Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Background document

to the Opinion on the Annex XV dossier proposing restrictions on

diisocyanates

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A.1 Summary

A.1.1 The identity of the substances

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, allophanate or isocyanurate linkages (i.e. the diisocyanate entity is not the result of prepolymerisation of a parent diisocyanate).

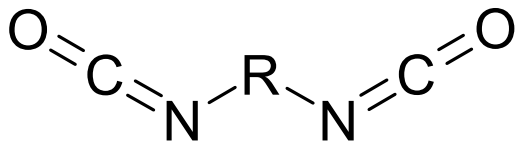

Figure 1: Chemical structure of diisocyanates

Further identity information on covered diisocyanates is given in Annex B.1.

It should be noted that in may publications dealing with hazards and risks of (di)isocyanates in practical applications, authors use the terms "diisocyanates" and "isocyanates" rather loosely in discussing effects from the formulations (i.e. mixtures) that are used in such applications. This becomes already apparent from the occupational disease which is always referred to as "isocyanate asthma", where, if specific allergens are investigated, it is the diisocyanates that are referred to.

In this dossier, we will use the term "diisocyanates" if we refer to specific data or discussions regarding diisocyanates according to the above definition and "isocyanates" if we refer to substances, mixtures, or formulations that may also contain (pre-)polymers or oligomers with isocyanate groups, or species with an isocyanate functionality other than 2. *Note: Also see remark in Annex B.1.2.*

A.1.2 Scope and conditions of the restriction(s)

The proposal limits the use of diisocyanates in industrial and professional applications to those cases where a combination of technical and organisational measures as well as a minimum standardised training package have been implemented. Information how to get access to this package is communicated throughout the supply chain.

Exemptions are defined for cases where the content of diisocyanates in the substance or mixture placed on the market or used is less than 0.1 wt%.

Exemptions are also defined for mixtures containing diisocyanates at ≥ 0.1 wt% for which a very low potential for exposure has been shown. This is the case if the TWA (8hrs) of the airborne cumulative concentration of all diisocyanates is demonstrated to be below 0.001 ppm and the indication for dermal exposure is demonstrated to be very low by the fact that the biological concentrations are below certain limits, or alternatively in cases where methods or data referring to biomonitoring are not available, a dermal assessment tool shows a "very low" potential for exposure. Details can be found in Appendix 7.

The DS would like to stress that after implementation the proposed restriction would apply without prejudice to existing occupational safety and health regulations, i.e. obligations from such regulations shall still be followed.

Regarding the scope of the proposed restriction, two other aspects should be mentioned:

1. All products that contain diisocyanates above the proposed concentration limit and are marketed to professionals or used by professionals are in the scope of the restriction. However, the scope of the restriction does not include products that are marketed exclusively to consumers or products that are used exclusively by consumers. These products were not included into the restriction because of the weaker data base on exposure and risks from diisocyanates in such products: There is no established monitoring system in the consumers sector that could distinguish asthma cases due to diisocyanate uses from other asthma cases. Moreover, it would be difficult to perform trainings for consumers or to collect measured data for exemptions of products if they were marketed exclusively in the consumers sector.

On the other side, researches performed by the dossier submitter on ECHA´s dissemination site did not detect registered consumer uses of diisocyanates that would not be covered by the existing Annex XVII restriction for MDI. According to indications from the consultation confirmed by own researches, spray paints containing a HDI-homopolymer are marketed in the internet. These paints are not in the scope of the existing MDI restriction. However, they would be in the scope of the restriction proposed by the dossier submitter if they contained HDI above the proposed concentration limit, because their use is not limited to consumers.

2. Monoisocyanates are not in the scope of the restriction. Monoisocyanates are mainly used for entirely different uses (production of pharmaceuticals and biocides, but not in polyurethane chemistry). Data on specific risks of uses of monoisocyanates are not available to the DS. If new data would give rise to a concern in this area, this should be dealt with in a separate process.

Assessment of RAC

There are indications that sensitisation in humans could also be induced by diisocyanate-free polyisocyanates, which are not covered by the Dossier Submitter´s proposal (Vandenplas et al., 1992a; Aalto-Korte K et al., (2010)). Scientific data on this issue are still very limited.

Another type of isocyanates that are not covered by this restriction proposal, but for which there is a concern that they could induce hypersensitivity in humans, are monoisocyanates, such as methyl isocyanate, isocyanic acid, tolyl isocyanate, ethyl isocyanate or phenyl isocyanate. According to the information provided by the Dossier Submitter and from the UK HSE report WATCH/2008/4 the primary use of methyl isocyanate is as a chemical intermediate in the production of carbamate pesticides. It is a potent respiratory irritant but although it is shown that it can induce immunological response in humans (IgE, IgG and IgM class, measured in subjects exposed to the industrial gas leak in Bhopal accident (Karol MH et al., (1987)), the primary concern for human health is its high acute toxicity if inhaled. Isocyanic acid is highly unstable and it does not have commercial uses, but occupational exposure may occur when it is generated as a thermal degradation product of other industrial processes. Ethyl isocyanate is used in production of pharmaceuticals and pesticides. Phenyl isocyanate is a trace constituent in commercial diphenyl methane diisocyanate products and is also an intermediate chemical. Animal experiments showed that it can induce contact sensitisation and humoral immune response (Karol and Kramarik, 1996). Tolyl isocyanate is an intermediate chemical in pharmaceutical industry. For this

substance it was also shown that it can induce immunologic response (IgE class) in humans (Baur X et al.). According to UK HSE report WATCH/2008/4 and more recent literature data, there is no direct evidence that any of the monoisocyanates can cause respiratory sensitisation in humans.

The Dossier Submitter points out that the use of monoisocyanates is not in the scope of the restriction, since they mainly have entirely different uses (e.g. as intermediates in the production of pharmaceuticals and biocides), and not in polyurethane (PU) chemistry. Data on specific risks of the uses of monoisocyanates were therefore not included in the Background Document. RAC also points out that workplace exposure to chemicals that are released due to thermal degradation (e.g. isocyanic acid) is not in the scope of this restriction.

To summarise, regarding other types of isocyanates, namely polyisocyanates (diisocyanate-free) and monoisocyanates, which are not in the scope of this restriction proposal, RAC considers that although there is no direct evidence for respiratory sensitisation in human population, indirect evidence from humans and animals stated above indicates that the risk of respiratory sensitisation in humans cannot be excluded. Nevertheless, RAC accepts that the scientific data on human health hazards and risks posed by these substances is rather limited, and why the Dossier Submitter decided not to include them in the scope of the restriction.

Consumer use of diisocyanates-containing products is not covered by this restriction proposal either. There is an existing European wide regulation for MDI (entry #56 to Annex XVII to Regulation (EC) No. 1907/2006 (REACH) which focuses on the risk of skin sensitisation to address the recognised risk. Spray applications are advised against for these substances. For the other two diisocyanates used at high tonnages in the European market (which together account for more than 95% of the market volume on diisocyanates), all consumer uses are either strongly advised against (HDI) or consumer uses are not relevant (TDI), according to the Chemical Safety Reports. There is no available information on health risk of application of diisocyanates-containing products by consumers (Lockey et al. 2015; Verschoor and Verschoor 2014; and Web of Science - All databases literature search performed by the rapporteurs), and no new information on exposure and health risks related to consumer use of diisocyanates was provided during the Public Consultation. RAC, therefore, agrees with the Dossier Submitter's justification for omitting the diisocyanate-containing consumers' product from the scope of this restriction proposal, but stresses that this issue should be reconsidered when more information on exposure and health risk in consumers becomes available.

A.1.2.1 Proposal of Text for Annex XVII

Column 1 Designation of the substance, of the group of substances or of the mixtures	Column 2 Conditions of restriction
Diisocyanates	1. Shall not be used as substances on their own, as a constituent in other substances or in mixtures for industrial and professional uses, unless

	a) the cumulative concentration of diisocyanates in the substance or mixture is less than 0.1 % by weight, or b) the substance or mixture in the form in which it is supplied to the user, including the combination of such substance or mixture, its packaging and any application aid is placed on the market in accordance with paragraph 2b), or c) the employer or self-employed worker ensures that measures and trainings are taken prior to the use of the substances or mixtures in accordance with the provisions described in Appendix 13[1] (Trainings and Measures). Member States may implement or continue to apply own provisions for the use of these substances and mixtures as long as the minimum requirements of Appendix Trainings and Measures are met. The employer or self-employed worker shall document the compliance to the requirements of Appendix 13 (Trainings and Measures). Proof of successful completion of a training according to Appendix 13 (Trainings and Measures) shall be recognised in all other Member States. 2. Shall not be placed on the market as substances on their own, as a constituent in other substances or in mixtures for industrial and professional uses, unless a) the cumulative concentration of diisocyanates in the substance or mixture is less than 0.1 % by weight, or b) the substance or mixture in the form in which it is supplied to the user, including the combination of such substance or mixture, its packaging and any application aid is compliant with Appendix 12 (Exemptions), or c) the supplier ensures that the recipient of the substance or mixture is provided with information according to paragraph 3. 3. For the purpose of 2c) manufacturers and importers of diisocyanates on their own or as a constituent in other substances and importers of mixtures containing diisocyanates shall develop a set of teaching material in accordance with the provisions of Appendix 13 (Trainings and Measures) in an official language of the Member State where the substance or mixture is placed on the market before placing the substance or mixture on the market. They shall ensure that training courses based on the training material are available to the recipients of such substances or mixtures. They shall review and update the training material after a maximum of 8 years, or without delay if new information, which may affect the risk management measures, becomes available and inform the recipients accordingly. Natural or legal persons formulating mixtures containing diisocyanates within the EU shall provide necessary information for the development of the teaching material upon request of their substance suppliers. All downstream users may be consulted for the purpose of the development and update of the teaching material.

Please note that in the way the proposal for the scope of the restriction has been formulated in Section A1.2.1, oligomers and prepolymers that contain ≥ 0.1 wt% of the diisocyanates that meet the above definition (of which a non-exhaustive list is shown in Section B1.1), would still be in scope of the restriction.

[1] The texts of Appendix 12 (Exemptions) and Appendix 13 (Trainings and Measures) should become part of the final legal text. Elements to be included in the final text are available in Appendix 7 and Appendix 8 to this proposal. A short summary can be found in A.2.2. Additional background information can be found in Appendix 5 to the dossier.

Assessment of RAC

Based on the comments provided in the public consultation of the Annex XV dossier regarding the complexity of the text of the restriction proposal, RAC and SEAC have reformulated the conditions of the restriction with the aim to streamline the requirements and structure them in a format compatible with an Annex XVII entry. The conditions of the restriction as formulated by RAC and SEAC are included as an Annex to the RAC and SEAC opinion.

A.1.2.2 Which substances are covered?

Section A1.1 gives a text description of the substances covered. Section B.1.1, Table 1 provides some examples of substances covered by this restriction proposal (non-exhaustive list).

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 restriction proposal covers all these diisocyanates, as well as other substances which contain residual diisocyanates. This includes prepolymers, oligomers and polymers of diisocyanates which still contain ≥ 0.1 % free diisocyanates.

A.1.3 Summary of the justification

A.1.3.1 Identified hazard and risk

Respiratory sensitisation has been an endpoint of major attention for the legislator and the regulatory authorities. REACH recital (115) places respiratory sensitisers among the "substances of the highest concern".
Diisocyanates are respiratory sensitisers and are important substances used in many applications (foams, sealants, coatings) throughout the European Union. The total tonnage is about 2.5 million tonnes/yr. With regard to diisocyanates, respiratory sensitisation therefore is seen as the endpoint of highest regulatory concern

The issue of occupational asthma (OA) caused by handling diisocyanates or formulations containing such substances has been known for decades and occupational diseases caused by these products are known in each Member State. The Dossier Submitter (DS) considers the annual number of new occupational diseases caused by diisocyanates (estimated to be more than 5000 cases) to be unacceptably high.

An already existing European wide regulation for MDI (entry #56 to Annex XVII to Regulation (EC) No. 1907/2006 (REACH)) focusses mainly on the risk of skin sensitisation for consumers and regulates the inclusion of protective gloves in packaging meant for the general public. This does, however, not solve the problem of occupational asthma described above.

A.1.3.2 Justification that the proposed restriction is the most appropriate Union-wide measure

In a Risk Management Option Analysis (RMOA, (German CA, 2013)) arguments for a REACH restriction for diisocyanates as a group have been discussed and concluded to be the best regulatory measure. The main arguments are in summary:

1. The risk of occupational disease (mainly occupational asthma) is present for all diisocyanates. Compared to authorisation, a restriction offers a more straightforward approach to address all diisocyanates in one regulatory action. A restriction may also cover prepolymers with residual diisocyanates.
2. It does not seem efficient to regulate the substances by means of the SVHC/Authorisation route because of the extreme complexity of the supply chain and the large number of uses. In view of the wide areas of uses, an extremely large number of Applications for Authorisation (AfA) has to be expected.
3. Based upon present information, socioeconomic benefits of the substances are likely to be much higher than the costs caused by the risks, making it likely that most AfAs would be granted. Pressure for substitution would be limited.
4. Because of unique properties of diisocyanates and the resulting polyurethane polymers, large scale substitution is unlikely.
5. The restriction route can concentrate on the conditions of supply and handling of formulations containing diisocyanates.
6. A voluntary "self-restriction" by industry has some attraction, but will suffer from the fact that no legal means are available to force companies that refuse to join such an initiative.

Long term experience with the application of the Chemical Agents Directive (CAD, Directive 98/24/EC) has shown that occupational safety and health measures are not efficient enough to reduce sensitisation by diisocyanates to an acceptable level. Therefore a restriction under REACH that aims at establishing stricter mandatory handling habits throughout the EU is considered as the option of choice. The restriction proposal will also create an incentive to develop and use products with very low potential of exposure. REACH as a regulation for the placing on the market of substances is much better suited to guarantee a comprehensive quality management from the top of the supply chain based on the knowledge of the manufacturers and importers.

A major point of attention has to be sought in the improvement of awareness of situations with potentially increased risks.

In addition the proposal is drafted in such a way that MS are still free to implement more stringent measures as long as they meet the minimum requirements as defined in this restriction.

The proposal for the restriction (Section A.1.2) also mentions two Appendices describing further details regarding use conditions and exemptions. More details on these Appendices are given in Section A.2.2. The full text of these Appendices can be found in two separate documents to this dossier. Additional information can be found in Appendix 5 to this dossier.

A.1.3.2.1 Effectiveness in reducing the identified risks

A restriction under REACH that aims at establishing stricter mandatory handling habits throughout the EU is considered as the option of choice. Apart from an incentive to use products with very low potential of exposure, establishing stricter mandatory handling habits will be reached by the obligation to train workers according to the potential risk met with during their work. This will improve the fundamentals of handling diisocyanates throughout the EU, and can be formulated in such a way that MS are still free to implement more stringent measures as long as they meet the minimum requirements as defined in this restriction. As will be discussed in Section A.3 (and in more detail in Annex E.6.1.1) it is assumed that mandatory standardised training may lead to a 50-70 per cent reduction in the yearly number of cases of newly reported occupational diseases due to handling diisocyanates.

A.1.3.2.2 Proportionality to the risk

As will be reported in Section A.3 the costs of the proposed measure in the form of the preferred option that combines both mandatory trainings and the option of exempted products have been evaluated to be proportionate with respect to the risks that are avoided by the measure.

A.1.3.2.3 Practicability, including enforceability

A number of aspects will be important in order to achieve an enforceable practical implementation:

- Measures will build upon an established system for customers at the top of the supply chain ("Walk the talk" (ISOPA, 2013) and "Safeguard – We care that you care!" from the trade associations "European Diisocyanate and Polyol Producers Assocation" (ISOPA) and "European Aliphatic Isocyanate Producers Association" (ALIPA)).
- Sharing common measures and trainings will improve communication and will help to get acceptance for the new duties throughout the supply chain.
- A dissemination strategy to allow access to the relevant trainings in various languages in all Member States will be made available by the manufacturers and importers of diisocyanates and their partners from industrial associations. This will need a certain transition time to be able to set up a structure to meet the new requirements.
- The restriction can be enforced by active checks of the training status of companies as proven by the necessary documentation, as well as checks for the implementation of the necessary risk management measures.

A.1.3.2.4 Monitorability

Monitorability of the restriction can in first instance be sought in tracking the degree of implementation of trainings throughout the various countries. However, in the long run (10-15 years) it should be possible to determine if the number of new occupational diseases because of handling diisocyanates is going down as assumed. In preparation of further activities the DS plans to update the survey on occupational diseases because of diisocyanates at regular intervals. In this way the awareness for respiratory sensitisation will be increased which will benefit future monitoring efforts in the Member States. In addition, industry is called upon to generate longitudinal epidemiological data that allow the evaluation of risks at current workplaces as well as its change that is expected to be achieved by this restriction.

A.2 The problem identified

A.2.1 The hazard, exposure/emissions and risk

A.2.1.1 Hazard assessment

A.2.1.1.1 Introduction and scope

The observation of diisocyanate-related occupational asthma (OA) is the main driver behind this restriction proposal. While respiratory sensitisation to diisocyanates is a pre-requisite for developing diisocyanate-related asthma, it is not possible to set a reliable exposure limit preventing sensitised individuals from developing manifest asthma. Therefore, any strategy for reducing the number of new diisocyanate-related asthma cases must aim at avoiding new cases of respiratory sensitisation. Moreover it should be noted that the sensitised state as such already adversely affects the individuals concerned because it triggers the need for

removal from their workplace as well as for long-term avoidance of diisocyanate exposure in both, their professional and private sphere. As a consequence the human health hazard assessment concentrated on markers of effects related to respiratory hypersensitivity (see next section).

Aromatic diisocyanates may potentially be degraded by hydrolysis or metabolism to yield primary aromatic amines known to be genotoxic carcinogens. Whether or not this is a relevant point when using diisocyanates at the workplace has been a matter of debate. In the present dossier this issue was, however, not considered further (for detailed reasons cf. Annexes B.5.8 and B.5.9), as the Dossier Submitter (DS) did not expect a relevant impact on the restriction proposal.

A.2.1.1.2 Hazard description based on REACH and CLP legal text and guidance

In analogy to skin sensitisation, the process of respiratory sensitisation is assumed to comprise two phases, i.e. induction and elicitation. For skin sensitisation it is known that elicitation thresholds apparently poorly correlate with induction potency and that there is large interindividual variability depending among other factors on the sensitising potency of the substance, the duration, site, and extent of exposure, the condition of the skin, and the extent to which the sensitisation has been acquired, cf. e.g. (ECHA, 2012; Holloway et al., 2010). For respiratory sensitisation, similar considerations apply, cf. e.g (Vercelli, 2016).

The major goal of this restriction proposal is to prevent new cases of sensitisation. As a consequence hazard assessment concentrated on the induction step of respiratory sensitisation. A more detailed description of the clinical picture in humans is provided in Annex B.5.6.2.1.

A.2.1.1.3 Summary of non-human data

For the assessment of respiratory sensitisation, currently no formally recognised and validated animal tests exist. In addition, even though in theory respiratory sensitisation (induction and elicitation) can be regarded as a threshold effect, the available methods are not suitable for threshold determination or DNEL derivation. In concert with human data, some types of animal data may play a supportive role in the qualitative assertion of respiratory sensitisation (ECHA, 2015; ECHA, 2016; European Parliament and Council, 2008).

All diisocyanates relevant under this restriction proposal are classified as Resp. Sens. 1 as well as Skin Sens. 1 according to CLP (cf. Annex B.3 on classification and labelling). In fact, MDI and TDI are recognised as potent, prototypic respiratory sensitisers and have been employed frequently as model substances in test method development. Qualitative assertion of the potential of diisocyanates to cause respiratory sensitisation was therefore unnecessary; nevertheless the large body of non-human experimental data on diisocyanates was evaluated with the following goals:

- to review the data with respect to the possibility to derive a DNEL (or DMEL) for respiratory sensitisation and
- to report the lowest dose levels (LOECs) at which in animal experiments sensitisation and/or respiratory effects have been observed after dermal or inhalation exposure.

To that end, variability and uncertainty have been considered for each aspect of hazard characterisation. Study reports were evaluated for all adverse effects on the respiratory system, and all effects indicative of sensitisation, i.e.:

- 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), as well as the ratio of IgE to IgG subtypes, and
- dermal contact hypersensitivity (as positive proof of the sensitised state).

The most important findings from the non-human database are summarised as follows:

- exposure to diisocyanates by inhalation, but also via the dermal route, can trigger both Type I (immediate) and Type IV (delayed) respiratory hypersensitivity in a variety of rodent species. Observed respiratory symptoms (increased respiratory rate, effects on respiratory flow, laboured breathing etc.) resemble those seen in humans with asthma;
- skin sensitisation has also been observed following inhalational induction;
- respiratory sensitisation can be evoked with diisocyanates and with diisocyanate serum albumin conjugates. Cross-reactivity with mono- and diisocyanates and polyisocyanate resin has been reported;
- species and strain differences appear to exist regarding the relative proportions in which individual traits of respiratory sensitisation are expressed;
- the severity of respiratory impairment following (single or repeated) short-term challenges ranged from moderate change in respiratory rate and other breathing parameters to anaphylaxis and mortality at high challenge concentrations;
- because in animal tests usually no follow-up data are available, no conclusion on reversibility (in the sense of remission of the sensitised state) can be drawn;
- overall, the interdependencies and quantitative contributions to sensitisation of factors such as the species and strain used, concentration and total dose received upon induction, or the temporal pattern of dosing are still poorly understood;
- NOAECs, where reported, could not be used as Points of Departure (PoDs) for risk characterisation, since most available studies only cover a limited spectrum of effect markers, the most relevant species to be used is unclear, agreement on critical effect levels is lacking, and many studies showed other deficiencies. Also there is great uncertainty regarding the extrapolation of results from animal experiments to humans.

For the analysis of LOECs, studies were selected by the following 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, dermal) and deselect those studies not matching pre-defined acceptance criteria (see Annex B.5.6.4.6);
- Tier 3: Record for the remaining studies 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.

An example of a study in mice using a single, 1-h inhalation challenge following a subchronic (6 wk) inhalation induction regime (4 h/d, 5 d/wk), which resembles, but might still underestimate continuous exposure of humans e.g. at the workplace was carried out by Matheson and co-workers in 2005. A spectrum of effects related to isocyanate-induced respiratory sensitisation in the animal model was observed in this study already at a dose

level of 20 ppb TDI (≙ 144.5 µg/m³), corresponding to about 10 ppb or 0.07 mg/m³ NCO[2]; a NOAEC was not determined (Matheson et al., 2005).

Both strategy and results are discussed in more detail in Annex B. Studies are summarised in tabular form in Appendix 1 to Annex B.

A.2.1.1.4 Summary of human data

The CLP regulation notes that evidence for chemical-induced respiratory sensitisation (asthma/rhinitis/conjunctivitis/alveolitis) will normally be based on human experience. "*The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated"* (European Parliament and Council, 2008).

Human data relevant for the assessment of respiratory sensitisation may comprise "*consumer experience and comments, preferably followed up by professionals (e.g. bronchial provocation tests, skin prick tests and measurements of specific IgE serum levels); records of workers' experience, accidents, and exposure studies including medical surveillance; case reports in the general scientific and medical literature; consumer tests (monitoring by questionnaire and/or medical surveillance); epidemiological studies."* (ECHA, 2016).

Nevertheless, studies in humans frequently suffer from limitations. The full spectrum of aspects such as the test protocol used, the substance or preparation studied, the extent of exposure, the frequency of effects, the persistence or absence of health effects, the presence of confounding factors, the relevance with respect to the group size, statistics, documentation, or the "healthy worker effect" which should all be reported (ECHA, 2016), is rarely, if ever, provided in these reports.

More than 100 case reports and epidemiological studies fulfilling elementary eligibility criteria have been evaluated. An overview of this evaluation is provided in Appendices 2 (case reports) and 3 (epidemiological studies). Moreover, an extensive review of isocyanate-related occupational diseases is provided in Annex B.5.6.5.3.

The Dossier Submitter 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 respective Competent Authorities (CAs) (further details in Section A.2.1.3).

Major findings from the evaluation are summarised as follows:

Remarkably, diisocyanates cause both immediate (seconds to minutes) and delayed-onset (up to several hours) type respiratory hypersensitivity in humans. A feature of particular concern is the delay between onset of (low-level) exposure at work and the manifestation of the asthmatic symptoms which may be as long as several years after the start of exposure.

Case reports provide overwhelming proof that humans exposed to diisocyanates may suffer from a broad spectrum of respiratory effects including asthma and pathological changes of the airways. Also a number of fatal cases have been reported, albeit not in recent years. While during the early stages of the development of the disease, respiratory symptoms may eventually be reversed upon removal from exposure, an irreversible remodelling of the airways will eventually take place when exposure is continued.

Data show that renewed contact with a respiratory sensitiser, even after prolonged times of non-exposure, may still evoke severe symptoms in affected subjects. Based on the available data in humans, and notwithstanding recession of symptoms after removal from exposure

[2] A table with conversion factors for ppm to mg/m³ and mg/m³ to ppm for all diisocyanates concerned can be found in Appendix 4.

during early stages or individual variability in the degree to which certain features of the disease are expressed, it is therefore concluded that once occupational asthma has been acquired caused by diisocyanate exposure, the disease is principally irreversible.

In addition, potential cross-reactivity with other structurally related sensitisers and increased sensitivity to non-specific stimuli as a consequence of sensitisation often further negatively impact on the quality of life of sensitised individuals.

On the other hand these case reports only allow for a qualitative assessment, as none of them includes 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. They are therefore principally unsuited for use in quantitative risk characterisation. However, for the purpose of illustrating certain aspects of the disease such as severity, delayed onset, irreversibility etc., some exemplary cases are described in detail in Annex B.5.6.5.1.

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

Epidemiological studies on diisocyanate-exposed workers conducted over 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 significant number of new cases of occupational diseases are reported in the EU.

Despite a large number of available studies, none of these studies is eligible for deriving a reliable ERR. Reasons for this are limitations of the studies, but it 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 contribute 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. However, it is obvious that every year isocyanates lead to a significant number of new disease cases in the EU. These cases serve as the basis for the risk characterisation in Section A.2.1.3. For most of the cases reported in Europe the specific isocyanate is not documented. This is one of the reasons for the proposed group approach.

A.2.1.1.5 Group approach

The common mechanistic understanding of skin and respiratory sensitisation caused by low-molecular weight chemicals in most cases is based on the assumption that in a first "molecular initiating event" (MIE) the chemical (hapten) must bind to a protein. In the course of this process the three-dimensional shape of this protein is altered which then triggers the immune system to recognise the protein-hapten complex as foreign to the body. The ability of diisocyanates to initiate the MIE, i.e. to bind to proteins, derives from the presence of the (double) isocyanate group. Therefore, it seems justified to address all diisocyanates under the same restriction proposal. Moreover, workers/professionals may be exposed to more than one diisocyanate and cross-reactivity between different diisocyanates has been demonstrated.

Arguably, depending on the non-isocyanate part of the molecular structure, the different diisocyanate congeners will possess different potencies, e.g. due to different binding affinities or different bioavailability. For the following reasons this was not further pursued in this dossier:

- A limited number of animal studies would have been available to at least compare the potency of some (but not all) of the congeners in a comparable experimental setting. However, since for respiratory sensitisation no validated and accepted test protocol is available in animals to be used for quantitative exposure-response assessment in humans, the result of such a comparison would have been of limited, if any, use for establishing relative potencies in humans.
- Also the available data in humans do not allow for potency comparison due to the absence of reliable exposure-response-relationships.
- Due to deficiencies in the registration of occupational diseases, the observed cases of diisocyanate-related occupational asthma cannot be attributed to specific diisocyanates.
- No thresholds could be established (cf. Section A.2.1.1.6), therefore the restriction proposal does not foresee a limit value for single or all diisocyanates.

However, as chemical reactivity of different substances should be compared on a molar and not mass basis, relevant dose metrics were converted to the concentration of NCO groups in order to compensate for differences in molecular weight. All conversion factors used in this dossier can be found in Appendix 4.

A.2.1.1.6 Discussion on DNELs and existing OELs

There has been a long-standing debate on the question of the existence of a threshold for respiratory sensitisation and on whether this threshold can be determined as a health-based DNEL from experimental (non-human or human) data. An extensive discussion of this issue is provided in Annex B.5.12. In essence the following reasoning has been applied:

For a given exposure scenario as characterised by route, duration, pattern and level of exposure, it is plausible to assume that in theory a level of exposure exists below which in a well-defined, previously unexposed human population no single case of induction of sensitisation will occur.

Respiratory sensitisation can be induced via both the dermal and the inhalation routes (see previous sections and (ECHA, 2016)). As the quantitative interaction between these routes is currently not understood, a "combined DNEL" cannot be set. Derivation of meaningful DNELs would only be possible for exposure scenarios for which the relevance of one of the two routes can be ruled out (and the following reasoning relates to this case only).

Due to biological variability and uncertainty caused *inter alia* by the inherent limitations of study designs and evaluation schemes, real-life thresholds can never guarantee 100 per cent protection. Therefore, a DNEL cannot simply be declared "safe" without further explanation. For instance, the nature of the critical effect and the critical effect size as well as the human target population to be protected, e.g. workers/general population, a certain fraction/percentile of that population, or even a specific sensitive sub-population, should be implicitly or explicitly transparent (cf. (IPCS, 2014), for a more profound treatment of these matters).

Also the confidence in the DNEL (the confidence that the protection goals are really achieved) should be addressed:

- As mentioned above (and shown in more detail in Annex B.5.6.4), animal tests are not suitable as PoDs for quantitative dose-response assessment in humans.
- Likewise the practical problems and limitations associated with human case reports/studies and epidemiological studies for use as PoDs have been discussed above (and in more detail in Annex B.5.6.5).
- With respect to differences in test design/exposure, the quantitative impact of different exposure designs (exposure duration, intermittent vs. continuous exposure, dose per

exposure) on the sensitisation outcome both in humans and animals is poorly understood, making any adjustment highly uncertain.

- There is insufficient quantitative knowledge regarding interspecies extrapolation. Likewise no reliable data exist on the amount of human interindividual variability, i.e. the difference in sensitivity between the median and sensitive sub-populations, towards respiratory sensitisation.
- In addition, data quality often is compromised, in particular with older studies and with studies designed for clarifying scientific questions in the academic setting rather than for addressing the design and documentation needs of regulatory toxicology.

In conclusion, in the view of the DS no reliable threshold value for risk assessment at the workplace can currently be derived from the available human and non-human data. Even if a DNEL for inhalational or epidermal induction could have been derived, additional problems would be posed by cumulative exposure (to other isocyanates, with the problem of cross-reactivity, or to other, e.g. unspecific stressors).

In contrast to the approach of this dossier, the registrants provide different occupational exposure limits (OELs) e.g. German AGW or MAK values for TDI, MDI, HDI as DNEL. These exposure limit values are mainly based on epidemiological studies on lung function decrement and are not explicitly designed to protect from sensitisation. Diisocyanates are designated as "Sa" in the German list of AGW which indicates that even in the case of adherence to the AGW (including the short time OEL) the induction of an allergy (sensitisation) and the elicitation of an allergic reaction cannot be ruled out (AGS, 2006).

A.2.1.1.7 Summary of hazard assessment results

Diisocyanates are respiratory sensitisers in animals and humans. In humans, this is observed in the form of occupational asthma (OA) to diisocyanates (or other agents with cross-reactivity) and accompanied by airway hyperresponsiveness (AHR, sometimes also termed "bronchial hyperresponsibeness, or BHR) to other chemical, biological, or physical stressors), as rhinitis, and/or in the form of extrinsic allergic alveolitis. The first manifestation of OA/AHR may be delayed by months or even years after the onset of exposure. The complex interplay between individual pre-disposition, exposure pattern, and other potential factors of influence on the one hand, and time-point of onset and extent of asthmatic disease in a specific individual on the other is still not understood in a quantitative way.

The approximate number of new cases of isocyanate-related occupational asthma in the EU is estimated to lie in the range of some thousands of new cases per year.

OA and AHR may be associated with severe, life-long impairment of the respiratory function and a decline in physical performance. Life-threatening or even fatal cases have been reported. If "reversibility" is defined as "the possibility of full restitution to the previous state", i.e. the health status expectable if exposure to the respiratory sensitiser had not occurred, respiratory sensitisation has to be considered an irreversible condition in many, if not most of the cases. Being an asthmatic requires long-term medical treatment. Partial loss of lung function will often impede physical activity in all areas of life and constitutes a permanent disablement.

Potential cross-reactivity and simultaneous exposure along both the dermal and inhalation routes constitute further problems. Meaningful quantitative risk characterisation cannot be performed based on the available non-human and human data, and a DNEL or DMEL of sufficient reliability (with respect to the desired protection goals) cannot be derived. For this reason, the DS has chosen an alternative risk characterisation approach based on the number of occupational diseases.

A.2.1.2 Exposure

A.2.1.2.1 Workers exposure

In addition to the described hazards, the following section shows a significant worker exposure and the wide spread use character of diisocyanates. The most likely routes of occupational exposure to diisocyanates are via inhalation and the dermal route.

The potential for inhalation exposure is determined by factors such as intrinsic substance properties (volatility) as well as by the ways how the substances are used and handled.

The volatility of diisocyanates highly correlates with their molecular size. 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.

Higher temperatures also increase the tendency of diisocyanates to become airborne as fumes and vapours. In this context, hot processes (e. g. hot melt adhesives, flame laminating) are of special interest. Also aerosol formation during spray applications (e. g. spray painting, blow foaming) can give rise to particularly high levels of inhalation exposure.

Dermal exposure is nearly always possible when diisocyanates are handled even if airborne concentrations are minimal (Cowie et al., 2005). Skin contact with diisocyanate containing products or with (partly) uncured products (e.g. production of polyurethanes) is a significant route of exposure and of particular relevance (Austin, 2007).

Diisocyanates are used in a wide range of sectors and applications in many products. However, within the scope of an exposure assessment for this dossier it is not envisaged to give an exhaustive description of all uses for all types of diisocyanates. Emphasis is laid on the most relevant species (namely MDI, TDI and HDI) and/or the most relevant uses with respect to amount / volume and workplace exposure. The identified uses for this sake have been grouped as follows:

- Manufacturing of diisocyanates
- Use in manufacture of polyurethanes and PU composite materials
- Use in manufacture of foam
- Use in spray foam applications
- Use in coatings
- Use in adhesives

The reported bandwidth of workplace exposure (including reported maximum values, where not all data sets allow indication of percentiles) results in the following ranking order of inhalation exposure levels to the respective diisocyanates and uses (where not all diisocyanates were found to be relevant for all of the uses):

Inhalation exposure levels to HDI and its oligomers in coatings
0.003 up to 5566.3 µg/m³ (90th percentile, total range: 0.003-245 000 µg/m³)
Inhalation exposure levels to MDI in spray foam applications
from LOQ up to 2050 µg/m³
Inhalation exposure levels to TDI in manufacture of foam
from LOQ up to 203 µg/m³
Inhalation exposure levels to TDI in manufacture of PU and PU composite materials
from LOQ up to 67.3 µg/m³

Inhalation exposure levels to TDI in adhesives
from LOQ up to 48.2 µg/m³
Inhalation exposure levels to MDI in adhesives
from LOQ up to 43 µg/m³
Inhalation exposure levels to MDI in manufacture of PU and PU composite materials
from LOQ up to 32.8 µg/m³
Inhalation exposure levels to TDI in coatings
from LOQ up to From LOQ up to 35 µg/m³
Inhalation exposure levels to MDI in manufacture of foam
from LOQ up to 29 µg/m³
Inhalation exposure levels to HDI in adhesives
from LOQ up to 1.0 µg/m³
LOQ: limit of quantification – not further specified here as they vary for the different data sources

The uses with the highest inhalation exposure levels are HDI (and its oligomers) in coatings and MDI in spray foam applications. In both the diisocyanates are applied by spraying, confirming that high exposures are to be expected when diisocyanate 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 less volatile diisocyanates leads to lower inhalation exposure levels. In general for most of the uses the majority of the measured data found 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 the 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.

However, as measurements of airborne isocyanates are particularly challenging some of the measurement methods might be less sensitive to highly reactive isocyanate species, 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, e.g. to isocyanate emissions linked to hot processes (like opening of moulds after polyurethane production or after hot gluing). As such emissions might be not detected by some of the standard measurement methods this might lead to some systematic underestimation of the exposure situation and associated risk when no additional risk management precautions are taken.

This assessment is supported by biological monitoring data (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). In this context it has to be highlighted that isocyanate adducts 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)). In this study by Creely et al. it was also confirmed that urinary levels of isocyanate metabolites of workers with observable dermal exposure were over two times higher than of workers who did not have evident skin contact, highlighting the significance of the dermal route. 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. A ranking of the described uses based on dermal exposure data is therefore not practicably feasible.

A.2.1.2.2 Bystander exposure

Exposure to diisocyanates from professional uses is not necessarily limited to the operators themselves, but it may affect other persons who enter the working area and/or have dermal contact to uncured materials that still contain free diisocyanates. This problem has been discussed in particular for construction and maintenance work with two-component spray polyurethane foams. Case reports have been published according to which residents developed respiratory and other symptoms after spray foam applications, and in some other studies, diisocyanate concentrations in the vicinity of the application area were monitored during and after work (see Appendix B.9.5.2.2 for details).

Two-component spray polyurethane foam applications typically produce high diisocyanate monomer and oligomer exposures, requiring full personal protection of the operator. In these cases the access to the working area must be restricted to trained and protected workers and dispersion of diisocyanate into other areas of the building must be avoided by technical means. When the application is finished, diisocyanate can still be detected in curing materials and in the air for some time. Key questions for bystander protection relate to the measures (e.g. enclosure, ventilation) to be taken after the application and to the time when the building can be safely occupied and used by the residents.

The curing time of spray polyurethane foam is affected by a variety of factors. In addition, mistakes or uncommon conditions can lead to curing problems and bystander exposure to diisocyanates and other foam components. Specific training and certification programs for spray polyurethane foam applications have been developed in order to avoid such conditions.

A.2.1.3 Risk

According to the previous Sections A.2.1.1 and A.2.1.2 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. Figure 2 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 diisocyanates in this dossier (see also Annex B5 for more details).

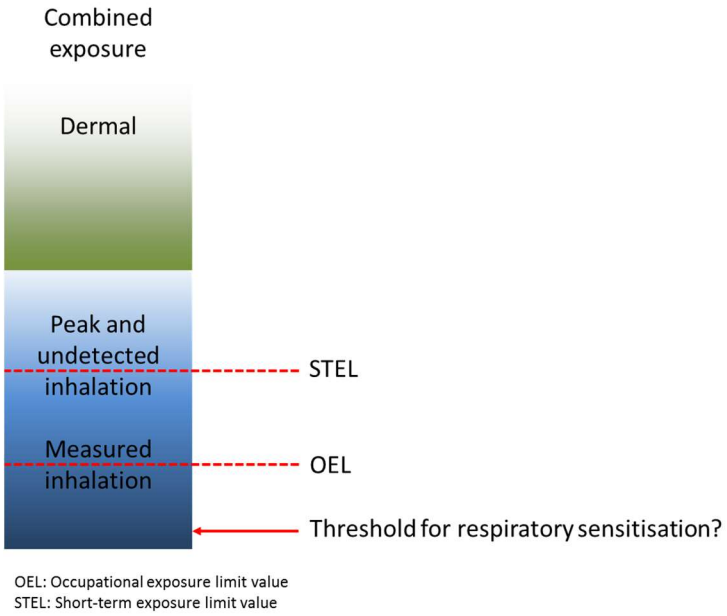

Figure 2: Relationship between toxicological and exposure related aspects of isocyanates

In addition, respiratory sensitisation to diisocyanates below the level of manifest asthma is not systematically monitored at workplaces in the EU (and arguably this would be practically impossible). However, occupational asthma (OA) due to diisocyanates is a problem identified and registered worldwide and diisocyanates are one of the most common causes of OA in the EU (see Annex B.5.6). Therefore, the following risk characterisation makes direct use of the occurrence of OA due to diisocyanates 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 a specific substance or group of substances.

A.2.1.3.1 Quantitative assessment of OA induced by isocyanates

In the following sections the term occupational asthma is used throughout for the estimation of new cases of respiratory disease in the EU. The DS is aware of the fact that this is not perfectly precise, because other respiratory diseases than asthma are also covered in the occupational disease statistics (Approach 1), whereas epidemiological studies (Approaches 1 and 2) use a narrower definition of asthma. However, asthma is by far the most frequently reported respiratory disease caused by diisocyanates and the added uncertainty caused by additional cases of other respiratory diseases to the estimation of the number of cases is considered negligible in comparison to other factors that add uncertainty to the estimation (such as underreporting in disease statistics).

Three different approaches to assess the occurrence of isocyanate OA in the isocyanate exposed workers in the EU are applied for this risk characterisation, which 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)

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
- In approaches 1 and 3 the incidence – as a measure of risk – is roughly estimated by relating the absolute number of cases to the number of exposed workers. The number of isocyanate exposed workers in the EU is based on estimations by industry (ISOPA; European trade association for producers of diisocyanates and polyols, See Table 4 in Section A.2.3). This results in 1.45 million workers who are exposed to a higher level of isocyanates and are at risk. In the following this group will be designated as "high risk".

Approach 1: Occurrence of isocyanate OA cases based on OA statistics

The cases of OA due to diisocyanates have been estimated on the basis of a survey carried out 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. Additionally, also the CAs were contacted (for details see Annex B.5.6). Based on 13 countries that provided data on occupational disease cases (respiratory as well as skin diseases), the annual number of cases was extrapolated to the working population of 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, 2013), 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.

A subgroup with higher exposure and risk are for example spray painters: Based on occupational disease statistics in the UK (SWORD) for 2005-2014 an incidence of occupational asthma in vehicle paint technicians of 0.066 % per year was calculated (HSE, 2016). For the period of 2009 to 2011, the calculated incidence also was 0.067 % per year. Applying a factor of 10 for underreporting leads to an annual incidence of 0.66 %. This value is corroborated by a large population-based study on the relation between occupational exposure and new-onset asthma, which allows to calculate an annual asthma incidence in spray painters of 0.85 % (Lillienberg et al., 2013) see Annex B 10). However, these studies may have included spray painters that worked with other respiratory sensitising components than just diisocyanates.

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 (≙ 36.1 µg/m³) 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 (≙ 144.5 µg/m³) (the present short-term exposure limit value e. g. in Germany and the acute DNEL) (Table 1). Undetected peak exposures are likely to be still present in recent workplaces (see Annex A.2.1.2). These studies were conducted in TDI production and foam production. Table 1 gives an overview of the studies.

Table 1: 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 (1 ppb ≙ 0.072 mg/m³)
(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, annual incidences between 0.2 % and 0.7 % were published (Tarlo et al., 1997), see Table 2.

The above cited studies indicate that in companies keeping 8h-TWA below 5 ppb, asthma cases still develop. This may be due to both the 5 ppb being not protective enough as well as peak exposures, undetected inhalation exposures or dermal contact. It has to be kept in mind that the working conditions in these studies may be different from the current situation (overestimation of incidence), but incidence might be underestimated in epidemiological studies prone to healthy worker effect.

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.

Table 2: Incidence provided by a Canadian case-control study (Tarlo et al., 1997)

	Incidence	
	As provided in the study (% in 4 years, 1984-1988)	% per year
Overall (223 companies)	0.9	0.2
High exposure companies (ever ≥ 5 ppb) with claims	2.7	0.7

Low exposure companies with claims (always < 5 ppb)	2.2	0.6

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 0.099 % based on new asthma symptoms and bronchial hyper-reactivity (Kogevinas et al., 2007). The population attributable fraction for adult asthma due to occupational exposures was estimated from different authors 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.. The working population in the EU is given as 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. Based on literature discussed in Annex B.10, as a reasonable average about 10 % of OA is due to isocyanates. The estimated number of OA cases due to isocyanates each year would be **6058**. Calculating with 300 cases per million people results 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.

Further disease cases not quantified in this section include the dermal occupational disease cases (see Annex 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 Annex B.9.5.2.2).

A.2.1.3.2 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 exposed workers of the high risk group (and even more in special occupations such as spray painters) become new asthma patients due to isocyanate exposure. The DS considers this to be unacceptably high.

Table 3: 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**	
	1 OD statistics		**2 Epidemiological studies**	**Assessment of asthma in the working population and quantifying the fraction due to isocyanates**	
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 million				
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).

A.2.2 Justification for an EU wide restriction measure

Diisocyanates are being used EU-wide, although the relative importance (and therefore the number of people involved and potentially at risk) may differ from country to country. Production of flexible foams appears to be of growing importance in some eastern European countries. Production locations of rigid foams are in many cases closely linked to the location of existing automotive suppliers (e.g. for seats and internal linings). Car repair shops handling aliphatic isocyanates (or their derivatives) are present in all countries and regions, as are uses of isocyanates in building and construction.

The analysis in Section A.2.1.3 with respect to occupational diseases has shown that handling diisocyanates leads to some thousands of new diseases yearly, mainly as occupational asthma.

The wide spread attention for isocyanates is shown by many publications. Reference is made to studies in the Netherlands (Pronk, 2007) and in the United Kingdom (HSE, 2015). Moreover, both TDI and MDI are part of the "List of undesirable Substances" in Denmark, which resulted in some additional publications (Christensen et al., 2014). The severeness of the problem is underlined by a recent publication describing the occupational health situation in a modern foam plant in Romania (Gui et al., 2014). Apart from these, additional literature is available from Sweden (Sennbro et al., 2004). And last but not least MDI also appears in a list of RIVM (NL) (ter Burg and Jongeneel, 2012) listing chemicals in need of further regulation. The existing REACH restriction for MDI has already been mentioned in Section

A.1.3. Outside the EU, isocyanates are under close observation of the EPA by the USA (US EPA, 2011).

As discussed in Section A.2.1 and the corresponding Annex B.9, the explanation of the still occurring new cases of occupational diseases because of handling diisocyanates cannot simply be found in large scale exceedances of existing exposure limits. In fact it is also not very clear to what extent the existing national OELs will protect workers against the risk of sensitisation. Validated animal models to derive such limits are not available and epidemiological studies also have their limits. Many investigators assume that unrecognised peak exposure of short duration because of lapses of attention in handling, or unrecognised situations of increased exposure contribute to new cases of OA. This includes situations of significant dermal exposures which because of a lack of quantitative measurements often go unnoticed. All such situations are a major contributor to the initiation of sensitisation (Hamada et al., 2012; Karol et al., 1981; Pronk et al., 2006).

This means that the way to reduce the number of occupational diseases cannot simply be to lower the OEL or to introduce better equipment. A major point of attention has to be sought in the improvement of awareness of situations with potentially increased risks. This should allow to avoid such situations altogether or to take immediate corrective actions and implement a stricter discipline in complying with the existing rules. The suppliers of diisocyanates have concentrated on the dissemination of such elements for several years, in the framework of their "Walk the talk" product stewardship programs (ISOPA, 2012; ISOPA, 2013). However, in first instance this only reaches the first layer of downstream users, mainly large industrial customers. The existing program should be critically reviewed and where necessary extended with new elements to advance the dissemination. In order to improve its effectiveness throughout the supply chain, and make it a clear element in the marketing of diisocyanates, means should be sought to make sure the necessary training is extended throughout the supply chain in a mandatory and standardised manner. Only in this way, it is possible to ensure that all workers handling diisocyanates eventually will possess the level of awareness and competencies needed to handle such products in a way that risks are reduced as far as possible. To reach this, initiatives from the top of the supply chain have to be transmitted to the end users, in such a way that the same basic standards and competencies are reached for all workers, depending on the uses they practice.

The above means that, in order to be effective, a regulatory action for limiting the risks of handling diisocyanates should definitely be targeted at the total group of substances in the various uses and be extended to cover all EU Member States. Moreover, in order to not disturb the internal market, the measures proposed in this restriction should result in similar obligations throughout all of Europe.

The result of the considerations in the RMOA (German CA, 2013) clearly shows that a restriction under REACH is the most promising option to reduce the risks for these substances, with a minimum of distortion of competition.

A.2.2.1 Why REACH?

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

As a reaction to this situation, many EU member states have introduced occupational exposure limits (OEL) for the use of such compounds (see section B.9.1.2). However, a harmonised EU-wide exposure limit does not exist. Furthermore, the available background information to the different OELs in the different member states does not always allow to judge if the value was derived from toxicological studies, epidemiological considerations, or represents a concentration that was deemed to be a reasonable technical achievable value.

In some MS additional measures and actions have been introduced (e.g. DE, UK, DK, SE) to support companies and workers in preventing adverse effects from handling diisocyanates by means of increasing the knowledge of such effects and disseminating 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. Within Europe these actions have never been harmonised, so that the level of knowledge and discipline of handling may differ significantly from country to country (and often within each country), see the data in section B.9.1.2.

Apart from national authorities, additional efforts were taken by the manufacturers and suppliers of diisocyanates to instruct and train their direct customers on a voluntary basis. However, this will only cover parts of the supply chain and cannot be made mandatory.

In an ideal world, the existing OSH regulations would be sufficient to protect workers and to prevent new cases of occupational asthma (OA). In reality each year a significant number of new cases of OA occur and additional action is deemed necessary to improve this situation. Reasons for these discrepancies are that the resulting level of occupational safety is highly dependent on the efforts of the individual companies and how well these fulfill their duties under OSH regulations. Undoubtedly there are many companies which take their duties under OSH regulations seriously. However, for handling chemicals in general there is ample evidence that in many cases necessary duties have not been fulfilled, e.g. see (Lenhardt and Beck, 2016).

The results of these OSH efforts in terms of reduction of new OA cases have never been analysed in sufficient detail on an EU-wide level. The present dossier (see section B.9.1.3) shows that targeted actions have led to a decrease in exposure in some countries. The number of registered new OA cases in some countries (see table 13 in B.5.6.5), as well as epidemiological investigations (Ott, 2002) indicate that compared to the situation of some decades ago definite improvements have been made. However, since 2005 further reductions of new registered OA cases (B.5.6.5, Table 13) seem to be minimal.

Also for diisocyanates there are reports from the field and visual evidence in the internet that show that handling of diisocyanates often ignores basic risk reduction measures. This happens in spite of the fact that the necessary technical measures to handle diisocyanates in a safe way are well defined in the product literature (Brandt, 2012; Leng et al., 2013).

The information regarding safe handling passed on through the supply chain of diisocyanates is variable. Although training and instruction are foreseen under OSH (as an EU-wide minimum standard in general OSH directives), frequency of training, duration and content have not been standardized, leaving ample room for variation and gaps.

In section B.10.1.1 of this dossier, three different methods were used to estimate the annual number of new cases of OA resulting from the handling diisocyanates. Although the data from different countries are difficult to compare, it is concluded that in spite of the efforts already taken, an unacceptable number of new OA cases are still reported each year. This provides the evidence that the already installed OSH measures are not yet sufficient. Information from practice, including the relevant industry organisations, and visual information from the internet demonstrate that to reach an improvement, behavioural changes seem suitable as an addition to technical measures or PPE. Thus awareness rising activities and information/training about adequate behavior and correct use of PPE were identified as the most effective measures to reduce this risk. The existing OSH obligation for information and training for workers needs to be supported by further measures.

In section E.6.1.1 several studies are cited that report the impact of specific training actions in various branches of industry in terms of a decrease in number of incidents, illness etc.

However, under the existing EU-OSH regulation a unified approach to improve this cannot be defined because there is no mechanism to make this mandatory throughout the EU for all users, irrespective of the company size, geographical location or their position in the supply chain.

This situation is different for REACH. Being a regulation for "placing on the market", REACH allows to establish duties for suppliers that need to be fulfilled if they want to sell their substances/mixtures/products to downstream users EU-wide.

One basic obligation for the manufacturers/importers/formulators under REACH is to define the safe use conditions of chemicals. For this particular group of chemicals (diisocyanates) a certain part of this responsibility is to define and train the safe use of these substances. Of course the practical implementation in their company still remains the obligation of the employers. The restriction will provide suppliers and employers with better defined tools and contents, which they can use to their advantage to improve their present performance. Finally, this will be in particular beneficial for the protection of the workers handling these substances. Also the prerequisite for an executable enforcement will be improved because part of the assessment will now be a simple check if trainings have taken place and the necessary documentation is in place.

The proposed risk management option will assign a duty to the manufacturers/importers/formulators of diisocyanates, or of substances and mixtures containing diisocyanates of establishing a set of unified instructions that are mandatory for each downstream user. The companies at the top of the supply chain support this approach and are therefore currently active in preparing concepts for the instruction/training materials in preparation of this restriction. After finalization, each member of the supply chain can refer to this material when complying with their duty to pass on information on substances or mixtures to a company down the supply chain. In this way, the complete supply chain will be covered by the same obligation and is forced to use the same material. The consortium of manufacturers/ importers/formulators (in the form of industry associations) will take care of the development and the dissemination structure of the material and setting up a suitable training structure. In this way, content, instruction method and training intensity should be the same for each member of the supply chain.

A.2.2.2 Why not the SVHC/Authorisation route?

Taking the experience collected for other respiratory sensitisers (Austrian CA, 2012; Dutch CA, 2012a; Dutch CA, 2012b), there is little doubt that diisocyanates with the classification Resp. Sens. 1 may be identified as SVHC under REACH, Art. 57(f) (Equivalent Level Of Concern). However upon consideration of the effects this may have in terms of improvement in occupational safety and health and the general impact on industry, this option does not look very attractive for the following reasons:

1. Because of the extreme complexity of the supply chain and the large number of uses. Either upstream applications will be unspecific and therefore of unsufficient effectiveness for occupational safety, or in case of down stream Applications for Authorisation (AfAs) an extremely large number has to be expected, which may overload the capcity of the system.
2. Because of the unique properties of diisocyanates and the resulting polyurethane polymers, large scale substitution is unlikely. Therefore socioeconomic benefits of the substances are likely to be much higher than the costs because of risks, making it likely that most AfAs will be granted.

An additional advantage of the restriction route is that it can deal with all relevant diisocyanates and their derivatives in one go and it can concentrate on the conditions of

supply and handling of formulations containing diisocyanates. This has been explained in more detail in the RMOA (German CA, 2013).

A.2.2.3 Structure of the proposal

A proposal for the wording of the restriction can be found in Section A.1.2. It is important to be aware of the proposed structure, especially with regard to the proposed exemptions:

In principle, the use of diisocyanates in industrial and professional uses is no longer allowed, neither as such nor in mixtures, unless the conditions for exemption are met. This is the case if either they contain < 0.1 wt% of free diisocyanate or they meet the conditions of the Appendix on Exemptions or the Appendix on Training and Measures. These Appendices will be attached to the final REACH Annex XVII entry for the restriction.

Justification for choosing 0.1wt% as cut-off limit

In absence of a generally agreed dose/response relationship for diisocyanates it is not possible to define a concentration limit for substances or mixtures that contain diisocyanates below which such a substance or mixture can be considered "safe". In the CLP Regulation this is accounted for by the fact that all substances and mixtures containing isocyanates are labelled with EUH 204 *"Contains isocyanates. May produce an allergic reaction"*, irrespective of the specific concentration limit (SCL) of the isocyanates involved. As can be seen from Table 7 (in Annex B.3.1.) for some diisocyanates an SCL of 0.1 % or 0.5 % has been derived while for others the generic limit (1 %) applies or there is yet no harmonised classification available.

It is generally accepted that the intrinsic reactivity properties of NCO groups are responsible for the sensitisation potential of substances that contain such entities. However, there are no reliable data about the relative potency of the isocyanate groups in different backbone structures. Recently introduced methods of monitoring isocyanates in the vapour phase or as aerosols tend to concentrate on a measurement of total content of isocyanate groups, (UK, DE) – i.e. there is no differentiation between aromatic and aliphatic diisocyanates.

In order to reach a practicable and manageable scope of the restriction proposal, the DS proposes to set a cut-off limit at 0.1 wt% of cumulative diisocyanate content in substances and mixtures. This corresponds to the lowest limit for classification as Resp. Sens. 1 for (aromatic) diisocyanates. This may be overly conservative in view of the higher SCLs for aliphatic diisocyanates, but has the advantage of being easier to use than a cut-off limit based on different SCLs, which leads to more questions in the case of mixtures. Moreover, as the restriction should cover all diisocyanates being respiratory sensitisers and not only those listed above a general limit for all diisocyanates seems to be the most sensible approach, both from the viewpoint of practicability and enforceability. It should be mentioned in this context that classification of mixtures containing respiratory sensitisers does generally not follow the principle of additivity (see Annex I 3.4.3.3.1 of CLP). However, since the toxicological mechanism for all diisocyanates is the same, a cumulative concentration at the same value as the lowest SCL seems pragmatic and precautionary.

The ideas behind the Appendices to the legal text are discussed below:

Appendix Exemptions

There might be situations in which the additional requirements of training and measures are likely to be disproportional compared to the potential risks involved. This is the case for a large amount of workers that use diisocyanate containing-products for a small fraction of their worktime only and under conditions where a reduced potential for exposure is highly likely. A lot of special glues, foams for windows and doorframes etc. fit this category. These products

may then probably qualify for an exemption. Trade associations have already indicated that providing a "free to use" product without the obligation for a special training (apart from the usual instruction of safety measures as described in the SDS), will be perceived as a significant positive factor on marketability. Additionally, the trade associations plan to strongly support their member companies in preparing "exemption dossiers". Despite the extra initial costs for developing and/or testing for "very low potential exposure" the more favourable marketability will be an incentive to stimulate the development and placing on the market of products with a "low risk" risk where before "high risk" products were used.

In Appendix 7 (Exempted products, etc) criteria are defined to systematically identify these products with potentially low exposure and risk. This is the case for products for which 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.

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 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.

However, the products identified by the rules set down in this Appendix are by no means "safe" products, which should already be obvious by the fact that they are still hazardous mixtures as defined by Article 4 of CLP (European Parliament and Council, 2008). They are to be classified as respiratory sensitisers and no threshold has been identified for the sensitising potential of diisocyanates.

Appendix Trainings and Measures

This Appendix contains requirements for training as well as technical and organisational measures. This is the core of the proposal aiming at disseminating appropriate handling instructions in a standardised way throughout the supply chain. The dissemination of this information throughout the supply chain is supported by the obligation for manufacturers/importers of diisocyanates to make the training accessible to all downstream users in the supply chain.

Member States are free to add measures within national OSH systems as long as the minimum conditions of this Appendix are met.

The main elements of this Appendix are listed below. Because of their multiple uses and different properties, the conditions of use and the associated potential risks of the different diisocyanates and diisocyanate containing substances will be different. This also means that the necessary risk management measures during handling in order 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 when handling diisocyanates in uses of varying potential risks in order to meet the requirements of the REACH restriction. It is beyond the possibility of the Appendix to list all uses of all diisocyanates in sufficient detail. In order to select the necessary risk management measures under the REACH restriction, a grouping approach is used. Apart from providing general safety instructions for all workers, the following actions have to be taken by a company in order to comply:

1. Identify the "measures group" for each worker that may be exposed to diisocyanates, depending on the product used and the activities performed by that worker or group

of workers. Based on an expert judgement approach, activities/uses are differentiated in qualitative exposure stages, describing the probability and magnitude of dermal and inhalation exposure. The latter includes contributions from vapour and aerosol exposure. These are ranked from minimal to high (3 stages).

2. Implement the technical and organisational measures as identified for that particular group and provide each worker with training incorporating the topics from the tables in the Appendix. New workers shall be incorporated into the training system at the start of their job.
3. Document the completion of the trainings.

Once the restriction is in force and the required training materials are in place it is important to gain experience with the system. Undoubtedly in the first phase some readjustments may become necessary. This can be accepted. However, to prevent that any monitoring efforts for the effectiveness of the restriction become too difficult, large changes should be avoided until enough experience has been collected. Because the system is built around a repeating four year cycle, it seems appropriate to wait up to the completion of 2 cycles (i.e. 8 years) before major revisions are undertaken.

A.2.3 Baseline

In understanding the baseline of the proposal it is important to know the number of workers that will be potentially impacted. Based on data supplied by ISOPA (in cooperation with related associations of downstream users) the following overview is achieved:

Table 4: Overview on exposed workforce in sectors

Sector	Workforce	Free of asthma*	Risk for healthy workers
Construction chemicals	1.8 million	1.62 million	Low
Automotive repair (excl. motor vehicle refinish, (MVR))	1.8 million	1.62 million	Low
Other sectors (e.g. metal treatment, insulating panels etc.)	1.6 million	1.45 million	High
All sectors	5.2 million	4.69 million	Low - high

Source: ISOPA, data modified (see Annex G.1.)

*Working population under asthma risk. Corrected for asthma prevalence of 10 % in the exposed population.

The data are taken from a summation of the indicated sectors in table 108 (Appendix G1) and corrected for the fact that ISOPA/ALIPA claim that their feedback represents about 80% of the market.

The exposure situation in the relevant sectors is not assessed on the basis of measurements but on an assessment of the potential for exposure under certain conditions and working characteristics in the various industry sectors. It can be recognised that certain activities, involving e.g. spraying and large scale foaming, as well as an increased probability of dermal contact, will lead to a higher potential for exposure (and therefore risk for OA). Based on the activity pattern of the groups mentioned in Table 4 this results in 1.45 million workers in the group with a potential for higher exposure. Consequently in the following this group will be designated as "high risk". Note that the differentiation in the Appendix "Trainings and

Measures" is not directly related to this, because the "Measures Groups" are based on a differentiation within the "high risk" group.

Estimations of the annual occurring asthma cases in the baseline scenario can be performed by the methods explained in Section A.2.1.3 with the results summarised in Table 4. 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 (about 3.2 million) or by performing activities of potentially lower risk.

The population of workers potentially exposed to isocyanates is expected to be more or less stable over the assessment period of 20 years, i.e. workers leaving the workforce because of retirement, work incapacity or job change will be replaced by new incoming workers to a similar degree.

If no further action is taken, it is to be anticipated that the number of occupational asthma (OA) cases, either being estimated from official statistics (approaches 1 and 2) or estimated via epidemiological investigations (approach 3) 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 and the already existing burden of old cases. In Table 5 the outcome is summarised.

Table 5: Overview on results of models for estimation of the annually occurring new asthma cases

Method	OA Assessment Approach 1 with reported numbers	OA Assessment Approach 1 with under-reporting factor 10	OA Assessment Approach 2	OA Assessment Approach 3
New OA cases /yr	235	2350	2900 – 10150	6058 -7269
Average cases/yr	235	2350	6525	6663
Cumulative number of cases after 20 years	4700	47000	58000 - 203 000	121 160 - 145 380

From the table above it can be calculated that the average value for method 2 (6525) is rather close to the average of method 3 (6663). **As the best estimate a value of 6500 will be used for the yearly number of new cases of occupational asthma in the EU.** This seems consistent with both ranges. Additional comparative calculations corresponding to some of the other methods will be shown in Annex E.9.1.1.

A.3 Impact assessment

A.3.1 Introduction

As indicated in Section B.5.6. (Table 12) also skin diseases caused by the handling of isocyanates are reported in the EU. However, it seems that cases of respiratory disease make

up the majority of the reported cases (> 80 %). Therefore, 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).

Although several data on skin diseases were included in the dossier (toxicological data, human case reports, EU-wide data request on reported cases), the DS decided for the subsequent, more detailed steps of hazard, risk and impact assessment, to focus mainly on respiratory sensitisation. This means that the health impacts of the use of diisocyanates will be even higher than presented below in this section and in more detail in Annex E, because each year somewhat more cases of occupational diseases will occur than what the DS takes into account (i.e. about 20% more because of skin sensitisations). As it is obvious that the behaviour based measures that are proposed in this restriction proposal will also be effective in reducing skin sensitisation, this means that for the same costs as calculated in this section and in Annex E, the net savings effects may even be higher than shown in these sections.

The major outcomes of the analysis of the three risk management options are presented in this section mainly in the form of tables and graphs. Furthermore, the conclusion on the most appropriate risk management option which is based on results from the impact assessment is provided. Details, background information and further calculations regarding the SEA can be found in Annex E to this dossier.

In principle the scope for estimation of the socio-economic impacts comprises the following two scenarios:

- baseline scenario – "business as usual" – i.e. without additional measures
- restriction scenarios (RMO1, 2, 3).

The socio-economic impacts result from the delta of the baseline and the restriction scenario for the number of cases of occupational asthma. Skin sensitisation will not be taken into account, although the proposed measures are expected to have the potential to reduce the number of skin sensitisation cases as well. 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 present values (PV). Based on the analysis of alternatives for diisocyanates and the feedback from 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.

A.3.1.1 Risk Management Options

The following restriction options will be considered:

- 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

As a further option authorisation was considered but not further assessed (see Section A.2) mainly because alternatives to isocyanates will not be available, or available alternatives will also have health risks (See Annex E.2).

The different restriction options were assessed according to the criteria effectiveness, practicality and monitorability (Annexes E.9 and E.10). As a result of this assessment, the restriction option RMO1 is proposed.

A.3.1.2 Restriction scenario(s)

The analysis of alternatives (see Annex E.2) has shown that given the large number of diisocyanate applications there will not be one or a few alternatives covering all these uses. In some areas (e.g. construction industry) alternatives are available and in commercial use. For several other applications alternatives having the beneficial properties of diisocyanates are not commercially available or available alternatives will not imply a shift to lower health risk (e.g. epoxy resins). Therefore, if the restriction proposal is followed only a shift to alternatives for some niche applications is expected (see Annex E.2). Thus the majority of the industrial and professional users of diisocyanates will implement the training measures and/ or use exempted products leading to economic impacts for these companies.

It is expected that the effort to comply with the restriction is viable for all companies concerned.

A.3.1.3 Basic Data

The data used for the calculations that were performed are summarised below. More details on these numbers can be found in Annexes E.5 and E.6.

Table 6: Overview on input parameters used for modelling of the costs for appendix on exemption and appendix on trainings and measures and on benefits for human health

Variable	Main Value	Range for sensitivity analysis		Source
		Low value	High value	
Prevalence of asthma in isocyanate exposed working population [%]	10	-	-	See Annex B.5.6.5.2
Exposed working population high risk group, all sectors, asthma free [million]	1.45	-	-	ISOPA and own appraisal;
Medical costs for asthma therapy [€/a]"	1700	-	-	BAuA
Ø Annual indirect cost: productivity loss all sectors [€/person 10 days]	1762	-	-	Own estimation based on EUROSTAT data
Indirect cost: Ø productivity loss all sectors [€/person h]	22	-	-	Own estimation based on EUROSTAT / ISOPA data

Variable	Main Value	Range for sensitivity analysis		Source
		Low value	High value	
Indirect cost: Ø productivity loss construction/automotive repair[€/person h]	23	-	-	Own estimation based on EUROSTAT / ISOPA data
Likelihood for loss in income [%]	32	-	-	(Ayres et al., 2010; Moscato et al., 1999; Nowak et al., 2011), own estimation
Ø Annual loss in income in all sectors [€/person]	31 700	-	-	Own estimation based on EUROSTAT / ISOPA data
WtP[3] for asthma [€/a]	1800	-	-	ECHA
Total effectiveness in 4 years period [%]	-	50	70	Own estimation mainly on basis of HSE study
Frequency of training [years]	4	-	-	This proposal
Ø Number of workers per company in all sectors	20	-	-	Analysis of EUROSTAT data, own assumption
Suppliers number for Isocyanates containing products	4600	-	-	ISOPA
Annual costs for product tests / Appendix Exemptions [€ million]	-	0.625	1.74	Own estimation based on expert judgement
Number of product tests needed for Appendix Exemptions	100	80	120	Personal communication with experts
Number of avoided trainings because of Appendix Exemptions [million]	3.6	-	-	ISOPA, own estimation based on expert judgement

It should be pointed out that the fact that the share of costs for productivity loss is between 20 and 90 % of the total costs, may lead to an underestimation of the costs/benefit ratio. The real economic impacts due to productivity loss by investment in training of one working day within 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 work disability.

A.3.1.4 Economic Impacts

Negative economic impacts for producers and industrial and professional users of diisocyanate containing products in RMO1 and 2 result predominantly from the additional costs for the

[3] Willingness to pay

training measures. In addition, costs may incur for testing of the products which might be eligible for an exemption according to the proposed Appendix on 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.

A.3.1.4.1 RMO1 and RMO2: Training Measures in Appendix Trainings and Measures

Different options exist to attend and complete the trainings. A specific company may choose one or the other form, depending on its circumstances. This will result in different costs.

The following training options were 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 Annex E.5.1.1, Table 72)
- Company size or number of workers per firm /course (this is explained in more detail in Annex E.5.1.1)
- The number of suppliers for isocyanate containing products (in option b)
- Frequency (validity period of training) (according to Appendix "Training and Measures" 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.

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 in the training course, the lower are the total costs for each single option. A supposedly near-optimum for acosts/benefit ratio can be achieved by grouping 20 participants in one course.

To avoid double counting, it was 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.

A.3.1.4.2 RMO1: Testing costs for identification of the exempted products

Apart from the training costs, this RMO also incorporates an option for testing products to be exempt from the restriction. Qualifying products for such an exemption may mean an additional test program, which will incur additional costs. The following factors are essential for the estimation of additional costs:

- Initial number of testing product groups or candidates for exemption
- One-off costs: testing the frame formulations and accordantly the conditions of use
- Annual running costs: additional efforts for data preparation and communication due to launching the new products and/ or information update

A.3.1.4.3 RMO2: Training and Measures for all workers

This involves the training costs for all workers exposed to diisocyanates. In addition to RMO1 in which only the workers at high risk will complete the training, it is assumed that the workers at low risk (Table 4), will complete the required training by the optionof e-learning, instead of using exempted products.

A.3.1.4.4 RMO3: Elimination in the supply chain (complete ban)

In case of a complete ban profit losses may arise due to stop of production of PU-based products, a shift to alternatives or a shift to import PU-based articles. These costs could not be quantified because of missing data. However, in order to get an estimation of the economic impacts the additional costs for premature vehicle obsolescence in case diisocyanate based repair coatings will be banned from the EU-market were extrapolated.

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 Dossier Submitter's opinion the largest economic impact in the EU-28 results from value added loss. This impact has been captured in Figure 7. (See Annexes E.5.2. and E.9.3E for more details).

A.3.1.4.5 Further implications of RMO3 (complete ban of the use of diisocyanates based products)

- Threat of import dependency on non-EU countries
- Reliability of supply may be negatively affected
- Additional investment costs for relocation of production outside the EU
- Additional costs for adjustment within the supply chain
    - Additional costs for suppliers certification/qualification in non-EU countries

- Additional administration and transport costs

- Adverse effects on competitiveness of the PU dependent European producers (particularly automotive industry)
- Negative impact on use of resources, e.g. in a rough estimation (see Annex E.5.2) a welfare loss of about € 5.5 billion per annum was obtained due to premature obsolescence of motor vehicles in EU-28 if repair coatings would no longer be available.
- Additional efforts to find alternatives.

A.3.1.4.6 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 % of the training costs. Using the basic data in Table 6 and in more detail in Annex E.5.2, the following results are obtained:

Table 7: Overview on results of costs estimation for each RMO (rounded)

	RMO1*	**RMO2***	**RMO3**
Additional costs (PV, million € in average per year over 20 years) as a range*	26 – 165	79 – 218	18126**
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 Annex A.3.1.3.1
** This represents the estimated value added for the total EU market for diisocyanates, calculated in Annexes E.5.2 and E.5.3

In the following some consideration on a "most probable" costs scenario suggesting a general qualitative pattern on response reaction with regard to each training option discussed in section E.3.1.4.1 are provided:

- For small firms with less than 20 exposed workers the training at the education centers (option A) is more economically attractive. Therefore, if such an option is likely to be chosen, if offered/established by industry associations.

  Estimation: If training option A is available, it will be in high demand.

- It could be anticipated that trainings provided by a supplier of diisocyanates or diisocyanate containing products (option B) will be attractive (if available). Moreover, in such way communication within the supply chain on the obligation for training can be ensured. Supposedly the additional costs for suppliers will be passed on further down the supply chainvia a higher price.

  Estimation: Very high demand for training via option B, if this training option is available.

- The option "training on the job" (option D) seems economically attractive for firms with more than three exposed workers. This allows realising a costs degression for a commissioned trainer in each firm. The optimal costs degression is achieved at 20 persons.

  Estimation: For firms with 3-20 exposed workers this option would be more preferred, because of the possibility of training on the job.

- If the sector specific industry association does not provide a training course the training can be taken as an external course (option C). However, as a stand-alone option, this is likely to be more expensive.

Estimation: Supposedly companies will try to avoid this option due to higher course costs.

- Because it may be assumed that e-learning (option E) is by far the cheapest option, it may be expected that this option would be the most preferred option. However, in the proposed "group measures" structure, this option is not available for all groups of workers.

  Estimation: In high demand where this is offered and the restriction conditions allow this.

With the exception of option C, the estimated costs for most of the identified training options are in the same range. For the reasons discussed above, the range of costs estimate for the options A/ B/ D/ F may indicate a likely realistic scenario for the costs dimension. Due to the higher costs for training option C it can be expected that this option will be chosen by only a small fraction of companies. Thus, in a more likely scenario the total costs would probably be slighty higher as estimated from the options: A, B, D, F.

In RMO2 it is most likely that workers in Measures Group 1 (the lowest risk group) will only get training via e-learning.

A.3.1.5 Human health impacts

Human health impacts are described as the result of the reduction of new asthma cases in the future, due to improvement in the standards of handling diisocyanates.

The estimation of the human health impacts is based on data presented in the baseline section A.2.3 and findings on effectiveness of the proposed measures.

As explained (e.g. section **Error! Reference source not found.** and B1.4), the adverse health effects are specifically linked to the functional isocyanate groups. These groups are present in all diisocyanates in the scope of the restriction. Also cases of cross-sensitisations have been reported (see section B.5.6.2.6). Moreover, data on occupational diseases also often use "isocyanates" as one group. Therefore, it seems sensible to use a group approach, where as a first approximation there is no distinction between the potency of the various diisocyanates.

A.3.1.5.1 Risk reduction capacity

RMO1 and RMO2: Effectiveness of the proposed restriction - training measures according to the Appendix Trainings and Measures

Effectiveness is expressed by the potential to avoid a certain fraction of asthma cases in the future relative to the baseline. A quantitative estimation for the reduction of the incidence rate after implementation of the proposed restriction measure is based on previous studies on safety training effectiveness. The assumptions for estimation of the effectiveness are based in particular on the results of the HSE's studies, describing the reduction of occupational exposure to isocyanates in the vehicle repair industry (Stocks et al., 2015) (Piney et al., 2015). Additional studies of more qualitative nature are found in (Bregnhøj et al., 2012; Cohen and Colligan, 1998).

There are distinct differences between the measures described in these studies and the current proposal. For more details see Annex E.6.1.1. Nevertheless, it seems plausible to take the upper limit of effectiveness as reported in these studies as the upper limit that may be achievable in the proposed restriction. This results in two different values for the effectiveness. Graphically this is shown in Figure 3 showing values for a main expectation of effectiveness ("low bound") and an optimistic ("high bound") scenario. In order to sustain the level of awareness and correct handling, it is necessary to repeat the training at regular intervals (four years is proposed). Resulting from the discussions with industry representatives, the Appendix Trainings and Measures describes four year training cycles. It

is reasonable to assume that a first training of all workers concerned would take four years to be completed. Therefore the effectiveness of the measure is expected to grow to the maximum over this period, with only minor improvements after that.

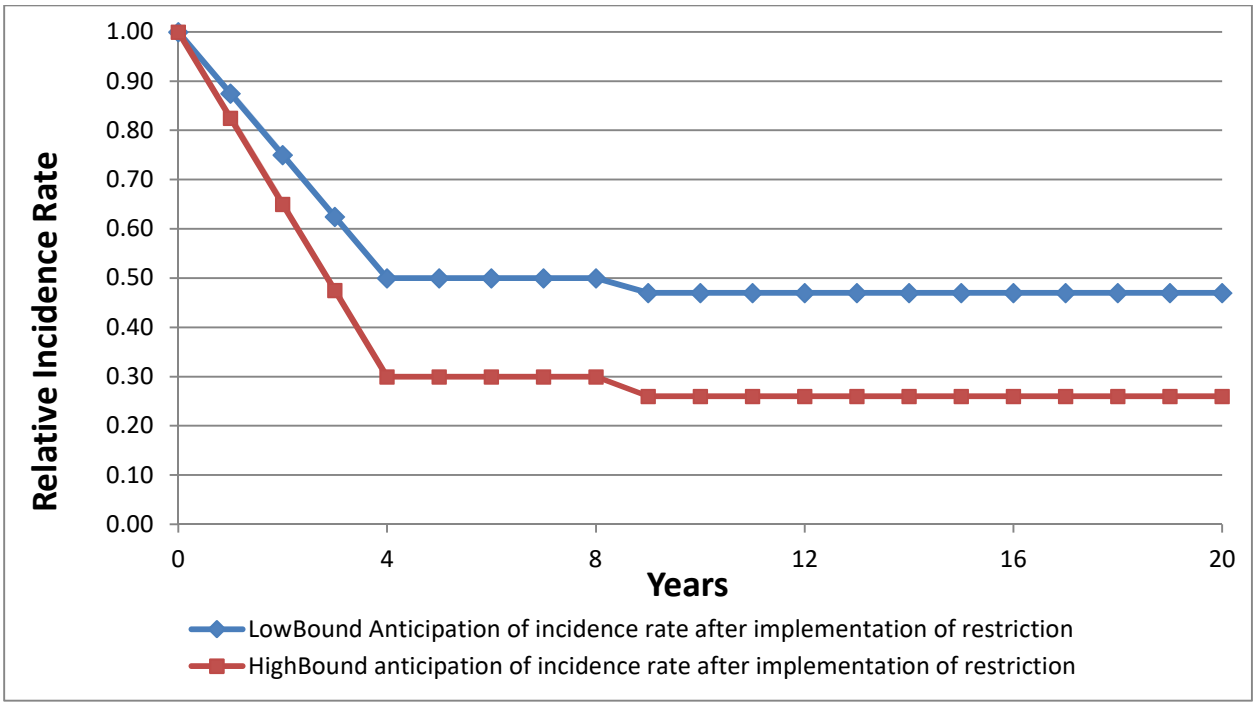

Figure 3: Forecast (low /high bound) for the relative development of the incidence rate after implementation of the proposed restriction measure

RMO1: Effectiveness of the measures in Appendix "Exemptions" with regard to workers at low risk.

Additional identification and placing on the market of exempted products with the potential for very low exposure for users in concerned sectors will lead to lower risks, in the case they replace products with a potential for higher exposure. This is also in line with the hierarchy of occupational protection measures. In such a case the delta in benefit would be positive. However, at the moment it is not possible to quantify this in detail.

RMO3: Complete ban

For this (extreme) risk management option the potential possible benefit which could be realised by a hypothetical risk reduction down to zero will be estimated. 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.

A.3.1.5.2 Valuation of human health impacts

The monetary effects are based on costs of medical treatment and productivity losses due to days of work disability. Welfare losses due to losses of life quality caused by asthma are also included in the valuation.

In the long-term workers may be driven to leave the job due to the risk of exposure to isocyanates. The concerned worker may change job internally in the company, change the company and the job as a whole, or will become unemployed (at least temporarily). In case of total work disability, the worker can ultimately be forced to leave the labour market and retire. Degradation of work qualification level or job experiences and corresponding work

capabilities or skills are included in health impact valuation as social costs due to occupational/ work-related asthma. In Annex E.6.1.2.3 possible constellations for employment of asthma suffering workers are analysed and combined with findings from several studies. Based on this, a weighted average for loss of income of 32 % is estimated.

The following cost components listed in Table 8 are used for the monetary valuation:

Table 8: Overview on costs components of the occupational asthma

Cost category	Costs driver	Annual value [€]
direct costs	Therapy/ medicine	1700*
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 personal costs]	0.32 x personnel costs
intangible costs	Pain & suffering/ Welfare loss	1800

Note: See Annex 6.1.2.3 for more details
* adapted to EU-28 by use of Medical Health Purchasing Power Parity (OECD, 2012)
** weighted average (cf. Annex E 6.1.2.3)

In general a positive net benefit for human health is expected which results from the reduction of asthma cases over a time period of 20 years.

Table 9: Results on human health impacts (based on 6500 cases of occupational asthma per year)

	RMO1*	RMO2*	RMO3
Cumulative number of avoided cases over 20 years (based on best estimate)	62465 – 87295**	62465 – 87295**	130 000
Monetary values (PV, € million) incl. social costs , average/year	271 – 378**	271 – 378**	627***

* Related only to trainings measure being the same for RMO1 and RMO2. Range for Low/High bound efficacy.

**Related only to worker groups at higher asthma risk. See explanation below.

*** Hypothetycal risk reduction down to zero.

Health impacts are only monetarily quantified based on the risk-reduction capacity of the implemented training measures. The risk reduction for the use of exempted products with regard to asthma cases cannot be quantified at this moment. Therefore, restriction option 1 and 2 show the same level of monetary health impacts because it is assumed that all asthma cases occur in the high risk group. Of course this is a simplification. If, against this assumption, some cases of disease would occur in the low risk group this would lead to a lower benefit for RMO1 than indicated in the table. On the other hand health benefits of RMO1 may be underestimated because the risk-reduction capacity of increasing development and introduction of low-exposure products is not included. In most cases the improvements for

human health of RMO3 may be less than expected. As described in the section "Alternatives" (Annex E.2) substances that have some credibility as alternative have human health risks themselves (often being skin sensitisers). The risk will not drop to zero because most downstream users of PU-products would forcefully have to shift to any kind of available alternative products if they want to stay in business.

A.3.1.6 Other impacts, practicability and monitorability

A.3.1.6.1 Social impacts

The social impacts in RMO1 and RMO2 can be expected in general to be positive. The avoidance of asthma disease has benefits regarding work ability with all consequences for employment and the individual income situation of workers. Social impacts are included in the calculation of human health impacts. In RMO3 the social impacts are inter alia described in the section economic impacts (See Annex E.5.2). For a ban of diisocyanates from the EU-market a negative impact for the European society is expected.

A.3.1.6.2 Wider economic impacts

In case of a total ban of isocyanates from the EU market an extreme disturbance of the smooth-running processes within the supply chain which comprises 240 000 (ISOPA, 2014) companies is to be expected. Particularly the direct producers, suppliers/subcontractors, direct isocyanate users e.g. foam, textile/PU-plastics producers are directly negatively affected, because their business model is exclusively 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 then be modified for other production or sunk costs due to non-utilisation. Theoretically the customers for PU primary articles 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, 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. The PU-articles do not contain diisocyanates anymore and can be thus imported into the EU-28. The possible consequences are in detail highlighted in the Annex "Stakeholder consultation".

A.3.1.6.3 Distributional impacts

Distributional impacts of the training costs are considered (model in Annex E.5.3.1.1.) for consumers and downstream users on the basis of vehicle repair services. In this case, even the most expensive training option c would only cause a price increase with up to 62 Eurocent per average service (e.g. a car repair job) and negatively impact the operating surplus with approximately 3 % per year if all workers need to be trained and not all costs can be passed on to the customer. In case of a complete passing on of the costs to the consumer the price of a service would increase by ca. 2 € per service.

The identification of exempted products would result in an estimated price increase of the end products of less than 1 Eurocent per unit. (e.g. a can of foam).

Positive distributional effects are increased business for institutions offering training for downstream users and laboratories that can perform tests for identifying low risk products that can be exempted from the restriction.

Analysis of distributional effects for additional costs due to the proposed Appendix Exemptions is carried out using another approach. In Annex E.5.3.1.1, it is analysed how the products unit costs in some sectors 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. Based on the fact that in Germany alone 25 million polyurethane foam cans are sold[4], it is assumed that at least 100 million products are being placed on the European market annually.

Section E.5.3.1.1 and table 84 (based on figure 10) provide information (based on a assumed model) on possible economic effects for the smallest enterprises (based on an example from the vehicle repair sector). The impact of exemptions are listed above. It is assumed that all additional costs will be passed on further down the supply chain.

A.3.1.6.4 Other impacts on the market

Introduction of this proposal will lead to a situation where the marketing and use of products containing diisocyanates will be subject to new conditions. It is to be expected that in the beginning some aspects of the proposal will lead to uncertainty in the supply chain on how the new obligations can be fulfilled. By itself, this situation may cause some negative economic impacts where people lose business because they have not fulfilled their duties on time. However, these effects are expected to be small and to be of a transient nature. They will disappear over time when the new processes and roles of the various partners in the supply chain become better defined.

An impact that seems already underway is the fact that discussions within the industry about the plans for a restriction for diisocyanates make downstream users aware that using diisocyanates in the future may become more challenging. At the moment it is unclear to what extent this will change the economic analysis of this restriction significantly.

A.3.1.6.5 Aspects of practicability

Some aspects of the practical implementation need to be considered. At this point in time, not all of these have yet been developed to the detail needed for a full implementation of the restriction. The following is a listing of aspects that need to be addressed. They also include suggestions/ assumptions from the DS that are needed to help the practical implementation of this restriction:

Responsibility for developing the necessary training material.

Bodies of the industry handling diisocyanates (manufacturers, importers, major formulators, industry sector associations) have committed themselves to the development of training material[5]. Preliminary discussions regarding practical aspects were carried out in the so called "PU exchange panel", organised by the manufacturer associations ISOPA and ALIPA. Stakeholders of all users of diisocyanates in the scope of the restriction were invited to

[4] https://www.regierung.oberfranken.bayern.de/umwelt/umweltinformationen/umweltinfo/umweltinfo2003_04.php

[5] See a.o. : Press Statement from ISOPA/ALIPA and trade associations of October 28, 2016, after submission of the dosser became public; Also see article in "Kunststoffland NRW Newsletter" on the occasion of K2016 (in German)

participate. A more permanent organisation (*"a not-for-profit body (under a status to be determined) to represent industry with the other stakeholders involved in the training process and in the maintaining of the training content. This body should be open for all contributing parties to the training material"[6]).*and further development of training content is being discussed in cooperation with an external consultant. Material tah thas bene developed will be cheked and screend by the not-for-profit-body mentioned above.

Actual training material (e.g. slides with a perticult lay-out and sequence) will then be prepared by training institutes.. Industrial representatives have indicated their willingness to take up the burden of translation of the materials in the EU languages needed. Material that is developed will take into account existing national regulations.

Post-course testing will be an integral part of the training course. Succesful completion will be confirmed by a written document.

Quality assurance on material that is developed.

To ensure the quality of the process, the main responsibility will rest with the platform indicated above, in exchange with the institutes/instructors that will provide the actual trainings. The DS expects that an evaluation questionnaire before/after each training session will provide an indication of what material works well or what is in need of change. In order to reach a level playing field in the EU a mutual recognition system should be in place to recognise trainings and the qualification of trainers across the EU. The DS recommends establishing an advisory board where competent independent outsiders have the possibility to provide input.

Organising the trainings in practice (or training licenced trainers).

"The developed training content (for example in the form of sets of slides or other material), will be made available to downstream users as well as existing (public and/or private) training institutes (e.g. Shield group, TÜV, DEKRA) to use it. This may be done by a licensing model. Conditions of this licensing still require discussion, but inspiration could be taken from other sectors where similar systems already apply. These institutes will also use their own tools of dissemination for the trainings. It is under discussion if the experts of the licensed downstream user or training institute may be instructed by the platform. Such institutes or downstream user would transform the licensed training content into proper education material, train qualified instructors, which in turn would train the workforce according to the terms of the restriction".[7] How to communicate the availability of trainings throughout the supply chains(with special attention to the lower segments of the supply chain – small companies and self-employed individuals).

To this end a number of activities can be foreseen induced by the diisocyanate industry:

- Referencing the existing restriction in an SDS (as is already mandatory anyway). This shall be combined with reference to a webpage where training information (general content for the company involved is available and ways to register for training in a specific area are indicated).
- Make it an obligation to meet restriction requirements with a provision in supply contracts.
- Targeted offerings in trade press in various countries.

[6] Text in italics as phrased by ISOPA/ALIPA (December 2016)

[7] Text in Italics as phrased by ISOPA (December 2016)

- Communication at trade fairs.
- Inclusion in programs for professional qualification/education
- Information dissemination via contact with occupational accident insurance companies.
- Communication via the network of chambers of commerce and inclusion of specific training sessions in their offerings.
- Use of flyers in product packaging (especially in a first stage of communication)
- Make information available via national REACH-CLP helpdesks

Special considerations have to be given to offerings for training schedules in regions where users of diisocyanates are few.

The case of self-employed workers (one-man companies)

- They will be made aware of their training duties in the communication actions provided on a national level or when purchasing products in the scope of the restriction.
- They will be able to provide evidence of successful completion of training by receiving a confirmation after completion of the required training. This confirmation can be presented while purchasing products that are in the scope of the restriction. (N.B. the DS expects that in many cases such people may purchase exempted products, which would eliminate training duties)

Roll-out planning

A considerable time period will be needed for a full implementation of this system in all member states and for all use sectors. From previous discussions, the DS assumes that approximately 3-5 years will be needed. A priority planning will be helpful to limit this period. A pilot project in an early stage is to be recommended in order to identify disconnects.

A.3.1.6.6 Aspects of monitorability

Regarding the monitoring of the effectiveness for the proposal a number of aspects has to be considered:

Responsibility for the scrutiny of the implementation and long term results of the trainings. In this respect it is important to distinguish between short, medium and long term aspects:

- Short term: National enforcement authorities can check if companies have fulfilled their training duties (i.e. do they have a confirmation of successful training completion for their workforce, as defined in Annex "Trainings and Measures").
- Medium term: Using the legal means available to them, MS can organise audits to check if companies have implemented the requirements as described in the Annex "Trainings and Measures". A coordinated union-wide action via SLIC (Senior Labour Inpectors Committee) may also be envisaged here.
- Long term: The most important objective of the restriction is to reduce the number of new cases of occupational asthma. Development in this area needs to be monitored by surveys by the DS at regular intervals (e.g. every three years). The DS has committed itself to initiate such surveys and the follow-up work. This should be seen on a time scale of 8-10 years.

Role for national enforcement authorities (NEAs) in this process.

The role of NEAs can be described as follows:

- NEAs have the right to request insight in the material used in the trainings.
- NEAs may require that, in case existing national regulations surpass the requirements as defined in the Annex Trainings and Measures", the provided material/instruction is modified by the "training work group" mentioned above, to include this specific information.

It should also be pointed out that the knowledge and awareness may by itself lead to an initial *increase* in new cases that are reported, not because more cases actually appear, but the awareness and the willingness to report, both from the side of the worker and from the side of the company and/or controlling physician, may be higher. Such a virtual increase is a well-known phenomenon in monitoring campaigns for occupational safety aspects. However, after a few years these effects will disappear and the actually underlying trends will become dominant. However, this effect should be considered in the timing of plans for concentrated efforts of data collection mentioned before.

A.3.1.7 Proportionality (including comparison of options)

To analyse proportionality, the estimated costs and benefits for human health of the proposed restriction are compared. In addition, a cost-effectiveness analysis will be presented which will show calculated figures indicating the investment costs needed to avoid a case of asthma (details are shown in Annex E.9.1.4). The affordability of the training costs for the individual company and consumers were also evaluated.

A.3.1.7.1 Comparison of costs and benefits of RMO1

In this summary only one result of the costs-benefit analysis for RMO1 is presented which is based on 6500 cases of OA/yr (Figure 4, see also Section A.2.3 Baseline). Benefits are shown for 50 % effectiveness (Lowbound) and 70 % effectiveness (Highbound).

The combination of costs and benefits will give two sets of curves in one diagram. One set will depend on the identified training option and its cumulative costs over 20 years. And the other one representing the cost savings related to the reduced number of cases of occupational asthma. Figure 4 provides information on the pay-off period. Depending on effectiveness, most training options would reach the **break-even point after 3-6 years** (low bound estimate of effectiveness) after implementation of the restriction. Only the training option c seems to be less cost-effective in this case (pay off about 13 years). Because of the external character inherent to option c, this is the most expensive training per worker (see Annex E.5.1.1). However, 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. Therefore in the Appendix Trainings and Measures, e-learning is only foreseen for the basic training module (with the lowest risk expected).

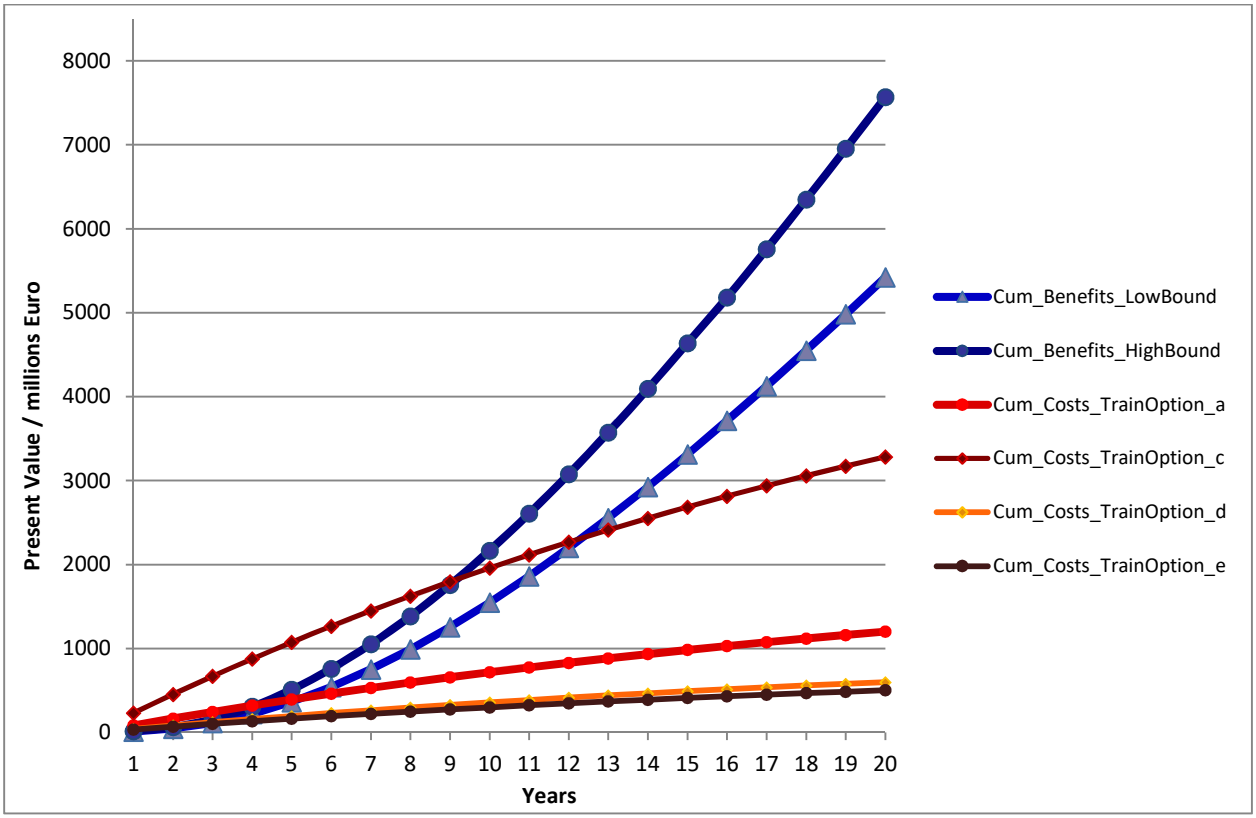

Figure 4: RMO1 over 20 years based on 6500 new cases of occupational diseases/year and several training options. The training options that are not shown fall between options e and a. (For reference: a = education center, c = external training, d = training at work, e = e-learning)

A.3.1.7.2 Cost effectiveness RMO1 (training for workers at high risk, exemptions for low risk products)

The cost-effectiveness analysis provides information on costs for avoidance of one asthma case over a period of 20 years. Considering the initial risk of 6500 cases/yr (see Section A.2.3), and depending on the training option and the assumed effectiveness of training measures a range of € 8000 – 53000 (lowbound) or € 6000 – 38000 (highbound) is derived for the costs to prevent one asthma case over a period of 20 years.

A.3.1.7.3 Comparison of costs and benefits RMO2 (No exemptions)

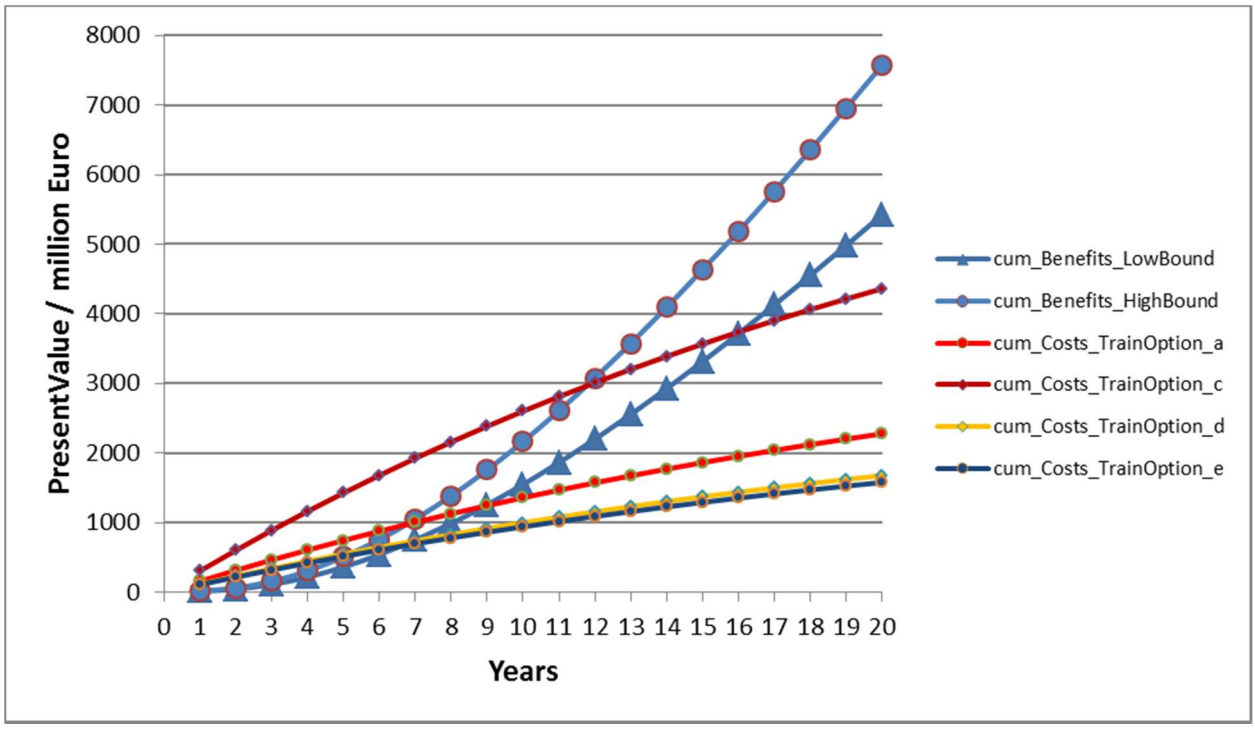

Figure 5: RMO2 over 20 years based on 6500 new cases of occupational diseases/year and several training options.

The training options that are not shown fall between options e and a (For reference: a = education center, c = external training, d = training at work, e = e-learning)

If no exempted products are identified, each downstream user (also in the "low risk" group) will be obliged to attend training according to the Appendix Trainings and Measures. This means much more workers need to participate in a training, leading to a considerable increase in costs. In such a case the basic training module defined in that Appendix ("stage 1") is

probably appropriate. In that case e-learning may be an appropriate model for training.

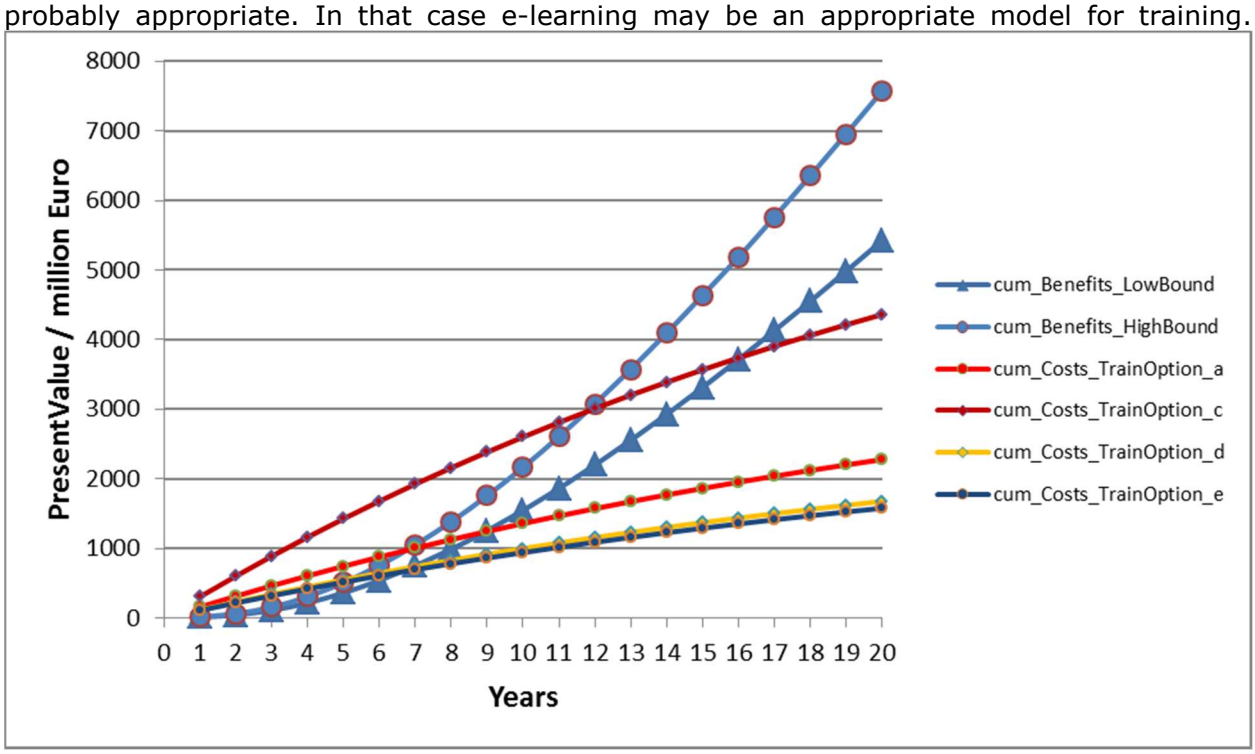

Figure 5 above indicates that the **break-even point would be realised after 7 - 9 years** (low bound estimate) – about twice as long as for RMO1. In case of training option c pay off about 17 years is expected. In overall consideration the RMO2 is still proportional, but the realisation of benefits may be related to more uncertainties because of the later pay-off period.

The cost-effectiveness analysis provides information on costs for avoidance of one asthma case in a period of 20 years. Considering the initial risk of 6500 cases/yr (see Section A.2.3), and depending on the training option and the assumed effectiveness of training measures a range of € 25000 – 70000 (lowbound) or € 18000 – 50000 (highbound) is derived for the costs to prevent one asthma case over a period of 20 years

A.3.1.7.4 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 Exemptions) or just adhere to the conditions of the Appendix on Trainings and Measures. Figure 6 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 in the range of about 45 – 120), even if the number of such products or the costs involved would be significantly underestimated. However, 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.

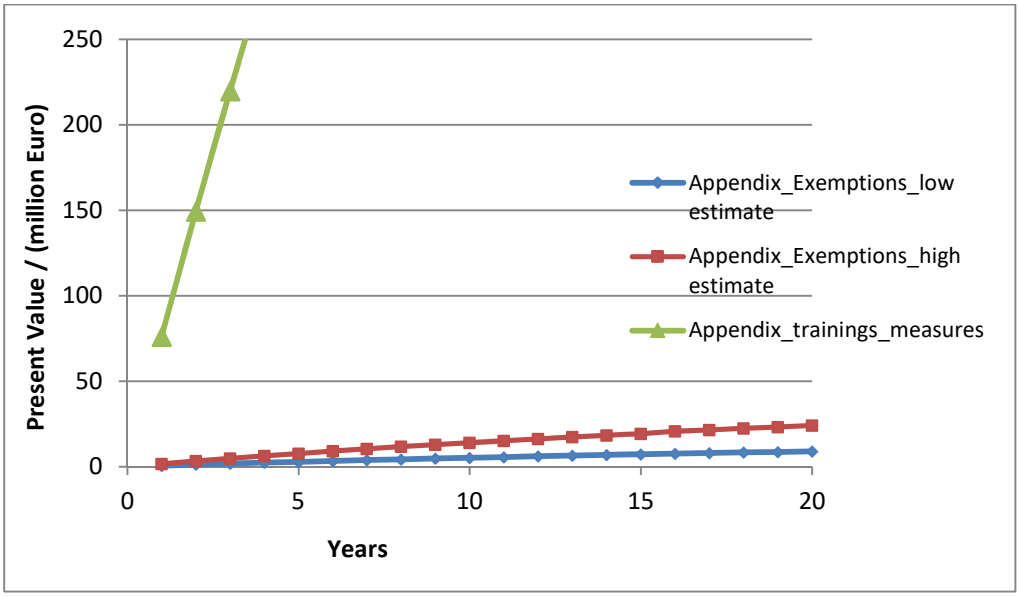

Figure 6: Comparison of costs for exemptions and e-learning

A.3.1.7.5 Cost and benefits of RMO3 (total ban)

An overall cost-benefit analysis resulting from a complete ban of isocyanates is very complex and beyond the DS's possibilities because of their widespread use.

In a first approach the cost over 20 years with regard to the lost added value generated by the PU-production sector was estimated. Figure 7 below compares this to the benefits under the assumption that the number of new asthma cases will drop to zero. It is obvious that the negative economic effects will be overwhelming. Thus, RMO3 is not a proportional measure for the reduction of new asthma cases.

The market for PU based products is a growing market. Therefore for modelling of the costs over 20 years in RMO3 in average 1 % ofannual 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.

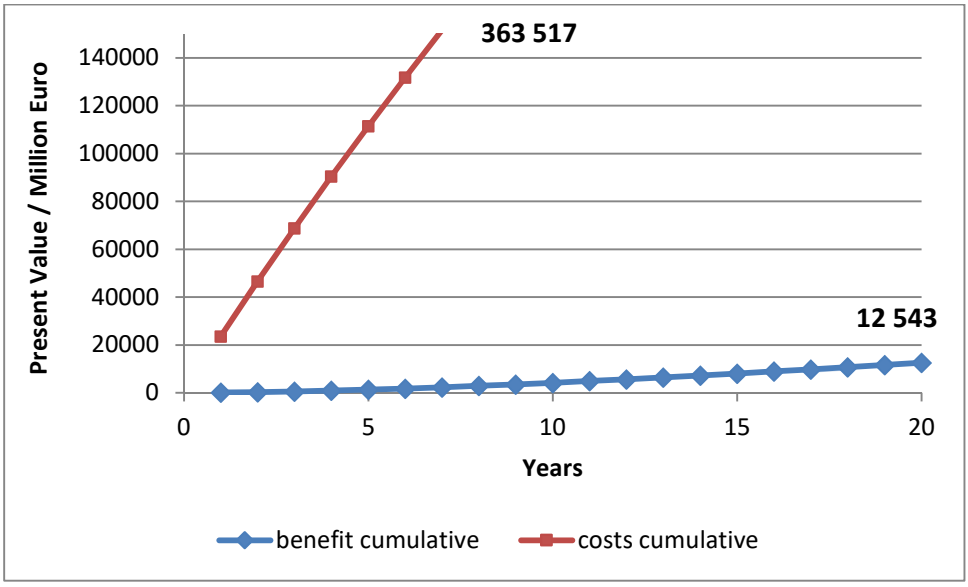

Figure 7: RMO3 comparison costs and benefits over 20 years

Table 10: Summary and overview on results for possible RMOs after 20 years. (rounded to 3rd position)

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	

RMO_n	Costs PV [€million]	Benefit PV [€million]	Benefit/cost ratio	Remark
RMO3: Complete ban (related to manufacturers and down-stream users)	362 500	13000	Costs are at least 28 times higher	• 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

The comparison of RMO1 with RMO2 is predominantly based on the balance of costs for the training measures against the costs for testing of the products as "exempted product" according to the proposed Appendix Exemptions. The costs for training measures in RMO2 are considerably higher because of the higher number of participants More details to these background data can be found in Annex E.5.1.1.

A.4 Assumptions, uncertainties and sensitivities

Declaration on uncertainties and possible factors for bias in the modelling of costs and benefits:

- 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 individuals with very low asthma prevalence will enter. So the prevalence rate would decrease over the medium term. Therefore, the number of workers under risk is potentially higher as assumed in modelling. In order to reduce the complexity these factors have been waived in the modelling.
- Prevalence of asthma in the working 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 at risk would be higher and the number of asthma cases could increase assuming the modelling based on the relative incidence rate approach.
- The assumed correlation of the isocyanates' market share with the number of workers might be incorrect because the degree of process automatisation in manufacturing could be essential for number of workers. 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.
- The statistics on gross value added, personal costs and turnover from 2012, 2013 and 2014 do not include the factor for purchasing power parity. According to EUROSTAT, since 2012 up to 2014 the price level indices have remained at the same level.
- Furthermore in the calculation of 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 Annex B.2) indicate that most of them would at least require the training for

group 2 defined in Appendix Trainings and Measures. It is assumed that only 10 % of uses or workers will be classified to stage 1 of that Appendix, where the training by e-learning could be a possible option. The costs of e-learning are definitely lower, so the effect for total costs will be very low due to the share of 10 %.

- For modelling of the costs over 20 years in RMO3 in average 1 % of annual growth of the value added is assumed. This premise is underpinned by the information provided by ISOPA and market forecasts.
- The costs values and savings based on asthma cases cannot be infinitely cumulated. Due to findings on 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.
- In this dossier, only the effects due to a reduction in asthmatic diseases are calculated. As discussed in section A.2.1, 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.

A.5 Conclusions

The DS is concerned by the fact that the risk of respiratory sensitisation resulting in occupational asthma caused by diisocyanates is not adequately controlled by means of the EU-wide existing regulations. The proposed approach was created with respect to established national regulations and in particular on 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 2350 – 10150 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 (safe) use of diisocyanates a possible option.
The proposed restriction is considered to be a balanced and justified measure as the benefits of risk reduction are estimated to outweigh the costs of the proposal after a reasonable time (3 - 6 years). It should be stressed that the real economic impacts due to productivity loss by one working day spending for training within a time period of 4 years might not be as significant as estimated. The loss of only one working day might have negligible effects due to the fact that the companies are not constantly working to 100 per cent capacity and personnel buffer is planned. Surely this short time effect cannot be deemed to be equivalent to productivity loss caused by working disability. 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 € 5.4 – 7.6 billion. Depending on the training option and the assumed effectiveness of training measures and considering the initial risk for 6500 cases/yr, the range of € 6000 – 38000 is derived for costs to prevent 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 an 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 10 the proposed RMO1 that combines both the measures described in the Appendices on Exemptions and on Trainings and Measures is the most costs-effective risk reduction measure. It provides the highest net benefit overall.

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