ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

SUBSTANCE NAME(S): N,N-dimethylacetamide (DMAC) and 1-ethylpyrrolidin-2-one (NEP)

IUPAC NAME(S): Dimethylacetamide / 1-ethyl-2-pyrrolidinon

EC NUMBER(S): 204-826-4 / 220-250-6

CAS NUMBER(S): 127-19-5 / 2687-91-4

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LIST OF ABBREVIATIONS

Acronym	Explanation
2-HESI	2-hydroxy-N-ethylsuccinimide
5-HNEP	5-hydroxy-N-ethyl-2-pyrrolidone
AC	Acetamide
ACSH	Advisory Committee on Safety and Health at Work
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredients
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BAT	Biological Tolerance Value
BDO	1,4 Butanediol Derivatives Sector Group
BLV	Biological Limit Value
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
BOEL	Binding Occupational Exposure Limit
BW	Body weight
CAD	Chemical Agents Directive
Cefic	European Chemical Industry Council
CfE	Call for Evidence
CI	Confidence interval
CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging
CMRD	Carcinogens, Mutagens and Reprotoxic substances Directive
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
CT	Computed Tomography
DART	Development And Reproductive Toxicity
DMAC	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one
DNEL	Derived No-Effect Level
DU CSR	Downstream User Chemical Safety Report
EWWA	European Winding Wire Association
GC-MS	Gas Chromatography–Mass Spectrometry
GD	Gestation Day
GLP	Good Laboratory Practice
GTP	Glutamyltranspeptidase
HMPA	Hexamethylphosphoramide
IOEL	Indicative Occupational Exposure Limit
IVC	Association of the German, Austrian and Swiss Man-Made Fibres Industries
LC50	Median (50%) Lethal Concentration

LD50	Median (50%) Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
MAK	Maximum Workplace Concentration
MVAC	N-methyl-N-vinylacetamide
NEP	1-ethylpyrrolidin-2-one
NMAC	N-methylacetamide
NMP	N-Methyl-2-Pyrrolidone
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OC	Operational Conditions
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OSH	Occupational Safety and Health
PAI	Polyamide-imide
PoD	Point of Departure
PROC	Process
QSAR	Quantitative Structure-Activity Relationship
RAC	Committee for Risk Assessment
RCR	Risk Characterisation Ratio
RIVM	National Institute for Public Health and the Environment
RMM	Risk Management Measures
RMO	Risk Management Option
RMOA	Risk Management Options Analyses
RPE	Respiratory Protective Equipment
SCOEL	Scientific Committee on Occupational Exposure Limit Values
SDS	Safety Data Sheet
SIDS	Screening Information Dataset
TG	Test guideline
TRA	Targeted Risk Assessment
TWA	Time-weighted average
UDS	Unscheduled DNA Synthesis

Summary

Proposed Restriction

Restriction on placing on the market and use of Dimethylacetamide (DMAC) and N-ethyl pyrrolidone (NEP)

Dimethylacetamide (DMAC) CAS-No. 127-19-5 EC-No. xxx	1. Shall not be placed on the market as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date] unless manufacturers, importers and downstream users have included in the chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 13 mg/m^3 for long-term exposure by inhalation and 0,53 mg/kg/day for long-term dermal exposure. 2. Shall not be manufactured, or used, as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date as in paragraph 1] unless manufacturers and downstream users take the appropriate risk management measures and take the appropriate operational conditions to ensure that exposure of workers is below both the DNELs specified in paragraph 1.
N-ethyl pyrrolidone (NEP) CAS-No. 2687-91-4 EC-No.xxx	1. Shall not be placed on the market as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date] unless manufacturers, importers and downstream users have included in the chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 4,0 mg/m^3 for long-term and 4,6 for acute exposures by inhalation and 2,4 mg/kg/day for long-term dermal exposure. 2. Shall not be manufactured, or used, as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date as in paragraph 1] unless manufacturers and downstream users take the appropriate risk management measures and take the appropriate operational conditions to ensure that exposure of

	workers is below both the DNELs specified in paragraph 1.

Summary of the justifications

To establish a more efficient and transparent restriction process and to prevent regrettable substitution, a group approach for dipolar aprotic solvents is used in this Annex XV restriction report. The proposed restriction is targeted to control risks identified at European Union (EU) wide level due to use of the substances DMAC and NEP in industrial settings and by professionals. Both substances are so-called dipolar aprotic solvents and are registered under REACH at substantial volumes. The substances have an EU harmonised classification in Annex VI of the CLP Regulation as reprotoxic category 1B based on developmental toxicity (Repro. 1B; H360D). Consumer applications are excluded from this document because both substances are classified as reprotoxic category 1B based on developmental toxicity (Repro.1B; H360D) in Annex VI of the Classification, Labelling and Packaging (CLP) Regulation which prohibits the use in consumer products up to a level of 0.3% through listing in Appendix 6 of entry 30 of REACH Annex XVII.

Identified hazard and risk

The hazard and risk of DMAC and NEP are assessed using information on the hazard from the registration dossiers, classification and labelling (CLH) proposals on both substances and the Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) dossier on DMAC. Exposure information is obtained from the registration dossiers, literature studies and monitoring data provided during the Call for Evidence (CfE).

DMAC is classified in Annex VI of CLP as harmful in contact with skin (Acute Tox. 4*; H312) and if inhaled (Acute Tox. 4*; H332) and as reprotoxic category 1B based on developmental toxicity (Repro. 1B; H360D). NEP is classified in Annex VI of CLP as reprotoxic category 1B based on developmental toxicity (Repro. 1B; H360D).

DMAC is studied extensively in the past decades showing a rather complete dataset of toxicological studies, including human studies. For NEP fewer toxicological studies are available. The focus of the Annex XV dossier is on the repeated dose toxicity endpoints and the developmental toxicity endpoint. In animal studies, the liver is the primary target organ for systemic repeated dose toxicity of DMAC and NEP. Developmental toxicity is observed in the form of reduced foetal body weight and increased incidences of malformation and variations for both DMAC and NEP. Increased post-implantation loss is also observed for NEP. In addition to systemic effects, NEP also induces local nasal irritation after inhalation exposure observed as degeneration/regeneration of the olfactory epithelium. Human studies have demonstrated liver effects in workers upon exposure to DMAC based on biochemistry parameters related to liver function and examination of the liver via ultrasonic and Computed Tomography (CT) imaging.

The benchmark dose (BMD) approach is used to determine the Point of Departure (PoD) for setting DNEL levels. The BMD approach is a scientifically more advanced method in comparison with the No Observed Adverse Effect Level (NOAEL) approach. In the BMD approach, the complete set of dose-response data are used to estimate the shape of the dose-response relationship of endpoints. The BMD is reported by its (90%) confidence interval (CI), which ranges from the lower to the upper confidence limits, the BMDL and BMDU respectively. BMD analyses for both substances is performed on the identified key studies for liver effects; developmental toxicity endpoints and for NEP local irritative effects. The following benchmark responses (BMRs) are considered for systemic effects: 10% change in organ or body weight and 10% extra risk in observed histopathology. For developmental toxicity a 5% decrease in foetal body weight, a 10% extra risk for foetal variations and a 1% extra risk for foetal

malformations and post-implantation loss are considered adverse, the latter due to its adversity. A 10% extra risk is taken as BMR for local irritative effects.

For DMAC, in an approach combining human and animal data, a systemic long-term inhalation DNEL of 13 mg/m^3 is proposed based on a $BMDL_1$ for foetal skeletal malformations and a $BMDL_{10}$ for foetal visceral variations in the animal developmental toxicity studies. Although the animal derived inhalation DNEL of 2.6 mg/m^3 for liver effects is lower, the inhalation DNEL of 22 mg/m^3 based on human data is considered more relevant for liver effects because the correct type of effects is assessed in the relevant population (workers) at relevant exposure conditions. In addition, the Dossier Submitter proposes a biological limit value for the metabolite of DMAC in urine of 15 mg N-methylacetamide (NMAC)/g creatinine corresponding to the DNEL of 13 mg/m^3. A systemic dermal DNEL of 0.53 mg/kg bw/day for workers is derived based on a $BMDL_{10}$ for increased relative liver weight after repeated exposure in animal toxicity studies and is also protective against developmental toxicity (head malformations).

For NEP, a systemic long-term inhalation DNEL of 4.0 mg/m^3 based on the absence of effects at the highest dose and a systemic long-term dermal DNEL of 2.4 mg/kg bw/day based on a $BMDL_{10}$ for increased relative liver weight are proposed. These DNELs are lower than the DNELs derived for developmental effects and are therefore also protective for developmental toxicity. An acute inhalation DNEL for local effects of 4.6 mg/m^3 is proposed based on a $BMDL_{10}$ for increased degeneration and/or regeneration of olfactory epithelium.

DMAC and NEP are used as solvents in the production of various formulations, e.g. in the production of agrochemicals, pharmaceuticals and fine chemicals. DMAC is used as solvent in coating and is extensively used in the production of man-made fibers and films and during the production of polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation. NEP is applied in cleaning agents and as binder and release agent. NEP is also used in oil field drilling and production operation processes, in functional fluids, in polymer processing, in water treatment, as excipient in agrochemicals and in road and construction applications. Both substances are used as laboratory agent. The manufacture of DMAC and NEP takes place in highly contained systems with exposure most likely to occur during sampling, transfer, maintenance and laboratory activities. Further down the supply chain DMAC and NEP are applied in formulations and used as process chemical. Exposure can occur during transfer activities, during (semi-closed) mixing/blending activities and during maintenance/cleaning activities. Exposure to DMAC may occur during its use as a solvent during fibre production or during the further processing of fibres, both due to inhalation or dermal contact. The application of coatings containing DMAC or NEP by spraying, brushing/rolling or dipping activities may also result in exposure.

A summary of the range of estimated exposure concentrations for DMAC and NEP per exposure scenario is presented in Table 1 and Table 2.

Table 1: Range of estimated exposure concentrations and inhalation measurement results for DMAC per exposure scenario

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		
		Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)	8-hour time weighted inhalation measurement results (mg/m^3)
Industrial use of DMAC				
Manufacturing	Low	0.036-10.69	0.034-1.37	<2.49
	High	0.036-178.16	0.034-1.37	
Formulation	Low	1.78-17.82	0.69-1.37	<0.07-<0.22
Charging and discharging	Low	0.89-17.82	0.69-1.37	<0.07-5.27
	Medium	4.45-17.82	0.69-1.37	

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		
		Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)	8-hour time weighted inhalation measurement results (mg/m^3)
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	Low	0.036-17.82	0.034-1.37	
Use as solvent in the production of man-made fibres and films	Low	0.036-10.69	0.034-14.14	Maximum values >36
	Medium	0.036-35.63	0.034-14.14	
Use as solvent in coatings	Low	2.14-10.69	0.82-2.57	<3.6
	Medium	10.69	0.82-1.65	
Manual maintenance (cleaning and repair) of machinery	Low	0.36-2.49	1.37	<8.66
Use as laboratory chemical	Low	1.78	0.034	
Professional use of DMAC				
Use as laboratory chemical	Low	3.56	0.068	

Table 2: Range of estimated exposure concentrations results for NEP per exposure scenario

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term	
		Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)
Manufacturing	Low	0.046-13.88	0.034-1.37
	Medium	0.046-46.28	0.034-1.37
Formulation	Low	0.046-13.88	0.034-1.37
	Medium	23.14	1.37
Charging and discharging	Low	1.16-46.28	0.69-1.37
Use as solvent in industrial processes	Low	0.046-13.88	0.034-1.37
Use as solvent in coatings	Low	2.78-13.88	0.82-2.57
	Medium	13.88	0.82-1.65
Manual maintenance (cleaning and repair) of machinery	Low	0.46-3.24	1.37
Use as laboratory chemical	Low	2.31	0.034
Binder and release agent	Low	1.39-13.88	0.21-2.57
Cleaning agents	Low	2.78-13.88	0.82-2.57
	Medium	13.88	0.82
Oil field drilling and production operations	Low	0.046-13.88	0.034-1.37
Functional fluids	Low	0.046-13.88	0.034-1.37
Polymer processing	Low	0.046-13.88	0.034-1.65
Water treatment	Low	0.046-13.88	0.034-1.37
Charging and discharging	Low	2.78-69.42	0.82-1.65
Use as solvent in coatings	Low	5.55-13.88	1.65-16.97
Manual maintenance (cleaning and repair) of machinery	Low	1.39-4.86	1.65
Use as laboratory chemical	Low	4.63	0.068
Binder and release agent	Low	5.55-13.88	1.65-12.86
Cleaning agents	Low	5.55-13.88	1.65-12.86
Use as excipient in agrochemicals	Low	46.28	2.74-21.43
Functional fluids	Low	13.88	0.21
Road and construction applications	Low	32.40-80.99	2.74-21.43
Polymer processing	Low	0.046-23.14	0.034-1.37

Conclusion

Based on the derived DNELs and exposure estimates for industrial and professional use of DMAC and NEP, risk characterisation ratios (RCRs) above one are calculated for most uses,

indicative of an unacceptable risk. The combined RCRs (inhalation and dermal RCRs) for DMAC range from 0.067 to 28.06 across all identified uses. Most RCRs are between 1 and 4. For NEP, combined RCRs range from 0.026 to 22.53. Most RCRs are between 1 and 4 for industrial uses and between 1 and 10 for professional uses, indicative of unacceptable workplace risks across sectors and uses.

It is therefore concluded that risks are not adequately controlled for several industrial and professional uses of DMAC and NEP, especially when it concerns processes under elevated temperatures, open processes, and processes that require manual activities.

Justification that action is required on a Union-wide basis

Total annual consumption of DMAC is estimated between 11 000 and 19 000 tonnes per year and EU manufacture ranges between 15 000 and 20 000 tonnes per year. DMAC is widely used in the EU as a solvent or processing agent across a range of industrial sectors such as textile fibre manufacture, electrical wire insulation and membrane manufacture. NEP manufacture and import ranges between 100 and 1 000 tonnes per year. Information on EU use of NEP is limited to the generic exposure scenario descriptions in the registration dossiers. There are some indications on uses in specialised coatings and as a cleaning agent in the manufacture of optical lenses. In general both substances are dipolar aprotic solvents that are used in specialised applications for which limited or no technically feasible alternatives are available. DMAC (since 2001) and NEP (since 2013) are both harmonized classified as "Reprotoxic 1B May damage the unborn child". For both substances a comprehensive hazard dataset is available and exposure of workers is expected in the various professional and industrial settings. Based on chemical safety assessment performed by the Dossier Submitter it is concluded that this occupational exposure results in unacceptable risks.

The identification of unacceptable risk is driven by establishment of DNELs for long-term systemic dermal and inhalation worker exposures that are more stringent than DNELs used in REACH registration dossiers. Therefore, action on a Community-wide basis is required to prevent EU-wide unacceptable risks for workers from exposure to DMAC and NEP. Applications of DMAC and NEP are traded freely and are used in all Member States of the EU. Action at EU level would ensure a 'level playing field' for all producers, importers and users of DMAC and NEP and products containing these substances. In view of the Dossier Submitter, a restriction targeted towards mandatory harmonised long-term inhalation and dermal DNELs combined with an obligation to implement operational conditions and risk management measures ensuring exposure below the DNELs is the most appropriate Community wide measure. In addition, the proposed restriction would offer legal consistency with existing restrictions on two other dipolar aprotic solvents N-Methyl-2-Pyrrolidone (NMP) and N,N-dimethylformamide (DMF).

Risk Management Options and effectiveness in reducing the identified risks

The Dossier Submitter has performed a Risk Management Options Analyses (RMOA) in which four options are considered to manage the identified risks of DMAC and NEP: authorisation, (update of) Occupational Exposure Limit (OEL) under Occupational Safety and Health (OSH) legislation, a restriction in the form of a ban with a maximum concentration limit and a restriction in the form of binding DNELs. All risk management options are expected to reduce or eliminate the risks related to the use of DMAC and NEP. A restriction with binding DNELs for the inhalation and dermal route for DMAC and NEP is concluded to be the most appropriate risk management option because it effectively reduces worker risks as a consequence of inhalation and dermal exposure, applies equally to all sectors and users in supply chains and allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve. In addition, the binding DNEL restriction offers a high level of flexibility for downstream users to implement where needed appropriate risk management measures and adapt operational conditions to ensure exposure below the respective DNELs. Finally, the

proposed restriction offers legal consistency with existing restrictions on two other dipolar aprotic solvents NMP and DMF.

Proportionality to the risk

The proportionality of the restriction proposal is assessed by a comparative approach. The net societal welfare changes are not quantified, instead costs and benefits of the proposed restriction are compared to the cost and benefits of the other two existing REACH restrictions of very similar nature targeted at dipolar aprotic solvents: NMP and DMF. Proportionality is assessed through comparison of the estimated costs per exposed worker to reduce the exposure below the imposed DNELs across all restriction dossiers for dipolar aprotic solvents. Cost estimates derived from the NMP and DMF dossiers serves as a benchmark to assess the proportionality of the proposed restriction on DMAC and NEP. The quantified costs of the proposed restriction are at least as cost-effective as some of the sectoral costs in the NMP restriction in terms of risk reduction per worker. Therefore, the proposed restriction is considered likely to be proportionate based on this comparative analyses.

Practicality

The proposed restriction is practical because it is implementable, manageable and enforceable:

Implementability and manageability

The practicality of implementing additional risk management measures to control dermal and inhalation exposure to DMAC and NEP below the DNELs depends on the company specific workplace situation. In general, the Dossier Submitter considers technical and operational workplace measures to reduce inhalation and dermal exposures below the DNELs technically feasible and proportionate to the risk. The restriction offers high flexibility for sectors and downstream users at company level in the type of measures taken to comply with the restriction, which renders the restriction practical and implementable. The proposed timing of the entry into force of the restriction positively affects implementability.

Enforceability

The Dossier Submitter concludes the restriction proposal to be enforceable. Enforcement of the compliance with the restriction may be carried out by national labour inspectors and/or REACH enforcement authorities depending on the Member State. Enforcement experiences with existing restrictions for NMP and DMF will be of added value as this restriction can be approached similarly. In checking compliance with the REACH restriction enforcement should pay special attention to adherence with the "hierarchy of control", as an established concept of the Chemical Agents Directive (CAD).

The Dossier Submitter recommends amending the existing NMP guideline as soon as a decision on the legal implementation of the DMAC and NEP restriction is taken to account for specific circumstances typical for these chemicals and their uses.

Monitorability

There are no specific concerns regarding the monitorability of the proposed restrictions on DMAC and NEP. This can be done through enforcement and would normally include verification of workplace exposure levels.

1. The problem identified

1.1. Hazard, exposure/emissions and risk

1.1.1. Identity of the substance(s), and physical and chemical properties

DMAC and NEP belong to the chemical class of dipolar aprotic solvents having high dielectric constants and high dipolar moments. Data in Table 3 and Table 4 is obtained from the public registration on the ECHA website (accessed January 2, 2022) or other public sources.

Table 3: Name and other identifiers of the substances[i]

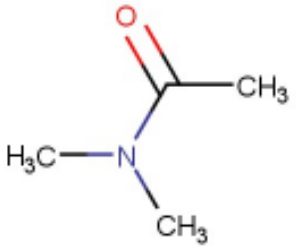
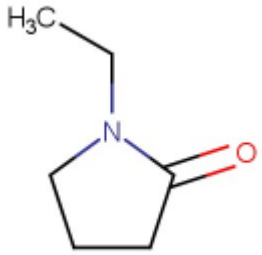
Substance name	N,N-dimethylacetamide (DMAC)	1-ethylpyrrolidin-2-one (NEP)
IUPAC name	Dimethylacetamide	1-ethyl-2-pyrrolidinon
EC number	204-826-4	220-250-6
CAS number	127-19-5	2687-91-4
Molecular formula	C_4H_9NO	$C_6H_{11}NO$
Structure formula		
Registration numbers	01-2119459339-27-0000 01-2119459339-27-0002 01-2119459339-27-0003 01-2119459339-27-0005 01-2119459339-27-0006 01-2119459339-27-0008 01-2119459339-27-0009 01-2119459339-27-0011 01-2119459339-27-0012 01-2119459339-27-0013 01-2119459339-27-0014 01-2119459339-27-0015 01-2119459339-27-0016 01-2119459339-27-0017	01-2119472138-36-0000 01-2119472138-36-0003 01-2119472138-36-0004 01-2119472138-36-0005 01-2119472138-36-0006

Table 4: Physicochemical properties of DMAC and NEP

	N,N-dimethylacetamide (DMAC)	**1-ethylpyrrolidin-2-one (NEP)**
Molecular weight (g/mol)	87.12	113.16
Physical state (at 20 °C and 1013 hPa)	Liquid	Liquid
Melting/freezing point (at 1013 hPa)	-20 °C	<-120 °C
Boiling point (at 1013 hPa)	166 °C	212.5 °C
Density (at 20 °C)	0.94 g/cm^3	0.997 g/cm^3
Vapour pressure	2 hPa (at 21.7 °C)	0.18 hPa (at 20 °C)

Surface tension	Not surface active (based on chemical structure, no surface activity is predicted)	69 mN/m. The test item is not surface-active
Water solubility	Miscible (at 20 °C)	Miscible (at 23 °C)
Partition coefficient n-octanol/water (log value)	-0.77 (25 °C)	-0.2 (20 °C)
Flash point (at 1013 hPa)	64 °C	91 °C
Flammability	No classification for flammability. The substance has no pyrophoric properties and does not yield flammable gases on contact with water	No classification for flammability. The substance has no pyrophoric properties and does not yield flammable gases on contact with water
Explosive properties	Non explosive	Non explosive
Self-ignition temperature (at 1013 hPa)	345 °C	245 °C
Oxidising properties	No oxidising properties	No oxidising properties
Granulometry	Not applicable	Not applicable
Stability in organic solvents and identity of relevant degradation products	Not applicable	Not applicable
Dissociation constant	-0.19 (at 25 °C)	Not applicable
Viscosity	0.92 mPas (at 25 °C)	2.1 mPas (at 20 °C)

The calculated conversion factor for DMAC from ppm to mg/m^3 is 1 ppm=3.624 mg/m^3 (at 20ºC and 1013 hPa).
The calculated conversion factor for NEP from ppm to mg/m^3 is 1 ppm=4.707 mg/m^3 (at 20ºC and 1013 hPa).

1.1.2. Justification for grouping

In order to establish a more efficient and transparent restriction process and to prevent regrettable substitution, a group approach for dipolar aprotic solvents is of interest for this restriction proposal.

By using the Organisation for Economic Co-operation and Development Quantitative Structure-Activity Relationships (OECD QSAR) Project Toolbox and Derek Nexus software several dipolar aprotic solvents are considered for grouping based on their structural similarity, the availability of toxicity data and developmental toxicity. The Development And Reproductive Toxicity (DART) scheme in the OECD QSAR Toolbox identifies DMAC as a (potential) teratogenic chemical due to its alkyl amide (N-alkyl) functionality. The presence of N-methyl groups results in a significant increase in teratogenic potency when compared to the N-unsubstituted analogues. N-methyl groups are present in NMP, DMF, DMAC, NEP, 1,3-dimethylimidazolidin-2-one (DMI), and N-methyl-N-vinylacetamide (MVAC). These six dipolar aprotic solvents are currently registered under REACH and are given priority for any further action. The following conclusions are drawn by the Dossier Submitter:

- NEP (CAS: 2687-91-4) is a likely candidate for inclusion in a grouped Annex XV Restriction dossier and restriction proposal as it also has an EU harmonised classification as Repro Cat. 1B like DMAC ;

- DMI (CAS: 80-73-9) is a likely candidate for a proposal for harmonised classification as it is self-classified as Repro Cat. 2 and is structurally related to DMAC. Harmonised classification for reproductive toxicity as such is however not a prerequisite for proposing a restriction. Therefore, the substance is not further considered for grouping;

- MVAC (CAS: 3195-78-6) is considered a likely candidate for screening for further evaluation (compliance check or substance evaluation) but not for inclusion in a grouped Annex XV Restriction dossier, as it, based on an initial assessment of QSARs, does not have an alert for reproductive toxicity and carries no (self) classification for reproductive toxicity. Furthermore, according to the public information on the ECHA website MVAC is used only in closed system industrial settings (including formulation), which renders the potential for exposure limited. Further evaluation in compliance check of substance evaluation processes could focus on the justification behind self-classifications as STOT-RE Cat. 1.

Based on the RMOA conclusions MVAC is not included in this restriction proposal. NEP and DMI are considered for grouping in addition to DMAC. The potential for worker exposure and the scale at which exposure may occur are estimated by collecting information on the uses from the available Chemical Safety Reports of registrants. Subsequently, information on the hazard profile of NEP and DMI specifically focussing on DNELs for workers is collected. An initial comparison of registrant DNELs with RIVM preliminary assessment and any available (indicative) OEL is made. The risk for workers which is not adequately controlled is identified. This is based on screening worker risk assessment focussing on finding the most critical human health endpoint, establishing preliminary DNELs for worker dermal and inhalation exposure and comparing these with DNELs applied by registrants and downstream users. In addition, inhalation DNELs are compared with available (indicative) OELs for the substance.

Based on the information above DMI is not included in this restriction proposal. Based on the availability of toxicity studies and the fact that DMAC and NEP are classified as reproductive toxicants category 1B (developmental toxicity), it is decided to include DMAC and NEP in this restriction proposal.

The type of restriction initially considered, namely the DNEL harmonization, does not lend itself to a broad group approach. The group approach chosen is limited to the two dipolar aprotic solvents which had a classification for reprotoxicity at the start of the dossier. This group restriction is characterized by two separate risk assessments and DNEL derivations. The group approach has little added value for this. The added value lies in the efficiency of describing the other parts of the file, e.g. the impact assessment, where there is partial overlap in the applications, the analysis of alternatives and the impacts.

1.1.3. Classification and labelling.

Table 5: Classification according to part 3 of Annex VI, Table 3 ((list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No.	International chemical identification	EC No.	Cas No.	Classification		Labelling			Specific Conc. Limits, M-factors
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)	
616-011-00-4	N,N-dimethylacetamide	204-826-4	127-19-5	Repr. 1B Acute Tox. 4* Acute Tox. 4*	H360D*** H332 H312	GHS08 GHS07 Dgr	H360D*** H332 H312		
616-208-00-5	N-ethyl-2-pyrrolidon; 1-ethylpyrrolidine-2-on	220-250-6	2687-91-4	Repr. 1B	H360D	GHS08 Dgr	H360D		

*Repr. 1B, H360D*** May damage the unborn child*
Repr. 1B, H360D May damage the unborn child
Acute Tox. 4, H332 Harmful if inhaled*
Acute Tox. 4, H312 Harmful in contact with skin*

1.1.4. Hazard assessment

Information on DMAC and NEP is obtained from a literature search, the registration dossiers, previous CLH proposals on DMAC (ECHA, 2013b) and NEP (ECHA, 2011b) and the OECD SIDS for DMAC (OECD, 2001). Study descriptions and No Observed Adverse Effect Concentrations/Levels (NOAEC(L)s) and/or Lowest Observed Adverse Effect Concentrations/Levels (LOAEC(L)s) are adopted in most cases with a preference for the summaries from the CLH reports if available.

Please review Annex section B for the study descriptions, tables and more comprehensive summaries of the toxicokinetics, repeated dose and reproductive toxicity studies.

1.1.4.1. Toxicokinetics (absorption, distribution, metabolism and excretion)

DMAC
Absorption occurs rapidly via all routes in rodents, primates and humans. It is, however, reasonable to assume that under non-exclusive conditions, dermal absorption is lower than inhalation absorption due to the relatively high volatility of DMAC. This is supported by studies with exposure to vapour in male volunteers where absorption of DMAC vapour occurred dermally, exclusively via inhalation or both. Absorption of DMAC vapour via the dermal route is smaller compared to the lungs. Data of individual dermal absorption rates (measured as urinary NMAC excretion) of twelve male human volunteers defined as dermal absorption over dermal plus respiratory absorption fluctuate widely between 12.9% and 73.3%, with a mean value of 40% (Nomiyama et al., 2000). Likewise, in another study with exposure to vapour with two human volunteers, dermal absorption is based on excretion of NMAC and estimate to be >two-fold lower (30%) as compared to absorption (70%) via inhalation (Maxfield et al. 1975). There is thus some uncertainty on the ratio of absorption between dermal and inhalation of DMAC vapour. Absorption of liquid DMAC (375 mg, once daily, five days) through the skin is between 10-53% (38-197 mg) of total dose applied in four male volunteers (Maxfield et al., 1975).

Based on the available data for DMAC, 100% absorption is assumed for oral and inhalation exposure. Substantial dermal absorption of DMAC vapour can occur, as observed in two human volunteer studies. The one human volunteer study with DMAC liquid indicates that dermal absorption can amount to 53%, but is considered too limited to deviate from the default of 100% under REACH Guidance R.7.12 for substances with a molecular weight <500 and a log P in the range of -1 and 4 (ECHA, 2017). Hence, a dermal absorption of 100% is assumed for DMAC.

DMAC undergoes demethylation to NMAC and is then further metabolized to acetamide (AC) via N-hydroxymethyl-acetamide. Plasma half-life range from 0.6 to 1.5 h for DMAC and 2.2 to 3.0 for NMAC in rats, and from 0.3 to 0.5 h for DMAC and 0.6 to 1.3 h for NMAC in mice after single and repeated inhalation exposure (Hundley et al., 1994). In humans, biological half-lives of urinary NMAC are 9.0 hours and 5.6 hours via skin and lung, respectively, as indicated by a study with twelve healthy male volunteers that were exposed twice to DMAC for four hours at intervals of 96 hours to 6.1 ppm for dermal (whole body with respiratory mask) and for inhalation exposure (nose-only). Saturation of metabolism seem to occur at concentrations ≥150 ppm in rats and ≥300 ppm in mice. In both species the plasma profiles, plasma AUC values and plasma half-lives are not affected by multiple exposures to DMAC. The parent substance and its metabolites are mainly excreted via urine, while fat and muscles are the major sites of retention in rats (Monsanto, 1982b).

A relationship of 10 ppm urinary NMAC for each 1 ppm DMAC inhaled is observed in five human workers of whom the urine was examined for four consecutive weeks (Kennedy Jr & Pruett, 1989).

NEP
Data on toxicokinetics of NEP is limited to a human volunteer study (Koch et al., 2014) and a recent toxicokinetics study with rats by Bury et al. (2019). Further information on toxicokinetics is adapted from the summary in the Chemical Safety Report (CSR) prepared by the lead registrant. This information is mainly derived based on toxicology studies. NEP is bioavailable via all routes as demonstrated by effects after NEP exposure via all routes.

Based on the available data for NEP, 100% absorption is assumed for oral and inhalation exposure. In the absence of a dermal absorption study, also for the dermal route 100% is assumed, given that NEP has a molecular weight <500 Dalton and a log P in the range of -1 and 4, and given its similarity to NMP (also 100% assumed for dermal absorption) (ECHA, 2014a).

Some more details on the metabolism and excretion of NEP are given by the studies of Koch et al. (2014) with human volunteers and with rats (Bury et al., 2019). NEP is predominantly metabolized to 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy-N-ethylsuccinimide (2-HESI) in both rats and humans. Both metabolites and the parent compounds are predominantly excreted via the urine. The Tmax in rats of 5-HNEP and 2-HESI are similar as the equivalent metabolites of NMP: 5-HNMP and 2-HMSI (Bury et al., 2019). In rats, the half-live of NEP is one to two hours. The interspecies (humans vs rats) differences of NEP and NMP for renal conversion factors and half-lives appears very similar according to Bury et al. (2019).

After repeated administration, elimination of NEP from plasma is slower in pregnant rats compared to non-pregnant rats with area under the curves (AUCs) and half-lives that are twice as high in pregnant rats (Bury et al., 2019). Metabolism is also affected with different plasma concentrations of the metabolites for pregnant/non-pregnant depending on the time of measurement after dosing. The placental transfer of NEP on gestation day (GD) 19 is rapid with similar concentrations of NEP and 5-HNEP in foetal plasma and amniotic fluid as compared to maternal plasma already one hour after dosage.

1.1.4.2. Acute toxicity

DMAC
DMAC has a harmonised classification as Acute Tox. 4*, H332 (harmful if inhaled) and Acute Tox. 4*, H312 (harmful in contact with skin). The LC_{50} values in rats range from 8.8 mg/L (one hour exposure) to in between 10.7 and 32 mg/L (four hour exposure). A dermal LD_{50} of 2100 mg/kg bw is reported in male rabbits. In pregnant animals, the approximate dermal lethal dose is 5000 (rabbits) or 7500 (rats) mg/kg bw. Orally, DMAC is not acutely toxic in rats (with LD_{50} values ranging between 4800 - 5830 mg/kg bw), mice (LD_{50} 4610 - 6020 mg/kg bw), and rabbits (LD_{50} 2820 mg/kg bw), whereas the dog seems more sensitive (lethality observed from 470 mg/kg bw). Reddened or irritated eyes and eyelid closure are common clinical signs observed in rats upon oral or inhalation exposure.

NEP
In oral, dermal and inhalation acute toxicity studies with rats, NEP appears not acutely toxic (oral LD_{50} 3200 mg/kg bw, dermal LD_{50} > 2000 mg/kg bw, and inhalation LC_{50} (air) > 5.1 mg/l/4h).

1.1.4.3. Irritation and corrosivity

DMAC
Several studies are available that indicate DMAC is only a slight skin irritant (not sufficient for classification), whereas it causes more severe eye irritation. It does not have a harmonised classification for the latter endpoint, but several notifiers have self-classified DMAC as eye irritant category 2 (H319).

NEP
NEP causes irreversible damage to the eye in an OECD 405 conform study but produce only minimal effects in a skin irritation study according to OECD 404. This can indicate Eye Dam. 1, H318, and the majority of notifiers have self-classified NEP as such.

1.1.4.4. Sensitisation

DMAC
No skin sensitisation is observed in a (pre-guideline) sensitisation study with guinea pigs.

NEP
NEP is tested in a Local Lymph Node Assay (LLNA) assay and appears not to cause skin sensitisation in this model.

1.1.4.5. Repeated dose toxicity

DMAC
In Table 6, a short summary is presented of the available repeated dose toxicity studies with DMAC and the critical effects observed at the lowest observed adverse effect concentration or level (LOAEC(L)). Unless stated otherwise these effects are statistically significantly different from control and dose dependent with larger effects at higher dose levels.

Table 6: Summary of NOAEC(L)s/LOAEC(L)s after repeated exposure to DMAC

Species	NOAEC(L)/LOAEC(L) (mg/m³ or mg/kg bw/day)	Critical effect(s) at LOAEC(L)	Study (similar as)	Study duration	Reliability (Klimisch)	Reference
Inhalation						
Rat	90/360	Liver effects in males (rel. weight 22%, n.s.; focal cystic degeneration; accumulation of pigments in Kupffer cells, hepatic peliosis, n.s)	OECD TG 453	lifetime – 2 years	1 – key study	DuPont (1994); Malley et al. (1995)
Rat	65/324	Liver effects in males and females (rel. weight 9-14%; ↑ cholesterol, triglycerides, phospholipids and gamma-GTP; adipose liver degeneration), kidney effects in males and females (renal tubular pigmentation; m: ↑ BUN and chronic progressive nephropathy)	OECD TG 451	lifetime – 2 years	2	Anonymous (2013a)
Rat	-/360 (local) 360/1040 (systemic)	Nasal irritation, liver effects (rel. weight 21-22%; f: ↑ cholesterol; hepatocellular hypertrophy), testicular atrophy	OECD TG 412	2 weeks	3	DuPont (1983b); Kelly et al. (1984)
Rat (males only)	1080/1730	BW (-12%)	-	2 weeks	3	Valentine et al. (1997)
Rat (males only)	360/1080	Liver effects (hepatocellular hypertrophy with margination of hepatocellular cytoplasmic contents and hepatic cellular cytoplasmic lipid-like vacuolation)	-	2 weeks	3	Kinney et al. (1993)
Mouse	90/360	Liver effects in males (accumulation of pigments in Kupffer cells; hepatocellular necrosis, n.s.)	OECD TG 453	Lifetime - 18 months	1 – key study	DuPont (1994); Malley et al. (1995)
Mouse	216/1080	Liver effects in males and females (rel. weight 34-65%, ↑ AST 160-560%; ↑ ALT 250-580%; ↑ nodules, eosinophilic foci, adenoma; f: ↑ carcinoma), kidney	OECD TG 451	lifetime – 2 years	2	Anonymous (2013b)

		effects in males and females (papillary necrosis; m: deformity and scarring)				
Mouse (young adult, males only)	360/1120	Testes effects (rel. weight -15%, n.s.; testicular lesions associated with ↓ number of sperm and ↑ germinal epithelium in epididymis)	-	2 weeks	3	Valentine et al. (1997)
Mouse (young pubescent, males only)	1080/1730	Testes effects (abs. weight -21%, testicular degeneration/atrophy)	-	2 weeks	3	Valentine et al. (1997)
Oral						
Rats - drinking water	-/100	↑ liver weight (rel. weight m: 23%)	OECD TG 453	Lifetime – 2 years	1 – key study	Monsanto (1980, 1990, 1993)
Rats - diet	60/-	No significant effects (only one low dose tested)	-	3 months	3	Kennedy and Sherman (1986)
Rats - gavage	-/290	↑ ALP (m), ↑ total lipids, ↓ abs. heart weight (m), ↓ abs./rel. adrenal weight (f), thin/filamentary uterine horns	OECD TG 407	4 weeks	3	BASF (1975)
m: male, f: female, ↑: increased, ↓: reduced, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BW: body weight, BUN: blood urea nitrogen, gamma-GTP: gamma glutamyltranspeptidase, rel.: relative, n.s.: not statistically significant, TG: test guideline						

A short summary of the key studies is presented below. For a detailed summary of all studies in the table or human studies, see Annex B – Section B.5.2.1 and Section B.5.2.2.

In a combined chronic toxicity and carcinogenicity study by Malley et al. (1995; key study), rats and mice were exposed to 0, 25, 100 or 350 ppm DMAC (0, 90, 360, 1260 mg/m^3, whole body, vapour) for six hours per day, five days per week, for two years (rats) or 18 months (mice). In both species, DMAC does not cause an increase in tumour incidences, nor local effects. Concerning non-neoplastic effects, the liver is the primary target organ in both sexes of rats and mice, with males (NOAEC 90 mg/m^3) somewhat more sensitive than females (NOAEC 360 mg/m^3). In rats, liver effects consist of increased relative weight (10-22%) and histopathological changes (generally of minimal severity), such as: accumulation of pigments in Kupffer cells in males and females, and focal cystic degeneration, hepatic peliosis and biliary hyperplasia in males. In mice, liver effects also include weight changes (females only), as well as hepatocellular necrosis (minimal to mild), accumulation of pigments in Kupffer cells (generally of minimal severity) and, in males only, centrilobular hepatocellular hypertrophy (minimal to mild). In rats also effects on the kidney are observed (increased relative weight (21-25%) in males and females), in association with (severe) chronic progressive nephropathy, a spontaneous age-related disease in rats for which the weight of evidence suggests no human counterpart. Rats additionally show changes in body weight (-5 to -11%) and body weight gain (-8 to -17%). The mechanism responsible for the pigment accumulation is not clear (no evidence of hepatocellular necrosis or increased apoptosis in rats and only few mice affected, no haematological evidence of damage to red blood cells, iron contamination in DMAC administered unlikely given 99.96% purity). According to the study pathologists, these liver weight changes most likely represent enzyme induction associated with metabolism of DMAC, whereas the histopathological changes collectively taken are suggestive of slight hepatotoxicity. Overall, the NOAEC for systemic effects (liver) in this key study in rats and mice was 90 mg/m^3.

Liver effects are also considered the most sensitive endpoint in another reported combined chronic toxicity/carcinogenicity inhalation study in rats and mice, and in other inhalation studies of shorter duration. At the LOAECs in the different studies, liver effects include increase in relative liver weight (9-65%), accompanied with histopathological findings (hypertrophy) and changes in biochemistry parameters related to liver function (gamma

glutamyltranspeptidase (gamma-GTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST)).

For DMF, a structural analogue to DMAC, minimal to moderate Kupffer cell hyperplasia with accumulation of lipofuscin and hemosiderin are also observed in rats and mice over a two-year or 18-month period, respectively, in inhalation studies performed in the same lab and with the same strains (Malley et al., 1994), and are determinative for the NOAEL in these studies.

Local effects in the nasal cavity (nasal irritation) are observed in one two-week study at 360 mg/m^3 (LOAEC) following whole-body exposure to DMAC via inhalation (DuPont, 1983b; Kelly et al., 1984). However, local effects are not noted in a two-week nose-only study at comparable concentrations, nor in any other inhalation study, including the combined chronic toxicity and carcinogenicity studies (Malley et al., 1995).

In a combined chronic toxicity and carcinogenicity study (Monsanto, 1980, 1990, 1993) in rats receiving 0, 100, 300 or 1000 mg DMAC/kg bw/day via drinking water for 24 months, males show an increased relative liver weight (23%) at the lowest dose of 100 mg/kg bw/day (LOAEL), without accompanying histopathological lesions. At doses ≥300 mg/kg bw/day, increased liver weights are seen in the presence of minimal to moderate (mostly minimal to slight) histopathological changes in liver (e.g. intracytoplasmic brown pigment hepatocellular hypertrophy and necrosis), similar to changes upon exposure via inhalation.

No reliable studies for repeated dose toxicity for DMAC via the dermal route are found.

Multiple case reports and cohort studies demonstrate liver effects in workers upon exposure to DMAC based on biochemistry parameters related to liver function (e.g. ALT, AST, gamma-GTP) and examination of the liver via ultrasonic and CT imaging (Corsi, 1971; Jung et al., 2007; Lee et al., 2006; Wang & Chen, 2020). However, the air concentrations of DMAC are not reported in these studies. On the other hand, two cohort studies and one clinical study with exposed workers or volunteers (respectively) are available including estimated concentrations of DMAC in the air (Antoniou et al., 2021; DuPont, 1974; Spies et al., 1995a, 1995b). No toxic effects are reported upon exposure to DMAC (36 mg/m^3, whole body, six hours per day, five days) in the clinical study but no long-term effect levels can be derived from this short-term effect study. No statistically significant DMAC exposure-related trends in hepatic serum clinical chemistry (serum levels of total bilirubin, AST, ALT, ALP, and gamma-GTP) are measured in a one-year cohort study of workers (highest exposed group geometric mean 10.8 mg/m^3 based on eight-hour time-weighted average (TWA)) in an acrylic fibre manufacturing facility (Spies et al., 1995a, 1995b). In a retrospective cohort study of workers in four man-made fibres factories (highest exposed group median 21.7 mg/m^3 based on eight hour TWA) no indication of a relationship between DMAC exposure and elevated levels of ALT and/or increased observations of liver injuries are noted (Antoniou et al., 2021).

For chronic exposure, an overall no-effect level in humans of six ppm (21.7 mg/m^3) eight-hour TWA can be deduced from the Antoniou et al. (2021) study. This study is given preference over the Spies et al. (1995a, 1995b) studies, given that it concerns more recent data from more workers, over more years and from work associated with the highest DMAC exposure.

NEP

In Table 7, a short summary is presented of the available repeated dose toxicity studies with NEP and the critical effects observed at the LOAEC(L). Unless stated otherwise these effects are statistically significantly different from control and dose dependent with larger effects at higher dose levels.

Table 7: Summary of NOAEC(L)s/LOAEC(L)s after repeated exposure to NEP

Species	**NOAEC(L)/LOAEC(L) (mg/m^3 or mg/kg bw/day)**	**Critical effects at LOAEC(L)**	**Study (similar as)**	**Study duration**	**Reliability (Klimisch)**	**Reference**
Inhalation						
Rat	60/200 - local 200/- systemic	degeneration and/or regeneration of olfactory epithelium	OECD TG 413	90 days	1 – key study	BASF (2013)
Rat	80/200 – local 400/- systemic	salivation, nose irritation, degeneration/regeneration of olfactory epithelium	OECD TG 412	28 days	1 – key study	BASF (2011)
Oral						
Rats - feed	100/300	↓ food consumption (m/f: up to -13.2/-7.5%), ↓ BW gain (m/f: -18.8/-23.5%), ↓ grip strength forelimbs (m: -33%), liver effects: ↑ rel. weight (m/f: +13/7%), centrilobular hypertrophy of hepatocytes (m)	OECD TG 408	90 days	1 – key study	BASF (2006)
Rats - gavage	250/-	-	OECD TG 407	28 days	2	Saillenfait et al. (2016)
m: male, f: female, ↑: increased, ↓: reduced, BW: body weight, rel.: relative, abs.: absolute, TG: test guideline						

A short summary of the studies is presented below. For a detailed summary of the studies in the table, see Annex B – Section B.5.2.1.

Two sub-chronic toxicity studies (oral/inhalation) and two sub-acute toxicity studies (oral/inhalation) with rats are available. In the inhalation studies, rats are exposed to NEP vapour for six hours per day, five days per week for either 13 or four weeks, via nose/head-only inhalation exposure. The target organ in both studies is the nasal cavity, with minimal to moderate degeneration and regeneration of the olfactory observed at the highest tested concentration of 200 mg/m^3 in the 90-day study (BASF, 2013), and at the mid and high dose (200 and 400 mg/m^3, respectively) in the 28-day study (BASF, 2011). An overall NOAEC of 80 mg/m^3 for local effects is derived from the sub-acute study. In the absence of systemic toxicity in both inhalation studies, the overall NOAEC for systemic effects is (at least) 200 mg/m^3.

Systemic effects are observed in the oral studies, with an overall NOAEL of 100 mg/kg bw/day. In the 90-day key study, rats administered NEP in the diet at doses of 0, 100, 300 or 1000 mg/kg bw/day show substance-related effects at 300 and 1000 mg/kg bw/day in both sexes of rats and at 100 mg/kg bw/day in males (BASF, 2006). Main target organs are the liver (with increased weight and centrilobular hypertrophy of the hepatocytes; in males at all doses, in females at the high dose) and the kidneys (with increased weight and, in male rats only, at all doses an increase of basophilic tubules and accumulation of hyaline droplets, confirm immunohistochemically as alpha 2µ globuline). The latter finding is considered not relevant to humans as it is due to a male rat specific mechanism. Rats also show lower body weight gain (-18.8 to -39.1% in males, -23,5 to -52.6% in females) and lower food consumption (up to -23.3%) at the mid and high dose. Additionally, grip strength in the forelimbs of male rats is significantly decreased at 300 and 1000 mg/kg bw/day, as is overall motor activity in female rats at 1000 mg/kg bw/day. Sperm examination shows an increased number of sperms with abnormal heads in males receiving 1000 mg/kg bw/day, without associated weight changes or (histo)pathological changes in the testis, or effects on the number of homogenization resistant spermatids, epididymal sperm count and sperm motility. Since the liver effects at the low dose in males are only small and probably more adaptive than adverse in nature, the NOAEL in this study is 100 mg/kg bw/day.

In the sub-acute gavage study, the systemic effects include mild renal and hepatic effects in male, but not female, rats at the highest dose tested of 250 mg/kg bw/day (Saillenfait et al., 2016). Similar to the 90-day study the observed kidney effects in male rats are related to alpha 2µ nephropathy, as confirmed immunohistochemically, and can thus be considered male rat specific. Given further that the liver effects (liver hypertrophy in combination with liver enzyme induction) are probably more adaptive than adverse, the NOAEL in this study is 250 mg/kg bw/day, the highest dose tested.

Additionally, two developmental toxicity studies in rabbits (performed according to Good Laboratory Practice (GLP) and to OECD 414 guidelines; (BASF, 2007a, 2007b)) show an increase in relative liver and kidney weight and enzymatic activity in pregnant animals after exposure to 200/220 mg/kg bw/day (see Annex B – section B.5.3.2.). This could indicate mild liver damage, but no histopathological analysis was performed. In combination, the two studies provide a NOAEL for maternal toxicity (conservatively set) of 60 mg/kg bw/day, based on indications for (mild) liver toxicity at 200/220 mg/kg bw/day. When integrating these rabbit studies with the rat studies described above, the overall NOAEL for repeated dose (liver) effects is 100 mg/kg bw/day.

No dermal studies are available.

No data is available on humans exposed to NEP.

1.1.4.6. Mutagenicity

A number of *in vitro* and *in vivo* studies are available for both DMAC and NEP that assess their mutagenic potential. *In vitro*, DMAC tests negative for gene mutations in bacteria and mammalian cells and for chromosomal aberrations and unscheduled DNA synthesis (UDS) in mammalian cells. *In vivo*, DMAC does not result in chromosomal aberrations and dominant lethal effects in rats following inhalation exposure, in dominant lethal effects in mice following intraperitoneal and dermal administration, or in sex-linked recessive lethality in *Drosophila melanogaster*. NEP tests negative for gene mutations in bacteria and mammalian cells (*in vitro*) and for chromosomal aberrations and micronuclei induction *in vivo* in mice after oral exposure.

The available studies do not indicate DMAC or NEP to have mutagenic/genotoxic potential.

1.1.4.7. Carcinogenicity

DMAC shows no carcinogenic potential when administered up to 350 ppm (1260 mg/m^3) in air to CD-1 mice and Crl:CD® BR rats, and when given in drinking water up to 1000 mg/kg bw/day to Long-Evans rats. In contrast, two Japanese studies show increased incidences of liver tumours in male F344 rats and male and female B6D2F1 mice following inhalation exposure to 450 ppm (1620 mg/m^3) and 300 ppm (1080 mg/m^3), respectively (section B.5.2). There are indications though that these concentrations may have exceeded the maximum tolerated dose in these animals.

No substance specific carcinogenicity studies are performed with NEP, therefore no conclusion about its carcinogenic potential can be made.

1.1.4.8. Reproductive toxicity

DMAC and NEP are both classified as Repr. 1B; H360D and may damage the unborn child. A number of studies are available for the endpoint toxicity to reproduction for DMAC.

1.1.4.8.1. Sexual function & fertility

DMAC
In Table 8, a short summary is presented of the available sexual function and fertility studies with DMAC and the critical effects observed at the LOAEC(L). Unless stated otherwise, these effects are statistically significantly different from control and dose dependent with larger effects at higher dose levels.

Table 8: Summary NOAEC(L)s/LOAEC(L)s for adverse effects on fertility after exposure to DMAC

Species	**NOAEC(L)/LOAEC(L) (mg/m³ or mg/kg bw/day)**	**Critical effect(s) at LOAEC(L)**	**Study (similar as)**	**Study duration**	**Reliability (Klimisch)**	**Reference**
Inhalation						
Rat	1080/-	No statistically significant differences in reproductive indices at any dose tested.	OECD TG 415	10-18 weeks	2	Ferenz and Kennedy Jr (1986)
Rat (males only)	1400/-	No statistically significant differences in reproductive indices at any dose tested.	-	15 weeks	2	Monsanto (1982a); Wang et al. (1989)

In a one-generation inhalation study (Ferenz & Kennedy Jr, 1986) and a fertility inhalation study (Wang et al., 1989) in rats, no effects on the reproductive performance are noted at any dose level tested (NOAEC of 1080 and 1400 mg/m^3, respectively). This may be due to too low doses tested, given that little to no general toxicity is observed in these studies. No reproduction toxicity studies to derive reliable NOAELs/LOAELs for DMAC via oral or dermal route are found.

In repeated dose toxicity studies, there is little evidence for effects on the reproductive organs in rats (unless at very high doses). In mice, some testicular lesions are noted in subacute studies with pubescent and young adult animals, but in long-term studies effects on reproductive organs are absent. No (multi) generation studies in mice are available to show absence or presence of functional impairment of reproduction.

NEP
No (multi) generation studies are available with NEP. In repeated dose toxicity studies no treatment-related effects on the reproductive organs are observed in a 28-day oral study (highest dose 250 mg/kg bw/day; according to OECD TG 407; (Saillenfait et al., 2016)), a 28-day inhalation study (highest dose 400 mg/m^3; according to GLP and OECD TG 412; BASF (2011)), and a 90-day inhalation study (highest dose 200 mg/m^3; according to GLP and OECD TG 413; BASF (2013)). In the latter study sperm motility and total sperm head count are also not affected. In a 90-day oral study, sperm analysis reveals an increased number of sperms with abnormal heads in males at the highest dose (2.0, 2.2, 2.8 and 11.4% in controls, 100, 300 and 1000 mg/kg bw/day groups, respectively; males with >4% abnormal sperm: 0, 1, 2, 8 in controls, low, mid and high dose, respectively), indicative of disrupted sperm maturation at very high dosages (according to GLP and OECD TG 408; BASF (2006)). There are however no histopathological changes in the testis, and the number of homogenization resistant spermatids, epididymal sperm count and sperm motility are not affected. Whether or not the effects observed at very high doses may actually result in functional impairment of reproduction is unclear, in the absence of (multi) generation studies.

1.1.4.8.2. Development

DMAC
In Table 9, a short summary is presented of the available developmental studies with DMAC and the critical effects observed at the LOAEC(L). Unless stated otherwise these effects are

statistically significantly different from control and dose dependent with larger effects at higher dose levels.

Table 9: Summary NOAEC(L)s/LOAEC(L)s for adverse effects on development after exposure to DMAC

Species	**Maternal NOAEC(L)/LOAEC(L) (mg/m^3 or mg/kg bw/day)**	**Developmental NOAEC(L)/LOAEC(L) (mg/m^3 or mg/kg bw/day)**	**Critical effect(s) at LOAEC(L) in foetuses**	**Study (similar as)**	**Reliability (Klimisch)**	**Reference**
Inhalation						
Rat	360/1080 (liver effects)	360/1080	↓ BW (m/f: -10/-8%), ↑ foetuses with ventricular septal defect (3.2% and in 2/10 litters vs. 0% in control, n.s.)	OECD TG 414 (GD 6-19)	2 – key study	Okuda et al. (2006)
Rat	1015/-	360/1015	↓ BW (-6%)	OECD TG 414 (GD 6-15)	2	DuPont (1983a); Solomon et al. (1991)
Rabbit	700/2000 (↓ placental weight)	200/700	↑ foetuses with skeletal variations ↑ (18% and in 7/14 litters vs. 11% and in 4/13 litters in control, n.s.), ↑ foetuses with accessory rib (11% and in 6/14 litters vs. 0% in control)	OECD TG 414 (GD 7-19)	2 – key study	BASF (1989); Klimisch and Hellwig (2000)
Oral						
Rat – gavage	150/400 (↓ food consumption, liver, kidney, placental effects)	65/150	↑ foetuses with malformations (n.s.) resembling the clear increase in malformations observed at the top dose	OECD TG 414 (GD 7-21)	1 – key study	DuPont (1997)
Rat – gavage	160/400 (↓ corrected BW gain)	65/160	↑ foetuses with 25 presacral vertebrae (variation; 8.1% and in 5/23 litters vs. 2.8% and in 2/22 litters, n.s.)	OECD TG 414 (GD 6-19)	2	Johannsen et al. (1987)
Rat – gavage	106/320 (↓ placental weight, vaginal bleeding)	106/320	↑ Dead implants (11.4% vs. 5.7% in control), ↓ BW (-18%), ↑ foetuses with: external malformations (6.8% and in 7/24 litters vs. 0.7% and in 1/22 litter in control), anasarca (3.5% and in 6/24 litters vs. 0% in control), aplasia of tail (1.2% and in 2/24 litters vs. 0% in control), atresia (0.6% and in 1/24 litter vs. 0% in control), malformed vertebrae (8.8% and in 7/24 litters vs. 2.1% and in 2/22 litters in control), hydroureter (1.1% and in 1/24 litter vs. 0% in control)	OECD TG 414 (GD 6-15)	2	BASF (1976b)
Mouse – gavage	240/400 (↓ placental weight)	240/400	↑ foetuses with: exencephalia (2.5% and in 5/24 litters vs. 0% in control), no eye lid closure (1.7% and in 3/24 litters vs. 0% in control), cleft palate (4.8% and in 3/24 litters vs. 1.4% and in 1/23 litter in control), fused ribs (4.1% and in 6/24 litters vs. 0% in control)	OECD TG 414 (GD 6-15)	2	BASF (1976c)

Rabbit – gavage	280/470 (clinical signs, mortality)	94/280	↑ resorptions (35.4% per dam vs. 16.7% in control, n.s.), ↓ BW (-19%), ↑ foetuses with malformations (13% and in 3/9 litters vs. 0% in control, n.s.): cleft palate (10.3% and in 2/9 litters vs. 0% in control), fused ribs or microphthalmia (each 2.6% and in 1/9 litter vs. 0% in control)	OECD TG 414 (GD 6-18)	2	BASF (1976a); Merkle and Zeller (1980)
Rabbit – gavage	280/850 (clinical signs, mortality)	94/280	↑ foetuses with malformations (5% in 2/10 litters vs. 0% in control): exencephaly and renal cyst (3.3% in 1/10 litter vs. 0% in control), cleft palate (1.6% in 1/10 litter vs. 0% in control)	OECD TG 414 (GD 6-18)	2	BASF (1974)
m: male, ↑: increased, ↓: reduced, BW: body weight, GD: gestational day, rel.: relative, n.s.: not statistically significant, TG: test guideline						

A short summary of the key studies is presented below. For a detailed summary of all studies in the table, see Annex B – Section B.5.3.2.

In an inhalation prenatal developmental toxicity study in rats exposed to DMAC (up to 2160 mg/m^3) on GD 6-19 (Okuda et al., 2006), liver effects (13% increased relative weight; 40% increased incidence of swelling of centrilobular hepatocytes vs 0% in the control, n.s.) are observed in dams at the LOAEC (maternal: 1080 mg/m^3). Foetal weight decrease in both sexes at the LOAEC of 1080 mg/m^3 (male/female: -10/-8%) and a (not statistically significant) increased incidence of cardiovascular malformations is noted in the form of ventricular septal defect (3.2% of foetuses and in 2/10 litters vs. 0% in control). At higher dose levels, these effects are observed more severely, indicating a dose response relationship. At 1620/2160 mg/m^3, foetal body weight is further decreased (-20 to -35%) and the incidence of cardiovascular malformations is increased (ventricular septal defect (11% in 6/10 litters; 45% in 8/8 litters, respectively) and persistent truncus arteriosus is observed (3.2% in 2/10 litters; 24% in 7/8 litters vs. 0% in control, respectively). Although a lower number of rats (n=10) is used in this study than required, this study is well-documented, and the clear developmental effects make this the key study. It is noted that no such effects are observed in a second developmental study in rats (DuPont, 1983a; Solomon et al., 1991), but in that study the concentrations tested are lower (0-1015 mg/m^3), during a shorter period (from GD 6-15).

In rabbits, placental weight (-18%) is statistically significantly decreased and substance-related at 2000 mg/m^3 in animals exposed to DMAC via inhalation in a prenatal developmental toxicity study (BASF, 1989; Klimisch & Hellwig, 2000). No other signs of maternal toxicity are noted. A maternal NOAEC of 700 mg/m^3 is derived based on decreased placental weight at 2000 mg/m^3. Foetal body weight is statistically significantly reduced and substance-related at 2000 mg/m^3. At LOAEC (700 mg/m^3), increased incidence of skeletal variations (18% and in 7/14 litters vs. 11% and in 4/13 litters in control, n.s.) are noted, in particular accessory ribs (11% of foetuses in 6/14 litters vs. 0% in control, n.s.). At the highest dose, increased incidence of soft tissue malformations (e.g. septal defects) and variations (separated origin on the carotids) are observed.

For DMAC exposure via the oral route, a prenatal developmental toxicity study in rats from DuPont (1997) is considered a key study. At the maternal LOAEL (400 mg/kg bw/day) reduced food consumption (-13%), white or tan outer edges of placentas (56% vs. 4% in control), and effects in liver (9% increased relative weight; 16% increased incidence of mitotic figures vs. 0% in control) and kidney (17% increased relative weight) are observed. Foetal effects noted at the LOAEL of 150 mg/kg bw/day are small and mostly not statistically significant different compared to control. Foetal effects observed include: lower body weight (-4%),

foetal malformations (2.5% of foetuses in 2/25 litters vs. 0.6% in 2/24 litters in control, n.s.) including distended brain ventricles (toxicological relevance unclear), as well as naris atresia, heart and vessel malformations, cleft palate, macroglossia, micrognathia, and synotia. At the high dose level (400 mg/kg bw/day), the number of live foetuses decrease (10.4 foetuses/litter vs. 14.1 in control) and resorptions increase (early/late resorptions: 2.8/0.3 resorptions/litter vs. 0.4/0 in control). Furthermore, foetal body weight is further decreased (-34%) and the incidence of malformations increased (sum-incidence: 69% of foetuses in 24/24 litters), as was the incidence of variations. The non-significant increase in malformations observed at 150 mg/kg bw/day might represent the bottom end of the dose-effect curve, as the type of foetal malformations are similar between the mid and high dose groups. Other oral prenatal developmental toxicity studies in rats show similar effects, with in one study the increase in variations already seen at 160 mg/kg bw/day. In mice and rabbits, treatment with DMAC result in comparable developmental effects, but reported LOAELs are typically slightly higher (maternal: 400-3000 mg/kg bw; foetal: 280-400 mg/kg bw).

Foetal developmental toxicity is observed in several oral studies at dose levels without, or limited maternal toxicity (such as increase in relative liver weight or lower body weight (gain)). Interestingly, the maternal LOAELs are higher as compared to the foetal NOAELs. There is also similarity in the type of developmental effects observed in most studies with malformation of the heart and blood vessels as the most typical effect, especially after a longer exposure to DMAC during gestation. In rats, the overall NOAEC/NOAEL is 360 mg/m^3 and 65 mg/kg bw (respectively) for developmental toxicity based on the inhalation and oral studies. The slightly higher NOAEL of 106 mg/kg bw/day for developmental toxicity reported in BASF (1976b) is considered less adequate as a shorter exposure window (GD 6-15 versus GD 7-21 in BASF (1976b) and DuPont (1997), respectively) is used. In rabbits, the overall NOAEC/NOAEL for developmental toxicity is 200 mg/m^3 and 94 mg/kg bw, based on inhalation and oral studies, respectively. For mice, there is only an oral NOAEL (240 mg/kg bw) available.

NEP

A short summary of the key studies is presented below. For a detailed summary of all key studies, see Annex B – Section B.5.3.2.

Table 10: Summary NOAECLs/LOAELs for adverse effects on development after exposure to NEP

Species	**Maternal NOAEL/ LOAEL (mg/kg bw/day)**	**Developmental NOAEL/LOAEL (mg/kg bw/day**	**Critical effect(s) at LOAEL in foetuses**	**Study (similar as)**	**Reliability (Klimisch)/key study**	**Reference**
Oral						
Rat – gavage	750/-	50/250	↓ Foetal BW (-7%), foetuses with skeletal variations: ↑ supernumerary ribs (32.2% vs. 17.9% in control).	OECD TG 414	1 – key study	Saillenfait et al. (2007)
Rabbit – gavage	60/200	60/200	↑ Litters with malformations (48% vs. 17% in control), ↑ litters with skeletal malformations (35% vs. 8.7% in control).	OECD TG 414	1 – key study	BASF (2007a, 2007b)
Dermal						
Rat	800/-	400/800	↓ Foetal BW (-11%), ↑ foetuses with skeletal variations (100% vs. 96.7% in control): incomplete ossification of basisphenoid (26% vs. 7.7% in control), unilateral ossification of sternebra (8.3% vs. 0.8% in control) and supernumerary	OECD TG 414	1 – key study	BASF (2005)

			14th rib (16.6% vs. 4.4% in control).			
Rabbit	1000/-	300/1000	↑ Foetuses with cardiovascular malformations altogether (3.5% vs. 0% in control), absent subclavian (0.7% vs. 0% in control), ventricular septum defect (1.4% vs. 0% in control), dextrocardia (2.1% vs. 0% in control).	OECD TG 414	1 – key study	BASF (2010)
m: male, ↑: increased, ↓: reduced, BW: body weight, GD: gestational day, rel.: relative, n.s.: not statistically significant, [1]: no statistical analysis reported, TG: test guideline						

Four guideline prenatal developmental toxicity studies are available, two administered dermally and two orally, one with rats and one with rabbits for each administration route.

In the oral rat study, at the higher dose levels of 500/750 mg/kg bw/day, an increase of implantation loss (20.8%/88.3% vs. 9.1% in control, respectively) and external malformations (30.4%/55.6% vs. 0% in control, respectively), skeletal malformations (39.1%/57.1% vs. 0% in control, respectively) and visceral malformations (22.7%/50.0% vs. 5.3% in control, respectively) and/or variations (100%/100% vs. 73.7% in control, respectively) is observed (Saillenfait et al., 2007). The visceral malformations induced by NEP are rare and severe malformations observed above historical control levels and with a statistical significance. These included cleft palate and anal atresia which cannot be attributed to the mild maternal toxicity in the form of reduced food consumption and body weight gain. A significant and dose-related decrease in foetal weight is also observed at 250 mg/kg and higher doses (-7, -28 and -42% respectively). The corrected maternal body weight on GD 21 (-3% for both 500 and 750 mg/kg bw/day) and corrected body weight gain (-17% and -11%, for 500 and 750 mg/kg bw/day respectively) is not statistically significantly lower at any dose level. Therefore, the oral NOAEL for maternal toxicity is considered 750 mg/kg bw/day based on an absence of adverse effects. The NOAEL for developmental toxicity is 50 mg/kg bw/day based on an increase in skeletal variations and reduced foetal weight.

In the oral study with rabbits, NEP induces an increase in relative liver and kidney weight and liver enzymatic activity at 200 mg/kg bw/day (BASF, 2007a, 2007b). This could possibly indicate mild liver damage, but no histopathological analysis was performed. NEP induces an increased incidence of litters with foetuses having malformations (48% vs. 17% in control) at the foetal LOAEL of 200 mg/ kg bw/day. It consists mainly of skeletal malformations (35% vs. 8.7% in control), but also few rare external malformations of the neural tube and of the cardiovascular system (including the rare absent subclavian) are reported. In the second study, the highest dose of 220 mg/kg bw/day induces decreased foetal body weight (-15%), increased incidence of litters with foetuses with visceral (54% vs. 24% in control) and skeletal (38% vs. 16% in control) malformations and increased skeletal variations. The NOAEL for maternal toxicity is conservatively set at 60 mg/kg bw/day, based on indications for (mild) liver toxicity. The oral NOAEL for developmental toxicity is set at 60 mg/kg bw/day based on an increase in skeletal malformations.

In the dermal study in rats, NEP has no significant effect on post-implantation loss and incidence of malformations (BASF, 2005). A decreased foetal weight (-11%) is observed at 800 mg/kg bw/day, as well as an increased incidence of some skeletal variations. Although these effects are seen in the presence of decreased maternal corrected weight and food consumption, it is noted that the decrease in foetal weight is greater than the corresponding decrease of corrected maternal weight. The latter is only slightly decreased (up to 5%) at GD 20, which is not considered adverse. Hence the NOAEL for maternal toxicity is 800 mg/kg bw/day based on the absence of adverse effects. The NOAEL for developmental toxicity is set at 400 mg/kg bw/day, based on reduced foetal weight and an increase of some skeletal variations.

In the dermal rabbit study, a few rare cardiovascular malformations are observed in the form of absent subclavian, membranous ventricular septum defect and dextrocardia which are above historical control data in the high dose foetuses (BASF, 2010). Similar cardiovascular effects are also observed in the oral study. The dermal NOAEL for maternal toxicity is considered to be 1000 mg/kg bw/day in absence of adverse effects. The dermal NOAEL for developmental toxicity is set at 300 mg/kg bw/day based on cardiovascular malformations.

1.1.4.9. BMD analysis

As alternative for the NOAEL approach, the benchmark dose (BMD) approach is used to determine the Point of Departure (PoD) for setting DNEL levels. The BMD approach is a scientifically more advanced method (ECHA, 2012b; EFSA, 2017) in comparison with the NOAEL approach. In the BMD approach, the complete set of dose-response data are used to estimate the shape of the dose-response relationship of endpoints. The BMD is reported by its (90%) confidence interval (CI), which ranges from the lower to the upper confidence limits, the BMDL and BMDU respectively. More information on the BMD analyses and used method can be found in Annex B.5.5. Detailed results of the BMD analyses are described in Appendix I.

The Dossier Submitter considers for systemic effects the following benchmark responses (BMRs): 10% change in organ or body weight and 10% extra risk in observed histopathology (Table 11). The Dossier Submitter considers changes in body weight (decrease) and relative organ weight (more specifically, the liver) to be adverse >10% change without the need for an additional assessment factor. It is recognized that changes in relative liver weight in absence of histopathological liver damage and relevant clinical chemistry changes can be considered more adaptive in nature than adverse. However, such interpretation is difficult within a BMD analyses with different BMDLs for liver effects, therefore a BMR of 10% change in relative liver weight is taken as adverse. For liver histopathology the default 10% extra risk is considered appropriate.

For local effects the default 10% extra risk is considered appropriate for histopathology related to irritative effects in the nasal cavity.

For developmental toxicity a decrease >5% in foetal body weight is considered adverse in accordance with the Committee for Risk Assessment (RAC) view in the RAC and Scientific Committee on Occupational Exposure Limit Values (SCOEL) Joint Opinion for NMP (RAC-SCOEL, 2016). The litter effect is taken into consideration for foetal body weight if individual data is available. In addition, the Dossier Submitter considers a 10% extra risk as BMR for foetal variations and a 1% extra risk as BMR for foetal malformations and post-implantation loss appropriate, the latter due to its adversity.

Table 11: Specifications of the BMR per endpoint used in BMD analyses in this dossier

Endpoint	**BMR**
Relative organ weight (liver)	10% change
Histopathology (liver)	10% extra risk
Histopathology (nasal cavity)	10% extra risk
Body weight	10% change
Foetal body weight	5% change
Foetal malformations	1% extra risk
Foetal variations	10% extra risk
Post-implantation loss	1% extra risk

1.1.4.9.1. BMD analysis DMAC

Repeated dose toxicity inhalation

The liver is considered the primary target organ for repeated dose toxicity of DMAC after inhalation. BMD analyses are done on the key study in rats and mice (chronic) for the main liver effects for both species and sexes (DuPont, 1994; Malley et al., 1995). In Table 12 an overview is presented of the BMD intervals derived for the various liver effects that show a dose response in the BMD analyses, unless stated otherwise. When possible, data from both rat and mouse studies are used per endpoint in a combined analysis with species as a covariate maximising the use of all available data and narrowing the confidence intervals.

Table 12: BMDL and BMDU derived for inhalation repeated dose toxicity for DMAC. BMDL/BMDU ratios ≥10 are presented in italics

Endpoint	**BMR**	**Sub-group**	**BMDL** (mg/m^3)	**BMDU** (mg/m^3)	**Reference**
Relative liver weight (terminal sacrifice)	10%	Rat f	480	1100	DuPont (1994); Malley et al. (1995)
		Rat m	470	1200	
		Mouse f	490	1100	
		Mouse m	480	1100	
Hepatic focal cystic degeneration	10%	Rat f	*1390*	*Inf*	
		Rat m	*2.0*	*810*	
Biliary hyperplasia	10%	Rat m/f	No significant dose-response		
Hepatic Kupffer cell pigment accumulation	10%	Rat f	270	1200	
		Rat m	180	600	
		Mouse f	*140*	*3800*	
		Mouse m	65	450	
Hepatic peliosis	10%	Rat m/f	No significant dose-response		
Centrilobular hepatocellular hypertrophy	10%	Mouse f	*1300*	*20000*	
		Mouse m	1000	1200	
Hepatic single cell necrosis	10%	Mouse f	660	1800	
		Mouse m	490	3000	

m=male
f=female

As can be seen from Table 12, some endpoints $BMDL_{10}$'s are not suitable as PoD. These are biliary hyperplasia and hepatic peliosis in rats (no dose response found), and the $BMDL_{10}$'s for hepatic focal cystic degeneration in rats, and for hepatic Kupffer cell pigmentation and centrilobular hepatocellular hypertrophy in female mice (BMDL-BMDU intervals too large). Of the $BMDL_{10}$'s that are suitable, the ones for Kupffer cell pigmentation are the lowest, both in rats and in mice. Whilst noting that the grading for this effect is generally minimal, together with the focal cystic degeneration in rats (trend seen, but interval too wide) the single cell necrosis in mice is considered suggestive of (slight) hepatotoxicity. The Dossier Submitter therefore considers the overall lowest $BMDL_{10}$ of 65 mg/m^3 for Kupffer cell pigmentation in male mice as most relevant PoD for DNEL derivation for the repeated dose toxicity of DMAC after inhalation.

Since local effects are only observed in one two week study (and one six month study by Horn (1961) of low reliability according the Dossier Submitter) but not in other inhalation studies (including the combined chronic toxicity and carcinogenicity studies) or in humans, no local DNEL are derived for DMAC.

Developmental toxicity inhalation

For developmental toxicity following exposure to DMAC via inhalation, reduced foetal body weight and increased incidence of malformations (visceral, skeletal and external) in rats and rabbits, and increased variations (skeletal and visceral) in rabbits are endpoints examined for a BMD analyses (Table 13). When looking at individual malformations, a clear increase in cardiovascular malformations is observed in the rat after inhalation and oral exposure (DuPont, 1997; Okuda et al., 2006). Therefore, it is also considered appropriate to analyse the incidence of cardiovascular malformations in the rabbit in addition to total visceral malformations. When possible, data from both rat and rabbit studies are used per endpoint in combined analyses with species as a covariate maximising the use of all available data and narrowing the confidence intervals.

Table 13: BMDL and BMDU derived for inhalation developmental toxicity for DMAC

Endpoint	BMR	Sub-group	BMDL (mg/m^3)	BMDU (mg/m^3)	Reference
Foetal body weight	5%	Rat[a]	730	900	Okuda et al. (2006)
		Rabbit[b]	1400	1900	BASF (1989); Klimisch and Hellwig (2000)
Foetal external malformations	1%	Rat	1800	2200	Okuda et al. (2006)
		Rabbit	1700	2100	BASF (1989); Klimisch and Hellwig (2000)
Foetal visceral malformations	1%	Rat	760	1300	Okuda et al. (2006)
		Rabbit	280	2400	BASF (1989); Klimisch and Hellwig (2000)
Foetal cardiovascular malformation	1%	Rat	750	1300	Okuda et al. (2006)
		Rabbit	550	1900	BASF (1989); Klimisch and Hellwig (2000)
Foetal skeletal malformations	1%	Rat	340	1600	Okuda et al. (2006)
		Rabbit	320	1900	BASF (1989); Klimisch and Hellwig (2000)
Foetal visceral variations	10%	Rabbit	320	1400	BASF (1989); Klimisch and Hellwig (2000)
Foetal skeletal variations	10%	Rabbit	430	1200	BASF (1989); Klimisch and Hellwig (2000)

[a] exposure on GD 6-19
[b] exposure on GD 7-19

Regarding foetal body weight, the $BMDL_5$ in rats (730 mg/m^3) is lower than the $BMDL_5$ in rabbits (1400 mg/m^3). However, as can be seen from Table 13, the foetal malformations and variations generally result in lower BMDL-values. The overall lowest BMDL derived for these effects is the $BMDL_1$ of 280 mg/m^3 for visceral malformations in rabbits. However, most of the visceral malformations in rabbits, and all in rats, consist of cardiovascular abnormalities, such as septal defect and truncus arteriosus communis, with an associated $BMDL_1$ in rabbits of 550 mg/m^3. The non-cardiovascular visceral abnormalities in rabbits do not show a dose-response. Therefore, the $BMLD_1$ for skeletal malformations and the $BMDL_{10}$ for visceral variations in rabbits (both 320 mg/m^3) provide the overall lowest BMDLs. Supported by a similar $BMDL_1$ for skeletal malformations in rats (340 mg/m^3), the value of 320 mg/m^3 is taken as PoD for DNEL derivation for the developmental toxicity of DMAC after inhalation.

Repeated dose toxicity dermal

In absence of reliable dermal repeated dose toxicity studies for DMAC, the key oral two year study in rats by Monsanto (Monsanto, 1980, 1993) is taken for BMD analyses on the observed increased relative liver weight and histopathological changes in the liver in this study (see Table 14). The Dossier Submitter considers the lowest oral $BMDL_{10}$ of 19 mg/kg bw/day in male rats (lowest BMDL) a suitable PoD to use for route-to-route extrapolation and subsequent derivation of a dermal DNEL for the repeated dose toxicity of DMAC.

Table 14: BMDL and BMDU derived for oral repeated dose toxicity for DMAC

Endpoint[a]	**BMR**	**Sub-group**	**BMDL** (mg/kg bw/day)	**BMDU** (mg/kg bw/day)	**Reference**
Relative liver weight	10%	Rat f	53	310	Monsanto (1980)
		Rat m	19	97	
Hypertrophy/hyperplasia	10%	Rat f	220	260	Monsanto (1993)
		Rat m	220	260	
Vesiculated/vacuolated hepatocellular cytoplasm	10%	Rat f	47	170	
		Rat m	48	180	
Hepatocellular necrosis	10%	Rat f	430	2800	
		Rat m	120	570	
Intracytoplasmic brown pigment	10%	Rat f	610	970	
		Rat m	350	590	

[a] Endpoints assessed of all animals at terminal sacrifice
m=male
f=female

Developmental toxicity dermal

In absence of reliable dermal developmental toxicity studies for DMAC, the oral prenatal developmental toxicity study in rats performed by DuPont (1997) is considered the best available study for the BMD analyses, taking into account effects of DMAC exposure on foetal body weight, external, cardiovascular, head and skeletal malformations (see Table 15). Besides malformations of the heart and/or greater vessels no other visceral malformations are observed. Incidences in variations, mostly skeletal, are increased in the highest dose. This incidence, reported in the summary tables as mean percent affected per litter, is however not suitable for BMD analyses.

Table 15: BMDL and BMDU derived for oral developmental toxicity for DMAC

Endpoint	**BMR**	**Sub-group**	**BMDL** (mg/kg bw/day)	**BMDU** (mg/kg bw/day)	**Reference**
Foetal body weight	5%	Rat[a]	120	190	DuPont (1997)
Foetal external malformations	1%		170	310	
Foetal cardiovascular malformation			140	290	
Foetal head malformation			92	150	
Foetal skeletal malformation			220	370	

[a] exposure on GD 7-21

The Dossier Submitter considers the overall lowest $BMDL_1$ of 92 mg/kg bw/day for head malformations (distended lateral brain ventricles and naris atresia) a suitable PoD to use for route-to-route extrapolation and subsequent derivation of a dermal DNEL for the developmental toxicity of DMAC.

1.1.4.9.2. BMD analysis NEP

Repeated dose toxicity inhalation (local effects)

Local effects are observed in rats after repeated exposure to NEP via inhalation. BMD analyses are performed on the key studies in rats for local effects for both sexes (BASF, 2011, 2013). In Table 16, an overview is presented of the BMD intervals derived for degeneration/regeneration of the olfactory epithelium at various locations in the respiratory tract (level I-IV) of the rats that showed a dose response in the BMD analyses. Initially both sex and exposure (resulting in four subgroups) are included as covariates in the BMD

analyses. For location level II and III it appears that the dose response of some male and female groups is the same. In that case these subgroups are analysed together with only exposure as covariate to improve the precision of the BMD estimate.

Table 16: BMDL and BMDU derived for local repeated dose toxicity for NEP after inhalation. BMDL/BMDU ratios ≥10 are presented in italics

Endpoint	BMR	Sub-group	BMDL (mg/m^3)	BMDU (mg/m^3)	Reference
Nasal cavity (location level I) Degeneration/ regeneration, olfactory epithelium	10%	Rat f 28	78	160	BASF (2011, 2013)
		Rat f 90	110	200	
		Rat m 28	83	150	
		Rat m 90	*500*	*inf*	
Nasal cavity (location level II) Degeneration/ regeneration, olfactory epithelium	10%	Rat mf 28	57	120	
		Rat mf 90	120	190	
Nasal cavity (location level III) Degeneration/ regeneration, olfactory epithelium	10%	Rat f 90	89	110	
		Rat m 90	170	190	
		Rat mf 28	74	120	
Nasal cavity (location level IV) Degeneration/ regeneration, olfactory epithelium	10%	Rat f 28	77	120	
		Rat f 90	78	120	
		Rat m 28	78	120	
		Rat m 90	78	120	

m=male
f=female
28 = 28-day exposure
90 = 90-day exposure

The occurrence of degeneration/regeneration of the olfactory epithelium is considered a consequence of irritant effects of NEP and should be regarded as an adverse effect. The difference in the exposure duration of the 28-day and 90-day study is not taken into account, since local effects are not primarily driven by exposure time but by exposure concentration. This is confirmed by the observation that for most histopathological effects, the BMDLs are in the same range for both studies. The Dossier Submitter therefore considers the overall lowest $BMDL_{10}$ of 57 mg/m^3 as most relevant PoD for DNEL derivation for the local toxicity of NEP after inhalation.

Repeated dose toxicity inhalation (systemic effects)
Two repeated dose toxicity inhalation studies with rats are available (BASF, 2011, 2013). No BMD analysis is performed for systemic endpoints since no adverse systemic effects are observed in the highest dose. Therefore, as a conservative approach the highest dose tested in the 90-day study (200 mg/m^3) is taken as PoD.

Developmental toxicity inhalation
In absence of inhalation developmental toxicity studies for NEP, the key oral studies in rats (Saillenfait et al., 2007) and rabbits (BASF, 2007a, 2007b) for developmental toxicity are taken for BMD analyses on the observed post-implantation loss, reduced foetal body weight and increased incidences of malformations (visceral, skeletal and external) and skeletal variations (Table 17). Of note is that the visceral malformations in rats and rabbits consists mainly of cardiovascular malformations, similar to the closely related substance NMP (ECHA, 2013a). Therefore, it is considered appropriate to analyse the incidence of cardiovascular malformations in rat and the rabbit in addition to total visceral malformations. When possible,

data from both rat and rabbit studies are used per endpoint in a combined analyses with species as a covariate maximising the use of all available data and narrowing the confidence intervals. The derived BMDL is used for route-to-route extrapolation to derive an inhalation DNEL.

Table 17: BMDL and BMDU derived for oral developmental toxicity for NEP. BMDL/BMDU ratios ≥10 are presented in italics.

Endpoint	BMR	Sub-group	BMDL (mg/kg bw/day)	BMDU (mg/kg bw/day)	Reference
Foetal body weight	5%	Rat	210	230	Saillenfait et al. (2007)
		Rabbit	160	310	BASF (2007a)
		Rabbit	130	160	BASF (2007b)
Foetal external malformations	1%	Rat	260	510	Saillenfait et al. (2007)
		Rabbit	*160*	*2500*	BASF (2007a)
		Rabbit	160	540	BASF (2007b)
Foetal visceral malformations	1%	Rat	150	510	Saillenfait et al. (2007)
		Rabbit	*80*	*5000*	BASF (2007a)
		Rabbit	*22*	*220*	BASF (2007b)
Foetal cardiovascular malformations	1%	Rat	210	540	Saillenfait et al. (2007)
		Rabbit	*130*	*25000*	BASF (2007a)
		Rabbit	38	210	BASF (2007b)
Foetal skeletal malformations	1%	Rat	190	470	Saillenfait et al. (2007)
		Rabbit	58	190	BASF (2007a)
		Rabbit	41	190	BASF (2007b)
Foetal skeletal variations	10%	Rat	160	270	Saillenfait et al. (2007)
		Rabbit	*130*	*218000*	BASF (2007a)
		Rabbit	82	180	BASF (2007b)
Post-implantation loss	1%	Rat	270	360	Saillenfait et al. (2007)
		Rabbit	170	370	BASF (2007a)
		Rabbit	170	360	BASF (2007b)

As can be seen from Table 17, the overall lowest BMDL is derived for visceral malformations in rabbits ($BMDL_1$ of 22 mg/kg bw/day). However, the BMDL/BMDU ratio for this BMDL is at the cut-off (10) of what is considered unwarranted for a PoD. When only taking the cardiovascular malformations into account, which make up the main part of the visceral malformations, the BMDL/BMDU ratio improves resulting in a $BMDL_1$ of 38 mg/kg bw/day. Supported by a similar $BMDL_1$ for skeletal malformations in rabbits (41 mg/kg bw/day), the value of 38 mg/kg bw/day is taken as PoD to use for route-to-route extrapolation and subsequent derivation of an inhalation DNEL for the developmental toxicity of NEP.

Repeated dose toxicity dermal

In absence of dermal repeated dose toxicity studies for NEP, the key oral 90-day study in rats (BASF, 2006) is taken for BMD analyses on the observed body weight decrease and increased relative liver weight in this study (see Table 18). The available data for liver histopathology (centrilobular hypertrophy of hepatocytes) is not suitable for BMD analysis, as in all the dose groups where this effect is seen it occurrs in 100% of the animals. The grip strength data is not selected for BMD analyses, because the observed decrease in grip strength in the male forelimbs is probably secondary to the decreased body weight (gain).

Table 18: BMDL and BMDU derived for oral repeated dose toxicity for NEP. BMDL/BMDU ratios ≥10 are presented in italics.

Endpoint	BMR	Sub-group	BMDL (mg/kg bw/day)	BMDU (mg/kg bw/day)	Reference
Body weight	10%	Rat f	270	620	BASF (2006)
		Rat m	260	670	
Relative liver weight	10%	Rat f	300	530	
		Rat m	170	330	

m=male
f=female

The Dossier Submitter considers the lowest $BMDL_{10}$ of 170 mg/kg bw/day for relative liver weight after oral exposure a suitable PoD to use for route-to-route extrapolation and subsequent derivation of a dermal DNEL for the repeated dose toxicity of NEP.

Developmental toxicity dermal

For developmental toxicity following dermal exposure to NEP two dermal developmental toxicity studies are available (BASF, 2005, 2010). Reduced foetal body weight, post-implantation loss, increased incidence of malformations (external, skeletal) and increases incidence in skeletal variation in rats and rabbits and visceral malformations in rabbits are endpoints examined by the BMD analyses (Table 19). It is considered appropriate to analyse the incidence of cardiovascular malformations in rabbits in addition to total visceral malformations as cardiovascular malformations occurred in both rats and rabbits after inhalatory exposure to NEP. No visceral malformations are observed in the dermal rat study (BASF, 2005). When possible, data from both rat and rabbit studies are used per endpoint in a combined analyses with species as a covariate maximising the use of all available data and narrowing the confidence intervals.

Table 19: BMDL and BMDU derived for dermal developmental toxicity for NEP. BMDL/BMDU ratios ≥10 are presented in italics.

Endpoint	BMR	Sub-group	BMDL (mg/kg bw/day)	BMDU (mg/kg bw/day)	Reference
Foetal body weight	5%	Rat	330	510	BASF (2005)
		Rabbit	830	1700	BASF (2010)
Post-implantation loss	1%	Rat	*9.2*	*inf*	BASF (2005)
		Rabbit	*0.00078*	*880*	BASF (2010)
Foetal external malformations	1%	Rat Rabbit	No significant dose-response		BASF (2005, 2010)
Foetal skeletal malformations	1%	Rat Rabbit	No significant dose-response		BASF (2005, 2010)
Foetal visceral malformations	1%	Rabbit	No significant dose-response		BASF (2010)
Foetal cardiovascular malformations	1%	Rabbit	*0.00023*	*910*	BASF (2010)
Foetal skeletal variation	10%	Rat Rabbit	No significant dose-response		BASF (2005, 2010)

As can be seen from Table 19, only foetal body weight results in a suitable PoD, with the $BMDL_5$ in rats (330 mg/kg bw/day) being lower than the $BMDL_5$ in rabbits (830 mg/kg bw/day). The lowest BMDL of 330 mg/kg bw/day is therefore taken as PoD for DNEL derivation for developmental toxicity of NEP after dermal exposure.

1.1.4.10. DNEL setting

Previously derived DNELs

SCOEL derived an indicative OEL of 10 ppm (36 mg/m^3) for DMAC in 1994, based on a limited dataset available at the time. This indicative OEL is used by most registrants in their registration dossiers and CSR as the inhalation DNEL, which is a possibility according to the ECHA Guidance Chapter R.8.2-7 (ECHA, 2012b). The OEL is based on the (slight) respiratory tract irritation observed in the inhalation study by Horn (1961) (of low reliability according the Dossier Submitter) with rats and dogs at 40 ppm (145 mg/m^3) (SCOEL, 1994). In absence of a NOAEC, an overall uncertainty factor of five was applied to the LOAEC of 40 ppm (145 mg/m^3). Taking into account the preferred value approach and the minimal nature of the effects, an OEL of 10 ppm (36 mg/m^3) was subsequently determined. Most member states have set an OEL equal to the SCOEL-derived indicative OEL (IOEL).

Recently, the German Maximum Workplace Concentration (MAK) Commission established a MAK value of five ppm (18 mg/m^3) derived from a NOAEC of 25 ppm (90 mg/m^3) for histological changes in the liver of male rats by Malley et al. (1995), an assessment factor of four (factor two for extrapolation animal study data to human and factor two for the higher respiratory volume of humans at the workplace compared to animals at rest (Hartwig & MAK Commission)) and the preferred value approach. France set a lower OEL of two ppm (7.2 mg/m^3) in 2006, based on a LOAEL of 200 ppm (700 mg/m^3) for skeletal variations in rabbits by Klimisch and Hellwig (2000) and an assessment factor of 100 (factor 10 for severity of adverse effects and factor 10 for animal to human extrapolation; (2003)). SCOEL did not derive an OEL for NEP.

Overall DNELs DMAC

A summary of the derived DNELs for DMAC by the Dossier Submitter is given in Table 20.

In conclusion, in an approach combining human and animal data, the Dossier Submitter proposes a systemic long-term inhalation DNEL of 13 mg/m^3 considering the DNEL of 22 mg/m^3 based on a NOAEC of 21.7 mg/m^3 in the Antoniou et al. (2021) study for liver effects in humans and the DNEL of 13 mg/m^3 based on a $BMDL_1$ for foetal skeletal malformations and a $BMDL_{10}$ for foetal visceral variations in the rabbit developmental study (BASF, 1989; Klimisch & Hellwig, 2000). The inhalation DNEL of 22 mg/m^3 based on human data is considered more relevant than the animal derived inhalation DNEL of 2.6 mg/m^3 for liver effects because the correct type of effects are assessed in the relevant population (workers) at relevant exposure conditions (eight hours per day, five days a week).

A systemic long-term dermal DNEL of 0.53 mg/kg bw/day for workers is derived based on the animal toxicity data and is protective against liver effects after repeated exposure to DMAC and developmental toxicity (head malformations).

Table 20: DNEL derivation for DMAC for workers

DNEL (endpoint)	BMDL, species	Type of study	BMR and type of effect	Correction for differences in exposure conditions	Corrected BMDL	Assessment factors	Resulting DNEL	Reference
Inhalation								
Repeated dose toxicity	65 mg/m^3, mouse	Combined chronic toxicity and	10% increased incidence of hepatic Kupffer cell pigmentation	6/8 6.7/10	32.7 mg/m^3	1 – (AS) 2.5 – (RD) 5 – (IS) Total: 12.5	2.6 mg/m^3	DuPont (1994); Malley et al. (1995)

		carcinogenicity study – life time						
Repeated dose toxicity	21.7 mg/m^3, human (workers)	Retrospective epidemiological study	No effect level based on blood liver function test (ALT levels)	-	-	-	22 mg/m^3	Antoniou et al. (2021)
Developmental toxicity	320 mg/m^3 rabbit	PNDT – GD 7-19	1% increased incidence of skeletal malformations and 10% increased incidence of visceral variations	6/8 6.7/10	161 mg/m^3	1 – (AS) 2.5 – (RD) 5 – (IS) Total: 12.5	13 mg/m^3	BASF (1989); Klimisch and Hellwig (2000)
Dermal								
Repeated dose toxicity	19 mg/kg bw/day, rat	Combined chronic toxicity and carcinogenicity study, oral drinking water– 2 years	10% increased relative liver weight	7/5 100% uptake assumed	26.6 mg/kg bw/day	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	0.53 mg/kg bw/day	Monsanto (1980, 1990, 1993)
Developmental toxicity	92 mg/kg bw/day, rat	PNDT oral gavage– GD 7-21	1% increased incidence of head malformations	100% uptake assumed	92 mg/kg bw/day	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	1.8 mg/kg bw/day	DuPont (1997)
AS: allometric scaling, GD: gestational day, IS: intraspecies factor, PNDT: prenatal developmental toxicity study, RD: remaining (toxicokinetic/dynamic) differences, ALT: alanine aminotransferase								

Biological limit value DMAC

Urinary excretion of NMAC could serve as biological limit value (BLV) for DMAC. Interpolation of the DNEL of 13 mg/m^3 DMAC and assuming the non-linear relationship described by Kennedy G.L (1990), used in the recent Biological Tolerance Value (BAT) re-evaluation Walter et al. (2020), leads to 23 mg NMAC/L urine after end of shift. Interpolation of the DNEL of 13 mg/m^3 DMAC and assuming a linear relationship between the log-transformed DMAC concentration (in ppm) and log-transformed NMAC concentration (in mg NMAC/g creatinine), as observed in Spies et al. (1995a), leads to a mean value of 25 mg NMAC/g creatinine. In addition, Nomiyama et al. (2000) exposed twelve healthy male volunteers for 4 hours to 6.1 ppm for dermal (whole body with respiratory mask) and for inhalation exposure (nose-only). The mean NMAC value after DMAC exposure is 11.2 mg NMAC/g creatinine (6.9 - 20.1 mg/g). Although not clearly stated in the manuscript, the mean value probably represents the total creatinine-adjusted NMAC concentration by adding the two values from the dermal and inhalation experiments. A four-hour exposure to 6.1 ppm results in a dose comparable to eight hours exposure to 3.05 ppm (equivalent to 11 mg/m^3), slightly below the DNEL of 13 mg/m^3.

In the determination of a BLV, both Spies et al. (1995a) and Nomiyama et al. (2000), suggest a lower value than the mean NMAC-value as potential BLV to avoid misclassification of a large

percentage of individuals as underexposed. Based on their datasets, Spies et al. (1995a) suggests to use approximately the 80th percentile (corresponding to a factor 1.84 from the mean) and (Nomiyama et al., 2000) the 90th percentile (corresponding to a factor 1.5 from the mean).

Overall, the Dossier Submitter prefers a creatinine-adjusted BLV value and considers the relation observed in (Spies et al., 1995a) sufficient (93 workers; 302 datapoints; r^2 0.54) to calculate the expected mean NMAC-value (mg/g creatinine) corresponding to the DNEL of 13 mg/m^3. Using the factors suggested by Spies et al. (1995a) and Nomiyama et al. (2000) to account for the inter and intra individual variation, the BLV would result in 14 and 17 mg NMAC/g creatinine, respectively. Using a pragmatic approach, the Dossier Submitter proposes a BLV of 15 mg NMAC/g creatinine corresponding to the DNEL of 13 mg/m^3. Considering the observed biological half-lives in Nomiyama et al. (2000) of urinary NMAC of 9.0 ± 1.4 hours and 5.6 ± 1.3 hours via skin and lung (respectively), post shift samples should be taken.

Overall DNELs NEP

A summary of the derived DNELs for NEP by the Dossier Submitter is given in

Table 21. In conclusion, a systemic long-term inhalation DNEL of 4.0 mg/m^3 and a systemic long-term dermal DNEL of 2.4 mg/kg bw/day are proposed for workers by the Dossier Submitter protecting liver effects after repeated exposure to NEP. These DNELs are lower than the DNELs derived for developmental effects and are therefore also protective for developmental toxicity.

The local inhalation effects are exposure concentration driven, therefore a local acute inhalation DNEL of 4.6 mg/m^3 is proposed.

Table 21: DNEL derivation for NEP for workers

DNEL (endpoint)	BMDL, species	Type of study	BMR and type of effect	Correction for differences in exposure conditions	Corrected BMDL	Asessment factors	Resulting DNEL	Reference
Inhalation								
Local toxicity	57 mg/m^3, rat	28-day RDT, inhalation	10% increased degeneration/regeneration of olfactory epithelium		57	2.5 – (RD) 5 – (IS) Total: 12.5	4.6 mg/m^3	BASF (2011)
Repeated dose toxicity	200 mg/m^3, rat	90-day RDT, inhalation	no systemic effects at highest dose (200 mg/m^3)	6/8 6.7/10	101	2.5 – (RD) 5 – (IS) 2 – (ED) Total: 25	4.0 mg/m^3	BASF (2013)
Developmental toxicity	38 mg/kg bw/day, rabbit	PNDT, oral-gavage GD 6-28	1% increased cardiovascular malformations	70/10	266	2.4 – (AS) 2.5 – (RD) 5 – (IS) Total: 30	8.9 mg/m^3	BASF (2007b)
Dermal								
Repeated dose toxicity	170 mg/kg bw/day, rat	90-day RDT, oral-feed	10% increased relative liver weight	7/5 100% uptake assumed	238	4 – (AS) 2.5 – (RD) 5 – (IS) 2 – (ED) Total: 100	2.4 mg/kg bw/day	BASF (2006)

DNEL (endpoint)	BMDL, species	Type of study	BMR and type of effect	Correction for differences in exposure conditions	Corrected BMDL	Asessment factors	Resulting DNEL	Reference
Developmental toxicity	330 mg/kg bw/day, rat	PNDT, dermal GD 6-19	5% decreased foetal body weight	6/8 100% uptake assumed	248	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	5.0 mg/kg bw/day	BASF (2005)
AS: allometric scaling, GD: gestational day, IS: intraspecies factor, PNDT: prenatal developmental toxicity study, RD: remaining (toxicokinetic/dynamic) differences, ED: exposure duration, RDT: repeated dose toxicity								

Biological limit value NEP
There are no available human studies to derive a BLV for NEP.

1.1.5. Exposure assessment

DMAC and NEP belong to the chemical class of dipolar aprotic solvents and there is some overlap in functionality and uses of the chemicals. Where this applies the use of DMAC and NEP is described in the same exposure scenario. DMAC and NEP are used as solvents in the production of various formulations, e.g. in the production of agrochemicals, pharmaceuticals and fine chemicals. DMAC is used as solvent in coating and is extensively used in the production of man-made fibers and films and during the production of polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation. NEP is applied in cleaning agents and as binder and release agent. NEP is also used in oil field drilling and production operation processes, in functional fluids, in polymer processing, in water treatment, as excipient in agrochemicals and in road and construction applications. Both substances are used as laboratory agent. The manufacture of DMAC and NEP takes place in highly contained systems with exposure most likely to occur during sampling, transfer, maintenance and laboratory activities. Further down the supply chain DMAC and NEP are applied in formulations and used as process chemical. Exposure can occur during transfer activities, during (semi-closed) mixing/blending activities and during maintenance/cleaning activities. Exposure to DMAC may occur during its use as a solvent during fibre production or during the further processing of fibres, both due to inhalation or dermal contact. The application of coatings containing DMAC or NEP by spraying, brushing/rolling or dipping activities may also result in exposure. An overview of the DMAC and NEP exposure scenario's is given in table 37 and table 38 in the Annex.

For the exposure assessment the following approach is applied by the Dossier Submitter:

- First the exposure assessments as presented in the various registration dossiers are evaluated. The Dossier Submitter does not attempt to recalculate the exposure estimations using other tools than applied by the registrants. In order to recalculate the worker exposure with other (higher tier) tools, a more detailed description of the worker tasks and worker environment is required, which is not available to the Dossier Submitter. The exposure scenarios and contributing scenarios as presented by the registrants in their CSRs are taken as starting point for this restriction proposal. For a few scenarios a Tier 2 exposure model (Advanced REACH Tool) is used by some registrants. To the Dossier Submitter it is not clear if these specific scenarios are representative for downstream use applications further down the supply chain. Therefore, instead ECETOC Targeted Risk Assessment (TRA) is used to estimate a more reasonable worst-case exposure concentration for these situations.

- Operational conditions (OC) and risk management measures (RMM) as applied by the registrant are evaluated. In some contributing scenarios, the Dossier Submitter deviates from the OC and RMM applied by the registrant for various reasons:
    - Applying RMM and OC that are considered common industry standard, e.g. the use of Local Exhaust Ventilation (LEV) for processes where exposure can occur, although these RMM/OCs may not be prescribed by all registrants in their CSRs. This may lead to an underestimation of exposure in some particular working situations.
    - For consistency reasons. The Dossier Submitter applies default (reasonable worst-case) protection factors for the use of gloves and respiratory protective equipment (RPE) in industrial and professional settings, assuming a basic level of training, and does not apply a broader range of protection factors as some registrants do. In most cases it is believed that this results in an overestimation of exposure when in practice a higher reduction can be reached, e.g. by more specific training and supervision.
    - The Dossier Submitter does not apply LEV, gloves or RPE for PROC1 (Process), PROC2 and PROC3 activities. These activities take place in closed continuous or batch processes, with limited manual interventions, including closed sampling. Because of the available level of containment in which these processes take place no additional LEV is considered of relevance.
    - As a reasonable worst-case exposure estimate no improved general ventilation is applied, because it cannot be excluded that activities take place in less well-ventilated areas. Therefore, only indoor use with basic ventilation is applied as a worst-case assumption.
    - When applying risk management measures the use of LEV is preferred over the use of RPE by the Dossier Submitter. Only in workplace situations where exposure cannot so easily be controlled by LEV, like spraying in a professional setting, or for maintenance work, the use of RPE is applied.
- No account is taken by the Dossier Submitter for possible consecutive tasks or processes for a worker when a specific process is time limited. It is acknowledged that exposure for a worker may be underestimated if he/she continues work in other processes, however as no information is available on the daily activities of workers for all exposure scenarios and all contributing scenarios, such correction is impossible to make. In this restriction dossier all exposure estimates are performed by applying an exposure duration of eight hours.
- Similar exposure scenarios in different CSRs with the same contributing scenarios are only included once in this dossier. This applies to the use of DMAC and NEP in charging and discharging activities, formulation activities and the use as a laboratory chemical.
- When registrants prescribe different RMM and OC for the same exposure scenario this is evaluated by the Dossier Submitter. When it is considered possible that different RMM and OC can be applied in workplace situations (e.g. the use of LEV or RPE, processes at elevated temperatures), this is taken into account by performing multiple exposure estimates.

The application of ECETOC TRA results in an overview of exposure scenarios with estimated inhalation and dermal exposure concentrations. Subsequently, a literature review is performed in order to find studies where exposure to DMAC or NEP is measured. Both public literature and confidential measurement results provided by industry in their CSR provided during the generation of the restriction dossier are reviewed. The measurements results, both inhalation (personal and area measurements) as well as biological monitoring results, are evaluated and included at the relevant exposure scenario.

Details on the exposure estimations, the selected operational conditions and risk management measures and the applied input exposure parameters are provided in the Annex B.9. A summary of the estimated exposure concentrations and inhalation exposure measurement results is given in Table 22 and Table 23.

Table 22: Inhalation and dermal exposure estimations for DMAC

Exposure Scenario and Process Categories (PROC)	Estimated exposure concentrations long-term		
	Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)	8-hour time weighted inhalation measurement results (mg/m^3)
Industrial use of DMAC			
Manufacturing			
Low fugacity category			
1	0.036	0.034	<2.49
2	3.56	1.37	
3	10.69	0.69	
High fugacity category			
1	0.036	0.034	
2	89.08	1.37	
3	178.16	0.69	
Formulation			
3	10.69	0.69	<0.07-<0.22
4	1.78	0.69	
5 (with LEV)	1.78	1.37	
5 (no LEV)	17.82	1.37	
Charging and discharging			
Low fugacity category			
8a	3.56	1.37	<0.07-5.27
8b (with LEV)	0.89	1.37	
8b (no LEV)	17.82	1.37	
9	1.78	0.69	
Medium fugacity category			
8a	17.82	1.37	
8b	4.45	1.37	
9	17.82	0.69	
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals			
1	0.036	0.034	
2	3.56	1.37	
3	10.69	0.69	
4 (with LEV)	1.78	0.69	
4 (no LEV)	17.82	0.69	
Use as solvent in the production of man-made fibres and films			
1	0.036	0.034	Maximum values >36
2	3.56	1.37	
3	10.69	0.69	
4	1.78	0.69	
13	3.56	1.37	
14	1.78	0.34	
19	3.56	14.14	
-	<9.5	-	
Medium fugacity category			
1	0.036	0.034	
2	17.82	1.37	
3	35.63	0.69	
4	7.13	0.69	
13	17.82	1.37	
14	17.82	0.34	
19	17.82	14.14	
Use as solvent in coatings			
Low fugacity category			

Exposure Scenario and Process Categories (PROC)	Estimated exposure concentrations long-term		
	Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)	8-hour time weighted inhalation measurement results (mg/m^3)
2	2.14	0.82	<3.6
7	10.69	2.57	
10	2.14	1.65	
13	2.14	0.82	
Medium fugacity category			
2	10.69	0.82	
10	10.69	1.65	
Manual maintenance (cleaning and repair) of machinery			
28 (indoors, with LEV and RPE)	0.36	1.37	<8.66
28 (outdoors, with RPE)	2.49	1.37	
Use as laboratory chemical			
15	1.78	0.034	
Professional use of DMAC			
Use as laboratory chemical			
15	3.56	0.068	

Table 23: Inhalation and dermal exposure estimations for NEP

Process Category (PROC)	Estimated exposure concentrations long-term	
	Inhalation (mg/m^3)	Dermal (mg/kg bw/ day)
Industrial use of NEP		
Manufacturing		
Low fugacity category		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
Medium fugacity category		
1	0.046	0.034
2	23.14	1.37
3	46.28	0.69
4	9.26	0.69
Formulation		
Low fugacity category		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
5	2.31	1.37
14	2.31	0.34
Medium fugacity category		
5	23.14	1.37
Charging and discharging		
8a (with LEV)	4.63	1.37
8a (no LEV)	46.28	1.37
8b (with LEV)	1.16	1.37
8b (no LEV)	23.14	1.37
9 (with LEV)	2.31	0.69
9 (no LEV)	23.14	0.69
Use as solvent in industrial processes		
1	0.046	0.034

2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
Use as solvent in coatings		
Low fugacity category		
2	2.78	0.82
7	13.88	2.57
10	2.78	1.65
13	2.78	0.82
Medium fugacity category		
2	13.88	0.82
10	13.88	1.65
13	13.88	0.82
Manual maintenance (cleaning and repair) of machinery		
28 (indoors, with RPE)	0.46	1.37
28 (outdoors, with RPE)	3.24	1.37
Use as laboratory chemical		
15	2.31	0.034
Binder and release agent		
6	1.39	1.65
7	13.88	2.57
10	2.78	1.65
13	2.78	0.82
14	1.39	0.21
Cleaning agents		
Low fugacity category		
7	13.88	2.57
10	2.78	1.65
13	2.78	0.82
Medium fugacity category		
13	13.88	0.82
Oil field drilling and production operations		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
Functional fluids		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
Polymer processing		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
5	2.31	1.37
6	1.39	1.65
13	2.78	0.82
14	1.39	0.21
Water treatment		
1	0.046	0.034
2	4.63	1.37
3	13.88	0.69
4	2.31	0.69
13	2.78	0.82
Professional use of NEP		
Charging and discharging		
8a (with LEV)	13.88	1.65

8a (no LEV)	69.42	1.65
8b (with LEV)	2.78	1.65
8b (no LEV)	27.77	1.65
9 (with LEV)	5.55	0.82
9 (no LEV)	27.77	0.82
Use as solvent in coatings		
10	13.88	3.29
11	5.55	12.86
13	5.55	1.65
19	13.88	16.97
Manual maintenance (cleaning and repair) of machinery		
28 (indoors with RPE)	1.39	1.65
28 (outdoors with RPE)	4.86	1.65
Use as laboratory chemical		
15	4.63	0.068
Binder and release agent		
10	13.88	3.29
11	5.55	12.86
13	5.55	1.65
Cleaning agents		
10	13.88	3.29
11	5.55	12.86
13	5.55	1.65
Use as excipient in agrochemicals		
5	46.28	2.74
11	46.28	21.43
13	46.28	2.74
Functional fluids		
20	13.88	0.21
Road and construction applications		
10	80.99	5.49
11	32.40	21.43
13	32.40	2.74
Polymer processing		
1	0.046	0.034
2	23.14	1.37
14	5.55	0.41
21[#]	-	-

[#] For PROC21 (the low energy manipulation and handling of substances bound in/on materials or articles), resulting in the release of dust, the registrant did not include an exposure estimate in the CSR. With ECETOC TRA v3.1 it is not possible to calculate possible exposure to NEP as a result of handling articles.

Manufacturing

The manufacturing process of DMAC is described by the registrants with contributing scenarios PROC1, PROC2 and PROC3. The estimated inhalation exposure concentrations for DMAC are in the range of 0.036-10.69 mg/m^3 (room temperature) and 0.036-178.16 mg/m^3 (elevated temperatures, high fugacity). The estimated dermal exposure concentrations (without the use of protective gloves) are in the range of 0.034-1.37 mg/kg bw/day.

Measurement data for DMAC from industry, collected between 1990-2020, during manufacturing activities indicate that the eight-hour time weighted average exposure is <2.49 mg/m^3. These results indicate that the model estimations are likely on the conservative side, especially for the exposure estimations at elevated temperatures.

The manufacturing process of NEP is described by the registrants with contributing scenarios PROC1, PROC2, PROC3 and PROC4. These PROCs include closed sampling activities. The estimated inhalation exposure concentrations for NEP are in the range of 0.046-13.88 mg/m^3

(room temperature) and 0.046-46.28 mg/m^3 (elevated temperatures). The estimated dermal exposure concentrations (with the use of protective gloves only applied for PROC4) are in the range of 0.034-1.37 mg/kg bw/day.

Formulation
DMAC and NEP are used in an industrial setting for the formulation of mixtures for different applications. The exposure scenario 'Formulation' is a generic scenario for all formulation activities.

Exposure may occur during formulation of DMAC (in batch formulation processes workers may have multiple and/or significant contact with DMAC), transfers of DMAC or of mixtures containing DMAC to and from large containers using either dedicated or non-dedicated facilities (ECHA, 2012a). According to comments by an industry association (EUROPACABLE) and one of the companies using DMAC in coatings, at all four sites involved in the formulation of enamel mixtures the process is carried out in closed systems (sealed circuits). Limited and short time exposure could occur during maintenance/filter sockets change and sampling operations. During these operations Personal Protective Equipment (PPEs) (inhalation and skin) and adequate ventilation would be employed as standard practice (ECHA, 2012c). The use of DMAC for the formulation of preparations is reflected by contributing scenarios PROC3, PROC4, PROC5. The estimated inhalation exposure concentrations for DMAC are in the range of 1.78-17.82 mg/m^3 (for PROC5 a scenario with and without LEV is estimated). Measurement data from industry (n=6) collected between 2010-2012 during formulation processes of preparations were not detectable with concentrations <0.07-<0.22 mg/mg^3 (BASF, 2012). The estimated dermal exposure concentrations (with the use of protective gloves applied for PROC4 and PROC5) are in the range of 0.69-1.37 mg/kg bw/day.

The use of NEP in formulation steps is reflected by contributing scenarios PROC1, PROC2, PROC3, PROC4, PROC5 and PROC14. The estimated inhalation exposure concentrations for NEP (with LEV applied for PROC4, PROC5 and PROC14) are in the range of 0.046-23.14 mg/m^3 (including a PROC5 contributing scenario at elevated temperature). The estimated dermal exposure concentrations (with the use of protective gloves applied for PROC4, PROC5 and PROC14) are in the range of 0.034-1.37 mg/kg bw/day.

Charging and discharging
Charging and discharging of DMAC and NEP concerns a generic exposure scenario describing the transfer and distribution processes of DMAC or NEP and mixtures containing DMAC or NEP. After manufacturing the end product is transferred into vessels/large containers at dedicated automated facilities. After transfer at the manufacturing sites DMAC and NEP are transported to downstream users where bulk transfer from Intermediate Bulk Container (IBCs), tankers or drums into the reactor or blenders takes place using closed pipelines or by using pumps. These processes are normally contained and/or equipped with LEV (ECHA, 2011a).

The charging and discharging of DMAC and NEP is reflected by contributing scenarios PROC8a, PROC8b and PROC9. For DMAC only industrial settings are considered by the registrants, for NEP both industrial and professional settings. The use of gloves and LEV are considered common industry standard and are applied in the exposure estimations.

The estimated inhalation exposure concentrations for DMAC are in the range of 0.89-17.82 mg/m^3. Inhalation eight-hour average measurement results during charging and discharging, collected between 1990-2020, are reported to be in the range of <0.07-5.27 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.69-1.37 mg/kg bw/day.

The estimated inhalation exposure concentrations for NEP are in the range of 1.16-46.28 mg/m^3 (industrial setting) and 2.78-69.62 mg/m^3 (professional setting). The estimated

dermal exposure concentrations are in the range of 0.69-1.37 mg/kg bw/day (industrial setting) and 0.82-1.65 mg/kg bw/day (professional setting).

Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals

Among the processes reported by industry to be carried out during those uses are: mixing with reactants, transfer/pouring from containers (described in the generic exposure scenario on transfer), separation from products (by filtration or distillation), re-use (after purification by distillation), and equipment cleaning and disposal (ECHA, 2012a).

According to information received during the CfE, the use of DMAC in the manufacture of active pharmaceutical ingredients (API) and associated intermediates is performed in enclosed reactor trains in accordance with Good Manufacturing Practice (ECHA, 2012c). Batch synthesis is run in multipurpose plants where workers' exposure would be reduced by the presence of LEV. Transfer systems are designed to minimize releases, while critical processes such as loading of the solvent, maintenance and cleaning are performed by trained personnel using appropriate protective equipment. In practice virtually all DMAC used in the pharmaceuticals industry would end/be handled in the waste streams. Automated filling and workers wearing gloves (butyl) and goggles could be regarded as common industry standard for large scale industrial installations.

The use of DMAC and NEP as solvent in industrial settings is reflected by contributing scenarios PROC1, PROC2, PROC3 and PROC4. The use of gloves is considered common industry standard and is applied for the PROC4 exposure estimations. LEV is not prescribed by all DMAC registrants for PROC4, therefore for this scenario exposure is estimated with and without the use of LEV.

The estimated inhalation exposure concentrations for DMAC are in the range of 0.036-17.82 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-1.37 mg/kg bw/day.

The estimated inhalation exposure concentrations for NEP are in the range of 0.046-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-1.37 mg/kg bw/day.

Use as solvent in the production of man-made fibres and films (DMAC)

The use of DMAC as solvent in the production of man-made fibres and films in an industrial setting is reflected by contributing scenarios PROC1, PROC2, PROC3 and PROC4. Specific activities like extrusion and the handling of treated objects are reflected by contributing scenarios PROC14 and PROC13 respectively. PROC19 is relevant for manual activities involving hand contact. For the reprocessing of fibres no adequate process category is available.

A DMAC weight fraction of 1 (>25-100%) is applied for all contributing scenarios except for the processing of fibres where a DMAC concentration of 1-5% is considered. For the reprocessing of fibres the exposure estimates are based on industry inhalation exposure measurements.

The estimated inhalation exposure concentrations for DMAC are in the range of 0.036-10.69 mg/m^3 (room temperature) and 0.036-35.63 mg/m^3 (elevated temperature). However, published measurement results in literature and measurement data reported by registrants in the CSRs indicate that the inhalation exposure estimations might not be conservative enough. Measured inhalation concentrations, collected between 1990-2020 (although sometimes based on stationary measurements), above 10 ppm (36 mg/m^3) are reported in the production of man-made fibres. Communication with industry for the use of DMAC in the production of films indicates that the inhalation exposure estimates might not be conservative

enough and that exposure is underestimated. The estimated dermal exposure concentrations are in the range of 0.034-14.14 mg/kg bw/day.

Use as solvent in coatings

DMAC is used in the production of PAI enamels (varnishes) used for electrical wire insulation, but manufacturers have indicated that DMAC is used for other coatings as well (ECHA, 2012a). NEP is used in coatings (like paints), ink, toners and adhesives. It is found in varnishing of hard plastic components in an automobile plant (Koslitz et al., 2014). The use of DMAC and NEP as solvent during the application of industrial coatings is reflected by contributing scenarios PROC7, PROC10 and PROC13. New type of enameling machines are associated with PROC2 scenarios. For NEP also professional use is described, reflected by contributing scenarios PROC10, PROC11, PROC13 and PROC19.

In general, the exposure of DMAC used in coatings may occur during the application of coatings by spraying, roller application/brushing or dipping. These coating applications are mentioned to be automated; therefore no worker exposure is associated with the respective registered processes such as industrial spraying / roller / brushing and pouring (ECHA, 2012a). Specifically for the use of DMAC in enamels (by the Dossier Submitter considered to be reflected by contributing scenario PROC10 and PROC2 for new type of enameling machines), industry indicates that the enamel application for copper wires for the electronics sector is a specific process where enamels are directly applied on the running wire in the ovens in a closed system. All plants in Europe are mentioned to be fitted with recycling ovens and catalyst systems, where DMAC is evaporated and mineralised (ECHA, 2012a).

An eight hour exposure duration and a weight fraction of 0.05-0.25 (5-25%) are selected for all contributing scenarios. For all contributing scenarios the use of gloves and LEV are applied in the exposure assessment. For spraying activities in a professional setting (PROC11) in addition the use of a respirator is selected. All activities are reported to be performed at room temperature, with PROC10 (DMAC, enamels) and PROC13 (NEP) also reported to be performed at elevated temperatures.

The estimated inhalation exposure concentrations for DMAC are in the range of 2.14-10.69 mg/m^3. Inhalation eight-hour average measurement results, collected between 2000-2020, during the use of DMAC as solvent in coatings are reported to be <3.6 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.82-2.57 mg/kg bw/day.

The estimated inhalation exposure concentrations for NEP are in the range of 2.78-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.82-16.97 mg/kg bw/day.

Manual maintenance (cleaning and repair) of machinery

Manual maintenance of machinery takes place at different stages of the life-cycle of DMAC and NEP. Depending on the life-cycle stage these activities occur more or less frequently, in indoor or outdoor situations and with varying duration of exposure. During manufacture exposures to DMAC are likely to be highest during maintenance operations, in particular in the absence of adequate PPE (ECHA, 2011a, 2012a).

Maintenance for cleaning and repair functions is reflected by contributing scenario PROC28. ECETOC TRA v3.1 does not provide exposure estimates for this PROC. Users are advised to adopt the values of an alternative PROC such as PROC8a (ECETOC, 2018). The Dossier Submitter applied the input parameters of PROC8a to estimate exposure during manual maintenance of machinery. According to industry (BASF, 2012) it is common practice to use gloves during maintenance work and a respirator if there is a possibility of exposure. For indoor maintenance activities the use of gloves, LEV and RPE are applied in the exposure assessment. For outdoor activities instead of LEV a ventilation (dilution) factor is applied (ECETOC, 2012).

The estimated inhalation exposure concentrations for DMAC are in the range of 0.36-2.49 mg/m^3. Published measurement results report inhalation exposure concentrations up to 8.66 mg/m^3. Inhalation eight hour average measurement results from industry during the maintenance and cleaning activities, collected between 1990-2020, indicate that the exposure concentration outside the respirator can highly exceed the DNEL. The estimated dermal exposure concentration is 1.37 mg/kg bw/day.

The estimated inhalation exposure concentrations for NEP are in the range of 0.46-4.86 mg/m^3. The estimated dermal exposure concentrations are in the range of 1.37-1.65 mg/kg bw/day.

Use as laboratory chemical
DMAC and NEP are used as laboratory chemicals in research and development activities. During manufacturing and use quality analysis takes place in laboratory settings. In the production of fibres linear density analysis are performed. Further down the supply chain DMAC is used as laboratory chemical in a wide range of applications.
The use of DMAC and NEP as laboratory chemicals in both industrial and professional settings is reflected by contributing scenario PROC15. Within a laboratory setting risk management measures like LEV or a fume cupboard can be considered available.

The estimated inhalation exposure concentrations for DMAC are in the range of 1.78-3.56 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-0.068 mg/kg bw/day.

The estimated inhalation exposure concentrations for NEP are in the range of 2.31-4.63 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-0.068 mg/kg bw/day.

Use of DMAC in other applications
Potential other uses of DMAC are identified. These include use of DMAC in petrochemical applications, filling / packaging for scientific research and development, adhesives, plastic / anti-set off agents in polymer molding/casting, and potentially in sealants, putty, paints, lubricants in metal working fluids, and the production of cellulose fibres such as cellophane (ECHA, 2012a). At the moment it is not clear if DMAC is still used for these applications. If so, many of these uses can be considered covered by other exposure scenarios already included in this dossier, e.g. the use of DMAC as solvent for the application of mixtures or articles, use in coatings or for the production of man-made fibres.

Use as binder and release agent (NEP)
NEP is used as binder and release agent in both industrial and professional settings.

The use of NEP as binder and release agent is reflected by contributing scenario PROC6, PROC7, PROC10, PROC13 and PROC14 for industrial settings and contributing scenarios PROC10, PROC11 and PROC13 for professional settings. The binders and release agents are mixtures in which NEP is assumed to be present in a weight fraction in the range of 0.05-0.25 (5-25%). The use of gloves and LEV are applied in the exposure assessment as well as RPE for spraying activities in a professional setting.

The estimated inhalation exposure concentrations for NEP are in the range of 1.39-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.21-12.86 mg/kg bw/day.

Use in cleaning agents (NEP)
NEP is used in cleaning agents in both industrial and professional settings.

The use of NEP in cleaning agents is reflected by contributing scenario PROC7, PROC10 and PROC13 for industrial settings and contributing scenarios PROC10, PROC11 and PROC13 for professional settings. NEP used in cleaning agents is assumed to be present in a weight fraction in the range of 0.05-0.25 (5-25%). The use of gloves and LEV are applied in the exposure assessment as well as RPE for spraying activities in a professional setting.

The estimated inhalation exposure concentrations for NEP are in the range of 2.78-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.82-12.86 mg/kg bw/day.

Use in oil field drilling and production operations (NEP)
The use of NEP in oil field drilling and production operations (industrial as well as professional setting) is described by one registrant. For this dossier only industrial use is considered to be relevant.

The use of NEP in oil field drilling is reflected by contributing scenario PROC1-4. The estimated inhalation exposure concentrations for NEP (with LEV applied only for PROC4) are in the range of 0.046-13.88 mg/m^3. The estimated dermal exposure concentrations (with the use of protective gloves only applied for PROC4) are in the range of 0.034-1.37 mg/kg bw/day.

Use in agrochemicals (NEP)
The professional use of NEP as excipient in agrochemicals is described by one registrant.

The use of NEP in agrochemicals is reflected by contributing scenario PROC1, PROC2, PROC4, PROC8a, PROC8b, PROC11 and PROC13. The manufacturing and formulation activities (PROC1, PROC2 and PROC4) and the charging and discharging activities (PROC8a and PROC8b) are described in separate exposure scenario elsewhere in this dossier. A mixing step is mentioned by the registrants. Therefore, in addition contributing scenario PROC5 is added to the exposure assessment. NEP used in agrochemicals is assumed to be present in a weight fraction in the range of 0.05-0.25 (5-25%). The use of gloves is applied for those situations where exposure arises (PROC5, PROC11 and PROC13). For spraying activities (PROC11) in addition the use of a respirator is selected. The estimated inhalation concentration for NEP is 46.28 mg/m^3. The estimated dermal exposure concentrations are in the range of 2.74-21.43 mg/kg bw/day.

Use in functional fluids (NEP)
The industrial and professional use of NEP in functional fluids is described by one registrant.

The industrial use of NEP in functional fluids is reflected by contributing scenarios PROC1, PROC2, PROC3, PROC4, PROC8a and PROC8b. The professional use of NEP in functional fluids is reflected by the registrant by contributing scenarios PROC1, PROC2, PROC3, PROC8a, PROC9 and PROC20. The Dossier Submitter however considers the professional use of NEP in functional fluids to be sufficiently covered by PROC20 only as this PROC includes filling and emptying of systems containing functional fluids (including transfers via the closed system). The charging and discharging activities (PROC8a, PROC8b and PROC9) are described in the exposure scenario charging and discharging.

A NEP weight fraction of 1 (100%) is considered for industrial use and of 0.05-0.25 (5-25% for professional use. For PROC4 LEV is applied as are the use of gloves for both PROC4 and PROC20. The estimated inhalation exposure concentrations for NEP are in the range of 0.046-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-1.37 mg/kg bw/day.

Use in road and construction applications (NEP)
The professional use of NEP in road and construction applications is described by one registrant.

The use of NEP in road and construction applications is reflected by contributing scenarios PROC8a, PROC8b, PROC9, PROC10, PROC11 and PROC13. The charging and discharging activities (PROC8a, PROC8b and PROC9) are described in the exposure scenario charging and discharging.

The NEP weight concentration used in road and construction applications is (based on information in the registration dossiers) considered to be >0.25 (>25%). Activities are assumed to be carried out outdoors for which a dilution factor is applied (ECETOC, 2012).The use of gloves are applied in the exposure assessment as well as the use of RPE for spraying activities. The estimated inhalation exposure concentrations for NEP are in the range of 32.40-80.99 mg/m^3. The estimated dermal exposure concentrations are in the range of 2.74-21.43 mg/kg bw/day.

Use in polymer processing (NEP)
The industrial and professional use of NEP in polymer processing is described by one registrant.

The industrial use of NEP in polymer processing is reflected by contributing scenarios PROC1, PROC2, PROC3, PROC4, PROC5, PROC6, PROC8a, PROC8b, PROC9, PROC13, PROC14 and PROC21. The professional use of NEP in polymer processing is reflected by contributing scenarios PROC1, PROC2, PROC8a, PROC8b, PROC14 and PROC21. The charging and discharging activities (PROC8a, PROC8b and PROC9) are described in the exposure scenario charging and discharging.

NEP used in polymer processing is assumed to be present in a weight fraction of 1 (100%) for the PROC1-5 contributing scenarios and in the range of 0.05-0.25 (5-25%) for the other scenarios. The use of LEV and gloves are applied for contributing scenarios where opportunity for exposure arises (PROC4-6, PROC13, PROC14 and PROC21). The estimated inhalation exposure concentrations for NEP are in the range of 0.046-23.14 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-1.65 mg/kg bw/day.

Use in water treatment chemicals (NEP)
The industrial use of NEP in water treatment chemicals is described by one registrant.

The industrial use of NEP in water treatment chemicals is reflected by contributing scenarios PROC1, PROC2, PROC3, PROC4, PROC8a, PROC8b and PROC13. The charging and discharging activities (PROC8a and PROC8b) are described in the exposure scenario charging and discharging.

NEP used in water treatment chemicals is assumed to be present in a weight fraction of 1 (100%) for the PROC1-4 contributing scenarios and in the range of 0.05-0.25 (5-25%) for PROC13. The use of LEV and gloves are applied for contributing scenarios where opportunity for exposure arises (PROC4 and PROC13). The estimated inhalation exposure concentrations for NEP are in the range of 0.046-13.88 mg/m^3. The estimated dermal exposure concentrations are in the range of 0.034-1.37 mg/kg bw/day.

1.1.6. Risk characterisation

The risk characterisation is performed using the estimated exposure concentrations (based on ECETOC TRA v3.1) and comparing these results with the DNELs (Table 24) derived in this dossier by the Dossier Submitter. The resulting RCRs for each industrial and professional use are described in Annex B.10 and Table 25 and Table 26 below.

- The derived RCRs are subsequently evaluated carefully using information on available exposure measurements and results from exposure model validation studies Exposure models are a simplification of the actual work situation. Tier 1 exposure models like ECETOC TRA v3.1 should offer a conservative exposure estimate, preferably the 90th percentile value, representing the reasonable worst case exposure level of a distribution within a generally suitable dataset (i.e. a dataset corresponding to the conditions described in a contributing scenario), should be used as the exposure value for the risk characterisation (ECHA, 2016). ECETOC TRA v3.1. presents the 75th percentile of the exposure distribution (ECETOC, 2012). It is assumed that exposure monitoring data provide a more realistic view of the exposure to DMAC or NEP at the workplace, although it is acknowledged by the Dossier Submitter that the number of studies is limited and do not reflect all workplaces within a sector. For exposure scenarios where measurement results are available these measurement results are thoroughly evaluated. If the measurement results are found to be reliable and reflective of the assessed exposure scenario, the measurement results are used to adjust or support the initially derived RCRs.
- In recent years ECETOC TRA has been validated by different research groups. In these studies the contributing scenario (PROCs) estimates are compared with exposure measurements results. Based on the available validation studies contributing scenarios (PROCs) are identified where the initial inhalation or dermal exposure concentration might be underestimated or the effect of LEV might be overestimated (Marquart et al., 2017; Schlueter & Tischer, 2020). Results of these validation studies are used by the Dossier Submitter to evaluate the derived RCRs. The main conclusions are presented below
    - For inhalation exposure a low level of conservatism is found for PROC5, PROC7, PROC14 and PROC19 contributing scenarios. An overestimation of the efficiency of LEV in actual workplaces is reported to occur for PROC7, PROC8a, PROC10, PROC13, PROC14, PROC19 contributing scenarios (Schlueter & Tischer, 2020).
    - For dermal exposure the validation results indicate that the model overestimates dermal exposure for situations where contact with the substance is expected to be very limited (PROC1-3), with a 75th percentile of measured concentrations for PROC3 <0.001 mg/kg bw/day. For situations where high exposure values are found the model tends to underestimate exposure. PROCs with the highest initial exposure values in ECETOC TRA v3.1 are PROC6, PROC7, PROC10, PROC11, PROC17 and PROC19. The reduction effect of gloves is evaluated by analysing 11 datasets with measurements inside and outside of gloves. The average reduction per data set ranges between 80.5-99.99%, with six of the data sets having a reduction of >95% and an overall average reduction factor of 34 (± 97% reduction) (Marquart et al., 2017).
- The registrants use a higher DNEL in their registration dossiers. In these dossiers no RCRs >1 are found. To the Dossier Submitter it is not clear if all OC and RMM available in daily practice are taken into account in the registrants' exposure assessments. This might not have been necessary for exposure scenarios where the RCR already is <1 by applying only a limited set of OC and RMM, resulting in a more worst-case exposure scenario. It is anticipated by the Dossier Submitter that for some processes the registrant could have applied OC and RMM used in practice, resulting in lower exposure estimates. Since specific workplace information is not available to the Dossier Submitter no refinements are considered in the exposure estimations and derived RCRs.

Table 24: DNELs for DMAC and NEP used in the calculation of RCRs

	DMAC	NEP
Inhalation DNEL (mg/m^3)	13	4.0
Dermal DNEL (mg/kg bw/day)	0.53	2.4

DMAC

The use of DMAC in various exposure scenarios, including different PROCs, results in RCRs above 1. In general, dermal exposure is the critical exposure route for DMAC. This means

that a risk is identified using DMAC. The results on the identified risks are described per exposure scenario and the conclusions are summarized in Table 25.

Manufacturing processes (PROC2 and PROC3) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 2.12-2.86 for activities at room temperature. For activities at elevated temperature the combined RCRs increase to 9.44-15.01 due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified, even though the processes take place in closed system. Calculations for PROC1 shows a combined RCR far below 1 (RCR=0.067) for activities at room temperature as well as activities at elevated temperate. Inhalation eight-hour average measurement results during manufacturing are reported to be <2.49 mg/m^3 (RCR=<0.20) indicating that the model estimations (especially for activities at elevated temperatures) are on the conservative side. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. Therefore no risk via inhalation and dermal exposure is identified.

Formulation processes (PROC3, PROC4 and PROC5) at room temperature can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.43-3.96. As the RCRs are above 1 a risk is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC3 situations. Therefore no risk is identified for PROC3. For PROC5 activities for liquids however, ECETOC TRA validation studies (Schlueter & Tischer, 2020) indicate a low level of conservatism. Therefore the identified risk for PROC5 remains.

Charging and discharging processes (PROC8a, PROC8b and PROC9) at room temperature as well as at elevated temperatures can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.43-3.96. As the RCRs are above 1 a risk is identified. Measurement results during charging and discharging show a wide variation in exposure, with measurement results reported to be below 5.27 mg/m^3 (RCR=0.41). It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a contributing scenarios. Together with the identified risk via dermal exposure the identified risks for these activities remain.

The use of DMAC as solvent for the production of agrochemicals, pharmaceuticals and fine chemicals (PROC1, PROC2, PROC3 and PROC4) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 0.067-2.86 for activities at room temperature. As the RCRs are above 1 a risk is identified, even though the processes take place in closed system. Calculations for PROC1 showed combined RCR far below 1 (RCR=0.067). Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. Therefore no risks via inhalation and dermal exposure is identified for PROC1-PROC3 situations.

The use of DMAC in the production of man-made fibres and films (PROC1, PROC2, PROC3, PROC4, PROC13, PROC14, PROC19 and reprocessing of fibres) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 0.067-26.96 for activities at room temperature. For activities at elevated temperature the combined RCRs increase to 0.067-28.06 mainly due to an increase in inhalation exposure. Especially for PROC19 a very high dermal exposure is estimated with a RCR of 26.68. As the RCRs are above 1 a risk is identified. Inhalation eight-hour average measurement results from industry during the production of man-made fibres indicate that the DNEL can be exceeded. Calculations for PROC1 show a combined RCR far below 1 (RCR=0.067) for activities at room temperature as well as activities at elevated temperate. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. Therefore no risk via inhalation and dermal exposure is identified for PROC1-PROC3 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC13, PROC14 and PROC19 contributing scenarios. In

addition ECETOC TRA tended to underestimate dermal exposure for PROC19 situations (Marquart et al., 2017). Therefore the identified risk for PROC4, PROC13, PROC14, PROC19 activities remains. For the reprocessing of fibres no adequate PROC is available. The inhalation RCR of <0.8 is based on confidential data reported in a CSR and reflects the 95-percentile value for the reprocessing of fibres based on air monitoring results of continuous monitoring analysers. Dermal exposure estimates for the reprocessing of fibres are not available. Therefore a risk cannot be excluded.

The use of DMAC in coatings can lead to exposure above the DNELs, resulting in combined RCRs of 1.72-5.67 for activities at room temperature. For activities at elevated temperature (PROC2 and PROC10) the combined RCR increases from 1.72 to 3.93, due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified. Inhalation eight-hour average measurement results during the use of DMAC in coatings are reported to be <3.6 mg/m^3 (RCR <0.28). Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC2 situations. Therefore no risk via inhalation and dermal exposure is identified for PROC2 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7 and PROC10 situations (Marquart et al., 2017). Therefore the identified risks for these activities remain.

Manual maintenance of machinery, reflected by contributing scenarios PROC28 (indoors and outdoors) can lead to exposure above the DNELs, resulting in combined RCRs of 2.61-2.78. As the RCRs are above 1 a risk is identified. Inhalation eight-hour average measurement results from industry during the maintenance and cleaning activities indicate that the exposure concentration outside the respirator can highly exceed the DNEL. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a (used for the calculation of PROC28) contributing scenarios. Together with the identified risk via dermal exposure the identified risks for these activities remain.

The use of DMAC in laboratory activities (PROC15) does not lead to exposure above the DNELS, with combined RCRs of 0.20 for industrial activities and 0.40 for professional activities. Therefore no risk via inhalation and dermal exposure is identified.

Table 25: Summary of calculated RCRs by the Dossier Submitter and conclusion of risk.

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
Industrial use of DMAC				
Manufacturing				
Low fugacity category				
1	<0.01	0.064	0.067	No risk is identified based on inhalation measurement results and model validation study results.
2	0.27	2.58	2.86	
3	0.82	1.30	2.12	
High fugacity category				
1	<0.01	0.064	0.067	
2	6.85	2.58	9.44	
3	13.70	1.30	15.01	
Formulation				
3	0.82	1.30	2.12	No risk is identified based on model validation study results for PROC3 activities. For PROC4 and PROC5 activities a risk is identified, especially via dermal exposure.
4	0.14	1.29	1.43	
5 (with LEV)	0.14	2.59	2.72	
5 (no LEV)	1.37	2.59	3.96	
Charging and discharging				

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
Low fugacity category				
8a	0.27	2.59	2.86	A risk via inhalation and dermal exposure is identified.
8b (with LEV)	0.069	2.59	2.66	
8b (no LEV)	1.37	2.59	3.96	
9	0.14	1.29	1.43	
Medium fugacity category				
8a	1.37	2.59	3.96	
8b	0.34	2.59	2.93	
9	1.37	1.29	2.66	
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals				
1	<0.01	0.064	0.067	No risk is identified based on inhalation measurement results and model validation study results for PROC1-PROC3 activities. For PROC4 activities a risk is identified, especially via dermal exposure.
2	0.27	2.58	2.86	
3	0.82	1.30	2.12	
4 (with LEV)	0.14	1.29	1.43	
4 (no LEV)	1.37	1.29	2.66	
Use as solvent in the production of man-made fibres and films				
Low fugacity category				
1	<0.01	0.064	0.067	No risk is identified based on inhalation measurement results and model validation study results for PROC1-PROC3 activities. For PROC4, PROC13, PROC14 and PROC19 a risk is identified via either dermal or inhalation exposure. For reprocessing of fibres a risk cannot be excluded as no dermal estimates are available.
2	0.27	2.58	2.86	
3	0.82	1.30	2.12	
4	0.14	1.29	1.43	
13	0.27	2.59	2.86	
14	0.14	0.65	0.78	
19	0.27	26.68	26.96	
-	<0.8			
Medium fugacity category				
1	<0.01	0.064	0.067	
2	1.37	2.58	3.96	
3	2.74	1.30	4.04	
4	0.55	1.29	1.84	
13	1.37	2.59	3.96	
14	1.37	0.65	2.02	
19	1.37	26.68	28.06	
Use as solvent in coatings				
Low fugacity category				
2	0.16	1.55	1.72	No risk is identified based on model validation study results for PROC2 activities. A risk is identified for PROC7, PROC10 and PROC13 activities, especially via dermal exposure.
7	0.82	4.85	5.67	
10	0.16	3.11	3.27	
13	0.16	1.55	1.72	
Medium fugacity category				
2	0.82	1.55	2.37	
10	0.82	3.11	3.93	
Manual maintenance (cleaning and repair) of machinery				
28 (indoors, with RPE)	0.027	2.59	2.61	A risk via dermal exposure is identified for PROC28 activities.
28 (outdoors, with RPE)	0.19	2.59	2.78	
Use as laboratory chemical				
15	0.14	0.064	0.20	No risk is identified.
Professional use of DMAC				
Use as laboratory chemical				

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
15	0.27	0.13	0.40	No risk is identified.

NEP

The use of NEP in various exposure scenarios, including different PROCs, resulted in RCRs above 1. In general, inhalation exposure is the critical exposure route for NEP. This means that a risk is identified using NEP. The results on the identified risks are described per exposure scenario the conclusions are summarized in Table 26.

Manufacturing processes (PROC2 and PROC3 at room temperature and PROC4 at elevated temperatures) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.73-3.76 for activities at room temperature. For activities at elevated temperature the combined RCRs increase to 2.60-11.86 due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified for these scenarios. Calculations for PROC1 showed combined RCR far below 1 (RCR=0.026) for activities at room temperature as well as activities at elevated temperate. Therefore for PROC1 no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. However, for PROC2 and PROC3 a risk is identified at both room temperature and elevated temperature, mainly due to inhalation exposure. For PROC4 a risk is identified for activities at elevated temperature.

Formulation processes (PROC2, PROC3 and PROC5) at room temperature can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.15-3.76. For activities at elevated temperature (PROC5) the combined RCR increases to 6.36 due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified. Calculations for PROC1, PROC4 and PROC14 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. In addition for PROC5 activities for liquids, ECETOC TRA validation studies (Schlueter & Tischer, 2020) indicate a low level of conservatism. For PROC2, PROC3 and PROC5 activities a risk is identified, mainly due to inhalation exposure, which cannot be excluded by model validation study results.

Charging and discharging processes (PROC8a, PROC8b and PROC9) in an industrial and professional setting (especially for those activities where no LEV is applied) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 6.07-12.14 (no LEV, industrial setting) and 7.29-18.04 (no LEV, professional setting). As the RCRs are above 1 a risk is identified. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a contributing scenarios. Therefore the identified risks via inhalation and dermal exposure cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

The use of NEP in industrial processes (PROC1-PROC4) can lead to exposures above the DNELs for PROC2 and PROC3 activities, resulting in calculated combined RCRs of 1.73-3.76. As the RCRs are above 1 a risk is identified for these scenarios. Calculations for PROC1 and PROC4 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. However, for PROC2 and PROC3 a risk is identified, mainly due to inhalation exposure. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

The use of NEP in coatings in both an industrial (PROC2, PROC7, PROC10 and PROC13) and a professional setting (PROC10, PROC11, PROC13 and PROC19) can lead to exposure above

the DNELs, resulting in combined RCRs of 1.04-4.54 (industrial setting) and 2.07-10.54 for professional setting. For activities at elevated temperature (PROC2, PROC10 and PROC13, industrial setting) the combined RCR increases from 1.04 to 4.16, due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified. No inhalation exposure measurements are available. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC2 situations. Therefore no risk via inhalation and dermal exposure is identified for PROC2 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7 and PROC10 situations (Marquart et al., 2017). Therefore the identified risks for these activities remain.

Manual maintenance of machinery, reflected by contributing scenarios PROC28 (indoors and outdoors, industrial and professional setting), can lead to exposure above the DNELs, resulting in combined RCRs of 1.38 (industrial setting, outdoor) and 1.03-1.90 (professional setting, indoors and outdoors). As the RCRs are above 1 a risk is identified for these scenarios. Calculations for PROC28 (industrial setting, indoors) show a combined RCR below 1 (RCR<0.69). Therefore for this activity no risk via inhalation or dermal exposure is identified, provided RPE is worn during the activities. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a (used for the calculation of PROC28) contributing scenarios. For outdoor activities and for maintenance in a professional setting the identified risks for these activities remain. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

The use of NEP in laboratory activities (PROC15) can lead to exposure above the DNELs, resulting in a combined RCR of 1.19 for use >4 hours in a professional setting. For use in an industrial setting, no risk via inhalation and dermal exposure is identified, with a combined RCR of 0.59.

The use of NEP as binder and release agent in both an industrial (PROC6, PROC7, PROC10, PROC13 and PROC14) and a professional setting (PROC10, PROC11, PROC13) can lead to exposure above the DNELs, resulting in combined RCRs of 1.03-4.54 (industrial setting, PROC6, PROC7, PROC10, PROC13) and 2.07-6.75 (professional setting). As the RCRs are above 1 a risk is identified for these scenarios. Calculations for PROC14 (industrial setting) show a combined RCR below 1 (RCR<0.43). Therefore for PROC14 no risk via inhalation or dermal exposure is identified. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 and PROC14 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10, PROC13 and PROC14 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC6, PROC7, PROC10 and PROC11 situations (Marquart et al., 2017). Therefore a combined risk via inhalation and dermal exposure is identified for all PROCs except PROC14.

The use of NEP as cleaning agent in both an industrial (PROC7, PROC10, PROC13) and a professional (PROC10, PROC11, PROC13) setting can lead to exposure above the DNELs, resulting in combined RCRs of 1.04-4.54 (industrial setting) and 2.07-6.75 (professional setting). For activities at elevated temperature (PROC13, industrial setting) the combined RCR increases from 1.04 to 3.81, due to an increase in inhalation exposure. As the RCRs are above 1 a risk is identified for these scenarios. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing

scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7, PROC10 and PROC11 situations (Marquart et al., 2017). Therefore a combined risk via inhalation and dermal exposure is identified for all PROCs.

In addition to the exposure scenarios described above, other exposure scenarios were initially described by two registrants. During the process of preparing this dossier one registrant withdrew their dossier. The remaining registrant indicated that the scenario's described below will not be included in their updated CSR. Until now no updated version is received and these uses are still described on the ECHA substance information page. The Dossier Submitter could only find a limited amount of information for some of the identified uses, indicating that NEP is used (in Europe) for these activities. However, because (small scale) use of NEP in these activities cannot be excluded, the Dossier Submitter decided to include these exposure scenarios in the dossier.

The use of NEP in oil field drilling and production operations (PROC1-PROC4) can lead to exposures above the DNELs for PROC2 and PROC3 activities, resulting in calculated combined RCRs of 1.73-3.76. As the RCRs are above 1 a risk is identified for these scenarios. No inhalation exposure measurements are available. Calculations for PROC1 and PROC4 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. However, for PROC2 and PROC3 a risk is identified, mainly due to inhalation exposure. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

The use of NEP in functional fluids (PROC1-PROC4 industrial use and PROC20 professional use) can lead to exposures above the DNELs for PROC2, PROC3 and PROC20 activities, resulting in calculated combined RCRs of 1.73-3.76. As the RCRs are above 1 a risk is identified for these scenarios. No inhalation exposure measurements are available. Calculations for PROC1 and PROC4 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. However, for PROC2, PROC3 and PROC20 a risk is identified, mainly due to inhalation exposure. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

The use of NEP as excipient in agrochemicals in a professional setting (PROC5, PROC11 and PROC13) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 12.71-20.50. As the RCRs are well above 1 a risk is identified for these scenarios. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC5 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC13. In addition ECETOC TRA tended to underestimate dermal exposure for PROC11 situations (Marquart et al., 2017). Therefore a combined risk via inhalation and dermal exposure is identified for all PROCs.

The industrial and professional use of NEP in polymer processing can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.03-3.76 (PROC2, PROC3, PROC5, PROC6, PROC13, industrial setting) and RCRs of 1.56-6.36 (PROC2 and PROC14). As the RCRs for these scenarios are above 1 a risk is identified. Calculations for PROC1, PROC4 and PROC14 (industrial) show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC5 and PROC14 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC13 and PROC14. Validation study results (Marquart et al., 2017) indicate that dermal exposure is

overestimated for PROC1-PROC3 situations and underestimated for PROC6 situations. For PROC2, PROC3, PROC5, PROC6 and PROC13 (industrial setting) and for PROC2 and PROC14 (professional setting) a risk is identified, mainly due to inhalation exposure, which cannot be excluded by model validation study results. The registrant includes contributing scenario PROC21, which is "the low energy manipulation and handling of substances bound in/on materials or articles" resulting in the release of dust. The registrant does not include an exposure estimate in the CSR. With ECETOC TRA v3.1 it is not possible to calculate possible exposure to NEP as a result of handling articles.

The use of NEP in water treatment operations (PROC1-PROC4 and PROC13) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.04-3.76 (PROC2, PROC3 and PROC13). As the RCRs for these scenarios are above 1 a risk is identified. Calculations for PROC1 and PROC4 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC13. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. For PROC2, PROC3 and PROC13 a risk is identified, mainly due to inhalation exposure, which cannot be excluded by model validation study results.

The professional use of NEP in road and construction applications (PROC10, PROC11 and PROC13) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 9.24-22.53. As the RCRs for these scenarios are well above 1 a risk is identified. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC10 and PROC11 situations (Marquart et al., 2017). Therefore the identified risks for these activities remain.

Table 26: Summary of calculated RCRs by the Dossier Submitter and conclusion of risk.

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
Industrial use of NEP				
Manufacturing				
Low fugacity category				
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified especially via inhalation at both room temperature and elevated temperature. For PROC4 a risk is identified for activities at elevated temperature mainly via inhalation.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
Medium fugacity category				
1	0.012	0.014	0.026	
2	5.79	0.57	6.36	
3	11.57	0.29	11.86	
4	2.31	0.29	2.60	
Formulation				
Low fugacity category				
1	0.012	0.014	0.026	For PROC2, PROC3 and PROC5 (at elevated temperatures) activities a risk is identified, mainly via inhalation. For PROC5 a risk is identified for the combined exposure.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
5	0.58	0.57	1.15	
14	0.58	0.14	0.72	
Medium fugacity category				
5	5.79	0.57	6.36	

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
Charging and discharging				
8a (with LEV)	1.16	0.57	1.73	A risk is identified, mainly via inhalation and mostly for activities without LEV.
8a (no LEV)	11.57	0.57	12.14	
8b (with LEV)	0.29	0.57	0.86	
8b (no LEV)	5.79	0.57	6.36	
9 (with LEV)	0.58	0.29	0.86	
9 (no LEV)	5.79	0.29	6.07	
Use as solvent in industrial processes				
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified, mainly via inhalation.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
Use as solvent in coatings				
Low fugacity category				For PROC7 (room temperature) and PROC2, PROC10 and PROC13 (at elevated temperatures) a risk is identified, mainly via inhalation. For PROC10 and PROC13 (at room temperature) a risk is identified for the combined exposure.
2	0.69	0.34	1.04	
7	3.47	1.07	4.54	
10	0.69	0.69	1.38	
13	0.69	0.34	1.04	
Medium fugacity category				
2	3.47	0.34	3.81	
10	3.47	0.69	4.16	
13	3.47	0.34	3.81	
Manual maintenance (cleaning and repair) of machinery				
28 (indoors, with RPE)	0.12	0.57	0.69	For outdoor activities a risk is identified for the combined exposure.
28 (outdoors, with RPE)	0.81	0.57	1.38	
Use as laboratory chemical				
15	0.58	0.014	0.59	No risk is identified.
Binder and release agent				
6	0.35	0.69	1.03	For PROC7 a risk is identified, mainly via inhalation. A risk is identified for the combined exposure for all PROCs except PROC14.
7	3.47	1.07	4.54	
10	0.69	0.69	1.38	
13	0.69	0.34	1.04	
14	0.35	0.086	0.43	
Cleaning agents				
Low fugacity category				
7	3.47	1.07	4.54	For PROC7 and PROC13 (at elevated temperatures) a risk is identified, mainly via inhalation. For PROC 10 and PROC13 (at room temperature) a risk is identified for the combined exposure.
10	0.69	0.69	1.38	
13	0.69	0.34	1.04	
Medium fugacity category				
13	3.47	0.34	3.81	
Oil field drilling and production operations				
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified, mainly via inhalation.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
Functional fluids				
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified, mainly via inhalation.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
Polymer processing				

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified, mainly via inhalation. For PROC5, PROC6 and PROC13 activities a risk via combined exposure is identified.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
5	0.58	0.57	1.15	
6	0.35	0.69	1.03	
13	0.69	0.34	1.04	
14	0.35	0.086	0.43	
Water treatment				
1	0.012	0.014	0.026	For PROC2 and PROC3 a risk is identified, mainly via inhalation. For PROC13 a risk via combined exposure is identified.
2	1.16	0.57	1.73	
3	3.47	0.29	3.76	
4	0.58	0.29	0.86	
13	0.69	0.34	1.04	
Professional use of NEP				
Charging and discharging				
8a (with LEV)	3.47	0.69	4.16	A risk is identified for all PROCs, mainly via inhalation and especially for activities without LEV.
8a (no LEV)	17.36	0.69	18.04	
8b (with LEV)	0.69	0.69	1.38	
8b (no LEV)	6.94	0.69	7.63	
9 (with LEV)	1.39	0.34	1.73	
9 (no LEV)	6.94	0.34	7.29	
Use as solvent in coatings				
10	3.47	1.37	4.84	A risk is identified for all PROCs.
11	1.39	5.36	6.75	
13	1.39	0.69	2.07	
19	3.47	7.07	10.54	
Manual maintenance (cleaning and repair) of machinery				
28 (indoors with RPE)	0.35	0.69	1.03	A risk via combined exposure is identified.
28 (outdoors with RPE)	1.21	0.69	1.90	
Use as laboratory chemical				
15	1.16	0.028	1.19	A risk via inhalation is identified.
Binder and release agent				
10	3.47	1.37	4.84	For PROC10 and PROC11 a risk via both inhalation and dermal exposure is identified. For PROC13 a risk is identified, mainly via inhalation.
11	1.39	5.36	6.75	
13	1.39	0.69	2.07	
Cleaning agents				
10	3.47	1.37	4.84	For PROC10 and PROC11 a risk via both inhalation and dermal exposure is identified. For PROC13 a risk is identified, mainly via inhalation.
11	1.39	5.36	6.75	
13	1.39	0.69	2.07	
Use as excipient in agrochemicals				
5	11.57	1.14	12.71	A risk via both inhalation and dermal exposure is identified for all PROCs.
11	11.57	8.93	20.50	
13	11.57	1.14	12.71	
Functional fluids				
20	3.47	0.086	3.56	A risk via inhalation exposure is identified.
Road and construction applications				
10	20.25	2.29	22.53	A risk via both inhalation and dermal exposure is identified for all PROCs.
11	8.10	8.93	17.03	

Process Category (PROC)	RCRs			Conclusion on risk
	Inhalation	Dermal	Combined	
13	8.10	1.14	9.24	
Polymer processing				
1	0.012	0.014	0.026	For PROC2 and PROC14 a risk is identified, mainly via inhalation. For PROC21 (the low energy manipulation and handling of substances bound in/on materials or articles), resulting in the release of dust, the registrant does not include an exposure estimate in the CSR. With ECETOC TRA v3.1 it is not possible to calculate possible exposure to NEP as a result of handling articles.
2	5.79	0.57	6.36	
14	1.39	0.17	1.56	
21	-	-	-	

1.2. Justification for an EU wide restriction measure

Total annual consumption of DMAC is estimated between 11 000 and 19 000 tonnes per year and EU manufacture ranges between 15 000 and 20 000 tonnes per year. DMAC is widely used in the EU as a solvent or processing agent across a range of industrial sectors such as textile fibre manufacture, electrical wire insulation and membrane manufacture. NEP manufacture and import ranges between 100 and 1 000 tonnes per year. Information on EU use of NEP is limited to the generic exposure scenario descriptions in the registration dossiers. There are some indications on uses in specialised coatings and as a cleaning agent in the manufacture of optical lenses. In general both substances are dipolar aprotic solvents that are used in specialised applications for which limited or no technically feasible alternatives are available. DMAC (since 2001) and NEP (since 2013) are both harmonized classified as "Reprotoxic 1B May damage the unborn child". For both substances a comprehensive hazard dataset is available and exposure of workers is expected in the various professional and industrial settings. Based on the chemical safety assessment (CSA) performed by the Dossier Submitter it is concluded that this occupational exposure results in unacceptable risks.

The identification of unacceptable risk is driven by establishment of DNELs for long-term systemic dermal and inhalation worker exposures that are more stringent than DNELs used in REACH registration dossiers. Therefore, action on a Community-wide basis is required to prevent EU-wide unacceptable risks for workers from exposure to DMAC and NEP. Applications of DMAC and NEP are traded freely and are used in all Member States of the EU. Action at EU level would ensure a 'level playing field' for all producers, importers and users of DMAC and NEP and products containing these substances. In view of the Dossier Submitter, a restriction targeted towards mandatory harmonised long-term inhalation and dermal DNELs combined with an obligation to implement operational conditions and risk management measures ensuring exposure below the DNELs is the most appropriate Community wide measure. In addition, the proposed restriction would offer legal consistency with existing restrictions on two other dipolar aprotic solvents NMP and DMF.

1.3. Baseline

The baseline scenario describes the current situation and trends in the foreseeable future of the use of DMAC and NEP without a restriction. The scenario is focussed on the volumes, the number of workers involved and market conditions per sector and use.

DMAC (since 2001) and NEP (since 2013) are both harmonized classified as "Reprotoxic 1B May damage the unborn child". According to information submitted to the CfE, this classification results at the very least in slower growth in production volumes or even a decline

in production (CfE, 2020). DMAC is included in the candidate list, NEP is not. No relevant impending legislation or modification to existing legislation concerning DMAC or NEP is expected to come into effect over the timescale considered for the assessment of impacts of the proposed restriction.

DMAC

As of 2010, total annual consumption of DMAC (as process chemical and in mixtures) in the EU was estimated to lie between 11 000 and 19 000 tonnes per year. The vast majority of DMAC used in the EU was produced locally, with EU manufacturing volumes being estimated to range from 15 000 to 20 000 tonnes. Between 1 000 and 2 000 tonnes were imported in 2010, while 3 000 to 4 000 tonnes were exported (ECHA, 2012a). No clear information on trends in manufacturing and import volumes are available to the Dossier Submitter. The estimation may therefore be regarded as an appropriate indication for 2022.

The main uses of DMAC are described in Annex A and summarised in the table below. Reported information is based on the background document for DMAC prepared by ECHA (ECHA, 2012a), inputs received through the CfE (CfE, 2020) and related follow-up communication. Relevant sites are rather evenly distributed across the EU (ECHA, 2012a).

Table 27: Summary of EU use volume, number of relevant companies and number of potential exposed workers by downstream use of DMAC described in Annex A.

Use	Tonnage share	Number of companies in the EU	Number of potentially exposed workers
Process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals	65-70%	>10	unknown
Process solvent for spinning of fibres of various polymers	20-25%*	4	750*
Solvent in coatings, e.g. PAI enamels (varnishes) used for electrical wire insulation	3-5%	15	1 500-2 000
Process solvent in the production of polysulphone membranes	<1%	6	500-1 000
Other uses	<3.5%	unknown	unknown

** This number includes the Dralon GmbH production site in Lingen (which ceased production July 2021) and the Asahi Kasei Spandex Europe GmbH site in Dormagen (which ceased production March 2022).*

The use of DMAC as process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals is based on a limited number of users consuming high DMAC volumes in closed industrial installations (ECHA, 2012a). According to the lead registrant this information is still valid. Demand for DMAC is limited by high recovery rates that have been reported by industry stakeholders in follow-up communications to the CfE. Recovery of DMAC from the final product is reported be very efficient and DMAC is reported to be re-used several times as solvent in chemical synthesis before ending up in chemical waste streams. The Dossier Submitter assumes that demand for DMAC in relation to this use is mainly driven by fluctuations in the global and European markets.

The use of DMAC as process solvent in the production of various fibres fluctuates in line with changes in production volumes of the main DMAC-related products – reported in the background document for DMAC prepared by ECHA (ECHA, 2012a), the CfE (CfE, 2020) and related follow-up communication as:

- Acrylic and polyurethanepolyurea copolymer (Spandex) fibres for textile

- Acrylic fibres as precursors for carbon fibres; and
- Meta-aramid fibres for various technical uses.

Described fibres are – to a certain extent – used in combination with other fibres. Spandex is for example used in mixes with cotton or polyester fibres, while meta-aramid fibres are for example mixed with fibre glass fibres for use in protective clothing (ECHA, 2012a).

The Association of the German, Austrian and Swiss Man-Made Fibres Industries (IVC) reports an annual use of around 1 900 tonnes of DMAC as of 2020 by six fibre producers located in the EU (CfE, 2020). As mentioned in relation to Table 27, two production sites in Germany have however ceased production in 2021 and 2022. The total annual use volume of the man-made fibre industry has thus likely decreased.

DMAC is recovered and repeatedly used in the fibre production process. Recovery rates lie above 99%, with the losses of DMAC (of between 0.5% and 1% per cycle) resulting from acid hydrolysis during the recovery processes, environmental releases, solvent residues in produced fibres and intentional disposal (ECHA, 2012a). Reported recovery rates were confirmed in follow-up communications to the CfE.

Residues of DMAC in fibres are decreasing during the processing of fabrics. While average residues of between 0.1% and 0.5% are reported for raw fibres, residual concentrations of DMAC in textile end-products are reported to be non-detectable or very low. Employed processing techniques are reported to have an influence on the residual content of DMAC. Spun dyed fibres, which are dyed during fibre production are, for example, found to contain higher residues than fibres dyed using conventional processes due to a comparatively lower use of water and other chemicals. As of 2012, 100 to 1 000 companies were estimated to be involved in the processing of raw fibres, while over 1 000 were estimated to produce textiles (ECHA, 2012a).

Acrylic and polyurethanepolyurea copolymer (Spandex) fibres for textile
The textile industry is reported to face very intensive international competition (ECHA, 2020 #193). In 2019, the turnover of the textile and clothing industry was €162 billion in the EU-27 according to Euratex (EURATEX, 2020). Man-made fibres alone account for 4% of this turnover; i.e. ~€6.5 billion (EURATEX, 2020). Man-made fibres include many other types of fibres in addition to acrylic fibre and polyurethanepolyurea copolymer (Spandex). Examples are nylon, polyester and polyolefin (ECHA, 2020a). From 2014 to 2018, the annual turnover related to man-made fibres ranged between €7.4 and €7.6 billion according to Euratex (EURATEX) . The decline in turnover in the man-made fibre sector is in line with developments in the EU textile and clothing industry for which a decline of 1.8% has been reported from 2018 to 2019 (EURATEX, 2020).

In the production of acrylic and Spandex fibres from polyacrylonitrile and polyurethane, DMAC (on its own) is reported to be used as a solvent (CfE, 2020). DMAC is reported to be predominantly used in the wet spinning process. As of 2022, 100% of acrylic fibres produced in the EU are produced by wet spinning production lines, while the global share of wet spinning processes is slightly lower at 90%. In 2019, 108 000 tonnes of acrylic fibres were produced in the EU-27 (including Northern Ireland) based on the wet spinning process in addition to 27 000 tonnes of Spandex. Due to closure of two production facilities in 2021 and 2022, the expected production volume for 2022 for the EU-27 (including Northern Ireland) is substantially lower with 43 000 tonnes of acrylic fibres and 20 000 tonnes of Spandex (industry consultation). As a result, the use volumes of DMAC are also expected to be significantly lower.

Similar to the textile industry, very intensive international competition is assumed for the European man-made fibre industry with generally low profit margins for acrylic and polyurethanepolyurea copolymer. Changes in labour costs, energy and raw material prices predominantly influence the profit margin. Closure of the Dralon production facility in Lingen

(Germany) has, amongst other factors, for example been initiated by increased costs of raw materials and energy.

Acrylic fibres as precursors for carbon fibres
Another important use of acrylic fibres, for which DMAC is used as solvent in the production process, is as precursor for the carbon fibre industry (CfE, 2020; ECHA, 2012a). Total annual global carbon fibre production is estimated at 160 000 tonnes in 2020 with an expected increase in production of ~9% in the short term (i.e. until 2022) and ~30% in the medium and long term (i.e. beyond 2022). Growth in the fibre composite market is therefore expected. Toray, the largest manufacture of carbon fibres, with an annual production volume of ~50 000 tonnes has production plants in several European countries. The second largest manufacture, in terms of tonnage, is Hexcel. It has, among others, production sites for carbon fibres in France and Spain. The strategy of Hexcel is to focus on the establishment and expansion of co-location plants, i.e. sites that have their own acrylic fibre precursor facility for internal processing into carbon fibres. Together with Hexcel's plant in the United States, those sites have been announced to be the focus of future capacity extensions (Sauer, 2021). Due to the expected growth in the fibre composite market, demand for EU-produced acrylic fibres as precursors for the carbon fibre industry could thus be increasing as could the use for DMAC.

Meta-aramid fibres for various technical uses
Meta-oriented aromatic polyamides can be processed into meta-aramid fibres or films on solution in dipolar aprotic solvents, e.g., hexamethylphosphoramide (HMPA), NMP, DMAC, and DMF (Bandyopadhyay et al., 2015; Vu, 2018). DMAC is reported to be the sole solvent used in the EU-27 (industry consultation). Meta-aramid fibres are highly resistant to temperature, chemical degradation, and abrasion and are reported to be used for protective clothing for firemen, military suits (used by Special Forces and pilots) and protective clothing in industrial settings to protect workers against electrical shock (industry consultation). The ECHA background dossier (ECHA, 2012a) furthermore mentions the uses of fibreglass/meta-aramid nonwoven (felt) fabrics in the aerospace sector; and the use of meta-aramid fibres in filters for hot gas filtration and in fibre-reinforced plastics. Short meta-aramid fibres, so-called floc, are also used for paper production – with relevant papers being used for the insulation of electrical equipment in transformers, motors and generators as well as structural composites (ECHA, 2012a). Examples of meta-aramid fibres, which are more commonly known by their trade names are the original Nomex® (DuPont) fibre and subsequently developed commercially available fibres, such as Conex® (Teijin), Apyeil® (Unitika), and Fenilon® (Russia), some of which may now no longer be available (Horrocks, 2016).

In 2019, ~ 6 000 tonnes of aramid fibres were produced in the EU-27 (including Northern Ireland). Meta-aramid fibre production volumes have remained stable over the recent years and are expected to remain stable in the absence of significant changes in the general economic situation (industry consultation).

The use of DMAC as solvent in coatings is mainly described for PAI enamels (varnishes) used for electrical wire insulation, although manufacturers of DMAC have indicated that the substances is used for other coatings as well (ECHA, 2012a). PAI-based enamel is one of the most important insulating enamels in electrical engineering and widely used for enamels on wires used for various electrical parts, e.g. electrical motors, generators and transformers. These electrical parts are used for a wide range of applications in vehicles, electrical appliances, electrical tools, and in relation to electricity production. Applications vary widely in size and range from small motors in watches to motors for high-speed trains as well as small transformers in cell phone battery recorders to transformers employed in power plants. Wire diameters and enamel application rates vary accordingly (industry consultation). According to the European Winding Wire Association (EWWA), the importance of PAI-based enamels is further increasing.

The production of coated wires for electrical engineering in Europe is mostly done within Europe. Imports represent only 5% of European consumption (CfE, 2020). One reason for the low import share are comparatively high transportation costs for coated copper wire (industry consultation). As of 2018, a turnover of around €2.2 billion is estimated for the EU winding wire industry based on information provided by EWWA. An increase in demand for coated wires for electrical engineering is anticipated due to the energy transition, and 'green' industry trends, e.g. the electrification of the automotive sector and the increase in wind turbines. In the EU, a negative trend in production volumes has however been observed in the last five years, i.e. between 2017 and 2021, in parts due to the COVID-19 pandemic but also due to the increasing cost of copper, the increasing production of less complex motors outside Europe and the fact that ongoing developments in relation to electrical applications have not yet translated in increased demand for wires. For 2021, production volumes of around 347 000 tonnes of copper winding wires and 18 000 aluminium winding wires have been estimated. Over the last five years, production volumes for copper winding wires are reported to have decreased by 3% per year, while the production of aluminium winding wires has increased by 6.5% per year (industry consultation). The EU winding wire sector is reported to operate with small margins in order to be able to compete with global prices and maintain its leading market position (CfE, 2020). Prices are mainly determined by the copper price. EWWA indicated that over the last years the price difference between winding wire end-products and the copper price decreased, therefore lowering potential profits for the winding wire sector. International competition, mainly from Asia, for European assembly lines using winding wires are mentioned as the mean reason for this. Two EU production plants have ceased production in 2020 (industry consultation).

According to EWWA, some companies in the wire coating sector need to invest in new production lines and additional risk management measures to comply with the NMP restriction entering into force in May 2024 for this sector. Investments of several million euros are reported to be needed for, for example, installing new machines and housings, ventilation and exhaust systems as well as increasingly sophisticated machine controls. As NMP and DMAC are used as solvents in the same formulations, the implementation of new production lines will also result in lower worker exposure to DMAC compared to the old production lines.

The use of DMAC as process solvent in the production of polysulphone membranes is mainly related to the medical device industry for the production of filters and membranes which are then used in dialysis treatment (used as renal replacement therapy) and other life-saving extracorporeal therapies (CfE, 2020; ECHA, 2012a). DMAC-based membranes produced in the EU are reported to be used for the regular treatment of over 100 000 patients in the EU and 500 000 patients worldwide (CfE, 2020). Production capacities for DMAC-related medical membranes have been steadily increased due to increasing patient numbers and market demand. A constant annual increase of the related DMAC demand in the EU (single digit) in the foreseeable future is expected, based on market growth worldwide. As for other sectors, DMAC demand is limited by solvent regeneration and re-use, which has been optimized over the last ten years (CfE, 2020). In follow-up communication on the CfE, margins are reported as sufficiently big to allow for investment in Research & Development activities for either alternative substances or to reduce worker exposures.

The use of DMAC for other applications is assumed to be limited. Other uses of DMAC reported in ECHA (2012a) are petrochemical applications, laboratory use, filling and packaging for scientific research and development, adhesives, plastic and anti-set off agents in polymer moulding/casting, and the potential use in sealants, putty, paints, lubricants in metal working fluids, and the production of cellulose fibres such as cellophane. According to information provided through the CfE, laboratory use of DMAC relates to quality assurance processes or laboratory research conducted in industrial or university settings (CfE, 2020). Further information on other uses was not received during the CfE. All reported applications are thus assumed to be niche applications.

NEP
Very limited information on NEP uses, use volumes and exposed workers, other than the information provided in the registration dossiers (described in Annex A) is available. A total volume of between 100 and 1 000 tonnes of NEP is manufactured or imported per year according to registration dossiers (ECHA, 2021). Based on aggregated information from chemical safety reports, a total manufacturing volume of between 1 000 and 10 000 tonnes per year is estimated by the Dossier Submitter. No additional information on manufacturing and import volumes was received during the CfE.

According to information on NEP uses provided during the CfE, NEP is not used as a solvent in coatings for wires nowadays (CfE, 2020). Follow-up communications to the CfE highlighted the use of NEP for cleaning of optical lenses during the production process, following substitution from NMP to NEP. The use of NEP for this application is reported for 2009 (industry consultation). Whether NEP is still used for this purpose nowadays is unclear.

Additional research on NEP uses in safety data sheets points to the use of NEP as solvent in cleaners/strippers, paint removers, lubricants, adhesives, coatings and putties. Concentrations of NEP used in these applications range from <0.5% in putties to 100% in relation to, amongst others, cleaners and paint removers. More specifically, safety data sheets point to the use of NEP as cleaning agents in the electronics industry, the medical sector and the automotive industry. In the building and construction sector, NEP appears to be used in some adhesives, coating and putties. Anti-friction coatings are one example of NEP-containing coatings mentioned in safety data sheets. The use of NEP in leather finishing agents is a further identified use.

Further enquiries directed at the relevant chapter of the European Chemical Industry Council (Cefic), the 1,4 butanediol Derivatives Sector Group (BDO), resulted in additional information on the use of NEP in coatings. The use of NEP in coatings has either already been phased out by companies or is expected to be phased out. Specialised coatings might still contain NEP although in very low concentration (<0.1%) (industry consultation).

The Dossier Submitter therefore assumes the use of NEP is limited and will remain stable under normal economic conditions.

2. Impact assessment

2.1. Introduction

The Annex XV restriction dossier on the use of DMAC and NEP is prepared by the Netherlands after a preliminary RMOA and a scoping study on the possibilities for grouping of dipolar aprotic solvents. The industrial and professional use of DMAC and NEP are considered to pose a health risk for workers that is not adequately controlled as concluded in section 1.1.6.

This impact assessment assesses whether restriction is the most appropriate risk management option to reduce or eliminate the identified health risks and to justify which of the identified restriction options is preferred. The restriction scenario describes the anticipated industry response per sector although working conditions can vary between sectors and within sectors at facility and workplace level. As details about the differences between facilities and workplaces are not available to the Dossier Submitter no precise description of measures or combinations of measures needed to sufficiently reduce exposure can be given.

The impact assessment estimates the costs and benefits for the preferred restriction option. For the benefits only human health effects are considered by the Dossier Submitter as the identified risks concerns a health risk for workers. The health impact is described qualitatively

using the elimination of health risks of exposed workers as proxy for the health impacts of the proposed restriction.

Economic impacts are estimated and quantified where possible focussing on the costs of implementing additional risk management measures to reduce exposure levels below the proposed DNELs and other foreseen compliance costs. Cost estimates are based on EU-27 averages and do not take into account country-specific price levels.

To assess proportionality a comparative approach is taken. The net societal welfare change is not quantified, instead costs and benefits of the proposed restriction are compared to the cost and benefits of the two existing REACH restrictions of very similar nature targeted at dipolar aprotic solvents: NMP and DMF. Proportionality is assessed through comparison of the estimated cost per worker to reduce the exposure below the imposed DNELs across all dipolar aprotic solvent restriction dossiers.

The geographical scope of the impact assessment is the EU-27 countries. To allow the comparison with the NMP and DMF dossiers a time frame of 15 years is used to estimate the economic impacts and proportionality.

2.2. Risk Management Options

In 2018, the European Commission and ECHA prepared a RMOA for the three dipolar aprotic solvents DMAC, DMF and NMP (European Commission & ECHA, 2018). At that moment, the restriction for NMP had been adopted and a dossier for the restriction of DMF had been submitted by Italy. The restriction for DMF was adopted by the REACH Committee (by written procedure) in April 2021 and published in November 2021 (European Commission, 2021).

The European Commission and ECHA observed that NMP, DMAC and DMF have similar hazard profiles and similar patterns of use. For some of the uses, the substances can be interchangeable (although usually not as drop-in alternatives). Although most uses appear to take place in closed systems, there are uses that involve high worker exposure such as spraying, roller application/brushing or dipping. RAC confirmed risks for NMP and the Annex XV dossier for DMF also pointed towards these risks according to the European Commission and ECHA (European Commission & ECHA, 2018). Those risks have since been confirmed by RAC in the opinion on the Annex XV dossier for a DMF restriction (ECHA, 2019c). Although at the time of the RMOA no detailed analysis had been performed for DMAC, risks for workers using DMAC could not be excluded. The analysis in this Annex XV restriction report confirms risks for workers using DMAC.

The European Commission and ECHA mentioned that the NMP restriction was a good example of a case where there is an added value of introducing legally binding DNELs via a REACH restriction, complementary to IOELs available under the EU OSH legislation (European Commission & ECHA, 2018). For DMAC and DMF, authorisation would result in a heavy burden on industry and authorities, due to the widespread uses of the solvents by industry and professionals and lack of safer alternatives on a short term. Furthermore, authorisation would not cover intermediate uses. Therefore, a restriction is the preferred risk management option under REACH for these substances.

Furthermore, it was noted in the RMOA that a REACH restriction with harmonised DNELs results in a higher degree of harmonisation than an update of the existing IOELs because national OELs may differ from the IOELs. The European Commission and ECHA concluded that due to the reasons above and for regulatory consistency, a restriction would be the best regulatory option for DMF and DMAC, as it was for NMP (European Commission & ECHA, 2018).

NEP was not part of the Commission RMOA. NEP has however also been classified as reprotoxic 1B in Annex VI of CLP and has similar (physico-chemical) properties as NMP, DMF and DMAC. NEP has not been included in the Candidate list and there currently is no European IOEL for the substance. The registration tonnage band is 100-1000 tonnes per annum, which is lower than the registration volumes for the other dipolar aprotic solvents. However, in the restriction dossiers for NMP and DMF and the Commission's RMOA this substance was identified as a possible substitute for several uses, which could lead to an increase in annual tonnage. Due to the classification and properties the same arguments are valid for NEP as for DMAC, and a restriction would be the preferred risk management option.

Authorisation

DMAC was placed on the Candidate list for authorisation in December 2011. It was included in ECHA's 4th recommendation for Annex XIV of REACH, but to date has not been included in Annex XIV due to the developments with regards to the restrictions for NMP and DMF. NEP has not been placed on the Candidate list but meets the criteria as it has a harmonised classification as Repr 1B. An Annex XV Substance of Very High Concern (SVHC) dossier proposing placement on the Candidate list would constitute an additional step towards regulating NEP through authorisation. However, such extra effort is not considered an obstacle as such. The Dossier Submitter notes that it will not be necessary to identify NEP as SVHC when the proposed restriction is in place. Authorisation could be a viable risk management option for both substances.

The primary aim of authorisation under REACH is to substitute SVHCs and it has proven to be an effective driver for this substitution (ECHA, 2020b; European Commission, 2018). However, it is questionable whether safer technically feasible alternatives are available for all uses of dipolar aprotic solvents. Their functionality relies highly on their specific properties, and therefore the group of substances that can be considered as alternatives is limited in scope. NMP, DMF, DMAC and NEP are the most widely used dipolar aprotic solvents and their uses may be interchangeable to some extent. They all have a harmonised classification as Repr 1B and substituting one with the other is not considered suitable as there will be no or limited health gains. Other possible substitutes, without (harmonised) CMR classifications, are not registered or are registered in lower tonnage bands. The availability of toxicity data may be limited, and some precaution is necessary when drawing conclusions with regards to their (human health) hazards and hence their potential to be suitable alternatives.

As shown in paragraph 1.1.4.9, the effects of both DMAC and NEP occur above a threshold exposure. If the exposure remains below this threshold, no health effects are expected and the use of the substances can be considered safe. The possibility of safe use under appropriate workplace conditions strongly reduces the urgency to substitute these substances and rather places the onus on achieving a set of binding rules to control risks.

DMAC and (to a lesser extent) NEP are used in many different sectors for a broad range of uses. If the substances are placed on Annex XIV, this would probably lead to a high number of applications for authorisation. This implies a high workload for both applicants and authorities. Although broad (upstream) applications are possible under REACH, the experience is that there is a lot of discussion about these applications due to uncertainties pertaining to the broadness of scope, use description, exposure scenario's and analyses of alternatives. Recent developments have shown that it takes longer before the authorisation is granted and review periods are often shorter compared to downstream use applications. Many downstream users making use of broad sector-wide upstream applications opted to file their own application at a later stage explaining their specific case and increase business certainty of a granted authorisation with a longer review period and including better case-specific conditions. Hence, based on recent experiences it is likely an authorisation requirement for DMAC and NEP would lead to multiple downstream applications, leading to a relatively high burden for industry and authorities.

Authorisation does not cover intermediate uses. The legal text regarding this exception for intermediate uses does not require "strictly controlled conditions" as referred to in articles 17 and 18 of REACH, although a recent Court Ruling (case C-650/15/P, "Acrylamide Judgment") has made clear that strictly controlled conditions are an essential condition for intermediate use. For DMAC, some intermediate use is reported (ECHA, 2012a). Both DMAC and NEP are not registered as intermediates under article 17 or 18 of REACH using strictly controlled conditions.

The Dossier Submitter concludes that authorisation is not the most appropriate EU-wide measure to manage the identified risks related to the uses of DMAC and NEP, based on the limited availability of alternatives, possibility of safe use without residual risks and expected high workload for both industry and authorities.

(Update of) OEL under OSH legislation

The main concern related to the use of DMAC and NEP is worker exposure. Options to regulate the use under the occupational safety and health legislation should therefore be considered. The main instrument under OSH to regulate exposure is the OEL. There are two types of OELs on a European level: IOEL and binding OELs (BOEL). When an IOEL is set, all member states must set a national OEL for the substance, taking the IOEL (and scientific documentation) into account, but the national OEL does not have to be equal to the IOEL. National OELs may thus be lower or even higher than an IOEL. Therefore, the IOEL cannot be considered as a tool that ensures harmonisation throughout Europe. Setting of a BOEL is a more elaborate process in which feasibility is also taken into account. National OELs may not exceed the BOEL, but they may be lower (stricter) than the BOEL.

Directive 96/94/EC introduced IOELs for DMAC (10 ppm or 36 mg/m^3 as 8-hour value and 20 ppm or 72 mg/m^3 for short term exposure) in 1996. This Directive was repealed by Directive 2000/39/EC, which also established new IOELs for DMAC at the same levels. Directive (EU) 2022/431 extends the scope of the former CMD (now Carcinogens, Mutagens and Reprotoxic substances Directive (CMRD)) to include reprotoxic substances. With this extension, the IOELs that are in place for reprotoxic substances will become BOELs. Member States will have to implement these changes in their national legislation before 5 April 2024. Until that date, there is a transitional period and in many countries the provisions for reprotoxic substances will still be based on the CAD (Directive 98/24/EC) rather than the stricter CMRD (Directive 2004/37/EC).

The OELs for DMAC are based on a SCOEL advice dating from 1994 (SCOEL, 1994). Since 1994, several relevant studies have been published (see paragraph 1.1.4), and in 2001 the substance was classified as toxic to reproduction. Therefore, the Dossier Submitter considers a revision of the OEL, taking newer studies into account, appropriate.

For NEP, to date no European (B)OEL has been set. Therefore, there is no obligation for member states to set an OEL for the substance and most of them have not done so. Although the directives concerning exposure to chemicals at work (CAD and CMRD) clearly state that the risks related to exposure should be prevented or minimised, the implementation of this obligation may vary between member states. For example, in absence of a national OEL, employers in the Netherlands have to derive their own OEL and use that in their risk assessment, a challenging task for (SME) companies that do not employ toxicologists. In other countries the risk assessment for these substances may be limited to a qualitative assessment, or a standard set of risk management measures may be prescribed. Setting a BOEL for NEP could help to assess and quantify risks.

The CAD and CMRD apply to employees and do not cover the self-employed. As with all Directives for Workplace Safety and Health, the obligations in these directives are a minimum requirement. Member States may choose to extend the validity to cover self-employed as well

or do so for a part of the obligations. On the other hand, CAD and CMRD cover all workplaces where exposure can occur, including activities that may be excluded from REACH e.g. waste handling.

Capacity to determine OELs is limited. Although in recent years the number of OELs (specifically BOELs) that have been set has increased, most of these are based on older evaluations. ECHA and the European Commission (DG EMPL) have agreed that ECHA will provide scientific opinions for up to five (groups of) substances per year (ECHA, 2019a). The Advisory Committee on Safety and Health at Work (ACSH) has recently adopted an opinion on priority chemicals for OEL setting (ACSH, 2021). The opinion contains two lists: one for chemicals that fall under the carcinogens and mutagens directive (at the time of publishing the opinion the scope did not include reprotoxic substances yet) and one for chemicals under the chemical agents directive. Combined, both lists contain around 40 substances or groups of substances. None of the dipolar aprotic substances is included in the list, meaning that they will probably not be evaluated by RAC in the coming years. Furthermore, contrary to the restriction process, there is no member state initiative in the OEL process. A member state cannot prepare a dossier for OEL setting, this has to be done by ECHA on request of the European Commission (DG EMPL).

Under OSH, there are no limit values for dermal exposure. When dermal exposure forms a significant part of the exposure to a substance, the OEL may get a 'skin' notation. This means that preventive measures should be taken to reduce dermal exposure. The assessment of dermal exposure is generally qualitative only.

The Dossier Submitter concludes that adjustment of the OEL for DMAC and establishment of an OEL for NEP would reduce the risk of inhalation exposure, but it does not reduce the risk of dermal exposure adequately. The Dossier Submitter notes that the substances are not included in the priority list to derive or adjust OELs. Therefore, the Dossier Submitter considers that setting (adjusted) BOELs for the substances under OSH is not the best regulatory management option to control the risks related to DMAC and NEP.

REACH restriction options

REACH restrictions offer a wide range of possibilities to control identified unacceptable risks due to use of hazardous substances, from a complete ban to the prescription of specific risk management measures for certain uses. The selection of the most effective option is a case-by-case decision and depends on the type of risks (and groups at risk), uses concerned and availability of alternatives. For DMAC and NEP two restriction options are considered: a maximum percentage (including complete ban) of DMAC and NEP, or a binding DNEL.

Maximum percentage of DMAC or NEP in a mixture

A complete ban of DMAC and NEP (maximum percentage of 0%) would eliminate all risks related to their use. A maximum percentage of DMAC or NEP in a mixture could reduce worker exposure to a safe level. However, the specific properties of aprotic solvents could be lost when they are used in a mixture, making it no longer suitable for certain uses. Therefore, for several uses a maximum percentage has the same effect as a complete ban.

As shown in Annex C.2, for many uses there are no viable safer alternatives. The uses would be transferred to countries outside of the EU, or the substances would be replaced by other aprotic solvents that are not (yet) restricted but are equally hazardous. Therefore, a complete ban or maximum percentage in the mixture seems to be not effective or not economically feasible.

Restriction with binding DNELs

This is the restriction option that is already in place for NMP and DMF. With binding DNELs for inhalation and dermal exposure, the safety of all uses can be evaluated in the CSA. The

registrant will have to advice his downstream users on the proper risk management measures. When downstream users follow these exposure scenarios, the workers' exposure will remain at a safe level (users may have to check combined exposure when workers perform multiple tasks). However, downstream users still have the freedom to make their own exposure assessment when the registrant's scenario does not match their situation.

When this option is chosen, users may continue to use DMAC or NEP and will not have to completely redesign production processes (depending on the height of the DNELs). It is expected that some companies will need to take additional risk management measures to reduce the exposure of their workers. In case of a low DNEL, it may be challenging for some sectors to comply with the restriction as soon as it becomes effective. In this case, authorisation would offer the possibility to do a socio-economic assessment to demonstrate that the benefits of continued use outweigh the risks related to that use. A restriction does not allow a similar assessment once it has been published, and if derogations are necessary they should be identified before publishing the restriction.

This restriction option is targeted at eliminating the risks related to the use of DMAC and NEP in all sectors rather than substitution. Users can continue to use DMAC or NEP where this is necessary, at safe exposure levels both for inhalation and dermal exposure. The Dossier Submitter therefore concludes that this option is effective in limiting the risks related to the use of DMAC and NEP. The Dossier Submitter considers this the preferred regulatory management option.

2.2.1. **Conclusion on most appropriate RMO**

Table 28 gives an overview of the risk management options that are considered. All risk management options mentioned above are expected to reduce or eliminate the risks related to the use of DMAC and NEP. However, based on other arguments presented above, the preferred option would be a restriction with a binding DNEL. This option is taken forward to the impact assessment.

Table 28: Summary of risk management options

Risk management option	***Description***	***Considerations with respect to risk reduction capacity, proportionality to the risk and practicability***
Authorisation	*Inclusion of the substances in Annex XIV. For NEP, SVHC identification through placement on the Candidate List should be included as a first step. Users will substitute or may apply for authorisation, thereby continuing the use of the substances under well described conditions and (in most cases) adequate control of risks for the threshold effects.*	*In case of adequate control, risks will be eliminated. When SEA route is used, there will be residual risks. In general, placement on Annex XIV may lead to regrettable substitution with substances that are not considered safer or for which appropriate information on safety is lacking.* *Due to the broad range of uses, a large number of applications for authorisation would be expected, leading to high workload for applicants and authorities.*
(Update of) OEL under OSH	*For DMAC an IOEL (BOEL per 5 April 2024) exists but it is based on old data and should be re-evaluated. For NEP, no IOEL or BOEL has been established to date.*	*This option is expected to have the capacity to reduce the risks of inhalation exposure. Risk reduction however depends on the value of the BOEL and on implementation by member states.* *Self-employed may not be covered by a BOEL and dermal exposure is regulated in a qualitative way only.* *Authorities have limited capacities to derive OELs and it may take years*

Risk management option	***Description***	***Considerations with respect to risk reduction capacity, proportionality to the risk and practicability***
		before DMAC and NEP will be evaluated under OSH. There is no Member state initiative for the derivation of OELs.
Restriction option 1	*maximum percentage in mixture, including complete ban*	*This would eliminate risks related to the use of DMAC and NEP but could lead to regrettable substitution with substances that are not considered safer.*
Restriction option 2	*Binding DNELs: the restriction will prescribe binding DNELs that should be used in CSAs Safety Data Sheets (SDSs) and including the need to implement operational conditions and risk management measures ensuring worker exposure below the DNELs.*	*This option covering two DNELs for inhalation and dermal exposure for both DMAC and NEP is assessed further in the impact assessment. This is the proposed restriction option.*

The detailed restriction conditions are the following:

Restriction on placing on the market and use of Dimethylacetamide (DMAC) and N-ethyl pyrrolidone (NEP)

Dimethylacetamide (DMAC) CAS-No. 127-19-5 EC-No. xxx	1. Shall not be placed on the market as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date] unless manufacturers, importers and downstream users have included in the chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 13 mg/m^3 for long-term exposure by inhalation and 0,53 mg/kg/day for long-term dermal exposure. 2. Shall not be manufactured, or used, as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date as in paragraph 1] unless manufacturers and downstream users take the appropriate risk management measures and take the appropriate operational conditions to ensure that exposure of workers is below both the DNELs specified in paragraph 1.
N-ethyl pyrrolidone (NEP) CAS-No. 2687-91-4 EC-No.xxx	1. Shall not be placed on the market as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date] unless manufacturers, importers and downstream users have included in the chemical safety reports and

	safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 4,0 mg/m^3 for long-term and 4,6 for acute exposures by inhalation and 2,4 mg/kg/day for long-term dermal exposure. 2. Shall not be manufactured, or used, as a substance on its own, as a constituent of other substances, or in mixtures in a concentration equal to or greater than 0,3 % after [date as in paragraph 1] unless manufacturers and downstream users take the appropriate risk management measures and take the appropriate operational conditions to ensure that exposure of workers is below both the DNELs specified in paragraph 1.

OELs and REACH (including restrictions and DNELs) have different ranges of validity. The CAD and CMRD apply to all employees that are exposed (or could be exposed) to hazardous substances. The self-employed are not covered by the CAD and CMRD. The user obligations under REACH apply to the (professional and industrial) users of chemicals, including the self-employed. However, there are exceptions to REACH, e.g. handling of waste, that are covered by the CAD and CMRD. Scientific research and development is excluded from REACH restrictions, but the exposure should be controlled under the CAD and CMRD. When the OEL and binding DNEL have different values, this could lead to unequal protection of workers in various sectors. Therefore, it may be advisable to set both REACH restriction DNELs and OELs at the same level.

2.3. Restriction scenario(s)

As described in the previous section on Risk Management Options, Restriction option two (Restriction prescribing binding DNELs to be used in CSAs, communicated in the supply chain and risks managed accordingly) is further assessed for both DMAC as NEP. More details on the anticipated response per industry sector (if applicable) is described in Annex C.3.

It is anticipated that registrants of DMAC and NEP will update their registration dossiers with additional OC and/or RMM for the various exposure scenarios and use first tier exposure models to estimate inhalation and dermal exposures. The Dossier Submitter assessed which additional OC and RMM could be implemented, next to those already described by most registrants, to reduce the exposure below the DNELs for DMAC and NEP based on the exposure scenarios provided by the Registrants. The identified additional OC and RMM are an indication of possible exposure reduction and are, but not limited to: i) a stricter gloves regime (with specific activity training), ii) implementation of LEV or increase the efficiency of existing LEV (to 95%), iii) task duration reduction and iv) use of a lower concentration (weight fraction). The latter is indicative of a further refinement of the exposure scenario rather than an actual RMM as the Dossier Submitter assumes DMAC or NEP concentrations used in formulation are not higher than technically needed. The efficiency of the different OC and RMM are further described in Annex B.9.1.2.

As described in section 1.1.5, some of the abovementioned OC and RMM may already be prescribed by some, but not all, Registrants in their CSR and working conditions can vary between sectors and within sectors at workplace level. The details of those workplaces are not in complete view to the Dossier Submitter hence making it difficult to precisely describe the measures or combinations of measures to reduce exposure sufficiently at workplace level.

In addition, some downstream users might prepare a downstream user CSR (DU CSR) with higher tier models and/or company-specific measurements to demonstrate compliance with the proposed DNELs instead of implementing all OC and RMM prescribed by the registrant.

It is noted that task duration limitations would offer a straightforward organizational measure to reduce the exposure of a worker. In case workers perform multiple tasks, the aggregate (*of combined*) exposure should not exceed the DNEL. It is advised to consider regular biomonitoring campaigns to ensure all necessary OC and RMM are sufficient to adequately reduce the combined exposure. Biomonitoring summary data in some registration dossiers and provided during the CfE indicate the possibility to use a BLV in order to evaluate the effectiveness of implemented OC and RMM in general and to further investigate trends and/or high individual results.

As a result of the proposed DNELs, the Dossier Submitter expects a restricted continued industrial use of DMAC as dipolar aprotic solvent. However, implementation of additional OC and RMM (see Annex C.3) will be needed in many sectors for specific uses and processes, mainly directed to reduce the dermal exposure and associated risks. For inhalation exposure additional exposure reduction measures might be necessary in the man-made fibre sector. During the development of the Annex XV restriction report this sector, as well as one registrant, have expressed their concerns about the feasibility to meet the dermal DNEL for DMAC as safe use cannot be demonstrated with ECETOC TRA for basic handling of DMAC like charging and discharging activities, even with a stricter gloves regime. The Dossier Submitter is of the opinion that OC, such as task duration reduction, could be applied for these kind of activities as it is not expected that workers in this sector will be charging/discharging 100% DMAC for their entire eight-hour shift.

As a result of the proposed DNELs, the Dossier Submitter expects a continued industrial use of NEP as dipolar aprotic solvent by most sectors. However, implementation of additional OC and RMM (see Annex C.3) will be needed in many sectors for specific uses and processes, mainly directed to reduce the inhalatory exposure and associated risks. For a few uses and processed additional OC and RMM will be needed to reduce the dermal exposure and associated risks. Based on the exposure scenarios provided by the Registrants the suggested OC and RMM described by the Dossier Submitter are an indication of possible exposure reduction measures. Task duration reduction can only be implemented if the inhalation exposure concentration does not exceed the local acute inhalation DNEL of 4.6 mg/m^3 at any given time during the work activity. Practically this implies that prescribing task duration reduction is not suitable for risk reduction related in most cases.

Limited information is available about the actual concentration of NEP in formulations used in coatings, binders and release agents and cleaning agents in industrial and professional settings. Information derived from SDSs of some formulations containing NEP shows a wide concentration range of NEP (0.5% up to 100%). In these settings, the use of formulations with high percentages of NEP and/or use of NEP at elevated temperatures might not be possible without considerable technical investments for exposure reduction or the use of RPE. Especially professional use of formulations with high NEP concentrations are assumed to cease due to the proposed restriction. Formulations with a lower NEP content might still be used with additional OC and RMM.

2.4. Economic impacts

This section focusses on estimating the costs incurred in relation to the proposed restriction. Estimated costs relate to the costs of implementing additional risk management measures to reduce exposure levels below the proposed DNELs – and thereby achieve compliance – and other foreseen compliance costs. As indicated in Section 2.3, the proposed restriction allows

the continued industrial use of DMAC and NEP provided that adequate risk management measures are taken.

An estimate of the total costs incurred by each sector cannot be provided by the Dossier Submitter as details of the exact working conditions and necessary additional risk management measures required by each affected company in each relevant sector are not known. The feasibility and related costs (per workplace) of administrative measures, for instance, a reduction of the time that a worker is tasked with an activity with a significant exposure potential, i.e. changes in staff rotation, could not be assessed as this requires detailed information of the company processes.

As the estimation of cost is not based on an assessment of the most likely reaction at company level, cost estimates are based on EU-27 averages and do not take into account country-specific price levels. All estimates are rounded to two significant figures. For exposure reduction measures that are anticipated to be implemented in part of the existing workplaces where DMAC and/or NEP are used, i.e. local exhaust ventilation (LEV) and a stricter glove regime, an estimation of the cost associated with the measure is attempted. In relation to LEV systems, such an estimation is not possible given the wide variety of (side-specific) parameters that need to be considered when designing an effective system and the resulting lack of generic cost estimates. Information on relevant cost components and factors that are beneficial for limiting operating costs is provided instead.

For NEP, it is furthermore anticipated that some professional uses, especially those with products containing high concentrations of NEP, will cease due to the proposed restriction. Substitution costs for the discontinuation of these NEP uses are expected to be minor given the generic product purposes (e.g. graffiti and paint remover, leather finishing agent and as hardener for isocyanate-based sealers used on flooring) with a small market share and the availability of less hazardous product alternatives. These costs are therefore not further assessed.

2.4.1. Cost estimates for risk reduction measures needed to comply with the proposed restriction

Installation and maintenance of local exhaust ventilation (LEV) extraction points or enhanced ventilation
Measures for preventing worker exposure are selected in line with a standard hierarchy of measures which favours substitution and process adaptions lowering the exposure potential, e.g. changes to process temperatures, over engineering means, such as LEV. Administrative measures, e.g. changes in staff rotation, and personal protective equipment should only be resorted to where the aforementioned measures do not constitute a feasible and effective approach (HSA, 2014). Hence, if substitution is not feasible and operational conditions are optimised towards exposure minimisation, implementing LEV is one of the most preferential measures for achieving compliance with the proposed restriction in relation to inhalation exposure.

Design of the LEV system is a complex but highly important process. In a guidance on LEV targeted at industry stakeholders requiring LEV and stakeholders designing and installing such systems, the Irish Health and Safety Authority stresses that poor design of an LEV system can in the worst-case increase exposure instead of preventing it. Leakage caused by poor design and/or maintenance may, for example, lead to concentrated local exposure spots. A poorly designed system can thus become an "expensive waste of expenditure and may give a false impression of hazard control" (HSA, 2014 p.7).

A good understanding of the process demands, in addition to the chemical to be controlled, is crucial for designing an LEV system that is fit for purpose and effective. Factors to be

considered when designing a suitable LEV system are, for example, whether the system needs to be adaptable to changing materials and processes and whether a simple or complex, i.e. multi-point, system is needed to cover identified exposure points. A suitably sized extraction fan system and ducting system are other examples of crucial factors for ensuring that the LEV system is effective in controlling exposure. Materials used also need to be compatible with the chemical to be controlled, e.g. in relation to corrosion- and fire resistance (HSA, 2014). Careful selection of the most suitable technical options for all components of the LEV system, i.e. the enclosure or hood[1], the ducting system, the air cleaner or filter[2], the air mover[3] and the discharge component, is thus crucial for ensuring effective exposure control (HSA, 2014). Given the variety of parameters relevant for designing a suitable and effective LEV system, no generic cost estimate for implementing a LEV system can be provided. Providers of LEV design services, in fact, work on the basis of providing site-specific quotes.

Adaptation and extensions of existing systems are also possible. The Irish Health and Safety Authority stresses, however, that a reconsideration of the entire design is needed to ensure that the system remains effective. A full technical commissioning process is also required in such a case (HSA, 2014). Whether such an adaption or extension is associated with (significantly) lower costs than the implementation of a new system is unknown.

In addition to selecting the most appropriate system, training of employees using the system as well as regular maintenance and record keeping are reported as crucial steps to ensure adequate and effective control of exposure over time. Besides the one-off investment costs associated with implementing LEV, additional operating costs will thus be incurred, e.g. for changing and cleaning filters, and training employees (HSA, 2014). The replacement of filters is reported to be a major cost component in relation to operating costs, with replacement being required every one to four years (HSE, 2017). Air cleaning systems or filters are however not part of all LEV systems. Depending on the process, captured emissions are either transported to an exhaust point or to a filter. Filtration is especially important where the captured chemical is posing a hazard to the environment (HSA, 2014). For the production of man-made fibres, releases to the environment are, as also mentioned in Section 1.3, one of the major described reasons for solvent losses during the production process (ECHA, 2012a; OECD, 2001). An assessment report of the OECD on DMAC furthermore states that releases of DMAC to the environment, are amongst other sources, expected through exhaust gas (OECD, 2001). This suggests that no filters are used to prevent emissions from reaching the environment. As a result, the Dossier Submitter assumes that filters are of relevance to at least some of the downstream users of DMAC and/or NEP. Required staff training should be explained in the specification provided by the LEV system provider, who should also provide a detailed user manual for training purposes. Staff training generally aims to develop knowledge on the system elements and how they work, on how to use the system effectively, limitations of the system and behavioural actions rendering the system ineffective. Apart from ensuring the effectiveness of the system, such training also enables staff to carry out routine checks by, for example, creating knowledge on how to recognise a damaged part based on visual inspections and how to use air flow measuring instruments (HSA, 2014).

To guarantee ongoing performance to design, more extensive testing of the LEV should also be carried out regularly – at least every 14 months according to authority recommendations

[1] *Technical options vary widely and range from small on-tool extraction devices to different types of hoods, booths and different forms of enclosures, i.e. small-scale, partial and total enclosures.*

[2] *Air filtering systems range from a simple filter system to a multi-component system including pre-filters and scrubbers. In some applications, no air cleaning system is needed at all.*

[3] *Available air movers include several types of fans, e.g. centrifugal fans, propellers and axial fans, as well as compressed-air-driven air movers.*

or more often, where this is recommended by the LEV manufacturer. Aspects to be tested include, amongst others, exhaust performance rates, checks of moving parts for wear and tear, e.g. fan motors, and checks for corrosion. Testing can either be carried out by a sufficiently qualified employee with competence in the operation of LEV systems or external service providers (HSA, 2014). Prices of external service providers appear to depend on the type, quantity and location of LEV systems (MBHS, 2022). As a general estimate, one UK-based service provider declares a cost for testing one LEV system, with up to 10 extraction points, of £190 (excluding value added tax) (MBHS, 2022). In the case of adaptations and extensions of existing LEV systems in response to the proposed restriction, changes in overall testing costs could be minor and are thought to be mainly related to the need for an additional testing round prior to expiration of the 14-month period and potentially higher costs for each test if the complexity of the system increases.

In relation to operating costs, an increase of the degree of enclosure and the isolation of unused hoods, by for example using dampers, are reported as beneficial for limiting operating costs. Where recirculation of air is possible following filtration, this is reported to help with limiting energy costs and reducing the costs for heating and cooling. It also limits the cost for make-up air needed to replace extracted air. If not replaced, sever draughts may occur with negative effects on the effectiveness of the system (HSE, 2017).

Implementation of a stricter glove regime (with specific activity training)
The Dossier Submitter anticipates that implementation of a stricter glove regime (with specific activity training) compared to the current situation is one of the most likely risk management measures to be implemented to reduce dermal exposure and achieve compliance with the proposed restriction. Such training can either be provided by in-house occupational hygienists or be outsourced to occupational health and safety service providers. Training costs are composed of direct costs for preparation and delivery of the training and indirect costs associated with attendance of the training, i.e. the loss of time that could have been spent on other tasks, henceforth referred to as lost productivity of the employees. When the training is provided by external training providers, the direct costs relate to the price paid by the downstream user for commissioning the training. In case the training is provided in house, additional direct costs are only incurred if additional personnel needs to be hired to have the capability and capacity to deliver such training in-house. As costs for additional full-time employees are deemed to exceed the costs associated with hiring external service providers, the Dossier Submitter assumes that companies affected by the restriction only decide to task in-house experts with delivering the training if such staff members have sufficient spare capacity for delivering the training. As a result, only indirect costs from lost productivity of participants are deemed to be relevant for the estimation of societal costs when the training is provided by in-house experts.

Costs associated with lost productivity are calculated by multiplying the training duration – estimated based on expert judgement – by an hourly cost estimate calculated based on the gross added value per employee (Eurostat, V91130) for the relevant sectors (see Table 29). The hourly cost for a commissioned trainer is estimated based on the turnover per employed person (Eurostat, V91100) in relevant sectors (see Table 30). All estimates are based on EU-27 average figures for the most recent year for which data is available and are inflation adjusted to 2021 prices (Eurostat, B1GQ price index). Yearly figures are adjusted to hourly costs assuming 250 working days per year (Eurostat, 2018) and eight hours of work per day. When more than one relevant NACE-R2 code is identified, the reported estimate represents the average.

Table 29: Lost productivity cost (per hour) per sector based on gross value added per employee. (Figures are EU-27 averages based on the most recent data available for the period between 2017 and 2019, 2000 working hours per year and adjusted to 2021 prices).

Sector	**NACE_R2 Labels (code)**	**Estimated lost productivity costs per hour (€)**
Formulation	Manufacture of chemicals and chemical products (C20) Manufacture of other organic basic chemicals (C2014)	85
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	Manufacture of pesticides and other agrochemical products (C202) Manufacture of other chemical products (C205) Manufacture of basic pharmaceutical products and pharmaceutical preparations (C21)	75
Use as solvent in the production of man-made fibres	Manufacture of man-made fibres (C206)	43
Use as solvent in coatings (wire coaters)	Treatment and coating of metals; machining (C256) Treatment and coating of metals (C2561) Manufacture of electrical equipment (C27)	30
Use as solvent in the production of polysulphone membranes	Manufacture of medical and dental instruments and supplies (C325)	37
Use as solvent in coatings (other)	Manufacture of paints, varnishes and similar coatings, printing ink and mastics (C203)	40
Binder and release agent	Manufacture of paints, varnishes and similar coatings, printing ink and mastics (C203)	40
Cleaning agents	Manufacture of soap and detergents, cleaning and polishing preparations (C2041)	43

Table 30: Hourly cost for a trainer based on turnover per employed person. (Figures are EU-27 averages from 2019,2000 working hours per year and adjusted to 2021 prices).

NACE_R2 Labels (code)	**Estimate of trainer costs per hour (€)**
Professional, scientific and technical activities (M) Management consultancy activities (M702) Engineering activities and related technical consultancy (M7112) Other professional, scientific and technical activities (M74) Other professional, scientific and technical activities n.e.c. (M749)	56

Based on expert judgement, the Dossier Submitter assumes the duration of the specific activity training to be between one and four hours for employees, depending on the specific daily tasks of the employee. The time investment of trainers, including preparation and delivery of the training as well as travel time, is estimated at between eight and 16 hours. A group size of 20 participants per training is assumed by the Dossier Submitter in line with what has been assumed in the Annex XV dossier proposing a restriction on diisocyanates. Based on desk research and data from practice, the Dossier Submitter for the restriction on diisocyanates identified 20 participants as the most optimal group size in terms of the cost-benefit ratio of such training activities. This evaluation also took into account maximum capacities declared by relevant identified training options, e.g. courses offered by education centres (ECHA, 2018). This group size for the specific activity training could be higher or lower depending on company specifics such as on-site facility capacities and the number of workers performing specific tasks. However, no specific information is available to deviate from the previously estimated most optimal group size. Implications of changing the group size are assessed in Annex D. To estimate the cost per worker associated with training provided by external occupational health and safety providers, one twentieth of the trainer cost is therefore added to the cost associated with lost productivity. The estimated costs per worker are displayed in Table 31. These cost estimates constitute a high-range estimate. If training is instead delivered by in-house experts, the average training costs are lower (14%-31%) due to only covering productivity losses of participants.

Table 31: Cost estimate per worker per training for the implementation of a stricter glove regime (with specific activity training).

Sector	**Cost estimate (€/worker)**		
	Min	**Max**	**Average**
Formulation	110	380	250
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	97	340	220
Use as solvent in the production of man-made fibres	65	210	140
Use as solvent in coatings (wire coaters)	52	160	110
Use as solvent in the production of polysulphone membranes	60	190	130

Use as solvent in coatings (other)	63	210	130
Binder and release agent	63	210	130
Cleaning agents	66	220	140

In the absence of further information, the Dossier Submitters considers a training frequency of once every four years – in line with the estimate made by the Dossier Submitter for the restriction on diisocyanate.

2.4.2. Other potential costs

Biomonitoring
Consideration of regular biomonitoring campaigns to ensure that operational conditions and risk management measures are sufficient to adequately reduce combined exposure is advisable, especially when workers perform multiple tasks that are associated with potentially high exposure levels during one shift. Participation in biomonitoring is not compulsory for workers.

Under certain conditions, workplace-specific biomonitoring data can be used to assess if combined exposures are below the BLV associated with the proposed DNEL (see also the section below on company-specific CSRs). A BLV could only be derived for DMAC, hence this section is only relevant in relation to the downstream use of DMAC.

A company or workplace biomonitoring campaign can be executed by in-house occupational hygienists or physicians or can be outsourced to occupational health and safety service providers. It is anticipated that the analytical work, i.e. the determination of the DMAC metabolite (NMAC) in urine samples, is performed by accredited analytical laboratories.

Based on expert judgement, the Dossier Submitter makes the following assumptions to produce a rough annual cost estimate per worker for biomonitoring:

- It is assumed that two measurements are taken per worker per year. Measurements consist of a post shift urine sample.
- Productivity losses for workers are assumed to be minor. Information on the biomonitoring scheme and sampling procedure can be provided by leaflets in combination with a short oral explanation on the first measurement day. Actual sampling is not considered to result in major productivity losses. A one-hour productivity loss is incorporated in the cost estimate to jointly account for these aspects.
- The time investment for occupational hygienists or physicians is estimated to consist of:
  - Preparatory work and information provision on site (one day);
  - Measurement days (two days per measurement round; i.e. four days in total); and
  - Analysis and reporting (two days per measurement round; i.e. four days in total).

Assumed time requirement for the occupational hygienist or physician on measurement days are based on an eligible group of between 10 and 40 workers. Sufficient time is needed for the occupational hygienist or physician to monitor the workers during their shift to accurately describe the performed tasks and report any relevant deviations that could influence the exposure to DMAC. The eligible group size per measurement round, and hence, the time investment needed for this monitoring can vary between sectors and companies.

Only one source for the analytical costs associated with biomonitoring could be identified. The United Kingdom Health and Safety Laboratory quotes a price of £66 (~€79[4]) per sample for a gas chromatography–mass spectrometry (GC-MS) analysis of NMAC in urine (HSE, 2022). In the absence of other data, this estimate is used for the cost assessment. Costs related to the time investment by external occupational hygienists are estimated using the same hourly rate as determined for the specific activity training (see Table 30). Table 32 states the calculated costs based on the aforementioned assumptions in euros per worker per year. Costs are expected to be lower (51%-57% less than the average) if sampling is undertaken by an in-house occupational hygienist or physician assuming that existing staff members have sufficient spare capacity.

Table 32: Cost estimate for a biomonitoring campaign per worker per year.

Sector	**Cost estimate (€/worker/year)**		
	Min	**Max**	**Average**
Formulation	340	650	490
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	330	640	480
Use as solvent in the production of man-made fibres	300	600	450
Use as solvent in coatings (wire coaters)	290	590	440
Use as solvent in the production of polysulphone membranes	300	600	450
Use as solvent in coatings (other)	300	600	450

Company-specific CSR based on own measurements or higher tiered models
The proposed restriction allows continued industrial use of DMAC and NEP with adequate risk management measures as indicated in Section 2.3. It is anticipated that registrants of DMAC and NEP will update their registration dossiers with additional OC and/or RMM for the various exposure scenarios and use first tier exposure models to estimate inhalation and dermal exposures. Details of all working conditions are not known by the Dossier Submitter; however some downstream users might not be able to meet all operational conditions and/or risk management measures prescribed by the registrant in the relevant exposure scenario whilst actual workplace exposures might be below the proposed DNELs. In that case the development of a company-specific CSA and preparation of a downstream user CSR (DU CSR) with higher tier models and/or company-specific measurements is imminent.

The Dossier Submitter estimates the costs for downstream users based on expert judgement and average EU-27 cost figures. Two options are foreseen by the Dossier Submitter, i.e.:

- The DU CSR is prepared based on higher tier models; and.
- The DU CSR is prepared based on measurements.

[4] *European Central Bank exchange rate of 17 March 2022: 0.84 EUR per GBP*

Under both options, the preparation of the DU CSR can be done by in-house occupational hygienists or can be outsourced to occupational health and safety service providers. The time investment for the preparation of the DU CSR is dependent on the number of exposure scenarios, associated contributing exposure scenarios and PROCs to be included in the DU CSR. On average about four exposure scenarios (i.e. formulation, charging and discharging, manual maintenance (cleaning and repair) of machinery and an exposure scenario describing the company-specific use) with between one and five associated PROCs are assumed to be included in the DU CSR. Based on expert judgement, the Dossier Submitter estimates the average time investment for the preparation of a DU CSR based on higher tier models as follows:

- One day for preparation and site visit
- One day per exposure scenario for higher tier based modelled exposure estimations (four days in total)
- One day for risk characterisations and reporting

No other costs components are considered under this option and the hourly service provider costs shown in Table 30 are used for the total cost estimate.

For the preparation of a DU CSR based on own measurements, the Dossier Submitter considers the costs of a biomonitoring campaign to represent the upper limit for measurement costs. Biomonitoring data reflects both dermal and inhalation exposure and could therefore be used to determine combined exposure. Especially for dermal exposure, where measurements in the workplace are particularly difficult, biomonitoring can be a useful alternative measurement approach to ensure that exposure through both the dermal and the inhalation route is adequately controlled - even if not all prescribed conditions of use could be implemented. Alternative measurements campaigns, for instance focussing on only inhalation exposure, would only be implemented if the costs are lower. This section describes only the additional costs for the preparation of a DU CSR. The costs for a measurement campaign are provided in Table 32.

Reported monitoring data is considered fairly compatible with the described exposure scenarios although some effort will be needed to incorporate the measurement data with the identified exposure scenarios. As a result, the time investment is anticipated to be similar as for the higher tier model estimations. Based on expert judgement, the Dossier Submitter estimates the time investment for the preparation of a DU CSR based on own measurements, excluding measurement campaign costs, to be:

- One day for preparation and the site visit;
- One day per exposure scenario to incorporate the reported measurements for exposure estimations (i.e. four days in total); and
- One day for risk characterisations and reporting.

No other costs components are considered under this option and the hourly costs shown in Table 30 are used for the total cost estimate.

The preparation of a DU CSR as a result of the proposed restriction is considered to be a one-off cost. Although the REACH Regulation requires companies to update their registrations on their own initiative 'without undue delay' when their chemicals data, tonnage band or company information changes, this does not apply to DU CSRs. Assuming that existing staff members have sufficient spare capacity, costs are expected to be significantly lower (down to zero costs) if the preparation is undertaken by an in-house occupational hygienist.

Table 33: Cost estimates for the preparation and update of a DU CSR (excluding measurement costs).

Cost description	**Cost estimate (€)**
Preparation of a DU CSR based on higher tier models or measurement campaign	2 700

2.4.3. Summary of cost estimates

A precise estimate of the total costs incurred by each sector cannot be provided by the Dossier Submitter as details of the exact working conditions, the number of exposed workers and the necessary additional risk management measures required by each affected company in each relevant sector are not known. Estimated costs relate to the costs of implementing additional risk management measures to reduce exposure levels below the proposed DNELs – and thereby achieve compliance – and other foreseen compliance costs. No generic cost estimate for implementing a LEV system or enhanced ventilation is provided given the variety of parameters relevant for designing a suitable and effective LEV. This is mainly relevant for exposure to DMAC in the man-made fibre sector and the all sectors working with NEP. In addition, feasibility and related costs (per workplace) of administrative measures, for instance, a reduction of the time that a worker is tasked with an activity with a significant exposure potential, i.e. changes in staff rotation, is not assessed as this requires detailed information of the company processes.

For the discontinuation of products with a high NEP content in professional settings, only minor substitution costs are expected given the generic product purposes (e.g. graffiti and paint remover, leather finishing agent and as hardener for isocyanate-based sealers used on flooring) with a small market share and the availability of less hazardous product alternatives. These are not quantified by the Dossier Submitter.

The cost elements that could be estimated are summarized in Table 34. Lower costs are expected if the training, sampling or preparation of the DU CSR are undertaken by in-house occupational hygienists. Cost differences between sectors are due to their respective difference in gross added value per employee and are indicative for the profit margins in those sectors. An estimate of the total costs incurred by each sector cannot be provided by the Dossier Submitter as details of the exact working conditions and necessary additional risk management measures required by each affected company in each relevant sector are not known.

Table 34: Summary quantified costs estimates per sector and measure to comply with the proposed restriction for DMAC and NEP.

Sector	**Cost description**		
	Implementation of a stricter glove regime	**Biomonitoring campaign**	**DU CSR**
	(€/worker/training) (min-max)	**(€/worker/year) (min-max)**	**(€/company)**
Formulation	250 (110-380)	490 (340-650)	2 700
Use as solvent in the production of agrochemicals,	220 (97-340)	480 (330-640)	2 700

pharmaceuticals and fine chemicals			
Use as solvent in the production of man-made fibres	140 (65-210)	450 (300-600)	2 700
Use as solvent in coatings (wire coaters)	110 (52-160)	440 (290-590)	2 700
Use as solvent in the production of polysulphone membranes	130 (60-190)	450 (300-600)	2 700
Use as solvent in coatings (other)	130 (63-210)	450 (300-600)	2 700
Binder and release agent	130 (63-210)	*Biomonitoring only relevant for use of DMAC, while this sector refers to a use of NEP*	2 700
Cleaning agents	140 (66-220)	*Biomonitoring only relevant for use of DMAC, while this sector refers to the use of NEP*	2 700

2.5. Human health and environmental impacts

Based on the current estimated worker exposures to DMAC and NEP in different industrial and professional settings, the risk characterisation leads to RCRs >1 for many uses. The main concern related to DMAC and NEP worker exposure are developmental health effects. Both DMAC and NEP are classified as reprotoxic category 1B. In addition to developmental effects, liver effects are identified as sensitive endpoint for both substances and local nasal irritation for NEP. The most sensitive health effect per exposure route is taken as point of departure for the derivation of the DNELs (see Table 20 and Table 21).

This section discusses the human health impacts of the proposed restriction. Any environmental impacts are outside the scope of this Annex XV dossier. A reduction in exposure, by means of prescribing binding DNELs to be used in CSAs, results in a reduction in health risks and consequently a reduction in negative health effects in humans for both substances. The potential adverse human health effects of DMAC and NEP are mainly based on results from animal studies. A qualitative description of these potential effects is given and its relevance to human health.

The Dossier Submitter considers the extrapolation and quantification of the identified health effects from animal studies to human health effects too uncertain. In addition, the proportionality of the proposed restriction is assessed through comparison of the estimated costs per worker for risk reduction across dipolar aprotic solvent restriction dossiers. As the net societal welfare change is not quantified, there is also no need for a quantified and monitised human health impact.

2.5.1. Qualitative description of health effects of DMAC

The most relevant human health endpoints of DMAC are developmental and liver effects, depending on route of exposure.

Exposure to DMAC via inhalation shows developmental effects in animal studies. Although liver effects are observed in animal studies at lower concentrations, human cohort data indicates safer higher exposures for humans for the inhalation route. The most sensitive observed effects in animal studies are an increase in visceral (internal organs) variations and an increase in skeletal malformations in foetuses. At higher exposure levels, indicative of the higher end of the estimated worker inhalation exposure to DMAC, additional effects are observed: an increase in cardiovascular malformations, an increase in skeletal variations and a reduced foetal body weight.

The human relevance of these effects cannot be assessed with certainty as no human case reports on DMAC-induced developmental toxicity are available. However, the clear developmental toxicity observed in two animal species support the assumption that human inhalation exposure to DMAC can lead to malformations and variations of different forms in foetuses and a reduced birth weight.

Oral exposure, used as proxy for the dermal exposure, to DMAC shows liver effects in animal studies as most sensitive endpoint. No human data is available to indicate safer higher exposures for humans for the dermal route. The most sensitive observed effect in animal studies is an increase in relative liver weight. At higher exposure levels, indicative of the higher end of the estimated worker dermal exposure to DMAC, additional liver damage is observed. At even higher exposure levels, reflecting the highest estimated worker dermal exposure to DMAC, developmental toxicity is observed in the form of increased head malformations in foetuses.

The human relevance of these effects cannot be assessed with certainty. Although human cohort studies demonstrate the liver toxicity potential of DMAC exposure (see Annex B.5.2.2.1), the data also indicates safer higher inhalation exposures for humans compared to the studied animals. In absence of human studies indicating safer higher dermal exposures, the observed liver effects in animals support the assumption that human dermal exposure to DMAC can lead to liver damage and malformation in foetuses, although the latter only at high exposures.

Overall, current occupational exposure to DMAC is associated with human health risks for i) malformations and variations of different forms in foetuses, ii) a reduced birth weight and iii) liver damage.

2.5.2. Qualitative description of health effects of NEP

The most relevant human health endpoints of NEP are developmental effects, liver effects and local nasal irritation depending on the exposure heights.

The DNEL for systemic effects of NEP via inhalation is based on the highest dose tested in animal inhalation studies although no systemic effect are observed in the highest dose. Therefore, it cannot be assessed what type of health effects are expected at higher concentrations and how this relates to human health effects. Given its similarity with NMP, it could be possible that similar effects are expected at higher concentrations as seen with NMP at higher concentrations. Animals exposed to NMP at concentrations five times higher than the highest dose tested with NEP showed reduced body weight, reduced body weight gain and reduced food consumption (ECHA, 2014a). The exposure level at which these effects of NMP are observed in the animal studies are indicative of the higher end of the estimated

worker inhalation exposure to NEP. Local effects in animal studies are observed t similar exposure levels to NEP as the DNEL for systemic effects. The most sensitive observed effect is an increase in degeneration and/or regeneration of olfactory epithelium. At higher exposure levels, indicative of the higher end of the estimated worker inhalation exposure to NEP, developmental toxicity is observed in the form of increased in cardiovascular and skeletal malformations in foetuses.

The human relevance of these effects cannot be assessed with certainty as no human (case) studies with NEP are available. For the systemic effects observed for NMP, the relevance for humans is described in the Annex XV dossier (ECHA, 2014a) as "a person would eat less and loose some body weight, probably combined with some loss in general well-being". The observed local effects of NEP in animal studies could be translated into some irritation of the mucous membranes in the nose. The observed effects in animal studies with NEP support the assumption that human inhalation exposure to NEP can lead to irritation of the mucous membranes in the nose, reduced food intake and some body weight loss, probably combined with some loss in general well-being and malformations in foetuses.

Oral exposure, used as proxy for the dermal exposure, to NEP shows liver effects in animal studies as most sensitive endpoint. The most sensitive observed effect in animal studies is an increase in relative liver weight. At higher exposure levels, indicative of the higher end of the estimated worker dermal exposure to NEP, body weights are also reduced. In addition, reduced foetal body weights are observed at this exposure level.

The human relevance of these effects cannot be assessed with certainty as no human studies with NEP are available. In analogy with NMP, the human relevance for the observed decrease in body weight could be described as a person losing some body weight probably with some loss in general well-being. The observed effects in animals support the assumption that human dermal exposure to NEP can lead to liver damage, some body weight loss, probably with some loss in general well-being and a reduced birth weight.

Overall, current occupational exposure to NEP is associated with human health risks for i) irritation of the mucous membranes in the nose, ii) liver damage, iii) reduced food intake and some body weight loss, probably combined with some loss in general well-being, iv) malformations in foetuses and v) a reduced birth weight

2.5.3. Risk reduction capacity

No human health effects are quantified, instead a proxy for the health impact of the proposed restriction is assumed: the risk reduction for health effects in the worker population exposed to DMAC and NEP. The proposed restriction reduces DMAC and NEP exposures, and subsequent health risks, to acceptable levels and ensures workers using DMAC or NEP are no more at risk for health effects such as: malformations and variations of different forms in foetuses, ii) a reduced birth weight, iii) liver damage, iv) irritation of the mucous membranes in the nose, v) reduced food intake and some body weight loss, probably combined with some loss in general well-being. The total worker population exposed to DMAC and NEP is not known, therefore no estimate can be made about the population at risk in absolute numbers and associated risk reduction capacity.

2.6. Other impacts, practicability and monitorability

2.6.1. Distributional impacts

The benefits of the proposed restrictions on the use of DMAC and NEP are mainly received by the workers in companies that have not yet implemented operational conditions and appropriate risk management measures to limit inhalatory and dermal workplace exposures

below the proposed DNELs. Their risk of developing long-term liver and developmental effects from occupational exposure to DMAC and/or NEP decreases. Also employers and European Member States may benefit e.g. due to savings in health care costs and reduced sick leave days. The costs are faced by the companies who have to change operational conditions and implement additional risk management measures. These costs are at least to some extent expected by the Dossier Submitter to be transferred to costumers in form of higher prices of products, while in other sectors it might effect profitability. Competitors who have already the proposed risk management measures in place may have a competitive advantage and could take over market shares from companies affected by the restriction.

2.6.2. **Enforceability**

Enforcing a restriction prohibiting use with occupational exposure over the DNEL is not always straightforward. Enforcement of the compliance with the restriction may be carried out by national labour inspectors and/or REACH enforcement authorities depending on the Member State.

In principle, a downstream user is compliant with the restriction when they apply the operational conditions and risk management measures from the SDS and exposure scenarios (provided that these are developed using the binding DNELs as reference values). However, when the use deviates from the exposure scenario, the user has to apply scaling or perform his own assessment. The user has to comply with OSH legislation as well, specifically the CAD. Most companies will have to perform a workplace risk assessment. This may overlap with the exposure scenario and can help to demonstrate compliance with the restriction as well. The compliance of downstream users can be checked by evaluating the exposure assessment performed by the company as part of a REACH CSA or an assessment under the CAD (98/24/EC), and by checking if the OC and RMM are implemented. However, some OC and RMM are not easily checked by inspectors (e.g. the effectiveness of a ventilation system or the frequency of a task). The risk assessment can be based on measurements during representative working conditions or on a quantitative risk assessment model like the tier 1 exposure assessment models under REACH. The inspector checking the restriction therefore has to have knowledge of the use and interpretation of both methods.

Manufacturers or downstream users may use air monitoring (preferably by personal sampling) to collect information allowing confirmation of compliance with the restriction with regards to inhalatory exposure. Performing actual workplace exposure measurements is for most inspectors not a viable option given that this requires careful planning. Instead, the inspector should be able to assess the representativeness and quality of the results of workplace measurements performed by the inspected company and use the data in a weight of evidence approach to conclude on compliance with the restriction.

In the workplace exposure assessment under OSH, the assessment of dermal exposure is generally performed in a qualitative manner. However, to assess compliance with the proposed restriction, a quantitative evaluation is necessary. The monitoring of dermal exposure is very complex and may not give results that are sufficiently accurate. In case of dermal exposure, modelling, biomonitoring or a combination of both could give more information about actual exposure levels (sum of all exposure routes). Biomonitoring can be used in the exposure assessment for substances with a clear relation between (external) exposure and concentration of the substance or its metabolites in biological media, and a standardised method to measure the biological concentration. Under those conditions, a biological limit value that corresponds to the DNEL can be derived. This is the case for DMAC as shown in paragraph 1.1.4, and therefore biomonitoring could be used to demonstrate compliance with the restriction for DMAC. The national regulations with regards to biomonitoring (implementation of OSH legislation) may vary between EU countries. In some countries biomonitoring data are regarded as exposure data, whereas in other countries they should be treated as medical (confidential) data. Similarly, some countries may not accept

the results of biomonitoring campaigns as an exposure assessment and require air monitoring as well. Worker participation in biomonitoring campaigns is usually on a voluntary basis. REACH and OSH enforcement authorities should discuss the national position before initiating actual enforcement activities. When a company has performed biomonitoring, inspectors should be able to assess the representativeness and quality of the results.

In general terms safe use in compliance with the proposed restriction should be guaranteed by the use of preventative measures that are applied in the order of the so-called "hierarchy of control", an established concept referred to in the CAD, i.e. substitution, enclosure, engineering controls (e.g. increased local exhaust ventilation), collective protection measures and organisational measures (e.g. increased general ventilation or task rotation) and if needed personal protective equipment. This hierarchy of risk management measures is mentioned in the REACH guidance on information requirements and CSA, chapter R14 (the STOP-principle): substitution, technical measures, organizational measures and/or personal measures (ECHA, 2016).

The proposed restriction on DMAC and NEP shows a high resemblance with the restriction on NMP that entered into force in April 2018 and entered into effect on May 9, 2020 for most uses (wire coating applications derogated until May 9 , 2024). Since the NMP restriction was the first restriction of the mandatory DNEL type, a guideline was developed by ECHA in cooperation with member states and industry representatives (ECHA, 2019b). The NMP guideline is an important point of reference for the currently proposed restriction as the approach how to comply with the REACH restriction and how to check for compliance will be largely comparable. The guideline was drafted to help users of NMP comply with the restriction and to help authorities understand what is expected and how to evaluate the compliance at a site. The guideline explains that its general approach can also be applied to other aprotic solvents similar to NMP (such as DMF and DMAC), if similar REACH restrictions are introduced for other aprotic solvents. In November 2021 the European Commission decided on a restriction for DMF (European Commission, 2021) .

The Dossier Submitter recommends the NMP guideline is updated as soon as a decision on the legal implementation of the DMAC and NEP restriction is taken. The NMP guideline should be amended to extend its scope and account for specific aspects relevant for uses of DMAC and NEP and the differences in regulatory status with respect to the presence of (I)OELVs under the CAD.

2.6.3. Practicality

The practicality of implementing adequate risk management measures to control dermal and inhalation exposure to DMAC and NEP below the DNELs depends on the company specific workplace situation. The Dossier Submitter considers technical and operational workplace measures to reduce inhalation and dermal exposures below the DNELs technically feasible and proportionate to the risk.

The fact that the proposed restriction does not specify or in any other way delimit the operational conditions and/or risk management measures to be implemented to reduce exposure levels below the DNELs in general increases the practicality of the restriction for industrial and professional users. The DNELs are binding and apply to all workplaces across sectors affected. The need to implement additional measures may vary widely across sectors and companies and the restriction offers flexibility in the implementation of operational conditions and risk management measures.

The timing of the entry into force of the restriction is an important aspect affecting its implementability. Registrants will need to make changes in their CSAs and communicate in the supply chain the changes made through the (e)SDS. Affected downstream users will need

time to implement measures to become compliant with the DNELs. Given the long period between the implementation of the NMP restriction, the Commission general RMOA on the polar aprotic solvents, the preparatory work for this restriction including several stakeholder consultations the Dossier Submitter considers a transition period of 18 months a reasonable timeframe positively affecting implementability.

2.6.4. **Monitorability**

There are no specific concerns with regard to the monitorability of the proposed restrictions on DMAC and NEP. This can be done through enforcement and would normally include verification of workplace exposure levels.

2.7. Proportionality (including comparison of options)

In line with the conclusions in the section on Risk Management Options (Section 2.2), only the second restriction option (i.e. a restriction prescribing binding DNELs to be used in CSAs, communicated in the supply chain and risks managed accordingly) is further assessed in the economic and health impact assessment. The proposed restriction reduces the number of workers at risk of developmental and/or liver health effects to zero at some costs for industry. The Dossier Submitter did not attempt to estimate the net societal welfare change of the proposed restriction via a cost-benefit analysis due to the uncertainties in the quantification of both health impacts and economic costs.

To assess proportionality, a comparative approach is taken. Instead of quantifying the net societal welfare change, costs and benefits of the proposed restriction are, where available information permits, compared to the cost and benefits of the two existing REACH restrictions of very similar nature that target other dipolar aprotic solvents: NMP and DMF. Proportionality is assessed by comparing the estimated costs per worker for reducing exposure below the imposed DNELs. Cost estimates derived in the NMP and DMF dossiers serve as a benchmark for assessing the proportionality of the proposed restriction on DMAC and NEP. If the estimated costs per worker for reducing DMAC and NEP exposures below their respective DNELs are similar or lower than the estimated costs per worker in other dossiers, the proposed restriction is considered likely to be proportionate. Given that no precise cost estimates at sector level could be developed for DMAC and NEP, this approach has limitations. As noted in Section 2.4, the Dossier Submitter does not have sufficient knowledge of all working conditions in affected companies in order to provide a complete overview of all necessary additional operation conditions and risk management measures. In addition, no generic cost estimate for implementing a LEV system can be provided by the Dossier Submitter (as noted in Section 2.4.1) given the variety of parameters relevant for designing a suitable and effective LEV system. The costs of other possible operational conditions such as a reduction of the time that a worker is tasked with an activity with a significant exposure potential, i.e. changes in staff rotation, could also not be assessed. Therefore, the aforementioned comparative approach does not provide a complete assessment of the proportionality of the proposed restriction as it is solely based on the anticipated operational conditions and risk management measures that could be quantified and does not provide an indication on the specific measures that will be implemented by affected companies in each sector. As a conservative approach, the total costs associated with implementing all measures for which cost could be quantified are computed. In practice, companies might however not implement all of these measures.

From a benefits perspective, this comparative approach is justified if the exposure reduction achieved by the assessed restrictions results in similar health benefits. NMP and DMF – the

benchmark cases – are dipolar aprotic solvents with a similar toxicological profile as DMAC and NEP. For both NMP and DMF, inhalatory and dermal DNELs are based on developmental effects. For DMAC, only the inhalatory DNEL is based on developmental effects. The dermal DNEL for DMAC is based on liver effects although high dermal exposures can also result in a risk for developmental effects, especially in combination with inhalation exposure. For NEP, both the inhalatory and dermal DNEL are based on other health effects than developmental effects. Estimated NEP exposure can in many scenarios however also lead to a developmental health risk. The Dossier Submitter therefore finds a comparative approach considering the cost of other highly similar restrictions on dipolar aprotic solvents, that are based on developmental effects, justified.

To allow for comparison with the cost estimates for DMAC and NEP, cost estimates for exposure reduction per worker need to be extracted from the NMP and DMF dossiers. During the opinion development on the DMF restriction, the Committee for Socio-Economic Analysis (SEAC) concluded that the costs reported by the Dossier Submitter, based on closure of 50% of companies in the polyurethane coating and membrane sector as well as the complete closure of the man-made fibre industry, were severely overestimated. Instead, SEAC found it more likely that additional personal protective equipment (PPE) and organisational measures (e.g. job rotation) would be implemented in cases where technical measures would not be sufficient or feasible (ECHA, 2019 #363). A more robust cost estimate could however not be developed by SEAC. Therefore, only the cost estimate for the NMP restriction is taken forward for the comparative assessment.

The SEAC opinion on the NMP dossier provides cost estimates for the automotive and wire coating sector. Costs are expressed in 2014 prices and constitute a present value per sector over a time period of 15 years. The SEAC opinion also refers to a statement made by the European Winding Wire Group on the number of workers employed at all production sites (ECHA, 2014b). For the automotive sector, the number of workers is stated in the Background Document (confidential information in ECHA, 2014a). Table 35: Restriction on NMP – Present value cost estimates and number of potentially exposed workers (ECHA, 2014a, 2014b). summarizes the available estimates and also provides the inflation adjusted present value in 2021 together with the cost per worker estimate.

Table 35: Restriction on NMP – Present value cost estimates and number of potentially exposed workers (ECHA, 2014a, 2014b).

Sector	**Number of workers potentially exposed**		**Cost estimate (in million €)**				**Cost estimate (in €/worker)**
	Min	**Max**	**2014**		**2021**		
			Min	**Max**	**Min**	**Max**	
Automotive sector	Confidential	Confidential	20	30	22	33	<150
Wire Coating	1 000		19*		22		22 000

**Corresponding to a transitional period of 10 years.*

The cost estimates of the proposed restriction (summarised in Table 34) need to be adjusted to present value estimates over a 15-year period to allow for a comparison with the cost estimate for NMP. A discount rate of 4% is used in line with the discount rate used in the NMP Background Document and ECHA guidance (ECHA, 2008, 2014a). For the stricter glove regime, a training frequency of once every four years is considered with the first training taking place in the first year. The cost associated with the preparation of a DU CSR is

estimated per company instead of per worker in Table 33. For the man-made fibre sector, the winding wire sector and the membrane sector, a sector-specific estimate of the average number of workers per company that are exposed to DMAC can be computed based on information on the number of companies in each sector and the number of potentially exposed workers provided in Table 27. For NEP and all other sectors using DMAC, the number of exposed workers per company is assumed to lie between 83 and 170 workers based on the widest range calculated from Table 27. This information is used to convert the cost per company into a cost estimate per worker.

To estimate the upper boundary for the costs per worker as a result of the proposed restriction, all quantified cost elements are combined in Table 36. Lower costs are expected if part of the time investments are undertaken by in-house occupational hygienists assuming that existing staff members have sufficient spare capacity.

Table 36: Cost estimates, i.e. cost per exposed worker, for DMAC and NEP of the proposed restriction in present value over a 15-year period.

Sector	**Cost description (€/worker) (min-max)**			
	Implementation of a stricter glove regime	**Biomonitoring campaign**	**DU CSR**	**All measures combined**
Formulation	790 (340-1 200)	5 700 (4 000-7 500)	24 (16-32)	6 500 (4 300-8 700)
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	710 (310-1 100)	5 600 (3 900-7 400)	24 (16-32)	6 300 (4 200-8 500)
Use as solvent in the production of man-made fibres	450 (210-690)	5 200 (3 500-7 000)	21	5 700 (3 700-7 700)
Use as solvent in coatings (wire coaters)	350 (170-520)	5 100 (3 300-6 800)	24 (20-27)	5 400 (3 500-7 400)
Use as solvent in the production of polysulphone membranes	410 (190-620)	5 200 (3 400-6 900)	24 (16-32)	5 600 (3 600-7 600)
Use as solvent in coatings (other)	430 (200-660)	5 200 (3 500-7 000)	24 (16-32)	5 700 (3 700-7 600)
Binder and release agent	430 (200-660)	*Biomonitoring only relevant for use of DMAC, while this sector refers to a use of NEP*	24 (16-32)	460 (220-700)
Cleaning agents	460 (210-700)	*Biomonitoring only relevant for use of DMAC, while this*	24 (16-32)	480 (230-730)

		sector refers to a use of NEP		

Based on Table 35 and Table 36 the Dossier Submitter concludes that the quantified costs of the proposed restriction are at least as cost-effective as some of the sectoral costs in the NMP restriction in terms of risk reduction per worker. The comparison between the upper boundary for quantified costs per worker, as a result of the proposed restriction, and the higher benchmark derived from the NMP restriction indicates that the non-quantified costs of the proposed restriction could comprise at least ~13 000 euro per worker (present value over 15-year period) before affecting the conclusion on proportionality.

Although not all costs could be quantified, the Dossier Submitter concludes the proposed restriction likely to be proportionate in reducing the health risks of dipolar aprotic solvents to acceptable levels based on the comparison of costs per exposed worker.

3. Assumptions, uncertainties and sensitivities

In this section, the Dossier Submitter assesses how uncertainties related to key assumptions of the impact assessment presented in the Annex XV restriction report would affect the conclusions about the restriction options and proportionality. The analysis of uncertainties is based on EFSA's guidance on uncertainty analysis and the communication of uncertainty in scientific assessments. In a pragmatic approach, not all assumptions or uncertainties are listed here, only those that are identified by the Dossier Submitter to potentially have an influence on the derived DNEL, identified risks or proportionality are described. Annex D describes the complete uncertainty analysis in more detail.

Based on the examination of every part of the previous assessment, a list of identified key uncertainties is compiled. Both uncertainties associated with the assessment inputs (e.g. data, estimates, other evidence) and uncertainties related to the methodologies (e.g. statistical methods, calculations or models, reasoning, expert judgement) applied to the scientific assessment are considered. In addition, uncertainties are assessed as standard or non-standard. Standard uncertainties are considered explicitly or implicitly addressed by the provisions of a standardised procedure or standardised assessment element. Normally, standard uncertainties do not need to be re-evaluated in each assessment that follows the defined standard procedure because they should have been assessed when the standard procedure was established. If this is not the case, the uncertainty is a non-standard uncertainty. As they are not addressed by any standardised assessment procedures, the identified non-standard uncertainties must be analysed in a case-specific way. This is done in the subsequent steps of the uncertainty analysis. Table 37 summarises the identified uncertainties.

Table 37: Identified uncertainties in the assessment. For more details see Annex D.

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
Section 1.1.4 and B.5., Hazard assessment	1	Study reliability, e.g. key study of Klimisch score 2. Studies of Klimisch score 1 could provide more reliable data.	[X]		S
	2	Differences in exposure conditions, e.g. higher respiratory volume human at the workplace versus rat in rest. This is corrected with default values.		[X]	S
	3	Route-to-route extrapolation, e.g. oral-to-dermal route and oral-to-inhalation route. Data of relevant exposure routes not always available. Extrapolation used to estimate exposure levels.		[X]	S
	4	Assessment factors, e.g. inter- and intraspecies differences. Individual differences and species differences. This is corrected with default values based on expert judgement.		[X]	S
	5	BMD analysis, e.g. setting of BMR at 1, 5 or 10% increased risk or change. The BMR can be set at a different level based on expert judgement.		[X]	NS
Section 1.1.5 and B.9, Exposure assessment	6	In line with the registrants' CSRs ECETOC TRA v3 is selected as first-tier model to estimate worker inhalatory and dermal exposure. Applying higher-tier exposure tools might result in more specific exposure scenario's with different exposure estimations, however this requires more detailed information of the working conditions, which is not available to the Dossier Submitter.		[X]	S

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	7	The exposure scenario and selected PROCs originate from the registration dossier. The Dossier Submitter is not sure if all described exposure scenarios and tasks (expressed in PROCs) are still performed. This concern is supported by communication with industry in which they indicate that some exposure scenarios will not be included in the updated CSR.	[X]		S
	8	ECETOC TRA v3 inhalation validation results indicate a low level of conservatism for PROC5, PROC7, PROC14 and PROC19 activities, possibly resulting in an underestimation of exposure via inhalation.		[X]	S
	9	ECETOC TRA v3 inhalation validation results indicate an overestimation of the efficiency of LEV for PROC7, PROC8a, PROC10, PROC13, PROC14, PROC19 activities, possibly resulting in an underestimation of exposure via inhalation.		[X]	S
	10	ECETOC TRA v3 validation results indicate an overestimation of dermal exposure for PROC1-PROC3 activities.		[X]	S
	11	ECETOC TRA v3 validation results indicate an underestimation of dermal exposure for PROC6, PROC7, PROC10, PROC11, PROC17 and PROC19 activities.		[X]	S
	12	RMM/OC are applied that are considered common industry standard, although these are not prescribed by all registrants in their CSRs. This may result in an underestimation of exposure in some particular working situations.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	13	Default (reasonable) worst-case RMM and protection factors are applied for the use of general ventilation systems, gloves and RPE. A broader range of protection factors is applied by some registrants. Applying default factors is believed to result in an overestimation of exposure when in practice a higher reduction can be reached.	[X]		NS
	14	For PROC1-PROC3 activities LEV, gloves or RPE are not applied by the dossier submitter, resulting in an overestimation of exposure when in practice these RMM are applied.	[X]		NS
	15	A full-shift eight hour is assumed by the dossier submitter for all activities, possibly resulting in an overestimation of exposure when in practice activities are performed during a shorter period and no other activities with the substance are performed.	[X]		NS
	16	Although the Dossier Submitter modelled identical processes with multiple variations of OC and RMM and provided information on the input data for the exposure modelling, resulting in exposure modifying factors, the representativeness of the modelled data for the different sites and uses remains uncertain.		[X]	S
	17	Process temperatures indicated in the CSRs might not correspond well with the actual temperature of the product to which the worker is exposed, resulting in some uncertainty with regard to the correctness of the selected volatility category.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	18	The lack of representative measured air concentrations (personal sampling) for each (sub-) sector leads to some uncertainty with regard to the inhalation exposure.	[X]		S
Section 1.1.6 and B.10 Risk assessment	19	The conclusion on risks is sometimes based on the combined RCRs although the most sensitive endpoint may differ between the inhalation and dermal route.		[X]	S
Section 1.3 and A.1-A.3 Baseline	20	There is limited information on the use of NEP and number of workers exposed to NEP.	[X]		NS
	21	The number of workers potentially exposed to DMAC is only described for a few sectors where DMAC is used.	[X]		NS
Section 2.3 and C.3 Restriction scenario	22	No details of working conditions at workplace level are available for DMAC and NEP, therefore it is not known, at a workplace level, which measures, or combination of measures, are needed to reduce exposure sufficiently.	[X]		NS
	23	Limited information is available about the actual concentration of NEP in formulations used in industrial and professional settings. The impact of the proposed restriction on the continued use of these formulations is uncertain.	[X]		NS
Section 2.4 Economic impacts	24	Not all anticipated OC or RMM could be monitised; e.g. increased ventilation or LEVs and task duration reduction.	[X]		NS
	25	The duration of the specific activity training for a stricter gloves regime, as well as the group size per training are based on judgement.	[X]		NS
	26	The time investment for occupational hygienists and number of measurements per worker in biomonitoring campaigns is based on expert judgement.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	27	The time investment for preparing a DU CSR is based on expert judgement.	[X]		NS
Section 2.7 Proportionality	28	Proportionality is assessed based on only a partial quantification of the costs.	[X]		NS
	29	Only one (NMP) of the two other restrictions on dipolar aprotic solvents had sufficient information to derive a benchmark. Benchmarks could only be derived for two sectors affected by the NMP restriction.	[X]		NS
	30	A discount rate of 4% is used.		[X]	NS

The key uncertainties that could affect the conclusions of the Annex XV restriction report are i) the BMR values in the derivation of the DNELs for DMAC (No. 5), ii) the variation in exposure estimates because of applying or not applying additional RMM by the Dossier Submitter (No. 12-15) and iii) the non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs (No. 24).

The Dossier Submitter deviated from the default BMR values for continuous data (5% change) for relative liver weight and body weight (10%) and for quantal data (10% extra risk) for malformations and post-implantation (1% extra risk). Using the default values would lower the proposed dermal DNEL by a factor of five (DMAC) and two (NEP) and subsequently change the risk assessment (higher dermal RCRs for DMAC, additional dermal risks identified for NEP) and impact assessment (significant additional investments are probably needed for DMAC to further reduce the dermal exposure). This will negatively affect the proportionality.

The deviation in applying RMM by the Dossier Submitter and subsequent variation in exposure will mainly result in an overestimation of exposure. The identified risks for DMAC and NEP would not apply to all working conditions as for some workplaces additional RMM would be in place. Consequently, industry sectors would need to implement less additional RMM or OC to comply with the restriction, positively affecting the total cost of the proposed restriction. Proportionality is assessed on a cost per exposed worker base, i.e. costs needed to reduce the exposure below the proposed DNELs, and is therefore not affected by this uncertainty.

The non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs will negatively affect the proportionality. The proportionality assessment indicates that some additional investments could be made before the conclusion on proportionality changes.

4. Conclusion

DMAC and NEP are dipolar aprotic solvents used in industrial settings and by professionals. Both substances are registered under REACH at substantial volumes and are, amongst others, classified in Annex VI of CLP as reprotoxic category 1B based on developmental toxicity (Repro. 1B; H360D).

DMAC and NEP are used as solvents in the production of various formulations, e.g. in the production of agrochemicals, pharmaceuticals and fine chemicals. DMAC is used as solvent in coating and is extensively used in the production of man-made fibers and films and during the production of PAI enamels (varnishes) used for electrical wire insulation. NEP is applied in cleaning agents and as binder and release agent. NEP is also used in oil field drilling and production operation processes, in functional fluids, in polymer processing, in water treatment, as excipient in agrochemicals and in road and construction applications. Both substances are used as laboratory agent. The manufacture of DMAC and NEP takes place in highly contained systems with exposure most likely to occur during sampling, transfer, maintenance and laboratory activities. Further down the supply chain DMAC and NEP are applied in formulations and used as process chemical. Exposure can occur during transfer activities, during (semi-closed) mixing/blending activities and during maintenance/cleaning activities. Exposure to DMAC may occur during its use as a solvent during fibre production or during the further processing of fibres, both due to inhalation or dermal contact. The application of coatings containing DMAC or NEP by spraying, brushing/rolling or dipping activities may also result in exposure.

In animal studies, the liver is the primary target organ for systemic repeated dose toxicity of DMAC and NEP. Developmental toxicity is observed in the form of reduced foetal body weight and increased incidences of malformation and variations for both DMAC and NEP. Increased post-implantation loss is also observed for NEP. In addition to systemic effects, NEP also induces local nasal irritation after inhalation exposure observed as degeneration/regeneration of the olfactory epithelium. Human studies have demonstrated liver effects in workers upon exposure to DMAC based on biochemistry parameters related to liver function and examination of the liver via ultrasonic and CT imaging.

DNELs are derived by the Dossier Submitter for both substances using the BMD approach that are lower than those used in the CSRs of registration dossiers of DMAC and NEP. Based on the derived DNELs and exposure estimates for industrial and professional use of DMAC and NEP, RCRs above one are calculated for most uses, indicative of an unacceptable risk. The combined RCRs (inhalation and dermal RCRs) for DMAC range from 0.067 to 28.06 across all identified uses. Most RCRs are between 1 and 4. For NEP, combined RCRs range from 0.026 to 22.53. Most RCRs are between 1 and 4 for industrial uses and between 1 and 10 for professional uses, indicative of unacceptable workplace risks across sectors and uses.

It is therefore concluded that human health risks are not adequately controlled for several industrial and professional uses of DMAC and NEP, especially when it concerns processes under elevated temperatures, open processes, and processes that require manual activities. A restriction with binding DNELs for the inhalatory and dermal route for DMAC and NEP is the most appropriate risk management option i) because it effectively reduces worker risks as a consequence of inhalation and dermal exposure, ii) applies equally to all sectors and users in supply chains and iii) allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve. In addition, the proposed restriction offers a high level of flexibility for downstream users to implement appropriate risk management measures where needed and adapt operational conditions to ensure exposure below the respective DNELs.

The proposed restriction is the most appropriate Community-wide measure as action on a Community-wide basis is required to prevent EU-wide unacceptable risks for workers from

exposure to DMAC and NEP. Applications of DMAC and NEP are traded freely and are used in all Member States of the EU. Action at EU level would ensure a 'level playing field' for all producers, importers and users of DMAC and NEP and products containing these substances. In addition, the proposed restriction offers legal consistency with existing restrictions on two other dipolar aprotic solvents NMP and DMF. The proposed restriction is practical because it is implementable, manageable and enforceable.

The proposed restriction is justified as the quantified costs are at least as cost-effective as some of the sectoral costs in the NMP restriction in terms of risk reduction per worker. Therefore, the proposed restriction is considered likely to be proportionate based on a comparative analysis.

The identified uncertainties that could affect the conclusions of the Annex XV restriction report are i) the BMR values in the derivation of the DNELs for DMAC, ii) the variation in exposure estimates because of applying or not applying additional RMM by the Dossier Submitter and iii) the non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs. Using default BMR values would lower the proposed dermal DNEL by a factor of five (DMAC) and two (NEP) and subsequently change the risk assessment and impact assessment. This would negatively affect the proportionality. The deviation in applying RMM by the Dossier Submitter and subsequent variation in exposure will mainly result in an overestimation of exposure affecting the risk and impact assessment but not the proportionality. The non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs would negatively affect the proportionality. The proportionality assessment however indicates that some additional investments achieving compliance would not affect the conclusion on proportionality.

In conclusion, in response to the identified human health risks and to prevent regrettable substitution of dipolar aprotic solvents, the restriction on the placing on the market, manufacturing and use of DMAC and NEP unless manufacturers, importers and downstream users have included mandatory DNELs in the chemical safety reports and safety data sheets is proposed. The proposed entry for the restriction is presented in 2.2.1.

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