income. In comparison with other adult asthmatics those whose disease is related to work may find employment more difficult (Cannone 1995, Labarnois 2002) and their financial loss may be greater (Santos 2007). Those employees who are relocated to jobs without exposure to the causative agent are more likely to remain in employment and are unlikely to leave those jobs because of their asthma (Dimich-Ward 2007).

Approximately one third of workers with occupational asthma are unemployed up to six years after diagnosis. Workers with occupational asthma suffer financially.(Nicholson et al., 2010)

Although the costs for e-learning for the workers at high risk have been calculated and compared with the benefits achievable at 50-70 % of risk reduction capacity, it is supposed that effectiveness of e-learning for workers in high risk group would be less as of a face-to-face training. Therefore e-learning will only be proposed as an allowed option for "stage 1" (basic module) of the trainings.

Estimation of income loss

The study of the British HSE (HSE 2006) estimated social costs of OA based on different exposures in the UK (**Ayres et al. 2010**). They calculated the costs for six hypothetical working population groups who are exposed to isocyanates based on a literature review

including the five studies mentioned before. Thus this study can be considered as summary of the literature on income loss in case of OA due to isocyanates and is used for the estimation of income loss here. Based on the literature survey the authors made the assumptions, that in 25 % of the cases the individual performs the same job at the same employer, and in 25 % of the cases switch jobs at the same employer. In both cases a reduction in take home salary of 20 % may result. 85 % of those 15 % who changed their employer may have a reduction in take home salary of 50 %. 15 % will retire from the labour force facing a full salary reduction. In 20 % of the cases individuals are at least unemployed facing also a full salary reduction of 100 % (see also Figure 16). In Ayres et al. 2010 it is assumed that these individuals will finally be reemployed again facing an average income loss of about 50 %.

For simplification in calculation of benefits for human health possible constellations in reduction of working abilities with economic consequences have been analysed and aggregated to one weighted average value. It expresses the likelihood of a loss in income of 100 per cent.

The study of Ayres et al. 2010 and others are used to estimate a range of possible income losses. The study indicates the different constellations for the estimation of the occurrence probability for loss in income (Figure 16) (Ayres et al., 2010). For this purpose, empirical results on employment status and connected income losses are applied to derive an expected income loss based on the frequencies of the different events.

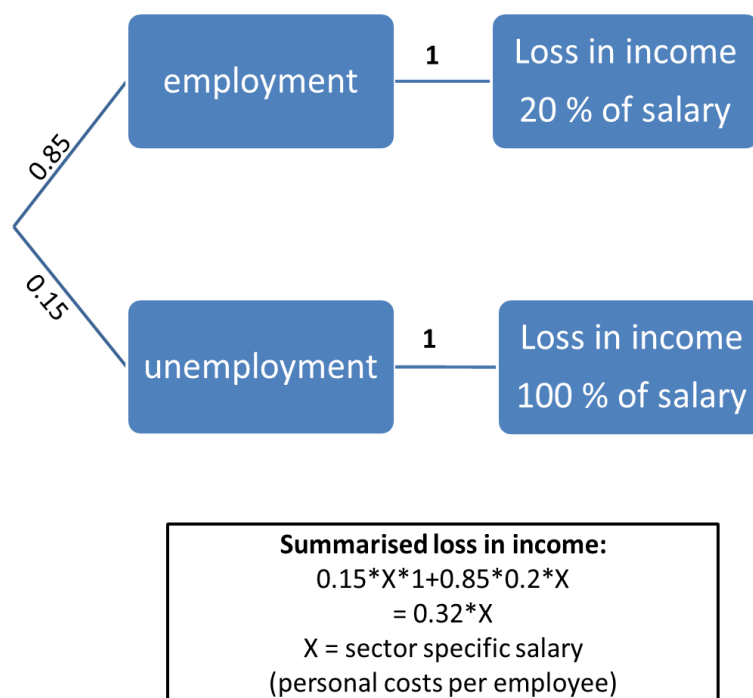
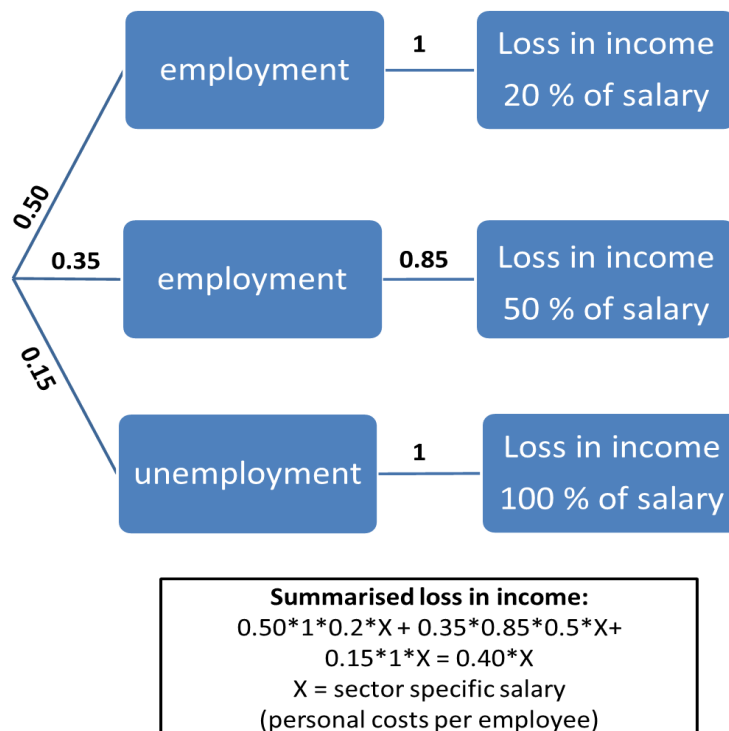


Figure 16: Likelihood tree for income loss due to work-related asthma source (Ayres et al., 2010)

The derived likelihood of round 40 % for total income loss seems to be very high. The derived likelihood of round 60 % for total income loss seems to be high. A more conservative constellation for unemployment has therefore been assumed ("best guess") (Figure 17). The derived likelihood in this figure of about 32 % (one third) is in the middle of the range of income losses between 20 % and 50 % which can be found in the literature referenced above.

In a German study on behalf of the Social Accident Insurance (DGUV) the frequency and degree of reduction in working capacity due to the work-related asthma were evaluated. The results on the reduction in working capacity for the examined sample of 121 patients are provided in Table 89. The average reduction in working capacity amounts 29 %, providing some evidence for an assumed income loss due to OA of about one third.

Taking into account the evidence obtained from the literature search (Table 90) 32 % is assumed as the "best guess" for the summarised likelihood for the occurrence of income



loss.

Figure 17: Likelihood tree own "best guess" on incomeloss due to work related asthma

Table 89: Overview on the DGUV's study results with own derivation on the summarised likelihood for reduction in working disability of people suffering asthma.

Frequency (relative number)	Degree of reduction in working capacity	weighted degree of reduction in working capacity
45 %	20 %	9 %

Frequency (relative number)	Degree of reduction in working capacity	weighted degree of reduction in working capacity
29 %	30 %	8.7 %
19 %	40 %	7.6 %
7 %	50 %	3.5 %
Summarised reduction in working capacity		29 %

Table 90: Overview on evidence from the literature search and own assumption

Source / publication year	Reduction [%] in working capacity unemployment
(HSE, 2015)	40 (aggregated)
(Nowak et al., 2011)	29 (aggregated)
(Nicholson et al., 2010)	33
(Larbanois et al., 2002)	22
(Moscato et al., 1999)	28
Own estimation	32 (best guess)

The monetary valuation of the social impacts regarding the annually estimated asthma cases is carried out on the basis of 32 % likelihood for total loss in income.

E.6.2 Human health impacts – results

Table 91: Overview on results of human health impacts (based on 6500 cases of occupational asthma per year)

Description	RMO1*	RMO2*	RMO3
Cumulative number of reduced cases over 20 years (based on best estimate)	62 465 – 87 295**	62 465 – 87 295**	130 000
Monetary values (PV, €million) incl. social costs, average/year	271 – 378**	271 – 378**	627***

* Related only to trainings measures. Range for Low/High bound efficacy

** Effectively it is assumed that all asthma cases will occur in the higher risk groups. See explanation below

The benefits for human health might be slightly higher as indicated, because the monetary effects resulting from reduction of skin diseases are not included (lack of data e.g. on effectiveness).

RMO1 – Benefit for human health resulting from the proposed Appendix Exemptions

As highlighted before, a quantitative estimation on risks in concerned sectors is not possible. According to expert judgement and personal communication 80 % of the

workers using products based on isocyanates are associated with a low risk. Only 20 % of workers apply the products by certain techniques which are associated with relatively medium risk.

The benefit for human health resulting from measures from the Appendix Exemptions is obvious. Namely, the identification and placing on the market of exempted products with the potential for very low exposure of users in concerned sectors. This would lead to low risks. The delta in benefit would be positive, but it is not possible at the moment to quantify it.

RMO3 – benefits for human health of a complete ban

Extreme scenario – risk reduction down to zero

For this (extreme) risk management option the potential possible benefit will be estimated which could be realised by a hypothetical risk reduction down to zero. The implications on the risk situation in non-EU countries in which the use of diisocyanates for goods production would increase and risk for occupational illnesses may be higher than in the EU, will not be considered.

Partial benefits of RMO3 (example vehicle refinish)

Coatings based on isocyanates contribute to a prolongation of the car life time and accordingly to the efficient use of resources and help to avoid early disposal.

On the other hand, a ban of diisocyanates would result in a reduction of asthma cases for spray painters of 100 per cent. A rough estimation indicates the PV value of annual costs savings of “€ 665 million” over a time horizon of 20 years or 33.2 million per annum due to a complete ban. According to the association “CEPE”, in the sector “150 000” workers which have direct contact with diisocyanates are employed. HSE has reported the annual incidence for asthma cases in the motor vehicle repair sector to be 66 on 100 000 employees (HSE 2014 (HSE, 2015)). The data are based on statistics for registered occupational diseases for asthma.

Table 92: Input parameter for calculation spray painters

Parameter	value
Number of exposed workers	150 000
Incidence rate [%/a] – baseline	0.26
Prevalence	10
Fraction of working population under risk [%]	90
Incidence rate [%/a] – restriction RMO3	0
years	20
CoI incl. WtP [€/a]	4942
likelihood for loss in income [%]	32

Parameter	value
loss in income [€/a]	23000*

E.7 Environmental impacts

The environmental impacts are not relevant for the proposed restriction scenario.

E.8 Basic Data for modelling of costs and benefits

Table 93: Overview on input parameter used for modelling of the costs for Appendix Trainings and Measures and Appendix Exemptions and benefit for human health

Variable	Main Value	Range for sensitivity analysis		Source
		Low value	High values	
Asthma prevalence in exposed workers [%]	10	-	-	See section B.5.6.5.2
Annual incidence rate in exposed working population [%]	0.46	0.07	1	(HSE, 2015) HSE Statistics incidence in MVR sector 66/100 000
Exposed working population MVR [mil]	0.15	-	-	ISOPA, verification by publication of OECD 2009
Exposed working population all sectors [mm]	1.6	1.34	-	ISOPA and own appraisal; 1.34 correlate with appr. 80 per cent
Medical costs for asthma therapy [€/a]	1700	-	-	(Aumann and Kreis, 2017)
Annual indirect cost: productivity loss in MVR [€/person 10 days]	1442	-	-	Own estimation by EUROSTAT data
Indirect cost: productivity loss in MVR [€/person h]	18	-	-	Own estimation by EUROSTAT data
Ø Annual indirect cost: productivity loss all sectors [€/person 10 days]	1762	-	-	Own estimation by EUROSTAT data
Indirect cost: Ø productivity loss all sectors [€/person h]	22	-	-	Own estimation by EUROSTAT / ISOPA data
Indirect cost: Ø productivity loss construction/automotive repair [€/person h]	23	-	-	Own estimation by EUROSTAT / ISOPA data
Likelihood for total loss in income [%]	32	-	-	(HSE, 2015; Moscato et al., 1999; Nowak et al., 2011), own estimation
Annual loss in income in MVR [€/person]	23000	-	-	Own estimation by EUROSTAT data
Ø Annual loss in income in all sectors [€/person]	32000	-	-	Own estimation by EUROSTAT / ISOPA data
WtP for asthma [€/a]	1800	-	-	ECHA (Máca and Scasny, 2014)

Variable	Main Value	Range for sensitivity analysis		Source
		Low value	High values	
Annual growth of effectiveness rate of the training [%] (case reduction factor)	-	12.5	17.5	Own guess mainly based on HSL (Piney et al., 2015)
Total effectiveness over a 4 years period [%]	-	50	70	Own estimation mainly on basis of HSE study
Frequency of training [years]	4	-	-	Own proposal
Ø Number of workers per firm in all sectors	20	-	-	Analysis of EUROSTAT data, own assumption
Number of Suppliers of Isocyanates containing products	4600	-	-	ISOPA
Number of body shops in MVR sector	40000	-	-	Own guess on basis of OECD 2009: 317,000 workers in 60,330 shops, at the moment 150,000 workers
Annual costs for product tests /Appendix Exemptions [€ mm]	-	0.9	1.74	Own estimation based on expert judgement
Number of product tests	100	80	120	Personal communication with experts
Number of exempted trainings [mm]	3	-	-	Own estimation based on expert judgement

N.B.: For a better overview, in the table several figures are rounded

E.9 Proportionality (including comparison of options)

In general, the socio-economic analysis is based on two scenarios with low and high uncertainty estimates respectively. The in-depth analysis of the case example of motor vehicle refinish thereby provides an estimation with a relatively high forecast certainty. The anticipation of figures for all relevant sectors is however attributed with some uncertainties with regard to the incidence rate for asthma disease. Nevertheless, the estimation provides a basis for assessment of proportionality.

The human health impacts are modelled from $n = 0$ up to $n = 20$ years. In both scenarios the valuation of the anticipated number of asthma cases is carried out by the identified cost units for CoI including the social costs (estimated in

Table 88). The costs will incur each year for new asthma cases as well as for all asthma cases that have occurred in previous years. Accordingly, the human health costs were in both scenarios cumulated as well. The net benefit in each year results from the difference in annual costs between both scenarios (baseline versus restriction low / high bound).

For an economic comparison the calculated monetary values of costs and benefits are cumulated and presented as net present values (PV) on a time scale of 20 years. The discount rate used hereby is 4 %. Thus, a pay-off period of costs could be estimated.

E.9.1 Cost-benefit analysis of the proposed restriction measure RMO1 – Appendix Trainings and Measures

The costs-benefit modelling is solely related to the industrial and professional sectors which are subject to higher risks associated with the use of diisocyanates. According to the initially postulated extrapolation /estimation methods, various values on empirical risk are used for the analysis in MVR and in all relevant sectors. In other words, the quantitative parameters of the risk of asthma are varied within an analysed use sector. The costs for the Appendix trainings and measures are set fixed in both sectors, respectively. As explained before the costs and benefits are given as cumulative net presented values²⁷.

The costs and benefits of RMO1 for the Appendix Training and Measures as well as Exemptions are reported separately. The target group of workers for the Appendix Exemptions has been identified. The workers related to the sectors automotive repair and construction are not supposedly subject to the same risks as other industrial and professional sectors involved in spraying and foaming processes using diisocyanates as monomers. Therefore, the costs-benefits analysis is only focused on the sectors subject to higher risks. The analysis in RMO1 is supplemented by a semi-quantitative analysis of the additional costs caused by the proposed Appendix Exemptions. The considerations of RMO2 comprise the calculation of additional costs for e-learning which would incur for the sectors exposed to very low risks. It was assumed that the health benefits with or without Appendix Exemptions are the same. However, it may be assumed that the benefits in case of RMO1 (with Appendix Exemptions) could be even slightly higher than in the case of RMO2 without the Appendix Exemptions. The incentives for the use of the exempted products associated with very low risks would increase. These considerations are underpinned by more incentives to use exempted products (with confirmed very low risk) instead of using products with low risk and attending the trainings defined in the Appendix Trainings and Measures.

E.9.1.1 Results on case example motor vehicle refinish (MVR)

Table 94: Overview of training options in MVR sector

Option	Assumption
a: courses at an established education centre / competence academy etc.	20 participants persons in one course with a commissioned trainer

²⁷ The modelling is performed in excel-files, which can be provided, if required.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Option	Assumption
b: integration of the training part into the product presentation/ suppliers technical customer support	500 firms producing coatings (producer of diisocyanates based products). The costs for their training are not included into the calculation because the benefit for coating suppliers is not covered in modelling of example for MVR sector.
c: external training course incl. training material and certificate	each worker attends the course at an accredited organisation
d: Training at work (in-house with a commissioned trainer)	Training with a commissioned trainer. Assuming 40 000 body shops exist within the EU-28. Due to small size of shops the economies of scale/ costs digression cannot be realised
f: train the trainer and internal instruction of workers	see above

Table 95: MVR: Extrapolation method 3 – estimation of health benefits based on reported asthma cases

Input parameter	Value
Number of exposed workers	150 000
Incidence rate [%/a] – baseline	≈ 0.07
Incidence rate [%/a] – restriction (RMO1 and RMO2)	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.
Prevalence [%]	10
Fraction of working population under risk [%]	90
Years	20
CoI incl. WtP [€/a]	4942
Likelihood for loss in income [%]	32
loss in income [€/a]	23000

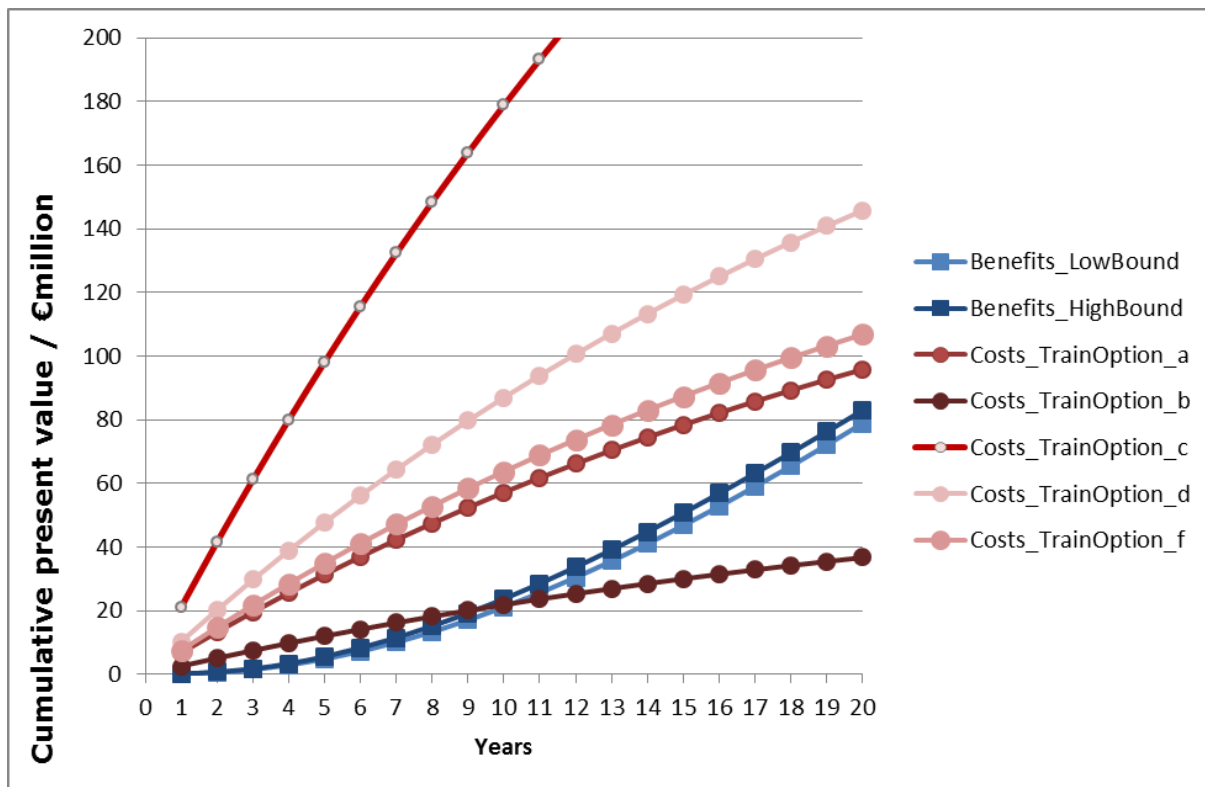


Figure 18: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma issue of 0.07 % per year

Assuming the asthma issue based on reported cases the costs-benefit analysis indicates that the training costs would be solely covered by the training model b. In such a case, taking the lower bound for effectiveness pay-off would be achieved after 16 years. In case of a better effectiveness as assumed for the high bound, pay-off can be expected after 11 years.

In principle, these results were predicted by the Dossier Submitter. The data on asthma risk is based on reported cases, which only represent the “tip of the iceberg” related to the asthma issue. On the other side, using the training option “b” no direct costs for training will incur for the MVR sector. The training integrated into supplier’s technical customer service only creates costs in terms of the productivity loss due to invested time. For the time period of 20 years the direct costs for suppliers were not modelled. The initial rough estimation indicates negligible low costs of around 45000 [€/a] for training of 500 coating suppliers. Furthermore, it can be assumed that suppliers can apply the obtained knowledge by training to instruct customers in other sectors beyond vehicle refinish. These costs to train the suppliers cannot be fully added to the calculation of overall costs in the considered case. The training in a course where a course fee is paid for each worker (training option “c”) would generate the highest costs.

Table 96: MVR: Extrapolation method 3 covering the underreporting issue

Parameter	Value
Number of exposed workers	150 000
Incidence rate [%/a] – baseline	≈ 0.3
Incidence rate [%/a] – restriction (RMO1 and RMO2)	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden. Fehler! Verweisquelle konnte nicht gefunden werden.
Underreporting factor	4
Prevalence [%]	10
Likelihood for working population under risk [%]	90
Years	20
CoI incl. WtP [€/a]	4942
Likelihood for loss in income [%]	32
loss in income [€/a]	23000

Taking into account the underreporting issue and not registered asthma cases which are previously highlighted in Section B.10 (“Risk characterisation”), the benefit for human health would be greater. With the exception of the training model via course option c the costs of other trainings would be outweighed by benefits for human health. According to the Figure 19 the training provided by supplier customer service is the most cost efficient measure, which would be paid-off after 4 years after implementation of the Appendix “Trainings and Measures”. Nevertheless the costs of trainings in a group of 20 persons or according to the principle “train the trainer” are also balanced by the benefits. Considering the low bound of effectiveness of the training, pay-off would be achieved after 8 or 12 years in the lower bound estimate. The relative higher costs for the training at work (option d) results from the sector structure. In many cases, body shops are micro firms with mostly 4 employees. Cost degression / economies of scale could not be achieved. Even taking into account the underreporting issue, the costs for attending the training course (option c) by each single worker could not be covered by the estimated benefit.

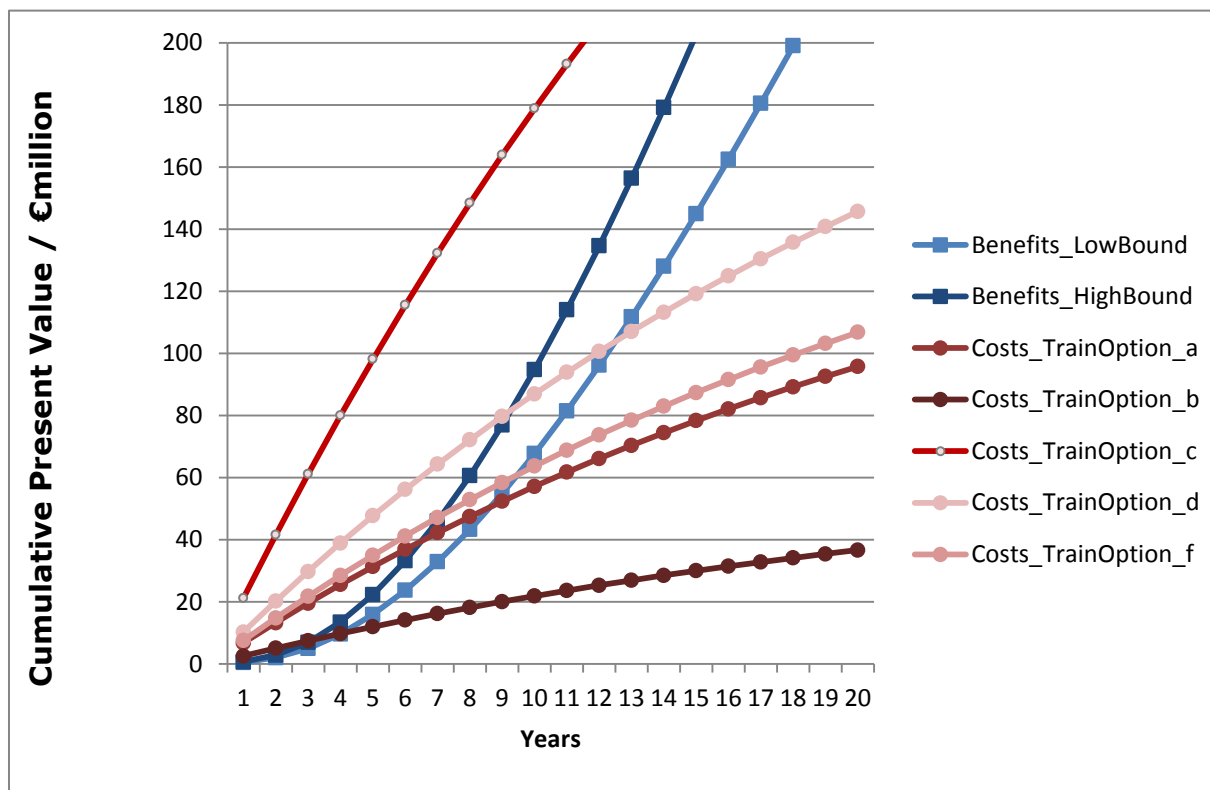


Figure 19: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma incidence issue of $\approx 0.3\%$ per year

Table 97: MVR: Extrapolation method 1 – calculation based on incidence rate epidemiological studies

Parameter	Value
Number of exposed workers	150 000
Incidence rate [%/a] – baseline	1
Incidence rate [%/a] – restriction	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.Fehler! Verweisquelle konnte nicht gefunden werden.
Prevalence [%]	10

Parameter	Value
Fraction of working population under risk) [%]	90
Years	20
CoI incl. WtP [€/a]	4 942
Likelihood for loss in income [%]	32

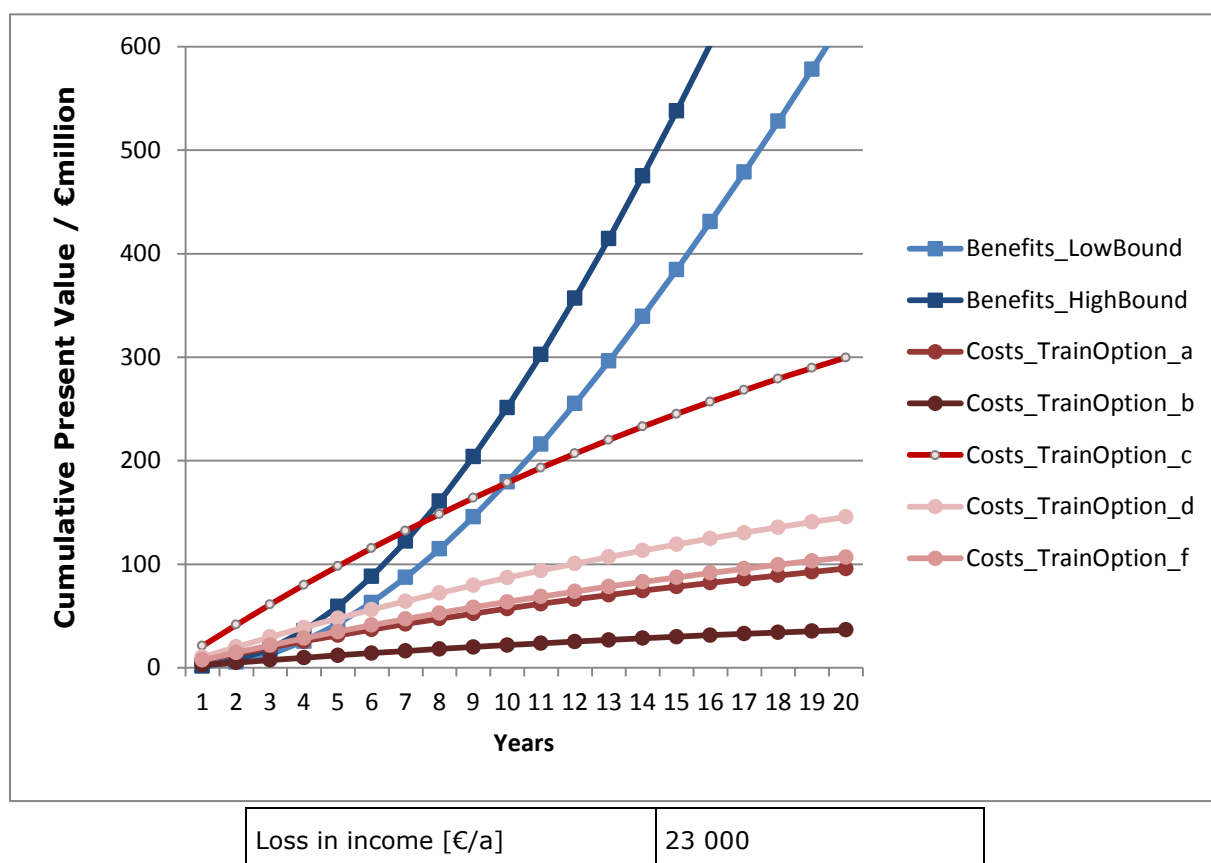


Figure 20: Modelling of the costs-benefit analysis over 20 years for various training concepts excluded e-learning in motor vehicle/refinish sector, assuming the initial asthma incidence issue of 0.7 % per year

Transferring the empirical based findings on an incidence rate of 0.7 per cent for modelling of the health benefits, the costs-benefit analysis is balanced very well. The critical issue is here the uncertainty regarding the representativeness of the random sample from the studies for all body shops in MVR sector.

The costs of all considered training options are covered by benefits associated with a reduction of asthma cases. Most training options are paid off at the latest after 3 or up to 5 years. Training in an external course (option c) would be paid off after 8 years (low bound) and 6 years (high bound).

E.9.1.2 Costs-benefit analysis results for overall affected sectors**Table 98: Overview on Training options in all relevant sectors**

Option	Remark
a: courses at an established education centre / competence academy etc.	20 participant in one course with a commissioned trainer
b: integration of the training part into the product presentation/ suppliers technical customer support	200 PU Chemicals Producers and 4.600 firms are PU Customers (producer of diisocyanates based products). 1 person per firm attend the training
c: external training course incl. training material and certificate	each worker attends the course at an accredited organisation
d: Training at work (in-house with a commissioned trainer)	On average cost distribution among a working collective of 20 workers. Manufacturing processes will be further continued and not stopped.
e: e-learning	E-Learning is only foreseen for sectors: construction chemicals and automotive repair (exempted vehicle refinishing with spaying application). Exemplary for around 1.6 mm workers the costs are calculated
f1: train the trainer and internal instruction for workers	course for trainer in a course according to the option c
f2: train the trainer and internal instruction for workers	course for trainer in a group according to the option a

The costs of the option f1 and f2 differ from each other, because there are two possibilities to train the trainer: in a course or in a group (education centre) are considered.

Table 99: All sectors – estimation of health benefits based on reported asthma cases (method 1)

Parameter	Value
Number of exposed workers under risk	1 447 475
Incidence rate absolute number of recorded cases – baseline	235
Incidence rate [%/a] – restriction	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.
Prevalence [%]	10
Years	20
CoI incl. WtP	5262

Parameter	Value
Likelihood for loss in income [%]	32
Loss in income [€/a]	31740

*Skin diseases are assumed as asthma cases, due to similar socio-economic impacts

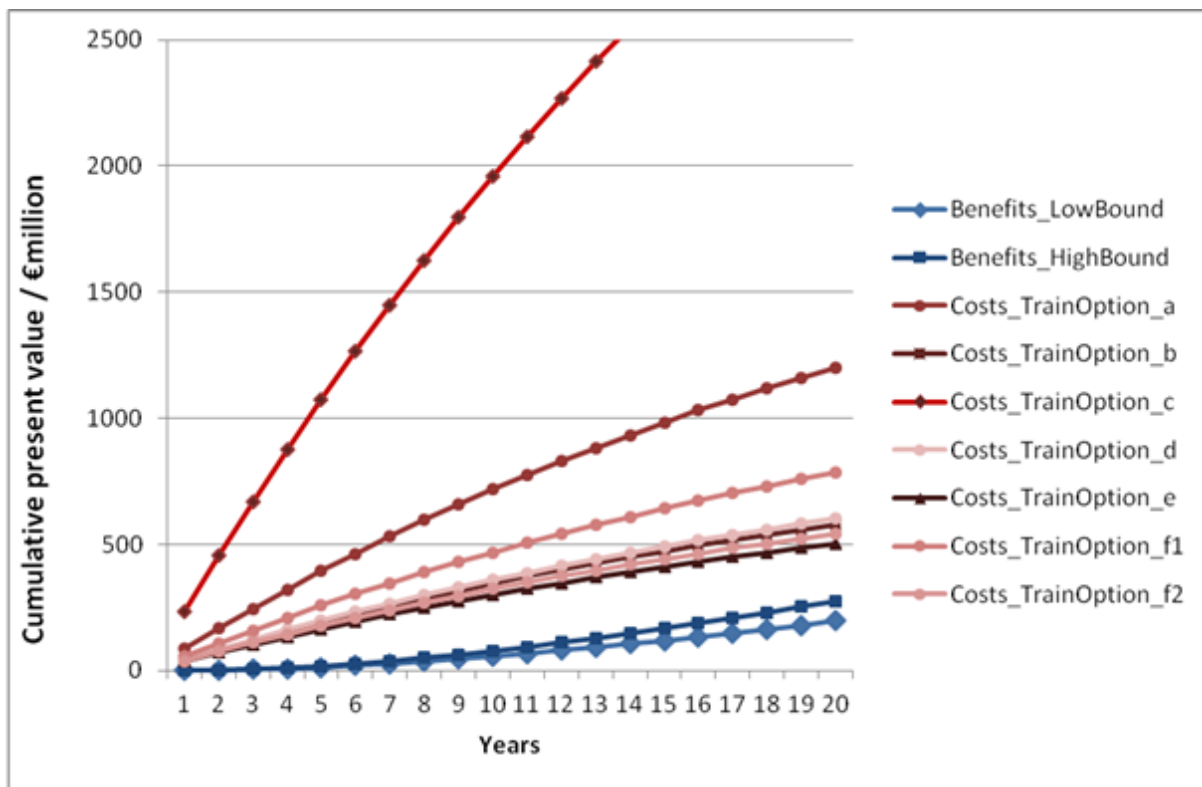


Figure 21: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 235 cases per year

Taking into account solely the recorded asthma cases, the benefits and costs are not proportional (Figure 21). Nevertheless it should be considered, that the cost calculation comprises the number of all exposed workers. The estimation of benefits is based on incomplete statistics within the EU-28. In addition the underreporting issue impacts the comprehensiveness of the estimation of the empirical based risk (incidence). Therefore the representativeness of 235 cases for the dimension of the asthma issue in all sectors is questionable. In this case the results on calculated costs of training could not be equally compared with the estimated benefits for human health.

Table 100: All sectors – estimation of health benefits based on reported asthma cases covering the underreporting issue (method 1)

Parameter	Value
Number of exposed workers under risk	1 447 475

Parameter	Value
Incidence rate absolute number of recorded cases – baseline	2350
Incidence rate [%/a] – restriction	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.
Prevalence [%]	10
Years	20
CoI incl. WtP [€/a]	5262
Likelihood for loss in income [%]	32
Loss in income [€/a]	31740

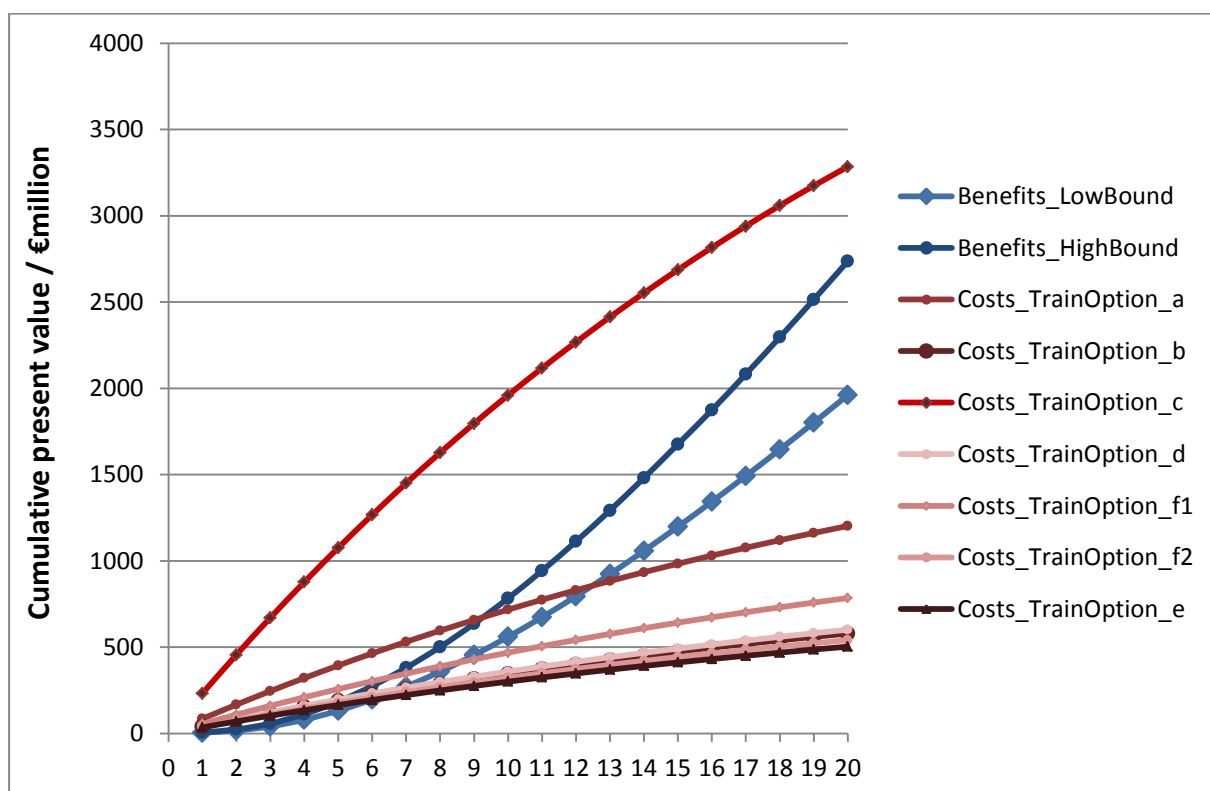


Figure 22: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 2350 cases per year

Covering underreporting by adjustment of recorded cases with an underreporting factor, the value of the benefits could be more equally comparable with the training costs. The costs will be outweighed by benefits reducing the number of asthma cases and are proportional to the benefits for human health. However, similar to the analysis in the MVR sector, the costs for the training via course (option c) are not covered by the benefits. Depending on the training concept the pay-off would be achieved at earliest after 5 (high bound estimate) and at latest after 15 years according to the low bound estimate.

Table 101: All sectors - indirect approach by extrapolation method 3

Parameter	Value
Working population [mil]	242.3
Fraction of isocyanates as causative agent for asthma [%]	10
Incidence rate for asthma* – baseline [persons per 1 mil. workers]	250
Incidence rate [quotient for reduction of cases [%/a] – restriction	The incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.Fehler! Verweisquelle konnte nicht gefunden werden.
Estimated number of cases caused by isocyanates/ incidence rate [%] – baseline	6058 (± 0.42 %)
Years	20
CoI incl. WtP [€/a]	5262
Likelihood for loss in income [%]	32
Loss in income [€/a]	31740

*all causative agents

The indirect approach is in principle a top-down method that underpins the appraisal regarding the real dimension of asthma cases caused by isocyanates. The results on calculated asthma cases of this approach are comparable with the underreporting approach.

The costs for the training option c are still less cost-efficient, but are outweighed by the estimated benefits. Other training measures are covered by benefits. Excluding the

training option c and depending on the training concept the costs for training would be paid off at the latest after 6 years after implementation of the training according to the Appendix "Trainings and Measures".

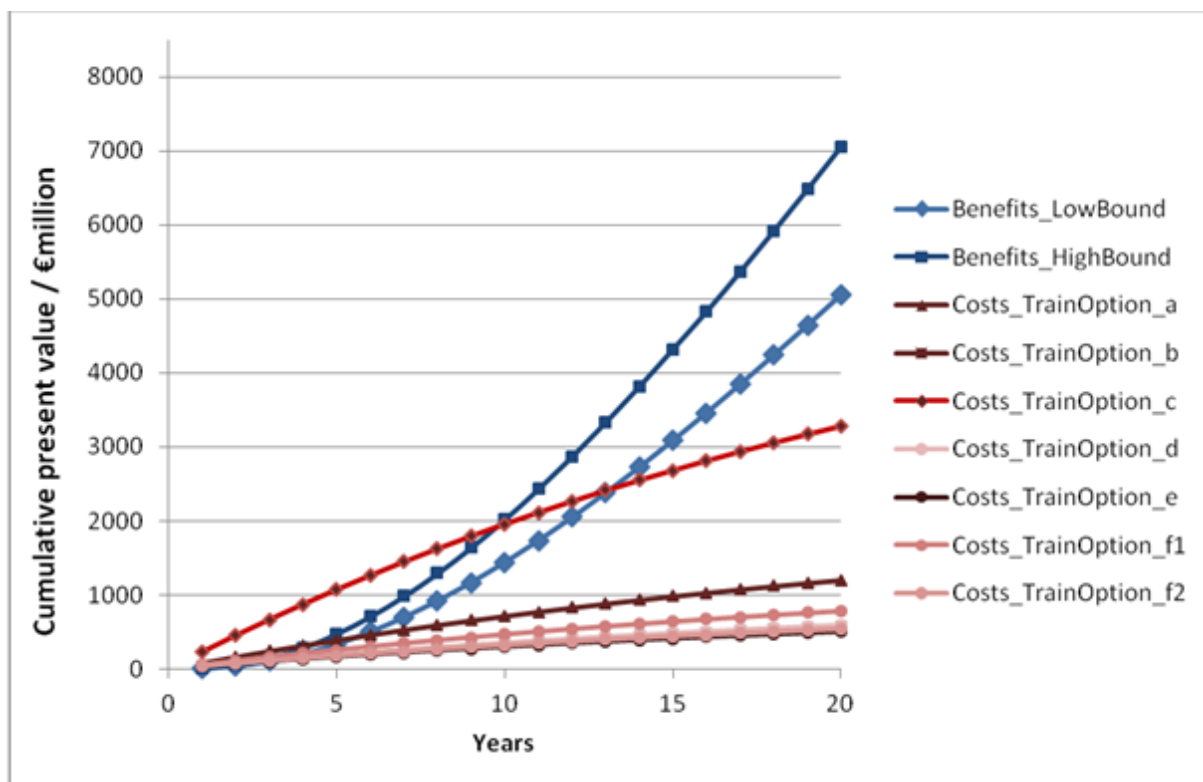


Figure 23: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming an absolute asthma incidence of 6058 cases per year.

Table 102: All sectors- random sample based incidence rate (method 2)

Parameter	Value
Number of exposed workers	1 608 306
Incidence rate [%/a] - baseline	0.7
Prevalence [%]	10
Fraction of working population under risk [%]	90
Incidence rate [%] - restriction	the incidence rate after implementation of the training measure is estimated according to the modelled forecast in Figure 13 and Table 85 Fehler! Verweisquelle konnte nicht gefunden werden.Fehler!

	Verweisquelle konnte nicht gefunden werden.
Years	20
CoI incl. WtP [€/a]	5262
likelihood for loss in income [%]	32
income loss [€/a]	31740

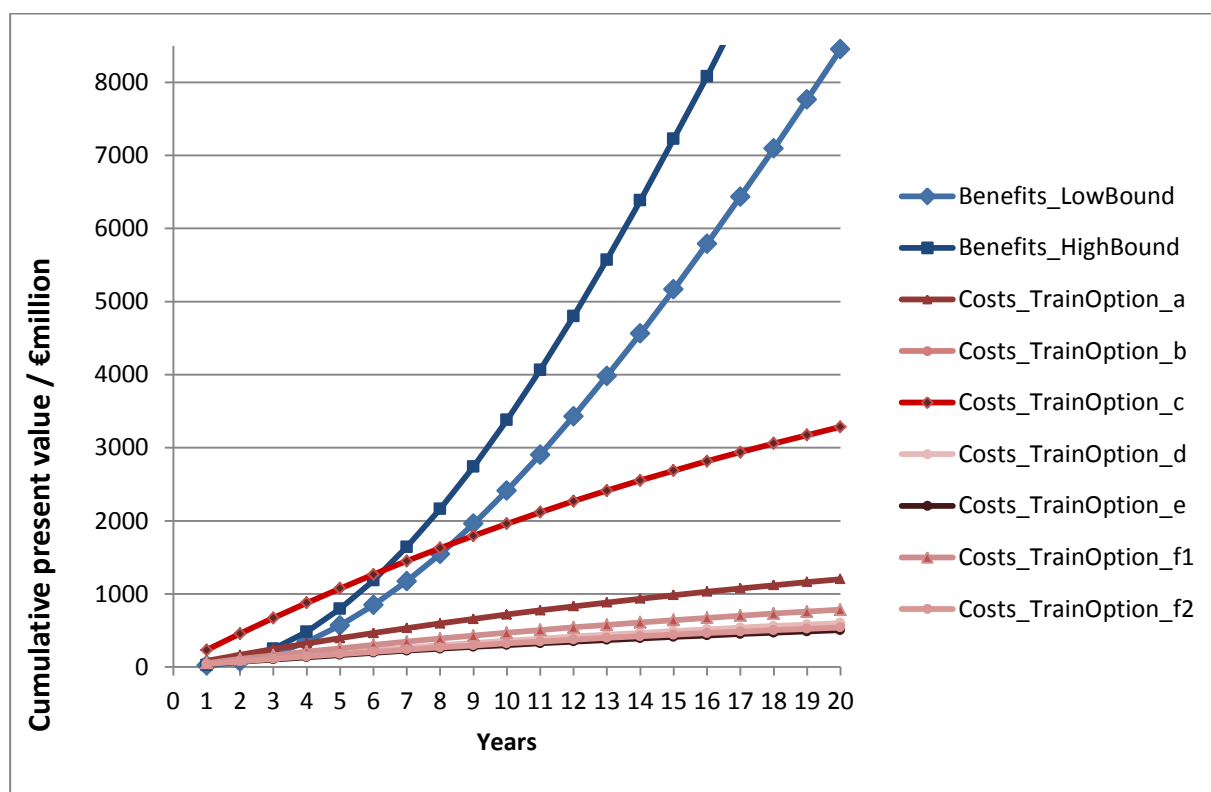


Figure 24: Modelling of the costs-benefit analysis over 20 years for various training concepts in all sectors, assuming the incidence rate of 0.7 % per year

The costs-benefits analysis applying the input parameters for an incidence rate of 0.7 % provides a similar chart as previously in the MVR sector. The costs of the training and the benefits are balanced very well. The investment for training would be returned at latest after 3 years, excluding the option c. Overall, a very positive benefit/cost ratio could be expected, in case an incidence rate of 0.7 % represent the real situation. However, some uncertainties exist regarding to representativeness of the results from random sample for all relevant sectors.

E.9.1.3 Costs-benefit analysis: overview on results for sectors at high risks

In conclusion regarding the costs evaluation it should be stressed that the real economic impacts due to productivity loss by one working day investment in training within a time period of 4 years might be not as significant as estimated in Figure 11. The loss of solely a working day might have negligible effects due to the fact that the companies are not

constantly working at 100 per cent capacity and personnel buffer is factored in. Surely this short time effect cannot be deemed equivalent to productivity loss caused by working disability. In case of asthma approx. additionally 10 working days per year are lost. Even with personnel buffer it is not trivial to compensate the lost personnel capacities.

Generally the training groups of e.g. 20 persons enable realisation of economies of scale and reduction of costs units per workers. However, finding a good balance between the group size and training success should be aimed for. It should be stressed that the effectiveness regarding risk reduction of training via e-learning may not be expected to be at the same level as face to face training options. Uncertainties exist regarding the number of not-registered or underreported cases of occupational asthma. Different methods were applied for the estimation of the possible extent of asthma caused by isocyanates in reality.

The bubble-diagram in the Figure 25 below provides an overview on results on benefit-costs ratios of RMO1 (solely trainings and measures) that result after 20 years. The diameter of bubbles represents the factor between benefits and the costs of each analysed training measure. In case of a ratio less than 1, the costs are not proportional to the benefits. The figure shows that in most scenarios the costs are proportional to the benefits. The results for the incidence rate of 0.1 % per year are not included because of underreporting issue.

E.9.1.3.1 Additional costs and benefits of the Appendix Exemptions

Generally, the benefit cost ratio for human health by identification of exempted products based on isocyanates can be assumed to be positive (i.e. benefits outweigh costs). At this moment a precise quantification for human health cannot be performed. In principle, an increase of certainty about the risks associated with products based on isocyanates can be perceived as a benefit for human health. Additionally an increase in the number of identified products for exemption could be considered as a qualitative indicator for measurement of the benefits after implementation of the Appendix Exemptions. An increase of exempted products in use correlates then with benefits for human health. The comparison of additional costs for RMO1 and RMO2 (with and without Appendix "Exemptions") provides an indication for most efficient RMO. (cf. E.9.4)

E.9.1.4 Costs-effectiveness analysis

The costs-effectiveness analysis is carried out only for the training measures under RMO1. The costs-effectiveness analysis provides information on costs of investment in order to avoid one asthma case over a period of 20 years. The analysis is performed for all identified risk situations (e.g. incidence rate absolute/relative) and for all trainings options. The results for the low bound of benefits are presented in Figure 26, Figure 27 and Figure 28 below. The calculated range for costs units which depend on the training model are summarised in a table below. For each assumed constellation, the calculated total costs are set in relation to the cumulated number of avoided cases over 20 years. The results on underreporting in the MVR sector and in other relevant sectors are presented in the charts below. Only the low estimate of the effectiveness of the training measure is selected for discussion.

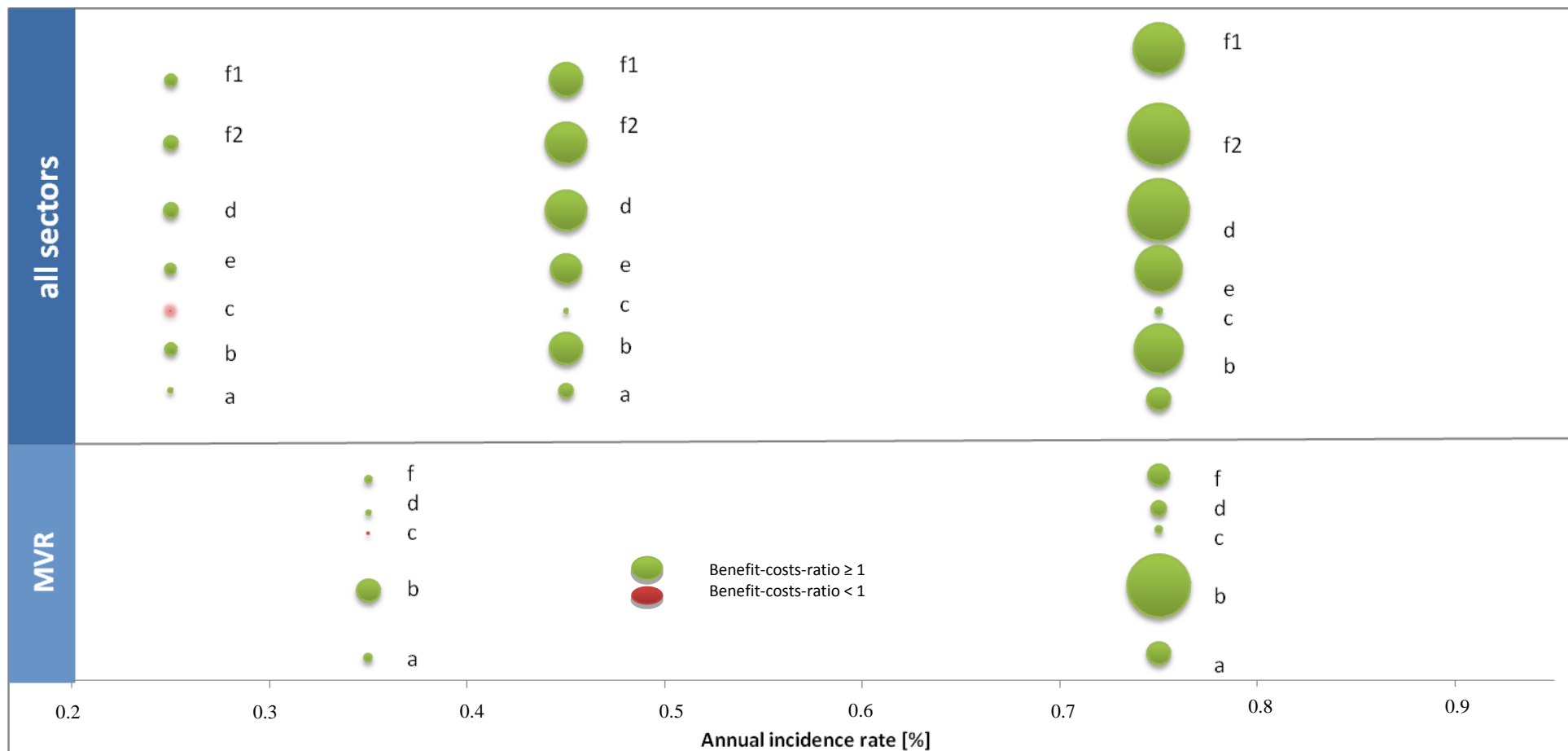


Figure 25: Overview on results for benefit-cost ratio after 20 years of training measure implementation – all considered scenarios (benefit in low bound)

Results case example motor vehicle refinish (method 1 covering the underreporting issue)

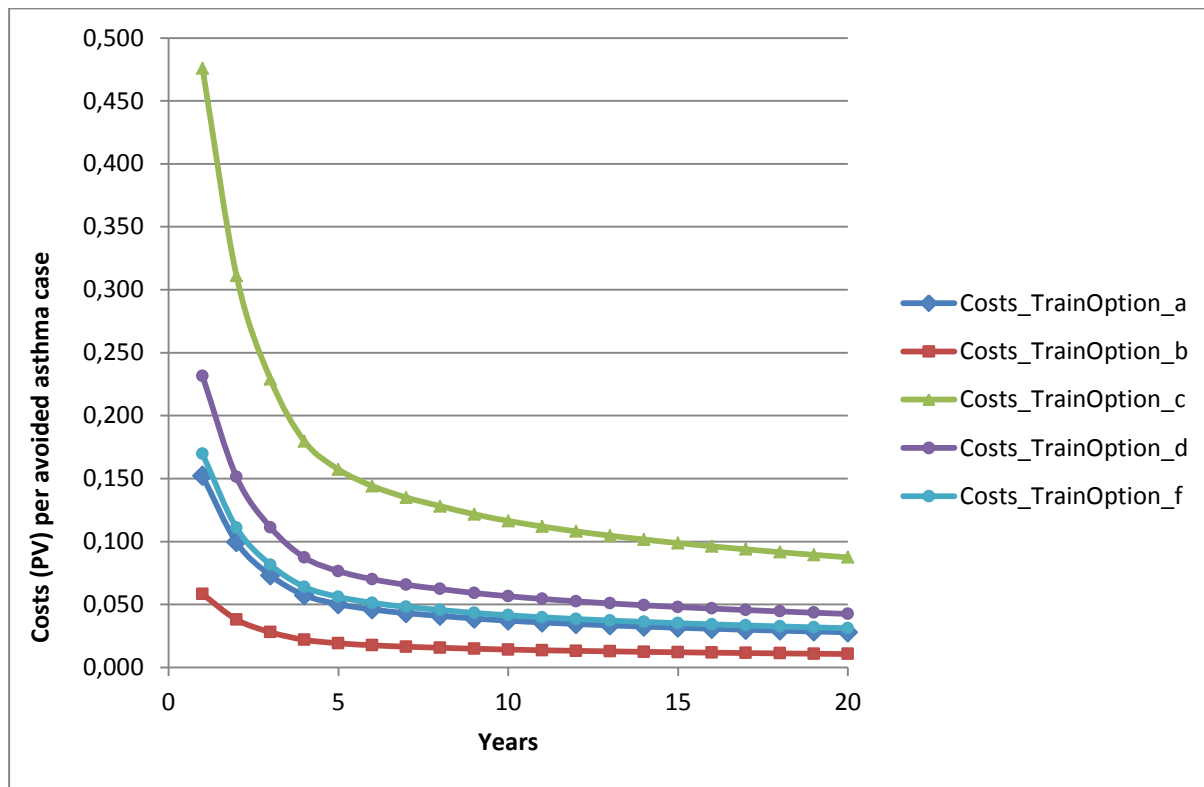


Figure 26: Development of the cost units per avoided asthma case over time in MVR – estimation based on statistics of reported asthma cases covered by underreporting factor 10

Results on overall affected sectors method 1 covering the underreporting issue

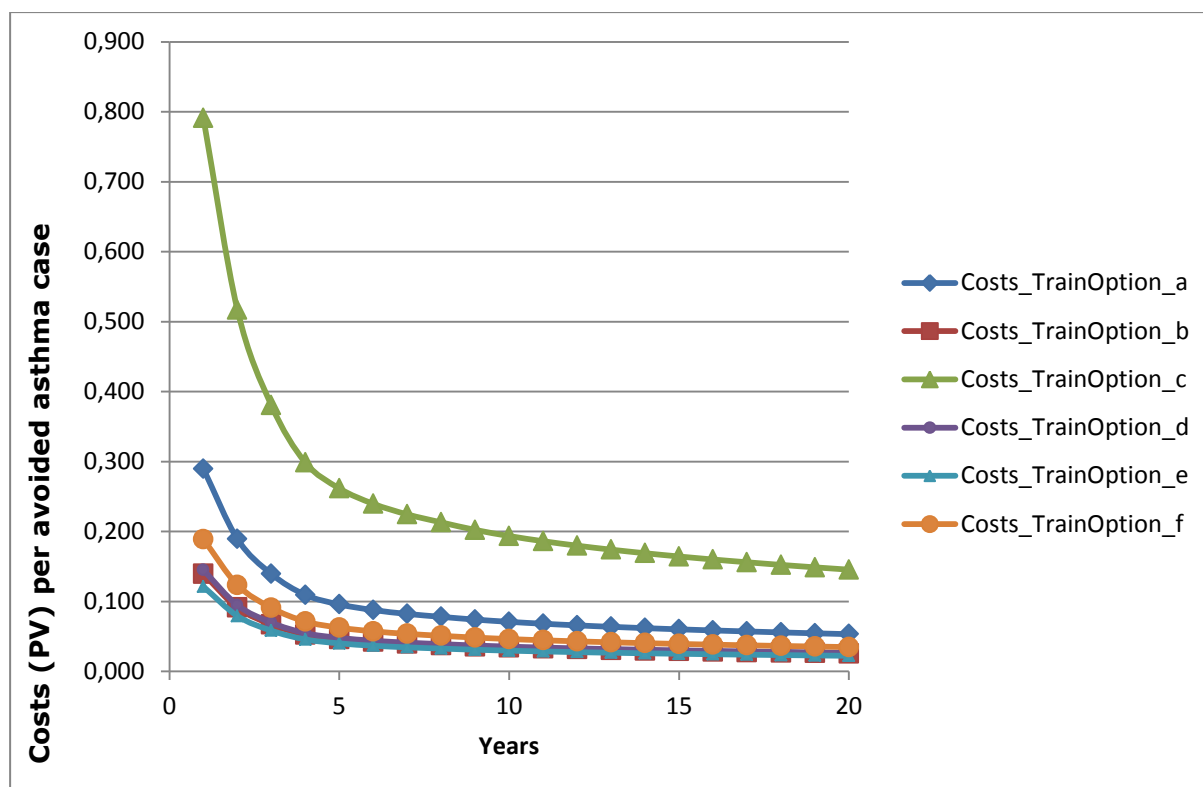


Figure 27: Development of the cost units per avoided asthma case over 20 years in all sectors – estimation based on statistics of reported asthma cases covered by underreporting factor 4

The charts in Figure 26 and Figure 27 present the costs only for selected training options. Option e indicates the similar results as options b, d and f.

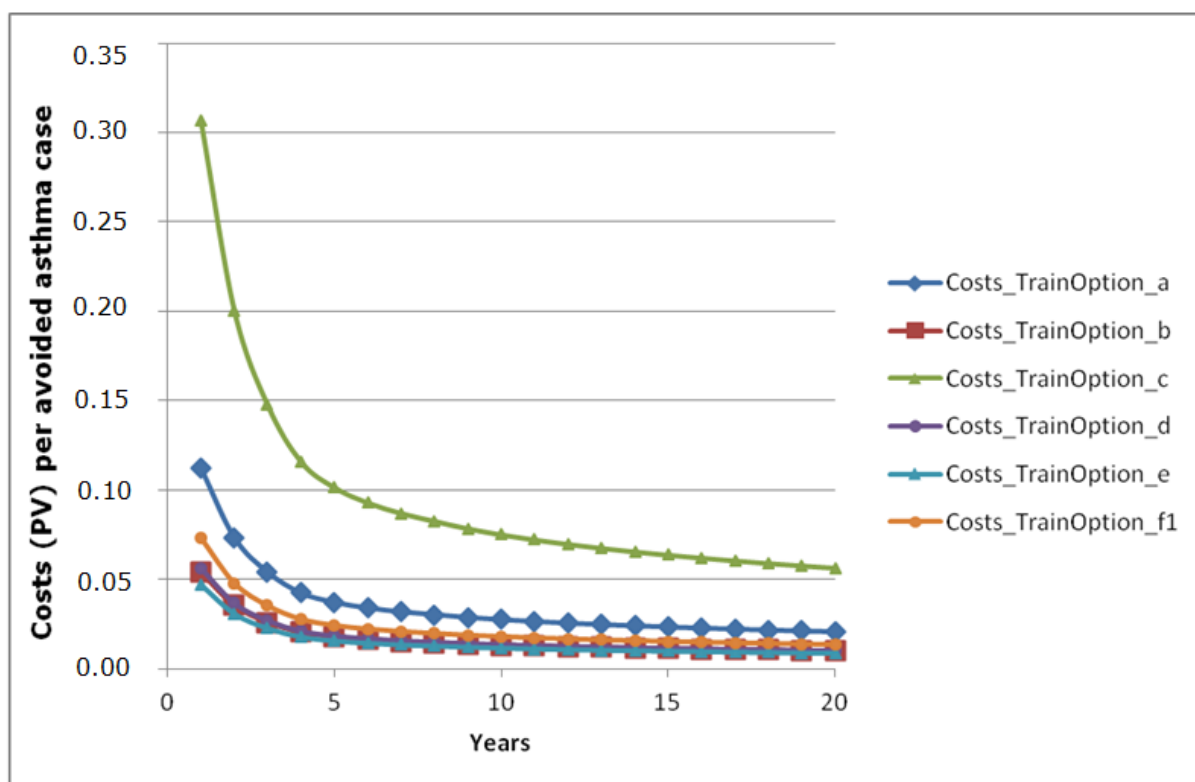


Figure 28: Development of the cost units per avoided asthma case over 20 years in all sectors – estimation based on method 2

Results on overall affected sectors method 3 (initial risk 6058 cases per year)

The charts on development of the cost units over time provide a clear picture on cost degeneration, which could be relatively quickly realised after implementation of the training measure. In the assumption, at the beginning (transient period) after the implementation of the restriction about one quarter of exposed workforce will attend training per year. Hence, not all potential asthma cases could be avoided in this period.

Thus, the consequence is that the most long term effects regarding to the reduction of asthma cases could be realised if the training as a prevention measure will be undertaken as soon as possible. The cost units per avoided case in the MVR sector are slightly lower than in all sectors because the incidence rate is assumed to be slightly higher. However the cost units per avoided asthma case are in the same order of magnitude (cf. Table 103).

Assuming the evaluated risk based on the underreporting issue represents the real situation in the practice, the cost units per avoided asthma case in all sectors are in a range between €5000 and €145 000 (low bound of effectiveness). In the high bound the costs units are correspondingly lower, in a range between €4000 and €104 000 (excluding the method 1 direct reports).

Table 103: Overview on results for costs-effectiveness analysis (after 20 years in €million/case avoided)

Estimation method for asthma cases	MVR		All sectors*	
	Low bound	High bound	Low bound	High bound
Reported cases Risk range: 0.02-0.07	0.043-0.35	0.031-0.25	0.223-1.454	0.159-1.041
Under-reporting Risk range: 0.2-0.26 %	0.011-0.087	0.008-0.063	0.022 - 0.145	0.016-0.104
Incidence rate Risk range: 0.7 %	0.004-0.033	0.003-0.024	0.068-0.053	0.005-0.038
Indirect Risk range: 0.42 %	Not applied	Not applied	0.005-0.034	0.004-0.024

*Excluded construction chemicals and automotive repair sectors (without MVR)

E.9.2 Cost-benefit analysis of the possible restriction measure RMO2

In contrast to RMO1, the costs for implementation of the Appendix Exemptions would not incur anymore. Instead, in addition to the estimated training costs for around 1.6 million workers (Appendix "Trainings measures") further training costs will incur for workers in the construction and automotive repair sector (excluding vehicle refinishing) (3.6 million).

The costs for e-learning of 3.6 million workers are modelled over 20 years and presented in the chart as cumulative present values. On average the annual costs of the training via e-learning are € 79 million. Without the exemptions procedure the additional costs for e-learning were estimated at round € 1572 million over a time period of 20 years.

Generally it can be presumed that the benefits for human health resulting from e-learning would be lower in comparison to the use of exempted products containing the isocyanate monomer below 0.1 % (w/w). This consideration is also in line with the hierarchy of occupational protection measures. In such a case the delta in benefit would be higher than for e-learning. However, at the moment it is not possible to quantify this in detail because in many cases already a low risk for the workers using such products is assumed. Hence, further reduction of risk will be small.

E.9.3 Comparison of impacts in RMO3

The benefits for human health for the EU-28 will increase extremely. However, in this case the asthma risks will be solely allocated to non-EU countries where in several cases, as is well known, lower occupational protection and safety standards may predominate. In such case, the overall balance of health impacts on the workers (world-wide) is expected to be negative.

Although a very rough calculation has been performed and the generated figures are not generally valid, a complete ban of the use of diisocyanates seems not to be the most cost-effective measure to obtain a proportional balance between the annual costs of the risk reduction measure \approx € 5.5 – 17 billion and the realisable annual health benefits of € 33.2 million. Even assuming the complete ban of use isocyanates within the EU, in case of underreported numbers of asthma /skin diseases around € 294 million per annum of benefits over the period of 20 years could be realised in all use sectors of isocyanates. Considering the incidence rate of 1 per cent, the annual benefit in all sectors would then amount to approx. € 1.6 billion, in case that the incidence rate could be reduced down to zero. Such effects seem to be unrealistic, because even when using alternatives remaining risks may occur.

The costs of non-use of isocyanate based coatings might be even higher than estimated in the case example. The coatings are being used for new vehicle production. The PU-based coatings protect the car body against the environmental conditions and prolongs therefore the vehicle life cycle. The PU-based coatings enable the protection of the vehicle value, efficient use of resources use for new vehicles as well as for vehicle in use.

Table 104: Summary and overview on possible RMOs

RMO_n	Costs PV [€million]	Benefit PV [€million]	Benefit/cost ratio	Remark
RMO1: Appendix Training and Measures and	500 – 3300	5400 – 7600	1.65 – 15	After 20 years, assessment. Range : figure for low and high bound of effectiveness
With additional Appendix Exemptions (compliance costs)	9 – 24	Quantification not possible	Quantification not possible	More incentives for introducing exempted (potentially low risk) products
RMO2: Only Appendix Training and Measures	1600 – 4400	5400 – 7600	1.2 – 4.8	

RMO3: Complete ban (related to manufacturers and down- stream users)	362 500	13000	Costs are at least 28 times higher	<ul style="list-style-type: none"> • Under premise: risk reduction up to zero • Risk relocation/ balance on risk reduction is not clear • Inefficient use of resources, additional costs within the supply chain
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E.9.4 RMO1 and RMO2 – Comparison of the costs

Costs of e-learning vs product exemption

In principle, companies using products in a potentially low risk environment (e.g. low temperature adhesives with automated application) have the option to qualify the product they use as “exempt” (according to the criteria in the Appendix on exemption) or just adhere to the conditions of the Appendix on trainings and measures. Figure 29 compares the economic impacts which result from costs incurred for obtaining exemptions and for e learning (one of the cheapest training options). The results clearly show that the option to go for an exemption procedure is much more cost-efficient (with a factor of about 45-120), even if the number of such products or the costs involved would be significantly underestimated. This is only true if the cost picture is considered for sufficiently large sectors, where the costs of qualifying products for an exemption may be shared by a number of companies.

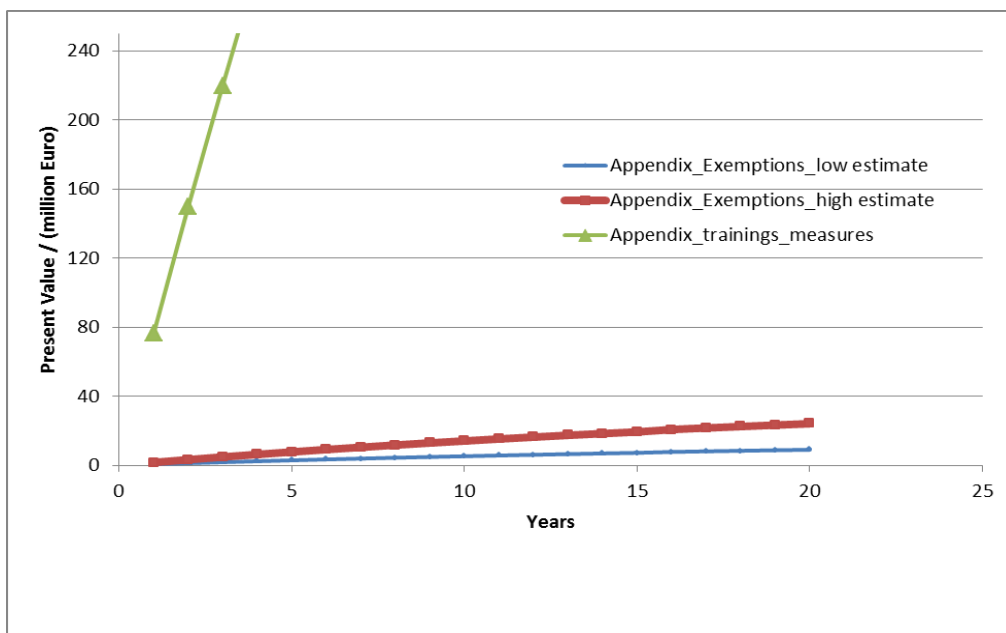


Figure 29: Comparison of the costs over 20 years for Appendix Exemption and training

On average the costs for RMO2 are 100 times higher than for RMO1. Thus RMO1 is the more costs-efficient risk management measure.

Substitution by the products with lower risks (implemented under Appendix Exemptions) is more beneficial for human health, than e-learning and further use of products associated with higher risks (implemented under Appendix Training and Measures).

E.10 Conclusion on risk management option analysis

The Dossier Submitter is concerned by the fact that the risk of respiratory sensitisation resulting in occupational asthma caused by diisocyanates is not adequately controlled yet by means of an EU-wide existing regulations. The proposed approach was developed with respect to established national regulations and in particular to EU Directives 98/24/EC and 89/391/EEC.

From data analysis of occupational asthma statistics and epidemiological research, it is concluded that in the EU the number of yearly new cases of occupational asthma is unacceptably high. The number of new asthma cases has been found to be in the range of 2300 -10000 cases/yr.

Therefore, regulatory action is required and this should be undertaken on a Union-wide level. The proposed restriction is the most appropriate EU-wide measure because it targets the risks from workplace exposure to diisocyanates while keeping the use of diisocyanates a possible option.

The proposed restriction is considered a balanced and justified measure as the benefits of risk reduction are estimated to outweigh the costs of the proposal after a reasonable time. The reduction of risk in the EU as a result of the proposed restriction is estimated to avoid over 3000 cases of occupational asthma per year, after full implementation of the restriction measures.

Benefits (PV after 20 years) have been estimated growing to a range of € 3 –5 billion. Depending on the training option and the assumed effectiveness of training measures and considering the assumed initial risk for 6500 cases/yr, a range of € 8000 – 82000 is derived for costs of preventing one additional new asthma case. It is expected that the effort to comply with the restriction is viable for all companies concerned.

It was demonstrated that the restriction would also have only a small impact on the prices of end-use services supplied.

The proposed restriction is a practical and monitorable measure for industry and enforcement authorities.

In conclusion, the restriction dossier demonstrates that action is required on an EU-wide level and the proposed restriction is the most appropriate measure. Even taking into consideration the existing uncertainties, the main conclusion will not change. According to the results provided in Table 104 the proposed RMO1 that combines both the measures described in the Appendix Exemptions and in the Appendix Trainings and Measures is the most costs-effective risk reduction measure. It provides the highest overall net benefit.

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Table 105: EUROSTAT data preparation for estimation of a daily fee [€] for a commissioned trainer

Member State	Professional, scientific and technical activities	Management consultancy activities	Engineering activities and related technical consultancy	Other professional, scientific and technical activities	Other professional, scientific and technical activities n.e.c.	Estimation of daily fee		weighted	
	Aggregated per working day	Aggregated per working day	per working day	per working day	per working day (2013)	min	max	min	max
Austria	1074	908	1035	709	990	709	1074		
Bulgaria	245	314	313	217	256	217	314		
Croatia	374	373	435	241	311	241	435		
Cyprus	589	785	313	365	566	313	785		
Czech Republic	582	573		578		573	582		
Denmark	1250	1490	1416	1051	1045	1045	1490		
Estonia	423	545	362	283	383	283	545		
Finland	976	1266	1003	787	1136	787	1266		
Greece	359	466	363	349	469	349	469		
Hungary	389	430	441	254	285	254	441		
Ireland	1098	1632	1072	650	770	650	1632		
Latvia	323	280	293	241	204	204	323		
Lithuania	275	391	192	184	311	184	391		
Luxembourg	1752	1825	1384	-	-	1384	1825		
Malta	918	471	-	837	1743	471	1743		
Norway	1999	1666	2871	1420	2133	1420	2871		
Slovakia	469	424	758	568	921	424	921		
Slovenia	637	548	884	339	474	339	884		
Sweden	1515	1266	1249	1544	2410	1249	2410		
Sum others / Average						584	1074	95.78	176.1

ANNEX XV RESTRICTION REPORT – DIISOCYANATES

Member State	Professional, scientific and technical activities	Management consultancy activities	Engineering activities and related technical consultancy	Other professional, scientific and technical activities	Other professional, scientific and technical activities n.e.c.	Estimation of daily fee		weighted	
	Aggregated per working day	Aggregated per working day	per working day	per working day	per working day (2013)	min	max	min	max
France	1355	1200	1423	649	998	649	1423	58.38	128
Germany (until 1990 former territory of the FRG)	949	1077	1024	943	1219	943	1219	166.1	214.6
Belgium	1592	1259	1481	803	1258	803	1592	41.74	82.79
Netherlands	1081	928	1099	1203		928	1203	42.68	55.32
Italy	756	1131	708	658	685	658	1131	85.57	147.1
Poland	402	443	332	389	402	332	443	36.54	48.69
Romania	310	383	337	170	176	170	383	5.087	11,5
Spain	663	771	919	454	470	454	919	32.68	66.18
United Kingdom	1134	1217	1440	1029	974	974	1440	97.39	144
ESTIMATION								662	1074
Average								868	

Table 106: Estimation of adjustment factors (source: ISOPA, EUROSTAT)

Market share by country according to ISOPA incl. Switzerland (2014)		Market share of isocyanates by MS according to ISOPA excl. Switzerland (own guess)	Price level indices 2014 [%] according to EUROSTAT	Estimated adjustment factor
UK	9.8 %	10 %	122	12.2
France	8.7 %	9 %	107	9.63
Spain	7.1 %	7.2 %	93	6.696
Belgium	5.0 %	5.2 %	111	5.772
Netherlands	4.4 %	4.6 %	113	5.198
Portugal	2.8 %	3 %	80	2.4
Romania	2.7 %	3 %	48	1.44
Germany	17.4 %	17.6 %	101	17.776
Italy	12.7 %	13 %	103	13.39
Poland	10.7 %	11 %	53	5.83
Sum weighted average (10 countries)	81.3 %	83.6 %		80.3
Others	18.7 %	16.4 %	93.6	15.35
Sum / Adjustment factor				95.7
DK			140	
SE			136	
LU			135	
IE			125	
FI			124	
AT			109	
CY			91	
EL			82	
SI			81	
MT			81	
EE			71	
LV			66	
SK			63	
HR			63	
CZ			59	
LT			58	
BG			43	
NO			158	

F. Assumptions, uncertainties and sensitivities

Different data sources are used. In most cases data are related to secondary sources, which are adjusted with assumptions and/or derived adjustment factors. The data provide a range. Therefore, quality assurance of the socio-economic analysis is provided by sensitivity analysis. The calculated values of critical parameters are varied. It will be checked if the conclusion changes in a fundamental way. The results are presented as a bandwidth.

Declaration on uncertainties and possible factors for bias in the modelling of costs and benefits:

- The factor fluctuation of employees is not considered for calculation of the training costs and health benefits. It is assumed, that this factor would impact the costs and benefit in proportional manner, so that the difference remains the same or of the same order.
- It is presumed that the workforce in the relevant sectors will remain at constant level, no growth or decrease is expected.
- The factors "retirement from employment" rate and "entry to the profession" rate were not considered in the calculation of the health impacts and the costs. Generally it should be assumed that more damaged persons leave the working collective and healthy individual with very low asthma prevalence will enter. So the prevalence rate would decrease in middle term. Therefore the number of workers under risk is potentially higher as in modelling assumed. In order to reduce the complexity these factors have been waived in the modelling.
- Prevalence of asthma in the exposed population could be lower than 10 % assumed (e.g. 5 % from cross sectional studies (Wild et al., 2005)). In such case the number of workers under risk would be higher and number of asthma cases could increase assuming the modelling based on the relative incidence rate approach.
- In the modelling, the input parameter growth of employment which could maximally correlate with the growth of GDP is neglected. According to a recent forecast of EU Commission (European Commission, 2016) the growth in GDP is estimated by 1 per cent. The number of workers impacts the costs and benefits in the same or proportional manner, so no significant impact on costs-benefit comparison will result.
- For the preparation of the EUROSTAT data which create the basis for the estimation of the trainer fee or productivity loss, 230 working days were assumed. These could vary in a negligible range from MS to MS
- From the EUROSTAT data base only "Turnover per person employed" in average could be obtained. Nevertheless, the estimated value falls within the range provided by the recommendation of the German Association (BDVT, 2012) of trainers, consultants and coaches on consulting fee for one day. For an adequate comparison the German price level will be taken into account.
- The hourly rate on figures for productivity loss and income loss could be only calculated on average. The EUROSTAT data provide no specific values related to the occupation in the sector.
- The number of exposed worker may be overestimated in several sectors (verification of data from ISOPA by EUROSTAT database on employee statistics). However the data on exposed workers may be underestimated in other sectors. Furthermore the number of exposed workers is an important input factor for both costs and benefits. Therefore the conclusion on overall impact is not affected significantly.

- The assumed correlation of the isocyanates market share with the number of workers might be incorrect, because the degree of the process automatisation in manufacturing could be essential for the number of employees. This aspect may have a marginal impact on the total training costs. At the moment no more exact data on distribution of the exposed workers within EU-28 are available to the dossier Submitter.
- The statistics from 2012, 2013 and 2014 were not prepared with the factor for purchasing power parity. According to EUROSTAT, since 2012 up to 2014 the price level indices have remained at the same level.
- A slight / negligible deviation of the estimated figures on gross value added and personal costs could be expected. In a representative random sample several economic activities (NACE codes) have been selected for the estimate for all relevant sectors.
- The number of participants in a course group of in a firm could possibly be over- or underestimated. The number of employees to train per firm is estimated at 20 persons on average. Presumably the number of workers per firm to train might be higher than the 20 persons assumed, so that in case of training by a commissioned trainer or training at work, the costs per person would be tendentially lower.
- Furthermore in the calculation of the overall costs (for about 1.6 million workers) in RMO1 a combination of each training concept with e-learning has not been considered. The listed uses (see section B.2) indicate that the most of them would at least require the training for group 2 defined in the Appendix Trainings and Measures. It is assumed that only 10 per cent of uses or workers will be classified to "measures group 1", where the training by e-learning could be a possible option. The costs of e-learning are thus definitely lower, so the effect for total costs will be very low due to the share of 10 per cent.
- In initial approximation 1-2.5 per cent deviation of total training costs for each option could be assumed. The German Employer's Liability Insurance Association indicated to offer for the members a cost free seminar for training. The fraction of workers in Germany represents around 50 per cent of the EU market. Furthermore according to experts, several products in construction sector have recently been optimised regarding the isocyanate monomer content. At the moment efforts also are undertaken to reduce the isocyanates monomer content to < 0.1 % (w/w) so that it is assumed that only few workers would have to attend the training. Thus the additional costs for such case could be assessed as negligible.
- For reduction of complexity in the modelling of training costs, it is assumed that all workers would attend the training at the time point zero in the investment period of 4 years. This means that 100 per cent of investments costs incur initially for the each training cycle (static method) and they are spread evenly over the period of 4 years. In reality the investment costs might be staggered, because it is more likely that 25 per cent of the workforce attend the training each year. However, the annual investment costs would additionally incur for trainings in each of the previous periods (dynamically staggered costs calculation model).
- For modelling of the costs over 20 years in RMO3, on average 1 per cent for annual growth of the value added is assumed. This premise is underpinned by the information provided by ISOPA and market forecasts. Although the forecasts provide a higher growth rate in the short term, market saturation is expected in the long term.
- The costs values and savings based on asthma cases cannot be infinitely cumulated. Due to findings on the average age of the asthma sufferers, number of working years

and statistical life expectancy the resulting modelling over 20 years is just a snapshot, which would not continue indefinitely.

- Depending on the training option chosen, the share of costs for productivity loss is between 20 and 90 % of the total. This is a conservative estimate. The real economic impacts due to productivity loss by investment in training of one working day over a time period of 4 years might be not as significant as estimated in the calculation of the costs if this is compared to productivity loss caused by working disability. In case of asthma approximately an additional 10 working days per year may be lost.
- Only the effects from a reduction in asthmatic diseases have been calculated. As discussed in section B.5.6.5.3., diisocyanates also cause skin sensitisation. (13 % of reported numbers of occupational diseases). The methods proposed in this restriction may be expected to also reduce cases of skin sensitisation in about the same proportion as asthmatic diseases. The positive human health impacts of this will add to the benefits.

G. Stakeholder information

G.1 Data on the number of exposed employees

In the discussions with industry stakeholders (ISOPA, ALIPA) the best estimation for the number of exposed employees in the various industry sectors has been extensively discussed, based on the Statistical Classification of Economic Activities in the EU (NACE code classification). Based on feedback from the various trade associations represented in the ISOPA/ALIPA exchange forum the following result was obtained:

Table 107: NACE codes for sectors – potentially exposed workforce downstream

NACE code*	Sector	Association	I= Industrial P=Prof.	Employed People	Thereof potentially exposed
C22.90: Manufacture of Plastic Products C20.16: Manufacture of plastics in primary form C22.10: Manufacture of plastic plates, sheets, tubes and profile	Flexible Foam	Europur	I	14 180	2694
C22.10: Manufacture of plastic plates, sheets, tubes and profile	Automotive Seating	Euromould.	I	13 489	5261
C20: Manufacture of chemicals and chemical products C23.52: Manufacture of lime and plaster C23.6: Manufacture of articles of concrete, cement and plaster	Construction Chemicals*	EFCC	P	n.a.	1 500 000
G45.20: Mechanical repairs and maintenance of motor vehicles.	Automotive Repair	FEICA	P	3 000 000	1 500 000
29.10; 29.20; 29.32	Automotive OEM	FEICA	I	n.a.	120 000
C22.22: Manufacture of plastic packinggoods; C17.21: Manufacture of corrugated paper and paperboard and of containers of paper and paperboard	Flexible Packaging	FEICA	I	n.a.	45000
multiple	Multiple Industry	FEICA	I	n.a.	231 000

NACE code*	Sector	Association	I= Industrial P=Prof.	Employed People	Thereof potentially exposed
24.30 : Manufacture of paints, varnishes and similar coatings, printing ink and mastics	Spraying/ Marine Coating	CEPE	P	6000	6000
24.30: Manufacture of paints, varnishes and similar coatings, printing ink and mastics	Printing Inks	CEPE	I	n.a.	50000
24.30: Manufacture of paints, varnishes and similar coatings, printing ink and mastics	Protective Coatings	CEPE	P	n.a.	500 000
24.30: Manufacture of paints, varnishes and similar coatings, printing ink and mastics	Vehicle Refinish	CEPE	P	n.a.	150 000
Aromatic spray resin 38249092 Aromatic prepolymer 39095090 Aliphatic spray resin 39072099 Aliphatic prepolymer 38249092	Construction Materials	PDA	P	1000	1000
C27.51: Manufacture of electric domestic appliances (email Marta Yuste/CECED 1.3.2016)	Cooling appliance	CECED	I	n.a.	2000
19.30: Manufacture of footwear	Footwear	CEC	I	~ 3750	1300
G46.75: Wholesale of chemical products. (email Irantzu Garmendia Aguirre 2.3.2016) "according to some of the distributors that handle isocyanates, they only handle closed packaging, store in warehouses and provide to customers. So no employee is exposed."	Distributors	FECC	I	n.a.	Not applicable Due to assessment by FECC
19.10: Tanning and dressing of leather	Textile/Leather	Contance	I	n.a.	2000
C22.21: Manufacture of plastic plates, sheets, tubes and profiles C22.23: Manufacture of builders' ware of plastic	Insulation boards and sandwich panels	PU Europe	I	n.a.	n.a.

NACE code*	Sector	Association	I= Industrial P=Prof.	Employed People	Thereof potentially exposed
F43.29: Other construction installation F43.33: Floor and wall covering F43.39: Other building completion and finishing F43.91: Roofing activities	Spray Foam	PU Europe	I/P	n.a.	n.a.
C16: Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials C16.1: Sawmilling and planning of wood C16.10: Sawmilling and planning of wood C16.2: Manufacture of products of wood, cork, straw and plaiting materials C16.21: Manufacture of veneer sheets and wood-based panels C16.22: Manufacture of assembled parquet floors C16.23: Manufacture of other builders' carpentry and joinery C16.24: Manufacture of wooden containers C16.29: Manufacture of other products of wood; manufacture of articles of cork, straw and plaiting materials	Furniture	EPF	I	1 016 000	4000
C31: Manufacture of furniture	Furniture	EFIC	I/P	1 100 000	220 000

*Partly own revision on nace code nomenclature. The data cover about 80 % of the market. Further data regarding socioeconomic contribution of the Polyurethane industry can be found in (ISOPA, 2014)

G.2 Stakeholder information – Call for evidence

Simultaneously with the notification of the restriction intention in ECHA's registry of intentions (RoI) industry stakeholders have been contacted by the DS and asked to answer a questionnaire on several issues related to the uses of diisocyanates. This questionnaire is attached below. In total 33 responses from a wide variety of companies in 10 different countries (15 DE, 3 AT, 3 UK, 1 from BE, FI, FR, IE, IT, NL, PL, 3 without country of origin) representing different application areas were received. A large majority of the respondents are rather big companies (25 report >100 employees). On the other hand, the number of exposed employees seems to be smaller (14 report 11-49, and only 8 report >100 employees)

From the analysis of replies the following remarks can be made:

1. Regarding the types of diisocyanates used, the answers show that from the list in section B.1 the emphasis seems to be on MDI (and its various isomers), TDI, HDI, IPDI.
2. Information regarding safe handling of diisocyanates is reported to come mainly from the Safety data Sheet (31 entries), secondly from National specific regulations (17 entries), followed by Industry sector associations (13 entries)
3. Regarding the tools used to communicate safety instructions to employees, first place is shared by written instructions (incl. computer aided) and Health and Safety Training courses (both 27 entries), third place is taken by verbal instructions (including videos) (23 entries)
4. Analysis specific for dermal contacts seems to be non-existent, apart from one company reporting swab analysis. There seems to be a dependence on indirect proof of dermal contact by comparing airborne levels of diisocyanates and biomonitoring data.
5. Regarding alternatives, specific proposals and ideas are lacking.

G.3 Further Comments from stakeholders

Apart from the above, in the course of the discussion with industry representatives the following statement was received on the importance of diisocyanates in the foam industry in view of the (hypothetical) possibility of introducing a complete ban:

"It is not possible to provide a reliable estimate of direct and indirect cost in case diisocyanates would be prohibited since a lot of influencing factors are difficult to quantify. The following paragraphs however aim at demonstrating on the Basis of existing data and publicly known information - that considering a prohibition on the use of diisocyanates would not only mean the end of flexible PU foam production in Europe but also risk wiping out tens of thousands of jobs in industries down the supply chain that use polyurethane foam.

To put things into perspective, there are today 107 slabstock foam plants in the EU28+CH+NO. Together they produce around 900,000 tonnes of foam. There are also 47 moulded foam production plants producing foam for the car seats of the around 15 million vehicles produced annually in the EU, representing another 140,000 tonnes of foam. There are also other plants producing flexible foam, for

example moulded foam for furniture, but their enter neither in the remit of EUROPUR or EURO-MOULDERS as trade associations and we do not have data on those plants.

It is impossible to produce PU foam without diisocyanates at an industrial scale. PU is by definition the resulting product of a reaction of an NCO group containing product (isocyanate) with an OH group (hydroxyl) containing compound (polyol).

It is also important to state that there are no free diisocyanates in PU foam. The diisocyanates it is produced from are consumed during the chemical reaction that creates polyurethane. They cannot be released into the air from polyurethane foam, which is an inert product (and an article under the REACH Regulation).

Therefore, if diisocyanates were to be prohibited in Europe, this would simply mean the end of PU foam manufacturing in the EU and where feasible replacement by imports of foam from Third Countries, where worker protection conditions are typically less controlled.

For example Turkey Russia or Ukraine, which are already major foam producers today. Plants in the EU would either have to close or be converted for other purposes. But these "other purposes" are impossible at this stage to foresee, considering the economic situation that is hardly geared towards massive re-industrialization in Europe today.

The consequences of the prohibition would not stop there since movements may be anticipated in customer industries as well. PU foam being a lightweight / high-volume cellular material, its cost of transport as compared to its weight can be relative important. For this reason, importing hundreds of thousands of tonnes of PU foam from outside of Europe may prove a costly exercise for the bedding, furniture and automotive industries, not even speaking of security of supply issues they may be facing. They might find it easier to relocate part of their production to lower-cost countries where the production of PU foam is well possible.

While this movement to be realistically anticipated in customer industries is hard to quantify, one has to note that further down our value chain, and linked to polyurethanes, around 29,000 companies in the EU are active in the furniture and bedding sector, representing an economic value of 45.5 billion EUR and employing over 122,000 people. Around 16,500 companies are active in the automotive parts supply chain, representing an economic value of 12.5 billion EUR and 69,000 jobs (source: ISOPA Socio-Economic Assessment (2014)). Clearly, if polyurethane foam could not be produced in Europe anymore, some of these jobs would also disappear.

Furthermore, major foam producers operating both in and outside the EU are headquartered in the EU where their research and development centres are located. Together with the quality of research in European Universities, these R&D centres provide the EU with the leading role in innovation in polyurethane foam technology. It can be expected that if production was not possible anymore in Europe, these research centres may also be relocated to Third Countries over time, since they typically need to have easy access to production sites where new formulations and processes can be tested.

White alternatives do exist for some applications of PU foam from a technical point of view, considering such alternatives to completely replace PU foam seems hardly feasible at a large-scale. We herewith prove a short overview of possible alternatives to the use in PU foam in major markets:

Bedding:

Out of the roughly 16 million mattresses being sold in the EU every year, close to half (48.8 %) are with a PU foam core, for a market value of close to 800 million EUR2. This market share has been in constant progression over the years. (Source European Bedding Industry Association (EBIA), 2012)

The second most sold category of mattresses are those with a spring core (41.3 %), but it should be noted in that regards that so-called "spring mattresses" usually also contain layers of polyurethane foam for softness and comfort. Mattresses with other filling (latex, fibres...) represent less than 10 % of the market and they also sometime include layers of polyurethane foam depending on the choice of the manufacturers.

Therefore, although in theory alternatives exist for PU foam in mattresses (latex, natural or synthetic fibres), the economic feasibility of such a replacement appears to be questionable. This view was substantiated in a report made by ICF International for the European Commission on formaldehyde (a raw material for the production of MDI), which looked at such alternatives and concluded that considering a restriction on formaldehyde would result in significant losses for the European economy and particularly for the European production of mattress and furniture, as well as increased costs for the consumer.

When discussing alternatives to PU foam in mattresses, one should also bear in mind that for alternative fillings, substances are used in production processes which may have hazardous properties too. This matter was discussed extensively during the process that led to the recent revision of the criteria for the EU Ecolabel for mattresses³, which also sets criteria for PU foam that are in line with EUROPUR's environment, health and safety standard, CertiPUR which has been applied by the foam industry for a long time.

Upholstered Furniture

It is estimated that around 90 % of upholstered furniture contains PU foam for upholstery. Alternative materials are the same as those for mattresses and the same issues as those stated for mattresses should be taken into account.

Automotive (car seats moulded foam)

Nearly all car seats are made of moulded PU foam. This is because the product provides a cost-effective solution for car seats while at the same time being lightweight which is an important factor to be kept in mind at a time where all car manufacturers seek to reduce CO₂ emissions from vehicles. To our knowledge, no car manufacturer is envisaging alternatives to PU foam on a large scale. On the contrary, the trend is more towards increased functional requirements for PU foam and assemblies with new materials, in order to support further weight reduction.

As for all materials, research in the automotive sector has been taking place in the past years to consider alternatives for PU foam, or to reduce the amount of chemicals poured to produce foam in order to save on raw materials. However none of the alternatives considered have shown the ability to match the performances of PU foam when it comes to comfort, low emissions of volatile organic compounds (VOCs), reduced weight and ease of end-of-life treatment. For example, currently, a

few car seats are produced with coconut fibers agglomerated with a latex mixture containing a copolymer of vinylidene chloride. This process is however being phased out from the market due to its complexity and cost.

Considering the above, and while we cannot provide an accurate estimate at this stage about the direct and indirect costs of prohibiting diisocyanates for our industry, we believe that it is obvious that doing so would seriously harm the European economy and destroy an entire industry branch in which the EU happens to be one of the world leaders in innovation.

We trust that this cannot be the purpose of European regulators and - as a responsible industry - look forward to discussing the best risk management options to guarantee the safe use of the substances we use."

H. References¹

- Aalto-Korte K., Pesonen M., Kuuliala O., Alanko K., and Jolanki R. (2010): Contact allergy to aliphatic polyisocyanates based on hexamethylene-1,6-diisocyanate (HDI). *Contact Dermatitis* 63 (6), 357-363. DOI: 10.1111/j.1600-0536.2010.01786.x (last accessed 2016-09-19)
- Aalto-Korte K., Suuronen K., Kuuliala O., Henriks-Eckerman M.L., and Jolanki R. (2012): Occupational contact allergy to monomeric isocyanates. *Contact Dermatitis* 67 (2), 78-88. DOI: 10.1111/j.1600-0536.2011.02049.x (last accessed 2016-09-19)
- ACC (2016): Reoccupancy. American Chemistry Council. <https://spraypolyurethane.org/reoccupancy> (last accessed 2016-09-21)
- ACEA (2016): Key figures. European Automobile Manufacturers Association (ACEA). <http://www.acea.be/statistics/tag/category/key-figures> (last accessed 2016-09-28)
- Adam N., Avar G., Blankenheim H., Friederichs W., Giersig M., Weigand E., Halfmann M., Wittbecker F.-W., Larimer D.-R., Maier U., Meyer-Ahrens S., Noble K.-L., and Wussow H.-G. (2005): Polyurethanes. In: *Ullmann's Encyclopedia of Industrial Chemistry*, volume 29, 546-603. Wiley-VCH. DOI: 10.1002/14356007.a21_665.pub2 (last accessed 2016-05-10)
- Adams W.G.F. (1975): Long term effects on the health of men engaged in the manufacture of tolylene di isocyanate. *British Journal of Industrial Medicine* 32 (1), 72-78. DOI: 10.1136/oem.32.1.72 (last accessed 2016-09-19)
- AGS (2006a): Begründung zu 2-Methyl-m-phenylendiisocyanat in TRGS 900 [Background document for 2-methyl-m-phenylendiisocyanate in TRGS 900], date: 2006-01. Ausschuss für Gefahrstoffe. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund, Germany. http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-2-methyl-m-phenylendiisocyanat.pdf?__blob=publicationFile (last accessed 2006-09-19)
- AGS (2006b): Technische Regeln für Gefahrstoffe, TRGS 900: Arbeitsplatzgrenzwerte [Technical rules for hazardous substances, TRGS 900: Occupational limit values], date: 2006-01. Ausschuss für Gefahrstoffe. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund, Germany. http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-900.pdf?__blob=publicationFile&v=21 (last accessed 2016-08-23)

¹ Explanatory note: Some of the references in the list contain up to two different entries for institutional authors and/or publishers. As a rule, a single entry or the second of two entries refers to the issuing/publishing institution (in the case of published reports) or the study sponsor(s) and/or data owners (as listed by IUCLID) in the case of confidential reports. If two entries are present, the first in general refers to the institution performing the work behind the reference (e.g. testing laboratory or consultancy), if different from the publisher/sponsor/data owner. Where the personal name(s) of the author(s) is/are not given, this latter entry is also used in abbreviated form instead. Cf. the following entry: 'Hazleton (1986): The toxicity and carcinogenicity of toluene diisocyanate vapour when administered to mice over a period of approximately two years. Volumes I and II. III project A-A-1, III Report 10382, date: 1986-01-03. Hazleton Laboratories Europe Ltd. International Isocyanate Institute, unpublished'. The study has been carried out at Hazleton Laboratories Ltd. and - according to the registration dossier - is sponsored and/or owned by the International Isocyanate Institute. Furthermore, this is a confidential report on a vertebrate experiment, therefore the personal name(s) of the author(s) have been replaced by an abbreviated version of the testing facility's name.

AGS (2009): TRGS 430: Isocyanate – Gefährdungsbeurteilung und Schutzmaßnahmen [TRGS 430: Isocyanates - hazard assessment and protective measures], date: 2009-03. Ausschuss für Gefahrstoffe (AGS). Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-430.pdf?__blob=publicationFile&v=3 (last accessed 2016-09-19)

Akbar-Khanzadeh F. and Rivas R.D. (1996): Exposure to isocyanates and organic solvents, and pulmonary-function changes in workers in a polyurethane molding process. *Journal of Occupational and Environmental Medicine* 38 (12), 1205-1212. <http://journals.lww.com/joem/pages/articleviewer.aspx?year=1996&issue=12000&article=00005&type=abstract>

Akimoto T., Tamura N., Uchida K., Dambara T., Nukiwa T., and Kira S. (1992): A case of hypersensitivity pneumonitis due to isocyanate exposure showing progression even two months after removal of the antigen. *Nihon Kyobu Shikkan Gakkai Zasshi* 30 (3), 458-463. https://www.jstage.jst.go.jp/browse/jjrs1963/30/3/_contents (last accessed 2016-09-19)

Alexandersson R., Gustafsson P., Hedenstierna G., and Rosen G. (1986): Exposure to naphthalene-diisocyanate in a rubber plant: Symptoms and lung function. *Archives of Environmental Health* 41 (2), 85-89. DOI: 10.1080/00039896.1986.9937414 (last accessed 2016-09-28)

Alexandersson R., Hedenstierna G., Plato N., and Kolmodin-Hedman B. (1987): Exposure, lung function, and symptoms in car painters exposed to hexamethylendiisocyanate and biuret modified hexamethylendiisocyanate. *Archives of Environmental Health* 42 (6), 367-373. DOI: 10.1080/00039896.1987.9934361 (last accessed 2016-09-28)

Alexandersson R., Hedenstierna G., Randma E., Rosen G., Swenson A., and Tornling G. (1985): Symptoms and lung function in low-exposure to TDI by polyurethane foam manufacturing. *International Archives of Occupational and Environmental Health* 55 (2), 149-157. <http://link.springer.com/article/10.1007/BF00378377> (last accessed 2016-09-28)

Ameille J., Pauli G., Calastreng-Crinquand A., Vervloët D., Iwatsubo Y., Popin E., Bayeux-Dunglas M.C., and Kopferschmitt-Kubler M.C. (2003): Reported incidence of occupational asthma in France, 1996–99: the ONAP programme. *Occupational and Environmental Medicine* 60 (2), 136-141. DOI: 10.1136/oem.60.2.136 (last accessed 2016-09-28)

Aoyama K., Huang J., Ueda A., and Matsushita T. (1994): Provocation of respiratory allergy in guinea pigs following inhalation of free toluene diisocyanate. *Archives of Environmental Contamination and Toxicology* 26 (3), 403-407. DOI: 10.1007/BF00203570 (last accessed 2016-09-19)

Arts J.H.E., de Jong W.H., van Triel J.J., Schijf M.A., de Klerk A., van Loveren H., and Kuper C.F. (2008): The respiratory local lymph node assay as a tool to study respiratory sensitizers. *Toxicological Sciences* 106 (2), 423-434. DOI: 10.1093/toxsci/kfn199 (last accessed 2016-09-19)

Arts J.H.E., Mommers C., and de Heer C. (2006): Dose-response relationships and threshold levels in skin and respiratory allergy. *Critical Reviews in Toxicology* 36 (3), 219-251. DOI: 10.1080/10408440500534149 (last accessed 2016-09-19)

Aul D.J., Bhaumik A., Kennedy A.L., Brown W.E., Lesage J., and Malo J.L. (1999): Specific IgG response to monomeric and polymeric diphenylmethane diisocyanate conjugates in subjects with respiratory reactions to isocyanates. *Journal of Allergy and Clinical Immunology* 103 (5 Pt 1), 749-755. DOI: 10.1016/S0091-6749(99)70415-X (last accessed 2016-09-28)

Aumann I. and Kreis K. (2017): Research on cost of illness and on indicators of severity of diseases for specific occupational diseases caused by isocyanates. Kompetenzzentrum

Versicherungswissenschaften GmbH, Leibniz Universität Hannover. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). <http://www.baua.de/en/Research/Research-Project/f2363.html?nn=4947596> (last accessed 2016-09-28)

Austin S. (2007): Biological monitoring of TDI-derived amines in polyurethane foam production. *Occupational Medicine* 57 (6), 444-448. DOI: 10.1093/occmed/kqm085 (last accessed 2016-09-19)

Avar G. (2008): Polyurethane (PUR). Wachstum durch Diversifizierung (Trendbericht) [Growth through diversification: Polyurethanes (PU)]. *Kunststoffe* 10, 205-211. <https://www.kunststoffe.de/kunststoffe-zeitschrift/archiv/artikel/wachstum-durch-diversifizierung-trendbericht-polyurethane-pur-540874.html>

Ayres J.G., Boyd R., Cowie H., and Hurley J.F. (2010): Costs of occupational asthma in the UK. *Thorax*. DOI: 10.1136/thx.2010.136762 (last accessed 2016-09-28)

Ban M., Hettich D., Goutet M., and Bonnet P. (1997): TDI inhalation in guinea-pigs involves migration of dendritic cells. *Toxicology Letters* 93 (2-3), 185-194. DOI: 10.1016/S0378-4274(97)00091-X

Ban M., Morel G., Langonné I., Huguet N., Pépin E., and Binet S. (2006): TDI can induce respiratory allergy with Th2-dominated response in mice. *Toxicology* 218 (1), 39-47. DOI: 10.1016/j.tox.2005.09.013 (last accessed 2016-09-19)

Banks D.E., Barkman H.W., Jr., Butcher B.T., Hammad Y.Y., Rando R.J., Glindmeyer H.W., 3rd, Jones R.N., and Weill H. (1986): Absence of hyperresponsiveness to methacholine in a worker with methylene diphenyl diisocyanate (MDI)-induced asthma. *CHEST* 89 (3), 389-393. DOI: 10.1378/chest.89.3.389 (last accessed 2016-09-19)

Banks D.E. and Rando R.J. (1988): Recurrent asthma induced by toluene diisocyanate. *Thorax* 43 (8), 660-662. DOI: 10.1136/thx.43.8.660 (last accessed 2016-09-28)

Banks D.E., Rando R.J., and Barkman H.W. (1990): Persistence of toluene diisocyanate-induced asthma despite negligible workplace exposures. *CHEST* 97 (1), 121-125. DOI: doi:10.1378/chest.97.1.121 (last accessed 2016-09-19)

Banks D.E., Sastre J., Butcher B.T., Ellis E., Rando R.J., Barkman H.W., Jr., Hammad Y.Y., Glindmeyer H.W., and Weill H. (1989): Role of inhalation challenge testing in the diagnosis of isocyanate-induced asthma. *CHEST* 95 (2), 414-423. DOI: 10.1378/chest.95.2.414 (last accessed 2016-09-19)

BASF (2009): IPDI Trimer - subchronic 90-day inhalation and lung toxicity study in Wistar rats - dust aerosol exposure. Report no. 99I0357/06026, date: 2009-02-19. BASF SE, Experimental Toxicology and Ecology. Bayer MaterialScience AG, BASF SE, Evonik Degussa GmbH, PERSTORP France, unpublished

Basketter D.A. and Gerberick G.F. (1996): An interlaboratory evaluation of the Buehler test for the identification and classification of skin sensitizers. *Contact Dermatitis* 35 (3), 146-151. DOI: 10.1111/j.1600-0536.1996.tb02332.x (last accessed 2016-09-19)

Baur X. (1983): Immunologic cross-reactivity between different albumin-bound isocyanates. *Journal of Allergy and Clinical Immunology* 71 (2), 197-205. DOI: 10.1016/0091-6749(83)90100-8 (last accessed 2016-09-19)

Baur X. (1995): Hypersensitivity pneumonitis (extrinsic allergic alveolitis) induced by isocyanates. *Journal of Allergy and Clinical Immunology* 95 (5), 1004-1010. DOI: 10.1016/S0091-6749(95)70101-X (last accessed 2016-09-19)

Baur X., Bakehe P., and Vellguth H. (2012): Bronchial asthma and COPD due to irritants in the workplace - an evidence-based approach. *Journal of Occupational Medicine and Toxicology* 7 (1), 1-31. DOI: 10.1186/1745-6673-7-19 (last accessed 2016-09-28)

Baur X. and Barbinova L. (2013): Occupational airborne exposure, specific sensitization and the atopic status: Evidence of a complex interrelationship. *Journal of Occupational Medicine and Toxicology* 8 (2). DOI: 10.1186/1745-6673-8-2 (last accessed 2016-09-19)

Baur X., Dewair M., and Römmelt H. (1984): Acute airway obstruction followed by hypersensitivity pneumonitis in an isocyanate (MDI) worker. *Journal of Occupational Medicine* 26 (4), 285-287

Baur X., Marek W., Ammon J., Czuppon A.B., Marczynski B., Raulf-Heimsoth M., Roemmelt H., and Fruhmann G. (1994): Respiratory and other hazards of isocyanates. *International Archives of Occupational and Environmental Health* 66 (3), 141-152. DOI: 10.1007/BF00380772

Bayer (1968): Isophorondiisocyanat - toxikologische Untersuchungen [Isophorone diisocyanate - toxicological studies]. Report no. 908, date: 1968-07-22. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1970): Desmodur H: Toxikologische Untersuchungen [Desmodur H: Toxicological studies]. Report no. 2146, date: 1970-07-08. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1983): Hexamethylen-1,6-diisocyanat (HDI): Untersuchungen zur sensibilisierenden Wirkung an der Meerschweinchenhaut [Hexamethylene-1,6-diisocyanate (HDI): Study of a sensitising effect in guinea pig skin]. Report no. 11703, date: 1983-04-08. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1984a): 4,4'-Diisocyanato-dicyclohexylmethan (H-MDI), Untersuchungen zur sensibilisierenden Wirkung an der Meerschweinchenhaut (modif. Maximierungstest mit nur intrakutaner Induktion) [4,4'-Diisocyanato-dicyclohexylmethane (H-MDI) - study on a sensitising effect in guinea-pig skin (modif. "maximisation test" with only intracutaneous induction)]. Report no. 13039, date: 1984-11-15. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1984b): Isophorondiisocyanat (IPDI) - Untersuchungen zur sensibilisierenden Wirkung an der Meerschweinchenhaut (modif. "Maximierungstest" mit nur intrakutaner Induktion) [Isophorone diisocyanate (IPDI) - study of a sensitising effect in guinea-pig skin (modif. "maximisation test" with only intracutaneous induction)]. Report no. 13041, date: 1984-11-15. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1985): 4,4'-Diisocyanato-dicyclohexylmethan (H-MDI), Prüfung auf sensibilisierende Wirkung an der Meerschweinchenhaut (Maximierungstest nach Magnusson/Kligman) [4,4'-Diisocyanato-dicyclohexylmethane (H-MDI), test for a sensitising effect in guinea-pig skin (maximisation test according to Magnusson/Kligman)]. Report no. 13787, date: 1985-08-29. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1993): Isophorondiisocyanat - Untersuchungen auf hautsensibilisierende Wirkung bei Meerschweinchen (Maximierungstest nach Magnusson und Kligman) [Isophorone diisocyanate - studies of a skin sensitising effect in guinea-pigs (maximisation test according to Magnusson and Kligman)]. Report no. 22645, company study no. T 1055173, date: 1993-11-04. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1994): MDI (Desmodur®44M) Evaluation of respiratory sensitization in guinea-pigs following intradermal induction and MDI-challenge. Report no. T7055340, date: 1994-11-18. Bayer AG, Department of Toxicology. International Isocyanate Institute, unpublished

Bayer (1995a): Desmodur W, pilot study for lung sensitization in Guinea-pigs following intradermal induction. Report no. 24199, date: 1995-07-26. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1995b): Diphenylmethane-4,4'-diisocyanate (MDI-monomer). Evaluation of respiratory sensitization in guinea-pigs following brief high-level inhalation induction exposure and challenge with ramped MDI concentrations. Report no. T1058323, III project 121-EU-MTX, III Report 11184, date: 1995-05-30. Bayer AG, Department of Toxicology. International Isocyanate Institute, unpublished

Bayer (1996a): IPDI (Isophorondiisocyanat), evaluation of respiratory sensitization in guinea-pigs following intradermal induction. Report no. 24967, T5055474, date: 1996-04-04. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (1996b): Vestanat T 1890/100 - study for lung sensitization in guinea-pigs following intradermal or inhalation induction. Report no. 24843, company study no. T6059147, date: 1996-02-28. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, Evonik Degussa GmbH, unpublished

Bayer (2003a): Desmodur Z 4470 MPA/X - local lymph node assay in mice (LLNA/IMDS). Report no. AT00334, date: 2003-03-26. Bayer AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

Bayer (2003b): Monomeric MDI: Lethality to rats following one hour inhalation of an inhalable aerosol. III report 11472, III project 216-AM-MTX, date: 2003-01-15. Bayer AG, PH-PD-P Healthcare Toxicology. International Isocyanate Institute, unpublished

Bayer (2008a): 90-Day inhalation study with a 4-week recovery period in Wistar rats. Report no. AT04587, company study no. T7076969, date: 2008-05-21. Bayer HealthCare AG. Bayer MaterialScience AG E.D.G., unpublished

Bayer (2008b): Isophorone diisocyanate (IPDI) 90-day inhalation study with a 4-week recovery period in Wistar rats. Report no. AT04738, company study no.: T6077598, date: 2008-07-31. Bayer HealthCare AG, GDD-GED-GT Inhalation Toxicology. Bayer MaterialScience AG, Degussa AG (Evonik Degussa GmbH), PERSTORP France SAS, BASF SE, unpublished

Bayer (2009): 1,6-Hexamethylene diisocyanate (HDI; CAS No. 822-06-0): Information/assumptions regarding toxicokinetics, date: 2009-08-27, unpublished

Bayer (2010a): 1,5-Naphthylene diisocyanate (NDI): 90-day inhalation study with a 1-month recovery period in Wistar rats. Report no. AT06097, study no. T 3080041, date: 2010-11-04. Bayer Schering Pharma AG, Department of General Toxicology - Inhalation. Bayer MaterialScience AG, unpublished

Bayer (2010b): 1,5-Naphthylene diisocyanate (NDI; CAS No. 3173-72-6): Information/assumptions regarding toxicokinetics, date: 2010-11-12

Bayer (2011): MDI22: Local lymph node assay in mice (LLNA/IMDS). Report no. AT06207, study no.: T3081851, date: 2011-02-09. Bayer Schering Pharma AG, Department of Toxicology. Bayer MaterialScience AG, unpublished

BDVT (2012): BDVT gibt Honorar-Empfehlung/Richtwerte für Tagessätze von Trainern, Beratern und Coaches [BDVT issues recommendations for daily fees for instructors, consultants, and coaches]. Berufsverband für Trainer, Berater und Coaches e.V. (BDVT). <http://www.verbaende.com/news.php/BDVT-gibt-Honorar-Empfehlung-Richtwerte-fuer-Tagessaetze-von-Trainern-Beratern-und-Coaches?m=85341> (last accessed 2016-09-28)

Belgian CA (2005): European Union risk assessment report. Methylenediphenyl diisocyanate (MDI), CAS No: 26447-40-5, EINECS No: 247-714-0, final report. European Commission.

<https://echa.europa.eu/documents/10162/9f8ad2fd-9b47-4eb6-9bf9-e0fc898f874d> (last accessed 2016-09-19)

Bello D., Herrick C.A., Smith T.J., Woskie S.R., Streicher R.P., Cullen M.R., Liu Y., and Redlich C.A. (2007): Skin exposure to isocyanates: Reasons for concern. *Environmental Health Perspectives* 115 (3), 328-335. DOI: 10.1289/ehp.9557 (last accessed 2016-09-19)

Bello D., Woskie S.R., Streicher R.P., Liu Y., Stowe M.H., Eisen E.A., Ellenbecker M.J., Sparer J., Youngs F., Cullen M.R., and Redlich C.A. (2004): Polyisocyanates in occupational environments: A critical review of exposure limits and metrics. *American Journal of Industrial Medicine* 46 (5), 480-491. DOI: 10.1002/ajim.20076 (last accessed 2016-09-19)

Bentley A.M., Maestrelli P., Saetta M., Fabbri L.M., Robinson D.S., Bradley B.L., Jeffery P.K., Durham S.R., and Kay A.B. (1992): Activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma. *The Journal of Allergy and Clinical Immunology* 89 (4), 821-829. DOI: 10.1016/0091-6749(92)90437-7 (last accessed 2016-09-28)

Bernstein D.I., Korbee L., Stauder T., Bernstein J.A., Scinto J., Herd Z.L., and Bernstein I.L. (1993): The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *Journal of Allergy and Clinical Immunology* 92 (3), 387-396. DOI: 10.1016/0091-6749(93)90117-X (last accessed 2016-09-19)

Bernstein I.L., Chang-Yeung M., and Malo J.L. (2013): Definition and classification of asthma in the workplace. In: *Asthma in the workplace* (Malo J.L., Chan-Yeung M., and Bernstein D.L., eds.), ed. 4, chapter 1. CRC Press, Boca Raton, London, New York. ISBN: 9781842145913

Bernstein I.L., Splansky G.L., Chen S.E., and Vinegar A. (1982): The guinea pig model of diisocyanate sensitization - II. Physiologic studies. *Journal of Allergy and Clinical Immunology* 70 (5), 393-398. DOI: 10.1016/0091-6749(82)90030-6 (last accessed 2016-09-19)

Bieler G., Thorn D., Huynh C.K., Tomicic C., Steiner U.C., Yawalkar N., and Danuser B. (2011): Acute life-threatening extrinsic allergic alveolitis in a paint controller. *Occupational Medicine* 61 (6), 440-442. DOI: 10.1093/occmed/kqr057 (last accessed 2016-09-28)

Bio-Dynamics (1984): A closed-patch repeated insult dermal sensitization study in guinea pigs with TDI, MDI, p-TMXDI, IPDI, m-TMXDI, HMDI and m-TMI (modified Buehler method). Report no. 4971-84, date: 1984-12-20. American Cyanamide, unpublished

Bio-Research (1984): Sensitization potential of inhaled AC-005 and AC-008 in guinea pigs. Report no. 81187/88, date: 1984-12-28. Bio-Research Laboratories Ltd. Cytec Industries, unpublished

Birdi K. and Beach J. (2013): Management of sensitizer-induced occupational asthma: Avoidance or reduction of exposure? *Current Opinion in Allergy and Clinical Immunology* 13 (2), 132-137. DOI: 10.1097/ACI.0b013e32835ea249 (last accessed 2016-09-19)

Blaikie L., Morrow T., Wilson A.P., Hext P., Hartop P.J., Rattray N.J., Woodcock D., Botham P.A., Woodcock D., and Botham P.A. (1995): A two-centre study for the evaluation and validation of an animal model for the assessment of the potential of small molecular weight chemicals to cause respiratory allergy. *Toxicology* 96 (1), 37-50. DOI: 10.1016/0300-483X(94)03007-O (last accessed 2016-09-19)

Bloemen K., Verstraelen S., van den Heuvel R., Witters H., Nelissen I., and Schoeters G. (2007): The allergic cascade: Review of the most important molecules in the asthmatic

lung. *Immunology Letters* 113 (1), 6-18. DOI: 10.1016/j.imlet.2007.07.010 (last accessed 2016-09-19)

Blomquist G.C., Dickie M., and O'Connor R.M. (2011): Willingness to pay for improving fatality risks and asthma symptoms: Values for children and adults of all ages. *Resource and Energy Economics* 33 (2), 410-425. DOI: 10.1016/j.reseneeco.2010.05.004 (last accessed 2016-09-28)

Bodner K.M., Burns C.J., Randolph N.M., and Salazar E.J. (2001): A longitudinal study of respiratory health of toluene diisocyanate production workers. *Journal of Occupational and Environmental Medicine* 43 (10), 890-897. <http://journals.lww.com/joem/pages/articleviewer.aspx?year=2001&issue=10000&article=00008&type=abstract> (last accessed 2016-09-19)

Boschetto P., Fabbri L.M., Zocca E., Milani G., Pivrotto F., Dal Vecchio A., Plebani M., and Mapp C.E. (1987): Prednisone inhibits late asthmatic reactions and airway inflammation induced by toluene diisocyanate in sensitized subjects. *Journal of Allergy and Clinical Immunology* 80 (3 PART 1), 261-267. DOI: 10.1016/0091-6749(87)90028-5 (last accessed 2016-09-28)

Botham P.A., Hext P.M., Rattray N.J., Walsh S.T., and Woodcock D.R. (1988): Sensitisation of guinea pigs by inhalation exposure to low molecular weight chemicals. *Toxicology Letters* 41 (2), 159-173. DOI: 10.1016/0378-4274(88)90089-6 (last accessed 2016-09-19)

Boulet L.P., Lemiere C., Gautrin D., and Cartier A. (2007): New insights into occupational asthma. *Current Opinion in Allergy and Clinical Immunology* 7 (1), 96-101. DOI: 10.1097/ACI.0b013e328013ccd8 (last accessed 2016-09-19)

Brandt B., Assenmacher-Maiworm H., and Hahn J.U. (2013): Messung und Beurteilung von Isocyanaten an Arbeitsplätzen unter Beachtung der TRGS 430 [Measurement and evaluation of isocyanates at workplaces according to TRGS 430]. *Gefahrstoffe - Reinhaltung der Luft* 73 (5), 209-218. http://www.dguv.de/medien/ifa/de/pub/grl/pdf/2013_122.pdf (last accessed 2016-09-29)

BRC (1981): Dermal sensitisation study of compound number 11583B15 and isophorone diisocyanate. Report no. 81-149, date: 1981-10-23. Biosphere Research Centre. Cytec Industries, unpublished

Brown W.E., Kennedy A.L., Aul D.J., Stock M.F., and Alarie Y. (1994): Comparative uptake and distribution of ¹⁴C labeled diisocyanates. *Toxicologist* 14 (1), 359

Bruckner H.C., Avery S.B., Stetson D.M., Dodson V.N., and Ronayne J.J. (1968): Clinical and immunologic appraisal of workers exposed to diisocyanates. *Archives of Environmental Health* 16 (5), 619-625. DOI: 10.1080/00039896.1968.10665117 (last accessed 2016-09-19)

Bruynzeel D.P. and van der Wegen-Keijser M.H. (1993): Contact dermatitis in a cast technician. *Contact Dermatitis* 28 (3), 193-194. DOI: 10.1111/j.1600-0536.1993.tb03393.x (last accessed 2016-09-19)

Brzezniński S. and Bonczarowska M. (2015): Occupational exposure to selected isocyanates in Polish industry. *Medycyna pracy* 66 (3), 291-301. DOI: 10.13075/mp.5893.00020 (last accessed 2016-09-28)

Bugler J., Clark R.L., and Hill I.D. (1991): The acute and long-term respiratory effects of aromatic di-isocyanates. A five year longitudinal study of polyurethane foam workers. III report 10848. International Isocyanate Institute, Manchester, UK

- Burge P.S. (1982): Non-specific bronchial hyper-reactivity in workers exposed to toluene diisocyanate, diphenyl methane diisocyanate and colophony. *European Journal of Respiratory Diseases Supplement* 123, 91-96. <http://www.ncbi.nlm.nih.gov/pubmed/6297950>
- Burke M.J., Sarpy S.A., Smith-Crowe K., Chan-Serafin S., Salvador R.O., and Islam G. (2006): Relative Effectiveness of Worker Safety and Health Training Methods. *American Journal of Public Health* 96 (2), 315-324. DOI: 10.2105/AJPH.2004.059840
- Butcher B.T., Jones R.N., O'Neil C., Glindmeyer H.W., Diem J.E., Dharmarajan V., Weill H., and Salvaggio J.E. (1977): Longitudinal study of workers employed in the manufacture of toluene diisocyanate. *American Review of Respiratory Disease* 116 (3), 411-421. DOI: 10.1164/arrd.1977.116.3.411 (last accessed 2016-09-19)
- Butcher B.T., Karr R.M., O'Neil C.E., Wilson M.R., Dharmarajan V., Salvaggio J.E., and Weill H. (1979): Inhalation challenge and pharmacologic studies of toluene diisocyanate (TDI)-sensitive workers. *Journal of Allergy and Clinical Immunology* 64 (2), 146-152. DOI: 10.1016/0091-6749(79)90049-6 (last accessed 2016-09-19)
- Butcher B.T., O'Neil C.E., Reed M.A., and Salvaggio J.E. (1980): Radioallergosorbent testing of toluene diisocyanate-reactive individuals using p-tolyl isocyanate antigen. *Journal of Allergy and Clinical Immunology* 66 (3), 213-216. DOI: 10.1016/0091-6749(80)90041-X (last accessed 2016-09-28)
- Calcagni P., Di Stefano A., Saetta M., Mapp C.E., Fabbri L.M., and Maestrelli P. (1993): Eosinophilia in induced sputum after asthmatic reactions to isocyanates in sensitized subjects. *Journal of Allergy and Clinical Immunology* 91 (1 PART 2), 221. DOI: 10.1016/0091-6749(93)90360-R (last accessed 2016-09-19)
- California EPA (2014): Priority product profile. Spray polyurethane foam systems containing unreacted diisocyanates, date: 2014-03. Department of Toxic Substances Control (DTSC). California Environment Protection Agency. <http://media.mofo.com/files/Uploads/Images/140313-Profile-Spray-Foam.pdf> (last accessed 2016-09-19)
- Carder M., Bensefa-Colas L., Mattioli S., Noone P., Stikova E., Valenty M., and Telle-Lamberton M. (2015): A review of occupational disease surveillance systems in Modernet countries. *Occupational Medicine* 65 (8), 615-625. DOI: 10.1093/occmed/kqv081 (last accessed 2016-09-28)
- Carder M., McNamee R., Turner S., Hussey L., Money A., and Agius R. (2011): Improving estimates of specialist-diagnosed, work-related respiratory and skin disease. *Occupational Medicine* 61 (1), 33-39. DOI: 10.1093/occmed/kqq164 (last accessed 2016-09-28)
- Carino M., Aliani M., Licitra C., Sarno N., and Ioli F. (1997): Death due to asthma at workplace in a diphenylmethane diisocyanate-sensitized subject. *Respiration* 64 (1), 111-113. DOI: 10.1159/000196653 (last accessed 2016-09-19)
- Cartier A., Grammer L., Malo J.L., Lagier F., Ghezze H., Harris K., and Patterson R. (1989): Specific serum antibodies against isocyanates: Association with occupational asthma. *Journal of Allergy and Clinical Immunology* 84 (4 PART 1), 507-514. DOI: 10.1016/0091-6749(89)90364-3 (last accessed 2016-09-19)
- Cassidy L.D., Molenaar D.M., Hathaway J.A., Feeley T.M., Cummings B.J., Simpson P., and Li S.H. (2010): Trends in pulmonary function and prevalence of asthma in hexamethylene diisocyanate workers during a 19-year period. *Journal of Occupational and Environmental Medicine* 52 (10), 988-994. DOI: 10.1097/JOM.0b013e3181f2e086 (last accessed 2016-09-19)

Castillon K. (2000): Overexposure to methylene bisphenyl isocyanate (MDI) in a motor vehicle parts manufacturing facility. *Applied Occupational and Environmental Hygiene* 15 (3), 251-252. DOI: 10.1080/104732200301557 (last accessed 2016-09-19)

Centre Laboratoire d'Etudes (1977): Pharmacokinetics of MDI after inhalation exposure of rats to labelled MDI, date: 1977-09. International Isocyanate Institute, unpublished

Chang K.C. and Karol M.H. (1984): Diphenylmethane diisocyanate (MDI)-induced asthma: Evaluation of the immunologic responses and application of an animal model of isocyanate sensitivity. *Clinical Allergy* 14 (4), 329-339. DOI: 10.1111/j.1365-2222.1984.tb02213.x (last accessed 2016-09-19)

Chappelle A.H., Shiotsuka R., N., and Bartels M.J. (2001): Some limitations in the use of urine biomonitoring for measuring TDI exposure. ASTM Special Technical Publication 1408, date: 2001-01. ASTM International. DOI: 10.1520/STP10461S (last accessed 2016-09-29)

Checkoway H., Pearce N., and Kriebel D., eds. (2004): Research methods in occupational epidemiology, ed. 2. Monographs in epidemiology and biostatistics. Oxford University Press, Oxford, New York etc. ISBN: 978-0195092424

Chen S.E. and Bernstein I.L. (1982): The guinea pig model of diisocyanate sensitization. I. Immunologic studies. *Journal of Allergy and Clinical Immunology* 70 (5), 383-392. DOI: 10.1016/0091-6749(82)90029-X (last accessed 2016-09-19)

Christensen F.N., N.H., Jeppesen C.N., and Clausen A.J. (2014): Survey of certain isocyanates (MDI and TDI). Part of the LOUS-review. Environmental Project No. 1537, 2014; ISBN: 978-87-93026-91-9. COWI A/S, Danish Technological Institute. Danish Environmental Protection Agency, Copenhagen, Denmark. <http://www2.mst.dk/Udgiv/publications/2014/01/978-87-93026-91-9.pdf> (last accessed 2016-09-19)

Cibulas W., Jr., Brooks S.M., Murlas C.G., Miller M.L., and McKay R.T. (1988): Toluene diisocyanate-induced airway hyperreactivity in guinea pigs depleted of granulocytes. *Journal of Applied Physiology* 64 (5), 1773-1778. <http://jap.physiology.org/content/64/5/1773.long>

Clark R.L., Bugler J., McDermott M., Hill I.D., Allport D.C., and Chamberlain J.D. (1998): An epidemiology study of lung function changes of toluene diisocyanate foam workers in the United Kingdom. *International Archives of Occupational and Environmental Health* 71 (3), 169-179. DOI: 10.1007/s004200050267 (last accessed 2016-09-19)

Clark R.L., Bugler J., Paddle G.M., Chamberlain J.D., and Allport D.C. (2003): A 17-year epidemiological study on changes in lung function in toluene diisocyanate foam workers. *International Archives of Occupational and Environmental Health* 76 (4), 295-301. DOI: 10.1007/s00420-002-0403-8 (last accessed 2016-09-19)

Clarke C.W. and Aldons P.M. (1981): Isophorone diisocyanate induced respiratory disease (IPDI). *Australian and New Zealand Journal of Medicine* 11 (3), 290-292

Clayton M. and Baxter N. (2015): Air-fed visors used for isocyanate paint spraying - potential exposure when the visor is lifted. *Annals of Occupational Hygiene* 59 (9), 1179-1189. DOI: 10.1093/annhyg/mev055 (last accessed 2016-09-29)

Clemmensen S. (1984): Cross-reaction patterns in guinea pigs sensitized to acrylic monomers. *Drug and Chemical Toxicology* 7 (6), 527-540. DOI: 10.3109/01480548409042817 (last accessed 2016-09-19)

Cochrane S.A., Arts J.H.E., Ehnes C., Hindle S., Hollnagel H.M., Poole A., Suto H., and Kimber I. (2015): Thresholds in chemical respiratory sensitisation. *Toxicology* 333, 179-194. DOI: 10.1016/j.tox.2015.04.010 (last accessed 2016-09-19)

- Cocker J. (2011): Biological monitoring for isocyanates. *Annals of Occupational Hygiene* 55 (2), 127-131. DOI: 10.1093/annhyg/meq083 (last accessed 2016-09-29)
- Cohen A. and Colligan M.J. (1998): Assessing occupational safety and health training. A literature review. DHHS (NIOSH) Publication No. 98-145, date: 1998-06. Centers for Disease Control and Prevention (CDC). National Institute for Occupational Safety and Health (NIOSH). <http://www.oshatrain.org/courses/pdf/assesstraining.pdf> (last accessed 2016-09-28)
- Collins M.A. (2012): Diisocyanate respiratory sensitization animal models and human experience, personal communication
- Cowie H.A., Hughson G.W., Creely K.S., Graham M.K., Hutchison P.A., and Aitken R.J. (2005): An occupational hygiene assessment of the use and control of isocyanates in the UK. Research report 311, ISBN: 0-7176-2959-7. Institute of Occupational Medicine. HSE Books, Edinburgh, UK. <http://www.hse.gov.uk/research/rrpdf/rr311.pdf> (last accessed 2016-09-19)
- Creely K.S., Hughson G.W., Cocker J., and Jones K. (2006): Assessing isocyanate exposures in polyurethane industry sectors using biological and air monitoring methods. *Annals of Occupational Hygiene* 50 (6), 609-621. DOI: 10.1093/annhyg/mel024 (last accessed 2016-09-21)
- Crespo J. and Galan J. (1999): Exposure to MDI during the process of insulating buildings with sprayed polyurethane foam. *Annals of Occupational Hygiene* 43 (6), 415-419. DOI: 10.1093/annhyg/43.6.415 (last accessed 2016-09-19)
- Cuno E., Brandt B., Assenmacher-Maiworm H., Buchwald K., Hahn J., and Hensel T. (2015): Emissionsverhalten von reaktiven Polyurethan-Schmelzklebstoffen [Emission behaviour of reactive polyurethane hotmelt adhesives]. Deutsche Gesetzliche Unfallversicherung (DGUV). http://www.dguv.de/medien/ifa/de/pub/grl/pdf/2015_215.pdf (last accessed 2016-09-28)
- Cvitanovic S., Zekan L.J., and Marusic M. (1989): Occurrence and specificity of IgE antibodies to isocyanates in occupationally exposed workers. *International Archives of Occupational and Environmental Health* 61 (7), 483-486. DOI: 10.1007/BF00386483 (last accessed 2016-09-19)
- Czuppon A.B., Marczyński B., and Baur X. (1992): Detection of protein changes in serum of workers following inhalation exposure to toluene diisocyanate vapors. *Toxicology and Industrial Health* 8 (6), 407-413. <http://www.ncbi.nlm.nih.gov/pubmed/7570621>
- Dahlin J., Spanne M., Dalene M., Karlsson D., and Skarping G. (2008): Size-separated sampling and analysis of isocyanates in workplace aerosols - Part II: Aging of aerosols from thermal degradation of polyurethane. *Annals of Occupational Hygiene* 52 (5), 375-383. DOI: 10.1093/annhyg/men018 (last accessed 2016-09-19)
- Dahlqvist M., Tornling G., Plato N., and Ulfvarson U. (1995): Effects within the week on forced vital capacity are correlated with long term changes in pulmonary function: Reanalysis of studies on car painters exposed to isocyanate. *Occupational and Environmental Medicine* 52 (3), 192-195. <http://www.jstor.org/stable/27730294> (last accessed 2016-09-28)
- de Jong W.H., Arts J.H.E., de Klerk A., Schijf M.A., Ezendam J., Kuper C.F., and van Loveren H. (2009): Contact and respiratory sensitizers can be identified by cytokine profiles following inhalation exposure. *Toxicology* 261 (3), 103-111. DOI: 10.1016/j.tox.2009.04.057 (last accessed 2016-09-19)

de Vooght V., Carlier V., Devos F.C., Haenen S., Verbeken E., Nemery B., Hoet P.H., and Vanoirbeek J.A. (2013): B-lymphocytes as key players in chemical-induced asthma. *PLoS One* 8 (12), e83228. DOI: 10.1371/journal.pone.0083228 (last accessed 2016-09-19)

Dearman R.J., Basketter D.A., and Kimber I. (1992a): Variable effects of chemical allergens on serum IgE concentration in mice: Preliminary evaluation of a novel approach to the identification of respiratory sensitizers. *Journal of Applied Toxicology* 12 (5), 317-323. DOI: 10.1002/jat.2550120505 (last accessed 2016-09-19)

Dearman R.J., Basketter D.A., and Kimber I. (1996a): Characterization of chemical allergens as a function of divergent cytokine secretion profiles induced in mice. *Toxicology and Applied Pharmacology* 138 (2), 308-316. DOI: 10.1006/taap.1996.0129 (last accessed 2016-09-19)

Dearman R.J., Basketter D.A., and Kimber I. (2013): Inter-relationships between different classes of chemical allergens. *Journal of Applied Toxicology* 33 (7), 558-565. DOI: 10.1002/jat.1758 (last accessed 2016-09-19)

Dearman R.J. and Botham P.A. (1990): Inhalation exposure to respiratory sensitising chemicals down-regulates guinea pig IgE and pulmonary responses. *International Archives of Allergy and Applied Immunology* 92 (4), 425-432. DOI: 10.1159/000235175 (last accessed 2016-09-19)

Dearman R.J., Moussavi A., Kemeny D.M., and Kimber I. (1996b): Contribution of CD4+ and CD8+ T lymphocyte subsets to the cytokine secretion patterns induced in mice during sensitization to contact and respiratory chemical allergens. *Immunology* 89 (4), 502-510. DOI: 10.1046/j.1365-2567.1996.d01-778.x (last accessed 2016-09-19)

Dearman R.J., Spence L.M., and Kimber I. (1992b): Characterization of murine immune responses to allergenic diisocyanates. *Toxicology and Applied Pharmacology* 112 (2), 190-197. DOI: 10.1016/0041-008X(92)90187-W (last accessed 2016-09-19)

Delebecq E., Pascault J.-P., Boutevin B., and Ganachaud F. (2013): On the versatility of urethane/urea bonds: Reversibility, blocked isocyanate, and non-isocyanate polyurethane. *Chemical Reviews* 113 (1), 80-118. DOI: 10.1021/cr300195n (last accessed 2016-09-19)

DFG (1997): 4,4'-Methylene diphenyl isocyanate (MDI) and "polymeric MDI" (PMDI) [MAK value documentation, 1997]. In: *The MAK Collection for Occupational Health and Safety*, volume 8. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, (ed.), 66-69. Deutsche Forschungsgemeinschaft (DFG). DOI: 10.1002/3527600418.mb10168stae0008 (last accessed 2016-09-19)

DFG (2003): Toluene diisocyanate [MAK Value Documentation, 2003]. In: *The MALK Collection for Occupational Safety and Health*, volume 20. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, (ed.). Deutsche Forschungsgemeinschaft (DFG). DOI: 10.1002/3527600418.mb58484isme0020 (last accessed 2016-09-19)

DFG (2008): 4,4'-Methylene diphenyl diisocyanate (MDI) [101-68-8] and "polymeric" MDI (PMDI) [9016-87-9] [MAK Value Documentation, 2008] In: *The MAK Collection For Occupational Health and Safety*. Deutsche Forschungsgemeinschaft (DFG), (ed.), 1-52. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area DOI: 10.1002/3527600418.mb10168stae4515 (last accessed 2016-09-01)

Diem J.E., Jones R.N., Hendrick D.J., Glindmeyer H.W., Dharmarajan V., Butcher B.T., Salvaggio J.E., and Weill H. (1982): Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. *American Review of Respiratory Disease* 126 (3), 420-428. DOI: 10.1164/arrd.1982.126.3.420 (last accessed 2016-09-28)

- Diepgen T.L., Purwins S., Posthumus J., Kuessner D., John S.M., and Augustin M. (2013a): Cost-of-illness analysis of patients with chronic hand eczema in routine care in Germany: Focus on the impact of occupational disease. *Acta Dermato-Venereologica* 93 (5), 538-543. DOI: 10.2340/00015555-1565
- Diepgen T.L., Scheidt R., Weisshaar E., John S.M., and Hieke K. (2013b): Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis* 69 (2), 99-106. DOI: 10.1111/cod.12038 (last accessed 2016-09-28)
- Dietemann-Molard A., Kopferschmitt-Kubler M.C., Meyer P.D., Tomb R., and Pauli G. (1991): Allergic asthma due to domestic use of insulating polyurethane foam. *The Lancet* 338 (8772), 953. DOI: 10.1016/0140-6736(91)91825-F (last accessed 2016-09-19)
- Diller W.F. (2002): Frequency and trends of occupational asthma due to toluene diisocyanate: a critical review. *Applied Occupational and Environmental Hygiene* 17 (12), 872-877. DOI: 10.1080/10473220290107075 (last accessed 2016-09-19)
- Diller W.F. and Herbert E. (1983): Lung function and other health parameters in workers in an isocyanate factory (MDI production). *Abstracts on Hygiene and Communicable Diseases* 58 (8), 524-525
- Dodge D.E. and Silva R. (2016a): Methylene diphenyl diisocyanate (monomer and polymeric forms) reference exposure levels. Technical support document for the derivation of noncancer reference exposure levels. Appendix D1, date: 2016-03. California Environmental Protection Agency, Oakland, CA, USA. <http://oehha.ca.gov/media/downloads/air/report-hot-spots/finalmdirelmarch2016.pdf> (last accessed 2016-09-20)
- Dodge D.E. and Silva R. (2016b): Toluene diisocyanate reference exposure levels. Technical support document for the derivation of noncancer reference exposure levels. Appendix D1, date: 2016-03. California Environmental Protection Agency, Oakland, CA, USA. <http://oehha.ca.gov/media/downloads/air/report-hot-spots/finaltdirelmarch2016.pdf> (last accessed 2016-09-20)
- Donnelly R., Buick J.B., and Macmahon J. (2004): Occupational asthma after exposure to plaster casts containing methylene diphenyl diisocyanate. *Occupational Medicine* 54 (6), 432-434. DOI: 10.1093/ocmed/kqg133 (last accessed 2016-09-19)
- Donovan J.C., Kudla I., and DeKoven J.G. (2009): Rapid development of allergic contact dermatitis from dicyclohexylmethane-4,4'-diisocyanate. *Dermatitis* 20 (4), 214-217. DOI: 10.2310/6620.2009.08098 (last accessed 2016-09-19)
- Dotson G.S., Maier A., Siegel P.D., Anderson S.E., Green B.J., Stefaniak A.B., Codispoti C.D., and Kimber I. (2015): Setting occupational exposure limits for chemical allergens - understanding the challenges. *Journal of Occupational and Environmental Hygiene* 12 Suppl 1, S82-S98. DOI: 10.1080/15459624.2015.1072277 (last accessed 2016-09-28)
- Dow (1992): Metabolic fate of 14C-toluene-2,4-diisocyanate in Fischer 344 rats. III report 10910, III project AM-AB-62, date: 1992-01-09. The Dow Chemical Company. International Isocyanate Institute, unpublished
- Dragos M., Jones M., Malo J.-L., Ghezzi H., and Gautrin D. (2009): Specific antibodies to diisocyanate and work-related respiratory symptoms in apprentice car-painters. *Occupational and Environmental Medicine* 66 (4), 227-234. DOI: 10.1136/oem.2007.038125 (last accessed 2016-09-19)
- DuPont (1971): Production of skin sensitization by inhalation of isocyanates. Report no. 161-71, date: 1971-05-20. DuPont, Haskell Laboratories. DuPont De Nemours & Co., unpublished

DuPont (1974): Immunopathological features of isocyanate compounds. Report no. 249-74, date: 1974-04-16. DuPont, Haskell Laboratories. DuPont De Nemours & Co., unpublished

DuPont (1977): Special primary skin irritation and sensitization tests on guinea pigs. Report no. 95-77, date: 1977-02-25. DuPont, Haskell Laboratories. DuPont De Nemours & Co., unpublished

Duprat P., Gradiski D., and Marignac B. (1976): Irritating and allergising power of two isocyanates. Toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI). *European Journal of Toxicology* 9, 41-53

Ebino K., Ueda H., Kawakatsu H., Shutoh Y., Kosaka T., Nagayoshi E., Lemus R., and Karol M.H. (2001): Isolated airway exposure to toluene diisocyanate results in skin sensitization. *Toxicology Letters* 121 (1), 79-85. DOI: 10.1016/S0378-4274(01)00325-3 (last accessed 2016-09-19)

ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. European Chemicals Agency, Helsinki, Finland. http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf (last accessed 2016-09-19)

ECHA (2015): Guidance on the application of the CLP criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, date: 2015-06. European Chemicals Agency. http://echa.europa.eu/documents/10162/13562/clp_en.pdf (last accessed 2016-09-19)

ECHA (2016): Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint-specific guidance. Version 5.0, date: 2016-12. European Chemicals Agency (ECHA). http://echa.europa.eu/documents/10162/13643/ir_csa_r7a_r7-3_caracal_draft_en.pdf (last accessed 2017-01-20)

Engels H.W., Pirkl H.G., Albers R., Albach R.W., Krause J., Hoffmann A., Casselmann H., and Dormish J. (2013): Polyurethane: Vielseitige Materialien und nachhaltige Problemlöser für aktuelle Anforderungen [Polyurethanes: Versatile materials and sustainable problem solvers for today's challenges]. *Angewandte Chemie* 125, 9596-9616. DOI: 10.1002/ange.201302766 (last accessed 2016-09-29)

Engfeldt M., Isaksson M., Zimerson E., and Bruze M. (2013): Several cases of work-related allergic contact dermatitis caused by isocyanates at a company manufacturing heat exchangers. *Contact Dermatitis* 68 (3), 175-180. DOI: 10.1111/j.1600-0536.2012.02167.x (last accessed 2016-09-19)

Engfeldt M. and Ponten A. (2013): Contact allergy to isocyanates after accidental spillage. *Contact Dermatitis* 69 (2), 122-124. DOI: 10.1111/cod.12071 (last accessed 2016-09-19)

Erban V. (1987): Isocyanat asthma in einer Graugießerei [Isocyanate asthma in a gray iron foundry]. *Arbeitsmedizin Sozialmedizin Präventivmedizin* 22, 249-253

European Commission (2003): Commission recommendation of 19 September 2003 concerning the European schedule of occupational diseases (notified under document number C(2003) 3297). http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2003.238.01.0028.01.ENG (last accessed 2016-09-28)

European Commission (2013a): Report on the current situation in relation to occupational diseases' systems in EU member states and EFTA/EEA countries, in particular relative to Commission Recommendation 2003/670/EC concerning the European schedule of occupational diseases and gathering of data on relevant related aspects, date: 2013-03. <http://ec.europa.eu/social/BlobServlet?docId=9982&langId=en> (last accessed 2016-09-19)

European Commission (2013b): Roadmap on Substances of Very High Concern, date: 2013-02-05. Council of Europe, Brussels, Belgium. <http://register.consilium.europa.eu/doc/srv?!=DE&f=ST%205867%202013%20INIT> (last accessed 2016-09-19)

European Commission (2014): Best Available Techniques (BAT) reference document in the large volume organic chemical industry, date: 2014-04. Joint Research Centre (JRC), Institute for Prospective Technological Studies, Sustainable Production and Consumption Unit, European IPPC Bureau. European Commission, Brussels, Belgium. <http://eippcb.jrc.ec.europa.eu/reference/BREF/LVOC042014.pdf> (last accessed 2016-09-29)

European Commission (2016): European Union inflation forecast 2015-2020, data and charts. <https://knoema.de/askertf/european-union-inflation-forecast-2015-2020-data-and-charts>

European Parliament and Council (2008a): Regulation (EC) no. 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (last amended by Commission Regulation (EU) 2015/491 of 23 March 2015). European Union,, Brussels. <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1272-20160101&from=EN> (last accessed 2016-09-19)

European Parliament and Council (2008b): Regulation (EC) no. 1338/2008 of the European Parliament and of the Council of 16 December 2008 on Community statistics on public health and health and safety at work. European Union,. <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1338&from=EN> (last accessed 2016-09-28)

Eurostat (2015): Employment (15-64 years) based on the European Union Labour Force Survey (EU LFS). European Commission,. http://appsso.eurostat.ec.europa.eu/nui/show.do?wai=true&dataset=lfsi_emp_a (last accessed 2015-10-12)

Fabbri L.M., Boschetto P., Zocca E., Milani G., Pivrotto F., Plebani M., Burlina A., Licata B., and Mapp C.E. (1987): Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. *American Review of Respiratory Disease* 136 (1), 36-42. DOI: 10.1164/ajrccm/136.1.36 (last accessed 2016-09-19)

Fabbri L.M., Danieli D., Crescioli S., Bevilacqua P., Meli S., Saetta M., and Mapp C.E. (1988): Fatal asthma in a subject sensitized to toluene diisocyanate. *American Review of Respiratory Disease* 137 (6), 1494-1498. DOI: 10.1164/ajrccm/137.6.1494 (last accessed 2016-09-28)

Fabbri L.M. and Mapp C. (1991): Bronchial hyperresponsiveness, airway inflammation and occupational asthma induced by toluene diisocyanate. *Clinical & Experimental Allergy* 21 Suppl 1, 42-47. DOI: 10.1111/j.1365-2222.1991.tb01705.x (last accessed 2016-09-19)

Farraj A.K., Boykin E., Haykal-Coates N., Gavett S.H., Doerfler D., and Selgrade M. (2007): Th2 cytokines in skin draining lymph nodes and serum IgE do not predict airway hypersensitivity to intranasal isocyanate exposure in mice. *Toxicological Sciences* 100 (1), 99-108. DOI: 10.1093/toxsci/kfm194 (last accessed 2016-09-19)

Fent K.W., Trelles Gaines L.G., Thomasen J.M., Flack S.L., Ding K., Herring A.H., Whittaker S.G., and Nylander-French L.A. (2009a): Quantification and statistical modeling - part I: Breathing-zone concentrations of monomeric and polymeric 1,6-hexamethylene diisocyanate. *Annals of Occupational Hygiene* 53 (7), 677-689. DOI: 10.1093/annhyg/mep046 (last accessed 2016-09-19)

Fent K.W., Trelles Gaines L.G., Thomasen J.M., Flack S.L., Ding K., Herring A.H., Whittaker S.G., and Nylander-French L.A. (2009b): Quantification and statistical modeling - part II: Dermal concentrations of monomeric and polymeric 1,6-hexamethylene diisocyanate. *Annals of Occupational Hygiene* 53 (7), 691-702. DOI: 10.1093/annhyg/mep048 (last accessed 2016-09-19)

Figovsky O., Shapovalov L., Leykin A., Birukova O., and Potashnikova R. (2012): Progress in elaboration of nonisocyanate polyurethanes based on cyclic carbonates. *International Letters of Chemistry, Physics and Astronomy* 3, 52-66. <http://figovsky.com/publications.html>

Finotto S., Fabbri L.M., Rado V., Mapp C.E., and Maestrelli P. (1991): Increase in numbers of CD8 positive lymphocytes and eosinophils in peripheral blood of subjects with late asthmatic reactions induced by toluene diisocyanate. *British Journal of Industrial Medicine* 48 (2), 116-121. DOI: 10.1136/oem.48.2.116 (last accessed 2016-09-28)

Fisseler-Eckhoff A., Bartsch H., Zinsky R., and Schirren J. (2011): Environmental isocyanate-induced asthma: Morphologic and pathogenetic aspects of an increasing occupational disease. *International Journal of Environmental Research and Public Health* 8 (9), 3672-3687. DOI: 10.3390/ijerph8093672 (last accessed 2016-09-19)

Fleming M. and Lardner R. (2002): Strategies to promote safe behaviour as part of a health and safety management system. Report no.: 430/2002, ISBN: 0 7176 2352 1. The Keil Centre. Executive H.a.S. http://www.hse.gov.uk/research/crr_pdf/2002/crr02430.pdf (last accessed 2016-12-15)

Frick M., Björkner B., Hamnerius N., and Zimerson E. (2003a): Allergic contact dermatitis from dicyclohexylmethane-4,4'- diisocyanate. *Contact Dermatitis* 48 (6), 305-309. DOI: 10.1034/j.1600-0536.2003.00123.x (last accessed 2016-09-19)

Frick M., Isaksson M., Björkner B., Hindsén M., Pontén A., and Bruze M. (2003b): Occupational allergic contact dermatitis in a company manufacturing boards coated with isocyanate lacquer. *Contact Dermatitis* 48 (5), 255-260. DOI: 10.1034/j.1600-0536.2003.00107.x (last accessed 2016-09-19)

Friedman S.A. (1982): Fibrosing alveolitis in man following exposure to diphenylmethane diisocyanate: First report. *American Review of Respiratory Disease* 125 (4)

Friedmann P.S. (2007): The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *British Journal of Dermatology* 157 (6), 1093-1102. DOI: 10.1111/j.1365-2133.2007.08162.x (last accessed 2016-09-19)

Fuchs S. and Valade P. (1951): Étude clinique et expérimentale sur quelques cas d'intoxication par le desmodur T (diisocyanate de toluylène 1-2-4 et 1-2-6) [Clinical and experimental study of some cases of poisoning by desmodur T (1-2-4 and 1-2-6 diisocyanates of toluene)]. *Archives des Maladies Professionnelles de Médecine du Travail et de Sécurité Sociale* 12 (2), 191-196

Fukuyama T., Tajima Y., Ueda H., Hayashi K., Shutoh Y., Harada T., and Kosaka T. (2010): A method for measuring mouse respiratory allergic reaction to low-dose chemical exposure to allergens: An environmental chemical of uncertain allergenicity, a typical contact allergen and a non-sensitizing irritant. *Toxicology Letters* 195 (1), 35-43. DOI: 10.1016/j.toxlet.2010.02.016 (last accessed 2016-09-19)

Fukuyama T., Ueda H., Hayashi K., Tajima Y., Shuto Y., Saito T.R., Harada T., and Kosaka T. (2008): Use of long term dermal sensitization followed by intratracheal challenge method to identify low-dose chemical-induced respiratory allergic responses in mice. *Toxicology Letters* 181 (3), 163-170. DOI: 10.1016/j.toxlet.2008.07.017 (last accessed 2016-09-20)

Gabriel S., Koppisch D., and Range D. (2010): The MGU - a monitoring system for the collection and documentation of valid workplace exposure data. *Gefahrstoffe - Reinhaltung der Luft* 70 (1/2), 43-49. http://www.berufsgenossenschaften.net/medien/ifa/de/pub/grl/pdf/2010_002.pdf (last accessed 2016-09-29)

Gad S.C., Dunn B.J., Dobbs D.W., Reilly C., and Walsh R.D. (1986): Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST). *Toxicology and Applied Pharmacology* 84 (1), 93-114. DOI: 10.1016/0041-008X(86)90419-9 (last accessed 2016-09-20)

Gagnaire F., Ban M., Cour C., Micillino J.C., Bonnet P., and Hettich D. (1997): Role of tachykinins and neutral endopeptidase in toluene diisocyanate-induced bronchial hyperresponsiveness in guinea pigs. *Toxicology* 116 (1-3), 17-26. DOI: 10.1016/S0300-483X(96)03517-2 (last accessed 2016-09-20)

Gagnaire F., Ban M., Micillino J.C., Lemonnier M., and Bonnet P. (1996): Bronchial responsiveness and inflammation in guinea-pigs exposed to toluene diisocyanate: a study on single and repeated exposure. *Toxicology* 114 (2), 91-100. DOI: 10.1016/S0300-483X(96)03415-4 (last accessed 2016-09-20)

Gaines L.G., Fent K.W., Flack S.L., Thomasen J.M., Ball L.M., Richardson D.B., Ding K., Whittaker S.G., and Nylander-French L.A. (2010): Urine 1,6-hexamethylene diamine (HDA) levels among workers exposed to 1,6-hexamethylene diisocyanate (HDI). *Annals of Occupational Hygiene* 54 (6), 678-691. DOI: 10.1093/annhyg/meq041 (last accessed 2016-09-20)

Gannon P.F.G., Weir D.C., Robertson A.S., and Sherwood Burge P. (1993): Health, employment, and financial outcomes in workers with occupational asthma. *British Journal of Industrial Medicine* 50 (6), 491-496. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1035473/> (last accessed 2016-12-01)

Garcia Gomez M., Urbanos Garrido R., Castaneda Lopez R., and Lopez Menduina P. (2012): Direct health care costs of occupational asthma in Spain: An estimation from 2008. *Archivos de Bronconeumologia* 48 (10), 355-361. DOI: 10.1016/j.arbres.2012.04.014 (last accessed 2016-09-28)

Gee J.B. and Morgan W.K. (1985): A 10-year follow-up study of a group of workers exposed to isocyanates. *Journal of Occupational Medicine* 27 (1), 15-18

Geens T., Dugardin S., Schockaert A., de Cooman G., and van Sprundel M. (2012): Air exposure assessment of TDI and biological monitoring of TDA in urine in workers in polyurethane foam industry. *Occupational and Environmental Medicine* 69 (2), 93-98. DOI: 10.1136/oem.2011.064840 (last accessed 2016-09-20)

Gezondheidsraad (2008): Prevention of work-related airway allergies. Recommended occupational exposure limits and periodic screening. Publication no. 2008/03E, ISBN: 978-90-5549-710-2, date: 2008-03-13. Gezondheidsraad (Health Council of the Netherlands), Den Haag, The Netherlands. <http://www.gezondheidsraad.nl/en/task-and-procedure/areas-of-activity/healthy-working-conditions/prevention-of-work-related-airway>

Gibson G., Brannigan C., Kaar A.-L., Kirsch F., Twisse F., Bonifazi E., Lorton C., Troncoso Ferrer M., Ruixo C., Izquierdo S.M., and Verbeek M. (2014): Study on the operation of the system of access to vehicle repair and maintenance information, date: 10/2014. Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs. European Commission. DOI: 10.2769/50934 (last accessed 2016-09-28)

Gledhill A., Wake A., Hext P., Leibold E., and Shiotsuka R. (2005): Absorption, distribution, metabolism and excretion of an inhalation dose of [¹⁴C] 4,4'-methylenediphenyl

diisocyanate in the male rat. *Xenobiotica* 35 (3), 273-292. DOI: 10.1080/00498250500057591 (last accessed 2016-09-20)

Goossens A., Detienne T., and Bruze M. (2002): Occupational allergic contact dermatitis caused by isocyanates. *Contact Dermatitis* 47 (5), 304-308. DOI: 10.1080/00498250500057591 (last accessed 2016-09-20)

Griem P., Goebel C., and Scheffler H. (2003): Proposal for a risk assessment methodology for skin sensitization based on sensitization potency data. *Regulatory Toxicology and Pharmacology* 38 (3), 269-290. DOI: 10.1016/j.yrtph.2003.07.001 (last accessed 2016-09-20)

Gries W. and Leng G. (2013): Analytical determination of specific 4,4'-methylene diphenyl diisocyanate hemoglobin adducts in human blood. *Analytical and Bioanalytical Chemistry* 405 (23), 7205-7213. DOI: 10.1007/s00216-013-7171-z (last accessed 2016-09-29)

Gui W., Wisniewski A.V., Neamtiu I., Gurzau E., Sparer J.A., Stowe M.H., Liu J., Slade M.D., Rusu O.A., and Redlich C.A. (2014): Inception cohort study of workers exposed to toluene diisocyanate at a polyurethane foam factory: Initial one-year follow-up. *American Journal of Industrial Medicine* 57 (11), 1207-1215. DOI: 10.1002/ajim.22385 (last accessed 2016-09-19)

Haag M., Leusink-Muis T., Le Bouquin R., Nijkamp F.P., Lugnier A., Frossard N., Folkerts G., and Pons F. (2002): Increased expression and decreased activity of cytochrome P450 1A1 in a murine model of toluene diisocyanate-induced asthma. *Archives of Toxicology* 76 (11), 621-627. DOI: 10.1007/s00204-002-0393-z (last accessed 2016-09-20)

Hagemeyer O., Monsé C., Brüning T., and Merget R. (2014): Expositionstests mit Diisocyanaten -zur Bedeutung von isolierten Spätreaktionen [Exposure tests with diisocyanates - on the relevance of isolated late-onset reactions]. *IPA-Journal* (2), 8-13. http://www.ipa.ruhr-uni-bochum.de/pdf/IPA-Journal_1402-AM-Fall.pdf (last accessed 2016-09-20)

Hathaway J.A., DeWilde A., Shepperly D.C., Nguyen L.T., and Johnson J.E. (1999): Evaluation of pulmonary function in workers exposed to hexamethylene diisocyanate. *Journal of Occupational and Environmental Medicine* 41 (5), 378-383. <http://journals.lww.com/joem/pages/articleviewer.aspx?year=1999&issue=05000&article=00005&type=abstract> (last accessed 2019-09-28)

Hathaway J.A., Molenaar D.M., Cassidy L.D., Feeley T.M., and Cummings B.J. (2014): Cross-sectional survey of workers exposed to aliphatic diisocyanates using detailed respiratory medical history and questions regarding accidental skin and respiratory exposures. *Journal of Occupational and Environmental Medicine* 56 (1), 52-57. DOI: 10.1097/jom.000000000000019 (last accessed 2016-09-20)

Hazleton (1984): The toxicity and carcinogenicity to rats of toluene diisocyanate vapour administered by inhalation for a period of 113 weeks. Addendum Report Volume. III project A-A-1, III report 10233, date: 1984-03-01. Hazleton Laboratories Europe Ltd. International Isocyanate Institute, unpublished

Hazleton (1986): The toxicity and carcinogenicity of toluene diisocyanate vapour when administered to mice over a period of approximately two years. Volumes I and II. III project A-A-1, III Report 10382, date: 1986-01-03. Hazleton Laboratories Europe Ltd. International Isocyanate Institute, unpublished

Heederik D., Henneberger P.K., and Redlich C.A. (2012): Primary prevention: exposure reduction, skin exposure and respiratory protection. *European Respiratory Review* 21 (124), 112-124. DOI: 10.1183/09059180.00005111 (last accessed 2016-09-29)

- Henriks-Eckerman M.L., Makela E.A., Laitinen J., Ylinen K., Suuronen K., Vuokko A., and Sauni R. (2015): Role of dermal exposure in systemic intake of methylenediphenyl diisocyanate (MDI) among construction and boat building workers. *Toxicology Letters* 232 (3), 595-600. DOI: 10.1016/j.toxlet.2014.12.012 (last accessed 2016-09-20)
- Hesbert A., Ban M., Bonnet P., Simon P., Bottin M.C., Lemonnier M., and de Ceaurriz J. (1991): Interdependence of polymorphonuclear neutrophils and macrophages stained for N-acetyl-beta-glucosaminidase in lavage effluents from toluene diisocyanate-exposed rat lungs. *Toxicology Letters* 56 (1-2), 53-59. DOI: 10.1016/0378-4274(91)90089-O (last accessed 2016-09-20)
- Hilton J., Dearman R.J., Basketter D.A., and Kimber I. (1995): Identification of chemical respiratory allergens: Dose-response relationships in the mouse IgE test. *Toxicology Mechanisms and Methods* 5 (1), 51-60. DOI: doi: 10.3109/15376519509066117 (last accessed 2016-09-20)
- Hilton J., Dearman R.J., Debicki R.J., Ramdin L.S.P., and Kimber I. (1994): Interleukin 6 production in vitro: An alternative read-out for the local lymph node assay. *Toxicology In Vitro* 8 (4), 711-713. DOI: 10.1016/0887-2333(94)90049-3 (last accessed 2016-09-20)
- Ho S.-M. (2010): Environmental epigenetics of asthma – an update. *Journal of Allergy and Clinical Immunology* 126 (3), 453-465. DOI: 10.1016/j.jaci.2010.07.030 (last accessed 2016-09-20)
- Hoffman T.E. (1982): Allergic contact dermatitis to new plastic resins. *Archives of Dermatology* 118 (12), 962. DOI: 10.1001/archderm.1982.01650240006009 (last accessed 2016-09-20)
- Hofmaier S., Comberiati P., and Matricardi P.M. (2014): Immunoglobulin G in IgE-mediated allergy and allergen-specific immunotherapy. *European Annals of Allergy and Clinical Immunology* 46 (1), 6-11. <http://www.eurannallergyimm.com/cont/journals-articles/18/volume-n-immunoglobulin-igemediated-allergy-allergenspecific-immunotherapy-33allasp1.pdf> (last accessed 2016-09-20)
- Holness D.L., Broder I., Corey P.N., Booth N., Mozzon D., Nazar M.A., and Guirguis S. (1984): Respiratory variables and exposure-effect relationships in isocyanate-exposed workers. *Journal of Occupational Medicine* 26 (6), 449-455
- Hostynek J.J. and Maibach H.I. (2004): Thresholds of elicitation depend on induction conditions. Could low level exposure induce sub-clinical allergic states that are only elicited under the severe conditions of clinical diagnosis? *Food and Chemical Toxicology* 42 (11), 1859-1865. DOI: 10.1016/j.fct.2004.06.017 (last accessed 2016-09-20)
- Hoymann H.G., Buschmann J., and Heinrich U. (1995): Untersuchungen zur chronischen Toxizität/Kanzerogenität von 4,4'-Methylenediphenyl-Diisocyanat (MDI) [Studies on the chronic toxicity/carcinogenicity of 4,4'-methylenediphenyl-diisocyanate (MDI)]. *Forschungsbericht* 116 06 084, date: 1995-09-01. Fraunhofer-Institut für Toxikologie und Aerosolforschung. Umweltbundesamt (UBA)
- HSE (2014): Controlling isocyanate exposure in spray booths and spray rooms. Health and Safety Executive. HSE books. <http://www.hse.gov.uk/pubns/priced/hsg276.pdf> (last accessed 2016-09-20)
- HSE (2015): Occupational asthma in Great Britain 2014, 1-17. <http://www.hse.gov.uk/statistics/causdis/asthma/asthma.pdf>
- HSE (2016): Index of data tables. THOR tables. Health and Safety Executive, <http://www.hse.gov.uk/Statistics/tables/index.htm#thor> (last accessed 2016-09-19)

HSL (2010): Reducing exposure to isocyanates in motor vehicle repair. Health & Safety Laboratory,. http://www.hsl.gov.uk/media/50529/reducing%20exposure%20to%20isocyanates_layout%201.pdf (last accessed 2016-09-28)

HSL (2016): Health & safety training courses. Health and Safety Laboratory,. <http://www.hsl.gov.uk/hsl-shop/health-and-safety-training-courses> (last accessed 2016-09-28)

Huang J., Wang X.P., Chen B.M., Ueda A., Aoyama K., and Matsushita T. (1991): Immunological effects of toluene diisocyanate exposure on painters. Archives of Environmental Contamination and Toxicology 21 (4), 607-611. DOI: 10.1007/BF01183884 (last accessed 2016-09-20)

Huang J., Wang X.P., Chen B.M., Zhou X.J., and Matsushita T. (1993): Dose-response relationships for chemical sensitization from TDI and DNCB. Bulletin of Environmental Contamination and Toxicology 51 (5), 732-739. DOI: 10.1007/BF00201652 (last accessed 2016-09-20)

Huang Y.C. and Tsuang W. (2014): Health effects associated with faulty application of spray polyurethane foam in residential homes. Environmental Research 134, 295-300. DOI: 10.1016/j.envres.2014.07.015 (last accessed 2016-09-21)

Huffman L.J., Judy D.J., Frazer D., Shapiro R.E., Castranova V., Billie M., and Dedhia H.V. (1997): Inhalation of toluene diisocyanate is associated with increased production of nitric oxide by rat bronchoalveolar lavage cells. Toxicology and Applied Pharmacology 145 (1), 61-67. DOI: 10.1006/taap.1997.8162 (last accessed 2016-09-20)

Huntingdon (1980): Screening test for delayed contact hypersensitivity with 1,3-Bis(Isocyanatomethyl)benzene in the albino guinea-pig. Report no. 80308D/TDA/77, date: 1980-04-24. Huntingdon Research Centre. Takeda Chemical Industries Ltd., unpublished

Huntingdon (1997): Takenate 500 skin sensitisation in the guinea-pig. Report no. TDA 217/971230, date: 1997-06-02. Huntingdon Life Sciences Ltd. Takeda Chemical Industries Ltd., unpublished

IAL (2014): Polyurethane chemicals and products in Europe, Middle East & Africa (EMEA), 2914. IAL Consultants,, London, United Kingdom. http://www.ialconsultants.com/uploads/CUBE_press_release/2014-09-30/polyurethane_EMEA_press_release_2014.pdf (last accessed 2016-09-29)

IBR (1977): Prüfung von "IPDI-T 1890" im epicutanen Sensibilisierungstest an der Meerschweinchenhaut (25 %ig in Sojabohnenöl) [Study of "IPDI-T 1890" in the epicutaneous sensitisation test in guinea-pig skin (25% in soy bean oil)]. Report no. 2-5-379-77, date: 1977-11-30. International Bio-Research. Evonik Degussa GmbH, unpublished

IBR (1983a): 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - Prüfung auf sensibilisierende Eigenschaften am Meerschweinchen nach B. Magnusson und A.M. Kligman (gemäß OECD Richtlinien) [3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanate - test for sensitising properties in the guinea-pig according to B. Magnusson and A.M. Kligman (following OECD guidelines)]. Report no. 2-5-120-83, date: 1983-07-11. IBR Forschungs GmbH. Evonik Degussa GmbH, unpublished

IBR (1983b): Polyisocyanat IPDI-T 1890S (monomeres IPDI: < 0,5 Gew. %) - Prüfung auf sensibilisierende Eigenschaften am Meerschweinchen nach B. Magnusson und A.M. Kligman (gemäß OECD Richtlinien) [Polyisocyanate IPDI-T 1890S (monomeric IPDI: < 0.5% by wt.) - test for sensitising properties in the guinea-pig according to B. Magnusson and A.M. Kligman (following OECD guidelines)]. Report no. 2-5-348-83, date: 1983-09-30. IBR Forschungs GmbH. Evonik Degussa GmbH, unpublished

IFA (2010): MEGA Auswertung zur Erstellung von REACH Expositionsszenarien für MDI und TDI (2000-2009) in Deutschland, date: 2010-06. Institut für Arbeitsschutz. Deutsche Gesetzliche Unfallversicherung (DGUV). http://www.dguv.de/medien/ifa/de/fac/reach/mega_auswertungen/mdi_tdi_d.pdf (last accessed 2016-09-29)

IFA (2012): MEGA-Auswertungen zur Erstellung von REACH-Expositionsszenarien für Hexamethylen-1,6-diisocyanat (HDI), date: 2013-05. Institut für Arbeitsschutz. Deutsche Gesetzliche Unfallversicherung (DGUV). http://www.dguv.de/medien/ifa/de/fac/reach/mega_auswertungen/hdi_dt.pdf (last accessed 2016-09-29)

IFA (2013): MEGA-Auswertungen zur Erstellung von REACH-Expositionsszenarien für 2,4-Diisocyanatoloul (2,4-TDI) und 2,6-Diisocyanatoloul (2,6-TDI), date: 2013-06. Institut für Arbeitsschutz. Deutsche Gesetzliche Unfallversicherung (DGUV). http://www.dguv.de/medien/ifa/de/fac/reach/mega_auswertungen/24_tdi_26_tdi.pdf (last accessed 2016-09-29)

Innocenti A., Cirila A.M., Pisati G., and Mariano A. (1988): Cross-reaction between aromatic isocyanates (TDI and MDI): A specific bronchial provocation test study. *Clinical Allergy* 18 (4), 323-329

Innocenti A. and Paggiaro P.L. (1983): A case of occupational asthma due to diphenylmethane diisocyanate (MDI). *Medicina del Lavoro* 74 (5), 391-393

International Isocyanate Institute (1998): Biochemical and histoautoradiographic characterization of the distribution of radioactivity following exposure to ¹⁴C-MDI aerosol. Project 103-AM-MTX, date: 1998-11-20, unpublished

IPCS (2004): IPCS risk assessment terminology. Part 1: IPCS key generic terms used in chemical hazard/risk assessment. Harmonization Project Document 1. International Programme on Chemical Safety (IPCS). World Health Organization (WHO), International Labour Organization (ILO), United Nations Environment Programme (UNEP), Geneva, Switzerland.

<http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf?ua=1> (last accessed 2016-09-20)

IPCS (2014): Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11. International Programme on Chemical Safety (IPCS). World Health Organization (WHO), International Labour Organization (ILO), United Nations Environment Programme (UNEP). http://www.who.int/ipcs/methods/harmonization/uncertainty_in_hazard_characterization.pdf (last accessed 2016-09-19)

ISOPA (2012): MDI: Final exposure scenarios in the e-SDS format. European Diisocyanate & Polyol Producers Association (ISOPA). http://www.isopa.org/media/1663/esds-for-mdi-_30_apr_2012_-1.pdf (last accessed 2016-09-29)

ISOPA (2013): GPS Safety Summary. MDI, Methylenediphenyl-diisocyanate, covers all commercially available products deriving from the pure 4,4'-MDI (CAS 101-68-8), its structural isomers 2,4'-MDI (CAS 5873-54-1) and 2,2'-MDI (CAS 2536-05-2), MDI mixed isomers (CAS 26447-40-5), both "oligomeric MDI" (CAS 32055-14-4) and "polymeric MDI" (CAS 9016-87-9) as well as the modified reaction products such as MDI Homopolymer (CAS 25686-28-6), MDI/DPG (CAS 88288-99-7), MDI/TPG (CAS 75880-28-3), MDI/1,3-BD/TPG/PG and MDI/MDI Homopolymer/1,3-BD/TPG/PG (EC 500-313-7), date: 2013-06. European Diisocyanate & Polyol Producers Association (ISOPA). <http://www.isopa.org/media/1093/gps-mdi.pdf> (last accessed 2016-09-29)

ISOPA (2014): Socio-economic contribution of the polyurethane industry to growth and jobs in Europe. European Diisocyanate & Polyol Producers Association (ISOPA). <http://isopa.org/media/1100/isopa-socioeconomic-report.pdf> (last accessed 2016-09-19)

Israeli R., Smirnov V., and Sculsky M. (1981): Vergiftungserscheinungen bei Dicyclohexylmethan-4-4'-diisocyanat-Exposition [Intoxication due to dicyclohexyl-methane-4-4' diisocyanate exposure]. *International Archives of Occupational and Environmental Health* 48 (2), 179-184. DOI: 10.1007/BF00378439 (last accessed 2016-09-20)

Jaakkola M.S. and Jaakkola J.J.K. (2012): Assessment of public health impact of work-related asthma. *BMC Medical Research Methodology* 12 (22). DOI: 10.1186/1471-2288-12-22 (last accessed 2016-09-28)

Jang A.S., Choi I.S., Koh Y.I., Moon J.D., and Lee K.J. (2000): Increase in airway hyperresponsiveness among workers exposed to methylene diphenyldiisocyanate compared to workers exposed to toluene diisocyanate at a petrochemical plant in Korea. *American Journal of Industrial Medicine* 37 (6), 663-667. DOI: 10.1002/(SICI)1097-0274(200006)37:6<663::AID-AJIM11>3.0.CO;2-H (last accessed 2016-09-20)

Jankowski M.J., Olsen R., Nielsen C.J., Thomassen Y., and Molander P. (2014): The applicability of proton transfer reaction-mass spectrometry (PTR-MS) for determination of isocyanic acid (ICA) in work room atmospheres. *Environmental Science. Processes & Impacts* 16 (10), 2423-2431. DOI: 10.1039/c4em00363b (last accessed 2016-09-28)

Jennings G.H. and Gower N.D. (1963): Thrombocytopenic purpura in toluene di-isocyanate workers. *The Lancet* 281 (7278), 406-408. DOI: 10.1016/S0140-6736(63)92301-8 (last accessed 2016-09-28)

Jin R. and Karol M.H. (1988): Diisocyanate antigens that detect specific antibodies in exposed workers and guinea pigs. *Chemical Research in Toxicology* 1 (5), 288-293. DOI: 10.1021/tx00005a006 (last accessed 2016-09-20)

Johnson A., Moira C.Y., MacLean L., Atkins E., Dybuncio A., Cheng F., and Enarson D. (1985): Respiratory abnormalities among workers in an iron and steel foundry. *British Journal of Industrial Medicine* 42 (2), 94-100. https://www.jstor.org/stable/27723898?seq=1#fndtn-page_scan_tab_contents (last accessed 2016-09-28)

Johnson V.J., Matheson J.M., and Luster M.I. (2004a): Animal models for diisocyanate asthma: Answers for lingering questions. *Current Opinion in Allergy and Clinical Immunology* 4 (2), 105-110. DOI: 10.1097/01.all.0000123966.96233.ce (last accessed 2016-09-20)

Johnson V.J., Yucesoy B., and Luster M.I. (2004b): Role of interleukin-1 in toluene diisocyanate asthma, Abst. 769.723. FASEB Meeting: Experimental Biology 2004, Washington, DC, USA, Federation of American Societies for Experimental Biology,. ISBN: 0892-6638 (ISSN print). <http://www.cdc.gov/niosh/nioshtic-2/20025079.html>

Jones K., Cocker J., and Piney M. (2013): Isocyanate exposure control in motor vehicle paint spraying: Evidence from biological monitoring. *Annals of Occupational Hygiene* 57 (2), 200-209. DOI: 10.1093/annhyg/mes056 (last accessed 2016-09-20)

Jones R.N., Rando R.J., Glindmeyer H.W., Foster T.A., Hughes J.M., O'Neil C.E., and Weill H. (1992): Abnormal lung function in polyurethane foam producers: Weak relationship to toluene diisocyanate exposures. *American Review of Respiratory Disease* 146 (4), 871-877. DOI: 10.1164/ajrccm/146.4.871 (last accessed 2016-09-19)

Kääriä K., Hirvonen A., Norppa H., Piirilä P., Vainio H., and Rosenberg C. (2001): Exposure to 4,4'-methylenediphenyl diisocyanate (MDI) during moulding of rigid polyurethane foam:

determination of airborne MDI and urinary 4,4'-methylenedianiline (MDA). *Analyst* 126 (4), 476-479. DOI: 10.1039/b009549o (last accessed 2016-09-20)

Kakooei H., Shahtaheri S.J., and Karbasi H.A. (2006): Evaluation of workers' exposure to methylene diphenyl diisocyanate (MDI) in an automobile manufacturing company, Iran. *International Journal of Occupational Safety and Ergonomics* 12 (4), 443-449. DOI: 10.1080/10803548.2006.11076701 (last accessed 2016-09-20)

Kalubi B., Takeda N., Irifune M., Ogino S., Abe Y., Hong S.L., Yamano M., Matsunaga T., and Tohyama M. (1992): Nasal-mucosa sensitization with toluene diisocyanate (TDI) increases preprotachykinin A (PPTA) and preproCGRP mRNAs in guinea pig trigeminal ganglion neurons. *Brain Research* 576 (2), 287-296. DOI: 10.1016/0006-8993(92)90692-3 (last accessed 2016-09-20)

Kanerva L., Grenquist-Nordén B., and Piirilä P. (1999): Occupational IgE-mediated contact urticaria from diphenylmethane-4,4'-diisocyanate (MDI). *Contact Dermatitis* 41 (1), 50-51. DOI: 10.1111/j.1600-0536.1999.tb06215.x (last accessed 2016-09-20)

Karjalainen A., Kurppa K., Virtanen S., Keskinen H., and Nordman H. (2000): Incidence of occupational asthma by occupation and industry in Finland. *American Journal of Industrial Medicine* 37 (5), 451-458. DOI: 10.1002/(SICI)1097-0274(200005)37:5<451::AID-AJIM1>3.0.CO;2-U (last accessed 2016-09-20)

Karol M.H. (1981): Survey of industrial workers for antibodies to toluene diisocyanate. *Journal of Occupational Medicine* 23 (11), 741-747. http://journals.lww.com/joem/Abstract/1981/11000/Survey_of_Industrial_Workers_for_Antibodies_to.7.aspx (last accessed 2016-09-22)

Karol M.H. (1983): Concentration-dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. *Toxicology and Applied Pharmacology* 68 (2), 229-241. DOI: 10.1016/0041-008X(83)90007-8 (last accessed 2016-09-20)

Karol M.H. and Dean J.H. (1986): Respiratory effects of inhaled isocyanates. *Critical Reviews in Toxicology* 16 (4), 349-379. DOI: 10.3109/10408448609037467 (last accessed 2016-09-29)

Karol M.H. and Hauth B.A. (1982): Use of hexyl isocyanate antigen to detect antibodies to hexamethylene diisocyanate (HDI) in sensitized guinea pigs and in a sensitized worker. *Fundamental and Applied Toxicology* 2 (3), 108-113. DOI: 10.1016/S0272-0590(82)80090-0 (last accessed 2016-09-20)

Karol M.H., Hauth B.A., Riley E.J., and Magreni C.M. (1981): Dermal contact with toluene diisocyanate (TDI) produces respiratory tract hypersensitivity in guinea pigs. *Toxicology and Applied Pharmacology* 58 (2), 221-230. DOI: 10.1016/0041-008X(81)90426-9 (last accessed 2016-09-19)

Karol M.H. and Kramarik J.A. (1996): Phenyl isocyanate is a potent chemical sensitizer. *Toxicology Letters* 89 (2), 139-146. DOI: 10.1016/S0378-4274(96)03798-8 (last accessed 2016-09-20)

Karol M.H. and Magreni C. (1982): Extensive skin sensitization with minimal antibody production in guinea pigs as a result of exposure to dicyclohexylmethane-4,4'-diisocyanate. *Toxicology and Applied Pharmacology* 65 (2), 291-301. DOI: 10.1016/0041-008X(82)90012-6 (last accessed 2016-09-20)

Kennedy A.L. (1990): Comparative analysis of the uptake and distribution of inhaled, ¹⁴C-labeled isocyanates in blood. *Toxicologist* 10, 236. <http://www.toxicology.org/pubs/docs/Tox/1990Tox.pdf> (last accessed 2016-09-20)

Kennedy A.L., Stock M.F., Alarie Y., and Brown W.E. (1989): Uptake and distribution of ¹⁴C during and following inhalation exposure to radioactive toluene diisocyanate. *Toxicology and Applied Pharmacology* 100 (2), 280-292. DOI: 10.1016/0041-008X(89)90314-1 (last accessed 2016-09-20)

Kennedy A.L., Wilson T.R., Stock M.F., Alarie Y., and Brown W.E. (1994): Distribution and reactivity of inhaled ¹⁴C-labeled toluene diisocyanate (TDI) in rats. *Archives of Toxicology* 68 (7), 434-443. DOI: 10.1007/s002040050094 (last accessed 2016-09-20)

Kerre S. (2008): Allergic contact dermatitis to DMDI in an office application. *Contact Dermatitis* 58 (5), 313-314. DOI: 10.1111/j.1600-0536.2007.01290.x (last accessed 2016-09-20)

Kidd P. (2003): Th1/Th2 balance: The hypothesis, its limitations, and implications for health and disease. *Alternative Medicine Review* 8 (3), 223-246. <http://www.altmedrev.com/publications/8/3/223.pdf> (last accessed 2016-09-20)

Kilgour J.D., Rattray N.J., Foster J., Soames A., and Hext P.M. (2002): Pulmonary responses and recovery following single and repeated inhalation exposure of rats to polymeric methylene diphenyl diisocyanate aerosols. *Journal of Applied Toxicology* 22 (6), 371-385. DOI: 10.1002/jat.872 (last accessed 2016-09-20)

Kim H., Kim Y.D., and Choi J. (1997): Seroimmunological characteristics of Korean workers exposed to toluene diisocyanate. *Environmental Research* 75 (1), 1-6. DOI: 10.1006/enrs.1997.3763 (last accessed 2016-09-28)

Kimber I. and Basketter D.A. (2014): Categorisation of protein respiratory allergens: The case of Subtilisin. *Regulatory Toxicology and Pharmacology* 68 (3), 488-492. DOI: 10.1016/j.yrtph.2014.02.004 (last accessed 2016-09-20)

Kimber I., Dearman R.J., and Basketter D.A. (2014): Diisocyanates, occupational asthma and IgE antibody: Implications for hazard characterization. *Journal of Applied Toxicology* 34 (10), 1073-1077. DOI: 10.1002/jat.3041 (last accessed 2016-09-20)

Kogevinas M., Zock J.P., Jarvis D., Kromhout H., Lillienberg L., Plana E., Radon K., Toren K., Alliksoo A., Benke G., Blanc P.D., Dahlman-Hoglund A., D'Errico A., Hery M., Kennedy S., Kunzli N., Leynaert B., Mirabelli M.C., Muniozgueren N., Norback D., Olivieri M., Payo F., Villani S., van Sprundel M., Urrutia I., Wieslander G., Sunyer J., and Anto J.M. (2007): Exposure to substances in the workplace and new-onset asthma: An international prospective population-based study (ECRHS-II). *The Lancet* 370 (9584), 336-341. DOI: 10.1016/s0140-6736(07)61164-7 (last accessed 2016-09-28)

Koschier F.J., Burden E.J., Brunkhorst C.S., and Friedman M.A. (1983): Concentration-dependent elicitation of dermal sensitization in guinea pigs treated with 2,4-toluene diisocyanate. *Toxicology and Applied Pharmacology* 67 (3), 401-407. DOI: 10.1016/0041-008X(83)90324-1 (last accessed 2016-09-20)

Kouadio K., Zheng K.C., Tuekpe M.K.-N., Todoriki H., and Ariizumi M. (2005): Airway inflammatory and immunological events in a rat model exposed to toluene diisocyanate. *Food and Chemical Toxicology* 43 (8), 1281-1288. DOI: 10.1016/j.fct.2005.03.005 (last accessed 2016-09-20)

Laboratoire d'Etude (1976a): A study of the diffusion of MDI in rats contaminated via the respiratory system, date: 1976-11. Laboratoire d'Etude du Metabolisme des Medicants, Commissariat a l' Energie Atomique. International Isocyanate Institute, unpublished

Laboratoire d'Etude (1976b): A study of the diffusion rate of TDI in rats contaminated via the respiratory system. Preliminary study. III report 10064, III project E-A-4, date: 1976-

01-01. Laboratoire d'Etude du Metabolisme des Medicants, Commissariat a l' Energie Atomique. International Isocyanate Institute, unpublished

Laboratoire d'Etude (1977): Pharmacokinetics of TDI after inhalation exposure of rats to labelled TDI. III report 10035, III project E-A-4, date: 1977-07-01. Laboratoire d'Etude du Metabolisme des Medicants, Commissariat a l' Energie Atomique. International Isocyanate Institute, unpublished

Laitinen J., Muittari A., and Sovijärvi A. (1984): Isosyanaatit astman ja alveoliitin aiheuttajina. *Duodecim* 100 (4), 220-225. http://www.terveysportti.fi/dhtm/articles/1984_4_220-225.pdf (last accessed 2016-09-20)

Lambrecht B.N. and Hammad H. (2012): The airway epithelium in asthma. *Nature Medicine* 18 (5), 684-692. DOI: 10.1038/nm.2737 (last accessed 2016-09-20)

Larbanois A., Jamart J., Delwiche J.P., and Vandenplas O. (2002): Socioeconomic outcome of subjects experiencing asthma symptoms at work. *European Respiratory Journal* 19 (6), 1107-1113. DOI: 10.1183/09031936.02.00272202a (last accessed 2016-09-28)

Laskin D.L., Sunil V.R., Gardner C.R., and Laskin J.D. (2011): Macrophages and tissue injury: Agents of defense or destruction? *Annual Review of Pharmacology and Toxicology* 51, 267-288. DOI: 10.1146/annurev.pharmtox.010909.105812 (last accessed 2016-09-19)

Latza U. and Baur X. (2005): Occupational obstructive airway diseases in Germany: Frequency and causes in an international comparison. *American Journal of Industrial Medicine* 48 (I), 144-152. DOI: 10.1002/ajim.20186 (last accessed 2016-09-20)

Latza U., Bittner C., and Baur X. (2007): Berufsbedingte, allergische und irritative obstruktive Atemwegserkrankungen im gewerblichen Bereich: Geschlechts-sensitive Identifikation von Präventionspotenzialen [Occupational, allergic and irritant obstructive respiratory diseases in the professional sector: Gender-specific identification of prevention potentials]. *Ergo Med - Praktische Arbeitsmedizin* 2 (1), 48-57. http://www.ergo-med.de/em/live/fachartikelarchiv/ha_artikel/show.php3?id=30939446&ps_alayout=l_2.inc (last accessed 2016-09-28)

Latza U., Haamann F., and Baur X. (2005): Effectiveness of a nationwide interdisciplinary preventive programme for latex allergy. *International Archives of Occupational and Environmental Health* 78 (5), 394-402. DOI: 10.1007/s00420-004-0594-2

Le Moual N., Kauffmann F., Eisen E.A., and Kennedy S.M. (2008): The healthy worker effect in asthma. *American Journal of Respiratory and Critical Care Medicine* 177 (1), 4-10. DOI: 10.1164/rccm.200703-415PP (last accessed 2016-09-20)

Lee H.S. and Phoon W.H. (1992): Diurnal variation in peak expiratory flow rate among workers exposed to toluene diisocyanate in the polyurethane foam manufacturing industry. *British Journal of Industrial Medicine* 49 (6), 423-427. <http://oem.bmj.com/content/49/6/423.abst> (last accessed 2016-09-28)

Lee Y.C., Kwak Y.G., and Song C.H. (2002): Contribution of vascular endothelial growth factor to airway hyperresponsiveness and inflammation in a murine model of toluene diisocyanate-induced asthma. *Journal of Immunology* 168 (7), 3595-3600. DOI: 10.4049/jimmunol.168.7.3595 (last accessed 2016-09-20)

Lee Y.M., Kim H.A., Park H.S., Lee S.K., and Nahm D.H. (2003): Exposure to toluene diisocyanate (TDI) induces IL-8 production from bronchial epithelial cells: Effect of preinflammatory cytokines. *Journal of Korean Medical Science* 18 (6), 809-812. DOI: 10.3346/jkms.2003.18.6.809 (last accessed 2016-09-20)

Leira H.L., Bratt U., and Slåstad S. (2005): Notified cases of occupational asthma in Norway: exposure and consequences for health and income. *Am J Ind Med* 48 (5), 359-364. DOI: 10.1002/ajim.20213

Lemière C., Cartier A., Dolovich J., Chan-Yeung M., Grammer L., Ghezzi H., L'Archeveque J., and Malo J.L. (1996): Outcome of specific bronchial responsiveness to occupational agents after removal from exposure. *American Journal of Respiratory and Critical Care Medicine* 154 (2), 329-333. DOI: 10.1164/ajrccm.154.2.8756802 (last accessed 2016-09-20)

Lemière C., Romeo P., Chaboulez S., Tremblay C., and Malo J.L. (2002): Airway inflammation and functional changes after exposure to different concentrations of isocyanates. *Journal of Allergy and Clinical Immunology* 110 (4), 641-646. DOI: 10.1067/mai.2002.128806 (last accessed 2016-09-20)

Lenaerts-Langanke H. (1992): Occupational lung diseases in coal miners: Isocyanate-induced respiratory problems, 929-933. Eighth International Conference on Occupational Lung Diseases, Prague, Czechoslovakia, Czech Medical Society,

Leng G., Gries W., Riedel W., and Hartz S. (2013): Biomonitoring im Rahmen der arbeitsmedizinischen Vorsorgeuntersuchung G 27 am Beispiel von Hexamethylen-1,6 - Diisocyanat (HDI) [Biomonitoring as part of the occupational medical examination G 27 showed by Hexamethylen-1.6-Diisocyanate (HDI)]. *Arbeitsmedizin Sozialmedizin Umweltmedizin* 48, 392-396

Lesage J., Stanley J., Karoly W.J., and Lichtenberg F.W. (2007): Airborne methylene diphenyl diisocyanate (MDI) concentrations associated with the application of polyurethane spray foam in residential construction. *Journal of Occupational and Environmental Hygiene* 4 (2), 145-155. DOI: 10.1080/15459620601133779 (last accessed 2016-09-21)

Lewalter J. and Biedermann P. (1994): Aromatic amines (Aniline, o-toluidine, m-toluidine, p-toluidine, 4-chloro-o-toluidine, 2,4-toluylenediamine and 2,6-toluylenediamine, 4-aminodiphenyl, 4,4'-diaminodiphenylmethane) [Biomonitoring Methods, 1994]. In: *The MAK Collection for Occupational Health and Safety*, volume 4. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, (ed.), 67-105. Deutsche Forschungsgemeinschaft (DFG). DOI: 10.1002/3527600418.bi6253e0004 (last accessed 2016-09-28)

Lewalter J., Skarping G., Ellrich D., and Schoen U. (2002): Hexamethylene diisocyanate (HDI) and hexamethylenediamine (HDA) - determination in urine. In: *The MAK Collection for Occupational Safety and Health*, volume 8. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, (ed.), 119 - 132. Deutsche Forschungsgemeinschaft (DFG),. DOI: 10.1002/3527600418.bi82206e0008 (last accessed 2016-09-28)

Liang J., Zhao H., Yao L., Tang H., Dong H., Wu Y., Liu L., Zou F., and Cai S. (2015): Phosphatidylinositol 3-kinases pathway mediates lung caspase-1 activation and high mobility group box 1 production in a toluene-diisocyanate induced murine asthma model. *Toxicology Letters* 236 (1), 25-33. DOI: 10.1016/j.toxlet.2015.04.011 (last accessed 2016-09-20)

Lidén C. (1980): Allergic contact dermatitis from 4,4'-diisocyanatol-diphenyl methane (MDI) in a molder. *Contact Dermatitis* 6 (4), 301-302. DOI: 10.1111/j.1600-0536.1980.tb04950.x (last accessed 2016-09-20)

Liljelind I., Norberg C., Egelrud L., Westberg H., Eriksson K., and Nylander-French L.A. (2010): Dermal and inhalation exposure to methylene bisphenyl isocyanate (MDI) in iron

- foundry workers. *Annals of Occupational Hygiene* 54 (1), 31-40. DOI: 10.1093/annhyg/mep067 (last accessed 2016-09-29)
- Lillienberg L., Andersson E., Janson C., Dahlman-Hoglund A., Forsberg B., Holm M., Glslason T., Jogi R., Omenaas E., Schlunssen V., Sigsgaard T., Svanes C., and Toren K. (2013): Occupational exposure and new-onset asthma in a population-based study in Northern Europe (RHINE). *Annals of Occupational Hygiene* 57 (4), 482-492. DOI: 10.1093/annhyg/mes083 (last accessed 2016-09-28)
- Lim R.H., Arredouani M.S., Fedulov A., Kobzik L., and Hubeau C. (2007): Maternal allergic contact dermatitis causes increased asthma risk in offspring. *Respiratory Research* 8, 56. DOI: 10.1186/1465-9921-8-56 (last accessed 2016-09-20)
- Lindberg H.K., Korpi A., Santonen T., Säkkinen K., Järvelä M., Tornaesus J., Ahonen N., Järventaus H., Pasanen A.L., Rosenberg C., and Norppa H. (2011): Micronuclei, hemoglobin adducts and respiratory tract irritation in mice after inhalation of toluene diisocyanate (TDI) and 4,4'-methylenediphenyl diisocyanate (MDI). *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 723 (1), 1-10. DOI: 10.1016/j.mrgentox.2011.03.009 (last accessed 2016-09-20)
- Littorin M., Axmon A., Broberg K., Sennbro C.J., and Tinnerberg H. (2007): Eye and airway symptoms in low occupational exposure to toluene diisocyanate. *Scandinavian Journal Of Work Environment & Health* 33 (4), 280-285. <http://www.jstor.org/stable/40967655> (last accessed 2016-09-28)
- Liu Y., Bello D., Sparer J.A., Stowe M.H., Gore R.J., Woskie S.R., Cullen M.R., and Redlich C.A. (2007): Skin exposure to aliphatic polyisocyanates in the auto body repair and refinishing industry: A qualitative assessment. *Annals of Occupational Hygiene* 51 (5), 429-439. DOI: 10.1093/annhyg/mem021 (last accessed 2016-09-20)
- Lob M. and Boillat M.A. (1981): Asthme retardé au diphenylmethane-diisocyanate (MDI). Importance de l'anamnèse professionnelle. Utilité et danger des tests inhalatoires. A propos de cinq cas [Delayed asthma on diphenylmethane diisocyanate (MDI). The importance of a professional history. The utility and danger of the inhalation tests. Apropos five cases]. *Schweizerische Medizinische Wochenschrift* 111 (5), 150-154
- Lockey J.E., Redlich C.A., Streicher R., Pfahles-Hutchens A., Hakkinen P.B., Ellison G.L., Harber P., Utell M., Holland J., Comai A., and White M. (2015): Isocyanates and human health: Multistakeholder information needs and research priorities. *Journal of Occupational and Environmental Medicine* 57 (1), 44-51. DOI: 10.1097/jom.0000000000000278 (last accessed 2016-09-29)
- Löfstedt H., Westberg H., Selden A.I., Bryngelsson I.L., and Svartengren M. (2011): Respiratory symptoms and lung function in foundry workers using the hot box method: A 4-year follow-up. *Journal of Occupational and Environmental Medicine* 53 (12), 1425-1429. DOI: 10.1097/JOM.0b013e3182363c17 (last accessed 2016-09-28)
- Löfstedt H., Westberg H., Selden A.I., Lundholm C., and Svartengren M. (2009): Respiratory symptoms and lung function in foundry workers exposed to low molecular weight isocyanates. *American Journal of Industrial Medicine* 52 (6), 455-463. DOI: 10.1002/ajim.20693 (last accessed 2016-09-28)
- Lozewicz S., Assoufi B.K., Hawkins R., and Newman Taylor A.J. (1987): Outcome of asthma induced by isocyanates. *British Journal of Diseases of the Chest* 81, 14-22. DOI: 10.1016/0007-0971(87)90103-3 (last accessed 2016-09-20)
- Ma-Hock L., Gamer A.O., Deckardt K., Leibold E., and van Ravenzwaay B. (2007): Determination of pulmonary irritant threshold concentrations of hexamethylene-1,6-diisocyanate (HDI) prepolymers by bronchoalveolar lavage in acute rat inhalation studies

according to TRGS 430. *Food and Chemical Toxicology* 45 (2), 237-243. DOI: 10.1016/j.fct.2006.08.016 (last accessed 2016-09-20)

Máca V. and Scasný M. (2014): Appendix: Willingness to pay for avoiding respiratory sensitisation outcomes. Service contract for the European Chemicals Agency no. ECHA/2011/123, date: 2014-09. Charles University in Prague (Environment Center). European Chemicals Agency (ECHA), Prague, Czechoslovakia. http://echa.europa.eu/documents/10162/13630/appendix_study_economic_benefits_avoiding_adverse_health_outcomes_1_en.pdf (last accessed 2016-09-19)

Maestrelli P., Calcagni P.G., Saetta M., Di S.A., Hosselet J.J., Santonastaso A., Fabbri L.M., and Mapp C.E. (1994a): Sputum eosinophilia after asthmatic responses induced by isocyanates in sensitized subjects. *Clinical and Experimental Allergy* 24 (1), 29-34. DOI: 10.1111/j.1365-2222.1994.tb00913.x (last accessed 2016-09-20)

Maestrelli P., Del Prete G.F., De Carli M., D'Elis M.M., Saetta M., Di Stefano A., Mapp C.E., Romagnani S., and Fabbri L.M. (1994b): CD8 T-cell clones producing interleukin-5 and interferon-gamma in bronchial mucosa of patients with asthma induced by toluene diisocyanate. *Scandinavian Journal Of Work Environment & Health* 20 (5), 376-381. <http://www.jstor.org/stable/40966279> (last accessed 2016-09-20)

Maestrelli P., di Stefano A., Occari P., Turato G., Milani G., Pivrotto F., Mapp C.E., Fabbri L.M., and Saetta M. (1995): Cytokines in the airway mucosa of subjects with asthma induced by toluene diisocyanate. *American Journal of Respiratory and Critical Care Medicine* 151 (3 Pt 1), 607-612. DOI: 10.1164/ajrccm/151.3_Pt_1.607 (last accessed 2016-09-20)

Maestrelli P., Occari P., Turato G., Papis S.A., Di Stefano A., Mapp C.E., Milani G.F., Fabbri L.M., and Saetta M. (1997): Expression of interleukin (IL)-4 and IL-5 proteins in asthma induced by toluene diisocyanate (TDI). *Clinical and Experimental Allergy* 27 (11), 1292-1298. DOI: 10.1111/j.1365-2222.1997.tb01174.x (last accessed 2016-09-20)

Mailhot B., Morlat-Thérias S., Ouahioune M., and Gardette J.-L. (2005): Study of the degradation of an epoxy/amine resin. Part 1: Photo- and thermo-chemical mechanisms. *Macromolecular Chemistry and Physics* 206, 575-584. DOI: 10.1002/macp.200400395

Malo J.L., Ghezzi H., and Elie R. (1999): Occupational asthma caused by isocyanates. *American Journal of Respiratory and Critical Care Medicine* 159 (6), 1879-1883. DOI: 10.1164/ajrccm.159.6.9806159 (last accessed 2016-09-28)

Malo J.L., L'Archevêque J., and Cartier A. (1989): Significant changes in nonspecific bronchial responsiveness after isolated immediate bronchospastic reactions caused by isocyanates but not after a late reaction caused by plicatic acid. *Journal of Allergy and Clinical Immunology* 83 (1), 159-165. DOI: 10.1016/0091-6749(89)90491-0 (last accessed 2016-09-20)

Malo J.L., Ouimet G., Cartier A., Levitz D., and Zeiss C.R. (1983): Combined alveolitis and asthma due to hexamethylene diisocyanate (HDI), with demonstration of crossed respiratory and immunologic reactivities to diphenylmethane diisocyanate (MDI). *Journal of Allergy and Clinical Immunology* 72 (4), 413-419. DOI: 10.1016/0091-6749(83)90508-0 (last accessed 2016-09-20)

Mapp C.E., Dal Vecchio L., Boschetto P., and Fabbri L.M. (1985): Combined asthma and alveolitis due to diphenylmethane diisocyanate (MDI) with demonstration of no crossed respiratory reactivity to toluene diisocyanate (TDI). *Annals of Allergy* 54 (5), 424-429

Mapp C.E., Lucchini R.E., Miotto D., Chitano P., Jovine L., Saetta M., Maestrelli P., Springall D.R., Polak J., and Fabbri L.M. (1998): Immunization and challenge with toluene diisocyanate decrease tachykinin and calcitonin gene-related peptide immunoreactivity in

guinea pig central airways. *American Journal of Respiratory and Critical Care Medicine* 158 (1), 263-269. DOI: 10.1164/ajrccm.158.1.9704061 (last accessed 2016-09-20)

Mapp C.E., Silva J.R.L.E., Lucchini R.E., Chitano P., Rado V., Saetta M., Pretolani M., Karol M.H., Maestrelli P., and Fabbri L.M. (1996): Inflammatory events in the blood and airways of guinea pigs immunized to toluene diisocyanate. *American Journal of Respiratory and Critical Care Medicine* 154 (1), 201-208. DOI: 10.1164/ajrccm.154.1.8680681 (last accessed 2016-09-20)

Marcali K. (1957): Microdetermination of toluenediisocyanates in atmosphere. *Analytical Chemistry* 29 (4), 552-558. DOI: 10.1021/ac50162a039 (last accessed 2016-09-20)

Matheson J.M., Johnson V.J., and Luster M.I. (2005a): Immune mediators in a murine model for occupational asthma: studies with toluene diisocyanate. *Toxicological Sciences* 84 (1), 99-109. DOI: 10.1093/toxsci/kfi051 (last accessed 2016-09-20)

Matheson J.M., Johnson V.J., Vallyathan V., and Luster M.I. (2005b): Exposure and immunological determinants in a murine model for toluene diisocyanate (TDI) asthma. *Toxicological Sciences* 84 (1), 88-98. DOI: 10.1093/toxsci/kfi050 (last accessed 2016-09-19)

Matheson J.M., Lange R.W., Lemus R., Karol M.H., and Luster M.I. (2001): Importance of inflammatory and immune components in a mouse model of airway reactivity to toluene diisocyanate (TDI). *Clinical and Experimental Allergy* 31 (7), 1067-1076. DOI: 10.1046/j.1365-2222.2001.01125.x (last accessed 2016-09-20)

Matheson J.M., Lemus R., Lange R.W., Karol M.H., and Luster M.I. (2002): Role of tumor necrosis factor in toluene diisocyanate asthma. *American Journal of Respiratory Cell and Molecular Biology* 27 (4), 396-405. DOI: 10.1165/rcmb.4614 (last accessed 2016-09-20)

Matsushima H., Takayanagi N., Tokunaga D., Maeno Y., Sato N., Kurashima K., Ubukata M., Yanagisawa T., Sugita Y., Kawabata Y., and Kanazawa M. (2003): [A case of combined hypersensitivity pneumonitis and bronchial asthma due to isocyanate (MDI)]. *Nihon Kogyaku Gakkai Zasshi* 41 (10), 760-765. http://www.jrs.or.jp/quicklink/journal/nopass_pdf/041100760j.pdf (last accessed 2016-09-20)

Meredith S.K., Bugler J., and Clark R.L. (2000): Isocyanate exposure and occupational asthma: A case-referent study. *Occupational and Environmental Medicine* 57 (12), 830-836. DOI: 10.1136/oem.57.12.830 (last accessed 2016-09-20)

Midland Thoracic Society (2016): Shield - surveillance scheme for occupational asthma. <http://www.occupationalasthma.com/shield.aspx> (last accessed 2016-09-28)

Militello G., Sasseville D., Ditre C., and Brod B.A. (2004): Allergic contact dermatitis from isocyanates among sculptors. *Dermatitis* 15 (3), 150-153

Miller G.W. and Jones D.P. (2014): The nature of nurture: Refining the definition of the exposome. *Toxicological Sciences* 137 (1), 1-2. DOI: 10.1093/toxsci/kft251 (last accessed 2016-09-20)

Miller R.L. and Ho S.-M. (2008): Environmental epigenetics and asthma: Current concepts and call for studies. *American Journal of Respiratory and Critical Care Medicine* 177 (6), 567-573. DOI: 10.1164/rccm.200710-1511PP (last accessed 2016-09-20)

Minov J., Karadzinska-Bislimovska J., Vasilevska K., Risteska-Kuc S., and Stoleski S. (2008): Work-related asthma in automobile spray painters: Two case reports. *Archives of Industrial Hygiene and Toxicology* 59 (2), 117-125. DOI: 10.2478/10004-1254-59-2008-1858 (last accessed 2016-09-28)

Mobay (1988): 90-Day inhalation toxicity study with 1,6-hexamethylene diisocyanate (HDI) in rats. Report no. 81-141-01, date: 1988-12-28. Bayer, unpublished

Mobay (1989): Chronic inhalation toxicity and oncogenicity study with 1,6 hexamethylene diisocyanate (HDI) in rats. Report no. 1157, company study no. 83-241-01, date: 1989-12-05. Bayer, unpublished

Moggs J.G., Terranova R., Kammüller M.E., Chibout S., Chapman V., Dearman R.J., and Kimber I. (2012): Regulation of allergic responses to chemicals and drugs: Possible roles of epigenetic mechanisms. *Toxicological Sciences* 130 (1), 60-69. DOI: 10.1093/toxsci/kfs207 (last accessed 2016-09-20)

Møller Christensen F., Nilsson N.H., Woldum Tordrup S., Warming M., Brinch A., and Kjølholt J. (2015): Alternatives to MDI in consumer products - with focus on coatings, adhesives and sealants. Environmental project No. 1709, 2015. COWI A/S and Danish Technological Institute. Danish Ministry of the Environment, Environmental Agency, Copenhagen, Denmark. <http://www2.mst.dk/Udgiv/publications/2015/05/978-87-93352-22-3.pdf> (last accessed 2016-09-28)

Moller D.R., McKay R.T., Bernstein I.L., and Brooks S.M. (1986): Persistent airways disease caused by toluene diisocyanate. *American Review of Respiratory Disease* 134 (1), 175-176. DOI: 10.1164/arrd.1986.134.1.175 (last accessed 2016-09-28)

Morimatsu Y., Akiyoshi H., Tajiri M., Hirai R., and Aizawa H. (2004): [A case of hypersensitivity pneumonitis showing acute respiratory distress syndrome due to exposure to dust containing diphenylmethane diisocyanate]. *Nihon Kokyuki Gakkai Zasshi* 42 (6), 502-508. http://www.jrs.or.jp/quicklink/journal/nopass_pdf/042060502j.pdf (last accessed 2016-09-20)

Moscato G., Dellabianca A., Perfetti L., Bramè B., Galdi E., Niniano R., and Paggiaro P. (1999): Occupational asthma: A longitudinal study on the clinical and socioeconomic outcome after diagnosis. *CHEST* 115 (1), 249-256. DOI: doi: 10.1378/chest.115.1.249 (last accessed 2016-09-20)

MRI (1987): Metabolism and disposition of 14C-labeled toluene diisocyanate (TDI) following oral and inhalation exposure: preliminary studies. III report 10434, III project NA-AB-37, date: 1987-06-12. Midwest Research Institute. International Isocyanate Institute, unpublished

Musk A.W., Peters J.M., and Berstein L. (1985): Absence of respiratory effects in subjects exposed to low concentrations to TDI and MDI: A reevaluation. *Journal of Occupational Medicine* 27 (12), 917-920. http://journals.lww.com/joem/Abstract/1985/12000/Absence_of_Respiratory_Effects_in_Subjects_Exposed.16.aspx?id=2-s2.0-0022384692&partnerID=40&md5=8c3cab998c523fc6012ce4fb66fb0445 (last accessed 2016-09-20)

Musk A.W., Peters J.M., DiBerardinis L., and Murphy R.L.H. (1982): Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. *Journal of Occupational Medicine* 24 (10), 746-750. http://journals.lww.com/joem/Abstract/1982/10000/Absence_of_Respiratory_Effects_in_Subjects_Exposed.11.aspx (last accessed 2016-09-20)

Nabe T., Yamauchi K., Shinjo Y., Niwa T., Imoto K., Koda A., and Kohno S. (2005): Delayed-type asthmatic response induced by repeated intratracheal exposure to toluene-2,4-diisocyanate in guinea pigs. *International Archives of Allergy and Applied Immunology* 137 (2), 115-124. DOI: 10.1159/000085466 (last accessed 2016-09-20)

Nanotech (2008): Safety data sheet according to 91/155 EC: ECPU 2851WCLS (Component A). Rev. 1. Nanotech Industries,. http://www.nanotechindustriesinc.com/pdf/MSDS_2851%20WCLS%20_part_A.pdf

Nanotech (2016): Green polyurethane. Nanotech Industries,. <http://nanotechindustriesinc.com/GPU.php> (last accessed 2016-09-29)

Nayak A.P., Hettick J.M., Siegel P.D., Anderson S.E., Long C.M., Green B.J., and Beezhold D.H. (2014): Toluene diisocyanate (TDI) disposition and co-localization of immune cells in hair follicles. *Toxicological Sciences* 140 (2), 327-337. DOI: 10.1093/toxsci/kfu079 (last accessed 2016-09-20)

Nemery B. and Lenaerts L. (1993): Exposure to methylene diphenyl diisocyanate in coal mines. *The Lancet* 341 (8840), 318. DOI: 10.1016/0140-6736(93)92682-J (last accessed 2016-09-20)

Nicholson P.J., Cullinan P., Burge P.S., and Boyle C. (2010): Occupational asthma: Prevention, identification & management: Systematic review & recommendations. ISBN: 978-0-9564979-1-8, date: 2010-03. British Occupational Health Research Foundation (BOHRF), London, United Kingdom. <http://www.bohrf.org.uk/downloads/OccupationalAsthmaEvidenceReview-Mar2010.pdf> (last accessed 2016-09-02)

NIEHS (1985): Disposition of 2,6-toluene diisocyanate in Fischer 344 rats. Report no. RTI/2227/00-06P, study no. N01-ES-1-5007, date: 1985-07-01. Research Triangle Institute. National Institute of Environmental Health Sciences, unpublished

Niewenhuis R., Scheel L., Stemmer K., and Killens R. (1965): Toxicity of chronic low level exposures to toluene diisocyanate in animals. *American Industrial Hygiene Association Journal* 26 (2), 143-149. DOI: 10.1080/00028896509342714 (last accessed 2016-09-20)

Niimi A., Amitani R., Yamada K., Tanaka K.I., and Kuze F. (1996): Late respiratory response and associated eosinophilic inflammation induced by repeated exposure to toluene diisocyanate in guinea pigs. *Journal of Allergy and Clinical Immunology* 97 (6), 1308-1319. DOI: 10.1016/S0091-6749(96)70200-2 (last accessed 2016-09-20)

Nippon Soda (2010): Toxicokinetic assessment of TODI. Report no.: 309-028. SCC. Nippon Soda Co. Ltd.

NOTOX (1996): Assessment of contact hypersensitivity to polyisocyanate resin 95222660 in the albino guinea pig (maximization test). Report no. 142649, date: 1996-02-02. NOTOX B.V. Bayer MaterialScience AG, unpublished

NOTOX (2004): Assessment of contact hypersensitivity to Vestanat T 1890 SV in the albino guinea pig (maximisation-test). Report no. 397496, date: 2004-04-05. NOTOX B.V. Evonik Degussa GmbH, unpublished

Nowak D. (2010): *Arbeitsmedizin und klinische Umweltmedizin [Occupational and clinical environmental medicine]*. Urban & Fischer/Elsevier GmbH,, München, Germany. ISBN: 978-3437411694

Nowak D., Ochmann U., and Kellberger J. (2011): Evaluation der stationären Rehabilitation von Atemwegs- und Lungenerkrankungen in den berufsgenossenschaftlichen Kliniken Falkenstein und Bad Reichenhall [Evaluation of the stationary rehabilitation of airway and lung diseases in the professional association hospitals of Falkenstein and Bad Reichenhall], date: 04/2011. Klinikum der Universität München, Institut und Poliklinik für Arbeits-, Sozial- und Umweltmedizin. Deutsche Gesetzliche Unfallversicherung (DGUV). http://www.dguv.de/medien/ifa/de/pro/pro1/ff-fb0094/abschlussbericht_final_21.4.11.pdf (last accessed 2016-09-28)

Nozawa S., Sato T., Sasagawa M., Suzuki E., Kioi S., and Arakawa M. (1989): [A case of hypersensitivity pneumonitis due to isocyanate (TDI)]. *Nihon Kyobu Shikkan Gakkai Zasshi* 27 (11), 1335-1341. DOI: 10.11389/jjrs1963.27.1335 (last accessed 2016-09-20)

Nuon (2013): Gespoten PUR vloerisolatie kan veilig worden toegepast [Spray PUR floor isolation can be used safely]. N.V. Nuon Energy. <http://www.nuon.com/nieuws/nieuws/2013/gespoten-pur-vloerisolatie-kan-veilig-worden-toegepast/>

O'Brien I.M., Harries M.G., Burge P.S., and Pepys J. (1979): Toluene di-isocyanates-induced asthma. I. Reactions to TDI, MDI, HDI and histamine. *Clinical Allergy* 9 (1), 1-6. DOI: 10.1111/j.1365-2222.1979.tb01516.x (last accessed 2016-09-28)

OECD (2011): Emission scenario document on coating application via spray-painting in the automotive refinishing industry. ENV/JM/MONO(2004)22/REV1. Organisation for Economic Co-operation and Development (OECD). <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282004%2922&doclanguage=en> (last accessed 2016-09-28)

OECD (2012a): The adverse outcome pathway for skin sensitisation initiated by covalent binding to proteins. Part 1: Scientific evidence. Document ENV/JM/MONO(2012)10/PART1, date: 2012-04-05. Organisation for Economic Co-operation and Development (OECD), Paris. <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282012%2910/part1&doclanguage=en> (last accessed 2016-09-20)

OECD (2012b): Asthma and COPD prevalence. In: *Health at a Glance: Europe 2012*, 46-47. ISBN: ISBN 978-92-64-18360-5. DOI: 10.1787/9789264183896-en

Olsen G.W., Shellenberger R., Bodner K.M., Flores G.H., Emmitte J.A., Bond G.G., and Saunders J.H. (1989): An epidemiologic investigation of forced expiratory volume at 1 second and respiratory symptoms among employees of a toluene diisocyanate production plant. *Journal of Occupational Medicine* 31 (8), 664-667 (last accessed 2016-09-20)

Omae K. (1984): Two-year observation of pulmonary function in workers exposed to low concentrations of toluene diisocyanate. *International Archives of Occupational and Environmental Health* 55 (1), 1-12. DOI: 10.1007/BF00378062 (last accessed 2016-09-20)

Omae K., Higashi T., Nakadate T., Tsugane S., Nakaza M., and Sakurai H. (1992): Four-year follow-up of effects of toluene diisocyanate exposure on the respiratory system in polyurethane foam manufacturing workers. II. Four-year changes in the effects on the respiratory system. *International Archives of Occupational and Environmental Health* 63 (8), 565-569. DOI: 10.1007/BF00386347 (last accessed 2016-09-20)

Orriols R., Costa R., Albanell M., Alberti C., Castejon J., Monso E., Panades R., Rubira N., and Zock J.P. (2006): Reported occupational respiratory diseases in Catalonia. *Occupational and environmental medicine* 63 (4), 255-260. DOI: 10.1136/oem.2005.022525 (last accessed 2016-09-20)

Ott M.G. (2002): Occupational asthma, lung function decrement, and toluene diisocyanate (TDI) exposure: A critical review of exposure-response relationships. *Applied Occupational and Environmental Hygiene* 17 (12), 891-901. DOI: 10.1080/10473220290107093 (last accessed 2016-09-19)

Ott M.G., Diller W.F., and Jolly A.T. (2003): Respiratory effects of toluene diisocyanate in the workplace: A discussion of exposure-response relationships. *Critical Reviews in Toxicology* 33 (1), 1-59. DOI: 10.1080/713611031 (last accessed 2016-09-19)

Ott M.G., Klees J.E., and Poche S.L. (2000): Respiratory health surveillance in a toluene diisocyanate production unit, 1967-97: Clinical observations and lung function analyses.

Occupational and Environmental Medicine 57 (1), 43-52. DOI: 10.1136/oem.57.1.43 (last accessed 2016-09-19)

Padoan M., Pozzato V., Simoni M., Zedda L., Milan G., Bononi I., Piola C., Maestrelli P., Boschetto P., and Mapp C.E. (2003): Long-term follow-up of toluene diisocyanate-induced asthma. *European Respiratory Journal* 21 (4), 637-640. DOI: 10.1183/09031936.03.00060703 (last accessed 2016-09-20)

Paggiaro P., Bacci E., Paoletti P., Bernard P., Dente F.L., Marchetti G., Talini D., Menconi G.F., and Giuntini C. (1990): Bronchoalveolar lavage and morphology of the airways after cessation of exposure in asthmatic subjects sensitized to toluene diisocyanate. *CHEST* 98 (3), 536-542. DOI: 10.1378/chest.98.3.536 (last accessed 2016-09-20)

Paris C., Ngatchou-Wandji J., Luc A., McNamee R., Bensefa-Colas L., Larabi L., Telle-Lamberton M., Herin F., Bergeret A., Bonnetterre V., Brochard P., Choudat D., Dupas D., Garnier R., Pairon J.C., Agius R.M., and Ameille J. (2012): Work-related asthma in France: Recent trends for the period 2001-2009. *Occupational and Environmental Medicine* 69 (6), 391-397. DOI: 10.1136/oemed-2011-100487 (last accessed 2016-09-20)

Park H., Jung K., Kim H., Nahm D., and Kang K. (1999): Neutrophil activation following TDI bronchial challenges to the airway secretion from subjects with TDI-induced asthma. *Clinical and Experimental Allergy* 29 (10), 1395-1401. DOI: 10.1046/j.1365-2222.1999.00682.x (last accessed 2016-09-20)

Park H.S., Kim H.A., Jung J.W., Kim Y.K., Lee S.K., Kim S.S., and Nahm D.H. (2003): Metalloproteinase-9 is increased after toluene diisocyanate exposure in the induced sputum from patients with toluene diisocyanate-induced asthma. *Clin Exp Allergy* 33 (1), 113-118. DOI: 10.1046/j.1365-2222.2003.01563.x (last accessed 2016-09-20)

Park H.S., Lee S.K., Lee Y.M., Kim S.S., and Nahm D.H. (2002): Longitudinal study of specific antibodies to toluene diisocyanate (TDI)-human serum albumin (HSA) conjugate in patients with TDI-induced asthma. *The Korean Journal of Internal Medicine* 17 (4), 249-251. DOI: 10.3904/kjim.2002.17.4.249 (last accessed 2016-09-20)

Park H.S. and Nahm D.H. (1997): Prognostic factors for toluene diisocyanate-induced occupational asthma after removal from exposure. *Clinical and Experimental Allergy* 27 (10), 1145-1150. DOI: 10.1111/j.1365-2222.1997.tb01151.x (last accessed 2016-09-20)

Park H.S., Park J.N., Kim J.W., and Kim S.K. (1992): Clinical and immunological evaluation of isocyanate-exposed workers. *Journal of Korean Medical Science* 7 (2), 122-127. DOI: 10.3346/jkms.1992.7.2.122 (last accessed 2016-09-28)

Parker D.L., Waller K., Himrich B., Martinez A., and Martin F. (1991): A cross-sectional study of pulmonary function in autobody repair workers. *American Journal of Public Health* 81 (6), 768-771. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1405165/> (last accessed 2016-09-28)

Patterson R., Harris K.E., Pruzansky J.J., and Zeiss C.R. (1982): An animal model of occupational immunologic asthma due to diphenylmethane diisocyanate, with multiple systemic immunologic responses. *Journal of Laboratory and Clinical Medicine* 99 (5), 615-623. <http://www.translationalres.com/article/0022-2143%2882%2990308-0/fulltext> (last accessed 2016-09-20)

Patterson R., Nugent K.M., Harris K.E., and Eberle M.E. (1990): Immunologic hemorrhagic pneumonia caused by isocyanates. *American Review of Respiratory Disease* 141 (1), 226-230. DOI: 10.1164/ajrccm/141.1.226 (last accessed 2016-09-28)

Pauluhn J. (1994): Assessment of chemicals for their potential to induce respiratory allergy in guinea pigs: A comparison of different routes of induction and confounding effects due to

pulmonary hyperreactivity. *Toxicology in Vitro* 8 (5), 981-985. DOI: 10.1016/0887-2333(94)90231-3 (last accessed 2016-09-20)

Pauluhn J. (1997): Assessment of respiratory hypersensitivity in guinea pigs sensitized to toluene diisocyanate: Improvements on analysis of respiratory response. *Fundamental and Applied Toxicology* 40 (2), 211-219. DOI: 10.1006/faat.1997.2393 (last accessed 2016-09-20)

Pauluhn J. (2000): Acute inhalation toxicity of polymeric diphenyl-methane 4,4'-diisocyanate in rats: Time course of changes in bronchoalveolar lavage. *Archives of Toxicology* 74 (4-5), 257-269. DOI: 10.1007/s002040000114 (last accessed 2016-09-20)

Pauluhn J. (2002a): Critical analysis of biomonitoring endpoints for measuring exposure to polymeric diphenyl-methane-4,4'-diisocyanate (MDI) in rats: A comparison of markers of exposure and markers of effect. *Archives of Toxicology* 76 (1), 13-22. DOI: 10.1007/s00204-001-0301-y (last accessed 2016-09-20)

Pauluhn J. (2002b): Short-term inhalation toxicity of polyisocyanate aerosols in rats: Comparative assessment of irritant-threshold concentrations by bronchoalveolar lavage. *Inhalation Toxicology* 14 (3), 287-301. DOI: 10.1080/08958370252809068 (last accessed 2016-09-20)

Pauluhn J. (2005): Brown Norway rat asthma model of diphenylmethane 4,4'-diisocyanate. *Inhalation Toxicology* 17 (13), 729-739. DOI: 10.1080/08958370500224631 (last accessed 2016-09-20)

Pauluhn J. (2008a): Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): Analysis of the elicitation dose-response relationship. *Toxicological Sciences* 104 (2), 320-331. DOI: 10.1093/toxsci/kfn098 (last accessed 2019-09-20)

Pauluhn J. (2008b): Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): Impact of vehicle for topical induction. *Regulatory Toxicology and Pharmacology* 50 (1), 144-154. DOI: 10.1016/j.yrtph.2007.09.003 (last accessed 2016-09-20)

Pauluhn J. (2011): Interrelating the acute and chronic mode of action of inhaled methylenediphenyl diisocyanate (MDI) in rats assisted by computational toxicology. *Regulatory Toxicology and Pharmacology* 61 (3), 351-364. DOI: 10.1016/j.yrtph.2011.09.007 (last accessed 2016-09-20)

Pauluhn J. (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. <http://www.asu-arbeitsmedizin.com/ASU-2013-3/Tiermodell-zur-Bestimmung-der-Asthma-Ausloeseschwelle-von-Diisocyanaten-und-seine-Relevanz-fuer-die-Ableitung-von-Arbeitsplatzgrenzwerten,QUIEPTM5Nzc1MCZNSUQ9MzAwMTA.html> (last accessed 2016-09-20)

Pauluhn J. (2014): Development of a respiratory sensitization/elicitation protocol of toluene diisocyanate (TDI) in Brown Norway rats to derive an elicitation-based occupational exposure level. *Toxicology* 319, 10-22. DOI: 10.1016/j.tox.2014.02.006 (last accessed 2016-09-20)

Pauluhn J. (2015): Analysis of the interrelationship of the pulmonary irritation and elicitation thresholds in rats sensitized with 1,6-hexamethylene diisocyanate (HDI). *Inhalation Toxicology* 27 (4), 191-206. DOI: 10.3109/08958378.2015.1026619 (last accessed 2016-09-20)

- Pauluhn J. (2016): Animal models for respiratory hypersensitivity. In: Encyclopedia of Immunotoxicology (Vohr H.-W., ed.), ed. 2, pp. 19-26. Springer, Berlin, Heidelberg, New York. ISBN: 978-3-642-54595-5. DOI: 10.1007-978-3-3642-54596-2
- Pauluhn J. and Eben A. (1991): Validation of a non-invasive technique to assess immediate or delayed onset of airway hypersensitivity in guinea-pigs. *Journal of Applied Toxicology* 11 (6), 423-431. DOI: 10.1002/jat.2550110608 (last accessed 2016)
- Pauluhn J., Emura M., Mohr U., Popp A., and Rosenbruch M. (1999): Two-week inhalation toxicity of polymeric diphenylmethane-4,4'-diisocyanate (PMDI) in rats: Analysis of biochemical and morphological markers of early pulmonary response. *Inhalation Toxicology* 11 (12), 1143-1163. DOI: 10.1080/089583799196637 (last accessed 2016-09-20)
- Pauluhn J. and Mohr U. (1998): Assessment of respiratory hypersensitivity in guinea pigs sensitized to toluene diisocyanate: A comparison of sensitization protocols. *Inhalation Toxicology* 10 (2), 131-154. DOI: 10.1080/089583798197790 (last accessed 2016-09-20)
- Pauluhn J. and Mohr U. (2001): Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymers (HDI-IC and HDI-BT): Results of subacute and subchronic repeated inhalation exposure studies. *Inhalation Toxicology* 13 (6), 513-532. DOI: 10.1080/089583701118600 (last accessed 2016-09-20)
- Pauluhn J. and Poole A. (2011): Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): Determination of the elicitation threshold concentration of after inhalation sensitization. *Toxicology* 281 (1-3), 15-24. DOI: 10.1016/j.tox.2011.01.005 (last accessed 2016-09-20)
- Pauluhn J., Thiel A., Emura M., and Mohr U. (2000): Respiratory sensitization to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs: Impact of particle size on induction and elicitation of response. *Toxicological Sciences* 56 (1), 105-113. DOI: 10.1093/toxsci/56.1.105 (last accessed 2016-09-20)
- Pauluhn J. and Vohr H.-W. (2006): Partial C-fiber ablation modulates diphenylmethane-4,4'-diisocyanate (MDI)-induced respiratory allergy in Brown Norway rats. *Toxicology* 228 (2-3), 188-199. DOI: 10.1016/j.tox.2006.08.031 (last accessed 2016-09-20)
- Pauluhn J., Woolhiser M.R., and Bloemen L. (2005): Repeated inhalation challenge with diphenylmethane-4,4'-diisocyanate in Brown Norway rats leads to a time-related increase of neutrophils in bronchoalveolar lavage after topical induction. *Inhalation Toxicology* 17 (2), 67-78. DOI: 10.1080/08958370590898434 (last accessed 2016-09-20)
- Perfetti L., Bram B., Ferrari M., and Moscato G. (2003): Occupational asthma (OA) with sensitization to diphenylmethane diisocyanate (MDI) presenting at the onset like a reactive airways dysfunction syndrome (RADS). *American Journal of Industrial Medicine* 44 (3), 325-328. DOI: 10.1002/ajim.10262 (last accessed 2016-09-20)
- Perrin B., Cartier A., Ghezzi H., Grammer L., Harris K., Chan H., Chan-Yeung M., and Malo J.L. (1991): Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *Journal of Allergy and Clinical Immunology* 87 (3), 630-639. DOI: 10.1016/0091-6749(91)90381-W (last accessed 2016-09-28)
- Petsonk E.L., Wang M.L., Lewis D.M., Siegel P.D., and Husberg B.J. (2000): Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *CHEST* 118 (4), 1183-1193. DOI: 10.1378/chest.118.4.1183 (last accessed 2016-09-20)
- Pham Q.T., Cavelier C., Mereau P., Mur J.M., and Cicoella A. (1978): Isocyanates and respiratory function: A study of workers producing polyurethane foam moulding. *Annals of Occupational Hygiene* 21 (2), 121-129. DOI: 10.1093/annhyg/21.2.121 (last accessed 2016-09-20)

- Pham Q.T., Teculescu D., Meyer-Bisch C., and Mur J.M. (1988): Effects of chronic exposure to diisocyanates. *Bulletin Européen de Physiopathologie Respiratoire* 23, 561-564
- Piirilä P., Lauhio A., Majuri M.L., Meuronen A., Myllärniemi M., Tervahartiala T., Vuorinen K., Laitinen A., Alenius H., Kinnula V.L., and Sorsa T. (2010): Matrix metalloproteinases-7, -8, -9 and TIMP-1 in the follow-up of diisocyanate-induced asthma. *Allergy* 65 (1), 61-68. DOI: 10.1111/j.1398-9995.2009.02146.x (last accessed 2016-09-20)
- Piirilä P.L., Meuronen A., Majuri M.L., Luukkonen R., Mäntylä T., Wolff H.J., Nordman H., Alenius H., and Laitinen A. (2008): Inflammation and functional outcome in diisocyanate-induced asthma after cessation of exposure. *Allergy: European Journal of Allergy and Clinical Immunology* 63 (5), 583-591. DOI: 10.1111/j.1398-9995.2007.01606.x (last accessed 2016-09-20)
- Piirilä P.L., Nordman H., Keskinen H.M., Luukkonen R., Salo S.P., Tuomi T.O., and Tuppurainen M. (2000): Long-term follow-up of hexamethylene diisocyanate-, diphenylmethane diisocyanate-, and toluene diisocyanate-induced asthma. *American Journal of Respiratory and Critical Care Medicine* 162 (2 Pt 1), 516-522. DOI: 10.1164/ajrccm.162.2.9909026 (last accessed 2016-09-20)
- Piney M., Llewellyn D., O'Hara R., Saunders J., Cocker J., Jones K., and Fishwick D. (2015): Reducing isocyanate exposure and asthma risk in motor vehicle repair. *International Journal of Workplace Health Management* 8 (4), 272 - 283. DOI: 10.1108/IJWHM-10-2014-0043 (last accessed 2016-09-28)
- Pisati G., Baruffini A., Bernabeo F., Cerri S., and Mangili A. (2007): Rechallenging subjects with occupational asthma due to toluene diisocyanate (TDI), after long-term removal from exposure. *International Archives of Occupational and Environmental Health* 80 (4), 298-305. DOI: 10.1007/s00420-006-0134-3 (last accessed 2016-09-20)
- Plitnick L.M., Loveless S.E., Ladics G.S., Holsapple M.P., Smialowicz R.J., Woolhiser M.R., Anderson P.K., Smith C., and Selgrade M.J.K. (2005): Cytokine mRNA profiles for isocyanates with known and unknown potential to induce respiratory sensitization. *Toxicology* 207 (3), 487-499. DOI: 10.1016/j.tox.2004.11.001 (last accessed 2016-09-20)
- Polish CA (2013): Substance evaluation report. Substance Name: m-tolylidene diisocyanate, EC Number: 247-722-4, CAS Number: 26471-62-5. Version number: 0.2. Bureau for Chemical Substances. <https://echa.europa.eu/documents/10162/043ec453-0d20-4554-a834-1dad960ef5c0> (last accessed 2016-09-29)
- Pollaris L., Devos F., de Vooght V., Seys S., Nemery B., Hoet P.M., and Vanoirbeek J.J. (2015): Toluene diisocyanate and methylene diphenyl diisocyanate: Asthmatic response and cross-reactivity in a mouse model. *Archives of Toxicology*, 1-9. DOI: 10.1007/s00204-015-1606-6 (last accessed 2016-09-20)
- Porter C.V., Higgins R.L., and Scheel L.D. (1975): A retrospective study of clinical, physiologic and immunologic changes in workers exposed to toluene diisocyanate. *American Industrial Hygiene Association Journal* 36 (3), 159-168. DOI: 10.1080/0002889758507230 (last accessed 2016-09-20)
- Pourabedian S., Barkhordari A., Habibi E., Rismanchiyan M., and Zare M. (2010): Effect of 1,6-hexamethylene diisocyanate exposure on peak flowmetry in automobile paint shop workers in Iran. *Archives of Industrial Hygiene and Toxicology* 61 (2), 183-189. DOI: 10.2478/10004-1254-61-2010-1994 (last accessed 2016-09-28)
- Pronk A., Preller L., Doekes G., Wouters I.M., Rooijackers J., Lammers J.W., and Heederik D. (2009): Different respiratory phenotypes are associated with isocyanate exposure in spray painters. *European Respiratory Journal* 33 (3), 494-501. DOI: 10.1183/09031936.00091408 (last accessed 2016-09-20)

Pronk A., Preller L., Raulf-Heimsoth M., Jonkers I.C., Lammers J.W., Wouters I.M., Doekes G., Wisnewski A.V., and Heederik D. (2007): Respiratory symptoms, sensitization, and exposure response relationships in spray painters exposed to isocyanates. *American Journal of Respiratory and Critical Care Medicine* 176 (11), 1090-1097. DOI: 10.1164/rccm.200702-2150C (last accessed 2016-09-20)

Pronk A., Yu F., Vlaanderen J., Tielemans E., Preller L., Bobeldijk I., Deddens J.A., Latza U., Baur X., and Heederik D. (2006): Dermal, inhalation, and internal exposure to 1,6-HDI and its oligomers in car body repair shop workers and industrial spray painters. *Occupational and Environmental Medicine* 63 (9), 624-631. DOI: 10.1136/oem.2005.023226 (last accessed 2016-09-19)

Puscasu S., Aubin S., Cloutier Y., Sarazin P., Tra H.V., and Gagné S. (2015): CIP10 optimization for 4,4-methylene diphenyl diisocyanate aerosol sampling and field comparison with impinger method. *Annals of Occupational Hygiene* 59 (3), 347-357. DOI: 10.1093/annhyg/meu100 (last accessed 2016-09-29)

Rachiotis G., Savani R., Brant A., MacNeill S.J., Taylor A.N., and Cullinan P. (2007): Outcome of occupational asthma after cessation of exposure: A systematic review. *Thorax* 62 (2), 147-152. DOI: 10.1136/thx.2006.061952 (last accessed 2016-09-20)

Rattray N.J., Botham P.A., Hext P.M., Woodcock D.R., Fielding I., Dearman R.J., and Kimber I. (1994): Induction of respiratory hypersensitivity to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. *Toxicology* 88, 1-3. DOI: 10.1016/0300-483X(94)90108-2 (last accessed 2016-09-20)

Redlich C.A. (2010): Skin exposure and asthma: Is there a connection? *Proceedings of the American Thoracic Society* 7 (2), 134-137. DOI: 10.1513/pats.201002-025RM (last accessed 2016-09-20)

Redlich C.A., Stowe M.H., Coren B.A., Wisnewski A.V., Holm C.T., and Cullen M.R. (2002): Diisocyanate-exposed auto body shop workers: A one-year follow-up. *American Journal of Industrial Medicine* 42 (6), 511-518. DOI: 10.1002/ajim.10143 (last accessed 2016-09-20)

Redlich C.A. and Wilson L.A. (2013): A case series of families with symptoms associated with home polyurethane spray foam insulation. *Isocyanates & Health Past, Present & Future*, Potomac, USA, April 3-4. http://www.cirpd.org/SiteCollectionDocuments/Conference%20Booklets/IsocyanatesProgramBook_SCREEN.pdf (last accessed 2016-09-21)

Reh C.M. and Lushniak B.D. (1984): Health Hazard Evaluation Report No. HETA-87-350-2084. Trailmobile, Inc., Charleston, Illinois. HETA 87-350-2084. Hazard Evaluations and Technical Assistance Branch. National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio, USA

Reuzel P.G., Arts J.H., Lomax L.G., Kuijpers M.H., Kuper C.F., Gembardt C., Feron V.J., and Loser E. (1994a): Chronic inhalation toxicity and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. *Fundamental and Applied Toxicology* 22 (2), 195-210. DOI: 10.1006/faat.1994.1024 (last accessed 2016-09-20)

Reuzel P.G.J., Kuper C.F., Feron V.J., Appelman L.M., and Loser E. (1994b): Acute, subacute, and subchronic inhalation toxicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. *Fundamental and Applied Toxicology* 22 (2), 186-194. DOI: 10.1006/faat.1994.1023 (last accessed 2016-09-20)

Ricci F., Chiesi A., Bisio C., Panari C., and Pelosi A. (2016): Effectiveness of occupational health and safety training: A systematic review with meta-analysis. *Journal of Workplace Learning* 28 (6), 355-377. DOI: 10.1108/JWL-11-2015-0087

Roberge B., Gravel R., and Drolet D. (2009): 4,4'-Diphenylmethane diisocyanate (MDI) - safety practices and concentration during polyurethane foam spraying. Report no. R-629, ISBN: 978-2-89631-411-9. Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), Montréal, Québec, Canada. <http://www.irsst.qc.ca/media/documents/PubIRSST/R-629.pdf>

Robert A., Ducos P., Francin J.M., and Marsan P. (2007): Biological monitoring of workers exposed to 4,4'-methylenediphenyl diisocyanate (MDI) in 19 French polyurethane industries. *International Archives of Occupational and Environmental Health* 80 (5), 412-422. DOI: 10.1007/s00420-006-0150-3 (last accessed 2016-09-29)

Robson L., Stephenson C., Schulte P., Amick B., Chan S., Bielecky A., Wang A., Heidotting T., Irvin E., Eggerth D., Peters R., Clarke J., Cullen K., Boldt L., Rotunda C., and Grubb P. (2010): A systematic review of the effectiveness of training & education for the protection of workers. Publication No. 2010-127, date: 2010-01. Institute for Work & Health. Health N.I.f.O.S.a. <https://www.cdc.gov/niosh/docs/2010-127/> (last accessed 2016-12-15)

RPS (2014): Sprayed PUR emissions from crawlspaces, date: 2014-02-25. RPS Advies- en Ingenieursbureau B.V., Delft, The Netherlands. <https://www.dropbox.com/s/932kqyk9e9b4exc/RPS%20report%20SPF%20-%2025%20February%202014.PDF> (last accessed 2016-09-21)

Rüegger M., Droste D., Hofmann M., Jost M., and Miedinger D. (2014): Diisocyanate-induced asthma in Switzerland: Long-term course and patients' self-assessment after a 12-year follow-up. *Journal of Occupational Medicine and Toxicology* 9, 21. DOI: 10.1186/1745-6673-9-21 (last accessed 2016-09-20)

Saetta M., Maestrelli P., Di Stefano A., De Marzo N., Milani G.F., Pivrotto F., Mapp C.E., and Fabbri L.M. (1992): Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. *American Review of Respiratory Disease* 145 (1), 169-174. DOI: 10.1164/ajrccm/145.1.169 (last accessed 2016-09-20)

Sætterstrøm B., Olsen J., and Johansen J.D. (2014): Cost-of-illness of patients with contact dermatitis in Denmark. *Contact Dermatitis* 71 (3), 154-161. DOI: 10.1111/cod.12231

Safepharm (1992): XDI: 1,3-Benzenebis(methyl isocyanate): Magnusson & Kligman maximisation study in the guinea pig. Project no. 458/13, date: 1992-09-28. Safepharm Laboratories Ltd. Mitsui Toatsu Chemicals Inc., unpublished

Safepharm (1998a): TODI: Magnusson & Kligman maximisation study in the guinea pig. Report no.: 235/224, date: 1998-02-26. Safepharm Laboratories Ltd. Nippon Soda Co. Ltd., unpublished

Safepharm (1998b): XDI (MR-6A): Magnusson & Kligman maximisation study in the guinea pig. Project No. 458/195, date: 1998-04-28. Safepharm Laboratories Ltd. Mitsui Toatsu Chemicals Inc., unpublished

Sales J.H. and Kennedy K.S. (1990): Epiglottic dysfunction after isocyanate inhalation exposure. *Archives of Otolaryngology - Head and Neck Surgery* 116 (6), 725-727. DOI: 10.1001/archotol.1990.01870060083016 (last accessed 2016-09-28)

Sangha G.K. and Alarie Y. (1979): Sensory irritation by toluene diisocyanate in single and repeated exposures. *Toxicology and Applied Pharmacology* 50, 533-547. DOI: 10.1016/0041-008X(79)90408-3 (last accessed 2016-09-20)

Sangha G.K., Matijak M., and Alarie Y. (1981): Comparison of some mono- and diisocyanates as sensory irritants. *Toxicology and Applied Pharmacology* 57 (2), 241-246. DOI: 10.1016/0041-008X(81)90285-4 (last accessed 2016-09-20)

Santos T., Romano D., and Gadea R. (2010): Trade Union priority list for REACH authorisation. Version 2.0, date: 2010-06. ISTAS (Union Institute of Work, Environment, and Health). European Trade Union Institute (ETUI). <https://www.etui.org/trade-union-priority-list> (last accessed 2016-10-04)

Sarlo K. and Clark E.D. (1992): A tier approach for evaluating the respiratory allergenicity of low molecular weight chemicals. *Fundamental and Applied Toxicology* 18 (1), 107-114. DOI: 10.1016/0272-0590(92)90202-S (last accessed 2016-09-20)

Scheerens H., Buckley T.L., Muis T., van Loveren H., and Nijkamp F.P. (1996): The involvement of sensory neuropeptides in toluene diisocyanate-induced tracheal hyperreactivity in the mouse airways. *British Journal of Pharmacology* 119 (8), 1665-1671. DOI: 10.1111/j.1476-5381.1996.tb16087.x (last accessed 2016-09-20)

Scheerens H., Buckley T.L., Muis T.L., Garssen J., Dormans J., Nijkamp F.P., and van Loveren H. (1999): Long-term topical exposure to toluene diisocyanate in mice leads to antibody production and in vivo airway hyperresponsiveness three hours after intranasal challenge. *American Journal of Respiratory and Critical Care Medicine* 159 (4), 1074-1080. DOI: 10.1164/ajrccm.159.4.9701012 (last accessed 2016-09-20)

Schweigert M., Sax S., House R., and Henderson B. (2002): Investigation of pulmonary function among employees exposed to low levels of monomeric isocyanates and solvents at an automobile finishing plant. *Journal of Occupational and Environmental Medicine* 44 (11), 1083-1090.

<http://journals.lww.com/joem/pages/articleviewer.aspx?year=2002&issue=11000&article=00015&type=abstract> (last accessed 2016-09-28)

Sebroski J.R. (2013): Developing ASTM standards for test specimen preparation and measuring emissions of volatile and semi-volatile organic compounds (VOCs and SVOCs) from spray polyurethane foam (SPF) insulation products. Polyurethanes Technical Conference, Phoenix, Arizona, US, September 23 - 25, 2013. <https://polyurethane.americanchemistry.com/Resources-and-Document-Library/Developing-ASTM-Standards-for-Test-Specimen-Preparation-and-Measuring-Emissions-of-Volatile-and-Semi.pdf> (last accessed 2016-09-21)

Selgrade M.K., Boykin E.H., Haykal-Coates N., Woolhiser M.R., Wiscinski C., Andrews D.L., Farraj A.K., Doerfler D.L., and Gavett S.H. (2006): Inconsistencies between cytokine profiles, antibody responses, and respiratory hyperresponsiveness following dermal exposure to isocyanates. *Toxicological Sciences* 94 (1), 108-117. DOI: 10.1093/toxsci/kfl094 (last accessed 2016-09-20)

Sennbro C.J., Lindh C.H., Ostin A., Welinder H., Jonsson B.A., and Tinnerberg H. (2004): A survey of airborne isocyanate exposure in 13 Swedish polyurethane industries. *Annals of Occupational Hygiene* 48 (5), 405-414. DOI: 10.1093/annhyg/meh034 (last accessed 2016-09-19)

Sennekamp J., Müller-Wening D., Amthor M., Baur X., Bergmann K.-C., Costabel U., Kirsten D., Koschel D., Kroidl R., Liebetrau G., Nowak D., Schreiber J., and Vogelmeier C. (2007): Empfehlungen zur Diagnostik der exogen-allergischen Alveolitis. *Pneumologie* 61 (1), 52-56. DOI: 10.1055/s-2006-944326 (last accessed 2016-09-29)

Simon J., Barla F., Kelemen-Haller A., Farkas F., and Kraxner M. (1988): Thermal stability of polyurethanes. *Chromatographia* 25 (2), 99-106. DOI: 10.1007/bf02259024 (last accessed 2016-09-20)

Singer R. and Scott N.E. (1987): Progression of neuropsychological deficits following toluene diisocyanate exposure. *Archives of Clinical Neuropsychology* 2 (2), 135-144. DOI: 10.1016/0887-6177(87)90041-2 (last accessed 2016-09-28)

Société de Pneumologie de Langue Française (2005): L'Observatoire national des asthmes professionnels: Un outil à préserver [The National Observatory for occupational asthma: A tool to preserve]. *Maladies Professionnelles* 67, 13-15

Song J., Zhao H., Dong H., Zhang D., Zou M., Tang H., Liu L., Liang Z., Lv Y., Zou F., and Cai S. (2013): Mechanism of E-cadherin redistribution in bronchial airway epithelial cells in a TDI-induced asthma model. *Toxicology Letters* 220 (1), 8-14. DOI: 10.1016/j.toxlet.2013.03.033 (last accessed 2016-09-20)

Sparer J., Stowe M.H., Bello D., Liu Y., Gore R.J., Youngs F., Cullen M.R., Redlich C.A., and Woskie S.R. (2004): Isocyanate exposures in autobody shop work: The SPRAY study. *Journal of Occupational and Environmental Hygiene* 1 (9), 570-581. DOI: 10.1080/15459620490485909 (last accessed 2016-09-20)

Spray Foam Distributors of New England (2015): Does spray foam smell? <http://sprayfoamsupply.com/does-spray-foam-smell/> (last accessed 2016-09-21)

Stadler J. and Karol M.H. (1984): Experimental delayed hypersensitivity following inhalation of dicyclohexylmethane-4,4'-diisocyanate: A concentration-response relationship. *Toxicology and Applied Pharmacology* 74 (2), 244-249. DOI: 10.1016/0041-008X(84)90149-2 (last accessed 2016-09-20)

Stadler J.C. and Karol M.H. (1985): Use of dose-response data to compare the skin sensitizing abilities of dicyclohexylmethane-4,4'-diisocyanate and picryl chloride in two animal species. *Toxicology and Applied Pharmacology* 78 (3), 445-450. DOI: 10.1016/0041-008X(85)90251-0 (last accessed 2016-09-20)

Statistisches Bundesamt (2016): Verkehrsunfälle. <https://www.destatis.de/DE/ZahlenFakten/Wirtschaftsbereiche/TransportVerkehr/Verkehrsunfaelle/Verkehrsunfaelle.html;jsessionid=CFEBC63A7DED8BBEDADA276731938> (last accessed 2016-06-06)

Stern M.L., Brown T.A., Brown R.D., and Munson A.E. (1989): Contact hypersensitivity response to isophorone diisocyanate in mice. *Drug and Chemical Toxicology* 12 (3-4), 287-296. DOI: 10.3109/01480548908999159 (last accessed 2016-09-20)

Stiftung Warentest (2007): Matratzen: Für erholsamen Schlaf [Mattresses: For a relaxing sleep]. *test* 10, 62-66. <https://www.test.de/Matratzen-Fuer-erholsamen-Schlaf-1577875-2577875/>

Stingeni L., Bellini V., and Lisi P. (2008): Occupational airborne contact urticaria and asthma: simultaneous immediate and delayed allergy to diphenylmethane-4,4'-diisocyanate. *Contact Dermatitis* 58 (2), 112-113. DOI: 10.1111/j.1600-0536.2007.01180.x (last accessed 2016-09-20)

Stocks S.J., Jones K., Piney M., and Agius R.M. (2015): Isocyanate exposure and asthma in the UK vehicle repair industry. *Occupational Medicine* 65 (9), 713-718. DOI: 10.1093/occmed/kqv108 (last accessed 2016-09-19)

Stoye D., Funke W., Hoppe L., Hasselkus J., Curtis L.G., Hoehne K., Zech H.-J., Heiling P., Yamabe M., Dören K., Schupp H., Küchenmeister R., Schmitthenner M., Kremer W., Wiczorrek W., H. G., Schneider W., White J.W., Short A.G., Blank W.J., Calbo, L.J., Plath D., Wagner F., Haller W., Rödder K.-M., Streitberger H.-J., Urbano E., Laible R., Meyer B.D., Bagda E., Waite F.A., Philips M., Köhler K., Simmendinger P., Roelle W., Scholz W., Valet A., Slongo M., Molz T., Hiller R., Thomer K.W., Vogel K., Schernau U., Hüser B., Brandt A., Milne A., Weyers H., Plehn W., and Lentze H.-A. (2000): Paints and coatings. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA. ISBN: 978-3527306732. DOI: 10.1002/14356007 (last accessed 2016-09-29)

Streicher R.P., Reh C.M., Key-Schwartz R., Schlecht P.C., Cassinelli M.E., and O'Connor P.F. (2002): Selecting isocyanate sampling and analytical methods. *Applied Occupational and Environmental Hygiene* 17 (3), 157-162. DOI: 10.1080/104732202753438234 (last accessed 2016-09-28)

Streicher R.P., Reh C.M., Key-Schwartz R.J., Schlecht P.C., Cassinelli M.E., and O'Connor P.F. (2000): Determination of airborne isocyanate exposure: Considerations in method selection. *American Industrial Hygiene Association Journal* 61 (4), 544-556. DOI: 10.1080/15298660008984567 (last accessed 2016-09-20)

Sulzer-Azaroff B. and Austin J. (2000): Does BBS Work? Behavior-Based Safety & Injury Reduction: A Survey of Evidence. *Professional Safety*, 19-24. http://www.safetybok.org/does_bbs_work_behavior-based_safety_injury_reduction_a_survey_of_evidence/ (last accessed 2016-12-15)

Sun L.Z., Elsayed S., Bronstad A.M., van Do T., Irgens A., Aardal N.P., and Aasen T.B. (2007): Airway inflammation and bronchial remodelling in toluene diisocyanate-exposed BALB/c mouse model. *Scandinavian Journal of Immunology* 65 (2), 118-125. DOI: 10.1111/j.1365-3083.2006.01882.x (last accessed 2016-09-20)

Svensson-Elfsmark L., Koch B.L., Gustafsson A., and Bucht A. (2009): Rats repeatedly exposed to toluene diisocyanate exhibit immune reactivity against methyl isocyanate-protein conjugates. *International Archives of Allergy and Immunology* 150 (3), 229-236. DOI: 10.1159/000222675 (last accessed 2016-09-20)

Swensson A., Holmquist C.E., and Lundgren K.D. (1955): Injury to the respiratory tract by isocyanates used in making lacquers. *British Journal of Industrial Medicine* 12 (1), 50-53. DOI: 10.1136/oem.12.1.50 (last accessed 2016-09-20)

Swierczynska-Machura D., Brzezinski S., Nowakowska-Swirta E., Walusiak-Skorupa J., Wittczak T., Dudek W., Bonczarowska M., Wesolowski W., Czerczak S., and Palczynski C. (2015): Occupational exposure to diisocyanates in polyurethane foam factory workers. *International Journal of Occupational and Environmental Health* 28 (6), 985-998. DOI: 10.13075/ijomeh.1896.00284 (last accessed 2016-09-28)

Swierczynska-Machura D., Nowakowska-Swirta E., Walusiak-Skorupa J., Piasecka-Zelga J., Swiercz R., Nocun M., and Palczynski C. (2014): Effect of inhaled toluene diisocyanate on local immune response based on murine model for occupational asthma. *Journal of Immunotoxicology* 11 (2), 166-171. DOI: 10.3109/1547691x.2013.818745 (last accessed 2016-09-20)

Swierczynska-Machura D., Walusiak-Skorupa J., Nowakowska-Swirta E., Piasecka-Zelga J., Swiercz R., and Palczynski C. (2012): Immunological determinants in a murine model of toluene diisocyanate-induced asthma. *International Journal of Occupational and Environmental Health* 25 (4), 492-498. DOI: 10.2478/s13382-012-0063-1 (last accessed 2016-09-20)

Syngenta (2003a): MDI: Biotransformation in the rat following inhalation exposure to [14C]-MDI at 2 mg/m³ for 6 hours. . III report 11481, III project 165-EU-MTX, date: 2003-07-07. Syngenta, Central Toxicology Laboratory. International Isocyanate Institute, unpublished

Syngenta (2003b): MDI: Excretion and tissue distribution in the rat following inhalation exposure to [14C]-MDI at 2 mg/m³ for 6 hours. III report 11480, III project 165-EU-MTX, date: 2003-07-07. Syngenta, Central Toxicology Laboratory. International Isocyanate Institute, unpublished

- Tanaka K., Kawai M., and Maekawa N. (1983): Experimental model of asthma by toluene diisocyanate (TDI). *Bulletin of the Chest Disease Research Institute of the Kyoto University* 16, 1-9. <http://hdl.handle.net/2433/52154> (last accessed 2016-09-20)
- Tanaka K.I. (1980): Contact sensitivity in mice induced by tolylene diisocyanate (TDI). *Journal of Dermatology* 7 (4), 277-280. DOI: 10.1111/j.1346-8138.1980.tb01969.x (last accessed 2016-09-20)
- Tanaka K.I., Takeoka A., Nishimura F., and Hanada S. (1987): Contact sensitivity induced in mice by methylene bisphenyl diisocyanate. *Contact Dermatitis* 17 (4), 199-204. DOI: 10.1111/j.1600-0536.1987.tb02713.x (last accessed 2016-09-20)
- Tarkowski M., Vanoirbeek J.A., Vanhooren H.M., de Vooght V., Mercier C.M., Ceuppens J., Nemery B., and Hoet P.H. (2007): Immunological determinants of ventilatory changes induced in mice by dermal sensitization and respiratory challenge with toluene diisocyanate. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 292 (1), L207-214. DOI: 10.1152/ajplung.00157.2005 (last accessed 2016-09-20)
- Tarlo S.M., Liss G.M., Dias C., and Banks D.E. (1997): Assessment of the relationship between isocyanate exposure levels and occupational asthma. *American Journal of Industrial Medicine* 32 (5), 517-521. DOI: 10.1002/(SICI)1097-0274(199711)32:5<517::AID-AJIM12>3.0.CO;2-5 (last accessed 2016-09-19)
- Thorne P.S., Hillebrand J.A., Lewis G.R., and Karol M.H. (1987): Contact sensitivity by diisocyanates: Potencies and cross-reactivities. *Toxicology and Applied Pharmacology* 87 (1), 155-165. DOI: 10.1016/0041-008X(87)90093-7 (last accessed 2016-09-20)
- Timchalk C., Smith F.A., and Bartels M.J. (1994): Route-dependent comparative metabolism of [14C]toluene 2,4-diisocyanate and [14C]toluene 2,4-diamine in Fischer 344 rats. *Toxicology and Applied Pharmacology* 124 (2), 181-190. DOI: 10.1006/taap.1994.1022 (last accessed 2016-09-20)
- Tinnerberg H., Broberg K., Lindh C.H., and Jonsson B.A. (2014): Biomarkers of exposure in Monday morning urine samples as a long-term measure of exposure to aromatic diisocyanates. *International Archives of Occupational and Environmental Health* 87 (4), 365-372. DOI: 10.1007/s00420-013-0872-y (last accessed 2016-09-20)
- Tinnerberg H. and Mattsson C. (2008): Usage of air monitoring and biomarkers of isocyanate exposure to assess the effect of a control intervention. *Annals of Occupational Hygiene* 52 (3), 187-194. DOI: 10.1093/annhyg/men006 (last accessed 2016-09-20)
- TNO (2013a): Evaluatie van gezondheidsrisico's voor bewoners op basis van resultaten van metingen in woningen tijdens en direct na aanbrenge van SPF-isolatie [Evaluation of health risks for residents on the basis of measurements in apartments directly after the installation of SPF isolations]. Report no. TNO2013 R11049, project no. 060.04501, date: 2013-08-21. TNO Earth, Environmental and Life Sciences. Nuon Isolatie. <http://www.purisolatieonderzoek.nl/documents/TNO-rapport-2.pdf> (last accessed 2016-09-21)
- TNO (2013b): Evaluatie van gezondheidsrisico's voor bewoners, op basis van resultaten van metingen in woningen waar SPF-vloerisolatie is aangebracht [Evaluation of health risks for residents, on the basis of measurements in apartments where SPF floor isolation is installed]. Report no. TNO2013 R10642, project no. 051.02876, date: 2013-05-31. TNO Earth, Environmental and Life Sciences. Nuon Isolatie. <http://www.purisolatieonderzoek.nl/documents/TNO-rapport-1.pdf> (last accessed 2016-09-21)

Toelle B.G., Peat J.K., Salome C.M., Mellis C.M., and Woolcock A.J. (1992): Toward a definition of asthma for epidemiology. *American Review of Respiratory Disease* 146 (3), 633-637. DOI: 10.1164/ajrccm/146.3.633 (last accessed 2016-09-20)

Tominaga M., Kohno S., Tanaka K.I., and Ohata K. (1985): Studies on toluene diisocyanate (TDI)-induced delayed type hypersensitivity. *Japanese Journal of Pharmacology* 39 (2), 163-171. DOI: 10.1254/jjp.39.163 (last accessed 2016-09-20)

Toren K. and Blanc P.D. (2009): Asthma caused by occupational exposures is common - a systematic analysis of estimates of the population-attributable fraction. *BMC Pulm Med* 9. DOI: 10.1186/1471-2466-9-7 (last accessed 2016-09-28)

Tornling G., Alexandersson R., Hedenstierna G., and Plato N. (1990): Decreased lung function and exposure to diisocyanates (HDI and HDI-BT) in car repair painters: Observations on re-examination 6 years after initial study. *American Journal of Industrial Medicine* 17 (3), 299-310. DOI: 10.1002/ajim.4700170302 (last accessed 2016-09-28)

Tsuang W. and Huang Y.-C.T. (2012): Asthma induced by exposure to spray polyurethane foam insulation in a residential home. *Journal of Occupational and Environmental Medicine* 54 (3), 272-273. DOI: 10.1097/JOM.0b013e31824d2da1 (last accessed 2016-09-21)

Tyl R.W., Neeper-Bradley T.L., Fisher L.C., Dodd D.E., Pritts I.M., Losco P.E., Lyon J.P., and Landry T.D. (1999): Two-generation reproductive toxicity study of inhaled toluene diisocyanate vapor in CD rats. *Toxicological Sciences* 52 (2), 258-268. DOI: 10.1093/toxsci/52.2.258 (last accessed 2016-09-28)

Ulvestad B., Melbostad E., and Fuglerud P. (1999): Asthma in tunnel workers exposed to synthetic resins. *Scandinavian Journal Of Work Environment & Health* 25 (4), 335-341. DOI: 10.5271/sjweh.443 (last accessed 2016-09-21)

Union Carbide (1988): Developmental toxicity study of inhaled toluene diisocyanate vapor in CD (Sprague-Dawley) rats. III report 10548, III project NA-AB-50, date: 1988-12-06. Union Carbide Chemicals and Plastics Company, Bushy Run Research Center. International Isocyanate Institute, unpublished

Union Carbide (1989): Two-generation reproduction study of inhaled toluene diisocyanate in CD (Sprague-Dawley) rats. III report 10608, III project NA-AB-50,, date: 1989-03-17. Union Carbide Chemicals and Plastics Company, Bushy Run Research Center. International Isocyanate Institute, unpublished

Union Carbide (1990): CT-329-87 fourteen-week vapor inhalation study with rats and mice Report no. 51-579, company study no. 87-57-80009, date: 1990-01-18. Union Carbide Chemicals and Plastics Company, Bushy Run Research Center. Cytec Industries, unpublished

Union Carbide (1992): Evaluation of sensory irritation potential and assessment of the respiratory response during exposure to meta-tetramethylxylene diisocyanate (CT-368-88) vapor. Report no. 52-506, date: 1992-05-22. Union Carbide Chemicals and Plastics Company, Bushy Run Research Center. Cytec Industries, unpublished

University of Louisville (1987): Preparation and immunologic evaluation of allergenic hapten-protein conjugates, date: 1983-11-23. American Cyanamide Co., unpublished

US EPA (2015): Potential chemical exposures from spray polyurethane foam. Curing rates. United States Environmental Protection Agency (EPA). <https://www.epa.gov/saferchoice/potential-chemical-exposures-spray-polyurethane-foam#curing-rates> (last accessed 2016-09-21)

Valentino M. and Rapisarda V. (2002): Evoluzione dell'asma da isocianati in rapporto alla cessazione dell'esposizione: Studio longitudinale su 50 soggetti [Development of isocyanate

asthma in relation to the cessation of exposure: Longitudinal study in 50 subjects]. *Giornale Italiano di Medicina del Lavoro ed Ergonomia* 24 (1), 26-31

Valks R., Conde-Salazar L., and Barrantes O.L. (2003): Occupational allergic contact urticaria and asthma from diphenylmethane-4,4'-diisocyanate. *Contact Dermatitis* 49 (3), 166-167. DOI: 10.1111/j.0105-1873.2003.0185j.x (last accessed 2016-09-21)

van der Putte I., Affourtit F., Qi S., and Blaauw M. (2012): A6. Data gathering sensitizers. VRM11.8079/Draft Final Report no.2 in reference to the supply of services on technical questions in support of activities of the Netherlands Bureau REACH. Report no. VRM11.8079, date: 2012-07-19. RPS advies, Nederlands Bureau REACH, Delft, The Netherlands, unpublished

van Och F.M.M., Slob W., de Jong W.H., Vandebriel R.J., and van Loveren H. (2000): A quantitative method for assessing the sensitizing potency of low molecular weight chemicals using a local lymph node assay: Employment of a regression method that includes determination of the uncertainty margins. *Toxicology* 146 (1), 49-59. DOI: 10.1016/S0300-483X(00)00165-7 (last accessed 2016-09-21)

Vandebriel R.J., de Jong W.H., Spiekstra S.W., van Dijk M., Fluitman A., Garssen J., and van Loveren H. (2000): Assessment of preferential T-helper 1 or T-helper 2 induction by low molecular weight compounds using the local lymph node assay in conjunction with RT-PCR and ELISA for interferon-gamma and interleukin-4. *Toxicology and Applied Pharmacology* 162 (2), 77-85. DOI: 10.1006/taap.1999.8841 (last accessed 2016-09-21)

Vandenplas O., Cartier A., Lesage J., Cloutier Y., Perreault G., Grammer L.C., Shaughnessy M.A., and Malo J.-L. (1993a): Prepolymers of hexamethylene diisocyanate as a cause of occupational asthma. *Journal of Allergy and Clinical Immunology* 91 (4), 850-861. DOI: 10.1016/0091-6749(93)90342-D (last accessed 2016-09-28)

Vandenplas O., Cartier A., Lesage J., Perrault G., Grammer L.C., and Malo J.L. (1992a): Occupational asthma caused by a prepolymer but not the monomer of toluene diisocyanate (TDI). *Journal of Allergy and Clinical Immunology* 89 (6), 1183-1188. DOI: 10.1016/0091-6749(92)90303-J (last accessed 2016-09-28)

Vandenplas O., Malo J.L., Cartier A., Perreault G., and Cloutier Y. (1992b): Closed-circuit methodology for inhalation challenge tests with isocyanates. *American Review of Respiratory Disease* 145 (3), 582-587. DOI: 10.1164/ajrccm/145.3.582 (last accessed 2016-09-21)

Vandenplas O., Malo J.L., Dugas M., Cartier A., Desjardins A., Lvesque J., Shaughnessy M.A., and Grammer L.C. (1993b): Hypersensitivity pneumonitis-like reaction among workers exposed to diphenylmethane diisocyanate (MDI). *American Review of Respiratory Disease* 147 (2), 338-346. DOI: 10.1164/ajrccm/147.2.338 (last accessed 2016-09-28)

Vandenplas O., Sherwood Burge S., Moscato G., and Malo J.-L. (2013): Functional assessment. In: *Asthma in the workplace* (Malo J.L., Chan-Yeung M., and Bernstein D.L., eds.), ed. 4, chapter 9. CRC. ISBN: 978-1-84214-591-3

Vanoirbeek J.A.J., de Vooght V., Synhaeve N., Nemery B., and Hoet P.H.M. (2009): Is toluene diamine a sensitizer and is there cross-reactivity between toluene diamine and toluene diisocyanate? *Toxicological Sciences* 109 (2), 256-264. DOI: 10.1093/toxsci/kfp065 (last accessed 2016-09-21)

Vanoirbeek J.A.J., Tarkowski M., Ceuppens J.L., Verbeken E.K., Nemery B., and Hoet P.H.M. (2004): Respiratory response to toluene diisocyanate depends on prior frequency and concentration of dermal sensitization in mice. *Toxicological Sciences* 80 (2), 310-321. DOI: 10.1093/toxsci/kfh155 (last accessed 2016-09-21)

- Venables K.M., Dally M.B., Burge P.S., Pickering C.A., and Newman Taylor A.J. (1985): Occupational asthma in a steel coating plant. *British Journal of Industrial Medicine* 42 (8), 517-524. DOI: 10.1136/oem.42.8.517 (last accessed 2016-09-28)
- Vercelli D. (2016): Does epigenetics play a role in human asthma? *Allergology International* 65 (2), 123-126. DOI: 10.1016/j.alit.2015.12.001 (last accessed 2016-09-19)
- Verschoor A.H. (2014): Reactie op het RPS rapport [Reaction to the RPS report], date: 2014-03-22. Expertise Centre Environmental Medicine (ECEMed). Kennisplatform gespoten PUR schuim, Velp, The Netherlands. <https://www.dropbox.com/s/44munlol07io9qo/reactie%20RPS%20rapport%20ECEMed.pdf> (last accessed 2016-09-21)
- Verschoor L. and Verschoor A. (2013): Woningisolatie met PUR moet in de ban [Isolation of apartments with PUR must be banned]. *Medisch Contact* 68 (10), 540-542. <https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/woningisolatie-met-pur-moet-in-de-ban.htm> (last accessed 2016-09-21)
- Verschoor L. and Verschoor A.H. (2014): Nonoccupational and occupational exposure to isocyanates. *Current Opinion in Pulmonary Medicine* 20 (2), 199-204. DOI: 10.1097/mcp.000000000000029 (last accessed 2016-09-21)
- Verstraelen S., Bloemen K., Nelissen I., Witters H., Schoeters G., and van den Heuvel R. (2008): Cell types involved in allergic asthma and their use in in vitro models to assess respiratory sensitization. *Toxicology in Vitro* 22 (6), 1419-1431. DOI: 10.1016/j.tiv.2008.05.008 (last accessed 2016-09-21)
- Vignoli M., Punnett L., and Depolo M. (2014): How to Measure Safety Training Effectiveness? Towards a More Reliable Model to Overcome Evaluation Issues in Safety Training. *Chemical Engineering Transactions* 36, 67-72. DOI: 10.3303/CET1436012 (last accessed 2016-12-14)
- Virchow J.C. (2013): What is asthma. In: *Global Atlas on Asthma* (Akdis C.A. and Agache I., eds.), chapter 1, pp. 2-3. EAACI, The European Academy of Allergy and Clinical Immunology. http://www.eaaci.org/GlobalAtlas/Global_Atlas_of_Asthma.pdf (last accessed 2016-09-21)
- Vogelmeier C., Baur X., and Fruhmans G. (1991): Isocyanate-induced asthma: Results of inhalation tests with TDI, MDI and methacholine. *International Archives of Allergy and Applied Immunology* 63 (1), 9-13. DOI: 10.1007/BF00406191 (last accessed 2016-09-21)
- Walters G.I., Kirkham A., McGrath E.E., Moore V.C., Robertson A.S., and Burge P.S. (2015): Twenty years of SHIELD: Decreasing incidence of occupational asthma in the West Midlands, UK? *Occupational and Environmental Medicine* 72 (4), 304-310. DOI: 10.1136/oemed-2014-102141 (last accessed 2016-09-21)
- Wang H., Wang Q.-s., He J.-j., Mao Z.-l., and Sun J.-h. (2013): Study on the pyrolytic behaviors and kinetics of rigid polyurethane foams. *Procedia Engineering* 52, 377-385. DOI: 10.1016/j.proeng.2013.02.156 (last accessed 2016-09-21)
- Wang J.D., Huang P.H., Lin J.M., Su S.Y., and Wu M.C. (1988): Occupational asthma due to toluene diisocyanate among velcro-like tape manufacturers. *American Journal of Industrial Medicine* 14 (1), 73-78. DOI: 10.1002/ajim.4700140109 (last accessed 2016-09-29)
- Wang M.L. and Petsonk E.L. (2004): Symptom onset in the first 2 years of employment at a wood products plant using diisocyanates: some observations relevant to occupational medical screening. *American Journal of Industrial Medicine* 46 (3), 226-233. DOI: 10.1002/ajim.20050 (last accessed 2016-09-21)

- Wass U. and Belin L. (1989): Immunologic specificity of isocyanate-induced IgE antibodies in serum from 10 sensitized workers. *Journal of Allergy and Clinical Immunology* 83 (1), 126-135. DOI: 10.1016/0091-6749(89)90487-9 (last accessed 2016-09-21)
- Wegman D.H., Musk A.W., Main D.M., and Pagnotto L.D. (1982): Accelerated loss of FEV-1 in polyurethane production workers: A four-year prospective study. *American Journal of Industrial Medicine* 3 (2), 209-215. DOI: 10.1002/ajim.4700030212 (last accessed 2016-09-21)
- Wegman D.H., Pagnotto L.D., Fine L.J., and Peters J.M. (1974): A dose response relationship in TDI workers. *Journal of Occupational Medicine* 16 (4), 258-260. http://journals.lww.com/joem/Abstract/1974/04000/A_Dose_Response_Relationship_in_TDI_Workers_.6.aspx (last accessed 2016-09-21)
- Wegman D.H., Peters J.M., Pagnotto L., and Fine L.J. (1977): Chronic pulmonary function loss from exposure to toluene diisocyanate. *British Journal of Industrial Medicine* 34 (3), 196-200. DOI: 10.1136/oem.34.3.196 (last accessed 2016-09-21)
- Weill H., Butcher B., Dharmarajan V., Glindmeyer H.W., Jones R.N., Carr J., O'Neill C., and Salvaggio J. (1981): Respiratory and immunologic evaluation of isocyanate exposure in a new manufacturing plant. NIOSH Publication No. 81-125. National Institute for Occupational Safety and Health (NIOSH). U.S. Government Printing Office
- Weyel D.A., Rodney B.S., and Alarie Y. (1982): Sensory irritation, pulmonary irritation, and acute lethality of a polymeric isocyanate and sensory irritation of 2,6-toluene diisocyanate. *Toxicology and Applied Pharmacology* 64 (3), 423-430. DOI: 10.1016/0041-008X(82)90238-1 (last accessed 2016-09-21)
- Weyel D.A. and Schaffer R.B. (1985): Pulmonary and sensory irritation of diphenylmethane-4,4'- and dicyclohexylmethane-4,4'-diisocyanate. *Toxicology and Applied Pharmacology* 77 (3), 427-433. DOI: 10.1016/0041-008X(85)90182-6 (last accessed 2016-09-21)
- White I.R., Stewart J.R., and Rycroft R.J.G. (1983): Allergic contact dermatitis from an organic di-isocyanate. *Contact Dermatitis* 9 (4), 300-303. DOI: 10.1111/j.1600-0536.1983.tb04395.x (last accessed 2016-09-21)
- WHO (2016): Occupational health. Occupational and work-related diseases. World Health Organisation,. http://www.who.int/occupational_health/activities/occupational_work_diseases/en/ (last accessed 2016-02-06)
- Wild D.M., Redlich C.A., and Paltiel A.D. (2005): Surveillance for isocyanate asthma: A model based cost effectiveness analysis. *Occupational and Environmental Medicine* 62 (11), 743-749. DOI: 10.1136/oem.2004.016147 (last accessed 2016-09-19)
- Williamson K.S. (1964): Studies of diisocyanate workers (1). *Occupational Medicine* 14 (1), 81-88. DOI: 10.1093/occmed/14.1.81 (last accessed 2016-09-21)
- Williamson K.S. (1965): Studies of diisocyanate workers. (2). *Occupational Medicine* 15 (1), 29-35. DOI: 10.1093/occmed/15.1.29 (last accessed 2016-09-28)
- Wisnewski A.V. (2007): Developments in laboratory diagnostics for isocyanate asthma. *Current Opinion in Allergy and Clinical Immunology* 7 (2), 138-145. DOI: 10.1097/ACI.0b013e3280895d22 (last accessed 2016-09-29)
- Wisnewski A.V., Herrick C.A., Liu Q., Chen L., Bottomly K., and Redlich C.A. (2003): Human gamma/delta T-cell proliferation and IFN-gamma production induced by hexamethylene diisocyanate. *The Journal of Allergy and Clinical Immunology* 112 (3), 538-546. DOI: 10.1016/S0091-6749(03)01865-7 (last accessed 2016-09-21)

Wisnewski A.V., Liu J., and Colangelo C.M. (2015): Glutathione reaction products with a chemical allergen, methylene-diphenyl diisocyanate, stimulate alternative macrophage activation and eosinophilic airway inflammation. *Chemical Research in Toxicology* 28 (4), 729-737. DOI: 10.1021/tx5005002 (last accessed 2016-09-21)

Wisnewski A.V., Liu Q., Liu J., and Redlich C.A. (2008): Human innate immune responses to hexamethylene diisocyanate (HDI) and HDI-albumin conjugates. *Clinical and Experimental Allergy* 38 (6), 957-967. DOI: 10.1111/j.1365-2222.2008.02982.x (last accessed 2016-09-21)

Wood R. (2013): CPI ventilation research project update. Polyurethanes Technical Conference, Phoenix, US, September 23 – 25, 2013. <https://polyurethane.americanchemistry.com/Resources-and-Document-Library#CPI> (last accessed 2016-09-21)

Wood R. (2014): CPI ventilation research project for estimating re-entry times for trade workers following application of three generic spray polyurethane foam formulations. Polyurethanes Technical Conference, Dallas, US, September 22 – 24, 2014. <https://polyurethane.americanchemistry.com/Resources-and-Document-Library#CPI> (last accessed 2016-09-21)

Woodbury J.W. (1956): Asthmatic syndrome following exposure to toluene diisocyanate. *Industrial Medicine & Surgery* 25, 540-543

Woolhiser M., Stephenson A., and Boverhof D. (2013): Sensitization potential of low-monomer diisocyanate prepolymers. http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_0869/0901b803808699bf.pdf?filepath=/polyurethane/pdfs/noreg/109-01865.pdf&fromPage=GetDoc (last accessed 2016-09-21)

Woolhiser M.R., Hayes B.B., and Meade B.J. (1998): A combined murine local lymph node and irritancy assay to predict sensitization and irritancy potential of chemicals. *Toxicology Methods* 8 (4), 245-256. DOI: 10.1080/105172398242835 (last accessed 2016-09-21)

Yamada K., Amitani R., Niimi A., and Kuze F. (1995): Interstitial pneumonitis-like lesions in guinea-pigs following repeated exposure to toluene diisocyanate. *European Respiratory Journal* 8 (8), 1300-1306. <http://erj.ersjournals.com/content/8/8/1300.long> (last accessed 2016-09-21)

Yang I.V. and Schwartz D.A. (2012): Epigenetic mechanisms and the development of asthma. *Journal of Allergy and Clinical Immunology* 130 (6), 1243-1255. DOI: 10.1016/j.jaci.2012.07.052 (last accessed 2016-09-21)

Yucesoy B., Johnson V.J., Lummus Z.L., Kashon M.L., Rao M., Bannerman-Thompson H., Frye B., Wang W., Gautrin D., Cartier A., Boulet L.P., Sastre J., Quirce S., Tarlo S.M., Germolec D.R., Luster M.I., and Bernstein D.I. (2014): Genetic variants in the major histocompatibility complex class I and class II genes are associated with diisocyanate-induced asthma. *Journal of Occupational and Environmental Medicine* 56 (4), 382-387. DOI: 10.1097/jom.000000000000138 (last accessed 2016-09-21)

Yucesoy B., Johnson V.J., Lummus Z.L., Kissling G.E., Fluharty K., Gautrin D., Malo J.L., Cartier A., Boulet L.P., Sastre J., Quirce S., Germolec D.R., Tarlo S.M., Cruz M.J., Munoz X., Luster M.I., and Bernstein D.I. (2012): Genetic variants in antioxidant genes are associated with diisocyanate-induced asthma. *Toxicological Sciences* 129 (1), 166-173. DOI: 10.1093/toxsci/kfs183 (last accessed 2016-09-21)

Zeiss C.R., Kanellakes T.M., Bellone J.D., Levitz D., Pruzansky J.J., and Patterson R. (1980): Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. *Journal of*

Allergy and Clinical Immunology 65 (5), 347-352. DOI: 10.1016/0091-6749(80)90211-0 (last accessed 2016-09-21)

Zhang Z. and Evans D. (2003): Investigation of fracture properties of epoxy at low temperatures. Polymer Engineering & Science 43 (5), 1071-1080. DOI: 10.1002/pen.10091

Zheng K.C., Ariizumi M., Todoriki H., and Shinjo M. (1998): Cytokine production by splenocytes and thymocytes in mice after intranasal exposure to toluene diisocyanate. Journal of Occupational Health 40 (4), 279-284. http://joh.sanei.or.jp/pdf/E40/E40_4_05.pdf (last accessed 2016-09-21)

Zheng K.C., Nong D.X., Morioka T., Todoriki H., and Ariizumi M. (2001): Elevated interleukin-4 and interleukin-6 in rats sensitized with toluene diisocyanate. Industrial Health 39 (4), 334-339. DOI: 10.2486/indhealth.39.334 (last accessed 2016-09-21)

Ziegler C. and Kersting K. (2012): Neue Entwicklungen zum sicheren Umgang mit Epoxidharzen [New developments for the safe handling of epoxy resins]. BauPortal 5, 42-44. <http://www.bgbau.de/praev/fachinformationen/gefahrstoffe/epoxidharze/downloads/neue-entwicklung-mit-epoxidharzen> (last accessed 2016-09-29)

Zissu D., Binet S., and Limasset J.C. (1998): Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. Contact Dermatitis 39 (5), 248-251. DOI: 10.1111/j.1600-0536.1998.tb05918.x (last accessed 2016-09-21)

Zocca E., Fabbri L.M., Boschetto P., Plebani M., Masiero M., Milani G.F., Pivrotto F., and Mapp C.E. (1990): Leukotriene B4 and late asthmatic reactions induced by toluene diisocyanate. Journal of Applied Physiology 68 (4), 1576-1580. <http://jap.physiology.org/content/68/4/1576.long>

Appendix 1 Tabular Overview of Relevant Animal Data Available for the Diisocyanates

Abbreviations:

2,2'-MDI: 2,2'-methylenediphenyldiisocyanate	F: Female	IVE: Intravenous
2,4'-MDI: 2,2'-methylenediphenyl diisocyanate	FCA: Freund's Complete Adjuvant	LPF: Liquid paraffin
2,4-TDI: 4-methyl-m-phenylene diisocyanate	FULL: Full text available	MDA: 4,4'-methylenediphenyldiamine
2,6-TDI: 2-methyl-m-phenylene diisocyanate	GP: Guinea pig	MDI: 4,4'-methylenediphenyldiisocyanate
ABST: Only abstract available	GPSA Guinea pig serum albumin	M: Male
AE: Aerosol	HDI: Hexamethylene diisocyanate	MO: Mouse
AMO: Acetone/mineral oil	HMDI: 4,4'-methylenedicyclohexyl diisocyanate	MT: Mortality
AOO: Acetone/olive oil	HO: Head-only	mTMXDI: 1,3-bis(1-isocyanato-1-methylethyl)benzene
AT: Acetone	HSA: Human serum albumin	mXDI: 1,3-bis(isocyanatomethyl)benzene
BN: Brown Norway	IC: Isocyanurate	N: No
BT: Biuret	IUCL: Only IUCLID summary available	NDI: 1,5-naphthylene diisocyanate
CO: Corn oil	IDE: Intradermal	NO: Nose-only
DH: Dunkin-Hartley	IF: Inflammation	NR: Not reported
DNBE: Di-n-butyl ether	INA: Intranasal	OPH: Oropharyngeal
DSA: Dog serum albumin	INH: Inhalation	PET: Petrolatum
DU: Dust	IPDI: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	PHDI: Polymeric HDI
ESH: English smooth-hair	ITR: Intratracheal	PIPDI: Polymeric IPDI
EtAc: Ethyl acetate		PMDI: Polymeric MDI

PTDI: Polymeric TDI	SDS: Sodium dodecylsulfate	TOP: Topical
PTMEG: Polytetramethyleneether glycol	SEB: Di-n-octyl sebacic acid ester	TRIDI: 2,4,6-triisopropyl-m-phenylene diisocyanate
RA: Rat	SS: Skin sensitisation	VP: Vapour
RB: Rabbit	TDI _{mix} : TDI, mixed isomers, isomer ratio 80:20 (2,4:2,6)	WB: Whole-body
RF: Respiratory function	TDI _{uc} : TDI, unknown composition	Y: Yes
RSA: Rat serum albumin	TDA: p-Toluylene diamine	
SCU: Subcutaneous	TODI: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	
SD: Sprague-Dawley		

Table 1-1: Overview of available animal studies and results of tier 1 evaluation²⁹

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
1	GP	INH	TDIuc	Y	sex, strain						FULL: (Niewenhuis et al., 1965)	
	RB											
	RA											
2	GP	IDE	IPDI	Y	N						IUCL: (Bayer, 1968)	
3	GP	TOP	HDI	N	N						IUCL: (Bayer, 1970)	
4	GP	INH	HMDI	Y	sex, strain						IUCL: (DuPont, 1971)	
5	GP	INH	HMDI	Y	sex, strain						(DuPont, 1974)	
6	GP	IDE	MDI	Y	strain						IUCL: (Duprat et al., 1976)	
7	GP	IDE	HDI	Y	N						IUCL: (DuPont, 1977)	
8	GP	TOP	PIPDI	N	free NCO, sex						IUCL: (IBR, 1977)	
9	MO	INH	2,4-TDI	Y	N	-	-		x		FULL: (Sangha and Alarie, 1979)	
10	GP	IDE+TOP	m-XDI	Y	N						(Huntingdon, 1980)	
11	MO	TOP	MDI	Y	sex						FULL: (Tanaka, 1980)	
			2,4-TDI									
12	GP	TOP	IPDI	Y	N	TOP	IPDI				x	IUCL: (BRC, 1981)
			mTMXDI	Y	N		mTMXDI					

²⁹ Tier 1 fields are shaded grey, where criteria for tier 2 inclusion were not met. If for a given "induction" agent and route a study contained experiments with negative test results as well as experiments demonstrating effects, only the latter are presented under tier 2. Experiments with knock-out animals are not reported, since the aim of this review was to identify LOECs in healthy animals.

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference			
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)					
								Antibodies	Resp. function		Inflammation	Skin sens.	
13	GP	IDE	HDI	Y	N	-	-	x			x	FULL: (Karol et al., 1981)	
			HMDI										
			MDI										
		TOP	TDImix										
14	MO	INH	HDI	Y	N	-	-		x				FULL: (Sangha et al., 1981)
15	GP	IVE	HDI-HSA	Y	N								(Bernstein et al., 1982)
			TDI-HSA										
16	GP	IPE	HDI-HSA	Y	sex							FULL: (Chen and Bernstein, 1982)	
			TDI-HSA										
			HDI-HSA										
		SCU	HDI-HSA	Y	N								
			TDI-HSA										
17	GP	IDE	CI	Y	N	-	-	x				FULL: (Karol and Magreni, 1982)	
			IPE										
			TOE										
			HMDI										
		TOP											
18	DO	ITR	MDI	Y	sex, strains								FULL: (Patterson et al., 1982)
19	MO	INH	HDI-BT	Y	free NCO								FULL: (Weyel et al., 1982)
20	GP	IDE	HDI	Y	N								IUCL: (Bayer, 1983)
21	GP	IDE+TOP	IPDI	Y	sex								IUCL: (IBR, 1983a)
22	GP	IDE+TOP	PIPDI	N	free NCO, sex								IUCL: (IBR, 1983b)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
23	GP	INH	TDImix	Y	N	-	-	x				FULL: (Karol, 1983)
						IDE	TDImix				x	
						INH	TDI-GPSA/ TMI-GPSA		x			
24	GP	TOP	2,4-TDI	Y	sex							FULL: (Koschier et al., 1983)
25	GP	INA	TDImix	Y	N							FULL: (Tanaka et al., 1983)
26	GP	IDE	HMDI	N	N							IUCL: (Bayer, 1984a)
27	GP	IDE	IPDI	Y	N							IUCL: (Bayer, 1984b)
28	GP	TOP	HMDI	Y	N	TOP	HMDI				x	(Bio-Dynamics, 1984)
			MDI	N								
29	GP	INH	mTMXDI-GPSA	N	N							IUCL: (Bio-Research, 1984)
30	GP	IDE	MDI	Y	free NCO							FULL: (Chang and Karol, 1984)
31	GP	IDE+TOP	HDI	Y	N							FULL: (Clemmensen, 1984)
			TDImix									
32	RA	INH	2,4-TDI	Y	N	-	-			x		IUCL: (Hazleton, 1984)
33	GP	INH	HMDI	Y	N	TOP	HMDI				x	FULL: (Stadler and Karol, 1984)
	MO	TOP+INH										
34	GP	IDE+TOP	HMDI	N	N							IUCL: (Bayer, 1985)
35	GP MO	TOP	HMDI	Y	N	TOP	HMDI				x	FULL: (Stadler and Karol, 1985)
36	MO	TOP	2,4-TDI	Y	N	TOP	2,4-TDI				x	FULL: (Tominaga et al., 1985)
37	MO	INH	HMDI	Y	N	-	-		x			FULL: (Weyel and Schaffer, 1985)
			MDI									
38	MO	TOP+FCA	TDIuc	Y	N							FULL: (Gad et al., 1986)
			HMDI									

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
39	MO	INH	2,4-TDI	Y	N	-	-			x		IUCL: (Hazleton, 1986)
40	GP	IDE	IPDI	Y	N					IUCL: (University of Louisville, 1987)		
		INH		N	N							
41	MO	TOP	MDI	Y	N	TOP	MDI				x	FULL: (Tanaka et al., 1987)
			2,4-TDI									
			2,4-TDI									
42	MO	TOP	HMDI	Y	N	TOP	HMDI				x	FULL: (Thorne et al., 1987)
			HDI									
			MDI									
			TDImix									
43	GP	INH	TDImix	Y	N	INH	TDI-GPSA	x	x			FULL: (Botham et al., 1988)
44	GP	INH	TDIuc	Y	N	-	-		x			FULL: (Cibulas et al., 1988)
45	GP	IDE	MDI	Y	N					FULL: (Jin and Karol, 1988)		
46	RA	INH	HDI	Y	N	-	-			x		IUCL: (Mobay, 1988)
47	RA	INH	TDImix	Y	N	-	-			x		IUCL: (Union Carbide, 1988)/FULL: (Tyl et al., 1999)
48	GP	INH	mTMXDI	Y	N	INH	mTMXDI-GPSA	x	x	x		IUCL: (Union Carbide, 1988)
49	RA	INH	HDI	Y	N	-	-			x		IUCL: (Mobay, 1989)
50	MO	TOP	IPDI	Y	N	TOP	IPDI				x	FULL: (Stern et al., 1989)
51	RA	INH	TDImix	Y	N	-	-			x		IUCL: (Union Carbide, 1989)/FULL: (Tyl et al., 1999)
52	GP	INH	MDI	Y	N	-	-	x				FULL: (Dearman and Botham, 1990)
						IPE	MDI-GPSA					

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
53	RA MO	INH	mTMXDI	Y	N	-	-			x		IUCL: (Union Carbide, 1990)
54	RA	INH	TDImix	Y	N	-	-			x		FULL: (Hesbert et al., 1991)
55	GP	INH IDE	HDI trimer	Y	free NCO							FULL: (Pauluhn and Eben, 1991)
56	MO	TOP	HMDI	Y	N	-	-	x			x	FULL: (Dearman et al., 1992a)
			IPDI									
			MDI									
57	MO	TOP	HMDI	Y	N	TOP	HMDI	x		x	x	FULL: (Dearman et al., 1992b)
			IPDI	Y	N		IPDI					
			MDI	Y	N		MDI					
58	GP	INA	TDIuc	Y	sex							FULL: (Kalubi et al., 1992)
59	GP	IDE+TOP	m-XDI	Y	N							IUCL: (Safeparm, 1992)
60	MO	INH	mTMXDI	Y	N	-	-			x	x	IUCL: (Union Carbide, 1992)
	RA											
61	GP	IDE+TOP	IPDI	Y	N							IUCL: (Bayer, 1993)
62	GP	INH	TDIuc	Y	N	INH	TDI-GPSA	x	x	x		FULL: (Huang et al., 1993)
63	GP	INH	TDImix	Y	N	INH	TDImix			x		FULL: (Huang et al., 1993)
64	GP	INH	TDImix	Y	N	INH	TDImix	x	x			FULL: (Aoyama et al., 1994)
65	GP	IDE	MDI	Y	N							IUCL: (Bayer, 1994)
66	MO	TOP	HMDI	Y	sex							FULL: (Hilton et al., 1994)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
67	GP	IDE	MDI	Y	sex					FULL: (Pauluhn, 1994)		
		INH	TDImix									
68	GP	IDE	MDI	Y	N	INH	MDI	x	x	x	FULL: (Rattray et al., 1994)	
		TOP				TOP						
		INH				INH						
69	RA	INH	PMDI	Y	N	-	-			x	FULL: (Reuzel et al., 1994a)	
70	RA	INH	PMDI	Y	N	-	-			x	FULL: (Reuzel et al., 1994b)	
71	GP	IDE	HMDI	Y	N					IUCL: (Bayer, 1995a)		
72	GP	INH	MDI	Y	sex					IUCL: (Bayer, 1995b)		
73	GP	IDE	TDImix	Y	N					FULL: (Blaikie et al., 1995)		
74	MO	TOP	HDI	Y	N	-	-	x		x	FULL: (Hilton et al., 1995)	
			MDI									
			TDIuc									
75	RA	INH	MDI	Y	N	-	-		x	x	IUCL: (Hoymann et al., 1995)	
76	GP	INA	2,4-TDI	Y	N					FULL: (Yamada et al., 1995)		
77	GP	TOP	HDI	Y	sex, strain					FULL: (Basketter and Gerberick, 1996)		
			2,4-TDI									
78	GP	IDE	IPDI	N	N					IUCL: (Bayer, 1996a)		
79	GP	IDE	PIPDI	N	free NCO					IUCL: (Bayer, 1996b)		
		INH										
80	MO	TOP	TDIuc	Y	N	TOP	TDIuc			x	x	FULL: (Dearman et al., 1996a)
81	MO	TOP	MDI	Y	N	-	-			x		FULL: (Dearman et al., 1996b)
82	GP	INH	TDImix	Y	N	-	-		x	x		FULL: (Gagnaire et al., 1996)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
83	MO	TOP	HDI TDImix	Y	sex	TOP	HDI TDImix	x		x	x	FULL: (Karol and Kramarik, 1996)
84	GP	IDE	TDImix	Y	N							FULL: (Mapp et al., 1996)
85	GP	INA	2,4-TDI	Y	N							FULL: (Niimi et al., 1996)
86	GP	IDE+TOP	Polyisocyanate resin	Y	free NCO, sex, strain							IUCL: (NOTOX, 1996)
87	MO	INA	TDIuc	Y	N	INA TOP	TDIuc	x	x	x		FULL: (Scheerens et al., 1996)
		TOP						x	x	x	x	
88	GP	INH	TDImix	Y	N	-	-			x		FULL: (Ban et al., 1997)
89	GP	INH	TDImix	Y	N	-	-			x		FULL: (Gagnaire et al., 1997)
90	RA	INH	TDImix	Y	N	-	-			x	x	FULL: (Huffman et al., 1997)
91	GP	IDE+TOP	m-XDI	Y	N							IUCL: (Huntingdon, 1997)
92	GP	INH+IDE	PTDI	N	free NCO							FULL: (Pauluhn and Mohr, 1998)
		INH	TDImix	Y	N	INH	TDImix/TDI-GPSA	x	x	x		
93	GP	IDE	TODI	Y	N							IUCL: (Safeparm, 1998a)
94	GP	IDE+TOP	m-XDI	Y	N							IUCL: (Safeparm, 1998b)
95	MO	TOP	TDIuc	Y	N	TOP	TDIuc			x	x	FULL: (Woolhiser et al., 1998)
96	MO	INA	2,4-TDI	Y	N							FULL: (Zheng et al., 1998)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference			
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)					
								Antibodies	Resp. function		Inflammation	Skin sens.	
97	GP	TOP	HDI	Y	N	TOP	HDI					x	FULL: (Zissu et al., 1998)
			HDI-BT				HDI-BT						
			HDI-IC				HDI-IC						
			HMDI				HMDI						
			IPDI				IPDI						
			PTDI				PTDI						
			TD-IC				TD-IC						
			TDImix				TDImix						
98	RA	INH	PMDI	Y	N	-	-		x	x			FULL: (Pauluhn et al., 1999)
99	MO	TOP	TDIuc	Y	N	TOP	TDIuc	x	x	x	x		FULL: (Scheerens et al., 1999)
100	RA	INH	PMDI	Y	N	-	-			x			FULL: (Pauluhn, 2000)
101	RA	INH	HDI-IC	Y	N	-	-		x	x			FULL: (Pauluhn, 2000)
102	GP	IDE	PMDI	Y	N	INH	PMDI	x	x	x			FULL: (Pauluhn et al., 2000)
		INH											
103	MO	TOP+SDS	2,4-TDI	Y	N								FULL: (van Och et al., 2000)
104	MO	TOP	2,4-TDI	Y	N	-	-				x		FULL: (Vandebriel et al., 2000)
105	GP	INA	TDImix	Y	N	TOP	TDImix					x	FULL: (Ebino et al., 2001)
		INH											
		ITR											
		TOP											
106	MO	SCU	TDImix	Y	N	INH							FULL: (Matheson et al., 2001)
107	RA	INH	HDI-BT	Y	N	-	-		x	x			FULL: (Pauluhn and Mohr, 2001)
			HDI-IC										
108	RA	INA	2,4-TDI	Y	N								FULL: (Zheng et al., 2001)
109	MO	TOP	TDImix	Y	N	INA	TDImix						FULL: (Haag et al., 2002)
110	RA	INH	PMDI	Y	free NCO								FULL: (Kilgour et al., 2002)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
111	MO	INA	TDIuc	Y	N						FULL: (Lee et al., 2002)	
112	MO	SCU	TDImix	Y	N						FULL: (Matheson et al., 2002)	
113	RA	INH	PMDI	Y	N	-	-			x	FULL: (Pauluhn, 2002a)	
114	RA	INH	HDI-IC PMDI	Y	N	-	-			x	FULL: (Pauluhn, 2002b)	
115	MO	TOP	IPDI-IC	Y	free NCO						IUCL: (Bayer, 2003a)	
116	RA	INH	MDI	Y	N	-	-		x		IUCL: (Bayer, 2003b)	
117	MO	INA	TDIuc	Y	N						FULL: (Lee et al., 2003)	
118	GP	IDE+TOP	IPDI-IC	Y	free NCO						IUCL: (NOTOX, 2004)	
119	MO	TOP	2,4-TDI	Y	N	INA	2,4-TDI	x	x	x	FULL: (Vanoirbeek et al., 2004)	
120	RA	INH	2,4-TDI	Y	N	-	-		x	x	FULL: (Kouadio et al., 2005)	
121	MO	INH	TDImix	Y	N	INH	TDImix	x	x	x	FULL: (Matheson et al., 2005a)	
122	MO	INH	TDImix	Y	N	INH	TDImix	x	x	x	FULL: (Matheson et al., 2005b)	
123	GP	TOP	2,4-TDI	Y	N	INH	2,4-TDI	x	x	x	FULL: (Nabe et al., 2005)	
124	RA	TOP	PMDI	Y	free NCO						FULL: (Pauluhn, 2005)	
125	RA	INH TOP	PMDI	Y	free NCO						FULL: (Pauluhn et al., 2005)	
126	MO	TOP	HMDI IPDI MDI 2,4-TDI TMXDI	Y	N	TOP - TOP - TOP -	HMDI - IPDI - MDI 2,4-TDI -			x x x x x	FULL: (Plitnick et al., 2005)	

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference							
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)									
								Antibodies	Resp. function		Inflammation	Skin sens.					
127	MO	INH SCU TOP+ITR	TDImix	Y	N	TOP	TMXDI			x		FULL: (Ban et al., 2006)					
						INH	TDImix	x		x							
						ITR											
128	RA	TOP	PMDI	Y		INH	PMDI			x		FULL: (Pauluhn and Vohr, 2006)					
		INH		Y	N	-	-		x	x							
129	MO	TOP	HMDI	Y	N	-	-	-	x	x	x	x	FULL: (Selgrade et al., 2006)				
			IPDI														
			MDI														
			TDIuc														
			TMXDI														
130	MO	TOP	HMDI	Y	N	-	-	-	x	x	x	x	FULL: (Farraj et al., 2007)				
			INA											HMDI		x	
			-											-			
			INA											IPDI		x	
			-											-			
			INA											MDI		x	
			-											-			
			INA											2,4-TDI		x	
-	-																
INA	TMXDI		x														
131	MO	TOP	TDIuc	Y	N	IPE+INH	TDIuc		x	x	x	FULL: (Lim et al., 2007)					

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference				
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)						
								Antibodies	Resp. function		Inflammation	Skin sens.		
132	RA	INH	HDI-IC PHDI/PTDI	Y	N	-	-			x		FULL: (Ma-Hock et al., 2007)		
133	MO	SCU	TDImix	Y	N							FULL: (Sun et al., 2007)		
134	MO	TOP	2,4-TDI	Y	N	INA	2,4-TDI	x	x	x		FULL: (Tarkowski et al., 2007)		
135	MO	INH	HDI	Y	N	-	-				x	x	FULL: (Arts et al., 2008)	
			IPDI											
			PIPDI											
			TDImix											
		free NCO												
		TOP	HDI		N	-	-			x	x			
			IPDI		N	-	-							
PIPDI														
TDImix	free NCO													
136	RA	INH	HMDI	Y	N	-	-			x		IUCL: (Bayer, 2008a)		
137	RA	INH	IPDI	Y	N	-	-			x		IUCL: (Bayer, 2008b)		
138	MO	ITR	2,4-TDI	Y	N	-	-						FULL: (Fukuyama et al., 2008)	
		TOP												ITR
139	RA	TOP	PMDI	Y	N	INH	PMDI		x	x		FULL: (Pauluhn, 2008a)		
140	RA	TOP	PMDI	Y	N	INH	PMDI		x	x		FULL: (Pauluhn, 2008b)		
141	RA	INH	IPDI trimer	Y	N	-	-			x		IUCL: (BASF, 2009)		
142	MO	INH	HDI	Y	N	-	-					x	x	FULL: (de Jong et al., 2009)
			IPDI											
			TDImix											
		TOP	HDI											
			IPDI											
			TDImix											

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
143	RA	INA	TDIuc	Y	N							FULL: (Svensson-Elfsmark et al., 2009)
144	MO	TOP	2,4-TDI	Y	N	INA	2,4-TDI	x	x	x		FULL: (Vanoirbeek et al., 2009)
145	MO	TOP	2,4-TDI	Y	N	INA	2,4-TDI	x	x	x		FULL: (Vanoirbeek et al., 2009)
146	RA	INH	NDI	Y	N	-	-		x	x		IUCL: (Bayer, 2010a)
147	MO	TOP	TDImix	Y	N	ITR	TDImix	x		x		FULL: (Fukuyama et al., 2010)
148	MO	TOP	2,2-MDI	Y	N	-	-				x	IUCL: (Bayer, 2011)
149	MO	INH	MDI TDImix	Y	N	-	-		x	x		FULL: (Lindberg et al., 2011)
150	RA	INH	PMDI	Y	N	INH	PMDI		x	x		FULL: (Pauluhn and Poole, 2011)
151	MO	INA	2,4-TDI	Y	N							FULL: (Swierczynska-Machura et al., 2012)
152	MO	TOP	2,4-TDI	Y	N	OPH	2,4-TDI	x	x	x		FULL: (de Vooght et al., 2013)
153	MO	TOP	2,4-TDI	Y	N	OPH	2,4-TDI		x	x		FULL: (Song et al., 2013)
154	MO	TOP	TDI-Adipate TDI-PTMEG	Y	free NCO							FULL: (Woolhiser et al., 2013)
155	MO	TOP	2,4-TDI	Y	N	-	-			x		FULL: (Nayak et al., 2014)
156	RA	INH TOP+INH	TDImix	Y	N	-	-		x			FULL: (Pauluhn, 2014)
157	MO	INA	2,4-TDI	Y	N							FULL: (Swierczynska-Machura et al., 2014)
158	MO	TOP	TDIuc	Y	N	INH	TDIuc	x	x	x		FULL: (Liang et al., 2015)
159	RA	TOP	HDI	Y	N	INH	HDI		x	x		FULL: (Pauluhn, 2015)
		INH	HDI HDI/PHDI	Y	free NCO	-	-		x			
160	MO	TOP	2,4-TDI MDI	Y	N	OPH	2,4-TDI	x	x	x		FULL: (Pollaris et al., 2015)

Report ID	Species	Tier 1 "Induction"				Tier 2 "Elicitation"				Reference		
		Route	Agent	Effects observed	Missing information (screening level)	Route	Agent	Endpoint(s)				
								Antibodies	Resp. function		Inflammation	Skin sens.
161	MO	TOP	MDI	Y	N	INA	MDI			x		FULL: (Wisnewski et al., 2015)

Table 1-2: Tier 2 and tier 3 assessment of studies using the inhalation route for induction. The respective references can be identified in Table 1-1 above via the field "Report ID"

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3							
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)	Total dose LOEC (mg NCO/m ³)x h	Critical effect		
Guinea pigs																		
23	1	ESH	F	TDImix	-	-	VP	HO	Y	8	2	3	5	3	5	6	33	AB
	12									1.3						19		
	8									5	0.4					6	SS	
	12									1.3	19					RF		
33	5	ESH	M	HMDI	TOP	HMDI	AE	HO	Y	4	3	2	7	1.0	6	SS		
43	6	DH	F	TDImix	INH	TDI-GPSA	AE	NO	Y	10	5	3	5	3	52	AB		
44	7	ESH	M	TDIuc	-	-	NR	NO	Y	12	1	0.17	1	12	2	RF		

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3					Critical effect	
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)	Total dose LOEC (mg NCO/m ³)x h		
48	8	Hartley	F	mTMXDI	INH	mTMXDI-GPSA	AE	WB	Y	12	5	3	15	11	160	AB/IF/RF	
52	9	DH	F	MDI	-	-	VP	NO	Y	5	5	3	21	4	54	AB	
	10				IPE	MDI-GPSA							22				
62	11	Hartley	MF	TDIuc	INH	TDI-GPSA	VP	WB	Y	6	5	3	26	0.7	10	AB/IF/RF	
63	12	Hartley	F	TDImix	INH	TDImix	VP	WB	Y	7	5	3	21	0.4	6	IF	
64	13	Hartley	F	TDImix	INH	TDImix	VP	WB	Y	6	5	3	26	0.7	10	AB/RF	
68	14	DH	F	MDI	INH	MDI	AE	NO	Y	16	5	3	18	7	98	AB	
82	15	DH	F	TDImix	-	-	VP	WB	Y	20	1	1	1	10	10	IF/RF	
	16											2					
	17											48	3	0.4	17		RF
	18											168	8	0.17	29		
88	19	DH	F	TDImix	-	-	VP	WB	Y	5	1	1	5	10	10	IF	
	20										4	4	15				
	21										2	4	4	30			
	22										1	48	1	0.2	11		
	23										5	3	2	3	52		
89	24	DH	F	TDImix	-	-	VP	WB	Y	10	1	1	1	10	10	RF	
	25											1344	56	0.1	141		
92	26	DH	F	TDImix	INH	TDImix/TDI-GPSA	VP	NO	Y	8	1	0.25	21	66	16	AB/IF/RF	
102	27	DH	F	PMDI	INH	PMDI	AE	NO	Y	16	1	0.25	21	43	11	AB/IF/RF	
105	28	Hartley	F	TDImix	TOP	TDImix	AE	NO	Y	8	1	4	15	4	16	SS	
Mice																	
9	29	SW	M	2,4-TDI	-	-	VP	HO	Y	4	1	0.5	1	0.7	0.3	RF	
	30											1		0.5	0.5		
	31											3		0.3	0.8		

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3					
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)	Total dose LOEC (mg NCO/m ³)x h	Critical effect
14	32	SW	M	HDI	-	-	VP	HO	Y	4	1	0.5	1	1.7	0.4	RF
	1											1.1		1.1		
	3											0.7		2		
33	35	BALB/cBy	M	HMDI	TOP	HMDI	AE	NO	Y	4	3	2	7	5	33	SS
37	36	SW	M	HMDI	-	-	AE	HO	Y	4	1	4	1	5	21	RF
	37			MDI										7	26	
39	38	CD-1	MF	2,4-TDI	-	-	VP	WB	Y	240	520	6	728	0.17	544	IF/RF
53	39	CD-1	MF	mTMXDI	-	-	VP	WB	Y	20	67	6	93	1.0	435	IF
60	40	SW	M	mTMXDI	-	-	VP	HO	Y	4	1	3	1	4	12	RF
121	41	C57BL/6	F	TDImix	INH	TDImix	VP	NO	Y	5	30	4	56	0.07	8	AB/IF/RF
122	42	C57BL/6	F	TDImix	INH	TDImix	VP	HO	Y	5	1	2	1	1.7	3	AB/IF/RF
	30										4	56	0.07	8		
135	44	BALB/c	M	HDI	-	-	VP	NO	Y	6	3	0.75	5	7	8	IF
	45											1.5			16	
	46											3			33	
	47											6			66	
	48											0.75			4	
	49			1.5			7									
	50			3			15									
	51			6			30									
	52			0.75			8									
	53			1.5			16									
	54			3			32									
55	6	64														
142	56	BALB/c	M	HDI	-	-	VP	NO	Y	6	3	0.8	3	4	8	IF

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3				Critical effect		
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)		Total dose LOEC (mg NCO/m ³)x h	
	57											1.5			17		
	58											2.0			22		
	59											6.0			67		
	60											0.8			6		
	61			IPDI								1.5	3		13		
	62											2.0				17	
	63											6.0			51		
	64											0.8	4		8		
	65			TDImix								1.5				16	
	66											2.0				22	
	67											6.0				65	
149	68	C57Bl6/6J	M		MDI	-	-	AE	HO	Y	8	5	1	5	4	10	IF
	69			TDImix	VP			0.5							3		
Rats																	
32	70	SD	MF	2,4-TDI	-	-	VP	WB	Y	126	565	6	791	0.17	591	IF/RF	
46	71	F344	MF	HDI	-	-	VP	WB	Y	40	65	6	91	0.03	14	IF	
47	72	SD	MF	TDImix	-	-	VP	WB	Y	25	10	6	16	0.07	4	IF	
49	73	F344	MF	HDI	-	-	VP	WB	Y	60	520	6	728	0.02	54	IF	
51	74	SD	MF	TDImix	-	-	VP	WB	Y	28	50	6	70	0.07	21	IF	
53	75	SD	MF	mTMXDI	-	-	VP	WB	Y	20	67	6	93	1.0	435	IF	
54	76	SD	M	TDImix	-	-	VP	WB	Y	10	1	4	1	1	4	IF	
60	77	SD	M	mTMXDI	-	-	VP	HO	Y	4	1	3	1	2	6	RF	
69	78	Wistar	MF	PMDI	-	-	AE	WB	Y	20	260	6	364	0,3	484	IF	
	79									120	520		728		967		
70	80	Wistar	MF	PMDI	-	-	AE	WB	Y	20	10	6	14	1.5	88	IF	

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3						
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)	Total dose LOEC (mg NCO/m ³)x h	Critical effect	
	81									40	10			4	254	MT	
	82									30	65			2	842	IF	
	83									60	65	91		1	480	IF	
75	84	Wistar	F	MDI	-	-	AE	WB	Y	8	436	17	610	0.08	572	RF	
	12																
	20									65	98						IF
										260	365						
										436	371						
	80									520	728						
90	90	SD	M	TDImix	-	-	AE	WB	Y	6	1	4	1	7	28	IF/RF	
98	91	Wistar	M	PMDI	-	-	AE	NO	Y	6	1	2.5	1	5	12	RF	
	92		MF							34	14	6	14	1.0	87	IF	
100	93	Wistar	M	PMDI	-	-	AE	NO	Y	6	1	6	8	2,5	15	IF/RF	
101	94	Wistar	F	HDI-IC	-	-	AE	NO	Y	30	1	6	1	12	72	IF/RF	
107	95	Wistar	MF	HDI-BT	-	-	AE	NO	Y	20	15	6	21	3	297	IF	
	65										91		1287		IF/RF		
	97		M	HDI-IC							10		14	4	215	IF	
	98		MF								15		21	3	297	IF	
	99										65		91		1287	IF/RF	
113	100	Wistar	F	PMDI	-	-	AE	NO	Y	41	14	6	18	4	336	IF	

Report ID	Experiment ID	Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Tier 2				Tier 3				Critical effect				
							Physical state	Inhalation type	Neg. control	Animals/group	No. of exposures	Hours/exposure	Total days	LOEC (mg NCO/m ³)		Total dose LOEC (mg NCO/m ³)x h			
114	101	Wistar	F	HDI-IC	-	-	AE	NO	Y	6	1	6	7	0.9	5	IF			
	102		M	PMDI	-	-	AE	NO	Y	6	1	0.38	1	18	7				
	103											0.75		8	6				
	104											1.5		4	6				
	105											3		2	6				
	106											6		1	6				
	107											6		1	6		7	0.2	1.3
	108											F		42	19		6	19	4
116	109	Wistar	MF	MDI	-	-	AE	NO	Y	5	1	1	1	752	752	RF			
120	110	Wistar	F	2,4-TDI	-	-	VP	WB	Y	10	5	4	5	1.3	27	IF/RF			
128	111	Wistar	M	PMDI	-	-	AE	NO	Y	6	1	6	1	5	28	IF			
132	112	Wistar	M	HDI-IC	-	-	AE	NO	Y	6	1	6	7	3	19	IF			
	113			PHDI/PTDI										0.5	3				
136	114	Wistar	MF	HMDI	-	-	AE	NO	Y	20	65	6	91	1.0	375	IF			
137	115	Wistar	MF	IPDI	-	-	AE	NO	Y	20	65	6	91	0.4	162	IF			
141	116	Wistar	MF	IPDI-IC	-	-	AE	NO	Y	20	65	6	91	3	1012	IF			
146	117	Wistar	MF	NDI	-	-	AE	NO	Y	10	65	6	91	0.4	157	IF			
150	118	BN	M	PMDI	INH	PMDI	AE	NO	Y	8	5	0.17	65	30	25	IF/RF			
	119											6		5	140		RF		
	120											0.17		291	243				
156	121	BN	M	TDImix	-	-	AE	HO	Y	4	1	0,5	1	2	1.2	RF			
159	122	Wistar	M	HDI	-	-	VP	NO	Y	5-6	1	0.5	1	2	1	RF			
	123						AE							54	27	RF			

Table 1-3: Tier 2 and tier 3 assessment of studies using topical induction, in which a positive sensitisation result was obtained³⁰. The respective references can be identified in Table 1-1 above via the field "Report ID".

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2					Tier 3								
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			Endpoint	
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)		
Guinea pigs																				
12	1	Hartley	MF	IPDI	TOP	IPDI	10	498	OO	N	Y	1	30	0.025	NR	1.5	NR	1.5	SS	
	2			mTMXDI		mTMXDI														
13	3	ESH	F	TDImix	-	-	6	300	OO	N	Y	1	60	0.05	NR	10	NR	10	AB	
					4	TOP													TDImix	8
17	5	ESH	F	HMDI	-	-	6	300	-	N	Y	2	343	0.1	NR	114	NR	114	228	AB
					6	IDE						HMDI-GPSA							12	SS
					7	INH						HMDI							12	RF
					8	TOP						HMDI							12	SS
28	9	Hartley	MF	HMDI	TOP	HMDI	15	390	AOO	Y	Y	3	1.7	0.05	NR	0.17	NR	0.5	SS	
35	10	ESH	M	HMDI	TOP	HMDI	8	350	AT	N	Y	1	0.3	0.1	NR	0.09	NR	0.09	SS	
68	11	DH	F	MDI	INH	MDI	8	300	CO	N	Y	1	44	0.4	NR	59	NR	59	RF	

³⁰ Experiments with knock-out animals are not reported, since the aim of this review was to identify LOECs in healthy animals.

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2					Tier 3							
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)	Endpoint
	12				TOP														SS
97	13	DH	F	HDI	TOP	HDI	20	350 ³¹	PET	Y	Y	1	5	0.5	NR	7	NR	7	SS
	14			HDI-BT		HDI-BT										123		176	
	15			HDI-IC		HDI-IC										255		365	
	16			HMDI		HMDI										7		10	
	17			IPDI		IPDI										20		28	
	18			PTDI		PTDI										76		109	
	19			TDI-IC		TDI-IC										4		6	
	20			TDImix		TDImix										30		43	
	105			-		Hartley										F		TDImix	
123	-	Hartley	M	2,4-TDI	INH	2,4-TDI	20-24	NR	EA	N	Y								
Mice																			
35	21	BALB/cBy	M	HMDI	TOP	HMDI	8	30	AT	N	Y	1	0.03	0.1	NR	0.09	NR	0.09	SS
36	-	ICR	M	2,4-TDI	TOP	2,4-TDI	5	NR	EA	N	Y								
41	-	C57BL/6	M	MDI	TOP	MDI	7	NR	EA	N	Y								
						2,4-TDI													

³¹ Only average body weight was reported.

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2					Tier 3							
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			Endpoint
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)	
				2,4-TDI		MDI 2,4-TDI													
42	22 23 24 25	BALB/cBy	M	HDI HMDI MDI TDImix	TOP	HDI HMDI MDI TDImix	4	NR ³²	AT	N	Y	1	NR ¹	0.1	NR	0.05 0.10 0.2 1.04	NR	0.05 0.10 0.2 1.04	SS
50	26	B6C3F1	F	IPDI	TOP	IPDI	4	20	AOO	N	Y	5	10.6	0.02	NR	4	NR	20	SS
56	-	BALB/c	F	HMDI IPDI MDI	-	-	4	NR	AOO	N	Y								
57	-	BALB/c	F	HMDI IPDI MDI	TOP	HMDI IPDI MDI	4-10	NR	AOO	N	Y								
74	-	BALB/c	F	HDI MDI TDIuc	-	-	4-6	NR	AOO	N	Y								

³² Not reported, but no reason for exclusion since dose levels were provided on a per body weight basis (estimated from Fig. 2 in (Thorne et al., 1987))

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2					Tier 3							
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)	Endpoint
80	-	BALB/c	F	TDIuc	TOP	TDIuc	5	NR	AOO	N	Y								
81	-	BALB/c	F	MDI	-	-	20	NR	AOO	N	N								
87	-	BALB/c	M	TDIuc	INA TOP	TDIuc	6-10	NR	AOO	N	Y								
95	27	B6C3F1	F	TDIuc	TOP	TDIuc	5	26	AT	N	Y	4	0.6	0.05	NR	1.2	NR	4.6	IF/SS
99	-	BALB/c	M	TDIuc	TOP	TDIuc	4	NR	AOO	N	Y								
104	-	BALB/c	MF	2,4-TDI	-	-	3-5	NR	AOO	N	Y								
109	-	BALB/c	M	TDImix	INA	TDImix	6	NR	AOO	N	Y								
119	28 29	BALB/c	M	2,4-TDI	INA	2,4-TDI	6	20	AOO	N	Y	1 3	6 1.8	0.04	NR	12 4	NR	12 11	AB/IF/RF
126	-	BALB/c	F	HMDI	TOP	HMDI	5-6	NR	AOO	N	Y								
				IPDI	-	-													
				IPDI	TOP	IPDI													
				MDI	-	-													
				2,4-TDI	TOP	MDI													
				TMXDI		MDI													
CBA/JHsd	TMXDI	-	-																
	TMXDI	-	-																
129	-	BALB/c	F	HMDI	-	-	6	NR	AOO	N	Y								
				IPDI															
				MDI															
				TDIuc															

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2				Tier 3								
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)	Endpoint
				TMXDI															
130	-	BALB/c	F	HMDI	-	-	6	NR	AOO	N	Y								
					INA	HMDI													
				IPDI	-	-													
					INA	IPDI													
				MDI	-	-													
					INA	MDI													
	2,4-TDI	-	-																
		INA	2,4-TDI																
		TMXDI	-	-															
			INA	TMXDI															
131	-	BALB/c	F	TDIuc	IPE/INH	TDIuc	3-5	NR	AMO	N	Y								
134	30	BALB/c	M	2,4-TDI	INA	2,4-TDI	17-23	20	AOO	N	Y	2	1.8	0.04	NR	4	NR	7	AB/IF/RF
135	-	BALB/c	M	HDI	TOP	HDI	6	NR	AOO	N	Y								
				IPDI		IPDI													
				TDImix		TDImix													
138	-	BALB/c	F	2,4-TDI	-	-	8	NR	AOO	N	Y								
					ITR	2,4-TDI													
142	-	BALB/c	M	HDI	-	-	3	NR	AOO	N	Y								
				IPDI															
				TDImix															
144	31	BALB/c	M	2,4-TDI	INA	2,4-TDI	4-10	20	AOO	N	Y	2	1.8	0.04	NR	4	NR	7	AB/IF/RF

Report ID	Experiment ID	Strain	Sex	"Induction" agent	"Elicitation" route	"Elicitation" agent	Tier 2					Tier 3							
							No. animals/group	Body wt. (g, max. or Mean + 2 SEM)	Vehicle	Occlusive	Negative control	No. of applications	Concentration (g NCO/L)	Volume (mL)	Area (cm ²)	LOEC			
																Dose NCO per exposure (mg/kg bw)	Area dose NCO per exposure (mg/cm ²)	Total dose received (mg/kg bw)	Endpoint
145	32	BALB/c	M	2,4-TDI	INA	2,4-TDI	4-10	20	AOO	N	Y	2	1.8	0.04	NR	4	NR	7	AB/IF/RF
147	-	BALB/c	F	TDImix	ITR	TDImix	6	NR	AOO	N	Y								
148	33	NMRI	F	2,2-MDI	-	-	6	32	AOO	N	Y	3	9	0.05	NR	14	NR	42	IF/SS
152	34	BALB/c	M	2,4-TDI	OPH	2,4-TDI	7-11	20	AOO	N	Y	2	1.8	0.04	NR	4	NR	7	AB/IF/RF
155	-	BALB/c	M	2,4-TDI	-	-	5	NR	AT	N	Y								
158	35	BALB/c	M	TDIuc	INH	TDIuc	6-8	20	AOO	N	Y	2	1.8	0.04	NR	4	NR	7	AB/IF/RF
160	-	C57Bl/6	M	MDI 2,4-TDI	OPH	2,4-TDI	7-10	NR	AOO	N	Y								
161	-	BALB/c	F	MDI	INA	MDI	18	NR	AT	N	Y								
Rats																			
128	36	BN	M	PMDI	INH	PMDI	8	240	-	N	Y	2	342	0.04	12.6	203	47	405	IF
139	37	BN	M	PMDI	INH	PMDI	8	245	AOO	N	Y	2	NR	0.003	0.8	13	4	26	IF/RF
140	38 39	BN	M	PMDI	INH	PMDI	8	250	AOO SEB	N	Y	2	220	0.2	10	55	1.37	110	IF/RF
159	40	BN	M	HDI	INH	HDI	8	240	AOO	N	Y	2	4	0.1	NR	4	NR	9	RF

Appendix 2 Overview of available human case reports and case studies

Table 2-1: Isocyanate-related cases documented in the literature (non-comprehensive)

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Swensson et al., 1955)	Case report (Sweden)	1953	Y	Patients with symptoms from the respiratory passages	3	1: Spray-painting with polyisocyanate lacquer 2: Painting with polyisocyanate plastic 3: Spray-painting, brush-painting with plastic lacquer	Painting	TDI	1: Asthmatic bronchitis 2: Asthmatic symptoms/attacks 3: Not specified (severe cough, pressure on the chest)	Y	N/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Jennings and Gower, 1963)	Case report (UK)	1962	Y	Subjects with asthmatic and purpuric symptoms	2	1: Inspector working in a process for insulating refrigerator units 2: Electrical engineer working in vicinity of the TDI process	Not specified (large factory that had introduced a polymerising process based on TDI)	TDI	Thrombocytopenic purpura	Y	N/N 2: A	Subject 1 was exposed to an unusually heavy exposure of TDI. Subject 2 was exposed to a high concentration of TDI vapour owing to the breakage of a pipe.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Williamson, 1965)	Case report (UK)	1962/1963	Y	Subjects having symptoms suggestive of diisocyanate sensitisation	6*	1: Engineer# 2/3/4/: laboratory assistant used TDI to make plastic foams 5: fitter dismantling equipment which was used in the making of foam	Chemical industry (Department in which isocyanates are handled in the course of developmental and experimental work on urethane foams and surface coatings)	TDI	TDI sensitization	Y	Y/Y 1: A	*: One worker was not accepted as a case of sensitisation as his symptoms were caused by anxiety as the main factor. #: 1 was known to be sensitised to TDI. Re-exposure occurred unintentionally due to an accident.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(O'Brien et al., 1979)	Worker examination by occupational-type bronchial provocation test for sensitivity to TDI (England)	Not specified	Y	Subjects handling diisocyanates and with respiratory disease	24	Not specified	Not specified	TDI, MDI, HDI	Asthma	N	N/N	Testing of sensitised subjects. Almost no data about the case histories
(Butcher et al., 1979)	Study to determine the mechanisms of bronchial hyperreactivity ("sensitivity") to TDI (USA)	Not specified	N	Workers with a history of sensitivity to TDI	28*	Workers in a TDI-producing plant	TDI production	TDI	Asthmatic reactions	N	N/N	*: 28 subjects were evaluated. 5 workers were defined as non-reactors by the inhalation challenge.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Lidén, 1980)	Case report (Sweden)	Not specified	N	Subject having contact dermatitis	1	Molder/preparing molds	Lymphoma clinic	MDI	Contact dermatitis	Y	N/Y	
(Zeiss et al., 1980)	Case report (USA)	1978	Y	Workers with respiratory symptoms	2	1: Production supervisor 2: Welder, exposed continuously to polyurethane foam fumes	Plant; not further specified	MDI	1: Occupational asthma 2.: Hypersensitivity pneumonitis	Y	N/N	
(Butcher et al., 1980)	Radioallergosorbent testing of TDI-reactive individuals (USA)	Not specified	Y	Subjects shown to react to provocative inhalation challenge with TDI	26	Not specified	Not specified	TDI	Asthma	N	N/N	Testing of sensitized subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Lob and Boillat, 1981)	Case report (France)	Not specified	N	Subjects diagnosed with asthma on MDI	4	Welding of polyurethane belts	Not specified	MDI	Asthma	Not determinable*	Not determinable*	*Publication in French. Data were extracted from the English abstract
(Israeli et al., 1981)	Case report (Israel)	not specified	Y	Workers showing allergic and non-allergic skin reactions	11	Workers involved in the production of polyurethane-coated glass bottles	Manufacture of glass bottles	DMDI	Skin lesions	N	N/N	
(Clarke and Aldons, 1981)	Case report (Australia)	1976	Y	Subject having developed severe asthma	1	Spray-painter	Panel beating industry	IPDI	Occupational asthma	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Friedman, 1982)	Case report (USA)	Not specified	Y	Man who received prolonged exposure to MDI several times	1	Manufacturing engineer	Not specified	MDI	Hypersensitivity pneumonitis and pleuritis progressing to fibrosing alveolitis	N	N/N	Data were extracted from an abstract.
(Burge, 1982)	Inhalative challenge tests in exposed workers (England)	Not specified	N	Workers with respiratory symptoms to TDI or MDI	51*, 40#	TDI: Printers and laminators of flexible packaging MDI: not specified	Not specified	TDI, MDI	Occupational asthma	N	Y/N	* 51 workers with respiratory symptoms to TDI were evaluated. 30 reacted. # 40 workers with respiratory symptoms to MDI were evaluated. 24 reacted.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Hoffman, 1982)	Case report (USA)	Not specified	N	Subject who developed a pruritic, erythematous dermatitis	1	Engineering aid in the manufacture of a new electronic part	Electronics industry	MDI	Allergic contact dermatitis	Y	N/N	
(White et al., 1983)	Case report (UK)	Not specified	Y	Individuals with cutaneous problems	7*	Operatives working with polyurethane resin	Factory making car badges	DMDI	Sensitisation/allergy to DMDI	Y	N/Y	*: 7 subjects were evaluated. 2 out of this 7 operatives were allergic to DMDI. None of the operators complained of respiratory troubles associated

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												with resin use.
(Malo et al., 1983)	Case report (Canada)	Not specified	Y	Subject with a history of shortness of breath, wheezing, malaise and chills	1	Foreman in a garage where painting was done using a polyisocyanate activator	Not specified	HDI	Combined alveolitis and asthma	N	N/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Diller and Herbert, 1983)	Retrospective analysis (Germany)	1965-1979	Y	Workers involved with MDI	109*	MDI-workers	MDI production	MDI	Chronic obstructive bronchial disease, contact dermatitis	Y	N/N	*: 109 MDI-workers were evaluated initially. 8 were diagnosed with chronic obstructive bronchial disease and 3 with contact dermatitis.
(Innocenti and Paggiaro, 1983)	Case report (Italy)	*	*	*	1	*	*	MDI	Occupational asthma	*	*	Publication in Italian. Data were extracted from the English abstract. *: Not

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												accessible due to Italian language.
(Baur et al., 1984)	Case report (Germany)	Approx. 1981	Y	Patient having symptoms of hypersensitivity pneumonitis	1	Worker in packing and shipping department, occasionally engaged in spraying a mixture of MDI and polyol to produce polyurethane foam	Automobile equipment firm	MDI	Hypersensitivity pneumonitis	Y	Y/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Chang and Karol, 1984)	Case report (USA)	1980, 1981, 1982	Y	Patient showing symptoms of severe asthma	1	Grain elevator operator/repairman cutting polyurethane plate made of MDI	Not specified	MDI	Occupational asthma	Y	N/N	
(Laitinen et al., 1984)	Case report (Finland)	Not specified	N	Patients having developed asthma and/or alveolitis	2	Paining, insulating	Not specified	HDI, MDI	Asthma, alveolitis	N	N/N	Publication in Finnish. Data were extracted from the English abstract.
(Mapp et al., 1985)	Mechanistic challenge study in subjects sensitized	1983	Y	Subjects exhibiting a late asthmatic response after TDI	6	Not specified	Not specified	TDI	Asthma	Y	N/N	Testing of sensitized subjects. Almost no data about the case

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	to TDI (Italy/England)			exposure								histories
(Johnson et al., 1985)	Case-control study (Canada)	1981	Y	Workers having respiratory symptoms	78 (372) *	Workers handling PepSet, a chemical binding system containing MDI	Iron and steel foundry	MDI	Asthma	Y#	Y/N	*: 78 workers were examined. 12 were diagnosed with asthma. 372 railway yard repair workers, representing 95 % of the work force, served as controls. #:

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												Calculable from data given in the publication
(Mapp et al., 1985)	Case reports (Italy)	Not specified	N	Workers who developed asthmatic symptoms	2	Injectors of MDI in the shoe-sole	Gym-shoe factory	MDI	1: Asthma and hypersensitivity pneumonitis 2: Asthma	Y	N/N	
(Banks et al., 1986)	Case report (USA)	Approx. 1985	N	Patient with a persuasive history of respiratory illness	1	Technical representative/exposed while unloading a railroad tank car containing MDI and further work-related intermittent	Chemical industry	MDI	Occupational asthma	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						exposure						
(Moller et al., 1986)	Case report (Not specified)	Not specified	Y	Patient having persistend asthma for 12 years after a single massive exposure to TDI	1	Not specified	Not specified	TDI	Asthma	Y	N/Y A (single massive exposure)	Data were extracted from an abstract.
(Singer and Scott, 1987)	Case report (USA)	Not specified	Y	Wharf workers experiencin g amongst others difficulty breathing	3	Wharf workers	Wharf	TDI	Continuing decrement in mental function	Y	N/Y A	The subjects were accidentally exposed during the unloading of a leaking drum filled with TDI

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Erban, 1987)	Case report (Germany)	1985	Y	Workers with respiratory symptoms	4	Core making, sand mixing and fettling associated with the Cold-Box process	Iron foundry	MDI#	Asthma bronchiale due to contact with isocyanates	Y	Y/N	#: Erban 1988 appears to be the same publication as this one, although in another language. In Erban 1988 MDI is specifically mentioned while in Erban 1987 only reference to IC (isocyanates) is made.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Boschetto et al., 1987)	Study on the inhibitive effect of prednisone on late asthmatic reactions and airway inflammation induced by TDI in sensitised subjects (Italy)	Not specified	Y	Subjects with previously documented late asthmatic reactions	8	Not specified	Not specified	TDI	Asthmatic reactions	N	N/N	Testing of sensitised subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Banks and Rando, 1988)	Case report (USA)	1974, 1985, 1987	Y	Patient having TDI induced asthma	1	Maintenance worker in a chemical plant	Chemical industry	TDI	Isocyanate induced Asthma	Y	N/N A (this peak exposure lead to onset of symptoms of asthma)	No hyperresponsiveness to challenge testing in 1985 (after 11 years of absence to TDI), positive in 1974 (after accident) and 1987 (after return to work with TDI).

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Fabbri et al., 1988)	Case report (Italy)	1980, 1986	Y	Patient diagnosed of asthma induced by TDI	1	Car painter	Self-employed	TDI	Death after an asthma attack	Y	Y/Y	The subject was recommended to cease working with isocyanates after diagnosis of asthma induced by TDI in 1980. Nevertheless he continued under usage of antiasthmatic drugs. He died 1986 within 1 hour after the second exposure to

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												a new kind of polyurethane paint in the workplace.
(Innocenti et al., 1988)	Challenge study examining cross-reaction between TDI and MDI (Italy)	Not specified	Y	Subjects having developed asthma to TDI	25	Workers in furniture industry handling polyurethane varnishes catalysed with TDI	Furniture industry	TDI	Occupational asthma	N	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Cvitanovic et al., 1989)	Case report (Yugoslavia)	Not specified	N	Patients with an unequivocal history of professional asthma	8	1: Employee in polyurethane foam car seat manufacture 3: Shoemaker 2,4,5, 6,7,8: Workers in shoemaking factory	Shoemaking factory (7); Polyurethane foam car seat factory (1)	TDI, MDI, HDI	Occupational asthma	Y	Y/Y	
(Cartier et al., 1989)	Assessment of specific IgE and IgG antibodies in workers	1984 to 1987	N	Workers with possible occupational asthma caused by isocyanate	62*	Workers in foam industry (TDI), spray painters (HDI/MDI),	Foam industry, secondary industries were isocyanate	HDI, MDI, TDI	Occupational asthma	Y	N/Y#	*: 62 subjects were evaluated. Specific inhalation challenges

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	with possible occupational asthma. (Canada)			s		various (MDI)	es were used but not manufactured					were positive in 29 subjects. #: For some of the preparations that the workers were exposed to, not all
(Malo et al., 1989)	Case reports (Canada)	Not specified	Y	Two subjects showing respiratory symptoms	2	Not specified	Not specified	MDI	Occupational asthma	Y	N/N	Almost no data on the case histories
(Banks et al., 1989)	Group-based report (USA)	1974-1988	N	Subjects with a diagnosis of probable isocyanate-induced	63*	Worker involved in the production of polyurethane	Manufacture of TDI, TDI foam manufacturing,	TDI	TDI-induced asthma	Y	N/N	*: 63 workers were evaluated. 30 were diagnosed

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
				asthma		e foam	refrigerator manufacturing facilities					with TDI-induced asthma.
(Nozawa et al., 1989)	Case report (Japan)	Not specified	N	Subject complaining of nocturnal dyspnea and dry cough	1	Worker in a paint processing plant	Paint processing plant	TDI	Hypersensitivity pneumonitis due to isocyanates	Y	N/N	Publication in Japanese. Data were extracted from the English abstract.
(Sales and Kennedy, 1990) and	Case report (USA)	Not specified	Y	Patient with symptoms of noncardiac chest pain probably secondary to pleuritis	1	Worker making award placques with a polyurethane coating resin containing MDI	Not specified	MDI	Isocyanate-induced Asthma	Y	N/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Banks et al., 1990)	Case report (USA)	1982, 1983, 1984, 1985, 1986	Y	Workers having respiratory complaints	6	1, 2, 3, 5: Workers manufacturing polyurethane foam 4: Research technician 6: Worker in the shipping department ; Later all six worked in areas with negligible/no exposure to TDI	Two plants producing polyurethane foam	TDI	TDI-induced occupational asthma	Y	Y/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Reh and Lushniak, 1984)	Health hazard evaluation report (USA)	1987	Y	Workers with respiratory symptoms consistent with asthma	13	Workers performing routine (i.e. waxing of former conveyor belt) and non-routine (unplugging jammed conveyors, repairs, adjustments) maintenance tasks	Company manufacturing waferboards	MDI	Occupational asthma (12 cases) and hypersensitivity pneumonitis (1 case)	Y	Y/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Patterson et al., 1990)	Case report (USA)	Not specified	Y	Patient having amongst others bilateral pleuritic chest pain and hemoptysis	1	Spray-painter spraying isocyanate-containing paint onto warm metal	Paint shop	HDI, another isocyanate (possibly TDI)	Hemorrhagic pneumonitis	N	N/N	
(Paggiaro et al., 1990)	Evaluation of the morphologic basis of the different outcomes of TDI asthma after quitting occupational	Not specified	Y	Patients with TDI asthma	10	Not specified	Not specified	TDI	Asthma	N	N/N	Testing of sensitised subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	exposure (Italy)											
(Dietemann-Molard et al., 1991)	Case report (France)	Approx. 1990/1991	N	Patient having bronchospasms after burning polyurethane packs and an immediate asthmatic reaction while working with polyurethane foam	1	Task at work: Burning polyurethane packs Task at home: insulating a window/drilling dry polyurethane foam Tasks unspecified to a location: painting cars with isocyanate-containing	Industry: not specified Home-use	MDI, TDI	Immediate bronchial hyperreactivity	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Perrin et al., 1991)	Study reassessing temporal patterns of bronchial obstruction after exposure to diisocyanates (Canada/USA)	1986-1989	Y	Subjects that were referred for investigation of occupational asthma and underwent specific inhalation challenges with positive results	23	paints 6 foam industry workers, 10 spray painters, 7 employees in various industries (plastics, foundries)	Foam industry, various industries	TDI, HDI, MDI	Occupational asthma	Y	Y/Y*	*: Given for the HDI formulation, not for the TDI oder MDI formulations that were used by the workers
(Finotto et al., 1991)	Study of blood parameters of subjects sensitised	Not specified	Y	Subjects, previously shown to develop a dual or late asthmatic	10	Not specified	Not specified	TDI	Occupational asthma	N	N/N	Testing of sensitised subjects. Almost no data about the case

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	to TDI (Italy)			reaction after inhaling TDI								histories
(Park et al., 1992)	Case report (South Korea)	Not specified	N	Employees complaining about work-related respiratory symptoms	23*	Paint mixers and spray painters	Zipper factory	TDI	Asthma	Y #	N/N	*: 23 subjects were evaluated. 3 of them were diagnosed with asthma. #: given for the 3 asthmatic subjects
(Vandenplas et al., 1992a)	Case report (Canada)	Not specified	Y	Workers having asthma	2	Wood-roof maintenance workers brushing/rolling	Wood-roof maintenance	TDI	Occupational asthma	Y	N/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						lacquers/varnishes containing TDI						
(Bentley et al., 1992)	Case-control study of activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma (Italy/England)	Not specified	Y	Patients with isocyanate-induced asthma	9 (12)*	Not specified	Not specified	TDI, MDI	Occupational asthma	Y	N/N	*: Nine occupationally sensitised subjects and 12 healthy non-atopic control subjects were tested. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Akimoto et al., 1992)	Case report (Japan)	1990	Y	Man with dry cough and exertional dyspnea	1	Handling paint spray containing isocyanates	Not specified	TDI, MDI	Hypersensitivity pneumonitis	Y	N/N	Publication in Japanese. Data were extracted from the English abstract.
(Lenaerts-Langanke, 1992)	Cross-sectional study (Germany)	1986	Y	Miners who were exposed to MDI and showed symptoms of work-related shortness to breath	216*	Miners working in rock consolidation with MDI	Coal mining	MDI	Specific bronchial hyperresponsiveness to MDI (4), isocyanate asthma (2)	N	N/Y	* 216 miners were evaluated. 6 were diagnosed with specific bronchial hyperresponsiveness to MDI or isocyanate asthma.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Czuppon et al., 1992)	Inhalative challenge test and serum examination (Germany)	Not specified	N	Workers with suspected asthma	10	Not specified	Not specified	TDI	Significant change in the chromatographic profile of the serum proteins	N	N/N	Testing of sensitised subjects. Almost no data about the case histories.
(Vandenplas et al., 1992b)	Evaluation of closed-circuit methodology for inhalation challenge tests (Canada)	Not specified	N	Consecutive subjects suspected of having isocyanate-induced asthma	20*	Not specified	Not specified	HDI, MDI, TDI	Occupational asthma	Y	N/N	* 20 workers were evaluated. 6 reacted.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Bruynzeel and van der Wegen-Keijser, 1993)	Case report (The Netherlands)	Not specified	Y	Patient showing symptoms of dermatitis	1	Cast technician	Hospital	MDI	Occupational allergic contact dermatitis	Y	N/N	
(Vandenplas et al., 1993a)	Inhalation challenge study on workers with possible occupational asthma (Canada)	Not specified	N	Workers with possible occupational asthma	20*	Workers exposed to spray paints	Not specified	HDI	Occupational asthma	Y	N/Y	*: 20 subjects were examined by specific inhalation challenges. A positive asthmatic reaction was found in 10 of the 20 subjects.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Vandenplas et al., 1993b)	Inhalation challenge study in workers having respiratory symptoms (USA/Canada)	Not specified	N	Subjects complaining of respiratory and generally symptoms related to workplace exposure	8*	1: Maintenance mechanic 2: Production line welder 3: Quality control laboratory 4: Electrician 5: Industrial mechanic 6: Production supervisor 7: Cleaning 8: Casual	Plant where a resin based on MDI was used in the manufacture of woodboard chips	MDI	Hypersensitivity pneumonitis	Y	Y/Y	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Calcagni et al., 1993)	Case-control study examining eosinophilia in induced sputum after asthmatic reactions to isocyanates in sensitised subjects (Italy)	Not specified	Y	Subjects with occupational asthma.	7 (3)*	Not specified	Not specified	TDI, MDI	Occupational asthma	N	N/N	*: Seven subjects with occupational asthma induced by TDI or MDI and 3 control subjects never exposed to isocyanates, were examined. Data were extracted from an abstract.
(Nemery and Lenaerts, 1993)	Case report (Belgium)	Not specified	N	Patient claiming compensation for bronchial	1	Surface worker in a coalmine involved in polyurethan	Coal mining	MDI	Occupational asthma	N	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
				asthma		e rock consolidation						
(Maestrelli et al., 1994a)	Case-control study of sputum eosinophilia after asthmatic responses induced by isocyanates in sensitized subjects (Italy)	Not specified	N	Subjects with occupational asthma induced by TDI or MDI	9 (4)*	Not specified	Not specified	MDI, TDI	Occupational asthma	N	N/N	Nine subjects with occupational asthma induced by TDI or MDI and 4 control subjects, never exposed to isocyanates, were examined. Testing of sensitised subjects. Almost no

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												data about the case histories
(Maestrelli et al., 1994b)	Study examining CD8 T-cell clones in bronchial mucosa of patients with asthma induced by TDI (Italy)	Not specified	Y	Subjects having occupational asthma	2	Exposure to polyurethane paint	Not specified	TDI	Occupational asthma	N	N/N	Testing of sensitised subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Baur, 1995)	Case report (Germany)	not specified	N	Patients suspected of having isocyanate-induced hypersensitivity pneumonitis.	14	1, 3, 10, 12, 14: Foam production 2, 8, 9: Paint spraying 4: Plastic welding 5, 11: Adhesive application 6, 7, 13: Injection molding	Polyurethane foam production, Injection molding in foundries; paint spraying; further work in various other industrial branches	MDI, TDI, HDI, TDA/TIPHP (in patient number four)	Hypersensitivity pneumonitis	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Lemière et al., 1996)	Study on the outcome of specific bronchial responsiveness to occupational agents after removal from exposure (Canada/USA)	Not specified	Y	Subjects with occupational asthma	15	Not specified	Not specified	MDI, TDI, HDI	Occupational asthma	Y	N/N	Testing of sensitised subjects. Almost no data about the case histories
(Carino et al., 1997)	Case report (Italy)	1986, 1992	Y	Subject with occupational asthma	1	Worker in mold and core processing where resins containing	Steel foundry	MDI	Occupational asthma (1986) followed by fatal asthma attack (1992)	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						MDI were used						
(Kanerva et al., 1999)	Case report (Finland)	Not specified	N	Subject with breathing difficulties.	1	Carpenter/ Glueing wood onto aluminium sheets	Manufacture of panels for ships	MDI	Asthma and contact urticaria	Y	N/Y	
(Malo et al., 1999)	Inhalation challenge study of symptomatic subjects (Canada)	Not specified	N	Symptomatic subjects.	24	Not specified	Not specified	TDI, HDI, MDI	Occupational asthma	Y	N/N	Almost no data on the case histories.
(Aul et al., 1999)	Analysis of specific IgG response to isocyanates in subjects	Not specified	N	Subjects having respiratory reactions.	13	Not specified	Not specified	MDI, TDI, HDI	Occupational asthma (12), Hypersensitivity Pneumonitis (1)	Y	N/N	Testing of sensitised subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	with respiratory reactions (USA)											
(Castillon, 2000)	OSHA inspection report (USA)	Not specified	N	Workers experiencing health-related symptoms including amongst others difficulty breathing	2	Workers cutting pressed automobile headliners that before had passed a three-ton press with an operating temperature of 350°F	Manufacturer of interior automobile trim	MDI	Not specified (Health-related symptoms including lightheadedness, nausea and difficulty breathing)	N	Y/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Goossens et al., 2002)	Case report (Belgium)	1978 to 2011	N	Patients diagnosed with occupation-related allergic contact dermatitis	22	1,3,4,5,6,9, 11: laboratory technicians involved in synthesis, analysis of isocyanates /polyurethanes 22: laboratory technician mixing paints and binders 2,7,10,14: maintenance technicians 8: worker in road	Automobile industry, offset-printing firm, car factory, telephone company car-manufacturing plant	Isocyanates and/or polyurethanes	Occupational allergic contact dermatitis	N	N/N A (Subject 8)	Accidental contact occurred in subject number 8 when a polyurethane prepolymer pipe burst.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						construction n 12: cast technician 13: painter 15-20: workers involved in manufacture of polyurethane floor mats 21: packing polyurethane foam						
(Frick et al., 2003a)	Case report (Sweden)	1999-2001	N	Workers with recent episodes of eczema.	16	Handling a glue based on the isocyanate DMDI (70%) and	Factory manufacturing medical equipment	DMDI (hydrogenated HMDI), TDI	Contact allergy	Y	N/Y A	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						TDI (5%)						
(Frick et al., 2003b)	Case report (Sweden)	Not specified	N	Workers with work-related skin lesions	4	Operators by a machine where MDI-based lacquer was sprayed.	Company producing flooring laminate boards	MDI	Occupational contact dermatitis	Y	N/Y	
(Perfetti et al., 2003)	Case report (Italy)	1997/98	Y	Worker showing respiratory symptoms	1	Spray painter/spray painting of polyurethane foam balls with a paint containing MDI	Toy manufacture	MDI	Occupational asthma	Y	N/N A (spill)	Subject was exposed for 3 years without developing sensitization. Probably the single high dose after the accidental spill

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
												represented the trigger for sensitisation
(Valks et al., 2003)	Case report (Spain)	Not specified	Y	Woman having breathing difficulties	1	Worker using a 2-component polyurethane glue	Manufacture of plastic components for the car industry	MDI	Occupational sensitisation to MDI causing contact urticaria and asthma, simultaneously	Y	N/N A	Symptoms started after a peak exposure (heavy and prolonged contact with the glue).

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Matsushima et al., 2003)	Case report (Japan)	Not specified	N	Man complaining about respiratory symptoms	1	Handling of paint spray containing isocyanate	Not specified	MDI	Combined hypersensitivity pneumonitis and bronchial asthma	N	N/N	Publication in Japanese. Data were extracted from the English abstract.
(Donnelly et al., 2004)	Case report (Ireland)	not specified	Y	Patient showing respiratory symptoms	1	Nurse working with MDI-containing synthetic plaster casts	Hospital	MDI	Occupational asthma	Y	N/N	
(Morimatsu et al., 2004)	Case report (Japan)	Not specified	Y	Man who reported coughing and fever	1	Breaking up a large refrigerator containing MDI	Not specified	MDI	Hypersensitivity pneumonitis with acute respiratory distress syndrome	Y	N/N	Publication in Japanese. Data were extracted from the English abstract.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Militello et al., 2004)	Case reports (Canada)	1: not specified 2: 2003	Y	Sculptors who developed dermatitis after contact with polyurethane sculpting materials	2	Sculptors using polyurethane molds	1: Sculptor studio 2: Circus	MDI, DMDI	Allergic contact dermatitis	N	N /Y	
(Pisati et al., 2007)	Re-examination of subjects having occupational asthma after long-term removal from	Not specified	Y	Spray-painters diagnosed with occupational asthma	25	Spray-painters using polyurethane varnishes	Not specified	TDI	Occupational asthma	Y	N/Y	Re-examination of subjects with occupational asthma after 58 ± 7 months after removal from exposure. 7

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
	exposure (Italy)											were still reactors, 18 had lost reactivity. The authors conclude that avoidance of the offending agent within few months after development of symptoms can lead to remission.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Kerre, 2008)	Case report (Belgium)	Not specified	N	Subject showing acute oedema and eczematous lesions	1	Making "3D" advertising labels using a polyurethane resin system	Advertising agency	DMDI	Acute allergic contact dermatitis	Y	N/N	The patient had suffered from a similar condition 1 year previously in the same advertising agency.
(Minov et al., 2008)	Case reports (Macedonia)	2006 and 2007	N	Subjects having respiratory symptoms suggestive of asthma	2	Spray painters/working with isocyanate-based aerosol paint	Two car repair shops	Not specified (isocyanate-based aerosol paint)	Allergic occupational asthma, work-exacerbated asthma	Y	N/N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Stingeni et al., 2008)	Case report (Italy)	Not specified	N	Subject complaining of breathing difficulties	1	Worker mixing polyurethane glues	Factory manufacturing adhesives	MDI	Asthma and urticaria (concomitant type I and type IV sensitivities to MDI)	Y	N /Y	
(Piirilä et al., 2008)	Follow-up study of patients diagnosed with diisocyanate-induced asthma after cessation of exposure (Finland)	Not specified	Y	Subjects diagnosed with diisocyanate-induced asthma	17	Not specified	Not specified	HDI, MDI, TDI	Diisocyanate-induced asthma	Y	N/N	Testing of sensitised subjects. Almost no data about the case histories

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Donovan et al., 2009)	Case report (Canada)	Not specified	Y	Subject who developed a severe eczematous eruption	1	Nameplate laminator	Not specified	DMDI	Allergic contact dermatitis	Y	N/Y	
(Aalto-Korte et al., 2010)	Case reports (Finland)	2000-2009	N	Patients having symptoms of an occupational skin disease	4	1: Packer; packing a hardener 2: Office worker; carrying samples of three hardeners 3: Painter; grinding of surfaces 4: Laboratory worker	1, 2, 4: Paint factory 3: Aircraft repair workshop	Aliphatic polyisocyanates based on hexamethylene-1,6-diisocyanate	Occupational allergic contact dermatitis/Occupational contact allergy	N	N/Y A (patient 2, spill)	HDI trimers as novel contact allergens; allergic reactions not explained by sensitisation to monomer

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Bieler et al., 2011)	Case report (Switzerland)	2009	Y	Patient having an acute respiratory event	1	Paint quality controller (laboratory)	Not specified	HDI	Occupational extrinsic allergic alveolitis	Y	Y/Y	Allergic reaction was life-threatening.
(Aalto-Korte et al., 2012)	Case reports (Finland)	1998-2010	N	Patients suspected of occupational skin disease	23	1: Composer of printed circuit boards 2: Electronics engineer 3: Boat builder 4. Electrical fitter 5. Train carriage fitter/Carriage repair 6: Painter	Motor vehicle industry; electronics industry; paint industry; polyurethane paint manufacture, painting and construction work	MDI, TDI, IPDI, HDI	Occupational allergic contact dermatitis; Occupational contact allergy; Contact allergy; Occupational irritant contact dermatitis	N	N/Y	Positive reactions: 12/23 to MDI, 9/23 to IPDI, 6/23 to TDI, 1/23 to HDI.

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						7: Carpet installer 8: Plate maker/aircraft fitter/ Aircraft workshop 9: Foreman in a foundry 10: Electronics engineer 11: Paint factory worker 12: Painter in the manufacture of windows and doors						

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						13: Set painter in a theatre 14: Floor coating worker 15: Machine assistant on ice breaker 16: Instrument fitter in aircraft workshop 17: Painter of buildings 18: Worker in flame cutting of scrap iron						

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						19: Plastics worker in manufacture of acrylonitrile-butadiene-styrene plastics 20: Wood industry worker in manufacture of windows, doors and frames 21: Warehouse worker in supermarket 22: Lamp						

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
						assembler 23: Salesperson in a plastic and rubber product store						
(Engfeldt et al., 2013)	Case report (Sweden)	approx. 2010	N	One patient with suspected occupational contact dermatitis and 6 patients with skin problems	7	1,2,3,4,5,6 : using polyurethane adhesive 7: not specified/sometimes in vicinity to PUR area	Company producing epoxy-lacquered aluminium heat exchangers	PMDI , MDI	Occupational contact allergy due to isocyanate-related test preparations in 4 of the 7 patients	Y	N	

Reference	Study design (Country)	Year(s) of examination	Post-examination information? Y=Yes; N=No	Subjects	n	Occupation/task	Industry	Agent(s)	Diagnosed disease/effect	Exposure duration given? Y=Yes; N=No	Exposure concentration (workplace (air)/in product) given? Y=Yes; N=No; A=Accident	Remarks
(Engfeldt and Ponten, 2013)	Case report (Sweden)	Not specified	Y	Patient suspected of having allergic contact dermatitis caused by isocyanates	1	Process operator changing a barrel containing a mixture mainly consisting of MDI when the hose burst	Manufacture of polyurethane adhesives	MDI, IPDI	Occupational allergic contact dermatitis	Y	N/Y A	Accidental spillage occurred on two occasions, around 5 years apart.

Appendix 3 Overview of available epidemiological data

Abbreviations

FEF₂₅₋₇₅: Forced expiratory flow between 25 and 75 % of FVC

FEV₁: Forced expiratory volume in one second

FEV₁ %: FEV₁/FVC x 100

FVC: Forced vital capacity

HDI: Hexamethylene diisocyanate

JEM: Job exposure matrix

LOD: Limit of detection

MDI: Methylenediphenyl diisocyanate

MMF: Maximum mid-expiratory flow

n. s.: not significant

OA: Occupational asthma

OR: Odds Ratio

PEFR: Peak expiratory flow rate

PR: Prevalence ratio

PU: Polyurethane

RR: Relative Risk

TDI: Toluene diisocyanate

TWA: Time-weighted average

Epidemiological data on the exposure-response relationship of diisocyanates and respiratory disease

Table 3-1: Reviews

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(DFG, 1997; DFG, 2008)	Derivation of a "MAK-value" → adoption as national OEL	MDI		<p>The OEL of 5 ppb for MDI and "polymeric MDI" was derived from occupational epidemiological studies with workers in plastic foam production, insulation foam production and MDI production. Available studies have a lot of limitations concerning exposure measurement, existing coexposures, disregard of both allergic aspects and preexposure to higher concentrations, lack of more objective outcome measurements (spirometry vs. whole body plethysmography). No significant changes in lung spirometry found when exposure was generally below 20 ppb. Whereas at this concentration there were sometimes respiratory symptoms (however not clearly attributable to isocyanates), such symptoms were not significantly more frequent at concentrations less than or equal to 10 ppb. At even lower concentrations of 0.05 mg/m³ or less, the workers, sometimes exposed for many years, were without symptoms and had better lung function than the control groups.</p> <p>Respiratory sensitisation: Long-term exposure to MDI concentration of 0.05 mg/m³ or less is thought to neither cause bronchial hypersensitivity and its associated symptoms nor the formation of specific</p>	

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				antibodies. For the induction of specific airway hypersensitivity (with or without immunological parameters) an exposure to MDI concentrations above 0.2 mg/m ³ or intensive skin contact is of great importance. To protect from increased peak exposure, 8-h TWA and short-term exposure limit value for 15 minutes have been put on the same level (0.05 mg/m ³). Ceiling exposure limit has been set to 0.1 mg/m ³ .	
(AGS, 2006a; DFG, 2003)	Derivation of a "MAK-value" → adoption as national OEL	TDI		The OEL of 5 ppb (0.035 mg/m ³) for TDI is based on gradual deterioration in lung function. This effect was evaluated in several occupational epidemiological studies with workers from polyurethane foam factories in Japan, North America and Europe. From these data it was deduced <i>"that with observance of an 8-hour-average value at the workplace of 0.005 ml/m³ and limitation of exposure peaks to 0.02 ml/m³ no significant deterioration in lung function is to be expected."</i> Concerning respiratory sensitisation it was concluded from three epidemiological studies, that under a TDI concentration below 0.01 to 0.02 ml/m ³ , <i>"generally no new cases of TDI asthma are observed (Karol, 1981; Olsen et al., 1989; Porter et al., 1975)"</i> .	
(Diller, 2002)	Incidence of OA due to TDI was estimated from nine longitudinal studies,	TDI Longitudinal studies:	Sparse and mostly qualitative information	TDI asthma: Reviewed studies are heterogeneous (population, case definition/validity of	Incidence data are not interpreted with regard to the exposure level.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>based on 2751 workers.</p> <p>Prevalence of OA due to TDI was estimated from ten cross-sectional studies, based on 788 workers.</p> <p>The 38-year period from 1954 to 1992 was covered.</p>	<p>Manufacture/ research and development/ flexible foam production</p> <p>Cross-sectional studies:</p> <p>Manufacture/foam production/ sewing laminated nylon/ laquer varnishing/ foam coating of steel/ adhesive tape production/varnish application/paint application</p>		<p>diagnosis of TDI asthma, industry, exposure), of limited validity and difficult to interpret.</p> <p>Annual incidence of TDI asthma shows downward trend over the past half century and was reported to be around 5 % in earlier times and between 0 and 0.7 % since 1980.</p> <p>The downward trend is attributed to the downward trend of TDI exposure.</p> <p>The prevalence of TDI asthma has been reported to be > 10 % before 1985 and between 0 and 10 % in the more recent years at workplaces with mean TDI exposures < 15 ppb.</p>	Reviewed studies overlap with those in Ott 2003 and Ott 2002.
(Ott, 2002)	<p>Review of studies on OA, lung function decrement and TDI exposure, with a focus on assessing exposure-response relationships</p> <p>TDI-induced asthma: Nine cross-sectional studies, eight longitudinal studies</p> <p>Lung function:</p>	<p>TDI</p> <p>Manufacture and TDI-using industries (PU foam production and others)</p>	<p>Earlier years (1950s and 1960s):</p> <p>60 ppb as mean area concentration or major portion of samples > 20 ppb, multiple spills reported</p> <p>Decline in exposure over the years</p> <p>More recent years (1980s and 1990s):</p>	<p>TDI asthma:</p> <p>Case definitions varied widely across studies.</p> <p>Prevalence across nine cross-sectional studies in TDI using industry ranged from 0 to 41 %.</p> <p>Annual incidence rates were 5-6 % in earlier times both in TDI manufacture and in TDI using industries.</p> <p>Rates declined to < 1 % with reduction of TDI concentrations to < 5 ppb (8h personal samples) (see Table C-2 below).</p>	Reviewed studies overlap with those in (Ott et al., 2003) and (Diller, 2002).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Three cross-sectional studies, eleven longitudinal studies		< 5 ppb TWA, short-term concentrations > 20 ppb	<p>Studies with more extensive exposure measurements indicate that majority of asthma cases may arise from TDI short-term concentrations > 20 ppb.</p> <p>Decline in lung function (FEV₁): Decrements in FEV₁ were seen in earlier studies and in follow-up studies of workers who continued to work after their diagnosis of OA.</p> <p>No consistent evidence of accelerated loss in FEV₁ was found in more recent studies with exposure up to 5 ppb (8h TWA) and even with short-term TDI concentrations > 20 ppb.</p>	
(Ott et al., 2003)	<p>Review of clinical/epidemiological literature on respiratory health effects of TDI and assessment of exposure-response-relationships in humans</p> <p>TDI-induced asthma: Nine cross-sectional studies, eight longitudinal studies</p> <p>Lung function: Three cross-sectional studies,</p>	<p>TDI</p> <p>Manufacture and TDI-using industries (PU foam production and others)</p>	<p>Different methods:</p> <p>Marcali method used in 1950s to 1970s</p> <p>Test-paper method developed 1968 and used in epidemiological studies published since 1980, equally sensitive to 2,4- and 2,6-isomers, not affected by presence of toluene diamine</p> <p>HPLC analytical methods since mid-1970s, lower LOD, separate determination</p>	<p>Hazards from single exposures are described, but will not be reported here.</p> <p>Hazards from repeated and long-term exposures:</p> <p>Asthma:</p> <p>Annual induction rates: About 5 % in earlier years (1950s-1970s) Between 0.7 to 1.1 % in four newer studies (1970s to 1990s). Here TWA concentrations mostly < 5 ppb, but short-term TDI concentrations > 20 ppb and occasionally > 80 ppb.</p> <p>Findings indicate a downward trend in incidence rate over time concurrent with lower TDI exposures.</p>	<p>Reviewed studies overlap with those in Ott 2002 and Diller 2002.</p> <p>Marcali method (Marcali, 1957) may have underestimated exposure to 2,6-TDI by as much as 47 %, positive interference if aromatic amines are present</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	eleven longitudinal studies		<p>of 2,4- and 2,6-isomers</p> <p>OSHA method 42</p> <p>Manufacturing:</p> <p>Early years: Concentrations up to 60 ppb, frequently > 20 ppb, peak concentrations up to 200 ppb during leaks, spills. After 1980: TWA < 5 ppb, short-term exposure > 20 ppb (less frequently).</p> <p>Foam production:</p> <p>Early years: similar to manufacturing. Since 1980: < 5 ppb (TWA), short-term exposure > 40 ppb, (less frequently)</p>	<p>OA cases might be attributable to overexposure incidents (> 20 ppb).</p> <p>Hypersensitivity pneumonitis: Incidence due to TDI exposure seems to be very low.</p> <p>Lung function decrement: Mostly no evidence for accelerated decline from the larger, more recent longitudinal studies (8h TWA mostly ≤ 5 ppb). However, decline in lung function in workers with symptoms or TDI-asthma and continued exposure.</p>	
(Belgian CA, 2005)	Human health assessment sections "respiratory sensitisation" and "repeated dose toxicity" cover eleven and nine studies in humans, respectively	MDI		<p><i>"MDI is a potential respiratory sensitiser in animals and humans...At the present time it is not possible to define reliable exposure-response relationships with regard to the risk of sensitisation for MDI."</i></p> <p><i>"In humans, some, but not all, epidemiological studies have found long-term decreases in ventilatory function and respiratory symptoms, in workers exposed</i></p>	Last literature search 2003

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				<p><i>to MDI even below current occupational standards."</i></p> <p>"... chronic exposure to even low levels (but mostly undetermined or below 0.05 mg/m³) of MDI involves a respiratory risk, "</p>	
(Dodge and Silva, 2016a)	<p>Methylene Diphenyl Diisocyanate (Monomer and Polymeric Forms)</p> <p>Reference Exposure Levels</p> <p>Technical Support Document for the Derivation of Noncancer Reference Exposure Levels</p>	MDI (monomer and polymeric forms)		<p>REL derived from animal data</p> <p>Acute REL = 12 µg/m³ (1.2 ppb)</p> <p>8-h REL = 0.16 µg/m³ (0.015 ppb)</p> <p>Chronic REL = 0.08 µg/m³ (0.008 ppb)</p>	Covers relevant published literature for MDI through spring 2015
(Dodge and Silva, 2016b)	<p>Toluene Diisocyanate</p> <p>Reference Exposure Levels</p> <p>Technical Support Document for the Derivation of Noncancer Reference Exposure Levels</p>	TDI (mixed isomers)		<p>Acute REL (infrequent 1-h exposures) = 2 µg/m³ (0.3 ppb)</p> <p>LOAEL = 71 µg/m³ (10 ppb) (≥ 100 % increase in Raw in asthmatics; (Baur et al., 1994; Vogelmeier et al., 1991))</p> <p>LOAEL uncertainty factor = 10 (for severe effect)</p> <p>Intraspecies toxicodynamic uncertainty factor = √10 (asthmatic children)</p> <p><i>"reasonably protective against sensitisation</i></p>	<p><i>"The RELs are intended to reasonably protect the general population from these health effects resulting from exposure to both 2,4- and 2,6-TDI, but may not protect all individuals previously sensitized to TDI."</i></p> <p>Covers relevant published literature for TDI through spring 2015</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				<p><i>under a scenario of infrequent exposures"</i></p> <p>8-h REL (repeated daily 8h-exposures up to 7 days/week) = 0.015 µg/m³ (0.002 ppb)</p> <p>LOAEL = 13.5 µg/m³ (1.9 ppb) (accelerated decline in FEV₁; (Diem et al., 1982)</p> <p>NOAEL = 0.9 ppb (6.4 µg/m³)</p> <p>time adjustment = 5/7</p> <p>subchronic uncertainty factor = $\sqrt{10}$</p> <p>intraspecies toxicokinetic uncertainty factor = 10</p> <p>intraspecies toxicodynamic uncertainty factor = 10</p> <p>Chronic REL (continuous exposure over a lifetime) = 0.008 µg/m³ (0.001 ppb)</p> <p>LOAEL and NOAEL see 8h REL</p> <p>time adjustment = 10/20 * 5/7</p> <p>subchronic uncertainty factor = $\sqrt{10}$</p> <p>intraspecies toxicokinetic uncertainty factor = 10</p> <p>intraspecies toxicodynamic uncertainty factor = 10</p>	

Table 3-2: Data taken from (Ott, 2002) (Tables I and III)

Study	Time period	Annual incidence of TDI-induced occupational asthma [%]	TDI concentration [ppb]	Exposure sampling
TDI production units				
(Adams, 1975)	1961 - 1970	5.6	1962 - 1964: 58 % - 72 % of samples > 20 1965 - 1966: 4 % - 21 % of samples > 20 1967 - 1970: 1 % - 2 % of samples > 20	Area samples
(Porter et al., 1975)	1956 - 1959	1.6	1956 - 1957: 60 (mean area conc.)	Area samples
	1960 - 1969	0.8	1960 - 1969: steady decline in area conc.	
	1970 - 1974	0.3	1974: < 4 (mean area conc.)	
(Weill et al., 1981)	1973 - 1978	1.0	1.6 - 6.8 (TWA; range by job) (STC > 20 5 % - 11 % of time in moderate to high exposure jobs)	Area samples 1973-75 Personal samples 1975-78
(Ott et al., 2000)	1967 - 1979	1.8	3.4 - 10.1 (TWA; range by job)	Area samples 1967-75 Personal samples 1976-96
	1980 - 1996	0.7	0.3 - 2.7 (TWA; range by job) (STC > 20 0.5 - 0.9 times/shift in moderate to high-exposure jobs)	
PU foam production facilities				
(Woodbury, 1956)	1954 - 1955	5	Multiple TDI spill episodes described in 18-month period	No sampling data
(Williamson, 1964)	1962 - 1963	> 2.7	Samples mostly < 20 (up to 200 detected during spills)	Area samples
(Bugler et al., 1991)	1981 - 1986	0.8	0.9 - 2.6 (TWA; range by job) 22 % of 8-hr samples with short-term conc. > 20 and 10 % > 40	Personal samples
(Jones et al., 1992)	1982 - 1986	0.7	1.4 - 4.5 (TWA; range by job) (STC > 20 3 % time in production and 0.1 % of time in finishing jobs)	Personal samples

STC: short-term concentration (9-12 minutes)

TWA: time-weighted average

Table 3-3: Longitudinal studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Adams, 1975)	<p>Prospective cohort study (9 years)</p> <p>2 plants</p> <p>565 have been employed for some period between 1961 to 1972</p> <p>A) Comparison of respiratory symptoms in TDI plant workers (n = 76) with control workers (n = 76) in another plant</p> <p>B) Lung function in healthy workers (n = 180)</p> <p>C) Long-term effects in men who were removed due to symptoms and had no exposure to TDI since two to 11 years (n = 46) compared to age-matched control group (n = 46)</p>	<p>TDI</p> <p>Manufacture</p>	<p>Area samples taken at points in the plant where free TDI might be expected (ca. 250 measurements a week; Marcali method, (Marcali, 1957))</p> <p>Samples > 20 ppb: 1962-64: 58 – 72 % 1965-66: 4 – 21 % 1967-70: 1 - 2 %</p>	<p>A) Respiratory symptoms (questionnaire): No significant difference in symptoms between men working in TDI plant and controls with the exception of higher frequency of wheezing in controls.</p> <p>B) Lung function: Duration of exposure had no effect on FEV₁ or FVC in the regression analysis.</p> <p>C) Respiratory symptoms (questionnaire): Prevalence of symptoms in TDI-sensitised men significantly higher than in controls → persistence of symptoms</p> <p>D) Lung function: FEV₁ and FVC smaller than predicted by equation obtained from a control group: FEV₁ -267 mL, FVC -269 mL</p>	<p>Reviewed in Ott et al. 2002</p> <p>Method of analysis did not calculate individual decline in lung function</p> <p>Regression analysis included duration of exposure, but no exposure level</p> <p>Area measurements</p> <p>Lung function measurements in the afternoon</p> <p>Only healthy workers included</p> <p>Smoking not included in regression analysis</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	D) Lung function in men who were removed due to symptoms and had no exposure to TDI since two to 11 years (n = 61)				
(Wegman et al., 1977)	<p>Follow-up of (Wegman et al., 1974)</p> <p>1972: n = 112</p> <p>1974: n = 63 (available for re-survey) n = 57 with personal exposure levels</p>	<p>TDI</p> <p>PU cushion manufacture</p>	<p>118 area samples + 14 personal samples taken during study period to characterise 20 work stations</p> <p>Marcali method (Marcali, 1957)</p> <p>Each individual was classed according to his or her usual work station</p> <p>Three exposure groups (ppm): ≤ 0.0015 (n = 20) $0.0020 - 0.0030$ (n = 17) ≥ 0.0035 (n = 20)</p>	<p>Lung function (because of acute effect seen on Monday: Monday morning following three-day weekend):</p> <p>Dose-response relationship for two-year change in FEV₁ (-12 mL/-85 mL/ -205 mL from low to high exposure groups).</p> <p>Only those in lowest exposure group showed normal declines in FEV₁.</p> <p>Those in highest group had three- to fourfold higher FEV₁ declines than expected (103 mL/year).</p> <p>Significant association between acute and chronic decrement in FEV₁.</p> <p>Respiratory symptoms (questionnaire): Prevalence of cough and phlegm increased with increase in exposure. Wheezing and dyspnea not associated with exposure.</p>	<p>High attrition rate</p> <p>Followed up: (Wegman et al., 1982)</p> <p>Possible confounding variables explored: age, months employed, smoking habits, variables related to lung size. Authors report that none of those was able to explain the differences.</p>
(Butcher et al., 1977)	<p>Prospective cohort, 2.5 years</p> <p>Visits: April 1973</p>	<p>TDI</p> <p>Manufacture</p>	<p>Area sampling (1973): frequent excursions of 8h-TWA value of 5 ppb; many above 20 ppb</p>	<p>Lung function changes (n = 102):</p> <p>Mean values of FVC and FEV₁ increased in all groups. Other lung function</p>	<p>Attrition rate = 7.2 %</p> <p>Two workers had left the study by October 1975</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>(before TDI production), November 1973 (after production had started), every 6 months thereafter</p> <p>Initially n = 166</p> <p>Study in TDI-sensitive persons (specific and unspecific challenge)</p>		<p>Personal monitoring (1975)</p> <p>Frequent and large discrepancies between simultaneously measured area and personal exposure levels</p> <p>Four groups:</p> <p>1) Mainly in TDI area: n = 77 2) Intermittently in TDI area: n = 36 3) Comparison group: n = 53 4) (added later) workers transferred from control group to exposure group after production had begun</p>	<p>parameters decreased slightly (n. s. different from zero or predicted).</p> <p>Paradoxical differences for lung volumes and diffusion capacity (greater declines in the groups with higher exposure).</p> <p>No exposure-related excess decline in lung function determined.</p> <p>Respiratory symptoms (questionnaire administered by interviewers):</p> <p>No significant increase in prevalence of bronchitis, atopic disorders, upper respiratory symptoms from April 1973 to October 1975.</p> <p>Significant proportion of exposed workers (26 of 89) reported onset of lower respiratory symptoms after beginning work in TDI areas (due to symptom development in non-smokers).</p> <p>Inhalation challenge with TDI: 9 out of 13 workers had an adverse bronchial response (immediate type, late type or dual type). Some reacted at 5 ppb, some to a higher concentration only.</p>	<p>after developing reactivity to TDI.</p> <p>No quantitative exposure estimation for the four exposure categories</p> <p>Smoking not considered in analysis of change in lung function</p>
(Pham et al., 1988)	<p>5 years follow up</p> <p>1976: n = 318 workers (104 women)</p>	<p>Mainly MDI</p> <p>Production of PU foam</p>	<p>Isocyanate concentration:</p> <p>1976: < 20 ppb 1981: ≤ 5 ppb</p> <p>1976: Group I (n = 83):</p>	<p>Lung function (flow volume curve, single breath CO diffusion test (D_{LCO})):</p> <p>Ventilatory function and lung transfer factors significantly impaired in male exposed workers compared to group I.</p>	<p>High loss to follow up (half of the initial cohort still active after 5 years)</p> <p>Rare information on exposure</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>1981: n = 156 (45 women)</p> <p>Two factories producing PU foam</p> <p>Follow up of Pham et al. 1978</p>		<p>unexposed</p> <p>Group II (n = 117): indirectly exposed</p> <p>Group III (n = 118) directly exposed</p> <p>1981: Only results for men reported for the longitudinal analysis.</p> <p>Group A (n = 45): unexposed at both studies</p> <p>Group B (n = 24): undirectly exposed at both studies</p> <p>Group C (n = 30): directly exposed at both studies</p> <p>Group D (n = 15): exposed in 1976, but removed in 1981</p>	<p>Only in the subgroup of workers exposed for more than 5 years.</p> <p>Decline of ventilatory function variables not significantly different between the groups.</p> <p>Significant larger loss of D_{LCO} in subjects with persisting exposure (group C) compared to reference group.</p> <p>Results returned to normal for the subjects no longer exposed (group D).</p> <p>Respiratory symptoms (questionnaire):</p> <p>Increased prevalence of asthma in group II men and group III women and of chronic bronchitis in both sexes.</p> <p>Number of workers with asthma or chronic bronchitis increased over the five years, but this was not limited to the exposed group.</p>	<p>In females, the proportion of smokers was the same in groups I – II. In males, there were slightly (n.s.) more smokers in groups II and III.</p> <p>Coexposure to other isocyanates? (“mainly MDI”)</p>
(Wegman et al., 1982)	<p>Four-year follow up (Wegman et al. 1974 and 1977)</p> <p>1972: n = 111</p> <p>1974: n = 63</p> <p>1976: n = 48 (all those who were still at work in 1976) → n = 37 with</p>	<p>TDI</p> <p>Automobile seat cushion manufacture</p>	<p>Environmental sampling at selected work sites on the same day as lung function was measured.</p> <p>Additional sampling during the first two years of the study.</p> <p>Personal sampling in</p>	<p>Lung function:</p> <p>Acute change in FEV₁ (during work shift) observed at the beginning of the study was weakly associated with long-term change in FEV₁.</p> <p>Chronic change in FEV₁ (over four years):</p> <p>Mean exposure to TDI was the best</p>	<p>Uncertainties in exposure assessment</p> <p>High attrition rate</p> <p>Lung function decline evaluated from 3 occasions only</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>exposure history and acceptable spiromograms</p> <p>On all three occasions workers were examined before work and as many as possible six to ten hours later.</p>		<p>production area, area samples in warehouse and nonproduction sites.</p> <p>Marcali method</p> <p>Occupational histories taken from personnel records</p> <p>Cumulative exposure of each worker calculated and from this the usual exposure level.</p> <p>Three exposure groups: Low (< 0.0020 ppm) Medium (0.002 – 0.0034 ppm) High (> 0.0033 ppm)</p>	<p>predictor of four-year change in FEV₁ in a stepwise regression model.</p> <p>Change in FEV₁ increased with exposure and was significantly different between the exposure groups.</p> <p>Decline in FEV₁ in high exposure group (60 mL/year) was higher than annual decline observed in other studies of normal populations (32-47 mL).</p> <p>Respiratory symptoms (questionnaire; upper respiratory symptoms: sneezing, sinus trouble or postnasal drip, hay fever; lower respiratory symptoms: coughing, wheezing, shortness of breath): Prevalence of respiratory symptoms was unrelated to exposure category.</p>	
(Musk et al., 1982)	<p>5 years follow-up</p> <p>n = 259 from three sites were examined in 1971; one of the sites closed in 1972 and there was high worker turnover; 107 subjects were available for re-examination in 1976</p>	TDI and MDI for the manufacture of PU automobile components	<p>2573 environmental samples were collected by plant personnel in the breathing zone of subjects pouring urethane plastic (exposure in areas with the highest exposures was measured)</p> <p>During lung function survey further measurements were made by plant personnel and study personnel at selected sites with highest TDI and MDI concentrations</p>	<p>Lung function (spirometry (FEV₁, FVC); change over 5 years/change over the course of a day/change between before and after two weeks of vacation):</p> <p>Mean annual decrement in FEV₁ of 0.02 L was interpreted as being only age-related</p> <p>No significant acute change in FEV₁ over the course of a day before or after vacation reported</p> <p>After two weeks of vacation FEV₁ was increased in those who had taken the</p>	<p>Uncertainties in exposure assessment and spirometry</p> <p>Smoking, age, height, sex were considered in the regression analysis of FEV₁.</p> <p>Healthy worker survivor effect (Although it is reported that subjects who left had similar lung functions to the remaining subjects, it seems possible</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>Marcali method (Marcali, 1957)</p> <p>All environmental measurements made over the 5 years together with the occupational history of the subjects determined the exposure category (No exposure/TDI/MDI/TDI and MDI).</p> <p>90 % of all measurements of TDI taken over the four years prior to the follow-up study were < 5 ppb (plant 1) and < 4 ppb (plant 2)</p> <p>Geometric mean TDI concentration: 1.5 ppb (plant 1) and 1 ppb (plant 2)</p> <p>MDI levels tended to be lower than TDI levels</p>	<p>vacation (n = 49, n. s.) and was decreased in those who had worked (n = 31, n.s.).</p> <p>Exposure category did not affect daily change in FEV₁/pre- to postvacation change in FEV₁/five-year change in FEV₁.</p> <p>Respiratory symptoms (questionnaire):</p> <p>No association between exposure to isocyanates and bronchitis or dyspnea found</p> <p>No acute exposure-related symptoms reported by subjects</p>	that workers left due to earlier symptoms of sensitisation).
(Diem et al., 1982)	<p>5 years prospective (9 surveys)</p> <p>First survey in 1973 (5 months before start of production)</p> <p>Initially: n = 168</p>	TDI manufacture	<p>2093 personal samples from 143 workers representing all job categories</p> <p>8h-TWA from 0.1 ppb - 25 ppb, geometric mean 2.00 ppb</p> <p>Average exposure:</p>	<p>Lung function (spirometry, annual change):</p> <p>Decrease in FEV, %FEV and FEF₂₅₋₇₅ was significantly larger in the high cumulative exposure category than in the low category (adjusted for pack-years of smoking).</p>	<p>No unexposed group</p> <p>"The present data do not identify a specific exposure below which no effect upon FEV₁ annual decline will occur. However, they do suggest that the NIOSH-recommended</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>After 5 surveys: n = 274 (males)</p> <p>Median follow-up time for n = 223 men who met inclusion criteria of spirometric data 4.1 years (1 – 5.5)</p>		<p>Three TWA exposure job categories: Geometric mean in ppb (time per shift < 20 ppb):</p> <p>Low: 0.02 (1.3 min)</p> <p>Medium: 2.0 (8.6 min)</p> <p>High: 4.5 (28.2 min)</p> <p>Cumulative exposure calculated from number of months spent in each of the three TWA exposure categories and their respective geometric means. Workers were divided into two groups using a division point of 68.2 ppb-months (= 1.1 ppb x 62 months). Low exposure group n = 149, high n = 74. Working time spent > 5 ppb: 2 % in low exposure group, 15 % in high exposure group.</p> <p>Peak exposure categories: division point 0.19 months > 20 ppb</p>	<p>No association of the other lung function annual changes with exposure.</p> <p>A more detailed analysis of FEV₁ and FEF₂₅₋₇₅ in six categories of cumulative TDI exposure and smoking showed a significant effect of TDI exposure in never smokers only and a significant effect of smoking in the low exposure group only. → effects not additive</p> <p>Effects similar for six categories of TDI peak exposure and smoking with the exception that a significant exposure effect was found in current smokers also. → higher TDI exposure seems to mask smoking effect → peak exposure analysis suggests additive effect (lacking in cumulative exposure analysis)</p> <p>Respiratory symptoms (questionnaire): No significant correlation in increase in prevalence from initial to final interview and exposure to TDI.</p>	<p>standard of a 5 ppb 8-h time-weighted average and a 20 ppb 10-min short-term exposure limit is reasonable.”</p> <p>Low cumulative exposure group was older and initially had higher prevalence of respiratory symptoms than high exposure group → possible underestimation of excess decline in lung function due to TDI</p> <p>75 % of the low exposure group had follow-up time > 2.5 years and 99 % of the higher exposure group</p> <p>Atopy, race and smoking were considered</p> <p>Age and FEV₁ level were considered in the more detailed analysis of FEV₁ and FEF₂₅₋₇₅</p>
(Omae, 1984)	<p>2-year follow up</p> <p>Four TDI-producing plants, two research laboratories</p>	<p>TDI</p> <p>Manufacture ; research laboratory</p>	<p>Mean duration of TDI exposure: 9.0 years (subjects in 1980) 11.2 years (subjects in 1982)</p>	<p>Lung function (Maximum expiratory flow volume curve, respiratory impedance):</p> <p>n = 8 workers with asthmatic reactions,</p>	<p>High loss to follow-up</p> <p>Co-exposures:</p> <p>TDI plant workers:</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>1980: n = 106 male exposed workers n = 39 male controls (office workers)</p> <p>1982 (one plant had closed): n = 64 workers (follow-up rate 60 %) n = 21 controls (follow-up rate 62 %)</p>		<p>Personal paper tape monitor (gives continuous profile; n = 161 samples in 1980, 106 in 1982)</p> <p>Means of individual TWA: 0.7 ppb (1980) 1ppb (1982)</p> <p>Short-term exposure \geq 20 ppb in 9.3 % (1980) and 1.9 % (1982) of collected samples</p>	<p>shortly after having begun work with TDI. Percentage of predicted values significantly less than 100 % in some of the expiratory flow parameters.</p> <p>No significant differences in lung function between the exposed workers and the referents.</p> <p>Change in lung function over the day (1980; n = 68 TDI workers + n = 31 controls): No meaningful daily changes in lung function in either group.</p> <p>Change in lung function over two years: When adjusted for aging, no remarkable intra-individual two-year decreases in lung function parameters in both groups and no significant difference between the groups.</p> <p>No difference in the two-year decrement between the workers with asthmatic reactions and the other TDI workers.</p> <p>Symptoms (interviewed by the use of a questionnaire): No significant differences in prevalence of respiratory symptoms between exposed workers and referents.</p> <p>Significantly higher prevalence of throat and eye irritation in exposed workers</p>	<p>occasionally various irritants such as phosgene, chlorine, nitric acid, sulfuric acid;</p> <p>Research laboratory workers: irritative amines, organic tin compounds , MDI, HDI during experimental mold foaming</p> <p>Effects of age, physical factors and smoking on lung function considered in analysis</p> <p>Survival worker effect considered to be small by the authors</p> <p>Hyperreactive persons to TDI may have already been transferred out of TDI sections</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				than in referents. May be due to peak exposures to TDI or other irritants (phosgene).	
(Musk et al., 1985)	Re-analysis of the data of (Musk et al., 1982)				The spirometers performed 1971 in the study by (Musk et al., 1982) were criticised ("inadequate", "lack of reproducibility", "leak in the spirometer"). (Musk et al., 1985) concluded that the original conclusions are valid.
(Gee and Morgan, 1985)	10-year follow up (includes significant proportion of subjects included in Musk et al. 1982) Examinations in 1971 and in 1981 n = 68 exposed n = 12 controls n = 65 subjects with pre- and post-shift measurement n = 42 studied in 1971 and 1981	TDI and MDI Manufacture of fittings, seat covers, other fixtures used in the interior of cars	Routine area and some individual sampling had been carried out monthly or more frequently Mean annual concentrations between 1973 and 1980 for TDI: 1- 5 ppb Mean annual concentrations between 1975 and 1981 for MDI: 1- 5 ppb	Lung function (compared to predicted values): Three subjects had impaired lung function (two exposed, one control). Lung function of subjects studied previously had mean FVC and mean FEV ₁ > 100 % of the predicted values. Control group of one plant had a significantly lower percentage of the predicted FVC and FEV ₁ than the exposed group. No other significant difference between any of the groups. Lung function (change over shift): Change not higher than 10 % in any subject. No comparison between controls and exposed.	Mean annual exposure values on factory level only Uncertainties in spirometry data (no reproducibility, leak in spirometer possible in 1971; learning effect from pre- to postshift measurements) Results on annual decline in lung function seen as "not realistic" (small increase in FVC, small decrease in FEV ₁).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Mean shift change in FEV ₁ was -57 mL in exposed and +69 in controls in one plant and -23 and -80 in the other plant, respectively.	
(Omae et al., 1992)	<p>4-year follow up (cross-sectional results see (Omae et al., 1992))</p> <p>Cross-sectional: 1981</p> <p>Follow-up visits: 1983 and 1985</p> <p>Japan:</p> <p>n = 57 PU foam workers (follow-up rate 66 %; n = 2 excluded)</p> <p>n = 24 reference workers (follow-up rate 61 %; n = 3 excluded)</p>	<p>TDI</p> <p>PU foam manufacture</p>	<p>Personal paper-tape monitors (n = 59 samples in 1981, 48 in 1983 and 52 in 1985)</p> <p>n = 28 group L (low exposure with little variation), 17.4 years in the PU foam factories (mean), TWA (mean, max) 0.1 ppb, 1 ppb; Peak exposure level < 1 ppb</p> <p>n = 29 group H (exposed workers), 16.5 years in the PU foam factories (mean), TWA (mean, max) 5.7 ppb, 30 ppb; Peak exposure level 3-80 ppb</p> <p>Two subgroups of group H:</p> <p>n = 15 group H1 (high short-term exposures), 13.8 years in the PU foam factories (mean), TWA (mean, max) 8.2 ppb, 30 ppb; Peak exposure level 30-80 ppb</p>	<p>Lung function (Flow-volume indices in 1981; Average annual loss of the indices during 1981-1985 (forced expiratory flow-volume test at follow-ups; slope of the regression equation for every subject)):</p> <p>No "noteworthy" differences in pulmonary function indices and average annual losses between groups H, L, reference.</p> <p>Group H1: Significantly larger average annual lung function losses (% MMF, %FEV₁ %, %MEF₂₅) than expected. Significantly larger average annual losses in some obstructive pulmonary function indices than in group L or reference group.</p>	<p>No individual exposure estimates</p> <p>No significant differences between group H1 and H2 (as suggested in the abstract)</p> <p>Workers in slab-type factories intermittently exposed to relatively high levels of TDI and concurrent other chemical gases/aerosol → group H divided into two subgroups</p> <p>Smoking rate significantly lower in group H than in group L and reference group</p> <p>Comparison of average annual losses of smokers and non-smokers in the 4 groups showed similar trends. Higher losses in smokers than non-smokers.</p> <p>Based on a comparison between lung function of</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			n = 14 group H2, 19.4 years in the PU foam factories (mean), TWA (mean, max) 1.7 ppb, 4 ppb; Peak exposure level 3-14 ppb		followed-up and lost workers, survival-worker effect was evaluated to be small.
(Tornling et al., 1990)	<p>Six years follow-up (initial study: (Alexandersson et al., 1987))</p> <p>1978:</p> <p>46 male car painters and 142 male controls (car platers and mechanics) randomly chosen from 14 garages in Stockholm</p> <p>Reinvestigation in 1984:</p> <p>Participation rate 78 % for car painters and 81 % for controls</p> <p>n = 36 car painters n = 115 controls</p>	<p>HDI monomer and HDI biuret trimer</p> <p>Car painting</p>	<p>Individual exposure assessments by industrial hygienist (interview about working routines, respirator use, hygienic standards).</p> <p>Exposure measurements at seven representative shops</p> <p>98 samples inside and outside the respirator</p> <p>Individual exposure was calculated from workplace data, proportion of work tasks, use of respirators.</p> <p>18 peak exposure measurements (sampling time < 3 min)</p> <p>Calculated TWA exposure:</p> <p>HDI: 0.0015 mg/m³</p> <p>HDI-BT: 0.09 mg/m³, frequently peak exposures > 0.2 mg/m³</p> <p>Calculated yearly number of</p>	<p>Decline in lung function over six years (1978: Monday morning values were used; 1984: Workers were examined during the first three hours of a working day):</p> <p>Smoking and ex-smoking car painters had significantly larger lung function decrease compared with respective controls.</p> <p>Nonsmoking car painters displayed no faster deterioration in lung function than corresponding controls.</p> <p>Decrease in FVC correlated significantly with number of HDI-BT exposure peaks, but not with mean exposure.</p> <p>IgG and IgE, specific IgE in car painters:</p> <p>No significant differences in Ig levels between car painters and controls.</p> <p>No specific IgE found.</p> <p>Symptoms: Car painters reported significantly higher frequency of wheezing than the controls. Differences</p>	<p>Participation rate at follow-up 78 % among car painters and 81 % among controls.</p> <p>Selection bias (drop outs may have quit job because of respiratory symptoms, one asthma case known)</p> <p>Smoking not quantified</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>peak exposure situations up to 6000 for each car painter</p> <p>No close correlation between exposure peaks and mean exposure</p>	for other symptoms n.s.	
(Dahlqvist et al., 1995)	<p>Reanalysis of data from (Tornling et al., 1990) and (Alexandersson et al., 1987)</p> <p>Evaluation if lung function decrease within the week is a marker of vulnerability of further decrement in lung function</p> <p>Six-year follow up, two study occasions</p> <p>Original group of workers were randomly chosen from 14 garages in Stockholm, 28 car painters participated in all three spirometric examinations, only those 20 were chosen who had been working during</p>	<p>HDI</p> <p>Monomer and biuret trimer</p> <p>Car painters working with polyurethane paints</p>	<p>Individual exposure assessments by industrial hygienist (interview about working routines, respirator use, hygienic standards).</p> <p>81 exposure measurements for three tasks in 25 spray painting chambers.</p> <p>Peak exposure measurements were performed (sampling time < 3 min)</p> <p>TWA between 1978 and 1984 for the workers studied: HDI: 0.0014 mg/m³ HDI-BT: 0.09 mg/m³</p>	<p>Lung function (1978: spirometry on Monday before work after two days of no exposure and on Friday; 1984: spirometry during the first three hours of a working day)</p> <p>Changes in FEV₁ and FVC within the week were dichotomised.</p> <p>Ten workers had a decrease in FVC within the week.</p> <p>Ten workers had a decrease in FEV₁ within the week.</p> <p>Car painters in the initial study who showed a decrease of FVC within the week in 1978 had a significantly greater decline in FVC from 1978 to 1984 than car painters who did not (adjusted for smoking).</p> <p>Significant correlation between changes within the week and six years decline in FVC.</p> <p>Decline in FVC was not significantly correlated with the mean exposure to HDI or HDI-BT estimated during the</p>	<p>Uncertainties in exposure assessment</p> <p>Current smokers had on average a higher yearly number of peak exposures to HDI-BT than did ever smokers. May indicate less use of protective equipment by smokers.</p> <p>Smoking not quantified</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	the entire six years period n = 20			entire follow up. Six year decline in FVC was correlated to the yearly number of peak exposures to HDI-BT. Respiratory symptoms reported (for example three of 10 workers with change in FVC within the week in 1984 have cough, dyspnoea and/or wheeze).	
(Jones et al., 1992)	Cross-sectional, follow up Two plants n = 394 at the start of the study, through the fourth examination n = 435 had ever worked in one of the plants	TDI Production of flexible PU foam products	258 workers wore monitors on 507 shifts resulting in 4845 12-min samples: 9 % > 5ppb 1 % > 20 ppb TDI concentrations were assigned to groups of jobs. Information on the number of months spent in each exposure grouping was taken from personal records. Mean by plant and job area ranged from 1.17 to 4.47 ppb. Exposure measures: cumulative exposure from hire to first study examination cumulative exposure from	Lung function (spirometry, standing position, nose clips): Significant adverse effect of cumulative TDI exposure on initial level of FVC and FEV ₁ in current smokers. TDI exposure had no significant effect on lung function decline. Respiratory symptoms (questionnaire administered by trained interviewers): Chronic bronchitis more prevalent among those with higher cumulative exposure (controlled for smoking, age, sex). Metacholine challenge (n = 303): Metacholine responsiveness in 22 % of tested workers. Skin prick test with common inhalant allergens Total IgE, RAST	Co-exposure to different amines and other substances in foam production healthy worker (predicted values) differential misclassification of exposure (large number of samples < LOD)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>hire to the end of study</p> <p>cumulative exposure during the study period</p> <p>length of time exposed to concentrations > 5 and 20 ppb</p>		
(Akbar-Khanzadeh and Rivas, 1996)	<p>1) Cross-sectional (daily, weekly changes)</p> <p>2) Longitudinal (2.5-year follow up)</p> <p>1) n = 16 urethane mold operators n = 19 controls (final assembly department, office area)</p> <p>2) Oct 1989 – March 1992: n = 65 exposed to diisocyanates and solvents n = 40 exposed to solvents n = 68 controls (office, assembly, hardware department)</p>	<p>HDI monomer and polyisocyanate, combined with organic solvents (MDI)</p> <p>Encapsulated automobile glass plant</p>	<p>1) HDI monomer, HDI polyisocyanate, volatile organic compounds</p> <p>Personal and area samples</p> <p>HDI: 92 % < LOD (set to 50 % of LOD); mean concentration (personal, area): 1.55 ppb (n = 6), 0.65 ppb (n = 3)</p> <p>HDI polyisocyanate: 75 % < LOD; mean concentration (personal, area): 0.09 mg/m³ (n = 6), 0.02 mg/m³ (n = 3)</p> <p>2) Mean concentration: HDI 1 ppb (n = 8 samples)</p> <p>HDI polyisocyanate 0.29 mg/m³ (n = 5 samples)</p>	<p>1) Lung function (spirometry on Monday and Friday before and after shift):</p> <p>No significant differences between exposed and control group</p> <p>No significant reduction in lung function during workshift or during week in the exposed group compared to the control group. Some findings in subgroups by sex.</p> <p>Respiratory symptoms (questionnaire): Some symptoms more prevalent in control group (n. s. or not tested?).</p> <p>2) Lung function (spirometry before the shift):</p> <p>Significant decrease in lung function parameters in isocyanate/solvent-exposed group.</p> <p>Significant differences in lung function</p>	<p>No individual exposure estimates</p> <p>Very small number of air samples</p> <p>Control group appropriate?</p> <p>1) HDI in control area 0.67 ppb</p> <p>Co-exposure</p> <p>Smoking was significantly more prevalent in the exposed group</p> <p>2) Co-exposure</p> <p>Controls had no occupational exposure “between the two tests”</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			MDI 0.45 ppb (n = 7 samples)	change (FEV ₁ and FVC) among groups Respiratory symptoms (questionnaire): Proportion of subjects who developed respiratory symptoms in the isocyanate-exposed group was not significantly greater than that of the non-exposed group.	
(Clark et al., 1998)	5 years longitudinal UK n = 780 workers in 12 factories (n = 623 original + 157 naïve workers)	TDI Manufacture of PU foam	Personal monitoring (2294 measurements) for 100 job categories. Cumulative exposure between first and last lung function measurement was calculated for each subject based on job histories. 8-h TWA exposure limit of 5.8 ppb (46 ppbh for an 8h working day) was exceeded on 107 (4.7 %) occasions. Five of the 780 subjects (0.6 %) had a mean daily exposure exceeding the limit value. Peak exposure limit value of 20 ppb was exceeded in 500 (19 %) samples. 8.8 % of the peak measurements > 40 ppb Exposed group (n = 521):	Longitudinal decline in lung function (spirometry; three or more measurements): No significant effect of TDI on annual lung function change. For the naïve population, regression analysis showed a significant effect of mean daily exposure on annual changes of FEV ₁ and FVC. Due to irritant effect? Respiratory symptoms (questionnaire): Increase in respiratory symptoms in exposed group and handling group, significant for wheezing. 24 cases of respiratory sensitisation were identified during the study.	Followed up by Clark et al. 2003 High attrition rate (47 %) Leavers reported excess breathlessness and wheeze compared to non-leavers of the total population. Linear regression considered sex, group, age, age ² , smoking, mean daily exposure, peak exposure, pre-study exposure.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>manufacture of PU foam or handling freshly manufactured products; mean daily exposure 9.6 ppbh (1.2 ppb 8-h TWA)</p> <p>Handling group (n =123): handling cold PU products</p> <p>Low-exposure group (n =136): shopfloor and office workers</p>		
(Hathaway et al., 1999)	<p>Follow up (9 years)</p> <p>Production began in 1988, follow up through 1997</p> <p>n = 43 "potential cases" and n = 42 "potential controls" of another unit at the same plant</p> <p>n = 32 matched pairs (by smoking, sex, age and by race and height if multiple possibilities were available)</p>	<p>HDI</p> <p>Production of HDI biuret and trimer from monomer</p>	<p>Average number of years of potential exposure: 8.4</p> <p>Area and personal sampling (different methods and equipment over time)</p> <p>Exposure when not wearing respiratory protection was considered</p> <p>1992-1995 (personal monitoring): average (range):</p> <p>TWA during work not requiring respiratory protection in the unit (1 – 4 hours/day): 0.5 ppb (0.0 – 2.0 ppb); calculated as 8h-TWA: 0.13 ppb</p> <p>Highest daily peak</p>	<p>Lung function (as part of annual evaluation of workers):</p> <p>Average number of available tests for calculating slope: 7.8 (exposed) and 8.2 (controls).</p> <p>No significant difference in annual change of lung function (slopes) between exposed and control group.</p> <p>By smoking status, the results show more variation.</p> <p>Results seen as being within the range of lung function declines reported in other studies.</p>	<p>Exposure not measured on individual level</p> <p>Smoking not quantified</p> <p>Height and race only partially controlled</p> <p>Co-exposure in control group reported (depending on work area): cerium and neodymium oxides, nitric acid, ammonia, kerosene, tributyl phosphate</p> <p>Qualitative information on potential drop outs: low turnover rate, few transfers between the units, subject attrition not been a problem</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>exposure: 2.9 ppb (1.0 – 10.0)</p> <p>Exposure before 1992 believed to be somewhat higher (no quantification)</p>		
(Petsonk et al., 2000)	<p>Health surveys prior to the use of diisocyanates and every six months thereafter over two years</p> <p>n = 276 workers were employed over the 2-year period; n = 144 had baseline and follow-up data as well as data on occupational history</p>	MDI oligomer and prepolymer for coating wood products	<p>Two exposure indices were assigned to individuals and to work areas, each with three categories.</p> <p>1) individual: reported involvement with diisocyanates or diisocyanate-containing products</p> <p>2) work area: level of potential exposure to liquid MDI resin, based on the percentage of workers reporting exposure</p>	<p>Asthma-like symptoms based on a questionnaire: initial asthma-like symptoms (IAS) follow-up asthma-like symptoms (FAS) new-onset asthma-like symptoms (NAS)</p> <p>Prevalence of NAS was 27 % in workers of the highest exposure potential to liquid MDI and 0 % in the lowest exposure category.</p> <p>Prevalence of NAS and FAS cases increased with categories of potential exposure to liquid MDI.</p> <p>FAS and NAS were significantly more prevalent among workers that reported that they had briefly removed respiratory protection than among workers who reported that they never do this.</p> <p>Prevalence of NAS and FAS were higher in the workers who reported a MDI stain on their skin than in workers that reported they had never observed a stain.</p> <p>Individual reports of work involving</p>	<p>Not suitable for deriving reference values because of missing exposure measurements</p> <p>Current smoking was considered in the logistic model of FAS.</p> <p>Prevalence data of FAS and NAS were stratified by current smoking (n = 32).</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				exposure to liquid MDI were significantly associated with FAS (logistic regression model).	
(Ott et al., 2000)	<p>Historic cohort study using medical records and exposure records from 1967 to 1997</p> <p>n = 313 employees ever assigned to the TDI production unit for >= 3 months; n =158 referent employees; 40 records were not found (16 of the study group and 24 of the reference group)</p>	TDI manufacturing	<p>Duration of TDI unit assignments:</p> <p>5.7 years (average, men)</p> <p>4.7 years (average, women)</p> <p>3 months to 30 years (range)</p> <p>1967 (area sampling): < 10 ppb in most areas and 25 ppb in the residue handling area</p> <p>1969-1973: < 10 ppb in most areas with 60 to 80 ppb in certain areas</p> <p>1976-1988 (personal 8 hour samples, paper type method): 5.9 ppb (average)</p> <p>1989-1997 (personal 8 hour samples, filter method); 2.8 ppb (average)</p> <p>JEM: Industrial hygiene measurements were linked to job-specific work history per person; peak exposure and 8h-TWA concentration were aggregated on a job and time specific basis for</p>	<p>Occupational asthma:</p> <p>Case identification was based on site physician. One episode of asthma-like symptoms was not enough to be an OA case.</p> <p>19 asthma cases presumed to be due to TDI, 9 skin allergies, 1 case of asthma and skin disease</p> <p>Yearly incidence: 19 cases in 1779 work-years = 1.1 %; before 1980: 1.8 %; since 1980: 0.7 %</p> <p>Cumulative incidence for people assigned to TDI unit at least 20 ys: 11.5 % (95 % CI 5.3-17.7 %)</p> <p>7 of 19 cases had reported previous incidents of exposure to TDI (2 related to rashes that had developed while handling TDI or waste products containing TDI)</p> <p>Respiratory symptoms:</p> <p>Since 1980 a standardised questionnaire was used that contained four questions with dichotomous answers (concerning wheezing/cough/chest discomfort/shortness of breath).</p>	<p>Long follow-up time</p> <p>Exposure concentration linked to the asthma incidence not clear. The review of Ott et al. 2003 reports for this study an exposure of 0.3 – 2.7 ppb (TWA; range by job) since 1980, assigning this to a yearly incidence of 0.7 %.</p> <p>Peak exposure and dermal exposure make it difficult to evaluate the 8h-TWA.</p> <p>Smoking, non-occupational asthma and allergy were assessed.</p> <p>Exposure to phosgene</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>three job groups (potentially low/moderate/high TDI exposure); cumulative dose estimates (ppb-months)</p> <p>Average TDI concentration: < 5 ppb for 59 % of the workers</p> <p>Cumulative TDI dose: < 500 ppb-months for 89 % of the workers</p> <p>Frequencies of peak exposure > 20 ppb per shift: 0.5 in moderate exposure jobs, 0.9 in high-exposure jobs</p>	<p>No significant associations with responses in the questionnaires were found for those exposed to TDI versus referents.</p> <p>Lung function (spirometry):</p> <p>Neither cross-sectional nor longitudinal analyses of FVC and FEV₁ showed significant dose-response findings relative to exposure to TDI across the total exposed population.</p>	
(Bodner et al., 2001)	<p>Longitudinal, data taken from routine medical surveillance examinations offered every 1 to 2 years</p> <p>Cross-sectional analyses (symptoms before entry and at last examination)</p> <p>Data from 1971-1997, mean follow-up ca. 8 years</p> <p>Dow Chemical, Texas, USA</p>	<p>TDI</p> <p>Manufacture</p>	<p>Mean observation period of TDI workers 7.8 years (SD 6.2)</p> <p>n = 449 8-h TWA TDI samples in 20 job categories; mean TDI exposure values per category calculated for start-up period (1971-1979) and full production period (1980-1997); individual work histories were matched to the 20 job categories to produce average exposure estimates and cumulative exposure estimates for each work segment for each</p>	<p>Clinical symptoms (questionnaire):</p> <p>One of the symptoms significantly more prevalent in controls than in exposed subjects at baseline (shortness of breath). Prevalence for all symptoms increased in both groups over time. Prevalence of symptoms not higher in TDI exposed subjects compared to controls at final examination.</p> <p>No effect of TDI on clinical symptoms reported during the study period found in regression models using four cumulative exposure categories or using a continuous cumulative variable or using quartiles of exposure.</p>	<p>Longest follow-up time (together with Ott et al. 2000) for TDI workers until then.</p> <p>Retrospective (change of formats of health surveys)</p> <p>Not enough exposure samples to derive annual TDI concentration estimates for each year for each job category</p> <p>Regression analyses for symptoms were adjusted for observation period and pack-years. Covariates</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>n = 305 TDI exposed workers</p> <p>n = 581 controls (hydrocarbons department)</p>		<p>worker</p> <p>Mean TDI concentration per individual: 2.3 ppb (SD 1.0), max. 5.2 ppb</p> <p>Average cumulative TDI exposure: 96.9 ppb-months (SD 110.6), max. 639 ppb-months</p> <p>Quartiles of the cumulative TDI estimates: 1-29 ppb-month, 30-70 ppb-month, 71-133 ppb-month, > 133 ppb-month</p> <p>Exposure categories with cut-points at 1 ppb for 1, 5, 10 years, expressed in ppb-month (distribution for all observations): 1-12 (8.3 %), 13-60 (36.6 %), 61-120 (27.1 %), > 120 (27.0 %)</p>	<p>Lung function (spirometry):</p> <p>Average annual decline in FEV₁ was 30 mL.</p> <p>No association of TDI and decline in lung function found with mixed regression models using different exposure terms and subgroups.</p>	<p>considered for the mixed models for longitudinal lung function change were initial FEV₁, initial FVC, age, observation period, height, race, sex, race, entry period, pack-years, asthma, shortness of breath</p> <p>No exposure to MDI (as in some foam-manufacturing operations)</p>
(Clark et al., 2003)	<p>17-year longitudinal 1981-1998</p> <p>UK</p> <p>Follow-up of Clark et al. 1998</p> <p>7 of 12 factories remained</p>	<p>TDI</p> <p>Manufacture of PU foam</p>	<p>Personal measurements:</p> <p>n = 1004 valid</p> <p>1.3 % in excess of 46.4 ppbh (5.8 ppb, 0.02 mg NCO/m³)</p> <p>Respiratory protection taken into account by subtracting 50 % of calculated exposure</p>	<p>Longitudinal decline in lung function (same spirometer as in previous study; earliest measurement during 1981-1986 + further measurement in 1997/1998 used): Significantly higher loss in FEV₁ and FVC in handling group vs. low exposure group. Annual decline of FEV₁ and FVC not associated to TDI exposure.</p> <p>Respiratory symptoms (questionnaire): Differences in</p>	<p>Study was not designed to identify cases of sensitisation</p> <p>Persons showing evidence of TDI sensitisation would be removed and would no longer be available for study</p> <p>High attrition rate</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 251 (217 were in the previous study)		<p>values</p> <p>Average daily dose for each exposed job at each factory calculated from the current and previous measurements</p> <p>Mean exposure for the period:</p> <p>Exposed group (n = 175): 8.4 ppbh</p> <p>Handling group (n = 26): 4.8 ppbh</p> <p>Low exposure group (n = 11): 2.3 ppbh</p>	<p>prevalence of respiratory symptoms between initial and final survey (reduction in some, increase in other symptoms).</p>	<p>Respiratory illness was the reason for leaving in 2.3 % of cases</p> <p>70 subjects out of 251 (28 %) changed groups during the 17-year period</p> <p>Number of present smokers fell from 129 (51 %) to 100 (40 %) between the two studies</p> <p>Only two data points used for lung function decline</p>
(Wang and Petsonk, 2004)	<p>Same cohort as in (Petsonk et al., 2000)</p> <p>(Initial survey before initial use of MDI in the plant, follow-up surveys at 2/8/14 and 20 months after initial use of MDI) n = 132</p>	MDI oligomer and pre-polymer for coating wood products	<p>Any contact with liquid MDI (respiratory or skin) reported: n = 39;</p> <p>no contact reported: n = 93</p> <p>(Further binary exposure groups for wood dust and smoking)</p>	<p>Five respiratory symptoms were assessed by a questionnaire (Attacks of dyspnoea with wheeze/attacks of dyspnoea or cough at rest/Chest tightness/Cough/Phlegm). Symptom incidence was recorded at a follow-up regardless of whether or not it had been reported on a previous or subsequent follow-up.</p> <p>Multiple logistic regression for repeated measurements of symptom onset showed that workers exposed to liquid MDI had about two to four times greater odds of developing these symptoms. Significant for all outcomes except for cough.</p>	<p>Not suitable for deriving reference values because of missing exposure measurements.</p> <p>Logistic regression adjusted for age, smoking, wood dust exposure, tenure</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Dragos et al., 2009)	<p>Prospective inception cohort study, 18 months</p> <p>n = 385 apprentice car-painters recruited between 1999 and 2002, complete data for n = 298</p> <p>First visit upon entry and second visit at the end of the training programme</p> <p>Montreal area, Canada</p>	HDI monomers and oligomers	<p>Personal breathing zone samples (n = 51) during regular and specific activities</p> <p>Area sampling (n = 41) in spray cabins and workplace background</p> <p>Duration for effective exposure to HDI max. 7 months, median 3 months</p> <p>Median (maximum) concentration in $\mu\text{g}/\text{m}^3$, personal samples: Monomer: Spraying 0.001 (0.006) Mixing 0.0003 (0.0003) Brush cleaning < LOD</p> <p>Oligomer: Spraying 0.283 (0.916) Mixing 0.4365 (0.6890) Brush cleaning 0.079 (0.079)</p> <p>Concentrations from area sampling were lower than</p>	<p>Health assessment included:</p> <ul style="list-style-type: none"> - Respiratory symptoms (questionnaire) - Lung function (spirometry) - Metacholine challenge - Skin prick tests (only first visit) - HDI-specific IgE, IgG and IgG4 <p>Aims:</p> <ul style="list-style-type: none"> - describe changes in specific antibodies to HDI - describe incidence of work-related symptoms - examine association between work-related symptoms and changes in specific antibody levels, and other potential risk factors <p>Increases in specific IgE and IgG levels > 97th and 95th percentile were significantly associated with duration of exposure (9 subjects increased their IgG levels /IgE levels above the cut-off of the 97th percentile).</p> <p>Increases in specific IgG and IgG4 showed a protective effect on the incidence of work-related lower and upper respiratory symptoms, respectively.</p> <p>13 subjects (4.4 %) developed work-related respiratory symptoms, 19 (6.4 %) developed work-related symptoms of rhinoconjunctivitis.</p>	<p>Subjects lost to follow-up 21.5 %</p> <p>Short observation period</p> <p>Pre-exposure possible</p> <p>No individual exposure estimates</p> <p>Masks worn when spraying, but not always those recommended and often removed inappropriately for inspecting the work.</p> <p>In regression analysis (dependent variable: IgE or IgG) only duration of exposure was used, but no concentration.</p> <p>At the exposure level in this study and after a few months, a small proportion shows increases in HDI-specific IgG and IgE</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			from personal sampling	No association between change in IgE levels and incidence of symptoms.	
(Cassidy et al., 2010)	<p>Matched retrospective cohort study</p> <p>Expands on Hathaway et al. 1999 (includes an additional plant)</p> <p>Observation period: Plant 1 1988-2007 Plant 2 1987-2006</p> <p>Southern US</p> <p>n = 57 potentially exposed in plant 1 and 43 in plant 2 (mainly exposed to HDI monomer)</p> <p>controls: plant workers without documented history of exposure to diisocyanates</p> <p>1:1 matching by age, gender, race, smoking status, date of birth, date of hire</p>	<p>HDI</p> <p>Two plants manufacturing or producing monomer and/or polyisocyanates</p>	<p>Industrial hygiene personal samples</p> <p>If record indicated that respiratory protection was used, sampling record was not considered</p> <p>Mean (range): Plant 1, 237 samples 0.79 ppb (Non detectable – 31 ppb) Plant 2, 29 samples 0.3 ppb (Non detectable – 2 ppb)</p> <p>Most of the study group reported some instances of dermal exposure</p>	<p>Asthma (annual medical surveillance history forms; suspect cases were inspected further by a company physician): No new asthma cases were reported.</p> <p>Changes in lung function over time (annual spirometry), examined by a random coefficient regression model: Decline in lung function (FEV₁, FVC) over time in the exposed group was significantly greater than in the control group.</p>	<p>No quantitative exposure estimations on the individual level</p> <p>Small number of exposure samples to reflect whole study period</p> <p>Smoking was assessed as binary variable. Controls may have been heavier smokers (significant difference in lung function decline between smoking controls and smoking exposed)</p> <p>Potential co-exposures reported:</p> <p>Exposed group: Other aliphatic diisocyanates, HDI polyisocyanates</p> <p>Control group from plant 1: dinitrotoluene, hydrazine, methylene chloride, maleic anhydride, toluene diamine, ethylene oxide</p> <p>Control group from plant 2: cerium, neodymium</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
					<p>oxides, nitric acid, ammonia, kerosene, tributyl phosphate (depending on work area)</p> <p>No employee had to be medically removed because of HDI exposure</p> <p>Individuals with asthma were excluded from work with potential exposure (only in plant 1) and there may have been self-deselection.</p>
(Löfstedt et al., 2011)	<p>4-year follow up after improvement in work environment 2001-2005 Sweden</p> <p>Original study see Löfstedt et al. 2009</p> <p>n = 25 (92 % male) foundry workers</p> <p>n = 55 (85 % male) referents</p>	Isocyanic acid, methyl isocyanate, formaldehyde	<p>Exposure measurements and lung function measurements on the same day</p> <p>Individual exposure measurements</p> <p>Exposure levels were reduced by 50 % at follow-up</p> <p>Geometric mean 2001 and 2005:</p> <p>ICA: 22 and 13 $\mu\text{g}/\text{m}^3$</p> <p>MIC: 6.0 and 3.1 $\mu\text{g}/\text{m}^3$</p> <p>Formaldehyde: 66 and 35</p>	<p>Lung function (spirometry before and after a day shift):</p> <p>Pre-shift FEV₁ slightly lower in exposed group than in referent group.</p> <p>No significant change in lung function over the shift.</p> <p>Respiratory and ocular symptoms (same questionnaire as in 2001):</p> <p>Lower airway symptoms were less frequent in both groups than in 2001, still a high prevalence of nasal and ocular symptoms in both groups.</p>	<p>Loss of almost 40 % of the participants of the original study</p> <p>Higher prevalence of nasal symptoms among workers exposed in 2001 but not exposed in 2005 than workers still exposed in 2005 → Healthy worker effect in the group that was still exposed in 2005</p> <p>Co-exposures present</p> <p>Unclear if respiratory symptoms are due to irritant or immunological response. Authors think immunological response is</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			<p>$\mu\text{g}/\text{m}^3$</p> <p>No respiratory protection for workers</p>		unlikely.
(Gui et al., 2014)	<p>Inception cohort study</p> <p>Evaluation of n = 49 newly hired workers pre-employment, after 6 months and after 12 months</p> <p>Grouping of workers in exposure risk groups, based on potential risk of TDI exposure: low n = 8, medium n = 28, high n = 13.</p>	TDI-based state-of-the-art PU foam production in Eastern Europe	<p>Continuous fixed-point air sampling in foaming hall and cutting areas.</p> <p>90 % of the samples < LOD (0.1 ppb).</p> <p>Maximum recorded 10.0 ppb (foaming hall), 5.4 ppb (cutting area)</p> <p>No air sampling period exceeded an 8h-TWA of 5 ppb</p> <p>Peak exposures recorded were below 20 ppb.</p> <p>Personal sampling performed on seven workers. All showed TDI levels < LOD.</p> <p>Dermal exposure occurred (uncured or just cured foam, contaminated surfaces).</p>	<p>Over the first year of employment, 7 workers (14 %) had findings that could indicate TDI-related health effects (Either new asthma symptoms, TDI-specific IgG, new airflow obstruction or a decline in $\text{FEV}_1 \geq 15 \%$).</p> <p>Twelve workers (25 %) were lost to follow-up. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up.</p> <p>No significant associations were found between the exposure risk group and health outcomes.</p> <p>Self-reported glove use differed significantly between the exposure risk groups (25 % of the workers in the low, 32 % in the medium, 100 % in high exposure risk group).</p> <p>Although this production facility is reported to be state-of-the-art with exposure below the OEL, the study suggests possible TDI-related health-effects.</p>	<p>Actual exposure of the individual is not known: TDI air levels may have been higher near the source. Dermal exposure occurred. Glove use differed between exposure risk groups.</p> <p>No unexposed control group</p> <p>No exposure quantification per exposed group</p> <p>Workers with spirometry data at baseline n = 23, with spirometry data at all three time points n = 16. Baseline spirometry conducted at another facility.</p>

Table 3-4: Case-control studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Tarlo et al., 1997)	Comparison of the level of isocyanate Concentration in 20 "case companies" (with compensated isocyanate asthma claims) with 203 "non-case companies"	TDI, MDI, HDI (or more than one)	Exposure data taken from a database of the Ontario Ministry of Labour (MOL): air samples collected during the same 4-year period during which the OA claims arose. Exposure determined on the basis of the highest level identified. Two categories: Always < 0.005 ppm Ever ≥ 0.005 ppm	56 accepted claims for OA (OA cases with identified isocyanate exposure during the 4-year period from mid-1984 to mid-1988 in the Ontario Workers' Compensation Board) Combined across isocyanate types: Companies with claims in the high exposure category: 10/20 (50 %) Companies without claims in the high exposure category: 50/203 (25 %) OR = 3.1 (95 % CI: 1.1–8.5, p = 0.03). MDI: OR = 1.7 (95 % CI: 0.4–7.6) TDI: OR = 2.7 (95 % CI: 0.7–10.6) Estimated incidence of OA in a 4 year study period: High exposure companies with claims: 2.7 % Low exposure companies with claims: 2.2 % Overall incidence in the total 223 companies surveyed: 0.9 % (56 out of 6308 workers).	Many high exposure companies without claims. Other factors may be important in isocyanate sensitisation, or there may have been quantitative or qualitative differences in exposure that were not assessed. Selection bias possible (some of the air sampling conducted in investigation of submitted claims for OA) Companies with claims had more employees than those without claims (higher probability of at least one employee becoming sensitized in a greater group of employees; larger companies may be more likely to implement a surveillance program).
(Meredith et al., 2000)	Company A: 27 OA cases were matched to 51 referents (sex, work area) Company B: 7	Company A: 24 cases attributed to TDI (manufacture of moulded and block flexible PU	Company A: Personal exposure measurements by job category (1979-1986) made for a separate	Asthma Data from the two sites were analysed separately. Company A:	Uncertainties in exposure assessment Regression analyses adjusted for smoking and different atopic diseases

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	cases; all non-cases (n = 12) served as controls, because matching was not possible (moving between work areas, few workers)	foam, flame bonding and surface coating of fabrics); 3 cases attributed to MDI (batch moulding of rigid PU components at 200°C) Company B: Cases attributed to MDI from a chemical plant in which MDI and poly-merric MDI mixtures were pro-cessed and poured into drums. Some processes involved heating the mixtures.	study + data collected after 1986 by occupational hygiene consultants were used to estimate 8h-TWA and peak exposure for each subject based on job title and date. Company B: Personal monitoring results from 1988 available (Marcali method to the middle of 1990, HPLC thereafter) For each subject, the proportion of measurements \geq LOD of the Marcali method (2 ppb) and $>$ 5 ppb were calculated. Measurements $<$ 2 ppb were treated as being 0. 90 % of the 269 TWA samples were $<$ 2 ppb	Conditional logistic regression: 8h-TWA as a binary variable (cut off: median concentration in control group) or continuous variable (0.1 ppb increments) Peak exposures: 1 – 50 ppb In 31 subjects peak exposure $>$ 20 ppb No difference between cases and controls. Mean 8-h TWA: cases: 1.5 ppb; controls: 1.2 ppb OR for exposure $>$ median of the control group: 3.2 (95 % CI 0.96 – 10.6; p = 0.06) Adjusted OR (for 0.1 ppb increase in 8h-TWA): 1.07 (95 % CI 0.99 – 1.16) Adjusted OR higher for smoking (2.4) as well as history of either hay fever, eczema or asthma (3.4), but also n.s. Company B: Association between reported chemical accidents and asthma.169/185 TWA samples for controls and 74/84 for cases were $<$ 2ppb. Mean and median exposures were $<$ LOD for cases and controls. Median of the highest concentration recorded for each subject was 3 ppb for both groups. Proportion of measurements \geq 2 ppb was 0.09 (controls) and 0.18 (cases). Proportion of measurements $>$ 5 ppb was 0.004 (controls) and 0.09 (cases).	Amines are used as catalysts in the manufacture of PU foams and they have been reported to cause respiratory symptoms

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				3/7 cases and 1/11 controls had at least one 8h-TWA exposure measurement > 5 ppb (OR 7.5; p= 0.09)	

Table 3-5: Cross-sectional studies with quantitative exposure-response estimates

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Pronk et al., 2007)	n = 581 (n = 241 spray painters n = 50 unexposed office workers n = 290 others) Workplace survey in several companies between 2003 and 2006	HDI monomer and trimers in spray painting (car body repair shops, furniture paint shops, industrial paint shops specialising in ships and harbour equipment or airplanes)	Personal exposure estimates were obtained combining personal task-based inhalation measurements for 23 different isocyanate compounds and time activity information Exposure of n = 241 spray painters, [$\mu\text{g NCO} \cdot \text{m}^{-3} \cdot \text{h} \cdot \text{mo}^{-1}$], median (min-max): Total isocyanate 3,682 (4-66464) HDI 27 (0.2-1427) Biuret 269 (0.2-13568) Isocyanurate	Prevalence ratios (PR) and 95 % CI for an interquartile range increase in exposure were calculated based on log-transformed exposure data. Respiratory symptoms (grouped into "asthma-like symptoms" and "COPD-like symptoms"), work-related symptoms (questionnaire): Respiratory symptoms were more prevalent in exposed workers than in office workers. Significant positive log-linear exposure-response associations were found for: Asthma-like symptoms PR (95 % CI) = 1.2 (1.0-1.5), COPD-like symptoms 1.3 (1.0-1.7), Work-related chest tightness 2.0 (1.0-3.9) and Work-related conjunctivitis 1.5 (1.0-2.1), but not for Work-related rhinitis	For subsample with BHR see (Pronk et al., 2009) Prevalence Ratios were adjusted for age, sex, current smoking and atopy (or some of those) Possible effect modification by atopy was explored

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			2250 (6-87623)	<p>1.3 (0.9-1.7)</p> <p>Different HDI-specific (for monomer and oligomers) IgE and IgG antibodies:</p> <p>Prevalence of specific IgE antibodies was low (up to 4.2 % in spray painters). Prevalence of specific IgG was higher (2-50.4 %). One of five specific IgE antibodies and four of five specific IgG antibodies were positively associated with exposure.</p> <p>Bronchial hyperresponsiveness (BHR) assessed by methacholine challenge in a subset of 229 workers</p> <p>Individuals with asthma-like symptoms were more likely to have BHR: PR (95 % CI) = 2.2 (1.5-3.2)</p> <p>For COPD-like symptoms, the association with BHR was less strong and n. s.</p>	
(Pronk et al., 2009)	<p>Subset of study by Pronk et al. 2007</p> <p>n = 229 from 38 companies</p> <p>(n = 91 spray painters n = 20 unexposed office workers n = 118 others)</p>	HDI monomer and trimers in spray painting	<p>Personal exposure estimates were obtained combining personal task-based inhalation measurements for 23 different isocyanate compounds and time activity information</p> <p>Exposure of n = 91 spray painters, [$\mu\text{g NCO}/\text{m}^3 \times \text{h}/\text{mo}$], median (min-max):</p> <p>Total isocyanate 4530 (15.4-66464) HDI</p>	<p>Prevalence ratios (PR) and 95 % CI for an interquartile range increase in exposure were calculated based on log-transformed exposure data.</p> <p>Lung function:</p> <p>Highly exposed workers had lower FEV1, FEV1/FVC and flow-volume parameters. Percentage of workers who met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD (FEV1/FVC <70 %):</p> <p>office workers 5 other workers 4 spray painters 15</p> <p>COPD clearly associated with exposure. PR (95 % CI): 2.7 (1.1-6.8)</p>	<p>Associations were adjusted for age, sex, current smoking and atopy</p> <p>Associations for lung function parameters: additionally adjusted for height and race</p> <p>Strengths: Quantitative inhalation exposure assessment based on > 500 measurements and detailed task activity information; Several objective respiratory effect measures investigated in one population</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			36.2 (1.3-472)	<p>Bronchial hyperresponsiveness (BHR) (defined as a provocative cumulative dose of methacholine of ≤ 2.5 mg (~ 10 μM) required to cause a 20 % fall FEV₁):</p> <p>Percentage of workers with hyperresponsiveness (BHR₂₀): office workers 0/ other workers 14.7/ spray painters 20.</p> <p>Hyperresponsiveness was found in 33 subjects and it was clearly associated with exposure expressed as total NCO. PR (95 % CI): 2.0 (1.1-3.8) (adjusted for smoking, age, sex and atopy)</p> <p>BHR combined with asthma-like symptoms was present in 19 subjects and the adjusted PR was 2.7 (1.0-6.8).</p> <p>Symptoms (see (Pronk et al., 2007)): Asthma-like symptoms, COPD-like symptoms, work-related chest tightness were more prevalent among workers with higher exposure (n. s.).</p> <p>Workers with asthma-like symptoms had sign. more BHR, sign. lower baseline FEV₁, FEV₁/FVC and maximal mid-expiratory flow.</p> <p>No sign. association between exposure and exhaled nitric oxide (eNO)</p> <p>IgE and IgE (see (Pronk et al., 2007)): The prevalence of specific IgE antibodies was low</p>	<p>Limitations: Use of personal protective equipment, previous exposures and dermal exposure was not taken into account; Complex exposure environment; Healthy worker effect possible</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				<p>(< ~4.4 %). The prevalence of specific IgG was higher (up to 47 % in spray painters). Specific IgG sensitisation was more common in highly exposed workers.</p> <p>Workers with specific IgE/IgG were more often hyperresponsive (overall; statistically significant only for one IgG).</p> <p><i>"The current study provides evidence that exposure to isocyanate oligomers is related to asthma with bronchial hyperresponsiveness as a hallmark, but also shows independent chronic obstructive respiratory effects resulting from isocyanate exposure."</i></p>	

Table 3-6: Further studies - cross-sectional studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Bruckner et al., 1968)	<p>Cross-sectional</p> <p>n = 26 with multiple exposures to diisocyanates</p> <p>n = 18 had never worked with or around isocyanates</p>	<p>TDI, polymeric isocyanates including MDI, xylylene diisocyanate</p> <p>Research, development and production</p>	<p>Exposed workers had accumulated exposure from 3 months to 11 years</p> <p>Air samples taken by industrial hygienist, modified Marcali method. Between 3 and 79 samples per year for single years between 1957 and 1967.</p> <p>Median concentration per year: 0-77 ppb</p>	<p>Symptoms (interview, physical examination)</p> <p>Immunologic reactivity to isocyanate antigen conjugates (several tests)</p> <p>Four groups:</p> <ul style="list-style-type: none"> - Exposed minimal response (minimal symptoms of mucous membrane irritation) n = 5 - Exposed overdose response (moderate to marked signs and symptoms of chemical irritation of the respiratory tract) n = 16 - Exposed sensitised (signs and symptoms of 	Groups built based on exposure and type of response

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		of isocyanates and other components of urethane plastics		<p>sensitisation) n = 5: With increasing number of exposure, the time to reaction became shorter and finally bronchospastic symptoms developed within seconds after exposure to minute amounts of isocyanates. All had irritative symptoms before developing symptoms indicative for sensitisation. All had exposures > 20 ppb.</p> <p>- Non-exposed n = 18</p> <p>n = 6 cases of irritant dermatitis</p> <p>Workers exposed to low levels (not given) of isocyanates developed eye, mouth and throat symptoms. According to the authors concentrations between 20-100 ppb "may predispose some workers to sensitivity to isocyanate compounds"</p>	
(Wegman et al., 1974)	<p>Cross-sectional</p> <p>1972</p> <p>Before and after shift on a Monday after three days away from work</p> <p>n = 111 (78 males)</p>	<p>TDI</p> <p>Manufacture of PU for mattresses and auto seat cushions</p>	<p>Area sampling on the day of lung function testing and on three subsequent days (Marcali method)</p> <p>All job areas were sampled and assigned exposure values and each worker was categorised according to his or her exposure to a measured mean concentration of TDI.</p> <p>Originally exposure categories were combined to four groups (ppm): A 0.002 - 0.003</p>	<p>Lung function (spirometry: FEV₁, FVC; in the morning before work and in the afternoon after eight hours work; only FEV₁ reported):</p> <p>All exposure groups showed significant loss in lung function (FEV₁) during the working day.</p> <p>Dose response relationship suggested (mean change in FEV₁ 0.078 L in group A and 0.180 L in group D). Confirmed by regression analyses. And confirmed by calculation of ratios of those showing no change or increase over those showing decrease per exposure group (ratio increases with exposure group).</p> <p>Greater fall in FEV₁ in workers with symptoms compared to workers without symptoms,</p>	<p>Followed up: (Wegman et al., 1982; Wegman et al., 1977)</p> <p>Age, height, years smoked, cigarettes smoked, duration of exposure was considered for stepwise regression analysis</p>

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			B 0.004 C 0.005 D 0.006 – 0.013	n. s. No trend of FEV ₁ across subgroups of age, years of smoking or years of employment.	
(Pham et al., 1978)	Cross-sectional Two factories producing mainly plastic foam automobile accessories n = 318 workers (214 men) who had been employed for at least a year	MDI PU foam moulding	Workers used MDI and some TDI for 1 to 10 years. Plant A: MDI consistently < 20 ppb Plant B: MDI peaks up to 87 ppb at foam injection workplaces Group I: Not exposed to any occupational hazard n = 83 (62 men) Group II: Indirect exposure risk due to foam plastics manufacture n = 117 (61 men) Group III: Definite, direct exposure risk due to foam plastics manufacture n = 118 (91 men)	Lung function (single breath carbon monoxide transfer factor test, spirometry): Lower values of VC and diffusion constant in the exposed groups and associated with length of exposure. Possibility of fibrosis in workers with long exposure suggested. Results for men not confirmed by results for women. Respiratory symptoms (questionnaire): Higher frequency of bronchitis in exposed groups compared to unexposed group (men and women).	Followed up by (Pham et al., 1988) Exposure on factory level Men and women analysed separately Exposure to stripping agents, solvents, polyvinyl vapour in exposed groups Exposure to TDI No statistically significant differences between the groups concerning age, height, weight, smoking. More men smoke than women and they are heavier smokers.
(Holness et al., 1984)	Cross-sectional, shift, intraday, intraweek 1982 Toronto area	TDI Use in foaming operations	Mean length of exposure to isocyanates of 6.5 years Monitoring of TDI and respirable dust during same shift as lung function analysis (area samples;	Lung function (spirometer, beginning and end of work shifts on Monday, Wednesday, Friday, sitting position using noseclips): Values of all lung function parameters (Monday morning) lower in the exposed than in the control group (not significant, adjusted	Respirable dust, mean for all exposed: 0.30 mg/m ³ Significantly lower frequency of family history of asthma, hay fever, bronchitis in exposed group (may be due to

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>Four companies</p> <p>n = 95 isocyanate-exposed workers (70 % males, n = 26 foam-line, 11 injection, 28 finishing, 21 miscellaneous)</p> <p>n = 37 control workers (62 % males; n = 16 plant, 21 Ministry of Labour)</p> <p>(n = 29 were excluded)</p>		<p>personal samples for 86 workers)</p> <p>Mean exposure concentration for five groups of workers: Area: 0.1 – 1.8 ppb Personal: 0.6 – 2.1 ppb</p> <p>Mean for all exposed: Area: 0.6 ppb Personal: 1.2 ppb</p> <p>Some analyses with three exposure categories: control, ≤1ppb, >1ppb</p> <p>One personal sample > 20 ppb</p> <p>Less than 3 % of the personal or area values > 5 ppb</p>	<p>for smoking).</p> <p>Significantly larger declines in lung function over the shift in exposed workers.</p> <p>Decline in FVC and FEV₁ over the shift increased over the three exposure categories, but was statistically significant only between controls and exposed groups.</p> <p>No significant relationships observed in regression analysis with continuous exposure.</p> <p>Respiratory and further symptoms: Slightly higher frequency of respiratory symptoms in exposed group, n. s..</p>	<p>screening prior to employment or workers with positive family history may have developed symptoms and left).</p>
(Venables et al., 1985)	<p>Cross-sectional (Outbreak of asthma was investigated)</p> <p>1979</p> <p>n = 221</p>	<p>TDI</p> <p>Steel coating plant; continuous process, coat was cured by passage through an</p>	<p>TDI:</p> <p>14 ppb at oven entry during normal processing, up to 26 ppb during 5 minute stoppage</p> <p>TWA 1979: 20 ppb</p>	<p>21 workers (9.5 %) with OA symptoms (questionnaire) in 7 years (onset of symptoms after 1971)</p> <p>Symptomatic groups had significantly lower FEV₁ than asymptomatic group.</p> <p>TDI was found to be the cause of the asthma outbreak. It was liberated by a coating modified by a supplier in 1971.</p>	<p>No individual exposure levels</p> <p>Affected individuals may have left the plant</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Alexander sson et al., 1985)	Cross-sectional n = 67 (57 males) n = 56 controls (11 with lung function tests)	TDI, MDI Seven PU foam manufacturing factories (two foam PU blocks, five cast PU in moulds)	Personal sampling on same day as lung function tests Day mean exposure to TDI in foaming of PU blocks: for the whole group: 0.008 mg/m ³ (0.001 ppm) Highest exposure in the group working by foaming machine: 0.023 mg/m ³ (0.008-0.060) Day mean exposure to MDI ≤ 0.001 mg/m ³ during casting in moulds. Highest measurement: TDI 0.275 mg/m ³ MDI 0.139 mg/m ³	Lung function (spirometry: FEV ₁ , FVC, FEV %, MMF; nitrogen washout: Phase III, Closing volume; in the morning prior to work; exposed workers were studied again in the afternoon after work): Lung function of non-exposed group similar to reference values. Lung function of exposed group significantly impaired as compared to reference values, but significant in subgroup of smokers only. No significant changes during work shift. Symptoms (standardised questionnaire): Frequency of symptoms significantly higher in exposed non-smokers than in non-exposed non-smokers (nose, throat, dyspnea). No significant difference in symptoms frequency between exposed and non – exposed smokers.	To calculate day exposure figures < detection limit (0.001 mg/m ³) were set to zero. Selection bias (underestimation of acute adverse effects of TDI as sensible individuals may tend to terminate their employment)
(Alexander sson et al., 1986)	Two cross-sectional studies 1977: n = 18 1980: n = 8 n = 23 males n = 5 males Employees who	NDI Rubber plant Manufacture of plastic polymer (component of tires),	Measurements in 1980: 8 subjects carried filter pumps, air samples were collected in breathing zone over 15 min during the course of various tasks on the day of the study Mean (range): Moulding 0.007 mg/m ³ (0.001 –	Lung function (spirometry: FEV ₁ , FVC, FEV %, MMF; nitrogen washout: Phase III, closing volume): Lung function impairment (of non-acute nature) observed as an increase in CV % (closing volume as percentage of the expired vital capacity) Symptoms (standardised questionnaire):	Exposure measurements from only one day, small number of samples High number of exposed subjects with eye irritation Selection bias (study was conducted because of complaints of airway irritation)

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	had been transferred because of severe symptoms n = 20 controls from the same factory	polymer is hardened in moulds	0.036) Preparation of moulds 0.002 mg/m ³ (0.001 – 0.011) Weighing and mixing of substances 0.008 (0.012 – 0.020)	Frequency of eye irritation significantly higher in exposed (12/17) than in controls (1/17). Frequency of productive cough, chronic bronchitis and exertion dyspnea higher in the exposed group than in control group, but n.s.	and the necessity to transfer employees to nonexposed work) Silicone oil sprayed in molds (not likely that this caused the irritation)
(Alexander sson et al., 1987)	Cross-sectional and over workweek 15 garages in Stockholm area n = 41 car painters n = 48 car platers (exposed to solvents, grinding dust, welding fumes like car painters, not to isocyanates n = 70 car mechanics Car painters and car platers were matched against a control by sex	HDI Monomer and biuret trimer Car painters working with polyurethane paints	Exposure questionnaire Exposure monitoring 278 samples of HDI and HDI-BT Exposure has been individually related to time, use of respiratory protections, working operation, ventilation. Individual exposure determined by industrial hygienist HDI-BT for car painting: mean (range): 115 µg/m ³ (10-385) High short-term peaks up to 13500 µg/m ³ HDI-BT HDI: 1.0 µg/m ³	Exposed workers were examined on Monday morning before work and on Friday afternoon Change in lung function within the week (spirometry: FEV ₁ , FVC, maximum mean expiratory flow MMF; Nitrogen washout: Phase III, Closing volume): Car painters did not differ from controls in any of the spirometric variables (before the workweek). Closing volume percent was significantly higher in exposed than in control workers. No significant difference in lung function in car painters before and after a workweek. Symptoms (interview by a nurse, standardised questionnaire): Eye, nose throat irritation more frequent in car painters and car platers than in controls, significant for platers only.	Uncertainties in exposure assessment Selection bias (some car painters had been relocated or their employment terminated)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	(only males), age, height, smoking				
(Wang et al., 1988)	Cross-sectional 1985 Taiwan n = 34, mostly females (38 of 45 workers had complete data, 4 were excluded because of smoking history) Follow-up (5 months after recommendations for improvement of worker protection by the study team)	TDI Velcro-like tape manufacture	Average length of employment 9.2 months Air samples, mean: weaving (n = 3) 12 ppb Packaging/storage (n = 3) 21 ppb Tape processing (n = 15) 47 ppb Highest concentration measured: 236 ppb 5 months after improvement: 7 of 9 air samples < 7 ppb at the processing area	Lung function (spirometry in the morning, during a usual working day, after 10 days holiday, 5 months after improvement of the workplace): Lung function of n = 21 workers after 10 days holiday: Greatest changes in pre- and post-exposure FEV1 and FVC for workers in the processing areas Asthma or asthmatic bronchitis (defined by development of cough for more than 1 month and shortness of breath or wheezing for 1 month after working in the factory): 14 workers met the case definition of asthma or asthmatic bronchitis. Overall prevalence of asthma = 14/34 = 41.2 % Significant trend in asthma frequency across the three exposure areas (0 % asthma cases in weaving, 37.5 % in packaging/storage, 84.6 % in tape processing). Follow up (5 months): No asthmatic symptoms. Lung function significantly improved (FEV ₁ and FVC) for 10 workers still employed.	No unexposed control group Difficult to distinguish between irritant and allergic reactions Reversibility may be due to irritant effect and due to short exposure duration. High turnover rate
(Olsen et al., 1989)	Cross-sectional Dow, Texas, USA n = 57	TDI Manufacture operations	Average TDI plant experience 4.1 years (< 1 – 9 years) Routine industrial hygiene	Lung function (spirometer, after at least two days away from work, standing or sitting, without the use of nose clips): TDI exposure (classified as current, highest, cumulative, cumulative highest-to-date) not associated	No individual exposure levels Age, height, smoking considered in regression analysis

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	<p>manufacturing workers (85 % participated)</p> <p>n = 89 unexposed workers (89 % participated)</p>		<p>measurements: TWA < 5 ppb, short-term exposure level 20 ppb for routine plant processes</p> <p>Use of self-contained breathing apparatus for breaking into lines for employees.</p> <p>Potential exposure was ranked by an industrial hygienist: None, low, moderate, high</p>	<p>with decline in FEV₁</p> <p>Respiratory symptoms (questionnaire):</p> <p>Prevalence of upper respiratory symptoms 68 % in nonexposed group, 34 % in exposed group</p> <p>Prevalence of lower symptoms 33 % in nonexposed group, 17 % in exposed group</p>	<p>Exposure misclassification possible, because rankings were applied to jobs regardless of calendar time</p>
(Parker et al., 1991)	<p>Cross-sectional Minnesota, USA</p> <p>n = 39 randomly selected autobody repair shops (out of 139 contacted shops 59 were eligible)</p> <p>n = 162 workers (160 males)</p>	<p>TDI, MDI</p> <p>Autobody repair</p>	<p>Mean number of years in autobody industry 11.4 ± 9.7</p> <p>Isocyanate samples from 32 shops</p> <p>8-h TWA total isocyanates: not detected to 60 ppb, mean 5 ppb</p> <p>Four percent of workers who spray painted at least one hour/week never used a respirator, 33 % sometimes, 63 % always.</p>	<p>Lung function (spirometry at the start and the end of the work day):</p> <p>Abnormal lung function (< 5th percentile) in 8 % (FEV₁, FVC) and 23 % (FEV₁/FVC) of never smokers.</p> <p>No significant change in lung function between morning and afternoon shifts.</p> <p>Working-years in the autobody industry, nonfunctioning spray booth, smoking were associated with a decrement in FEV₁/ FVC (regression analysis).</p> <p>No relationship between shop isocyanate concentration and lung function.</p> <p>Respiratory symptoms (self-administered questionnaire):</p>	<p>No individual exposure levels</p> <p>Exposure to dust, solvents</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				<p>Significant increase of wheezing across categories of respirator use (always, sometimes, never) while spray painting and for coughing and wheezing while sandblasting for non-smokers.</p> <p>No trends for respiratory symptoms and respirator use while sanding.</p>	
(Huang et al., 1991)	<p>Cross-sectional</p> <p>1988-1989</p> <p>Asia</p> <p>n = 48 workers (25 males) in three factories: Factory A n = 15 Factory B n = 29 Factory C n = 13</p> <p>n = 18 controls (9 males)</p>	<p>TDI</p> <p>Furniture manufacture factories; painters exposed to TDI aerosol while brushing PU varnish to the surfaces of wood furniture</p>	<p>Area sampling at five spots</p> <p>Day mean exposure calculated from four measurements taken one, three, five, seven hours after the start of the work shift</p> <p>Marcali method</p> <p>Mean (range):</p> <p>Factory A: 0.79 mg/m³ (0.49-1.18)</p> <p>Factory B: 0.31 mg/m³ (0.22-0.89)</p> <p>Factory C: 0.11 mg/m³ (0.07-0.24)</p> <p>Aerosol</p>	<p>Lung function parameters (spirometry): Impairment of some lung function parameters significant in workers of factories A and B compared to the control group.</p> <p>Symptoms of the respiratory tract, skin, eyes (structured questionnaire administered by occupational physicians):</p> <p>Prevalence of symptoms was significantly higher in factory A as well as in factory B compared to the control group.</p> <p>No significant difference was detected between workers in factory C compared to the control group.</p> <p>Symptoms of the eyes, nose, throat in all workers in factory A, 60 % in factory B. No symptoms of the eyes in factory C and in the control group, 11 to 15 % reported symptoms of the nose or throat.</p> <p>Asthma-like symptoms (dyspnea and wheezing during work): 4 workers (26.7 %) in factory A 3 workers in factory B (15 %)</p>	<p>Cited in Diller (Diller, 2002)</p> <p>Exposure measured only on one day and not on an individual level</p> <p>High exposure levels make it difficult to differentiate between irritant and allergic reactions.</p> <p>No information on potential differences in PSA between the factories.</p> <p>Medical history, smoking habits, duration of exposure, weight, height, age was assessed.</p> <p>All subjects had no history of respiratory or skin diseases.</p>

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			Dermal exposure likely (at least in factories A and B)	<p>no subject in factory C and of the control group.</p> <p>Patch test (0.1 % TDI): Positive patch test in 5 and 2 painters in factories A and B (including three and two workers with contact dermatitis, respectively) and no subject in factory C or the control group.</p> <p>Mast cell degranulation test: Significantly higher mast cell degranulation percentage (MCDP) in painters from factories A and B than for the controls (specific to TDI-OA conjugates).</p> <p>No significantly higher MCDP in painters in factory C compared to the control group.</p>	
(Omae et al., 1992)	<p>Cross-sectional (4-year follow up see (Omae et al., 1992))</p> <p>1981</p> <p>Japan</p> <p>n = 90 workers (male)</p> <p>n = 44 reference workers in the same factories</p>	<p>TDI</p> <p>PU foam manufacture</p>	<p>Working in PU foam factories for 0.5-25 years, mean 13.3</p> <p>129 personal samples: arithmetic mean: 3.2 ppb geometric mean: ppb 90th percentile: 8.4 ppb maximum: 26 ppb</p> <p>Short-term exposure peaks > 20 ppb in 16/129 samples</p>	<p>Lung function, change over working day (3 methods: forced expiratory flow-volume test, respiratory impedance, airway resistance and specific airway conductance):</p> <p>No significant differences in lung function between PU foam workers and referents, except for lower PEF and %PEF in the exposed group.</p> <p>No change of lung function during work shift in both groups.</p> <p>Symptoms (questionnaire with interview): Significantly higher prevalence of respiratory symptoms, nasal symptoms, eye symptoms in the exposed workers.</p>	<p>Exposure to tertiary amines, organic tin compounds, polyols, silicon oil, dichloromethane, freons, flame-resisting agents, pigments etc.</p> <p>Possibly a survivor population</p> <p>Current smoking did not affect the results</p>
(Lee and	Cross-sectional	TDI	24 personal breathing	Lung function:	Cited in (Diller, 2002)

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Phoon, 1992)	n = 26 exposed workers ("mixers") n = 26 controls (workshop maintenance and field staff from government departments), matched by age, race, smoking state	PU foam manufacture	zone samples: Mean: 0.16 ppm Range: 0.01 – 0.50 ppm	Mean diurnal variation in PEFR (in one week period): Significantly higher diurnal variation in PEFR in mixers than in controls. FEV ₁ /FVC significantly lower in exposed (83.0 %) than in controls (89.3 %) Mixers with ten or more years of exposure showed evidence of chronic airways obstruction. Respiratory symptoms (questionnaire): About 50 % of mixers had eye irritation or cough during work (significant higher prevalence than in controls). No overt cases of OA	High exposure level Survivor population
(Bernstein et al., 1993)	Cross-sectional 1991 n = 243 (n = 175 males) 3-year old plant	MDI Urethane mould plant that had been designed to minimise exposure to MDI	Average duration of employment: 18.2 months (range: 0-32 months) Continuous monitoring of MDI area levels: < 5 ppb Occasional spills reported by workers, but not detected by monitors	Methods: Workers with at least one lower respiratory symptom (questionnaire) and workers with specific antibodies were instructed to perform serial PEFR studies for two weeks (n = 43). PEFR studies were also done in 23 control subjects (no symptoms, no antibodies). Workers with PEFR variability were evaluated by a physician (including methacholine test) for final diagnosis of OA/non-OA. Workers who were assigned final diagnosis of OA/non-OA/work-related urticaria were reevaluated in 1992 (n = 6).	No unexposed control group

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				<p>Results:</p> <p>PEFR variability detected in 3/9 workers with questionnaire diagnosis of OA, in 2/4 workers with non-OA, in 2/23 control workers without symptoms.</p> <p>Three cases of physician diagnosed OA (3/234, prevalence ca. 1 %) and two cases of physician diagnosed non-OA.</p> <p>Two workers had specific IgE and IgG to MDI-HSA. One of those had urticaria.</p> <p>Cases are considered to be due to intermittent higher than normal exposures to MDI during non-routine working activities.</p> <p>Cases were removed from exposure. After 1 year clinical status of OA was described as "inactive".</p>	
(Kim et al., 1997)	<p>Cross-sectional</p> <p>Korea</p> <p>n = 81 workers (41 males)</p>	<p>TDI</p> <p>Spray painters</p> <p>Workshops manufacturing furniture or musical instruments or repairing motor</p>	<p>Area samples (n = 41)</p> <p>Range 0.5 – 10 ppb</p> <p>Mean 3.5 ± 2.3 ppb</p> <p>Four samples (9.8 %) > 5 ppb</p>	<p>Examinations: Respiratory symptoms (questionnaires and interviews), Chest auscultation, IgE, IgG, FVC, FEV₁</p> <p>Diagnosis of TDI OA was made if there was a decrease of PEFR over 20 % of baseline and if the changing pattern was closely related to workshift.</p> <p>PEFR was recorded in the following cases:</p> <p>Subject complained of sputum, cough, and dyspnea aggravated by work</p>	<p>Cited in (Diller, 2002)</p> <p>No control group</p> <p>No individual exposure data</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
		vehicles		<p>Wheezing audible by auscultation</p> <p>FVC or FEV₁₀ < 80 % of the normal Korean reference value</p> <p>Positive IgE RAST for TDI</p> <p>PEFR was checked for 15 workers. Eight workers (9.9 %) were diagnosed with TDI-OA.</p>	
(Ulvestad et al., 1999)	<p>Cross-sectional Norway?</p> <p>n = 19 injection workers (previous tunnel workers who were grouped into a department set up for sealing work; exposed to PU and acrylic resins; all the workers employed in this department in 1996 were included)</p> <p>n = 104 other tunnel workers, 6 different sites</p>	<p>MDI monomer and prepolymer</p> <p>Sealing work in tunnels</p>	<p>Job-years; mean (range): injection workers: 21 (1-42) tunnel workers: 13 (1-46)</p> <p>MDI monomer (personal sampling, 20 samples): mostly below the LOD (< 1 µg/m³); 1.9 and 3.0 µg/m³ at 2 occasions where isocyanate resin was spilled during injection work</p> <p>Pre-polymer:</p> <p>n = 4 shift samples: 5.5 – 300 µg/m³ (median 7.1);</p> <p>n = 18 short-term exposure values: 18-4300 (median 103) µg/m³</p> <p>Stationary sampling (n = 6): monomer < 4 µg/m³, prepolymer < 4 - 31</p>	<p>Examinations: Respiratory symptoms (questionnaire), lung function (spirometry), IgE (TDI, MDI, formaldehyde, eight common allergens), Metacholine provocation test, Clinical examination</p> <p>Higher prevalence of respiratory symptoms, airflow obstruction, BHR, asthma in injection workers compared to other tunnel workers.</p> <p>Two TDI-HSA-specific IgE positive injection workers (with work-related respiratory symptoms)</p>	<p>No exposure measurements available from the years the "injection department" had existed → most common exposure situations for workers during the last ten years were simulated.</p> <p>No individual exposure data</p> <p>Workers had not been informed about health hazards of the chemicals they worked with and did not report any use of airway protection.</p> <p>Exposure to acrylic resins</p> <p>Previous exposure to TDI</p> <p>Underestimation of exposure possible</p> <p>Years in the same job and smoking status were</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			$\mu\text{g}/\text{m}^3$		considered in the regression model
(Jang et al., 2000)	Cross-sectional Korea n = 64 randomly selected workers n = 27 controls (23 males)	TDI (n = 44) MDI (n = 20) Petrochemical plant Manufacture	60 personal breathing zone samples Sampling during manufacture, sampling time 30-60 min Mean (maximum): TDI $17.4 \mu\text{g}/\text{m}^3$ ($42.9 \mu\text{g}/\text{m}^3$) MDI $\mu\text{g}/\text{m}^3$ ($6.4 \mu\text{g}/\text{m}^3$)	Airway hyperresponsiveness (AHR) (definition: $\text{PC}_{20} \text{FEV}_1 < 16 \text{ mg}/\text{mL}$ of methacholine; continuous index of bronchial responsiveness: BRindex): Prevalence of AHR higher in MDI-exposed workers (4/20; 20 %) than in TDI-exposed workers (2/42; 5 %) and in controls (read from Figure: 2/27; 7 %). Significantly higher BRindex in MDI-exposed workers than in controls, but not significantly higher than in TDI-exposed workers. Differences statistically significant?	No individual exposure measurements Medication, work history, atopy, smoking was assessed by questionnaire
(Schweiger et al., 2002)	Cross-sectional Ontario, Canada n = 41 (isocyanate exposure, medium solvent category) n = 153 (no isocyanate exposure, three categories of solvent exposure: low solvent n = 6	HDI (polymeric, $< 0.1 \%$ monomeric) Automobile paint manufacture	Four summary exposure categories Personal sampling: HDI monomer: 0.1 – 0.6 ppb Polymeric isocyanate: $< 0.01 \text{ ppb}$	Lung function (performed at least every 2 years, data taken from medical charts): Significant negative correlation between total years of solvent exposure and FEV_1 and FVC. No correlation of smoking status and FEV_1 and FVC. No differences in lung function between the two isocyanate exposure categories (yes/no) in the workers with medium solvent exposure. Respiratory symptoms were not assessed. However, no respiratory illnesses have been reported.	Survivor effect possible (less physically conditioned workers move to an area where no respirators have to be worn) Smoking status classification may have resulted in a bias towards the null

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	medium solvent n = 92 high solvent n = 55				
(Kakooei et al., 2006)	Cross-sectional Iran n = 39 employees in an automobile manufacturing company n = 117 unexposed employees at other work stations	MDI Window fixation, window glue processes	Personal samples Average concentration of MDI: Window fixation 34.53 µg/m ³ Window glue workplaces 27.37 µg/m ³	Lung function: %FEV1/FVC, %PEF significantly smaller in the exposed group than in the control group. Respiratory symptoms (questionnaire): Skin, respiratory, eye, mental symptoms significantly more prevalent in the exposed group. Respiratory, eye, mental symptoms significantly more prevalent in workers exposed to higher concentrations compared to lower concentrations than the mean value of 31.22 µg/m ³ . Respiratory symptoms increased with the duration of service. However, symptoms not significantly correlated to years or intensity of exposure.	Occupational health and hygiene problems due to missing application of adequate engineering controls and proper safe work practice. This can cause great exposure to air pollutants. Study was conducted in the summer. Higher exposure levels in the winter likely, because windows are kept closed then. No significant differences between the two groups in age, height, duration of service. However, duration of service was shorter in the exposed group. No information on smoking.
(Littorin et al., 2007)	Cross-sectional Southern Sweden n = 136 exposed to TDI in eleven plants	TDI or TDI-based PU MDI used in 4/5 moulding plants (low or non-	Median personal 8h exposure to TDI (ppb): continuous-foaming: 0.63-4.0 flame lamination: 0.76-1.5 molding: 0.17-0.64 low heating or nonheating processes: 0.02-0.05	Respiratory and eye symptoms (structured interview, physical examination): Comparison between exposed and unexposed group: Total symptoms: significant increase in symptoms of the lower airways, nose	Symptoms may have been caused by combined exposures. Coexposures: dusts, other diisocyanates, organic solvents, thermal degradation products of ready-made PU in flame lamination plants (mix of mono-and diisocyanates,

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 118 unexposed workers from different activities	detectable) . IPDI used in 1 of these plants. 5 moulding plants, 2 continuous-foaming plants, 2 flame-lamination plants, 2 plants with low heating or non-heating processes	Individual airborne exposure: measured during one shift (n = 79 workers), estimated based on department, task, air measurements (n = 57). Biomonitoring: 2,4-TDA and 2,6-TDA Urine: LOD – 623 and 353 noml/L Plasma: LOD-254 and 509 nmol/L Correlations between air measurements and biomarkers in urine as well as biomarkers in plasma. Biomarkers in urine and plasma also correlated. Skin exposure certainly present	bleeding (as the only nose symptom investigated), eye symptoms for the exposed group. Work-related symptoms: strong associations with exposure, in particular for attacks of eye symptoms (OR = 10), "wheezing etc" (OR = 21) and dry cough (OR = 11). Continuous measure of exposure within the exposed cohort: Only eye symptoms significantly associated with exposure measures (air, plasma, urine; OR from 1.6 to 4.2) Effect of 2,4-TDI on the eyes was more pronounced compared to 2,6-TDI No clear patterns for other exposure-response relationships.	aminoisocyanates, amines) High number of workers with airway symptoms is seen as remarkable by authors, because of the selected workforce. However, no dose-response relationship with TDI. Individual airborne exposure was measured for a part of the workers only. Logistic regression model included age, gender, smoking. Atopy was considered. Preemployment health examinations should lead to a selected workforce in the Swedish PU industry (rather healthy concerning airway disease).
(Löfstedt et al., 2009)	Cross-sectional, shift 2001 4 Swedish foundries n = 64 foundry workers	Isocyanic acid, methyl isocyanate, formaldehyde Hot box binder technique (to produce	Individual exposure measured on the same day as lung function ICA and MIC: measured in 4-5 randomly selected intermittent short-term samples (5 min) from the shift Formaldehyde: full shift	Lung function before and after a day shift: Both groups had reduced lung function before shift compared to reference values. Lung function decrease (VC and FEV1) over shift was significantly greater among exposed workers than in referents. No significant effects of IC, MIC, formaldehyde, smoking during day on lung	Follow up: Löfstedt et al. 2011 Coexposures Findings not related to current exposure → other irritants in the foundry might be the cause Swedish legislation is aimed at preventing asthmatics from working in such environments

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>n = 134 controls</p> <p>n = 10 persons in the exposed group (14 %) declined to participate</p> <p>n = 59 of the invited referents (31 %) declined to participate</p>	cores for hollow castings)	<p>sample</p> <p>Geometric mean: ICA: 24 µg/m³ MIC: 4.9 µg/m³ Formaldehyde: 120 µg/m³</p>	<p>function change.</p> <p>Respiratory symptoms (questionnaire):</p> <p>Higher prevalence of 6 out of 8 symptoms in exposed group than in referents, but for most symptoms difference was not significant.</p> <p>Ocular irritation and coughing without infection significantly more prevalent among exposed workers, especially coremakers.</p>	<p>Non-participating rate higher in referents → overrepresentation of referents with symptoms → underestimation of risk</p> <p>Tendency to overreport symptoms possible</p> <p>Selective loss of exposed symptomatic individuals possible</p>
(Pourabedian et al., 2010)	<p>Cross-sectional, shift</p> <p>Iran</p> <p>n = 43 car painters (healthy on enrolment) exclusion criteria: respiratory disorders including asthma, cigarette smoking, use of respiratory drugs</p>	<p>HDI</p> <p>Car body paint shop</p>	<p>Mean daily exposure: 15 minutes</p> <p>Mean daily HDI TWA air concentration in the breathing zone: 0.42 ± 0.1 mg/m³</p> <p>Mean weekly HDI TWA: 0.13±0.059 mg/m³</p>	<p>Lung function: Variation in PEF (peak flow meter, before and after the shift, over one week):</p> <p>Mean peak flow at the end of the shift on painting day was significantly lower than at the start of the shift</p> <p>72 % of the workers had >10 % variation in PEF on painting days</p> <p>Effects of exposure remained till the day after painting</p> <p>Significant difference between the two days</p> <p>Significant correlation between HDI and percentage of decrease in peak flow as well as mean peak flow on painting day</p>	<p>High exposure levels</p> <p>No unexposed control group</p> <p>Questions concerning statistical analysis/ reporting of results</p> <p>Organic solutions</p>
(Hathaway et al., 2014)	<p>Cross-sectional</p> <p>Southern USA</p>	<p>Plant 1: Manufacture of HDI, IPDI,</p>	<p>Duration of work not determined (12 years on average in previous study)</p>	<p>No cases of OA identified (more detailed respiratory medical history questionnaire than in (Cassidy et al., 2010))</p>	<p>Follow up of (Cassidy et al., 2010)</p> <p>No control group</p>

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	<p>n = 73 employed in 2011 in 2 plants (71 males, 1 female, 1 unknown)</p> <p>Participation rate > 80 %</p>	<p>H12MDI and their polyisocyanates</p> <p>Plant 2: Manufacture of HDI polyisocyanates from HDI</p>	<p>Industrial hygiene monitoring (2007-2012):</p> <p>Airborne HDI monomer, respirator worn (n = 33 samples):</p> <p>Nondetectable n = 14 ≥ 5 ppb n = 3</p> <p>Airborne HDI monomer, respirator not worn (n = 100 samples):</p> <p>Nondetectable n = 60 all samples < 2 ppb</p> <p>Airborne IPDI and H12MDI: all samples < 2 ppb</p> <p>Authors think it likely that exposure was ≥ 5 ppb for at least some of the reported instances when odors of HDI were reported.</p>	<p>Accidental unprotected inhalation and skin exposures (questionnaire included questions concerning detection of odor, being in the vicinity of leak or spill, unprotected skin exposure): 15 persons answered one or more of the questions on respiratory symptoms with "yes".</p>	<p>No individual exposure assessment</p> <p>Some employees indicated that they noted a characteristic irritation (mostly eye irritation)</p> <p>Detection of odor and skin exposure self-reported and odor subjective</p> <p>Smaller percentage of workers with chronic cough, wheezing and smaller percentage of smokers than in control groups in other studies</p> <p>Healthy worker effect possible (Self-selection)</p>
(Hathaway et al., 2014) ctd.			<p>Detection of odor:</p> <p>HDI: n = 68 (93 %) IPDI: n = 32 (76 % of those working with IPDI)</p> <p>Work in vicinity of leak/spill:</p>		

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			HDI: n = 62 IPDI: n = 31 Unprotected skin contact reported [more than 15 times]: HDI monomer: n = 39 (53 %) [n = 6] HDI polyisocyanates: n = 27 (37 %) [n = 5] Estimations: Odor: once per 4 years per employee leak/spill: once per 5-6 years unprotected skin exposure: once every 4-5 years		

Appendix 4 Conversion factors

Table 4-1: Conversion factors used in the assessment of diisocyanates

Substance	EC no.	CAS	Molecular formula	M (g/mol)	Conversion factors ((AGS, 2006b))		NCO mass fraction	Density	
					mg/m ³ → ppmV	ppmV → mg/m ³		Value (g/cm ³)	at T = ...°C
HDI	212-485-8	822-06-0	C ₈ H ₁₂ N ₂ O ₂	168.195	0.143286067	6.979045643	0.499623651	1.05	20
HMDI	225-863-2	5124-30-1	C ₁₅ H ₂₂ N ₂ O ₂	262.351	0.091861666	10.88593361	0.320312101	1.07	25
IPDI	223-861-6	4098-71-9	C ₁₂ H ₁₈ N ₂ O ₂	222.2864	0.108418689	9.223502075	0.378044721	1.06	NA
2,2' MDI	219-799-4	2536-05-2	C ₁₅ H ₁₀ N ₂ O ₂	250.2562	0.09630131	10.38407469	0.33579268	1.32	20
2,4' MDI	227-534-9	5873-54-1							
4,4'-MDI	202-966-0	101-68-8							
NDI	221-641-4	3173-72-6	C ₁₂ H ₆ N ₂ O ₂	210.1916	0.114657294	8.721643154	0.399798089	1.40	20
2,4-TDI	209-544-5	584-84-9	C ₉ H ₆ N ₂ O ₂	174.1586	0.138379615	7.226497925	0.482515362	1.24	20
2,6-TDI	202-039-0	91-08-7						NA	NA
TDImix	247-722-4	26471-62-5						1.22	20
mTMXDI	220-474-4	2778-42-9						1.07	25
TODI	202-112-7	91-97-4	C ₁₆ H ₁₂ N ₂ O ₂	264.283	0.091190126	10.96609959	0.317970509	1.33	20
TRIDI	218-485-4	2162-73-4	C ₁₇ H ₂₂ N ₂ O ₂	286.373	0.084155978	11.8826971	0.293443167	1.05	20
mXDI	222-852-4	3634-83-1	C ₁₀ H ₈ N ₂ O ₂	188.1854	0.128065195	7.808522822	0.446550051	1.20	19

Appendix 5 Additional material regarding Appendix Exemptions and Appendix Trainings and Measures

Further information to Appendix Exemptions

Background of "Exempted Products"

There are situations where the additional requirements of training and measures are likely to be disproportional compared to the potential risks involved. Therefore, this Appendix (full text in separate document) provides the possibility for an exemption in cases where it can be shown that the use of a product (including chemicals, packaging, application aids) presents a very low risk during normal and foreseeable conditions of use. This is the case for example in the building sector, where a lot of diisocyanate containing products (e.g. building foams, glues) are only used for special short term steps during the worktime.

Products are eligible for this exemption if they are shown to have a reduced risk potential (e.g. they do not emit aerosols under ambient use conditions) and/or if specific application equipment is used that has especially been developed to minimise exposure. An example is the combination of a small foam cartridge with a special application nozzle preventing potential for dermal contact and minimising inhalation exposure.

In the Appendix Exemptions criteria are defined to systematically identify these products with potentially low exposure and risk. In order to determine whether a product fulfils these criteria, an application specific assessment considering the exemption criteria laid down in this Appendix is to be conducted. If the criteria are met, the requirements of the Appendix Training and Measures can be omitted.

The products identified by the rules set down in this Appendix are by no means "safe" products, which should already be clear by the fact that they are still hazardous mixtures as defined by Article 4 of CLP (European Parliament and Council, 2008a). They are to be classified as respiratory sensitisers and no threshold has been identified for the sensitising potential of diisocyanates.

Extensive discussions have taken place on the possibility of a substitution for diisocyanate containing products, but alternatives could only be identified for some highly specific uses. General "alternatives" also exist, namely epoxides and solvent based paints and glues.

Epoxides are known as highly potent skin sensitizers and are seen as a major problem at workplaces especially in the building sector and isocyanate containing products are actually recommended as alternatives for epoxide products. Therefore a substitution to epoxides is seen as a no-go.

Solvent based paints and glues are mainly not problematic from a toxicological viewpoint, but from a physical viewpoint. The products are flammable and can create explosive atmospheres. Based on the amount of workplace accidents happening with such products, two German technical rules have been created to promote substitution of solvent based glues and paints [TRGS 617-618] and diisocyanate containing products have, in full knowledge of their toxicological profile, been identified as recommended alternatives.

The expert opinion at the current level of existing products is, that diisocyanates are the best of a large amount of bad choices and the use, especially in the building industry, is still needed.

Parallel to the discussion, the German liability insurance for the building sector started an evaluation of their occupational disease cases based on diisocyanates. It shows for the building sector in Germany that, based on the high amount of diisocyanate containing products used, only a really small amount of occupational disease cases exist.

Based on missing alternatives and the indication of a small incidence for occupational disease cases based on diisocyanate containing products in the building industry, the decision was taken, to create criteria to identify the less risky part of the existing diisocyanate products. For these products, an application specific assessment on dermal and inhalation criteria has to be conducted.

For inhalation exposure, standardized workplace measurements, following the analytical methods set down in Table 5-1 below, have to be conducted. The measurements have to take into account unfavourable conditions like e.g. seasonal influences. Additionally, all tasks in the context of the application, including steps like e.g. mixing and cleaning, have to be taken into account.

The number of measurements needed depends on the validity and values of the measurement results, the representativeness, kind of conditions and evaluation indices. Exposure results shall be assessed in line with ECHA guidance R14.

The sum of the concentrations for all isocyanates has to be smaller than 0.001 ppm as time weighted 8 hours average.

The value of 0.001 ppm is in no way to be seen as a toxicological threshold or as a limit for safe use. The value is a purely practical value based on the limit of quantification of the measurement methods and orientating itself at the OEL's of the European Member States.

Table 5-1: Measurement Methods for diisocyanates in the context of Appendix Exemptions

Method	Measurable diisocyanates
DFG Air Monitoring Methods, 2009	2,4-TDI, 2.6-TDI, 4,4'MDI, IPDI, HDI, NDI
DFG Air Monitoring Methods, 1991	2,4-TDI, 2.6-TDI, HDI
DFG Air Monitoring Methods in German language, 2006	2,4-TDI, 2.6-TDI, 4,4'MDI, IPDI, HDI, NDI
HSE MDHS 25/3 Organic isocyanates in air. (Januar 1999)	2,4-TDI, 2.6-TDI, 4,4'MDI, IPDI, HDI, NDI
IFA 7670 "Isocyanate", 2009	Total NCO
IFA 7120 "Diisocyanate, monomer", 2010	2,4-TDI, 2.6-TDI, 4,4'MDI, IPDI, HDI, NDI
NIOSH 5522 (1998)	2,4-TDI, 2.6-TDI, 4,4'MDI, HDI
NIOSH 5521 (1994)	2,4-TDI, 2.6-TDI, 4,4'MDI, HDI, NDI
NIOSH 5525 (2003)	Total NCO

For the dermal assessment a special assessment tool for dermal exposure potential of diisocyanates has been created³³. The tool is applications specific and takes into account working conditions, product characteristics and specific application risks. The tool has been evaluated by BG Bau and Bundesverband Klebstoffe, the German liability insurance for the building sector and the German industry association on glues. So far, the assessment tool seems to be conservative.

In cases where the assessment tool does not show very low potential for exposure, biomonitoring data, using the methods shown in Table 5-3, have to show exposure below the limits shown in this table. Biomonitoring shows the combined exposure and not just the dermal exposure, and is a good tool to assess the exposure of workers. If biomonitoring data shows an exposure above the limits in Table 5-3, then the product can never be exempted, no matter what the assessment tool or workplace measurements show.

Since a full ban of diisocyanates is out of proportion, specific rules for the use of diisocyanates have to be implemented (see Appendix Trainings and Measures). The proportionality of using the rules of Appendix Trainings and Measures for every kind of diisocyanate-use has been discussed. Especially in the building industry a lot of diisocyanate containing products (e.g. building foams, glues) are used and the experts opinion is that the big majority of all workers in the building sector use products containing diisocyanates. In contrast to the industrial use of diisocyanates most of the products are only used for special short term steps during the worktime. Therefore no exposure of eight hours per day for five days a week can be assumed. Additionally, in the majority of cases only small amounts are used. Therefore the idea was discussed whether it is possible to identify product/use combinations with a low exposure per use and a low total amount of uses per worktime.

Identification of products:

Identification as products fulfilling the criteria for an exemption from the authorisation:

The restriction proposed gives three possible ways to still use isocyanates. That being:

- a) the cumulative concentration of diisocyanates in the substance or mixture is less than 0.1 %
- b) the product is labelled as compliant with Appendix Exemptions according to paragraph 3, or
- c) the substance or mixture is used in accordance with the provisions described in Appendix Trainings and Measures.

Appendix 12 (Exemptions) states that a product may only be identified as compliant with Appendix Exemptions if the evaluation as described in Appendix Exemptions has shown that the product qualifies for an exemption according to the criteria described in that Appendix.

The idea of Appendix Exemptions is the identification of "products" with a "very low potential for exposure" for all used "applications".

For the purposes of this entry the term product shall be regarded as the substance or mixture containing diisocyanates in the form in which it is supplied to the user. This includes

³³ Available as EXCEL spreadsheet

the combination of a substance or mixture, packaging, and any application aids, if it is sold within the same unit.

Application is to be understood as a highly specific use of the product. Examples of applications can be found in Table 5-2. An application is more specific than a typical use under REACH. An application normally contains different steps conducted after each other either by the same worker or by different workers.

Table 5-2: Examples for applications and steps

Application	Steps
One Component Foam (Window Frames)	Sputtering foam from can, Cutting excess foam
Floor Coating	Opening of pails, Transfer of component, Mixing of components, Pouring and spreading, Detail distribution by trowel

“Very low potential for exposure” are defined by criteria for dermal, inhalation and combined exposure. All demanded criteria need to be fulfilled for a product in combination with all its applications for it to be of “very low potential for exposure”.

Products which fulfil the criteria for “Very low potential for exposure” for all applications are named as “Exempted Products” since they are exempted from the requirements of Appendix Trainings and Measures.

Table 5-3: Biological limits

Parent substance	Urinary metabolite (after hydrolysis)	Limit	Detection Limit	Method
MDI	MDA	10 µg/g Creatinine	0.5 µg/L	(Lewalter and Biedermann, 1994)
HDI	HDA	15 µg/g Creatinine.	0.5 µg/L	(Lewalter et al., 2002)
TDI	TDA	5 µg/g Creatinine.	0.5 µg/L	(Lewalter and Biedermann, 1994)
IPDI)	IPDA	5 µmol/g Creatinine.	0.5 µg/L	(Lewalter et al., 2002)
NDI	NDA	5 µmol/g Creatinine	0.5 µg/L	(Lewalter and Biedermann, 1994)

Further information to Appendix Trainings and Measures”

Introduction:

All diisocyanates and some of their oligomers are respiratory and skin sensitisers. Because of their multiple uses and different properties, the conditions of use and the associated potential risks of the diisocyanate substances will be different. This also means that the necessary risk management measures during handling to reach a level of minimal risk need to be different.

The Appendix contains a systematic overview of the necessary measures that are to be implemented in handling diisocyanates in uses of varying potential risks in order to meet the requirements of the REACH restriction.

It is beyond the possibility of this Appendix to list all uses of all diisocyanates in sufficient detail. In order to select the necessary risk management measures under the REACH restriction, we use a grouping approach.

Apart from providing general safety instructions for all employees, a company or employer has to take following actions in order to comply:

1. Identify the “measures group” (see below) for each employee that may be exposed to diisocyanates, depending on the activities performed by that employee or group of employees.
2. Implement the technical and protective measures as identified below for that particular group
3. Ensure completion of training for each employee according to the determined measures group. Training topics for different measures groups can be combined into one unit taking the combined time for the respective groups.
4. Keep documentation on the completion of steps 1 and 2. Check validity of documentation at least once per year

(Full details can be found in the Appendix “Trainings and Measures” itself)

Although implementation of measures and trainings is the responsibility of an employer or company management, it is possible to transfer the practical support for this responsibility to external experts.

Based on an expert judgement approach, activities/uses are differentiated in qualitative exposure stages, describing the probability and magnitude of dermal exposure and inhalation exposure. The latter includes contributions from vapour and aerosol exposure. These are ranked from minimal to high (3 stages)³⁴ as shown in Table 5-4.

To make this fit for use in this context, the highest rating of the exposure stages (be it inhalation exposure or dermal exposure) for a particular workplace/activity determines the “measures group”. This group represents a combination of necessary technical, organisational and personal protective measures, and a certain combination of training requirements appropriate for this activity.

³⁴ Similar to TRGS 430 Exposure scenarios, page 2 Link: http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/Katalog-Expositionsszenarien.pdf?_blob=publicationFile&v=3

An employee with various tasks needs to complete the training for the highest stage of his working tasks. Training for stages 2 and 3 can be organized in such a way that all content and time are added together, so that one session includes the parts of stage(s) 1 and/or 2 respectively.

Table 5-4: Exposure stages (expert judgement)

Route of Exposure	Exposure Stage	Probability of Exposure
Dermal	1	Potential skin contact rare, small areas and immediately appropriately removed e.g. splashes
	2	Potential repeated short term skin contact (max 4*15 min per 8 hr shift)
	3	Potential repeated prolonged skin contact (more than 60 min per 8 hr shift)
Inhalation	1	Low vapour formation
	2	Moderate vapour and/or aerosol formation
	3	High vapour and/or aerosol formation

Measures Groups:

“Group 1”: These uses should be performed with precautions that represent the basic requirements for operations with diisocyanates. They may need specific measures, skills, and knowledge beyond the minimum needed to handle hazardous materials in general.

“Group 2”: This is the group of uses that encompasses many uses in industrial and professional applications where a higher potential risk is expected. Special skills and competencies being a prerequisite for safe application of these uses need to be acquired in extra training.

“Group 3”: These uses have strong indications for a high risk potential. This includes operations that may be infrequent and additional standard procedures. They will require specific skills and RMMs for that particular activity or use. They may be supervised in a special way and may follow special dedicated protocols (like those described in external certification schemes).

An (e)SDS of a substance or mixture will list general reference to the restriction in sections 1.2 or 15.1. If an indication for a measure group is specified by the supplier this shall be included in Section 16 (Other information). Where available, this shall be followed. For general reference, Table 5-5 lists generic use/activity descriptions, and provides their proposed “exposure stages” and “measures groups. For other activities not listed here, or if specific use conditions differ significantly, a risk assessment needs to be performed in order to determine the relevant measure group. The result shall be documented.

Table 5-5: Generic uses and the corresponding “measures groups” – Industrial & professional

Activities	Inhalation Exposure	Dermal Exposure	Measures group
Loading/Unloading Trucks	1	1	1
Pumping /Loading using closed systems	1	1	1
Application of Sealants and adhesives (including foam application from cans)	1	1	1

Activities	Inhalation Exposure	Dermal Exposure	Measures group
Handling cold fibres and composite materials after manufacturing	1	1	1
Polyurethane operation with dedicated closed machinery, like foaming, adhesives, sealants, elastomers	1	1	1
Working in a laboratory	1	1	1
Handling open mixtures at ambient temp. (incl. foam tunnels)	2	2	2
Handling incompletely cured articles (e.g. freshly cured, still warm)	1	2	2
Spraying in a ventilated booth	2*	2	2
Application by roller	2	2	2
Application by brush	2	2	2
Application by dipping and pouring	2	2	2
Foundry applications	1	2	2
Mechanical post treatment (e.g. cutting) of not fully cured articles	1	2	2
Cleaning and waste	2	2	2
Maintenance and repair that needs access to equipment	2	2	2
Change Management	2	2	2
Open handling of warm or hot formulations (>45 C)	3	2	3
Spraying in open air, with limited or only natural ventilation (includes large industry working halls) and spraying with high energy (e.g. foams, elastomers)	3	3	3

For each "measures group" the Appendix "Trainings and Measures" lists:

- a. A minimum of competencies and knowledge that needs to be acquired in mandatory training packages that a worker needs to complete in order to be able to recognise, assess and control risks caused by diisocyanates appropriately. For group 3 the listing is more activity-specific in order to address the special tasks with high risks.
- b. Specific measures related to technical equipment, organisation and personal protective equipment that, as a minimum, need to be in place in order to work safely.

Training topics covering competencies and knowledge that needs to be acquired by a company's management are listed in a specific table. In this context, the term "management" refers to persons with direct authority upon workers potentially exposed to diisocyanates as well as to qualified trainers in charge of training such workers. Such as for example site managers, shift leaders, plant managers or EHS staff.

For each use of diisocyanates, the corresponding level of RMMs and training requirements are derived from Table 5-5. This happens without prejudice to other mandatory national or local measures. RMMs defined in the eSDS or SDS are followed.

The content of the required training shall allow reaching the competences and level of knowledge mentioned in Table 5-5. This content shall be based on information available from manufacturers of diisocyanates, formulators or suppliers of mixtures of diisocyanates on how to safely handle diisocyanates or such mixtures. Where available, information from trade associations of producers or downstream users of such substances and mixtures can also be used as a basis for the content of the required training. Companies shall document their need of the training level and how they implement the trainings and the specific modules taught.

In addition technical requirements are listed that are a general prerequisite to work with isocyanates.

The provisions of the Appendix shall also cover (external) contractors or temporary workers that may carry out relevant activities with potential exposure to diisocyanates. Their employer is obliged to provide documentation which shows that they have been trained in accordance with the provisions set out in the Appendix before they can be put to work in activities with potential exposure.

Parts of the required trainings may be combined with training modules in existing training programs or management systems related to occupational safety, if documentation is provided to show how these trainings reach the same level of competencies.

Methods suitable for the training sessions

The training modules will make use of some concepts that were identified as particular effective in other studies (See section E.6.1.1.). It should be stressed that the main objective of the trainings is to achieve behavioural changes, not increase in knowledge per se. It should also be indicated that a too detailed formal prescription of methods and concepts to be used for different groups of trainees is not considered helpful, as it would limit continuous improvements based on new didactic insights or on feedback from practice. Nevertheless, The DS expects that some of the specific concepts that need to be used are the following:

1. Classroom training (e.g. for basic facts and simple chemistry teachings).
Note: professional users without chemical training will benefit most of using simple visual materials, whereas for people with specialist or academic training more in-depth concepts may be used
2. Video instruction showing correct behaviour and typical actions (e.g. regarding handling sequences of diisocyanates and formulations containing them).
Note: This is a method that will be useful for all trainees, irrespective of formal education levels.
3. Pictures with "Do's and Don'ts" (e.g. to describe (in)correct actions like the use of PPE)
Note: This is a method that seems especially be suited for professional workers in an SME environment
4. Hands-on exercises where this is appropriate (e.g. correct use of PPE)
Note: Especially for PPE, this is an aspect that will be useful for all trainees.
5. Discussion at the actual work place (or a simulated one).
6. Use of questionnaires pre- and post-training to detect improvement in knowledge and/or attitude (and behavioural changes in later training cycles).
7. Supervised work assignments as foreseen in Measures Group 3. This is most likely to represent applications of diisocyanate substances in potentially high risk situations where external certification may be required in anyway.

Depending on the formal level of education of trainees, some concepts will be preferably used. It is foreseen that for professional users visual material and hands-on exercises will play a larger role.

Experience gained during implementation and further development of general educational insights may lead to use of additional methods in the future.

Appendix 6 Information regarding alternatives.

Below is presented the summary of the external market search for alternatives to diisocyanates with emphasis on the building industry. The full report is available upon request.

Market research of available alternative products (with content of isocyanates less than 0.1 % (w/w)) as possible substitutes for diisocyanate-containing products in the skilled crafts sector

Abstract

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Principal: Federal Institute for Occupational Safety and Health

Introduction

Polyurethane plastics are formed by the reaction of diisocyanates or polyisocyanates with polyols. The reactive groups of isocyanates react with hydroxyl groups of polyols to polyurethane. Polyurethanes play a major role in industrial applications, e.g. the production of rigid and flexible foams (mattresses, shoe soles, insulations, seat upholstery etc.) but are also used in the skilled crafts sector where they are produced "in situ" in various fields of application. These reactive systems, which are used as foams, coatings or glues, are attributed to high flexibility concerning rigidity, firmness and elasticity in connection with lightfastness, resistance to weather and colour stability (Dt. Bauchemie 2012, p. 6).

"The spectrum ranges from highly wear resistant and crack-bridging coatings for park garages and industrial floors or collecting tanks in chemical plants to tread-friendly, decorative floor coatings, e.g. for floors in sports halls or running tracks in stadiums all the way to jointless waterproofing for roofs, walls or bridges. But you also find polyurethanes in places where they are not always immediately visible such as liquid polymer waterproofing under structures, beneath tiles or in cracks that have been closed with expansion capable materials." (loc cit)

Diisocyanate can cause severe allergic reactions of the respiratory tract (e.g. asthma) even at low concentrations. Therefore, the Federal Institute for Occupational Safety and Health plans the compilation of a restriction proposal for diisocyanates as an entry to Annex XVII of REACH regulation. The restriction shall combine the use of diisocyanate-containing products with special qualifications of the employees as well as with minimum standards for technical

and organisational measures. Uses of products that can be shown to have clearly reduced risks should be exempted from the restriction.

As a basis for an estimation of changes of costs and risks caused by converting to diisocyanate-free products available alternatives to diisocyanate-containing products/product groups with applications in the skilled crafts sector had to be described in this project.

Research was structured in the following work packages:

- Literature and internet research to identify
 - Fields of application in the skilled crafts sector
 - Diisocyanate-containing products in the relevant fields of application
 - Viable lower risk alternatives
- Consultation with experts
 - Online survey of users
 - Identification and establishment of contact to experts (users, manufacturers, others, e.g., associations, research institutes etc.)
 - Expert interviews

Products and viable alternatives were documented as follows:

- Specific use
- Restrictions to the use (of the diisocyanate-containing product or the alternatives)
- Essential technical safety measures and/or equipment
- In case of hazardous substances/mixtures: classification according to CLP and use profile

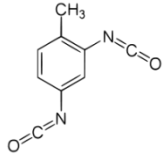
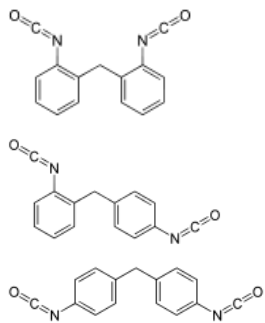
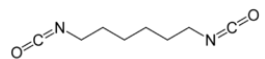
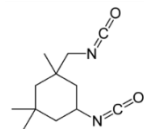
If possible the following aspects were documented:

- Costs (product price, material consumption, investments, time involved)
- Service life
- Availability on the market
- Feasibility and acceptance
- Market relevance of the use (widespread/niche market or similar)

Characterisation of diisocyanate-containing products in the skilled crafts sector

Reactive systems in products used by professionals can be distinguished by means of the used diisocyanates. Table 6-1 shows frequently used diisocyanate monomers.

Table 6-1: Frequently used diisocyanates

Chemical product	Abbreviation	CAS-Nr.	Spec. boundary concentration (% w/w)	Formula
Toluene 2,4-diisocyanate (technical toluene diisocyanate is a mixture of 2,4- and 2,6-isomers, CAS: 26471-62-5)	TDI	584-84-9	H334: $\geq 0,1$	
Methylene diphenyl diisocyanate (2,2'-methylene diphenyl diisocyanate, 2,4'-methylene diphenyl diisocyanate, 4,4'-methylene diphenyl diisocyanate)	MDI	26447-40-5 (mixed isomers)	H319: ≥ 5 H315: ≥ 5 H334: $\geq 0,1$ H335: ≥ 5	
Hexamethylene diisocyanate	HDI	822-06-0	H334: $\geq 0,5$ H317: $\geq 0,5$	
Isophorone diisocyanate (5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-cyclohexane)	IDPI	4098-71-9	H334: $\geq 0,5$ H317: $\geq 0,5$	

Products can be distinguished as 1- and 2-component systems (1-C and 2-C systems). In case of the latter polyol ("resin") and diisocyanate component ("hardener") are mixed on site with curing caused by reaction of the reactive groups. 1-C systems cure as air moisture acts as reaction partner of isocyanate-groups. During the reaction of water with isocyanate carbon dioxide is released, which acts as foaming agent. In systems with latent hardeners (e.g. oxazolidine, Kittel 1998) foam generation is suppressed. Therefore, 1-C systems can be used as varnishes, glues or other unfoamed products as well (Dt. Bauchemie 2012).

Commonly used polyols are polyesters, polyethers, polyacrylates as well as polycarbonates depending on purpose. Moreover, amines are used in combination with polyols (e.g. polyaspartic ester, see Dt. Bauchemie 2012).

Method

Apart from a literature and online research, an anonymous online survey with approx. 1,200 crafts enterprises was carried out in North Rhine-Westphalia, Rhineland-Palatinate and

Baden-Württemberg. Contact data were retrieved from publicly accessible registers of guilds and other professional organisations. The following crafts were addressed:

- Mason and concrete workers
- Painters and varnishers
- Joiners
- Carpenters
- Floor tilers and pavers
- Parquet recliners
- Electricians
- Car body painters
- Tilers
- Interior decorators

The questionnaire was divided in four sections:

- Business characteristics (number of employees, branch, services)
- Technical aspects of the use of diisocyanate-containing products
- Economic aspects
- Questions regarding the willingness to participate in follow up interviews

The survey provided a total of 27 responses (2.2 % of 1,234 potential participants). Thus the results cannot be considered as representative. However, the objectives to get a first impression on applications as well as to identify users as interview partners were achieved.

The distribution of the participants on the trade branches is shown in Figure 6-1. Seven participants did not answer the question with regard to their branch. The responses are dominated by the branches parquet layer and painter/varnisher. Reasons for this could not be determined.

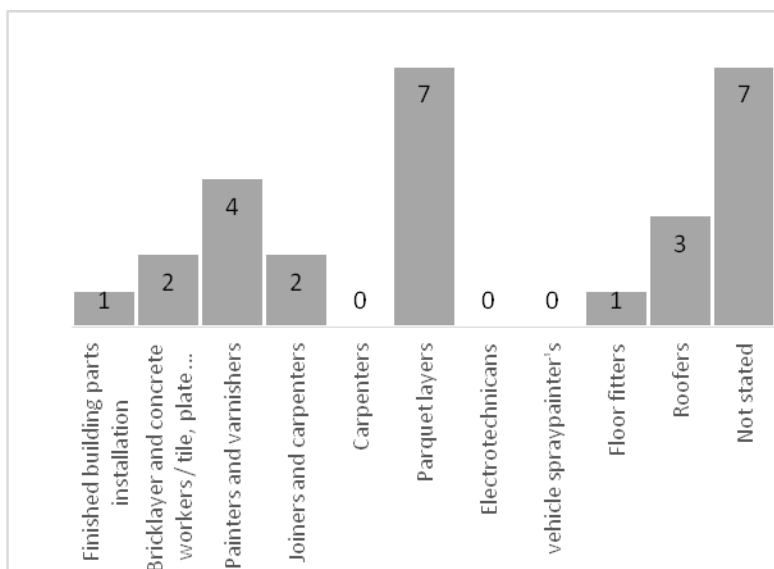


Figure 6-1: Distribution of responses of the online survey on craft sectors

The following table shows the service spectrum of the companies. There appear partly clear overlappings. With masons, concrete workers, floor tilers, pavers as well as parquet layers the same services are often offered. Therefore, they were summarised into one category.

Table 6-2: Distribution of services on craft sectors

Trade	Services
n/a	Application of parquet / carpet / lino / vinyl
Installation of finished product for construction	Window installation
Flooring expert	Painting, varnishing and wallpapering work
Roofer	Roof, façade, solar, woodwork, insulating materials
	Roofing
Floor fitters	Floor covering works in accordance with DIN 18365
Painters and varnishers	Wall, floor and ceiling coating, varnishing
	All works of painting and varnishing (except WDVS)
	Coating and plastering
	Work of painters and varnishers
Concrete worker, tile and mosaic layers	Work of concrete worker, tile and mosaic layers
	Garden and landscape construction
Parquet layer	Interior design, floor covering work
	Application of parquet, work on old parquet
	Parquet and floor covers
	Sale and laying of parquet and resilient floor coverings
	Application, renovation, trade
Interior designer and floor covering worker	Interior designer and floor covering worker
Repair of buildings	Repair and building redevelopment, parquet and floor covers
Carpenter / joiner	Joinery, interior construction
	Furniture, windows, doors

Five participants answered that they are already using isocyanate-free products, nevertheless, mostly the composition of used products was not known.

As possible alternatives to the application of diisocyanate-containing products the interviewees named, for example

- Water based coatings (for wooden substrates)
- Parquet adhesives: silyl modified hybrid resin ("MS" hybrid resin)
- Parquet lacquer: natural surfaces with oil and wax
- Silyl modified products
- Dispersions (without information on ingredients)

Interviewees named the following drawbacks of alternatives when compared with diisocyanate-containing polyurethane products:

- „Insulating material thickness considerably higher, pressure resistance lower“
- „Lower stability of varnish“
- „Other drying times, strains and processing methods“
- „Other processing times and processing temperatures“

This online survey was appropriate to get a first overview on applications and products. Moreover, some used products were named specifically. Six persons were willing to participate in further interviews. It concerned a roofer, a carpenter as well as four parquet recliners. This numerical ratio coarsely corresponds to the branch distribution in the totality of responses.

After finishing online-survey and literature and online research representatives of the following enterprises/institutions were interviewed:

- Manufacturers (companies, associations)
 - Soudal Deutschland
 - German Adhesives Association (Industrieverband Klebstoffe e.V.)
 - Sika AG
 - Henkel AG & Co. KGaA
 - Covestro AG
 - Deutsche Bauchemie e.V.
 - Adolf Würth GmbH & Co. KG
 - Wacker Chemie AG
 - Kemper System GmbH & Co. KG
- Users (companies, associations)
 - Central Association of the German Construction Industry (Zentralverband des Deutschen Baugewerbes e.V.)
 - German Federation for Motor Vehicle Trades and Repairs (Zentralverband des Deutschen Kfz-Gewerbes e.V.)
 - Confederation Colour, Design, Construction protection (Bundesverband Farbe, Gestaltung und Bautenschutz)
 - Carpenter Ceglarek
 - Glomsda Surface Technology
 - PSL Trading Company
 - Carpenter MassivHolz Kütter
 - Carpenter Kubat
- Others
 - Employers Liability Insurance Associations for the building trade (Bau-Berufsgenossenschaft)
 - German Institut for Building Technology (Deutsches Institut für Bautechnik)
 - Institute for Underground Infrastructure IKT (Institut für unterirdische Infrastruktur gGmbH)
 - German Association for Water, Wastewater and Waste DWA (Deutsche Vereinigung für Wasserwirtschaft, Abwasser und Abfall e.V.)

The results of these interviews have been considered with the documentation of the applications.

Results

Uses shown in Table 6-3 were selected for further research.

Table 6-3: Uses of products containing diisocyanates in craft sector

Insulating and sealing
Installation of doors and windows Roof refurbishment and insulation Insulation of operational facilities and buildings Refurbishment of sewers and sewage shafts
Adhesives
Bonding of wall and floor covering Bonding wood elements Windshield replacement Bonding / assembling of vehicle components Bookbinding Adherence of insulating boards Bonding of building components Bonding of machine components
Painting and coating
Painting and coating of surfaces Anticorrosive coating Coating/sealing of wall and floor covering Sealing floors (wood) Coating wood elements Coating vehicle components Coating machine components Coating floors Chemical resistant floors Food compatible floors Drivable floors Conductive floors Stairway floors / ramps Entrance area / foyer Swimming pool Bathroom floors Tile floor / vinyl/ linoleum Basement floors Balcony and terrace floors

Research showed that diisocyanate-containing polyurethane products in most cases are used due to specific technical requirements. In many use cases with especially high technical demands, e.g. with regard to the mechanical and/or chemical surface robustness, epoxy-based products were found to be the only suitable alternatives. Therefore, no lower-risk alternatives could be identified in these cases. In particular, in construction chemistry many products or procedures are either liable to approval or their use is regulated by technical standards or comparable technical regulations. In Germany the "Deutsches Institut für Bautechnik" (DIBt) grants national technical approvals for construction products and types of construction. For new alternatives to be applicable suitable approval has to be granted.

The availability of alternative MDI based products with low diisocyanate content (< 0.1 %) is limited as only few manufacturers deliver the necessary monomer-diminished MDI. Another group of alternative lower-risk products, which are based on silane-terminated polymers, are not feasible in all application fields. The use of silane-based assembly foams,

e.g., is restricted by certain basic conditions or demands (application temperature, fire prevention standards or similar). In most cases where low-risk alternatives could be identified in principle neither product costs nor costs of application were relevant decision criteria against them, but putative or factual superior technical product features of the diisocyanate-containing polyurethane products.

The following table shows the summarised results with "X" depicting positive answers to the following questions:

- Are there any lower-risk alternatives available at all? ("Lower risk alternatives available?")
- If so, are there any technical constraints limiting their feasibility? ("Technical constraints?")
- Are there any procedural differences between the alternatives? ("Procedural differences?")
- Are there problems known with regard to availability of the alternative(s)? ("Restricted availability?")
- Are there any economic restrictions limiting their feasibility? ("Economical restrictions?")

The interpretation of Table 6-4 is to be clarified by the following examples:

For "*roof refurbishment and insulation*" there are lower risk alternatives available, but technical constraints apply. There are no procedural differences between the processes and there is no restriction with regard to availability in the market, although there are economic restrictions.

For "*coating of sewers and shafts*" there are no lower risk alternatives available at all.

For "*coatings for balconies/terraces*" there are lower risk alternatives available, and neither restrictions nor limitations have been identified.

Table 6-4: Summary of research results

Application	Lower risk alternatives available?	Technical constraints?	Procedural differences?	Restricted availability?	Economic restrictions?
Insulation and Sealing					
Installation of doors and windows	X	X	X ¹		X
Roof refurbishment and insulation	X	X			X
Coating of sewers and shafts					
Insulation of operational facilities and buildings	X		X		
Adhesives					
Bonding of insulating boards	X				
Laying parquet: Underground preparation for resin					
Laying parquet: Precoat	X				
Laying parquet: Trowel application	X				
Laying parquet: Parquet adhesives	X				
Laying parquet: Sealing parquet	X				

Application	Lower risk alternatives available?	Technical constraints?	Procedural differences?	Restricted availability?	Economic restrictions?
Bonding of elastic floor coverings	X				
Bonding of floortiles	X	X ²			
Bonding of construction parts	X	X			
Bonding of vehicle parts	X	X			X
Bonding of machine parts	X				
Installation of windshields	X				
Bookbinding	X	X			
Bonding of shoes					
Coating and varnishing					
Chemical-resistant grounds					
Food-grade coatings					
Accessible ground coatings					
Conductive ground coatings					
Pool-coatings	X				
Coatings for stairs and ramps					
Coatings of parking garages / basement garages					
Coatings of tiles and bathroomfloors	X	X	X		
Coating of basement floors					
Coatings for balconies/terraces	X				
Marking					
Coatings of vehicle parts (Top Coat)					
Corrosion protection					

¹: Alternatives available, both with and without procedural differences

²: Normally tiles are bonded to powdery, cement-based products. 2 K-PU- tile adhesives are used for laying ceramic tiles on difficult substrates.

Literature

Deutsche Bauchemie e. V. (2012): Polyurethane in der Bauwirtschaft und Umwelt. Sachstandsbericht. 2. Ausgabe, Juni 2012, Frankfurt am Main

Kittel, Hans (1998): Lehrbuch der Lacke und Beschichtungen. Band 2: Bindemittel für lösemittelhaltige und lösemittelfreie Systeme. 2. Auflage, Stuttgart.

Appendix 7 Appendix 12 to the future Annex XVII entry: Exempted substances and mixtures according to 2b) containing Isocyanates ≥ 0.1 % w/w

1. Substances or mixtures containing diisocyanates $\geq 0.1\%$ w/w may only be placed on the market or used if the provisions of Appendix 13 (Trainings and Measures) are fulfilled.
2. By way of derogation from Appendix 13 (Trainings and Measures) substances and mixtures according to 2b) may be placed on the market or used if they are in accordance with the criteria set out in this Appendix and the information according to number 6 is provided in the safety data sheet (SDS).
3. Exemptions only apply to substances and mixtures according to 2b) if very low potential for exposure both via the dermal and the inhalation route has been shown according to the rules set out in this Appendix. This applies to all typical /expected applications of the substance or mixture according to 2b). Exemptions are not possible for applications where aerosols are sprayed, at temperatures above 45 °C or if personal protection equipment of Category III³⁵ or technical ventilation is needed during the application.
4. In case the use of the derogation is planned, the evaluation whether the conditions of 'very low potential exposure' is fulfilled shall be performed by the manufacturer or importer of a substance or the importer or formulator of the mixture according to 2b). The evaluation, including all data used, shall be documented in a comprehensible manner and, on demand, made available to enforcement authorities within 10 working days free of charge either in English or an official language of the Member State where the substance or mixture according to 2b) is placed on the market. If references to other substances or mixtures according to 2b) are used (see number 9-11), the data referenced shall be made available at the same time in the same language. Additionally, the supplier shall show that he is allowed to use the referenced data.
5. The measurement methods used shall be taken from the 'Compendium on analytical methods to enforce restrictions published³⁶'. This applies for inhalation and biological monitoring methods. The measurements shall take into account unfavourable conditions like e.g. seasonal influences. Additionally, all tasks in the context of the application, including steps like e.g. mixing and cleaning, shall be taken into account. The number of measurements needed depends on the validity and values of the measurement results, the representativeness, kind of conditions and evaluation indices.
6. If the evaluation of a substance or mixture containing diisocyanates in accordance with number 7 leads to the conclusion that the substance fulfils the requirements for an exemption this may be communicated in the safety data sheet (SDS) in accordance with Annex II of this Regulation. In that case the SDS shall contain:
 - a. In section 15 a statement that the evaluation in accordance with to number 7 was performed and the name and address of the manufacturer, importer or formulator according to number 4,
 - b. In section 1.2 a comprehensive description of the applications,

³⁵ As defined by [Regulation \(EU\) No 2016/425](#)

³⁶ http://echa.europa.eu/view-article/-/journal_content/title/compendium-on-analytical-methods-to-enforce-restrictions-published

- c. In section 7 the reoccupation time, when the room of the application can be normally used and all objects within the application area can be safely touched by the occupants or a re-use time for articles (e.g. in case of glues used for textiles),
 - d. In section 16 safety information for bystanders shall be provided,
 - e. In section 16 a short summary of the data used to prove that the exemption according to the criteria set out in this Appendix is fulfilled.
7. For both routes (inhalation and dermal), representative and validated measurements shall be conducted. For the inhalation route workplace exposure measurements may be used. For the dermal route biomonitoring measurements methods may be used. The substance or mixture according to 2b) fulfils the criterion of very low potential for exposure if the cumulative concentration of all diisocyanates is demonstrated to be below 0.001 ppm as time weighted 8 hours average and the biological concentrations are demonstrated to be below the values set down in Table 1 for each diisocyanate.
 8. The Dermal Assessment Tool³⁷ may be used to assess the potential dermal exposure. If it shows "very low" as a result, the dermal criteria are fulfilled. In any other case, biomonitoring (see number 7) shall be conducted.
 9. Grouping is allowed if it is clearly possible to identify for a specific application the substance or mixture according to 2b) with the highest potential exposure fulfilling the criteria of number 7. Other substances or mixtures can be regarded as being of 'very low potential exposure' if they exhibit lower potential exposure than the reference.
 10. Generalised statements on the exposure potential of different applications for the inhalation and the dermal route may be formulated. If, for a specific product, an application fulfils the criteria for 'very low potential exposure' set down in number 7, all applications with a lower potential exposure also fulfil the criteria for 'very low potential exposure'.
 11. It is possible to combine the rules set down in 9 and 10.

Table 7-1 : Biological limits

Parent substance	Urinary metabolite (after hydrolysis)	Limit	Detection Limit	Method
MDI	MDA	10 µg/g Creatinine	0.5 µg/L	DFG, 1994
HDI	HDA	15 µg/g Creatinine.	0.5 µg/L	DFG, 2003
TDI	TDA	5 µg/g Creatinine.	0.5 µg/L	DFG, 1994
IPDI)	IPDA	5 µmol/g Creatinine.	0.5 µg/L	DFG 2003
NDI	NDA	5 µmol/g Creatinine	0.5 µg/L	DFG 1994

³⁷ Available as Excel sheet.

Appendix 8 Elements to be included into Appendix 13 Trainings and Measures to the future Annex XVII entry

This Appendix contains the required elements that are to be used in a final legal text of "Appendix 13"

The provisions of an Appendix 13 shall also cover (external) contractors or temporary workers that may carry out activities from Table 1 with potential exposure to diisocyanates.

The employer or self-employed worker shall

1. Identify the "measures group" for each employee that may be exposed to diisocyanates, depending on the activities performed by that employee or group of employees according to Table 1. This shall be done without prejudice to other mandatory national or local measures. RMMs defined in the eSDS or SDS shall be followed.

Table 8-1: Generic uses and the corresponding "measures groups" – Industrial & professional

Activities	Inhalation Exposure	Dermal Exposure	Measures group
Loading/Unloading Trucks	1	1	1
Pumping /Loading using closed systems	1	1	1
Application of Sealants and adhesives (including foam application from cans)	1	1	1
Handling cold fibres and composite materials after manufacturing	1	1	1
Polyurethane operation with dedicated closed machinery, like foaming, adhesives, sealants, elastomers	1	1	1
Working in a laboratory	1	1	1
Handling open mixtures at ambient temp. (incl. foam tunnels)	2	2	2
Handling incompletely cured articles (e.g. freshly cured, still warm)	1	2	2
Spraying in a ventilated booth	2*	2	2
Application by roller	2	2	2
Application by brush	2	2	2
Application by dipping and pouring	2	2	2
Foundry applications	1	2	2
Mechanical post treatment (e.g. cutting) of not fully cured articles	1	2	2
Cleaning and waste	2	2	2
Maintenance and repair that needs access to equipment	2	2	2
Change Management	2	2	2
Open handling of warm or hot formulations (>45 C)	3	2	3
Spraying in open air, with limited or only natural ventilation (includes large industry working halls) and spraying with high energy (e.g. foams, elastomers)	3	3	3

For other activities not listed in Table 1, or if specific use conditions differ significantly, a risk assessment shall be performed in order to determine the relevant measure group. The result shall be documented.

2. Implement the technical, organisational and personal protective measures for each measures groups as indicated below.

Measure groups 1, 2 and 3:

Basic requirements for technical measures and equipment for all measures groups
RMMs as defined in the supporting documents (e.g. in exposure scenarios in eSDS for substances, or measures prescribed in SDSs for mixtures) are in place
Application equipment is properly maintained
Equipment critical for safety protection (e.g. temperature indicators, overheating safety switches, ventilation systems) is working according to specification and has been checked according to predefined schedules. This shall be proven by relevant documentation.
If heated application systems are used, this equipment is equipped with an overheating switch off protection that will bring the equipment temperature to a safe level.
If exhaust equipment is used (both fixed or mobile) this is constructed in such a way that fresh air replaces exhaust air and that nobody is exposed to exhaust air.
Equipment in storage areas containing isocyanates is constructed in such a way that any spills and leakages are contained.

Measures group 1:

All basic requirements listed above and the following:

Measures	Downstream User Category/Remarks
Technical measures	
Air monitoring once a year is advised.	Industrial users
Where required (e.g. in (e)SDS) exhaust equipment is available.	Industrial and professional users
Emergency kits (cleaning small spills, splashes) are available.	Industrial and professional users
Cleaning solutions, cured waste and isocyanate rests shall only be stored in dedicated areas, in separate containers outside the normal working area.	Industrial users
Organisational measures	
Companies have documented proof that their employees have been trained according to the requirements of this Appendix.	Industrial and professional users
Employees are offered to undergo a medical consultation at the start of job and offered after that yearly. The offer for such a consultation shall be documented.	98/24/EC Art 6.3 and Art 10 [Chemical agents directive] – Industrial and professional
Companies have documented the risk for neighbouring workplaces and bystanders both during normal use and during emergencies.	Industrial and professional users
Companies have tools or system that prevent non-workers from entering the work area when in use and during specified time of restricted access, unless accompanied by a person trained according to the specifications of this Appendix. Access shall only be permitted with PPE specified for the ongoing work stage.	
Companies have a check & maintenance schedule for their ventilation equipment	2009/104 EC Art 4.2 and Art 5.1 and 5.2.a, b, 5.3
Written instructions are available for the performed tasks.	
Personal protective measures	
Protective equipment has been defined and has been made available dependent on product properties and use.	EC89/391

Sufficient skin cleaning and conditioning materials are made available.	
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Measures group 2

All measures of Measures group 1 and additionally the following:

Measures	Downstream User Category/Remarks
Technical measures	
Qualitative detection tools (e.g. wiping tissues) for detection of deposited isocyanate are available	
Companies provide evidence that technical equipment is sufficient for risk management	
Organisational measures	
Effectiveness of protection measures should be regularly checked and documented	
If open systems are used, reasons to use these have been documented. This includes steps like maintenance and repair	

Measures group 3

All measures of Measures Group 2 and additionally the following:

Measures	Downstream User Category/Remarks
Technical measures	
Facilities, machines and tanks shall be constructed and arranged in such a way that also when an equipment part fails, uncontrolled release of isocyanate at the workplace is prevented.	
Organisational measures	
Quantities available during use and quantities stored are limited to the amount necessary to allow a smooth workflow.	
The emergency planning is appropriate for release of large amounts of isocyanate. Appropriate protection equipment for first aiders and/or technical personnel is available	Industrial, fits to local permit.
Documented work procedures exist for the task carried out. These list specific precautions needed (e.g. installation of LEV, sealing rooms to prevent uncontrolled emissions)	
Define and communicate a minimum time to re-entry of the working area to avoid exposure of other workers, and a minimum time to re-occupation of rooms by persons from the general population, according to information in SDS.	Industrial and professional
Tools, including written instructions, are made available to those concerned in order to communicate and control blocking of workspaces for bystander access.	Directive : 92/58/EEC
Companies have introduced a behavioural based management system for performance improvement. For professional BBP is part of training.	For industrial use
Biomonitoring options are offered	

3. Ensure completion of training for each employee according to the determined measures group. Training topics for different measures groups can be combined into one unit taking the combined time for the respective groups.

The content of the required training shall allow reaching the necessary competences and level of knowledge for each measures group respectively. An employee with various tasks shall complete the training for the highest measures group of his working tasks.

This content shall be based on information available from manufacturers of diisocyanates, formulators or suppliers of mixtures of diisocyanates on how to safely handle diisocyanates or such mixtures. Where available, information from trade associations of producers or downstream users of such substances and mixtures can also be used as a basis for the content of the required training.

Any such training shall cover at least the following aspects.

Training for managers / qualified trainers - Measures Group 1, 2 and 3:

Training Format	Optional offering: Classroom, Written, Workplace
Training length (hrs)	4
Repeat frequency (yrs)	4
Trainer qualification	Commissioned expert (e.g. safety or occupational health specialist)

Training topics	Educational objective
Basic information on restriction, training requirements and implementation.	Participants are aware of rationale, scope and requirements of the restriction for their specific use(s).
Measuring devices and their limitations	Participants know when personal or stationary measuring methods are suited
Deposition and Distribution	Participants are aware that diisocyanates can be deposited in areas away from machines.
Protecting Bystanders	Participants are aware that bystander may be exposed and at risk as well and know how to minimise risk. Rules for bystander protection have been defined for the work and have been implemented.
PPE needed	If need for PPE is indicated, the specified type of mask and gloves will be defined and made available for each person. In addition, an instruction has been performed where use of PPE is needed (practising, maximum time of wearing, disposal of contaminated PPE).
PPE and their limitations	Participants know the limitations of the different PPEs (respiratory protection equipment, eye protection, skin protection). This includes special PPE required in emergency situations.
Storage	Participants know how diisocyanates are to be stored for their specific use.
Behavioural based safety management	Participants are aware of the principle of behavioural based safety management. A behavioural-based

	safety organisation has been introduced.
Emergency plans	Participants know how to react in case of an emergency related to isocyanates.
Management of Change	Participants understand and apply the principles of management of change
Certification	For those applications where such is required (e.g. some activities in measure group 3), a valid national or international certificate for such a specialized task has been obtained.
Evaluation	Participants have reached a success rate of >70 percent in a corresponding test of the requisite qualification

Employees Measures Group 1:

Training Format	Optional offering: Classroom, Written, e-learning, Workplace
Taining length (hrs)	4
Repeat frequency (yrs)	4
Trainer qualification	Employer, or commissioned expert (e.g. safety or occupational health specialist)

Training topic	Educational objective
Chemistry	Participants have basic knowledge what are diisocyanates and know about the hazards for human health
How you can be exposed	Participants are aware of exposure routes via inhalation, dermal, oral and the possibility of contamination because of deposition, including basics on industrial hygiene
Signs of sensitisation	Participants can recognize warning signs (dripping nose, sore throat, short breath) and will warn their supervisor.
Hazard of odour	Participants know that detectable odour indicates large exceedance of exposure limits and can act accordingly.
Importance volatility / Viscosity/ Temperature / Mol. Wt	Participants can rationalize when risk level increases
Personal Hygiene	Participants are aware that high hygiene standard prevents exposure
PPE needed	If need for PPE is indicated, participants know which type of mask and which gloves are needed. In addition participants <ul style="list-style-type: none"> - have practised to put on - are aware of maximum time of wearing - know how to take off contaminated PPE (especially gloves) in a safe way - will dispose single use gloves directly after use, and normal gloves at end of shift.
Clothing	Participants know what contaminated clothing shall be changed directly (risk of cross-contamination)
Risk of dermal contact	Participants can recognize activities with increased risk of dermal contact.

Risk of exposure to not fully cured polyurethane	Participants are aware that not fully cured PU may still present a risk and take appropriate actions.
A skin protection scheme has been taught	Participants know which skin care products they need to use.
Ventilation	Understand the basics of ventilation; Participants know that ventilation need to be checked.
Cleaning , leakages, maintenance	Participants have been instructed for cleaning and maintenance, also after spills and when applicable for empty drum handling and drum decontamination
Discarding empty packaging	Participants are aware where empty packaging should be put und how it should be treated
Protecting bystander	Participants use warning signs to restrict access to working area. Professional use in buildings: restrict access to work area for time specified by supplier in SDS or work instructions, follow specification for ventilation and re-occupation time in SDS or work instructions ³⁸ .
Identification of critical handling stages	With regard to the potential risk of exposure, participants are able to mention the most critical stages of their personal work assignments.
Special national code systems (If applicable)	Participants know how to interpret and use external reference codes that allow to recognise or obtain additional safe handling instructions (e.g. GISCODE in DE)
Behavioural based safety	Participants are aware of the principle of behavioural based safety
Evaluation	Participants have reached a success rate of >70 percent in a corresponding test of the requisite qualification.

Employees Measures Group 2:

Training Form	Optional offering: Class room / workplace
Training length (hrs)	Additional 4
Repeat frequency (yrs)	4
Trainer qualification	Employer, or commissioned expert (e.g. safety or occupational health specialist)

Topic	Educational objective
Training Stage Measure Group (1)	Training topics for measures group 1 can be combined with the topics from measures group 1 in to one unit taking the combined time for group 1 and 2
PPE and their limitations	Participants know the limitations of the different PPE's.

³⁸ These times will be related to the total formulation and may also be determined by other substances than diisocyanates

	respiratory protection equipment, eye protection, skin protection. Including special PPE required in emergency situations.
Behavior based aspects	Do's and don't's during special applications (e.g. PPE, handling, machinery, communication)
Maintenance	Participants are aware that equipment can hold diisocyanates, need to know PPE, bystander protection procedures.
Management of change.	Participants understand and apply the principles of management of change.
Evaluation of safety instructions	Related to use of PPE, use of equipment in a safe way.
Risk and application process used	Participants know how to recognize applications with higher risks
Evaluation	Participants have reached a success rate of >70 percent in a corresponding test of the requisite qualification.

Employees Measures Group 3

Training Form	Class room / On-Site instructions where required
Training length (hrs)	Additional 4, if combined with application specific trainings
Repeat frequency (yrs)	4
Trainer qualification	Employer, or commissioned expert (e.g. safety or occupational health specialist)

Topic	Educational objective
Feedback	Participants have completed typical work under supervision (if applicable). Suggestions for improvement have been documented.
Additional certification	Where an external certificate is required, participants have a valid certificate for such a specialised task.
Spray in open air	<p>Specific training modules related to the risk associated with spraying in areas with no or insufficient general or local exhaust. (This includes large industrial halls)</p> <p>Special attention for product / use items that potentially create a greater risk. As a minimum this includes</p> <ul style="list-style-type: none"> - Activity planning and preparation - PPE requirements - Bystander protection <p>For sprayfoam, specific training modules based on the sprayfoam product stewardship. This especially includes specific product / use items that potentially create a greater risk.</p> <p>Apart from what has been mentioned in stages 1 and 2 , such a training shall include as a minimum:</p> <ul style="list-style-type: none"> - specific prescriptions for ventilation(minimum number of air exchanges/hr, - ventilation time after application), - Necessary PPE - Bystander protection as defined in procedure (including a minimum reoccupation time) - in case of confined areas: A second person should always be

	available for direct communication. - for confined spaces a schedule of maximum uninterrupted working time/ mandatory break time has been defined .
Open handling of hot or warm formulations (>45°C)	Focuses on the potential higher risks due to working open handling of formulations with elevated temperatures (>45 C). This shall include: - Special ventilation requirements, - PPE, - Bystander protection.
Evaluation	Participants have received positive go-ahead on supervised work.

4. Document the completion of steps 1 – 3 and check the validity of the documentation at least once per year.

If a supplier specifies a specific measure group for any of his substances or mixtures, this shall be documented in Section 16 of the the safety data sheet. This shall be taken into account by the downstream user.