Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Annex XV dossier proposing restrictions on

N,N-dimethylacetamide (DMAC); 1-ethylpyrrolidin-2-one (NEP)

ECHA/RAC/RES-O-0000007225-77-01/F

ECHA/SEAC/RES-O-0000007300-87-01/F

9 June 2023

OPINION ON AN ANNEX XV DOSSIER PROPOSING RESTRICTIONS ON DMAC and NEP

Opinion of the Committee for Risk Assessment

and

Opinion of the Committee for Socio-economic Analysis

on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation and the Committee for Socio-economic Analysis (SEAC) has adopted an opinion in accordance with Article 71 of the REACH Regulation on the proposal for restriction of

Chemical name(s):	**N,N-dimethylacetamide (DMAC); 1-ethylpyrrolidin-2-one (NEP)**
EC No.:	**204-826-4; 220-250-6**
CAS No.:	**127-19-5; 2687-91-4**

This document presents the opinions adopted by RAC and SEAC and the Committee's justification for its opinions. The Background Document, as a supportive document to both RAC and SEAC opinions and their justification, gives the details of the Dossier Submitters proposal amended for further information obtained during the consultation and other relevant information resulting from the opinion making process.

PROCESS FOR ADOPTION OF THE OPINIONS

The Netherlands has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV report conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at https://echa.europa.eu/restrictions-under-consideration on **20 June 2022**. Interested parties were invited to submit comments and contributions by **20 December 2022**.

ADOPTION OF THE OPINION

ADOPTION OF THE OPINION OF RAC:

Rapporteur, appointed by RAC:	**Tiina SANTONEN**
Co-rapporteur, appointed by RAC:	**Urs SCHLÜTER**

The opinion of RAC as to whether the suggested restrictions are appropriate in reducing the risk to human health and/or the environment was adopted in accordance with Article 70 of the REACH Regulation on **13 March 2023**.

The opinion takes into account the comments of interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The opinion of RAC was adopted **by consensus**.

OPINION ON AN ANNEX XV DOSSIER PROPOSING RESTRICTIONS ON DMAC and NEP

ADOPTION OF THE OPINION OF SEAC

Rapporteur, appointed by SEAC: **Andreas LÜDEKE**

Co-rapporteur, appointed by SEAC: Jernej ISKRA

The draft opinion of SEAC

The draft opinion of SEAC on the proposed restriction and on its related socio-economic impact has been agreed in accordance with Article 71(1) of the REACH Regulation on **9 March 2023.**

The draft opinion takes into account the comments from the interested parties provided in accordance with Article 69(6)(a) of the REACH Regulation..

The draft opinion takes into account the socio-economic analysis, or information which can contribute to one, received from the interested parties provided in accordance with Article 69(6)(b) of the REACH Regulation.

The draft opinion was published at https://echa.europa.eu/restrictions-under-consideration on **15 March 2023**. Interested parties were invited to submit comments on the draft opinion by **22 May 2023** (due to IT error a longer time was given).

The opinion of SEAC

The opinion of SEAC on the proposed restriction and on its related socio-economic impact was adopted in accordance with Article 71(1) and (2) of the REACH Regulation on **9 June**.

The opinion takes into account the comments of interested parties provided in accordance with Article[s 69(6) and][5] 71(1) of the REACH Regulation.

The opinion of SEAC was adopted **by consensus**.

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1. OPINION OF RAC AND SEAC

The restriction proposed by the Dossier Submitter is:

Table 1: Proposed restriction

Dimethylacetamide (DMAC) CAS-No. 127-19-5 EC-No. 204-826-4	Conditions of the restriction 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. 220-250-6	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 mg/m^3 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.

1.1. THE OPINION OF RAC

RAC has formulated its opinion on the proposed restriction based on an evaluation of information related to the identified risk and to the identified options to reduce the risk as

documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. RAC considers that the proposed restriction on **N,N-dimethylacetamide (DMAC); 1-ethylpyrrolidin-2-one (NEP)** is the most appropriate Union wide measure to address the identified risk in terms of the effectiveness in reducing the risk, practicality and monitorability as demonstrated in the justification supporting this opinion, provided that the conditions are modified, as proposed by RAC.

The conditions of the restriction proposed by RAC are:

Table 2: Restriction proposed by RAC

Substance Identity (or group identity)	Conditions of the restriction
Dimethylacetamide (DMAC) CAS-No. 127-19-5 EC-No. 204-826-4	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 1.8 mg/kg bw/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. 220-250-6	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 [acute exposure value removed] exposure 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.

Note for the attention of the Commission: Since DMAC and NEP can be readily absorbed via exposed skin (see p. 15 and 16), RAC has derived biomarker DNELs to enable biomonitoring, in line with previous restriction opinions on NMP (Annex XVII – entry 71) and DMF (Annex XVII – entry 76). RAC notes that biomonitoring is not needed for REACH enforcement but may provide additional protection for workers.

1.2. THE OPINION OF SEAC

SEAC has formulated its opinion on the proposed restriction based on an evaluation of the information related to socio-economic impacts documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. SEAC considers that the proposed restriction on **N,N-dimethylacetamide (DMAC); 1-ethylpyrrolidin-2-one (NEP)** is the most appropriate Union wide measure to address the identified risks, as concluded by RAC, taking into account the proportionality of its socio-economic benefits to its socio-economic costs provided that the conditions are modified, as proposed by RAC or SEAC, as demonstrated in the justification supporting this opinion.

The conditions of the restriction proposed by SEAC are:

Table 3: Restriction proposed by SEAC

Substance Identity (or group identity)	Conditions of the restriction
Dimethylacetamide (DMAC) CAS-No. 127-19-5 EC-No. 204-826-4	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[1]] 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 1.8 mg/kg bw/day for long-term dermal exposure. 2. Shall not be manufactured, or used, as a substance on its own, as a constituent of

[1] The restriction report states that the Dossier submitter considers a transition period of 18 months a reasonable general timeframe for this restriction (Restriction report ch.2.6.3 p.87(22 April 2022)). SEAC agrees with the general transition period of 18 months with the exception for Dimethylacetamide (DMAC) spelled out in point 3.

	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. 3. The entry into force of the restriction: paragraph 1 and 2 shall apply after 18 months as proposed by the Dossier Submitter, however, after 4 years for the companies in Man-Made Fibre sector.
N-ethyl pyrrolidone (NEP) CAS-No. 2687-91-4 EC-No. 220-250-6	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 – see the footnote 1] 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 exposure 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. 3. The entry into force of the restriction: paragraph 1 and 2 shall apply after 18 months as proposed by the Dossier Submitter.

2. SUMMARY OF PROPOSAL AND OPINION

2.1. Summary of the proposal

The proposed restriction is targeted to control risks identified in the European Union (EU) due

to use of the substances DMAC and NEP in industrial settings and by professionals[2].

Both substances are registered under REACH at substantial volumes and are, amongst others, classified in Annex VI of CLP as toxic to reproduction category 1B based on developmental toxicity (Repro. 1B; H360D).

DMAC and NEP are dipolar aprotic solvents used in the production of various formulations, e.g. in agrochemicals, pharmaceuticals and fine chemicals.

DMAC is also used as a solvent in coatings 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 a 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 an excipient in agrochemicals and in road and construction applications. Both substances are used as a 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 fiber production or during the further processing of fibers, 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.

Regarding human health effects, the liver is the primary target organ in animal studies 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 Dossier Submitter proposed Derived No Effect Levels (DNEL) for both substances using the benchmark dose (BMD) approach. RAC notes that hese are lower than those used in the Chemical Safety Reports of the registration dossiers of DMAC and NEP by the lead registrants. . The Dossier Submitter proposed the following DNELs for workers:

DMAC

- systemic long-term inhalation DNEL: 13 mg/m^3
- systemic long-term dermal DNEL: 0.53 mg/kg bw/day
- biomarker DNEL: of 15 mg N-methylacetamide (NMAC)/g creatinine (mean)

[2] 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. By listing in Appendix 6 of entry 30 of REACH Annex XVII both substances are prohibited for the use in consumer products in concentrations equal or greater than 0.3 %.

NEP

- local acute inhalation DNEL: 4.6 mg/m^3
- systemic long-term inhalation DNEL: 4.0 mg/kg bw/day
- systemic long-term dermal DNEL: 2.4 mg/kg bw/day
- biomarker DNEL: 20 µg 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) plus 2-hydroxy-N-ethylsuccinimide (2-HESI)/L urine (mean)

Based on the 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.

- For DMAC, the combined RCRs (inhalation and dermal) 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.

The Dossier Submitter 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. The Dossier submitter states that a restriction with binding DNELs for the inhalation 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) it applies equally to all sectors and users in supply chains and
iii) it allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve. In addition, the Dossier Submitter finds the proposed restriction offers a high level of flexibility for downstream users to implement appropriate risk management measures (RMM) where needed and adapt operational conditions (OC) to ensure exposure below the respective DNELs.

The Dossier submitter notes the proposed restriction is the most appropriate Community-wide measure as unacceptable risks for workers from exposure to DMAC and NEP occur across the EU. Formulations 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 Dossier Submitter notes the proposed restriction offers consistency with existing restrictions on two other dipolar aprotic solvents 1-methyl-2-pyrrolidone (NMP; EC number 212-828-1) and N,N-dimethylformamide (DMF; EC number 200-679-5) with similar uses and that the proposed restriction is practical because it is implementable, manageable and enforceable and monitorable.

The Dossier submitter finds 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 Dossier Submitter notes 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 benchmark response (BMR) values in the derivation of the DNELs for DMAC, ii) the variation in exposure estimates depending on the RMM taken into account by the Dossier Submitter in their assessment and iii) the non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs.

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 is proposed unless manufacturers, importers and downstream users have included mandatory DNELs in the chemical safety reports and safety data sheets.

2.2. Summary of opinion

2.2.1. RAC opinion summary

RAC derived a different systemic long-term dermal DNEL for DMAC and did not consider a local acute DNEL for NEP as proposed by the Dossier Submitter to be justified . The following DNELs are derived by RAC:

DMAC

- systemic long-term inhalation DNEL: 13 mg/m^3
- systemic long-term dermal DNEL: 1.8 mg/kg bw/day
- biomarker DNEL: 20 mg NMAC/L urine corresponding to 15 mg NMAC/g creatinine collected post-shift at the end of the working week.

NEP

- systemic long-term inhalation DNEL: 4.0 mg/kg bw/day
- systemic long-term dermal DNEL: 2.4 mg/kg bw/day
- biomarker DNEL: sum value of 20 mg 5-HNEP plus 2-HESI /L urine corresponding to 15 mg 5-HNEP plus 2-HESI /g creatinine collected pre-shift the day following exposure and at the end of the working week OR 10 mg 2-HNEP /L urine (7 mg 2-HNEP/g creatinine) measured from post-shift samples and 8 mg 2-HESI/L urine (6 mg 2-HESI/g creatinine) measured pre-shift the day following exposure.

The systemic long-term dermal DNEL for DMAC is higher than that derived by the Dossier Submitter leading to lower risks for the use of DMAC. However, taking this into account, risk characterisation ratios (RCR) above one are still estimated for many of the uses that are described by the Dossier Submitter. **Therefore, RAC concluded in line with the Dossier Submitter that human health risks are not adequately controlled for several industrial and professional uses of DMAC and NEP.**

RAC concludes that a restriction with binding DNELs for the inhalation and dermal route for DMAC and NEP is the most appropriate risk management option because:

i) it effectively reduces worker risks in the case that the DNELs are observed at workplaces,
ii) it applies equally to all sectors and users in supply chains,
iii) it allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve and
iv) DMAC and NEP are not currently prioritised for setting or updating of a binding occupational exposure limit value (BOELV), .
v) In addition, the proposed restriction offers consistency with existing restrictions on two other dipolar aprotic solvents (1-methyl-2-pyrrolidone and N,N-dimethylformamide).

In the opinion of RAC, the proposed restriction is the most appropriate Community-wide measure as uncontrolled risks for workers from exposure to DMAC and NEP occur across 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.

The main uncertainties that could affect the conclusions of the RAC opinion are related especially to the exposure assessment due to limited measurement data from relevant occupational activities. In the hazard assessment, conservative assumptions have been used

to cover related uncertainties, which may result in some overestimation of risks.

RAC recommends an update of the ECHA (2019) NMP guideline[3] to include also other restricted aprotic solvents as soon as a decision on the legal implementation of the DMAC and NEP restriction is taken.

RAC further recommends to derive corresponding Binding Occupational Exposure Limits (BOELs) for NEP and DMAC under the Carcinogens, Mutagens or Reprotoxic substances Directive (CMRD) to ensure a harmonised maximum inhalation exposure level under relevant legislation across the EU and covering of all possible exposure scenarios including e.g. waste management activities.

2.2.2. SEAC opinion summary

SEAC has developed its opinion on the proposed restriction based on an evaluation of the information related to socio-economic impacts documented in the Annex XV report and submitted by interested parties, the opinion of RAC, Forum's advice on enforceability as well as other available information as recorded in the Background Document.

SEAC supports the view that any necessary action to address risks associated with N,N-dimethylacetamide (DMAC) and 1-ethylpyrrolidin-2-one (NEP) should be implemented on an EU-wide basis, based on the key principles of ensuring a consistent level of protection of human health and the environment across the EU and of maintaining the free movement of goods within the union. SEAC notes restrictions of the two other aprotic solvents DMF and NMP when considering the restriction proposal of DMAC and NEP.

SEAC noted that the Dossier Submitter had performed a Risk Management Options Analyses (RMOA) considering: i) authorisation, ii) (an update of) Occupational Exposure Limit (OEL) under Occupational Safety and Health (OSH) legislation, iii) a restriction in the form of a ban with a maximum concentration limit, and iv) a restriction in the form of binding DNELs. The Dossier submitter proposed a restriction in the form of binding DNELs with an 18 months transition period as the preferred risk management option (See section 2.6.3. "Practicality" in Restriction proposal and/or Final Background document).

SEAC noted that the proposed restriction option with binding DNELs would allow continued use of DMAC and NEP but induce additional risk management measures. Concerning the complete ban, SEAC agrees with the Dossier submitter that a complete ban would not be economically feasible.

SEAC concluded that for both substances, DMAC and NEP, setting a binding OEL (BOEL) would ensure a harmonised maximum exposure level across the EU and could be an acceptable risk management option, comparable to a harmonised DNEL for inhalation and dermal exposure if accompanied by a technical guidance document of how to comply with the DNELs (inhalation and dermal). However, SEAC observes the level of the current BOEL for DMAC under the CMRD and that for NEP no indicative or binding OEL on EU level is available and, separately, SEAC agrees that even if prioritised for BOEL setting, the implementation of the limit value would be delayed, and consequently the identified unacceptable risks (in section 3.3) could persist.

Furthermore, SEAC agrees that authorisation under REACH would not be an effective risk management option for either substance since for several of the uses no suitable alternatives are available, and regrettable substitution could take place. Furthermore, intermediate uses

[3] How to comply with REACH Restriction 71, guideline for users of NMP (1-methyl2-pyrrolidone). https://echa.europa.eu/documents/10162/17233/entry_71_how_to_comply_en.pdf/c6e09198-c0b1-44e3-abae-6b3d0bc909a8

would not be covered.

For both substances, SEAC agrees with the Dossier Submitter's listing of the main elements of the company costs relating to the risk reduction measures. These measures comprise, engineering controls (e.g. containment, Local Exhaust Ventilation (LEV)), administrative measures (e.g. staff rotation to limit exposure times), and Personal Protective Equipment (e.g. by training for stricter glove regime, use of gloves, protective cloth and respiratory protection equipment). SEAC agrees that substitution, although effective in principle, may not be a technically (or economically) feasible solution in most cases and SEAC notes that, according to the Dossier Submitter, for some professional uses use of DMAC and NEP will cease. In addition to the RMM costs, the Dossier Submitter considers that the implementation of the restriction proposal may induce biomonitoring costs per worker and company specific costs for downstream user companies updating their CSRs.

SEAC found Dossier Submitter's explanation plausible that, an estimate of the total costs by each sector cannot be provided due to lack of information. However, there were some company-specific comments in the consultation of the Annex XV report stating that in some companies compliance is already reached and no compliance costs of this restriction are expected. SEAC views the cost information and the qualitative statements about compliance and compliance costs to be, although to some degree vague, credible and sufficient to be used for the proportionality assessment.
Concerning the benefits, SEAC notes that RAC has confirmed the negative health impacts due to inhalation and dermal exposure to DMAC and NEP. SEAC agrees that inhalation and dermal DNELs for DMAC and NEP, and adequate risk management measures chosen to reduce exposure such as to comply with these DNELs will reduce the health risks. SEAC also agrees that this risk reduction can be used as a proxy for the health benefits.
Based on the RAC´s conclusion on risk assessment, the proposed restriction is expected to yield health benefits. However, SEAC notes that the dossier submitter's benefit assessment provides only limited information for quantitative benefit assessment. Based on the information available, benefits of this restriction for both DMAC and especially NEP, appear limited in general. However, SEAC notes the proposed restriction would yield benefits also by ensuring that the risk levels would not increase in the future as a result of e.g. increased use of DMAC or NEP.

SEAC notes that for the case of NEP, conclusions about health benefits are not possible. In the absence of opposing information, it is likely that due to adaptions of RMM to former NMP and DMF restrictions the economic impacts and also the health benefits of this restriction are very limited.

SEAC agrees with the Dossier Submitter's proposed entry into force, however, agreeing with the sector-specific transition period of 4 years for DMAC as requested by European Man Made Fibres sector in the consultation.

As a starting point for assessing proportionality, SEAC notes that RAC is of the opinion that the proposed restriction would be effective in risk reduction. It should be possible for most companies to reduce the exposure by adaptation and improvement of OCs and RMMs to a level below the DNELs derived by RAC.

SEAC notes that health benefits were not quantified, but mainly qualitatively described, and the cost information largely consist of qualitative information with some general cost information, however, difficult to directly tie with a certain company size or a cost per employee. Information on aggregated compliance costs per sector is not available, however, indications of compliance costs per company in a sector are derived. As a result, SEAC concludes that a proportionality assessment comparing quantified costs and benefits is not possible. Instead, proportionality has been analysed and assessed by a semi-qualitative cost-benefit comparison, and by a benchmarking approach.

SEAC concludes on the proportionality for DMAC and in the same context proposes a 4-year

transition period to Man-made-Fibre sector such that more costly risk reduction technologies can be gradually implemented. In case of NEP, SEAC also considers the restriction would be proportional in the absence of opposing information as it is likely that due to adaptations of RMMs due to earlier NMP and DMF restrictions the economic impacts and similarly the health benefits of this restriction are limited.

SEAC takes note of the Forum advice and concludes that the proposed restrictions would be practicable and monitorable.

3. JUSTIFICATION FOR THE OPINION OF RAC AND SEAC

3.1. RISK ASSESSMENT

3.1.1. Hazard(s)

Summary of Dossier Submitter's assessment:

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 was studied extensively in recent decades, showing a rather complete dataset of toxicological studies, including human studies. For NEP, fewer toxicological studies are available. In animal studies, the liver is the primary target organ for systemic repeated dose toxicity of both 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 repeated inhalation exposure, observed as degeneration/regeneration of the olfactory epithelium. Human studies have demonstrated liver effects in workers following exposure to DMAC based on biochemistry parameters related to liver function and examination of the liver via ultrasonic and Computed Tomography (CT) imaging.

The Dossier Submitter has used the benchmark dose (BMD) approach to determine the point of departure for setting DNEL levels. The following benchmark responses (BMRs) were 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. A 10 % extra risk is taken as BMR for local irritative effects.

DMAC / inhalation DNEL(s)

For DMAC, a systemic long-term inhalation DNEL (liver toxicity) was derived from chronic inhalation toxicity and carcinogenicity studies in rats and mice (Malley et al., 1995). A $BMDL_{10}$ of 65 mg/m^3 was used as a point of departure which is based on hepatic Kupffer cell pigmentation in male mice. This was corrected for exposure duration (6 to 8 h) and breathing volume activity (6.7 to 10 m^3). Assessment factors were applied as follows:

- an interspecies remaining differences factor of 2.5 (default) and
- an intraspecies factor of 5 (default worker).

This resulted in a systemic long-term inhalation DNEL of 2.6 mg/m^3 for workers.

However, there are two occupational cohort studies available for inhalation exposure to DMAC resulting in no-effect levels of 10.8 or 21.7 mg/m^3 (8-h TWA equivalent) based on liver function (Antoniou et al., 2021; Spies et al., 1995a; 1995b). The study by Antoniou et al. (2021) concerns more recent data from more workers, over more years and from work associated with the highest DMAC exposure compared to the studies by Spies et al. (1995a, 1995b). No assessment factors were used considering the size of the study and the availability of other human studies. This resulted in a systemic long-term inhalation DNEL for workers of 22 mg/m^3.

The inhalation DNEL of 22 mg/m^3 (for liver effects) based on human data (workers) is considered more relevant than the DNEL derived based on animal data (2.6 mg/m^3).

Inhalation developmental toxicity studies with rats and rabbits were used to derive a developmental toxicity inhalation DNEL for DMAC (Okuda et al., 2006; Klimisch and Hellwig, 2000). A point of departure of 320 mg/m^3 was used, based on the $BMDL_1$ for skeletal malformations and the $BMDL_{10}$ for visceral variations in rabbits. This point of departure is corrected for exposure time (6 to 8 h) and breathing volume activity (6.7 to 10 m^3). No additional correction for exposure duration (7 to 5 days) was suggested for developmental toxicity as it is unknown what the most sensitive period for DMAC-induced developmental adverse effects is or whether such a sensitive period exists at all. The following assessment factors were applied:

- an interspecies remaining differences factor of 2.5 (default) and
- an intraspecies factor of 5 (default worker).

This resulted in a systemic long-term inhalation DNEL for workers of 13 mg/m^3.

The Dossier Submitter therefore proposed a systemic long-term inhalation DNEL of 13 mg/m^3 to be used for risk characterisation.

DMAC / dermal DNEL(s)

The oral chronic toxicity and carcinogenicity study (Monsanto, 1980; 1990; 1993) in rats was used for the derivation of a systemic long-term dermal DNEL (liver toxicity) for DMAC. A $BMDL_{10}$ of 19 mg/kg bw/day for increased relative liver weight in male rats was used as a point of departure. For route-to-route extrapolation, oral and dermal absorption of DMAC was assumed to be 100 %. Therefore, the dermal $BMDL_{10}$ was considered identical to the oral $BMDL_{10}$ (19 mg/kg bw/day). Correction for exposure duration (7 to 5 days) was suggested. The following assessment factors were used:

- an allometric scaling factor of 4 (default rat),
- an interspecies remaining differences factor of 2.5 (default), and
- an intraspecies factor of 5 (default worker).

A systemic long-term dermal DNEL for workers of 0.53 mg/kg bw/day was thus derived. There are no human data available on dermal repeated dose toxicity.

A developmental toxicity dermal DNEL was derived for DMAC by using an oral prenatal developmental toxicity study in rat (DuPont, 1997). The $BMDL_1$ of 92 mg/kg bw/day was selected as a point of departure based on foetal head malformations in rats. For route-to-route extrapolation, oral and dermal absorption of DMAC was assumed with 100 %. Therefore, the dermal $BMDL_1$ was considered identical to the oral $BMDL_1$ (92 mg/kg bw/day). The following assessment factors were applied:

- an allometric scaling factor of 4 (default rat),
- an interspecies remaining differences factor 2.5 (default) and
- an intraspecies factor of 5 (default worker).

This resulted in a systemic long-term dermal DNEL for workers of 1.8 mg/kg bw/day.

The Dossier Submitter proposed a systemic long-term dermal DNEL of 0.53 mg/kg bw/day to be used for risk characterisation.

NEP / inhalation DNEL(s)

For NEP, a local acute inhalation DNEL and a systemic long-term inhalation DNEL were derived from inhalation toxicity studies in rats.

A $BMDL_{10}$ of 57 mg/m^3 was used as a point of departure for a local acute inhalation DNEL, based on the occurrence of degeneration/regeneration of the olfactory epithelium in a 28-day rat study (BASF, 2011). No correction for exposure duration was used since local effects are not primarily driven by exposure time but by exposure concentration. The following assessment factors were applied:

- an interspecies remaining differences factor of 2.5 (default) and
- an intraspecies factor of 5 (default worker).

This resulted in a local acute inhalation DNEL for workers of 4.6 mg/m^3.

A systemic long-term inhalation DNEL for NEP was derived from a 90-day inhalation rat study (BASF, 2013), where no systemic effects were observed at the highest concentration of 200 mg/m^3. This concentration was selected as a point of departure. It was corrected for exposure duration (6 to 8 h) and default breathing volume during activity (6.7 to 10 m^3). The following assessment factors were used:

- an interspecies remaining differences factor of 2.5 (default),
- an intraspecies factor of 5 (default worker), and a factor 2 for exposure duration (sub-chronic to chronic).

This resulted in a systemic long-term inhalation DNEL for workers of 4 mg/m^3.

The oral developmental toxicity studies with NEP in rats and rabbits (Saillenfait et al., 2007; BASF, 2007a, 2007b) were used to derive a developmental toxicity inhalation DNEL by using route-to-route extrapolation in accordance with the REACH guidance R.8 (ECHA, 2012). A $BMDL_1$ of 38 mg/kg bw/day for foetal cardiovascular malformations in rabbits was used as a point of departure. No correction for differences in absorption was conducted since 100 % was assumed for both oral and inhalation absorption. No correction for exposure duration (7 to 5 days) was suggested for developmental toxicity as it is unknown what the most sensitive period for NEP-induced developmental adverse effects is or whether such a period exists at all. The following assessment factors were applied:

- allomatric scaling factor 2.5 (default)
- an interspecies remaining differences factor 2.5 (default) and
- an intraspecies factor of 5 (default worker).

This resulted in a systemic long-term inhalation DNEL for workers of 8.9 mg/m^3 (assumption of the 70 weight worker with an inhalation volume of 10 m^3/8 h working day)

The Dossier Submitter proposed a local acute inhalation DNEL of 4.6 mg/m^3, and a systemic long-term inhalation DNEL of 4.0 mg/m^3 to be used for risk characterisation.

NEP / dermal DNEL, long-term systemic

A systemic long-term dermal DNEL for NEP was derived from the oral sub-chronic toxicity study in rats (BASF, 2006). The $BMDL_{10}$ of 170 mg/kg bw/day for increased relative liver weight was used as a point of departure. For route-to-route extrapolation, oral and dermal absorption of NEP was assumed with 100 %. Therefore, the oral $BMDL_{10}$ was assumed identical with the dermal $BMDL_{10}$ (170 mg/kg bw/day). The exposure duration was corrected (7 to 5 days). The following assessment factors were applied:

- an allometric scaling factor of 4 (default rat),
- an interspecies remaining differences factor of 2.5 (default),
- an intraspecies factor of 5 (default worker), and a factor 2 for exposure duration (sub-chronic to chronic).

This resulted in a systemic long-term dermal DNEL for workers of 2.4 mg/ kg bw/day.

A developmental toxicity dermal DNEL was derived from the dermal prenatal developmental toxicity studies in rats (BASF, 2005) and in rabbits (BASF, 2010). A $BMDL_5$ of 330 mg/kg bw/day based on decreased foetal body weight in rats was used as a point of departure. A correction factor for exposure duration (6 to 8 h) was applied but no correction for exposure duration (7 to 5 days) for developmental toxicity was performed. The following AFs were used:

- an allometric scaling factor of 4 (default rat),
- an interspecies remaining differences factor of 2.5 (default) and
- an intraspecies factor of 5 (default worker),

This resulted in a systemic long-term dermal DNEL for workers of 5.0 mg/kg bw/day.

The Dossier Submitter proposed a systemic long-term dermal DNEL of 2.4 mg/kg bw/day to be used for risk characterisation.

Biomonitoring DNEL

Urinary excretion of NMAC could serve as a biological limit value (BLV) for DMAC. Previously, published correlation data were used for the derivation of a biomarker DNEL for DMAC (Spies et al., 1995a; Nomiyama et al., 2000). Using the factors suggested by Spies et al. (1995a) and Nomiyama et al. (2000) to account for inter- and intra-individual variation, interpolation of the DNEL of 13 mg DMAC/m^3 resulted in a mean value of about 15 mg N-methylacetamide (NMAC)/g creatinine.

The Dossier Submitter notes that there are no human studies available for NEP to provide a measured correlation between NEP air levels and urinary metabolite levels for deriving a biomarker DNEL. However, as an alternative, a urinary mass balance approach (as described by David et al., 2021) can be used to derive a rough estimate of a biomarker DNEL. The Dossier Submitter used this approach to derive a biomarker DNEL of 20 mg/L for combined urinary excretion of the metabolites 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy-N-ethylsuccinimide (2-HESI) corresponding to a DNEL of 4 mg NEP/m^3. The most appropriate sampling time was proposed to be pre-shift on the day following exposure and, if possible, at the end of the working week since e.g., due to the slow dermal absorption urinary excretion is likely to be delayed.

RAC conclusion(s):

DMAC

- RAC agrees with the Dossier Submitter about the selection of key studies for assessing the hazards (liver effects and developmental toxicity endpoints).
- RAC agrees with the Dossier Submitter about the BMD modelling being used for the point of departure derivation for setting DNELs for relevant endpoints and the BMRs used for relevant toxicity endpoints.

Long-term inhalation DNEL:

- RAC agrees with setting of an overall DNEL for systemic long-term inhalation of 13 mg/m^3 based on a $BMDL_1$ for foetal skeletal malformations and a $BMDL_{10}$ for foetal visceral variations, the most sensitive effects, observed in a prenatal developmental toxicity study in rabbits,. RAC agrees that a DNEL based on liver effects would be higher at 22 mg/m^3 based on human data (workers) which is considered more relevant than the DNEL based on animal data (2.6 mg/m^3) from a chronic inhalation toxicity study in mice.

Long-term dermal DNEL:

- RAC does not agree with the setting of a systemic long-term dermal DNEL of 0.53 mg/kg bw/day based on a $BMDL_{10}$ for increased relative liver weight in rats. RAC notes that humans are not as sensitive for liver effects as rats. Using human data with a NOAEC of 22 mg/m^3 a systemic NOAEL of 3.1 mg/kg bw/day can be derived. This is higher than the dermal DNEL of 1.8 mg/kg bw/d derived by the Dossier Submitter from an oral prenatal developmental toxicity study in rats.
- RAC therefore proposes to use a systemic long-term dermal DNEL of 1.8 mg/kg bw/day for risk characterisation which is derived from an oral prenatal developmental toxicity study in rats. This is considered the most sensitive endpoint and is consistent with the approach for the setting of the systemic long-term inhalation DNEL for DMAC.

Biomarker DNEL ($DNEL_{biomarker}$)

- RAC agrees with the Dossier Submitter about setting a $DNEL_{biomarker}$ of 15 mg NMAC/g creatinine (corresponding to 20 mg/L NMAC in urine) which on average corresponds to the proposed systemic long-term inhalation DNEL of 13 mg/m^3 for DMAC. Measurement should be made post-shift at the end of the work week.

NEP

- RAC agrees with the Dossier Submitter about the selection of key studies for assessing the hazards (liver effects, developmental toxicity endpoints and local irritative effects).
- RAC agrees with the Dossier Submitter about the BMD modelling being used for point of departure derivation for setting DNELs for relevant endpoints and the BMRs used for relevant toxicity endpoints.

Long-term inhalation DNEL:

- RAC agrees with setting a DNEL for systemic long-term inhalation of 4.0 mg/m^3 in the absence of effects at the highest concentration of a 90-day inhalation toxicity study in rats. RAC also agrees with the fact that this DNEL for NEP is lower than the DNEL derived for prenatal developmental toxic effects (8.9 mg/m^3) observed in an oral study with rabbits, which is therefore protective also for developmental toxicity.

Short-term local inhalation DNEL:

- RAC does not agree with setting a local acute inhalation DNEL of 4.6 mg/m^3 based on a $BMDL_{10}$ for increased degeneration and/or regeneration of the olfactory epithelium in a 28-day inhalation toxicity study in rats.
- RAC proposes **not to give any separate acute local DNEL**. Local effects seen in the 28-day (and 90-day) inhalation toxicity studies in rats are not representing acute irritation seen after short-term (15 min) exposure, but effects caused by repeated exposure. No acute value has been given for other aprotic solvents, including NMP, either. In addition, the proposed acute DNEL was not used in risk characterization by the Dossier Submitter. Furthermore, the long-term inhalation DNEL value of 4 mg/m^3 is considered sufficient to prevent local respiratory tract effects in continuous repeated NEP exposure.

Long-term dermal DNEL:

- RAC agrees with setting a systemic long-term dermal DNEL of 2.4 mg/kg bw/day based on a $BMDL_{10}$ for increased relative liver weight observed in a 90-day oral toxicity study in rats. RAC agrees with the fact that this DNEL is lower than the DNEL derived for developmental effects (5 mg/kg bw/d) observed in a dermal prenatal developmental toxicity study in rats and is therefore protective for developmental toxicity.

Biomarker DNEL ($DNEL_{biomarker}$)

- RAC agrees with the Dossier Submitter that the urinary mass balance approach can be used to make an estimate on the biomarker DNEL although RAC acknowledges that there are some uncertainties related to this approach since the method estimates the steady-state urinary metabolite levels which may result in overestimation of exposure and risk if peak urinary levels are measured.
- RAC agrees with the Dossier Submitter's proposal of 20 mg/L (rounded value, corresponds approximately 15 mg/g creatinine) for combined urinary excretion of 5-HNEP plus 2-HESI corresponding to the systemic long-term inhalation DNEL of 4 mg/m^3 for NEP.
- In addition, RAC calculated biomarker DNELs for these specific metabolites. These are 10 mg/L (7 mg/g creatinine) for 2-HNEP and 8 mg/L (6 mg/g creatinine) for 2-HESI. 2-HNEP can be used to assess recent inhalation exposure if measured post-shift. 2-HESI should be measured always next morning due to the slow excretion. In all cases measurement should be made at the end of the work week.

Key elements underpinning the RAC conclusion(s):

BMD approach and setting of BMRs

RAC agrees that when suitable data is available, the BMD analysis is a scientifically more advanced method in comparison with the NOAEL approach to determine a dose response relationship. The PROAST software (versions 70.2 and 70.3) was used for the BMD analysis; this is a commonly used and openly available software for benchmark dose modelling (https://www.rivm.nl/en/proast).

The BMDL confidence intervals can become wider with smaller BMRs. To reduce the uncertainty, the Dossier Submitter assessed the confidence intervals of the BMDLs and selected those data sets that were adequate for the calculation of such a small increase in incidence with sufficient precision. The Dossier Submitter did not consider BMDL as a point of departure when the 90 % confidence intervals of BMDL/BMDU were ≥ 10. The EFSA guidance (EFSA, 2017) on the BMD approach recommends to always report BMD confidence interval rather than the value of the BMD. BMDL is needed as a potential reference point, and the BMDU is needed for establishing the BMDL/BMDU per ratio reflecting the uncertainty in the BMD estimate.

RAC agrees on using default BMRs of 10 % for changes in organ or body weight and 10 % extra risk in histopathological changes. The Dossier Submitter used a BMR of 5 % for decrease in foetal body weight (Table **4**), which is in accordance with RAC's view in the RAC and SCOEL Joint Opinion for NMP (RAC-SCOEL, 2016). The litter effect was taken into consideration by the Dossier Submitter for foetal body weight if individual data was available. The Dossier Submitter considered also a 10 % extra risk as BMR for foetal variations and a 1 % extra risk as BMR for foetal malformations and post-implantation loss. RAC agrees about the use of

modified BMRs for developmental toxicity due to the severity of the effects although recognises the conservativeness of $BMDL_1$ used for foetal malformations. $BMDL_1$ has been used earlier for deriving DNELs for developmental effects of lead (EFSA, 2010).

Table 4: Specifications of the BMR per endpoint used in BMD analyses for DMAC.

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

The guidance on BMD analysis and setting of BMRs do not have default values for developmental toxicity. In the REACH Guidance R8 (ECHA, 2012) it is referred to a BMR of 5 % as, on average, comparable to a NOAEL. If other BMD indicators are used it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed. The EFSA guidance (EFSA, 2017) on the BMD approach describes for quantal data that the median of the upper bounds of extra risk at the NOAEL was close to 10 %, suggesting that the $BMDL_{10}$ would be an appropriate default assumption. For continuous data, a re-analysis of studies showed that the $BMDL_5$ was close to the NOAEL derived from the same data. The EFSA Scientific Committee has noted that these default BMRs may be modified based on statistical or biological considerations.

DMAC

Inhalation exposure

RAC agrees with setting of an overall DNEL for systemic long-term inhalation of 13 mg/m^3.

The Dossier Submitter performed benchmark dose modelling for several endpoints and based on several datasets. In case of inhalation effects, similar BMDLs (320 mg/m^3) were derived for both foetal skeletal malformations ($BMDL_1$) and for foetal visceral variations ($BMDL_{10}$) giving more confidence to the established BMDL. A lower $BMDL_{10}$ (65 mg/m^3) was derived for liver effects in animals, but RAC agrees that available data from exposed humans lessens the concern for these effects and should be considered for DNEL derivation. This human evidence comes from the study by Antoniou et al. (2021), which gives a NOAEC of 22 mg/m^3 for the liver effects. In addition, in a re-analysis by Antoniou et al. (2022) a sensitivity analysis was performed for the data using the DMAC median distribution. Like the original data analysis (Antoniou et al. 2021), the re-analysis found no association between DMAC exposure and hepatoxicity among European workers. In the highest exposure group with median exposure level of 4 to 6 ppm (15 to 22 mg/m^3) no cases of liver injury or elevated liver parameters were seen. RAC notes, however, that in contrast to animal data in humans it is not possible

to get histopathological information which could be more sensitive to indicate early, subclinical liver effects.

Concerning the application of assessment factors, RAC supports the use of standard assessment factors for interspecies extrapolation, and an intraspecies factor of 5 for workers. This latter has been set in line with REACH guidance and in line with RAC opinion on NMP, noting that there is no scientific reason to assume a different sensitivity to developmental effects in a working mother compared to a mother from the general population (for which an intraspecies AF of 10 would be used).

Dermal exposure

RAC disagrees with the Dossier Submitter proposal of a dermal DNEL of 0.53 mg/kg bw/day.

The Dossier Submitter based this DNEL on an oral $BMDL_{10}$ of 19 mg/kg bw for increased relative liver weight in rats and used standard assessment factors (4 x 2.5) for interspecies extrapolation. However, as discussed above, data from humans lessens the concern for liver effects at these exposure levels and should be considered for DNEL derivation. Assuming 100 % absorption of DMAC via inhalation, the NOAEC of 22 mg/m^3 observed by Antoniou et al. (2021) results in a systemic dose (NOAEL) of 3.1 mg/kg bw/day. 15 mg/m^3, which was the lower end of the median exposure in the highest exposed group of workers in Antoniou et al. (2021), corresponds to 2.1 mg/kg bw/day. If also 100 % dermal absorption is assumed, a NOAEC of 22 mg/m^3 will result in a dermal DNEL of 3.1 mg/kg/day based on human data.

In a semi-chronic dermal toxicity study (Horn, 1961), one male and one female dog per group (2 lowest doses) or two male dogs per group (2 highest doses) received 0, 94, 300, 940, 3760 mg DMAC/kg bw/day to the clipped skin (open; 5 days/weeks; washing after 5 h exposure/day) for 6 months. Animals at the two highest doses showed progressive impairment of health, with weight loss, clinical signs, and dogs dying after 15 to 16 days (at 3 760 mg/kg bw/day) or sacrificed moribund after 6 weeks (at 940 mg/kg bw/day). These animals showed skin irritation, skin lesions and liver damage (fatty degeneration), but kidneys were unremarkable. No effects on body weight or ALP/BSP were observed in the other dog at 300 mg/kg bw/day, but this dog developed an ulcer. Both dogs at 300 mg/kg bw/day showed marked scaliness of the skin. The livers at the two lowest doses showed slightly reticulated cytoplasm. The skin showed only some slight thickening and/or inflammatory reaction. The NOAEL of the study was 94 mg/kg bw/d, concluded by the author to be a safe level with respect to liver damage and for the local skin effects. This study was not considered reliable by the Dossier Submitter because there was only 2 dogs/dose group and it was not a GLP study and had limited documentation. RAC agrees that this study can only be considered supportive for the liver effects of DMAC. However, it supports the conclusion that rats and mice may be more sensitive than some other species, like dogs and humans for liver effects.

Overall, RAC proposes to use a systemic long-term dermal DNEL of 1.8 mg/kg bw/day for risk characterisation. This is based on an oral developmental toxicity in rats, which is considered the most sensitive endpoint. This is also consistent with the approach for setting the DMAC inhalation DNEL.

Biomarker DNEL

The Dossier Submitter proposed a $DNEL_{biomarker}$ of 15 mg NMAC/g creatinine which was considered to correspond to the proposed systemic long-term inhalation DNEL of 13 mg/m^3 for DMAC when samples are taken at the end of the work week and after the shift. RAC agrees

with the Dossier Submitter on this $DNEL_{biomarker}$ value. To allow normalisation to specific gravity or osmolarity, RAC has calculated that this corresponds approximately to 20 mg/L NMAC in urine when a mean creatinine value of 1.36 g/L is used for conversion (Cocker et al. 2011). Validated analytical methods are available to measure the sum of metabolically formed NMAC and NMAC thermally cleaved from DMAC's primary metabolite N-hydroxymethyl-N-methylacetamide (HMMAC). The thermal cleavage step is a prerequisite for the comparison of NMAC levels to the biomarker-DNEL.

RAC notes that in the recent update of MAK and BAT values for DMAC, the German MAK Commission (Walter et al., 2020) has used the correlation equation by Kennedy (1990) to derive a BAT value of 25 mg/L corresponding (on average) to an 8 h inhalation exposure to the MAK value of 5 ppm (18 mg/m^3). The non-linear relationship by Kennedy (1990) results in 23 mg/L NMAC corresponding to the systemic long-term inhalation DNEL of 13 mg DMAC/m^3.

Other studies on correlations between DMAC in the air and urinary excretion of the DMAC metabolite NMAC include studies by Spies et al. (1995) and Nomiyama et al. (2000). These studies assumed a linear relationship between the log-transformed DMAC concentration in the air and log-transformed NMAC concentration in urine which results in 25 mg NMAC/g creatinine corresponding to the DNEL of 13 mg DMAC/m^3. Spies et al. (1995a) and Nomiyama et al. (2000) suggested a lower value than the mean NMAC value as potential biological limit value to avoid misclassification of a large percentage of individuals as underexposed. Based on their datasets, Spies et al. (1995a) suggested 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), resulting in NMAC values of 14 and 17 mg NMAC/g creatinine. Based on this, the Dossier Submitter proposed a DNEL biomarker of 15 mg NMAC/g creatinine corresponding to the DNEL of 13 mg DMAC/m^3. RAC agrees with the Dossier Submitter to use 15 mg NMAC/g creatinine ~ 20 mg/L NMAC (normalised to specific gravity or osmolarity) in urine as biomarker DNEL for DMAC, also taking into account the Kennedy (1990) data used by the German MAK Commission. The samples should be taken post-shift in the end of the work week.

NEP

Inhalation exposure, systemic long-term

RAC agrees with the Dossier Submitter's proposal for a systemic long-term inhalation DNEL of 4 mg/m^3 based on no systemic effects observed up to the highest concentration (200 mg/m^3) of a 90-day inhalation toxicity study in rats and by applying standard correction and assessment factors. RAC also agrees with the fact that this DNEL for NEP is lower than the DNEL derived for prenatal developmental toxic effects (8.9 mg/m^3) which is based on cardiovascular malformations ($BMDL_1$ 38 mg/kg bw/day) observed in an oral prenatal developmental toxicity study with rabbits. The DNEL for systemic long-term inhalation is therefore protective also for developmental toxicity.

Inhalation exposure, local, acute

RAC does not agree with the Dossier Submitter proposal to set a local acute inhalation DNEL of 4.6 mg/m^3 based on a $BMDL_{10}$ for increased degeneration and/or regeneration in the olfactory epithelium in rats in a 28-day inhalation toxicity study. The local effects seen in 28-day (and 90-day) rat toxicity studies are not considered to represent acute irritation but

effects caused by repeated exposure.

RAC notes that in the rat inhalation toxicity studies, clinical signs of irritation were seen only at 200 mg/m^3 in both 28- and 90-day studies. The stronger irritative effects in the 28-day study, compared to the 90-day study, could be attributed to the fact that the exposure atmosphere contained aerosol fraction in addition to vapour. Degeneration of olfactory epithelium was related to the continuous, repeated irritation, which can be prevented by the systemic long-term inhalation DNEL of 4 mg/m^3. RAC considers the approach used by the Dossier Submitter very conservative since in addition to the point of departure derived from the 28-day toxicity study, the Dossier Submitter applied the default assessment factors of 2.5 x 5 to account for uncertainties related to interspecies and intraspecies extrapolation. Brüning et al. (2014) made a comparison between animal repeated dose data and human sensory irritation data. In this study they proposed a default assessment factor of 3 for setting of occupational limit values based on local effects observed in the upper respiratory tract in animal repeated dose studies. However, RAC notes that the data is based on only limited number of substances and is focused on sensory irritation and does not consider this approach applicable either.

Overall, RAC proposes not to set an acute local DNEL for NEP. RAC notes that no acute DNEL value has been derived for DMAC or other aprotic solvents, including NMP. In the RAC opinion on the restriction proposal on NMP, developmental toxicity effects were considered the most sensitive toxicity endpoint over questionable irritation effects (ECHA, 2014). RAC also notes that NEP does not have a harmonised CLP classification for any irritation effects. In addition, NEP - and NMP - are not an acutely toxic substance and do not cause respiratory irritation effects in acute toxicity tests. The proposed acute DNEL for NEP was not used in the risk characterisation by the Dossier Submitter.

However, the relevance of these local effects seen in rats after repeated exposure for human long-term exposure needs to be considered. The Dossier Submitter did not derive a long-term DNEL for local respiratory tract effects since these effects were considered as acute irritant effects. RAC considers these effects caused rather by repeated exposure than short term exposure. Since the data was derived from 28-days study, the default approach would be to apply an additional assessment factor of 3 for time extrapolation which would result in an overall assessment factor of 2.5 x 5 x 3. This is, however, very conservative approach. In humans the olfactory epithelium covers 3 % of the nasal cavity, while in rats this tissue covers 50 % of the intranasal surface and extends to anterior parts of the nasal cavity (Brüning et al., 2014). It has been also observed that air stream over the human olfactory epithelia amounts to only 50 % of that of the rat (Frederick et al. 1998). This might increase the sensitivity of the rat olfactory epithelium for the cytotoxic effects when compared to the human olfactory epithelium. Although it has not been proven that the local effects seen in rats are caused by direct cytotoxic effects after repeated exposure or if they require metabolism, the direct cytotoxicity at these high levels seems likely and therefore e.g. the use of a default assessment factor of 2.5 for toxicodynamics might not be justified. It can be also argued that since the 90-day study resulted in a higher $BMDL_{10}$ (78 mg/m^3 vs. 57 mg/m^3 in a 28-day study), this additional assessment factor is not necessary. However, the BMDL could have been lower if the aerosol fraction would have been higher in the 90-day study.

Overall, there are several reasons that justify a deviation from the default assessment factors in this case. If an assessment factor of 5 for intraindividual differences and a total assessment factor up to 3 accounting for time-extrapolation and possible remaining uncertainties for interspecies extrapolation are applied, this will result in ≥3.8 mg/m^3. Since this is close to the

systemic long-term inhalation DNEL value of 4 mg/m^3 derived based on developmental effects, a DNEL of 4 mg/m^3 is considered sufficient to protect also from local inhalation effects following repeated exposure.

Dermal exposure

RAC agrees with setting a systemic long-term dermal DNEL of 2.4 mg/kg bw/day. There are no relevant dermal toxicity studies on target organs including liver effects available for NEP, except two dermal prenatal developmental toxicity studies with rat and rabbit. Therefore, the Dossier Submitter used the oral 90-day toxicity study when deriving the dermal DNEL. The Dossier Submitter based this DNEL on an $BMDL_{10}$ of 170 mg/kg bw for increased relative liver weight in rats and used standard correction (7/5) and standard assessment factors (4 x 2.5 x 5 x 2). In route-to-route extrapolation the Dossier Submitter assumed default 100 % oral and dermal absorption for NEP. RAC agrees with the Dossier Submitter to use the conservative default absorption rate of 100 % since relevant animal studies or human volunteer dermal studies are not available on NEP and data on other, similar substances (like NMP and DMAC) suggest high dermal absorption. In addition, NEP falls into a category of substances favourable for absorption with a molecular weight lower than 500 and a log P in the range of -1 and 4 (REACH Guidance R.7.12.) A similar approach has been used also for the other aprotic solvents DMF and NMP.

Biomarker DNEL

There are no human studies available for NEP to derive a biomarker DNEL. However, human biomonitoring guidance values (HBM GV) have been derived for the general population (urinary NEP metabolites 5-HNEP and 2-HESI) using a urinary mass balance approach (David et al., 2021). Using this same approach, the proposed long-term inhalation DNEL of 4 mg NEP/m^3 would result in a mean biomarker DNEL of 20 mg/L of the total concentration of 5-HNEP and 2-HESI in urine (corresponding 15 mg/g creatinine when a mean creatinine value of 1.36 g/L is used for conversion (Cocker et al., 2011)). The Dossier Submitter proposes urinary samples to be collected pre-shift the day following exposure and, if possible, at the end of the working week since there might be delayed excretion due to the slower dermal absorption compared to inhalation absorption. RAC agrees with the approach chosen and the proposal on biomonitoring DNEL. RAC acknowledges the uncertainties which are related to the fact that the mass balance approach estimates the steady state urinary levels. This means that if the biomonitoring measurement is made at the sampling time representing peak levels in the urine, the biomonitoring approach is likely to overestimate the exposure and risk. Assuming the excretion kinetics of NEP resemble that of NMP, peak levels of 5-HNEP metabolites in urine are likely to occur 8 to 16 hours after the beginning of the work shift in inhalation exposure. In the inhalation exposure study by Bader et al. (2007), 5-HNEP peak occurred during this period. However, following dermal exposure this may be delayed. Excretion kinetics of 2-HMSI was slower with peak occurring only after 24 to 32 hours after inhalation exposure.

However, RAC recognises that a sum value may present challenges for the interpretation of the biomonitoring results in case of variable occupational exposure. In addition, a sum value may not be available in all cases. Therefore (and in line with NMP), RAC has also calculated biomarker DNELs for these specific metabolites which are 10 mg/L (7 mg/g creatinine) for 2-HNEP and 8 mg/L (6 mg/g creatinine) for 2-HESI. The 2-HNEP value can be used to assess recent inhalation exposure if measured post-shift. 2-HESI is recommended to be measured next morning due to the slow excretion half-life of 22 to 27 h whereas for 2-HNEP the half-

life is 7 h. In all cases measurement should be made at the end of work week to account for cumulation during the week.

Summary

Summary of the DNELs for DMAC and NEP proposed by RAC are presented in Table 5 and Table 6.

Table 5: DNELs for DMAC and NEP proposed by RAC

Substance	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, systemic long-term									
DMAC	Develop-mental toxicity	320 mg/m^3 rabbit	PNDT, inhalation, 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
NEP	Repeated dose toxicity	200 mg/m^3 rat	90-day RDT, inhalation	no systemic effects at highest concentration (200 mg/m^3)	6/8 6.7/10	101 mg/m^3	2.5 – (RD) 5 – (IS) 2 – (ED) Total: 25	4 mg/m^3	BASF 2013
Dermal, systemic long-term									
DMAC	Develop-mental 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
NEP	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 mg/kg bw/day	4 – (AS) 2.5 – (RD) 5 – (IS) 2 – (ED) Total: 100	2.4 mg/kg bw/day	BASF 2006
AS: allometric scaling, ED: exposure duration, GD: gestational day, IS: intraspecies factor, PNDT: prenatal developmental toxicity study, RD: remaining (toxicokinetic/dynamic) differences, RDT: repeated dose toxicity									

*Concerning the application of assessment factors, RAC supports the use of standard assessment factors for interspecies extrapolation, and an intraspecies factor of 5 for workers. This latter has been set in line with REACH guidance, noting that there is no scientific reason to assume a different sensitivity to developmental effects in a working mother compared to a mother from the general population (for which an intraspecies AF of 10 would be used).

Table 6: Biomarker DNELs for DMAC and NEP proposed by RAC

Substance	Corresponding DNEL	Urinary metabolites	Resulting DNEL[1]	Sampling	Calculation method	Reference
Biomarker						
DMAC	Systemic long-term inhalation 13 mg/m^3	NMAC	20 mg NMAC/L urine corresponding to 15 mg NMAC/g creatinine	Post-shift samples at the end of the work week	Linear relationship between the log-transformed DMAC concentration and log-transformed NMAC concentration	Spies et al. 1995ab; Nomiyama et al. 2000
NEP	Systemic long-term inhalation 4 mg/m^3	5-HNEP and 2-HESI	sum value: 20 mg 5-HNEP plus 2-HESI /L urine corresponding to 15 mg 5-HNEP plus 2-HESI /g creatinine 10 mg 2-HNEP /L urine (7 mg 2-HNEP/g creatinine) 8 mg 2-HESI/L (6 mg 2-HESI/g creatinine)	Urinary samples collected pre-shift the day following exposure and at the end of the working week (delayed excretion due to the slow dermal absorption). In case high inhalation exposure is expected, 5-HNEP can be measured from post-shift samples to capture recent exposure.	Urinary mass-balance method	David et al. 2021

[1] A mean creatinine value of 1.36 g/L was used for conversion (Cocker et al. 2011)

3.1.2. Emissions and exposures

Summary of Dossier Submitter's assessment:

DMAC and NEP are used as solvents in a variety of sectors and for different uses. The Dossier Submitter identified important uses in the production of various formulations, e.g., in the production of agrochemicals, pharmaceuticals and fine chemicals. DMAC is used as solvent in coatings and is extensively used in the production of man-made fibres 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 a 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 a 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.

RAC conclusion(s):

For most of the occupational settings, detailed exposure information is not available. Therefore, the exposure assessment performed by the Dossier Submitter is based on information from the registration dossiers using modelled data, developed with the tier 1 assessment tool ECETOC TRA v3 worker module. In the registration dossiers usually the EasyTRA model was used and not ECETOC TRA. The use of modelled data may better reflect the exposures resulting from the use of a substance in a wide variety of industrial and professional settings and in many countries than limited data sets of workplace monitoring with unknown representativeness. The registration dossiers demonstrate safe use in most scenarios with tier 1 exposure modelling tool. Refinement using more detailed, higher tier models was not pursued by the Dossier Submitter in the absence of necessary information required to perform such higher tier modelling.

RAC concludes that the input parameters are in principal well chosen and documented transparently. Therefore, RAC accepts the modelling as provided by the Dossier Submitter and makes only some minor adjustments.

Some measured data (air- and biomonitoring) are available and discussed in the Background Document. Additional information was provided by some contributors during the Annex XV consultation. But it is difficult to know how representative measured data are for such widely used substances.

RAC is of the opinion that the exposure estimates presented by the Dossier Submitter can be used as the basis for the risk characterisation, because the modelling seems adequately conservative (and is supported by some monitoring data) and may acceptably represent the average conditions of a high number of occupational settings.

Key elements underpinning the RAC conclusion(s):

RAC evaluated the modelling in some detail. This seems necessary due to this dependence on a tier 1 model for occupational exposure assessment for both DMAC and NEP. RAC identified some minor differences in the exposure levels (that does not affect the conclusions drawn from the risk characterisation) that are caused by different temperatures (conversion inhalation exposure estimastes from ppm to mg/m^3). Additionally, for some uses RAC concluded that the Dossier Submitter used very conservative input parameters (see some details in the confidential annex to the Background Document).

Table 7 and Table 8 present a summary of the range of estimated exposure concentrations for DMAC and NEP per exposure scenario. Additionally, the modelling results are complemented by a limited data set of workplace air and biomonitoring (last two columns of the tables). Some of this information is considered confidential by the relevant affected industry sectors and is presented in annex 3 to the Background Document; confidential information was made available to RAC members.

Table 7: Range of estimated exposure concentrations and workplace air and biomonitoring data for DMAC per exposure scenario

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		8 h time weighted inhalation measurement results (mg/m^3)	Post-shift urinary NMAC levels (mg NMAC/g creatinine)
		Inhalation (mg/m^3)	Dermal (mg/kg bw/day)		
Industrial use of DMAC					
Manufacture	Low	0.036 – 10.89	0.03 – 1.37	4.1	
	High	0.036 – 181.5	0.03 – 1.37		
Formulation	Low	1.81 – 18.15	0.69 – 1.37	< 0.22	
Charging and Discharging	Low	0.91 – 18.15	0.69 – 1.37	9.3	Up to 3.5[4] 90th percentile Conf. data
	Medium	4.53 – 18.15	0.69 – 1.37		
Use as solvent in the production of agrochem., pharmaceuticals and fine chemicals	Low	0.036 – 18.15	0.03 – 1.37		
Use as solvent in the production of man-made fibres and films	Low	0.036 – 10.89	0.03 – 14.14	20 mg/m³ This is a conservative 90th percentile based on different available studies.	21 90th percentile
	Medium	0.036 – 36.3	0.03 – 14.14		
Use as solvent in the production of films or	According to the Dossier Submitter this use is covered by the exposure scenario 'Use as solvent in the production of man-made fibres'.				

[4] The workers recruited for this biomonitoring have several tasks, only some are related to charging and discharging.

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		8 h time weighted inhalation measurement results (mg/m^3)	Post-shift urinary NMAC levels (mg NMAC/g creatinine)
		Inhalation (mg/m^3)	Dermal (mg/kg bw/day)		
hollow fibre spinning					
Use as solvent in coatings	Low	2.18 – 10.89	0.82 – 2.57	< 4.1	
	Medium	10.89	0.82 – 1.65		
Manual maintenance (cleaning and repair) of machinery	Low	0.36 – 2.54	1.37	< 44.4	AM: 6.45
Use as laboratory chemical	Low	1.81	0.03	0.184	3.56 90^{th} percentile
Professional use of DMAC					
Use as laboratory chemical	Low	3.63	0.068		

The Dossier Submitter evaluated a number of studies that report about air- and biomonitoring of DMAC (urinary NMAC levels). RAC notes that most of these studies deal with the use of DMAC as a solvent in the production of man-made fibres. For other uses of DMAC, only little biomonitoring data is available but some limited information about workplace air monitoring was provided by the Dossier Submitter and during the consultation of the Annex XV report. For the use "anual maintenance (cleaning and repair) of machinery" the modelled exposure levels appear to be lower than the corresponding measured levels. Tier 1 exposure models do have known deficiencies in modelling these uses. Therefore, those modelling results need to be evaluated with caution.

During the consultation of the Annex XV report, contributors submitted information about workplace exposure (including data) of DMAC that was evaluated by RAC. Some of the information submitted was already provided by industry during the call for evidence to the Dossier Submitter. This information is therefore already reflected in the Background Document. However, some information is new and adds to the exposure assessment.

The information provided in the consultation regarding worker exposure to DMAC in the man-made fiber sector is much more detailed than for other uses and provides a clearer picture of the workplace situation in that sector. As most of the information is considered as confidential, this evaluation is presented in annex 3 to the Background Document.

The biomonitoring data for the man-made fibre sector provided in publications and during the consultation was evaluated by RAC. Detailed information and the RAC interpretation of biomonitoring data is presented in annex 3 to the Background Document; confidential information was made available to RAC members. It must be noted that the biomonitoring data vary considerably. The range of absolute values varies between 1 and 200 mg NMAC/g creatinine. In the publications, often only the geometric mean or the 50^{th} percentile is provided. However, neither the 50^{th} percentile nor the geometric mean are sound and

conservative enough for risk assessment due to the wide range. RAC decided to use the 90th percentile. Unfortunately, based on the available information, it is not possible to derive the 90th percentile retrospectively for all data. Furthermore, some biomonitoring data was not considered because only a small number of measurements are available and/or the data are clearly outdated. In sum, the exposure assessment performed by RAC is based on recent biomonitoring data with a high number of measurements. Here the 90th percentile values still vary between < 5 and 26 mg NMAC/g creatinine, which may be also related to the variability in tasks performed by the workers prior to the sampling campaign. As the contextual information is often missing a rather conservative value of **21 mg NMAC/g creatinine** is used for the worker exposure assessment of the "use as solvent in the production of man-made fibres and films".

Even less relevant studies are available about the workplace exposure situation for the different uses of NEP. The exposure assessment for NEP therefore relies fully on the tier 1 exposure modelling. Only for a low number of uses workplace air- or biomonitoring data are available (see Table 8).

Table 8: Range of estimated exposure concentrations and workplace air and biomonitoring data for NEP per exposure scenario

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		8 h time weighted inhalation measurement results (mg/m³)	Post shift urine concentrations of 5-HNEP and 2-HESI (mg/g creatinine)
		Inhalation (mg/m³)	Dermal (mg/kg bw/day)		
Industrial use of NEP					
Manufacture	Low	0.047 – 14.14	0.03 – 1.37		
	Medium	0.047 – 47.15	0.03 – 1.37		
Formulation	Low	0.047 – 14.14	0.03 – 1.37		
	Medium	23.58	1.37		
Charging and discharging	Low	1.18 – 47.15	0.69 – 1.37	personal & static: < 25 personal: < 1.2	
Use as solvent in industrial processes	Low	0.047 – 14.14	0.03 – 1.37		
Use as solvent in coatings	Low	2.83 – 14.14	0.82 – 2.57		0.01 – 3.47 (5-HNEP) 0.04 – 4.52 (2-HESI) n = 12 (Koslitz et al., 2014)
	Medium	14.14	0.82 – 1.64		
Manual maintenance (cleaning and repair) of machinery	Low	0.47 – 3.30	1.37		
Use as laboratory chemical	Low	2.36	0.03		
Binder and release agent	Low	1.41 – 14.14	0.20 – 2.57		
Cleaning	Low	2.83 – 14.14	0.82 – 2.57		Max. 17

Exposure Scenario	Fugacity category	Estimated exposure concentrations long-term		8 h time weighted inhalation measurement results (mg/m^3)	Post shift urine concentrations of 5-HNEP and 2-HESI (mg/g creatinine)
		Inhalation (mg/m^3)	Dermal (mg/kg bw/day)		
agents	Medium	14.14	0.82		(5-HNEP) Max. 4.63 (2-HESI) n = 2 (Koslitz et al., 2014)
Oil field drilling and production operations	Low	0.047 – 14.14	0.03 – 1.37		
Functional fluids	Low	0.047 – 14.14	0.03 – 1.37		
Polymer processing	Low	0.047 – 14.14	0.03 – 1.65		
Water treatment	Low	0.047 – 14.14	0.03 – 1.37		
Professional use of NEP					
Charging and discharging	Low	2.83 – 70.72	0.82 – 1.65		
Use as solvent in coatings	Low	5.66 – 14.14	1.65 – 16.97		
Manual maintenance (cleaning and repair) of machinery	Low	1.41 – 4.95	1.65		
Use as laboratory chemical	Low	4.72	0.068		
Binder and release agent	Low	5.66 – 14.14	1.65 – 12.86		
Cleaning agents	Low	5.66 – 14.14	1.65 – 12.86		
Use as excipient in agrochemicals	Low	47.15	2.74 – 21.43		
Functional fluids	Low	14.14	0.21		
Road and construction applications	Low	33.00 – 82.51	2.74 – 21.43		
Polymer processing	Low	0.047 – 23.58	0.03 – 1.37		

There have been no contributions on NEP in the Annex XV consultation. The exposure assessment for NEP relies fully on the Dossier Submitter's assessment.

RAC identified a number of uncertainties in the workplace exposure assessment (details are described in section 3.5 of this document):

- The exposure modelling of the Dossier Submitter relies almost fully on a tier 1 model for occupational exposure assessment (ECETOC TRA worker module).

- The number of monitoring datasets (workplace air monitoring and biomonitoring) is very limited regarding range and quality:
    - Not all uses are covered by monitoring. Especially some uses with comparably high exposure levels are not covered by monitoring.
    - Some of the uses with monitoring data, seem to show higher exposure values than the modelled values. This is an unusual situation and cannot be clarified satisfyingly.
- The contributions in the Annex XV consultation provide contradictory information on the different applications of DMAC. The contradictory contributions relate to exposure levels, OCs/RMMs, appropriate measurement methods and the organisation of occupational health and safety in the industries concerned.

Following a request from RAC, the Dossier Submitter reported that, similar to the workplace exposure, the general population can also be exposed to DMAC and NEP. For example, recent human biomonitoring in Germany shows widespread exposure to NEP, although the measured concentrations do not give reason for toxicological concerns (Schmied-Tobies et al., 2021). There is no information where this exposure would come from.

Following a recommendation from RAC, the Dossier Submitter contacted the German Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) and was able to provide – towards the end of the opinion making process of RAC – two reports about workplace air monitoring. These reports include data for DMAC and NEP for inhalation exposure in German workplaces 2012 to 2021. RAC evaluated this additional information[5] and concluded that overall the above exposure assessment is supported. The data include the analytical prove of DMAC and NEP in the air at workplaces where these solvents are used. The levels are comparable to other air monitoring levels that were available for DMAC. The situation regarding monitoring data for NEP is clearly improved, because relevant air monitoring data for NEP is now available. The two reports are available on the IFA website[6].

3.1.3. Risk characterisation

Summary of Dossier Submitter's assessment:

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 uncontrolled 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

[5] RAC evaluation presented in the Background Document Annex 3.

[6] DMAC: https://www.dguv.de/medien/ifa/de/gestis/mega/onlinebericht_dmac.pdf

NEP: https://www.dguv.de/medien/ifa/de/gestis/mega/onlinebericht_nep.pdf

temperatures, open processes, and processes that require manual activities.

RAC conclusion(s):

While it is noted that the modelling is likely to be of a conservative nature (a tier 1 modelling tool is used) and may have overestimated the exposure for some uses (e.g. man-made fibre), there is a significant number of occupational settings using DMAC and NEP with an RCR above one.

The DNELs for workers derived by RAC are considered as robust. During the Annex XV consultation some of the contributors agreed to these DNELs, whereas the Dossier Submitter's systemic long-term dermal DNEL was considered as too conservative.

RAC therefore supports the concern, while noting the uncertainties in the exposure assessment.

It is therefore concluded that risks are not sufficiently controlled for all workers in some uses.

Key elements underpinning the RAC conclusion(s):

Based on the DNELs presented above, calculated by the Dossier Submitter or RAC, respectively, and the exposure estimates from the registration dossier, the Annex XV consultation and RAC, RCRs are calculated and presented below in Table 9 for DMAC and in

Table 10 for NEP. For almost all uses, the RCRs for some of the contributing worker scenarios exceed the value of 1. More specifically, using the DNELs calculated by RAC, **27** out of **46** worker contributing scenarios for DMAC have RCRs > 1. For NEP **70** out of **94** exposure scenarios are above one.

Depending on the tasks and the corresponding exposure pattern, for some uses, the inhalation route contributes most to the total exposure (e.g., manufacturing of DMAC) and for others the dermal route is more relevant (e.g., charging and discharging of DMAC).

For DMAC, the combined exposure gives RCRs for workers that range between 0.02 and 14.34, with the majority of them between one and two. For NEP the RCRs have a wider range (0.02 – 23). Most of them are between one and six.

Table 9: RCRs calculated by RAC for DMAC

Process Categories	Used reduction factors, OCs and PPE	Exposure estimation with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighted results	RCR	post-shift urine concentrations of NMAC	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine (unless otherwise indicated)	
		ppm	mg/m³	mg/kg bw/day							
Industrial use of DMAC											
Manufacturing											
Low fugacity category								4.1	**0.32**		
1	8 h full shift, 100 % conc. no elevated temp → low fugacity	0.01	0.036	0.03	0.003	0.017	**0.02**				
2		1	3.63	1.37	0.28	0.76	**1.04**				
3		3	10.89	0.69	0.84	0.38	**1.22**				
High fugacity category											
1	8 h full shift, 100 % conc. Temp up to 180 °C → high fugacity, Gloves 90 %	0.01	0.036	0.03	0.003	0.017	**0.02**				
2		25	90.75	1.37	6.98	0.76	**7.74**				
3		50	181.5	0.69	13.96	0.38	**14.34**				
Formulation											
3	8 h full shift, 100 % conc. no elevated temp → low fugacity, Gloves 90 % (not for PROC 3), LEV for PROC 4 & 5 (90 %)	3	10.89	0.69	0.84	0.38	**1.22**	<0.22	**0.02**		
4 (LEV)		0.5	1.81	0.69	0.14	0.38	**0.52**				
5 (LEV)		0.5	1.81	1.37	0.14	0.76	**0.90**				
5 (no LEV)		5	18.15	1.37	1.40	0.76	**2.16**				
Charging and discharging											
Low fugacity category								9.3	**0.72**	Up to 3.5[7] 90th percentile (Conf. data)	**0.23**
8a (LEV)	8 h full shift, 100 % conc. Gloves 90 % LEV (PROC 8b (95 %)), otherwise 90 %	1	3.63	1.37	0.28	0.76	**1.04**				
8b (LEV)		0.25	0.91	1.37	0.07	0.76	**0.83**				
8b (no LEV)		5	18.15	1.37	1.40	0.76	**2.16**				
9 (LEV)		0.5	1.81	0.69	0.14	0.38	**0.52**				

[7] The workers recruited for this biomonitoring had several tasks, only some were related to charging and discharging.

Process Categories	Used reduction factors, OCs and PPE	Exposure estimation with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighted results	RCR	post-shift urine concentrations of NMAC	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine (unless otherwise indicated)	
		ppm	mg/m³	mg/kg bw/day							
Medium fugacity category											
8a (LEV)	8 h full shift, 100 % conc. Elevated temp (40 °C) → medium Gloves 90 %, LEV (PROC 8b (95 %), otherwise 90 %)	5	18.15	1.37	1.40	0.76	**2.16**				
8b (LEV)		1.25	4.53	1.37	0.35	0.76	**1.11**				
9 (LEV)		5	18.15	0.69	1.40	0.38	**1.78**				
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals											
1	8 h full shift, 100 % conc. No elevated temp → low Gloves 90 % (only PROC 4) LEV 90 % (only PROC 4)	0.01	0.036	0.03	0.003	0.02	**0.02**				
2		1	3.63	1.37	0.28	0.76	**1.04**				
3		3	10.89	0.69	0.84	0.38	**1.22**				
4 (LEV)		0.5	1.81	0.69	0.14	0.38	**0.52**				
4 (no LEV)		5	18.15	0.69	1.40	0.38	**1.78**				
Use as solvent in the production of man-made fibres and films											
Low fugacity category								20	**1.53**	21	**1.4**
1	8 h full shift, 100 % conc. No elevated temp → low Gloves 90 % (not for PROC 1-3) LEV 90 % (not for PROC 1-3)	0.01	0.036	0.03	0.003	0.02	**0.02**				
2		1	3.63	1.37	0.28	0.76	**1.04**				
3		3	10.89	0.69	0.84	0.38	**1.22**				
4		0.5	1.81	0.69	0.14	0.38	**0.52**				
13		1	3.63	1.37	0.28	0.76	**1.04**				
14		0.5	1.81	0.34	0.14	0.19	**0.33**				
19		1	3.63	14.14	0.28	7.86	**8.13**				
Medium fugacity category											
1	8 h full shift, 100 % conc. elevated temp → medium	0.01	0.036	0.03	0.003	0.02	**0.02**				
2		5	18.15	1.37	1.40	0.76	**2.16**				
3		10	36.3	0.69	2.79	0.38	**3.18**				

Process Categories	Used reduction factors, OCs and PPE	Exposure estimation with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighted results	RCR	post-shift urine concentrations of NMAC	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine (unless otherwise indicated)	
		ppm	mg/m³	mg/kg bw/day							
4	120 °C (up to 300 °C)[8] Gloves 90 % (not for PROC 1-3), LEV 90 % (not for PROC 1-3)	2	7.26	0.69	0.56	0.38	**0.94**				
13		5	18.15	1.37	1.40	0.76	**2.16**				
14		5	18.15	0.34	1.40	0.19	**1.59**				
19		5	18.15	14.14	1.40	7.86	**9.25**				
Use as solvent in coatings											
Low fugacity category								4.1	**0.32**		
2	8 h full shift, 5-25 % conc. No elevated temp → low Gloves 90 % (not for PROC 1-3) LEV 90 % (not for PROC 1-3)	0.6	2.18	0.82	0.17	0.46	**0.62**				
7		3	10.89	2.57	0.84	1.43	**2.27**				
10		0.6	2.18	1.65	0.17	0.92	**1.08**				
13		0.6	2.18	0.82	0.17	0.46	**0.62**				
Medium fugacity category											
2	s.a. but slighty elevated temp (30 °C) → medium	3	10.89	0.85	0.84	0.47	**1.31**				
10		3	10.89	1.65	0.84	0.92	**1.75**				
Manual maintenance (cleaning and repair) of machinery											
28 (indoors, LEV & RPE)	PROC 8a used as basis 8 h full shift, 100 % conc., No elevated temp → low Gloves 90 %, RPE 90 % LEV 90 % or 30 % reduction for outdoors	0.1	0.36	1.37	0.03	0.76	**0.79**	<44.4	**3.42**	AM: 6.45	**0.3**
28 (outdoors, with RPE)		0.7	2.54	1.37	0.20	0.76	**0.96**				

[8] [8] Fugacity category should actually be "high" instead of "medium", as process temperature exceeds 100 °C, therefore the inhalation exposure values would be 5 times higher (except for PROC 1).

Process Categories	Used reduction factors, OCs and PPE	Exposure estimation with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighted results	RCR	post-shift urine concentrations of NMAC	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine (unless otherwise indicated)	
		ppm	mg/m³	mg/kg bw/day							
Use as laboratory chemical[9]											
15	8 h full shift, 100 % conc., No elevated temp → low Gloves 90 %, LEV 90 %	0.5	1.81	0.03	0.14	0.02	**0.16**	0.184	**0.01**	3.56 90th percentile	**0.24**
Professional use of DMAC											
Use as laboratory chemical											
15	8 h full shift, 100 % conc., No elevated temp → low Gloves 80 %, LEV 80 %	1	3.63	0.068	0.28	0.04	**0.32**				

[9] There are indications that analyses are also carried out in the laboratory at higher temperatures (→ medium or high fugacity category). This would lead to inhalation exposure values that are higher by a factor of 2 or 10, respectively.

Table 10: RCRs calculated by RAC for NEP

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total				
		ppm	mg/m³	mg/kg bw/day				mg/m³		mg/g creatinine	
Industrial use of NEP											
Manufacture											
Low fugacity category											
1	8 h full shift, 100 % conc., No elevated temp → low Gloves 90 % (for PROC 4) LEV 90 % (for PROC 4)	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
Medium fugacity category											
1	8 h full shift, 100 % conc., elevated temp (precise temp. not known) → medium Gloves 90 % (for PROC 4) LEV 90 % (for PROC 4)	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		5	23.58	1.37	5.90	0.57	**6.47**				
3		10	47.15	0.69	11.79	0.29	**12.08**				
4		2	9.43	0.69	2.36	0.29	**2.65**				
Formulation											
Low fugacity category											
1	8 h full shift, 100 % conc., elevated temp (precise temp. not known) → medium LEV 90 % (for PROC 4, 5 & 14) Gloves 90 % (for PROC 4, 5 & 14)	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
5		0.5	2.36	1.37	0.59	0.57	**1.16**				
14		0.5	2.36	0.34	0.59	0.14	**0.73**				
Medium fugacity category											
5	8 h full shift, 100 % conc., elevated temp → medium LEV 90 % & gloves 90 %	5	23.58	1.37	5.90	0.57	**6.47**				
Charging and discharging											

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
8a (LEV)	8 h full shift, 100 % conc. No elevated temp → low LEV 90-95 % Gloves 90 %	1	4.72	1.37	1.18	0.57	**1.75**	<25 (personal & static) <1.2 (personal)	**6.25** **0.3**		
8a (no LEV)		10	47.15	1.37	11.79	0.57	**12.36**				
8b (LEV)		0.25	0.13	1.37	0.03	0.57	**0.60**				
8b (no LEV)		5	23.58	1.37	5.90	0.57	**6.47**				
9 (LEV)		0,5	2.36	0.69	0.59	0.29	**0.88**				
9 (no LEV)		5	23.58	0.69	5.90	0.29	**6.18**				
Use as solvent in industrial processes											
1	8 h full shift, 100 % conc. No elevated temp → low LEV 90 % and gloves 90 %	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
Use as solvent in coatings											
Low fugacity category										5-HNEP: 0.01-3.47 2-HESI: 0.04-4.52 n = 12	**≤ 0.5** **≤ 0.75** **Sum: 0.53**
2	8 h full shift, 5-25 % conc. → 40 % reduction, No elevated temp → low LEV 90-95 % (not for PROC 2), Gloves 90 %	0.6	2.83	0.82	0.71	0.34	**1.05**				
7		3	14.14	2.57	3.54	1.07	**4.61**				
10		0.6	2.83	1.64	0.71	0.68	**1.39**				
13		0.6	2.83	0.82	0.71	0.34	**1.05**				
Medium fugacity category											
2	8 h full shift, 5-25 % conc. → 40 % reduction, elevated temp (PROC 2 > 30 °C & PROC 13 up to 130 °C) → medium LEV 90 % (not for PROC 2) Gloves 90 %	3	14.14	0.82	3.54	0.34	**3.88**				
10		3	14.14	1.64	3.54	0.68	**4.22**				
13		3	14.14	0.82	3.54	0.34	**3.88**				
Manual maintenance (cleaning and repair) of machinery											

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
28 (indoors, with RPE)	PROC 8a used for calculation 8 h full shift, 100 % conc., No elevated temp → low Gloves 90 %, RPE 90 %, LEV 90 % or 30 % reduction for outdoors	0.1	0.47	1.37	0.12	0.57	**0.69**				
28 (outdoors, with RPE)		0.7	3.30	1.37	0.83	0.57	**1.40**				
Use as laboratory chemical											
15	8 h full shift, 100 % conc., No elevated temp → low Gloves 90 %, LEV 90 %	0.5	2.36	0.034	0.59	0.01	**0.60**				
Binder and release agent											
6	8 h full shift, 5-25 % conc. → 40 % reduction No elevated temp → low Gloves 90 % LEV 90-95 %	0.3	1.41	1.65	0.35	0.69	**1.04**				
7		3	14.14	2.57	3.54	1.07	**4.61**				
10		0.6	2.83	1.65	0.71	0.69	**1.40**				
13		0.6	2.83	0.82	0.71	0.34	**1.05**				
14		0.3	1.41	0.20	0.35	0.08	**0.44**				
Cleaning agents (e.g. paint removers, cleaners, degreasers)											
Low fugacity category										5-HNEP: up to 17 2-HESI: up to 4.63 n = 2	**≤2.43** **≤0.77** **Combined: 1.44**
7	8 h full shift, 5-25 % conc. → 40 % reduction, No elevated temp → low Gloves 90 %, LEV 90-95 %	3	14.14	2.57	3.54	1.07	**4.61**				
10		0.6	2.83	1.65	0.71	0.69	**1.40**				
13		0.6	2.83	0.82	0.71	0.34	**1.05**				
Medium fugacity category											
13	8 h full shift, 5-25 % conc. → 40 % reduction, Temp. up to 130 °C → medium Gloves 90 %, LEV 90-95 %	3	14.14	0.82	3.54	0.34	**3.88**				
Oil field drilling and production operations (one registrant)											
1	8 h full shift, 100 % conc.	0.01	0.047	0.03	0.012	0.013	**0.02**				

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
2	No elevated temp → low Gloves 90 % & LEV 90 % only for PROC 4	1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
Functional fluids											
1	8 h full shift 100 % conc. No elevated temp → low Gloves 90 % & LEV 90 % only for PROC 4	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
Polymer processing (one registrant)											
1	8 h full shift 100 % conc. (PROC 1-5) 5-25 % conc. → 40 % reduction (PROC 6, 13, 14) No elevated temp → low Gloves 90 % (PROC 4, 5, 6, 13, 14) LEV 90 % (PROC 4, 5, 6, 13, 14)	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
5		0.5	2.36	1.37	0.59	0.57	**1.16**				
6		0.3	1.41	1.65	0.35	0.69	**1.04**				
13		0.6	2.83	0.82	0.71	0.34	**1.05**				
14		0.3	1.41	0.21	0.35	0.09	**0.44**				
Water treatment (one registrant)											
1	8 h full shift 100 % conc. (PROC 1-4) 5-25 % conc. → 40 % reduction (PROC 13) No elevated temp → low Gloves 90 % (PROC 4, 13) LEV 90 % (PROC 4, 13)	0.01	0.047	0.03	0.012	0.013	**0.02**				
2		1	4.72	1.37	1.18	0.57	**1.75**				
3		3	14.14	0.69	3.54	0.29	**3.82**				
4		0.5	2.36	0.69	0.59	0.29	**0.88**				
13		0.6	2.83	0.82	0.71	0.34	**1.05**				
Professional use of NEP											

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
Charging and discharging											
8a (LEV)	8 h full shift 5-25 % conc. → 40 % reduction No elevated temp → low LEV 80-90 % Gloves 80 %	3	14.14	1.65	3.54	0.69	**4.22**				
8a (no LEV)		15	70.72	1.65	17.68	0.69	**18.37**				
8b (LEV)		0.6	2.83	1.65	0.71	0.69	**1.40**				
8b (no LEV)		6	28.29	1.65	7.07	0.69	**7.76**				
9 (LEV)		1.2	5.66	0.82	1.42	0.34	**1.76**				
9 (no LEV)		6	28.29	0.82	7.07	0.34	**7.41**				
Use as solvent in coatings											
10	8 h full shift, 5-25 % conc. → 40 % reduction No elevated temp → low LEV 80 %, Gloves 80 % RPE 90 % for PROC 11	3	14.14	3.29	3.54	1.37	**4.91**				
11		1.2	5.66	12.86	1.42	5.36	**6.77**				
13		1.2	5.66	1.65	1.42	0.69	**2.10**				
19		3	14.14	16.97	3.54	7.07	**10.61**				
Manual maintenance (cleaning and repair) of machinery											
28 (indoors with RPE)	PROC 8a used for calculation 8 h full shift, < 25 % conc. → 40 % reduction, No elevated temp → low, Gloves 80 %, RPE 90 %, LEV 80 % (indoors), outdoors 30 % reduction	0.3	1.41	1.65	0.35	0.69	**1.04**				
28 (outdoors with RPE)		1.05	4.95	1.65	1.24	0.69	**1.93**				
Use as laboratory chemical											
15	8 h full shift, 100 % conc., No elevated temp → low Gloves 80 %, LEV 80 %	1	4.72	0.068	1.18	0,03	**1.21**				
Binder and release agent											
10	8 h full shift, 5-25 % conc. → 40 % reduction, No elevated	3	14.14	3.29	3.54	1.37	**4.91**				
11		1.2	5.66	12.86	1.42	5.36	**6.77**				

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
13	temp → low, Gloves 80 %, LEV 80 %, RPE 90 % for PROC 11	1.2	5.66	1.65	1.42	0.69	**2.10**				
Cleaning agents											
10	8 h full shift, 5-25 % conc. → 40 % reduction, No elevated temp → low, Gloves 80 %, LEV 80 %, RPE 90 % for PROC 11	3	14.14	3.29	3.54	1.37	**4.91**				
11		1.2	5.66	12.86	1.42	5.36	**6.77**				
13		1.2	5.66	1.64	1.42	0.68	**2.10**				
Use as excipient in agrochemicals (one registrant)											
5	8 h full shift, 100 % conc. No elevated temp → low Gloves 80 %, RPE 90 % for PROC 11	10	47.15	2.74	11.79	1.14	**12.93**				
11		10	47.15	21.43	11.79	8.93	**20.72**				
13		10	47.15	2.74	11.79	1.14	**12.93**				
Functional fluids (one registrant)											
20	8 h full shift, 5-25 % conc. → 40 % reduction, No elevated temp → low, Gloves 80 %	3	14.14	0.21	3.54	0.09	**3.62**				
Road and construction applications (one registrant)											
10	8 h full shift, 100 % conc. No elevated temp → low Gloves 80 %, Outdoors 30 % reduction, RPE 90 % for PROC 11	17.5	82.51	5.49	20.63	2.29	**22.92**				
11		7	33.00	21.43	8.25	8.93	**17.18**				
13		7	33.00	2.74	8.25	1.14	**9.39**				
Polymer processing											
1	8 h full shift, 100 % conc. (PROC 1 & 2), 5-25 % conc. → 40 % reduction (PROC 14) No elevated temp → low	0.01	0.047	0.03	0.012	0.013	**0.024**				
2		5	23.58	1.37	5.90	0.57	**6.47**				

Process Categories	Used reduction factors, OCs and PPE	Estimated exposure with ECETOC TRA v3						Air measurements		Biomonitoring	
		concentrations long-term			RCR			8 h time weighed results	RCR	Post shift urine concentrations of 5-HNEP and 2-HESI	RCR
		Inhalation		Dermal	Inhalation	Dermal	Total	mg/m³		mg/g creatinine	
		ppm	mg/m³	mg/kg bw/day							
14	Gloves 80 % (PROC 14) LEV 80 % (PROC 14)	1.2	5.66	0.41	1.42	0.17	**1.59**				

In some cases, according to the modelling being used, the RCRs could be reduced below 1 by considering advanced exposure estimation methodolgy (such as tier 2 modelling and monitoring), or change of input parameters in the tier 1 modelling (e.g. duration of exposure, currently assumed to be 8 hours a day in most scenarios).

3.1.4. Existing risk management measures and operational conditions

Summary of Dossier Submitter's assessment:

The practicality of implementing additional RMM 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

RAC conclusion(s):

The uses of DMAC and NEP are very diverse for both substances, ranging from high volume industrial uses in large installations with a high level of containment to small scale manual activities in laboratories. RAC concludes that:

- for some uses (see section 3.1.3) the RMMs and OCs implemented and recommended by the manufactures and/or importers are not sufficient to control the risk as RCRs are above one also with
    - additional information received in the Annex XV consultation and
    - the less conservative DNELs that were derived by RAC compared to the Dossier Submitter's proposals,
- it is not possible to evaluate all possible existing RMMs and OCs as they are too diverse in the different uses and sectors,
- risk management at the different workplaces – making use of technical and organisational RMMs – seem to be feasible and proportionate to address the identified risks, as these are in most cases of a level that can be reduced adequately by technical RMMs,
- RMM need to be tailor-made to reduce inhalation or dermal exposures below the DNELs, as the relevance of both exposure paths can differ from workplace to workplace and from use to use.

Key elements underpinning the RAC conclusion(s):

Different OCs and RMMs seem to be the standard for different uses (industrial and professional) as different contributions to the consultation from different industrial sectors provide contradicting information about the state of the art at workplaces dealing with DMAC. No information in this regard is available for NEP. This is also reflected by the different use of OCs and RMMs as input parameters for modelling (indicating different OCs and RMMs in the evaluated workplaces).

For DMAC combined exposures result in RCRs for workers that range between 0.02 and 14 , with the majority of them between one and two. For NEP the RCRs have a wider range between 0.02 and 23. Most of them are between one and six. These are risk levels that can be addressed by technical RMMs (usually reducing exposure levels by at least 90 %) or improved exposure assessment (higher tier modelling or monitoring).

3.1.5. Uncertainties in the risk assessment

See section 3.5.1.

3.2. JUSTIFICATION THAT ACTION IS REQUIRED ON A UNION WIDE BASIS

Summary of Dossier Submitter's assessment:

The Dossier Submitter has concluded that action is required on a Union-wide basis. 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. 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. 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.

Action on a Community-wide basis is required to prevent EU-wide non adequately controlled 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.

RAC conclusion(s):

Based on the key principle of ensuring a high level of protection across the Union RAC concludes that any necessary action to address the risk(s) associated with the occupational exposure to DMAC and NEP should be implemented in all Member States.

Key elements underpinning the RAC conclusion(s):

As concluded above,

- in several scenarios, risks were observed (see section 3.1.3). The RMMs and OCs implemented and recommended by the manufactures and/or importers are not sufficient to control these risks. RCRs are above one even with the less conservative DNELs that were derived by RAC compared to the Dossier Submitter's proposals.
- The use of DMAC/NEP is wide-spread over the EU. RAC agrees that EU level action is needed to ensure the same level of protection across the EU.

SEAC conclusion(s):

- SEAC agrees on both, DMAC and NEP, that the action is required on a Union wide basis. Based on the key principle of maintaining the free movement of goods within the Union, SEAC concludes that any necessary action to address risks associated with DMAC and NEP should be implemented in all Member States.

Key elements underpinning the SEAC conclusion(s):

- Both, DMAC and NEP are placed on the market and used throughout the European Union. Therefore, exposure can potentially take place in any/all EU Member States. RAC and SEAC consider that a Union-wide action is needed to address the risks associated with several industrial and professional uses of DMAC and NEP to ensure a harmonised high level of protection of human health across the Union.

3.3. ANALYSIS OF ALTERNATIVES

3.3.1. Approach to the analysis of alternatives

Summary of Dossier Submitter's assessment:

The Dossier Submitter discusses the alternatives and their assessment mainly as part of the risk management options. The assessment of alternatives refers to earlier work by European Commission and ECHA (e.g. European Commission, & ECHA. (2018). Regulatory Management Option Analysis Conclusion Document. Substance Name: N, N-Dimethylacetamide (DMAC); Dimethylformamide (DMF); N-methyl pyrrolidone (NMP).

SEAC conclusion(s):

Information on the use of DMAC and NEP and information on available alternatives was gathered from various sources – CSRs, communication with ECHA, industry sources and literature. Based on the restriction report, SEAC concludes that relevant information was taken into consideration in the analysis on alternatives. The main uses of both substances, DMAC and NEP, were covered and information on possible alternatives was thoroughly reviewed.

The methodology used for the identification of alternatives was based on the similarities in the properties of the solvents DMAC and NEP with better known DMF and NMP. The shortlisting of identified alternatives was based on these properties, literature data and information from industry. SEAC concludes that concerning both substances, the methodology for identifying and shortlisting of alternatives is credible. The approach is clearly described and the scope of the analysis is clearly stated.

Key elements underpinning the SEAC conclusion(s):

SEAC acknowledges, that uses of NEP are in many cases closely related to uses of NMP and DMF. The same applies to DMAC, however, to a lesser extent. DMAC and NEP are solvents with somewhat similar properties and uses compared to DMF and NMP, respectively. Therefore, for many uses they are considered alternatives to DMF and NMP. The use of NEP increased after NMP was classified as reprotoxic. The decision to base the analysis of alternatives on the use of DMF and NMP is reasonable because more information is available for the latter two solvents. DMAC and NEP are used as solvents in various applications due to their physicochemical properties, such as polarity, density and solvating power. Alternatives should have similar properties to retain their function in the process. Due to the combination of different properties that give DMAC or NEP their role in the process, it is difficult to find a general substitute for either substance, rather certain alternatives are limited to specific processes. The main alternatives for using DMAC as a process solvent are stated to be DMSO, DMI, acetonitrile, ethanol, cyclic carbonates, 2-methylTHF, dimethylisosorbide. NEP is often used as a substitute to NMP and information on alternatives for NEP is more scarce and therefore no list of such alternatives is available.

3.3.2. Availability and technical and economic feasibility of alternatives

Summary of Dossier Submitter's assessment:

Both substances are dipolar aprotic solvents that are used in specialised applications for which limited or no technically feasible alternatives are available. The Dossier submitter referred that 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).

According to the Dossier submitter, 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.

The Dossier submitter reminds that the primary aim of authorisation under REACH is to substitute SVHCs, however, notes that it is questionable whether safer technically feasible alternatives are available for all uses of dipolar aprotic solvents as their functionality relies highly on their specific properties, and therefore the group of substances that can be considered as alternatives is limited in scope. 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 one reason being the limited availability of alternatives.

Furthermore, the Dossier submitter states, that for many uses there are no viable safer alternatives, and 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. Based on this, the Dossier submitter finds a complete ban or maximum percentage in the mixture seems to be not effective or not economically feasible.

SEAC conclusion(s):

In the Annex XV report, some potential alternatives have been listed and briefly assessed, however, information on alternatives in case of DMAC is very case specific and in case of NEP scarce if existent. As a summary, SEAC concludes that there is no general alternative to **DMAC** as a process solvent. However, SEAC acknowledges, that for some uses (e.g. man-made fibre production and uses where phase separation and phase inversion are of relevance) alternatives appear to exist, often different aprotic solvents suitable for certain uses, at least in the developmental stage, however, little information is available. DMAC is also used in production of graphene and in perovskite-based solar cells, in these cases alternatives exist, in the latter one at least in lab scale.

Concerning **NEP**, SEAC considers, based on the restriction report, that it could be used as an alternative of NMP. However, its use as a solvent in the manufacture of pharmaceuticals is negligible. Alternatives for (NMP and) NEP as ingredients in paint removers, cleaners, and degreasers appear to exist although requiring higher use (and costs) of other inputs. For some uses (cement, concrete production), information on alternatives is lacking.

SEAC is not able to assess the economic feasibility as information available in the Annex XV report and in the Annex XV report consultation comments on technical and economic feasibility is scarce.

Key elements underpinning the SEAC conclusion(s):

Concerning **DMAC**, SEAC notes that it is mainly used as a dipolar aprotic solvent for its good solvating power for a wide range of organic and inorganic compounds and for its good miscibility with other solvents, including water. DMF, DMAC, NMP and NEP tend to share

similar physico-chemical and toxicological properties. However, even substituting one with another generally requires process adaptation (comment from Cefic #3588). There are no alternative solvents which could be used as simple "drop-in" replacements due to their different properties, so feasibility of any potential alternative depends always on the application in question. The main alternatives for using DMAC as a process solvent are stated to be DMSO and DMI. However, the potential alternatives tend to also have their own safety and health risk issues. According to the dossier a few potential new alternative solvents (e.g. $ScCO_2$ and ionic liquids) have been reported as substitutes for hazardous solvents, however, no examples of DMAC substitution were found. SEAC concludes that there is no general alternative to DMAC as a process solvent.

Besides the process solvent, the restriction report lists several other uses for DMAC. It is used for the production of man-made fibres by wet spinning from DMAC solution, especially for heavier yarns (polyacrylonitrile, polyurethanes, aromatic polyamides). SEAC notes that in the production of man-made fibres alternative technologies exist and alternative solvents are also used. However, little information is available. As explained in a comment #3590 out of many solvents studied none was found to be able to solvate spandex polymer.

DMAC is also used for preparation of dope solution and for casting in the production of polymers, coatings, resins, paints, films, enamels, varnishes and membranes. Phase separation and phase inversion are of relevance in these applications. The type of solvent used to prepare the doping solution depends on the structure of the polymer and DMAC, DMF, NMP and DMSO are used. Information provided by the Dossier Submitter states that DMAC has been used as a substitute for DMF, although there are other alternatives. In the production of enamels no economically feasible alternative is known for insulation for winding wires for DMAC other than replacing it with NMT (#3609). DMAC is part of solvent system in high performance enamels for high performance applications like electric cars. The situation is similar for membrane fabrication, where polar aprotic solvents are used while several potential alternatives are being developed. Less information is available on their use in industry. SEAC notes the Annex XV report consultation comment (#3602), which states that no alternatives for DMAC exist in the production of medical membranes, which are crucial elements in filters acting as artificial kidney in haemodialysis. The comment justifies this referring to strict criteria for safety, biocompatibility, treatment outcome and medical treatment costs worldwide.

Production of graphene by exfoliation is often done in NMP or water, but ethanol and DMAC are also used. SEAC notes that based on the Annex XV restriction report DMAC is not an exclusive solvent in this process and that alternatives exist.

DMAC is also used in perovskite-based solar cells, which have a 5% market share. SEAC notes that lab-scale alternatives to DMAC are reported to be available.

Regarding **NEP**, SEAC notes that NMP is used as a co-formulant in herbicide, pesticide, and fungicide formulations and agrees that NEP could replace NMP in these uses. Based on the information provided SEAC considers the use of NEP as a solvent in the manufacture of pharmaceuticals to be negligible.

SEAC observes that NMP and NEP are also used as ingredients in paint removers, cleaners, and degreasers due to their good solubilising power of plastics, resins, oils, and greases. SEAC acknowledges that there are alternatives for these uses, however, in some cases higher energy consumption is required for the same effect.

SEAC concludes that there is no information available in the Annex XV restriction report on alternatives to the use of NEP in products used to seal cement or concrete products.

3.3.3. Risk of alternatives

Summary of Dossier Submitter's assessment:

The group of substances that can be considered as alternatives is limited in scope. According to the Dossier submitter for many uses there are no viable safer alternatives.

RAC conclusion(s):

Without a more detailed assessment, RAC cannot come to appropriate conclusions on the potential risks of the alternatives. However, the intention of this restriction proposal is to limit the workplace exposure rather than require substitution. Therefore no further detailed assessment of the risks of alternatives is needed.

Key elements underpinning the RAC conclusion(s):

SEAC concludes that there is no single drop-in alternative which would apply to all uses of DMAC or NEP.

In some uses, aprotic solvents are interchangeable but may share the same developmental toxic properties as DMAC/NEP and are therefore not recommended.

Several other potential alternatives for some potential uses have been mentioned in the Background Document but not assessed in detail.

No information on alternatives was provided during the Annex XV consultation for either DMAC or NEP.

3.3.4. Conclusion on analysis of alternatives

SEAC conclusion(s):

SEAC concludes that the scope of the analysis of alternatives in case of DMAC and NEP is clearly defined.

SEAC concludes that the relevant information was considered in the analysis on alternatives. The major uses of both substances, DMAC and NEP, were covered and the information on potential alternatives was thoroughly reviewed.

SEAC concludes that concerning both substances, the methodology for identifying, and shortlisting of alternatives is credible.

SEAC concludes that there is no general alternative to DMAC as a process solvent rather alternatives may be available on a case-by-case basis. SEAC concludes that for the major uses (textile fibre manufacture, electrical wire insulation and membrane manufacture) no suitable alternatives to DMAC and NEP are available. SEAC acknowledges that alternatives exist only at the developmental stage. For some niche applications alternatives may exist (e.g. production of graphene and in perovskite-based solar cells), while in some cases (sealing of cement or concrete products) there is not enough information to assess the situation.

SEAC concludes that it is not able to assess the economic feasibility of alternatives because the technical feasibility is not determined. SEAC concludes that the available information on the use of DMAC provides an overview of the uses and available alternatives, while information on the uses of NEP is more scarce.

Key elements underpinning the SEAC conclusion(s):

Information on the use of DMAC and NEP and available alternatives was gathered from various sources – CSRs, communication with ECHA, industry sources and literature. Analysis was in many occasions linked to DMF and NMP that have similar properties and uses. Relevant

information was taken into consideration in the analysis on alternatives. The methodology for identification of alternatives was based on the properties of the solvents DMAC and NEP and similarly, the shortlisting of alternatives was based on these properties, as well as on literature data and information from industry.

DMAC and NEP are used as solvents in various applications due to their physicochemical properties, such as polarity, density, solvating power. Alternatives should have similar properties to retain their function in the process. Due to the combination of different properties that give DMAC or NEP their role in the process, it is difficult to find a general substitute for either substance, rather certain alternatives that are limited to specific processes.

Some potential alternatives have been listed and briefly assessed in the Annex XV report, however, information on alternatives in case of DMAC is scattered and in case of NEP scarce if existent. DMAC is used as process solvent, where there is no general alternative. However, the several alternatives (for single uses) are listed, e.g. DMSO, DMI, acetonitrile, ethanol, cyclic carbonates, 2-methylTHF, dimethylisosorbide. SEAC acknowledges, that for some uses (man-made fibres, electrical wire insulation and sulphone membranes for hemodialysis) alternatives appear to exist. Those are often different aprotic solvents suitable for certain uses, and even if not fully developed, generally at least in the developmental stage. However, SEAC notes, that generally quite a little information is available. DMAC is also used in production of graphene and in perovskite-based solar cells and for those cases alternatives exist, in the latter one at least in lab scale.

Even less information is available on the use of NEP. Alternatives for NEP in paint removers, cleaners, and degreasers appear to exist, however, normally requiring higher use (and costs) of other inputs. For some uses (cement, concrete production), information on alternatives is lacking.

In general, for most of the uses, SEAC is not able to assess the economic feasibility as technical feasibility tends to be not determined.

3.4. JUSTIFICATION THAT THE SUGGESTED RESTRICTION IS THE MOST APPROPRIATE EU WIDE MEASURE

Summary of the proposed restriction

The Dossier Submitter has targeted the restriction towards mandatory harmonised long-term inhalation and dermal DNELs. According to the Dossier submitter, this combined with an obligation to implement OC and RMM ensuring exposure below the DNELs would be the most appropriate Community wide measure.

When assessing the restriction, the Dossier Submitter notes that the European Commission and ECHA promoted the NMP restriction as a good example of a case where there is an added value of introducing legally binding DNELs via a REACH restriction, complementary to IOELVs available under the EU occupational safety and health (OSH) legislation (European Commission & ECHA, 2018). Following this, the Dossier submitter concludes that a restriction with binding DNELs for the inhalation and dermal route for DMAC and NEP is 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. Specifically, the binding DNEL restriction offers a high level of flexibility for sectors and downstream users to implement where needed

appropriate RMM and adapt OC at a company level to ensure exposure below the respective DNELs. In addition, the proposed restriction would offer legal consistency with existing restrictions on the two other dipolar aprotic solvents NMP and DMF. This together with the proposed timing of the entry into force support implementability and manageability.

3.4.1. Targeting of the proposed restriction

Summary of Dossier Submitter's assessment:

The proposed restriction is targeted to control risks identified at EU-wide level due to use of the substances DMAC and NEP in industrial settings and by professionals. Both substances are 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).

The Dossier Submitter proposes to restrict the placing on the market for DMAC and NEP unless the supplier communicates the inhalation and dermal DNELs as specified in this restriction to the downstream users and manufacturers and downstream users take the appropriate OC and RMM, when DMAC and NEP are manufactured or used, to ensure that exposure of workers is below the DNELs.

Reasons for this proposal are:

- prevent regrettable substitution of other dipolar aprotic solvents that are already restricted (i.e. NMP, DMF)
- control risks identified at EU-wide level due to use of the substances DMAC and NEP in industrial settings and by professionals
- both substances have an EU harmonised classification reprotoxic category 1B (Repro. 1B; H360D)

Consumer applications were excluded from the proposal because both substances are classified as reprotoxic category 1B based on developmental toxicity (Repro.1B; H360D) in Annex VI of CLP Regulation which prohibits the use in consumer products in concentrations equal or greater than 0.3 % through listing in Appendix 6 of entry 30 of REACH Annex XVII.

RAC conclusion:

RAC concludes that the scope for the restriction proposal is clear and comparable to the restriction of other dipolar aprotic solvents that are already restricted (i.e. NMP, DMF). Therefore, the proposal will be able to prevent regrettable substitution of these substances.

The proposal focuses on occupational health, as, based on the harmonised classification of the substances, all consumer uses of the substances or in mixtures are already restricted (entry 30 of Annex XVII of REACH). RAC agrees with this focus.

The Dossier Submitter has made a hazard assessment based on the toxicological data available in the open literature and registration dossiers, and an exposure assessment based on the information in the respective registration dossiers. The Dossier Submitter identified risks for industrial and professional uses and for inhalation and dermal exposure pathways. RAC agrees with this concern (see chapter risk characterization 3.1.3).

Under the provisions of worker protection legislation, an EU-wide inhalation BOELV has been

established for DMAC but not for NEP. RAC however notes that the underlying evaluation of this BOELV is rather old and can be considered outdated. Dermal occupational exposure limits or biological limit values have not been established, but a skin notation has been assigned with the BOELV for DMAC.

Key elements underpinning the RAC conclusion:

Unacceptable risks for occupational uses of DMAC and NEP are demonstrated by the Dossier Submitter and confirmed by RAC's assessment. This restriction proposal is comparable to the restrictions for DMF and NMP and results in an equal treatment of interchangeable aprotic solvents.

This restriction covers also dermal exposure at workplaces and proposes a biomonitoring approach to control combined exposure via multiple routes. For DMAC a BOELV based on outdated information (1994) is in place. For NEP neither a BOELV nor an IOELV is available. The restriction is problably the faster risk management option compared to the derivation or update of BOELVs.

RAC agrees with the focus on occupational risks but notes that measurable levels of NEP metabolites have been also detected in the urine of German children and adolescents (Schmied-Tobies et al., 2021). The source of this exposure is unclear, but it is likely that this restriction proposal will also indirectly reduce the exposure of the general public.

SEAC conclusion(s):

The scope of the proposed restriction of the substances DMAC and NEP in industrial settings and by professionals has a broad coverage and is clearly defined. The scope is comparable to the restriction of other dipolar aprotic solvents already restricted (i.e. NMP, DMF) which helps to prevent regrettable substitution of both of these substances. SEAC notes that the two substances are assessed separately not as a group of substances.

No derogations are proposed.

Key elements underpinning the SEAC conclusion:

The Dossier submitter has considered a grouping approach for dipolar aprotic solvents based on structural similarity, and the availability of toxicity data and developmental toxicity. NMP, DMF, DMAC, NEP, 1,3-dimethylimidazolidin-2-one (DMI), and N-methyl-N-vinylacetamide (MVAC) are registered under REACH and are given priority for any further action. NMP and DMF are already restricted. DMAC and NEP have a harmonised classification as Repro Cat. 1B. DMI (CAS: 80-73-9) does not have harmonised classification as Repro Cat. 1B but is self-classified as Repro Cat. 2. MVAC (CAS: 3195-78-6) does not have either a harmonised classification as Repro Cat. 1B, nor a self-classification as Repro Cat. 2. Therefore, MVAC could be considered first as a candidate for screening for further evaluation (compliance check or substance evaluation), and DMI should be considered first as candidate for a proposal for harmonised classification.
Based on the availability of toxicity studies and the fact that DMAC and NEP are already classified as reproductive toxicants category 1B (developmental toxicity), it was decided to include DMAC and NEP in this restriction proposal.

3.4.2. Other regulatory risk management options

Summary of Dossier Submitter's assessment:

The Dossier Submitter has performed a RMOA in which four options were considered to manage the identified risks of DMAC and NEP: authorisation, (update of) Occupational Exposure Limit (OEL) under OSH legislation, a restriction in the form of a ban with a maximum concentration limit and a restriction in the form of binding DNELs.

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. According to the Dossier Submitter, in case of 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.

According to the Dossier submitter, the main concern related to the use of DMAC and NEP is worker exposure. Therefore, options to regulate the use/exposure under the occupational safety and health legislation should be considered the main instrument being the OEL.

For DMAC the OELs are based on a SCOEL advice dating from 1994 (SCOEL, 1994). Since that, several relevant studies have been published, and the substance has been classified as toxic to reproduction. Therefore, the Dossier Submitter considers a revision of the OEL appropriate.

For NEP, no European (B)OELV has been set, and as there is no obligation for member states to set an OEL for the substance, 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. Setting a BOELV for NEP could help to assess and quantify risks.

The CAD and CMRD apply to employees and do not cover the self-employed. The number of BOELVs set has increased in recent years. However, contrary to the restriction process, there is no Member State initiative in the OEL process, rather this has to be done by ECHA on request of the European Commission (DG EMPL). Concerning dermal exposure, there are no limit values under OSH and therefore dermal exposure is generally qualitatively assessed but provided with a 'skin' notation. 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 not the risk of dermal exposure. Furthermore, as the substances are not included in the priority list to derive/adjust OELs, the setting of (adjusted) BOELs for the substances under OSH will take time and is not the best regulatory management option to control the risks related to DMAC and NEP.

Finally, the Dossier Submitter points out that also 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 (European Commission & ECHA, 2018).

RAC conclusion(s):

RAC notes that in addition to setting binding DNELs under a REACH restriction, setting of BOELVs (or binding biological limit values) under the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD, 2004/37/EC) would ensure harmonised maximum exposure levels across the EU and could also be acceptable risk management options, comparable to harmonised DNELs for inhalation exposure.

RAC does not consider that the implementation of dermal DNELs will bring any substantial benefit compared to the "skin notation" given under CMRD since it is currently not established to quantitatively measure dermal exposure.

However, RAC points out that, in order to avoid confusion at workplaces due to the different limit values in the safety data sheets, it would in any case be useful to subsequently set BOELVs corresponding to the inhalation DNELs given in this restriction proposal under CMRD. Similar observations can be made for the biomarker DNELs for DMAC and NEP and the corresponding binding BLVs according to the CMRD.

Key elements underpinning the RAC conclusion(s):

The current BOELV for DMAC is clearly outdated (1994) and higher than the DNELs proposed by RAC. There is no BOELV or IOELV for NEP. If DMAC and NEP are not prioritised for evaluation within this year, implementation of BOELVs may take substantially longer than implementation of binding DNELs under a REACH restriction.

RAC notes that some waste management activities may remain unregulated under this restriction but would be covered by BOELVs given under CMRD.

RAC also recognises that the similar aprotic solvents NMP and DMF have been also regulated under a REACH restriction. This might be the main reason to favour a restriction also in case of DMAC and NEP as this option would be a harmonised approach for the four solvents (NMP, DMF, NEP and DMAC) that have similar uses.

SEAC conclusion(s):

For both substances, DMAC and NEP, SEAC notes that setting a binding OEL (BOEL) under the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD, 2004/37/EC) would ensure a harmonised maximum exposure level across the EU and could be an acceptable risk management option, comparable to a harmonised DNEL for inhalation and dermal exposure if accompanied by a technical guidance document of how to comply with the DNELs (inhalation and dermal). However, the current BOEL for DMAC under the CMRD (amended according to Directive (EU) 2022/431) is clearly higher than the proposed DNEL; for NEP no indicative or binding OEL on EU level is available. If DMAC and/or NEP are not prioritised for evaluation within this year, SEAC considers it likely that over the next 5 to 10 years, no update of the BOEL for DMAC or setting of a BOEL for NEP can be expected. SEAC agrees that even if prioritised for BOEL setting, the implementation of the limit value would be delayed, and consequently the identified unacceptable risks (in section 3.3) could persist.

SEAC notes that N,N-dimethylformamide (DMF) restriction dossier was submitted in October 2018 and that Commission Regulation on amending Annex XVII as regards DMF was published in November 2021.

The proposed dermal DNELs for DMAC and NEP are not directly applicable since no accepted monitoring methodology is available. However, supervision of biological limit values by biomonitoring may allow under specific conditions evaluation of the combined (systemic) effects from inhaled and dermally absorbed DMAC/ NEP. However, any biological monitoring undertaken in association with a biological limit value (BLV) usually needs to be conducted on a voluntary basis i.e. with the fully informed consent of employees. SEAC concludes that this might limit the effectiveness of harmonised dermal DNELs for cases e.g. when downstream users deviate from the proposed exposure scenarios and must undertake own monitoring of DMAC/ NEP dermal exposure (and if exposure modelling or transfer of exposure data from comparable workplaces is not possible).

SEAC agrees that authorisation under REACH would not be an effective risk management option for either substance since for several of the uses no suitable alternatives are available, and regrettable substitution can take place (see section 3.3). Also intermediate uses would not be covered which is of special relevance for uses in sector of Manufacture of chemicals and chemical products (C20).

SEAC agrees with the Dossier submitter that a complete ban would not be economically feasible, as for most of the uses sufficient risk reduction can be realised by implementation of adequate technical, organisational or personal protective equipment.

Key elements underpinning the SEAC conclusion(s):

Authorisation under REACH

SEAC agrees that authorisation would not be an effective risk management option. SEAC believes that authorisations would not induce a shift to less hazardous alternatives since according to the Dossier Submitter for most uses no suitable alternatives are currently and for the near future available. Instead, due to widespread use of DMAC and NEP, the authorisation requirement would likely induce numerous applications for authorisation causing administrative burden both for authorities and applicants. Furthermore, as intermediate uses are not covered by the authorisation obligation, such uses (reported for DMAC) would not be part of the authorisation obligation.

(Update of) OEL under OSH legislation

The proposed restriction only targets the protection of workers. Under the OSH legislation, for **DMAC** an indicative OEL (IOEL) was already established at the EU level according to the Chemical Agents Directive (CAD, 98/24/EC), which became a binding OEL (BOEL) under the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD, 2004/37/EC) with the last amendment Directive (EU) 2022/431). For NEP no indicative OEL (IOEL) was established at the EU level so far. Member states shall implement the provisions of the Directive (EU) 2022/431 by 5 April 2024. The current BOEL for DMAC (36 mg/m^3 as 8-hour value) is about 3 times higher than the DNEL for exposure via inhalation proposed by the Dossier Submitter. Currently, at least two EU member states have implemented an OEL (France and Germany 7.2 mg/m^3 and 18 mg/m^3 respectively) as an 8-hour value in the range of the proposed value by the restriction for DMAC. The other member states are within the range of the upper maximum limit of the present BOEL.

Harmonised DNELs under a REACH Restriction

SEAC agrees with the Dossier submitter that setting a harmonised DNEL for inhalation exposure could be a risk management option comparable to a binding OEL under CMRD in order to ensure a harmonized maximum exposure level across the EU. SEAC takes note of the assessment by RAC concerning the Dossier submitter's claim that an adequate protection level at the workplace could only be guaranteed by a much lower limit value than the existing BOEL for DMAC. The Advisory Committee on Safety and Health at Work (ACSH) did not prioritise DMAC, so far. SEAC acknowledges the Dossier Submitter's point that if DMAC and NEP would be prioritised within the year 2022, it could be taken up in the next action plan. A revision of an OEL could be expected within approximately the next five years. If a prioritisation does not occur within this year, SEAC considers it plausible that, no update of the BOEL for DMAC could be expected over the next five years or that setting a harmonised DNEL for NEP could be faster than BOEL setting under the CMRD.

SEAC also agrees with the Dossier Submitter's argument that a BOEL setting would avoid a potential overlap in regulation between REACH and the OSH legislation, and that enforcement of a BOEL would be well known to enforcement authorities of OSH legislation. Furthermore, SEAC notes the Dossier Submitter's stating that the use of BOEL appears simpler and generally more applicable to different workplaces.

SEAC notes that one advantage of basing a restriction on a DNEL for DMAC and NEP under REACH restriction would be a possibility to develop a harmonised EU-guidance for safe handling at the workplace like done for NMP. SEAC understands such a guidance could support the practical implementation of safe working conditions in the member states although, SEAC notes that an evaluation of the effectiveness of a DNEL implementation of NMP or of the subsequent guidance has not yet been undertaken. Furthermore, the restriction proposal of DMAC and NEP is in line with a coherent regulation of the aprotic solvents.

SEAC recognises possible disadvantages of BOEL setting as mentioned by the Dossier submitter, namely, that self-employed are not covered, and no quantitative exposure levels for dermal exposure are foreseen under the OSH legislation. However, SEAC notes that currently there are not any well-established methodologies to monitor for a DNEL for dermal exposure available. In addition, the skin notation linked to the BOEL for **DMAC** signals that dermal exposure of DMAC shall be avoided and may already induce adequate measures to avoid skin contact. For NEP neither an indicative nor a binding OEL was established so far, and thus no skin notation linked to a BOEL is available. SEAC takes note of RAC conclusions on whether limitations in monitoring methodologies might reduce the practicality of supervision of dermal DNELs for DMAC and NEP.

As an alternative approach to conclude on compliance with the dermal DNELs, the Dossier Submitter considers biomonitoring for evaluation of the combined (systemic) effects from inhaled and dermally absorbed DMAC/ NEP, and to contribute to the assessment of working conditions and the checking of the effectiveness of occupational safety measures. However, the legal conditions for application and use of results of biomonitoring vary across the EU since biomonitoring as occupational health surveillance is part of OSH legislation ((CAD, 98/24/EC)).

E.g. for Germany for uses of DMAC or NEP, no mandatory or optional occupational health surveillance is required according to ArbMedVV (Ordinance on Occupational Health Care). Exposed employees must be given regular check-ups if they so wish (elective occupational health surveillance). Thus, physical and clinical examinations within health surveillance can be refused by employees according to German law, and biomonitoring results if treated as medical data are confidential data. Biomonitoring for DMAC and NEP for exposure control implemented via a company agreement must not undermine the regulations on health surveillance. Due to legal limitations the use of BLVs for DMAC and NEP for exposure control may not be possible in all EU MS. In a comment received in the consultation of the Annex XV report concerning DMAC (#3587), the European Man-made Fibres Association (CIRFS) states that methods for measuring the dermal exposure are not available.

SEAC also notes two Annex XV report consultation comments (#3592, #3682), where the Danish Working Environment Authority and European Apparel and Textile Confederation (EURATEX) express their general viewpoint that the regulation of risk of hazardous substances at work places should be done under the OSH regulation to avoid double regulation, and that REACH or other regulations only are instruments that should be used exceptionally to complement OSH-regulation to further increase the protection of workers. The Danish Working Environment Authority refers to the recent amendment to Directive 2004/37/EC which entered into force in April 2022 and now allows to set binding occupational exposure limits (BOELs) for reprotoxic substances. Further it is underlined, that setting a BOEL involves the tripartite dialogue in the Advisory Committee on Health and Safety at Work (ACSH) to address the feasibility of proposals.

<u>REACH restriction options</u>

The Dossier submitter has discussed a complete ban of DMAC and NEP (maximum percentage of 0% in mixtures), and binding DNELs as two possible restriction options. SEAC agrees with the Dossier Submitter that a complete ban is not economically feasible for either substance since specific properties of aprotic solvents are required for several uses. SEAC also notes that in case of the complete ban a regrettable substitution could take place with other aprotic

solvents not restricted but having similar hazards.

The proposed restriction option with binding DNELs would allow continued use of DMAC and NEP but induce additional risk management measures. RAC has agreed that this option is expected to reduce exposures effectively. SEAC agrees with the Dossier Submitter that practical and economic challenges of complying with the DNELs could, in principle, be addressed by derogations for specific uses and transitional periods for specific sectors. The Dossier submitter did not initially identify any needs for derogations or transitional periods for any specific sectors, however, in the consultation on the Annex XV report the Man-made Fibre industry requested a 4-year transition period to smoothen the adjustment to the proposed restriction. The proportionality of this restriction option are discussed further below.

3.4.3. Effectiveness in reducing the identified risks

Summary of Dossier Submitter's assessment:

The Dossier Submitter has targeted the restriction 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 necessary, at safe exposure levels both for inhalation and dermal exposure. The Dossier Submitter concludes this option to be effective in limiting the risks related to the use of DMAC and NEP.

When assessing the four risk management options (authorisation, Occupational Exposure Limit (OEL), a restriction with a maximum concentration limit and a restriction with binding DNELs) the Dossier Submitter found that all risk management options are expected to reduce or eliminate the risks related to the use of DMAC and NEP. Furthermore, the Dossier Submitter concludes that the proposed restriction with binding DNELs for the inhalation and dermal route for DMAC and NEP is the most appropriate risk management option because it i) 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, according to the Dossier Submitter iv) the binding DNEL restriction offers a high level of flexibility for downstream users to implement necessary RMM and adapt OC to ensure exposure below the respective DNELs. Finally, v) the proposed restriction offers legal consistency with existing restrictions on two other dipolar aprotic solvents NMP and DMF.

RAC conclusion(s):

A restriction with binding DNELs for the inhalation route and for biomonitoring for DMAC and NEP can be considered to effectively reduce the risks in case these DNELs are complied with in the relevant workplaces.

The proposed restriction offers a high level of flexibility for downstream users to implement tailor-made appropriate OCs and RMMs as needed or adapt already existing OCs and RMMs.

RAC agrees with the Dossier Submitter that it should be possible for most companies to reduce the exposure by adjustment and improvement of OCs and RMMs to a level below the DNELs derived by RAC.

Key elements underpinning the RAC conclusion(s):

The risks to workers resulting from exposure to DMAC and NEP can be effectively reduced through the implementation of technical RMMs.

DNELs apply equally to all sectors and users in supply chains; however some uses especially in waste management might not be covered by a restriction. A restriction allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve.

Although RAC considers the proposed restriction effective in reducing the risks, it is recognized that there are no studies available yet on the success of the practical implementation and on the effectivity of existing NMP and DMF restrictions at workplaces.

3.4.4. Socioeconomic analysis

3.4.4.1. Costs

Summary of Dossier Submitter's assessment:

According to the proposal, the proposed restriction would achieve adequate control of risks with limited costs for the industry.

According to the Dossier Submitter no precise estimate of the total costs incurred by each sector is available. Estimated costs relate to the costs of implementing additional risk management measures to reduce exposure levels below the proposed DNELs – i.e. to describe compliance costs. No generic cost estimate for implementing a LEV system or enhanced ventilation is provided. In addition, feasibility and related costs (per workplace) of administrative measures, i.e. changes in staff rotation, are not assessed.

Quantitative costs estimates per worker are provided for a staff training program to protect against dermal exposure, and for biomonitoring for combined exposure to DMAC. Additionally, one-off costs are available for update of CSR in case a downstream user deviates from the Registrant´s exposure scenarios.

For the special case of discontinuation of products with a high NEP content in professional settings, only minor substitution costs are expected given the generic product purposes with a small market share and the availability of less hazardous product alternatives (non-quantified estimates by the Dossier Submitter).

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.

Summary of proposed derogations:

Originally, no derogations were proposed by the Dossier submitter. In the consultation of the Annex XV restriction report, the European Man Made Fibres Association requested a transition period of 4 years. The association described the compliance costs for enlargement and adaption of Local Exhaust Ventilation (LEV) systems to be significant and requested the transition period for the industry sector to be able to cover those costs (comment #3587, #3667).

SEAC conclusion(s):

Concerning both substances, SEAC agrees with the Dossier Submitter's listing of the main elements of the company costs relating to the risk reduction measures. These measures comprise, engineering controls (e.g. containment, Local Exhaust Ventilation (LEV)), administrative measures (e.g. staff rotation to limit exposure times), and Personal Protective Equipment (e.g. by training for stricter glove regime, use of gloves, protective cloth and respiratory protection equipment).

SEAC agrees with the Dossier Submitter that substitution in principle would be an effective measure to eliminate the identified risk from both DMAC and NEP. However, it is not a technically (or economically) feasible solution in most cases (see section 3.3 Analysis of alternatives). SEAC notes that, according to the Dossier Submitter, for some professional uses in chemical products (e.g. graffiti cleaning products) uses of DMAC and NEP will cease. However, the Dossier submitter has considered these as minor uses and has not assessed the economic impacts of withdrawal of these products from the market or potential product performance losses. In the Annex XV report consultation additional information on this was requested. SEAC notes that, with the information currently available, no final conclusion on estimated magnitude of substitution costs is possible.

SEAC notes that the Dossier Submitter states the Local Exhaust Ventilation (LEV) to be the preferred measure to reduce inhalation exposure according to hierarchy of control principle (assuming that process conditions are already optimised to minimise exposure). However, due to the variance of parameters of a LEV system (number of exposure points, type of filter, filter size, fan system performance etc.) the Dossier Submitter does not consider it possible to provide generic (quantitative) cost information for the implementation or upgrade of a LEV system. SEAC recognises the difficulties and the resulting uncertainties in quantification of these costs. For getting an indication about the order of magnitude of LEV costs SEAC proposes to use the LEV costs estimates from NMP restriction proposal. Because of different numbers of exposed workers, and different production conditions in different industry sectors only a rough adaption of these costs to different company sizes and industry sectors was possible. As such SEAC recognizes some uncertainty in the LEV cost estimates.

SEAC notes that the Dossier Submitter discussed job rotation as an organisational risk management measure and agrees that these costs can be considered insignificant. Similarly, SEAC notes the training for glove use and the subsequent (quantified) training costs per worker plausible as provided by the Dossier Submitter.

In addition to the RMM costs, the Dossier Submitter considers that the implementation of the restriction proposal may induce biomonitoring costs per worker and company specific costs for downstream user companies updating their CSRs. Expert judgement is used to quantify these costs. With the current information, no conclusion on the assumptions used and the resulting cost estimates is possible. The consultation of the Annex XV report did not bring significant further information on this matter.

SEAC acknowledges, that according to the Dossier Submitter, an estimate of the total costs by each sector cannot be provided since information on the share of companies needing to adapt their RMMs to comply with the DNELs is lacking and details of the exact working conditions and necessary additional risk management measures required by each affected company in each relevant sector are not known. This seems plausible to SEAC. As a result, SEAC cannot conclude on total compliance costs or sector specific total compliance costs due to adaptation of risk management measures to comply with DNELs. However, based on comments received in the consultation of the Annex XV report, some quantitative information about company-specific compliance costs, and some qualitative information stating that compliance is already reached and no compliance costs of this restriction are expected can be found in comments 3587, 3602, 3609, 3664, 3668, 3708, 3714.

Concerning the proposed derogation SEAC notes that increased time to react to the proposed restriction is normally expected to decrease the costs. This could allow e.g. some of the adaptation to be undertaken as a part of normal periodic maintenance and service activities. For instance, costly risk reduction technologies like investments in LEV, can be implemented gradually. It may also help to time planned instrument installations in a way to minimise the number of breaks and/or delays in the production process. As such, SEAC finds the proposed transitional period cost saving, however, that would naturally need to be compared to value of consequent postponement of benefits.

Assessing the cost information provided by the Dossier submitter as well as the comments

received in the consultation SEAC views the cost information and the qualitative statements about compliance and compliance costs to be, although to some degree vague, however, credible and to be used for the proportionality assessment because strongly contradictory and/or opposing responses have been few.

Key elements underpinning the SEAC conclusion(s):

SEAC notes, that the Dossier Submitter has identified relevant cost items. However, they are only partly quantified. Quantified information is available on the following cost items: i) training costs to implement a stricter glove regime, ii) biomonitoring costs, iii) CSR update costs (relevant if higher tier models or additional measurement campaigns are implemented). Other costs (e.g. implementation of technical measures (LEV)) were assessed qualitatively by the Dossier Submitter.

Thus, in the light of the proportionality assessment, this cost information can be used to assess the proportionality of the proposed restriction. SEAC notes quantitative information related to some potential risk management measures is available, however, the information tends to be scattered i.e., cost information is not always clearly linked to company size or number of employees being affected. SEAC also notes that quantitative data about technical risk reduction measures does not reflect all different company sizes and production conditions in different industry sectors. This sparsity of data hinders the generalisation of it, and its use for sector level conclusions. As such the cost information tends to, at the most, shed light at some specific industry sectors and/or describe exemplary cases helping to better understand the situation, however, it is not able to provide a holistic picture about the costs in general.

Training costs

SEAC understands the company specific training costs are based on direct and indirect costs. As explained in the Background Document, the indirect costs are due to the productivity losses (valued with gross value added per employee) when employees are trained during working time and the direct costs are e.g. the price for hiring an external trainer. SEAC agrees with the treatment of the costs in the restriction report and found the way the costs have been calculated in the report (p. 76-79) clear and acceptable.

Assuming for training duration between one and four hours, and a group size of 20 participants for training on average, sector-specific training costs in the range **€110 to €250 per workers** per training session are estimated which SEAC considers the approach to value the productivity losses of employees during training time which follows the diisocyanate restriction plausible. A training repetition once every four years seems also reasonable and is in-line with the restriction of diisocyanates.

The Dossier Submitter assumes that the training shall focus on more effective use of **gloves** to protect against dermal exposure. SEAC plans to seek RAC's advice whether a training measure could also address a use of **respiratory protective equipment**. This is mainly of importance for professional uses of NEP when technical measures like LEV cannot be applied especially for specific outdoor professional uses. Training duration, and expertise of the trainer would be similar, and thus similar training costs per worker are assumed **€110 to €250 per workers** per training session. Respiratory protective equipment (RPE) ranges from simple filtering masks (respirators) to special breathing apparatus (BA) with an independent source of air (e.g. air cylinder or air compressor).

Biomonitoring costs (DMAC only)

SEAC understands that the biomonitoring is the only option for combined exposure assessment (dermal and inhalation). The dossier submitter has derived a Biological limit value (BLV) only for DMAC, RAC has done this also for NEP in the opinion.

According to the restriction report sector-specific biomonitoring costs are estimated to be in

the range of **€440 to €490 per worker** per year depending on the sector. The estimate is based on assumptions about number of measurements, analytical costs, number of employees monitored (assumption: #10, #40), productivity loss during sampling, and time investment for occupational hygienists or physicians as listed in the restriction report (p. 79-80). SEAC finds the assumptions plausible. However, SEAC notes that the biomonitoring costs will be lower in case the company is already doing biomonitoring on a regular basis for other occupational exposures. In the best-case the time investment of the occupational hygienists for biomonitoring will be sufficient to monitor the occupational burden of DMAC/NEP exposure such that only analytical costs for the sample arise of about **€160 per worker per year** (around €80 per sample times 2 measurements).

Development of a downstream user Chemical Safety Report (CSR)

The Dossier Submitter clarifies that the registrants will need to update their exposure scenarios with additional OC and adequate RMMs such that compliance with the DNELs can be assumed if downstream users follow to the exposure scenarios. However, some downstream users may deviate from these exposure scenarios and demonstrate with higher tier models (option 1) and/or company-specific measurements (option 2) compliance with the DNELs. These companies have to prepare a company-specific CSR prepared by an in-house occupational hygienist or by an external OSH service provider (service provider costs: 56€/h). SEAC notes the monetary estimate used appears moderate and an hourly cost can also be clearly higher than this. SEAC notes the preparation is costly to the company. The time (and costs) needed for update is driven by the number of exposure scenarios and the associated number of worker contributing exposure scenarios (WCS, ECS) and product categories (PROCs) which have to be adapted. SEAC finds the Dossier submitter has estimated the costs for updating the CSR and explained the assumptions used in the calculations in an acceptable way in the report (p. 80-82). The resulting total one-off cost for CSR update is estimated to be **€2 700**. In case internal OSH staff is available for this task the costs may be significantly lower.

Based on information provided in the consultation of the Annex XV restriction report (#3714), the Dossier Submitter revised the total one-off costs for the CSR-updates in the Background Document. In the comment, it was indicated that the average time investment for the preparation of an updated Downstream user (DU) CSR could be twice as high as estimated by the Dossier Submitter. Based on this information, the number of workdays needed to update a DU CSR is adjusted to about 12 days by the Dossier Submitter (before: 6 days) resulting in total one-off cost for the CSR update of €4 900 instead of €2 700. SEAC has considered this plausible and has taken forward a total one-off cost for CSR update of €4 900 for its cost assessment. In addition to more working days needed, this comment (#3714) provides higher estimates also for consultancy costs for CSR-updates such that the total CSR-update costs are indicated to range from €13 000 to €14 000. These are to be considered more plausible based on significant hourly costs, and the costs for evaluation of monitoring data which were not included in the Dossier Submitter's cost estimation. Based on this information, the earlier used €2 700 costs (and also the €4 900 costs updated by dossier submitter) are considered to be an underestimation. The same comment also states that, typically, the professional expertise to perform a complex assessment needed for the preparation of a CSR is not available in DU companies.

In case compliance is demonstrated by company-specific measurements (option 2) biomonitoring costs per worker as estimated above are assumed. These monitoring costs may represent an upper value to determine combined exposure. In case only the inhalation exposure route is of relevance and if air measurements are less costly these would be chosen.

Table 11: Total Downstream user (DU) CSR preparation costs

	DU CSR prepared based on higher tier models	DU CSR prepared based on measurements
	€4 900	€4 900

No. of employees assumed for measurement campaign: #10		€5 600
No. of employees assumed for measurement campaign: #40		€10 400
Total cost for DU CSR per company		Lower value: €10 500 Higher value: €15 300
Total cost for DU CSR per company per year (time horizon: 15 years)	€180	Lower value: €700 Higher value: €1 020

For impact assessments of NMP and DMF restrictions a time horizon of **15 years** was assumed. To make cost impact of DMAC/NEP restriction comparable with these restrictions the same time horizon was assumed.

SEAC considers the valuation approach plausible. Similarly, the estimates for the time spent for CSR update seem plausible. The Annex XV report consultation has provided some support on the approach taken.

Costs of technical measures: Local exhaust ventilation

The Dossier submitter has presented a qualitative discussion on factors that would have an impact on the operating costs of LEV systems, namely, i) regular maintenance, ii) frequency of replacement of filters, iii) training of employees, iv) performance testing by internal staff or external service provider (at least every 14 months[10]). SEAC considers that these factors are all valid and would have an impact on the operating costs of LEV systems. Furthermore, SEAC requested additional information on such costs in the Annex XV report consultation to have information to be used to generate a range of costs for the cost assessment. Due to the wide variance in company specific conditions the Dossier submitter decided not to quantify costs of technical measures, especially the implementation and operation of ventilation systems. SEAC recognises these difficulties and the resulting uncertainties in quantification. For getting an indication about the order of magnitude of LEV costs, SEAC reports the cost data for ventilation units which were used for impact assessment of Binding Occupational Exposure limit values under the Carcinogens Mutagens Directive (CMD, 2004/37/EG) based on estimates from LEV suppliers (IOM 2011).[11] These cost data were also used for NMP restriction proposal (2013). The costs are reported per company.

Table 12: Indicative RMM costs per enterprise (annualised per year, updated to 2021 €) (Annex XV Restriction REPORT, N-Methylpyrrolidone (NMP), Appendix B Costs analysis)

	Annual LEV costs		**Effectiveness (%)**
	Low	High	
Stationary LEV*	€7 114	€31 118	83

LEV units are assumed to have a lifetime of 20 years, and comprise capital costs, annual maintenance and testing costs, and filter changes every 5 years. The discount rate for annualisation is 4%. It is estimated that the average number of exposed employees per

[10] Based on authority recommendations.

[11] IOM (2011a): Health, socio-economic and environmental aspects of possible amendments to the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work, 1,2Dichloroethane, IOM research project P937/17.

company is 44 to 54.

LEV costs were also assessed for Cobalt restriction based on Industry survey/CfE. Based on that, annual costs per LEV system are estimated to be in the range of **€170 - €1 700**, covering investment costs in the range of €1 000 - €10 000[12]. These annual costs (derived from Cobalt restriction) are lower compared to NMP annual LEV costs, but the costs are given per LEV system, and not per company. Thus, without more specific information about the conditions of production calculation of LEV costs per company is not possible.

In an impact assessment for polymer registration and evaluation under REACH costs of various risk management measures in the workplace were gathered by an industry survey (capital and operating costs). The LEV capital costs are in the broad range between €7,000 (small company) and €1.7 million (large company), and the annual operating costs are estimated to be 10% of capital costs (i.e. €700 – €170 000).[13] (Annualized LEV costs over 20 years with discount rate 4%: **€570 – €126 000**.) Since information about the number of exposed workers assumed for the LEV cost assessment is not available, cost transfer to companies with different numbers of workers exposed to DMAC and NEP is not possible.

The European Man-made Fibres Association (CIRFS) stated in their Annex XV report consultation comment (#3587) that according to their members the man-made fibre (MMF) manufacturing companies have already installed LEV systems (e.g. wet-spinning companies using aprotic solvent DMF). Based on their experience, further adaptation and extension of LEV might be needed to maintain a safety margin given the proposed inhalation DNEL for DMAC. This was also supported by the European Apparel and Textile Confederation (EURATEX) in their Annex XV report consultation comment (#3682), and in their comment to the consultation of the SEAC draft opinion. According to those comments, for some companies of the textile industry, ventilation needs to be improved. The related costs are expected to be of the same order of magnitude as for the man-made-fibre sector.

In a further comment (#3667) LEV investment costs based on LEV costs for DMF restriction are indicated to be in the range €5-€10 million per company (annualized over 20 years with discount rate 4%: **€368 000 – €736 000**). To adapt to the proposed DNELs adaptation and expansion of existing LEVs additional investments are expected for improved ventilation for some companies. In addition to the investment costs, there would be further costs from reduced DMAC recovery efficiency (due to lower concentration in the exhaust stream as a greater volume of air is drawn through the system), potential additional heating costs, and increased emissions to the environment. For comparison with LEV costs as shown in Table 12 it has to be taken into account that the number of workers per company in Man-Made-Fibre industry on average is larger (about 4 to 5 times) than was assumed for estimated LEV costs in NMP restriction. In comment #3587 it was also stated that local exhaust ventilation is already installed in MMF companies for fibre production with DMAC as shown to the dossier submitter during online site visit and using similar production techniques as for wet-spinning DMF plants with regard to requirements of the OSH-regulation. The binding OEL is about 3 times higher than the proposed inhalation DNEL for DMAC. Therefore, for SEAC the need for adaption of RMMs is plausible, but it is not clear whether compliance could at least partly be reached with less costly measures like PPE, and organisational measures like job rotation. Furthermore, the identified risks are mainly caused by dermal exposure on which LEV have only a minor effect. SEAC also notes that costly investments in LEV could also be at least partly shifted to planned investment cycles for substitution and modernisation of the LEV systems. Therefore, the LEV costs raised in the comment # 3667 are considered as a very conservative cost estimate and could be lower. However, SEAC also notes that in cases where

[12] Background Document to the Opinion on the Annex XV dossier proposing restrictions on cobalt sulphate; cobalt dinitrate; cobalt dichloride; cobalt carbonate; cobalt diacetate, (p. 39).

[13] European Commission, Scientific and technical support for the development of criteria to identify and group polymers for Registration/Evaluation under REACH and their impact assessment. Final Report. 2020.

LEV already exist but has to be adapted to e.g. to make it more efficient, the costs are expected to be lower.

In summary, because the assumptions for the LEV costs assessment for NMP restriction are well documented and plausible, SEAC decided to use these cost figures for cost assessment for average size companies in the following manner: **€7 100 - €31 100** per company per year (rounded). To cover "larger" companies of e.g. Man-made fibre sector with about 250 exposed workers per company, SEAC notes that for such companies the LEV costs could be considered to be 5 times higher than the aforementioned average LEV cost figures.

Further costs

Concerning the assessment methods, SEAC notes the European Man-made Fibres Association (CIRFS) Annex XV report consultation comment (#3587), which states that the dermal DNEL for DMAC in practice leads to a substance ban when applying the highest dermal protection foreseen in the ECETOC TRA model (glove incl. specific training). This in turn would lead to closure of plants as even bulk charging/discharging operation in an industrial environment cannot calculated to be safe and all industrial handling requires a charging/discharging operation of liquid DMAC at some stage.

In a further comment (#3714) site closure was also considered as a possible consequence of considerably low DNELs (as originally proposed by Dossier submitter). Consequently, for instance, EEA production of Spandex/Elastane fibres could suffer and would need to be imported from non-EU production sites at higher costs for the downstream uses of the fibres.

Per company cost estimation

The above considered costs of risk management measures (RMM) and the biomonitoring and CSR update costs will arise depending on whether companies in the different sectors need to adapt their RMMs to be compliant with the DNELs. Based on the risk assessment in the Restriction Report and the information from the CfE a conclusion on this is not possible. The Annex XV report consultation has delivered more information on this. These information and Dossier Submitter´s cost estimates for risk management measures (training for glove use), biomonitoring, CSR-update have been used to estimate compliance costs per company and compliance costs per worker. Additionally, SEAC has assessed whether there appears to be cost estimates available from data for ventilation units to shed light on the order of magnitude of these costs. The information is summarised with the tables below, however, information applies only to DMAC. For NEP no cost information was submitted during the consultation of the Annex XV dossier.

Table 13: Risk measurement measures already in place and possible RMM adaptation for compliance in different sectors (RMO1)

DMAC **Sector (NACE R2 Labels (code))**	**DNEL compliance with current measures (inhalation, dermal)**	**Adaption of RMM based on identified risk and further information**
Manufacture of chemicals and chemical products (C20) Manufacture of other organic basic chemicals (C2014)	Cefic BDO & Derivatives sector group of Cefic (#3588): We refer to the measures for the implementation of the NMP Directive: All necessary measures (LEV, Training, PPE) to comply with the NMP limits are also effective for the DMAC emissions. The adaptation of the conditions in the process, infrastructure and individual protective measures are being implemented or have already been carried out.	No additional RMM
Manufacture of man-made fibres (C206)	European Man-made Fibres Association (#3587): Local exhaust ventilation is already installed in MMF companies for fibre production with DMAC because of OSH requirements, but not considered sufficient to comply with proposed DNELs.	Increased efficiency of LEV Adaptation and extension of exhaust ventilation might be needed within the technical limits possible to maintain a safety margin to the proposed inhalation DNEL.
Apparel and textile manufacturing sector (Some companies of Apparel and textile sector are also involved in production of synthetic yarns and using DMAC)	The European Apparel and Textile Confederation (EURATEX) (#3682, comment to SEAC draft final opinion): Adaptation and expansion of existing LEVs is required because the DNELs are much lower than the existing national OELs for which the LEVs were developed and installed	Increased efficiency of LEV
Manufacture of medical and dental instruments and supplies (C325) • Use as solvent in the	Company name name confidential (#3602) – medical (dialyzer) membranes for	No additional RMM

production of polysulphone membranes	hemodialysis: Local exhaust ventilation systems (LEV) are already installed in DMAC-relevant workplaces. With regards to the currently proposed inhalation DNEL only, no need to install or adapt LEV is expected to meet this air/inhalation limit. Adequate OHS training is already required and established in line with applicable OHS regulations on a regular basis. This also covers dermal exposure and use of required PPE. This topic was also discussed in comment #3708 (company name confidential): According to the results of the inhalation exposure measurements, no need for LEV system and training program is expected.	
Manufacture of electrical equipment (C27) – Use as solvent in coatings (wire coaters)	European Wire Winding Association (EWWA) (#3609, #3668): Measures to comply with the NMP restriction DNELs are also effective for the DMAC emissions (see REACH Restriction 71, guideline for users of NMP). The adaptation of the conditions in the process, infrastructure and individual protective measures are being implemented or have already been carried out. RMM are already in place: LEV, PPE, Regular training on yearly base, special training for new workers or due to special events or changes in the process.	Depending on exposure assessment, case-by-case adaptation of risk management measures might be required to be compliant with dermal DNEL
Other sectors: Petrochemical applications, filling and packaging for scientific research and development, adhesives,	No further information received in CfE; considered as niche applications by Dossier submitter	-

plastic and anti-set off agents in polymer moulding/casting, potential use in sealants, putty, paints, lubricants in metal working fluids, production of cellulose fibres such as cellophane ECHA (2012a).		

DMAC is also used for **manual maintenance** (cleaning and repair) of machinery, and for use as **laboratory chemical** on some sectors. For these uses no information about compliance costs were received in consultation to Annex XV dossier. There is very limited information on NEP uses, use volumes and number of exposed workers available in addition to the information provided in the registration dossiers (described in Annex A). A total volume of between 100 and 1 000 tonnes of NEP is manufactured or imported per year according to registration dossiers (ECHA, 2021). Only little information on NEP use was received in the Annex XV dossier consultation.

The following table provides compliance costs per company and per worker for different combinations of risk management measures, monitoring and CSR-update.

Table 14: Cost items and total compliance costs per company per year– DMAC/NEP

	Training (Glove use)	**LEV**	**Biomonitoring**	**CSR update (w/o monitoring)**	**CSR update (with monitoring)**	**Total costs**
Combinations of RMM and monitoring	€391 - €1,664	€7,100 - €31,100	€373-€693	€327	€700 - €1020	
RMM	X	X				**€7,491 – €32,764**
RMM + Biomonitoring	X	X	X			**€7,864-€33,457**
RMM + CSR	X	X		X		**€7,818 – €33,091**
RMM + CSR with monitoring (analytical costs only)	X	X			X	**€7,870 - €33,301**
RMM + CSR with monitoring	X	X			X	**€8,191 - €33,784**

Assumptions: Time horizon for assessment: 15 years; 10 and 40 employees per company for training and biomonitoring campaigns assumed; Training repetition every 4 years; LEV depreciation rate: 20 years

The numbers indicate the order of magnitude of costs. SEAC is aware that the costs are not representative for the industry as a whole, but rather examples from different size companies from different industrial sectors.

3.4.4.2. Benefits

Summary of Dossier Submitter's assessment:

The benefits accrue from the (positive) 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. The Dossier Submitter considers the extrapolation and quantification of the identified health effects from animal studies to human health effects too uncertain. In general, the Dossier Submitter acknowledged uncertainties in the quantification of health impacts and instead, a qualitative description of potential effects is given and its relevance to human health. The Dossier submitter also views that there is no need for a quantified and monetised human health impact as the net societal welfare change is not quantified.

Summary of proposed derogations:

No derogations were proposed by the Dossier submitter.

In the consultation a transition period of 4 years was requested by European Man Made Fibres Association to be able to cover significant compliance costs for enlargement and adaptation of Local ventilation systems. The derogation would postpone occurrence of benefits for the same 4 years but are not seen to affect the level of benefits otherwise.

SEAC conclusion(s):

SEAC notes that RAC has confirmed the negative health impacts due to inhalation and dermal exposure to DMAC and NEP.

SEAC agrees that inhalation and dermal DNELs for DMAC and NEP, and adequate risk management measures chosen to reduce exposure such as to comply with these DNELs will reduce the health risks. The health risks are effectively zero if compliance with the DNELs is reached. SEAC also agrees that this risk reduction can be used as a proxy for the health benefits.

The health effects of the proposed restriction are qualitatively described with reference to the negative health impacts which may arise if exposures with DMAC/NEP are larger than DNELs. No quantification of health impacts was provided.

The developmental effects like foetus malformations leading to lower birth weight and birth defects are considered as very severe health effects which is also reflected by comparatively high willingness-to-pay values to avoid these adverse health impacts.

Based on the RAC´s conclusion on risk assessment, the proposed restriction is expected to yield health benefits. However, SEAC notes that the dossier submitter's benefit assessment provides only limited information for quantitative benefit assessment, and thus hinders quantitative proportionality assessment by comparison of benefits and costs. Furthermore, based on the information available, benefits of this restriction for both DMAC and especially NEP, appear limited in general. Besides direct benefits, the proposed restriction would yield benefits by ensuring that the risk levels would not increase in the future as a result of e.g.

increased use of DMAC or NEP.

SEAC notes that for the case of NEP, conclusions about health benefits are not possible. No information about RMM adaptations costs to be linked with the proposed DNELs were submitted in the consultation. Compared to DMAC, use of NEP can be considered as a niche use. In the absence of opposing information, it is likely that due to adaptions of RMM to former NMP and DMF restrictions the economic impacts and also the health benefits of this restriction are very limited. Because of the moderate risk levels of industrial uses of DMAC and NEP which were derived by the Dossier Submitter (with one exception) it seems very likely that the RCRs could be reduced below 1 by considering advanced exposure estimation methodology (such as tier 2 modelling and monitoring).

Key elements underpinning the SEAC conclusion(s):

For both aprotic solvents, DMAC and NEP, developmental effects and liver effects are observed in animal studies. Health risks due to inhalation exposure to DMAC related with the developmental toxicity of DMAC may lead to malformations of different forms in foetuses, and a reduced birth weight. Oral exposure used as a proxy for dermal exposure to DMAC may cause liver damage. These health effects are also observed for exposure to NEP in animal studies. In addition, for exposure to NEP due to similarity with NMP systemic effects are considered likely resulting in body weight loss combined with some loss in general well-being. Inhalation exposure of NEP may also lead to irritation of the mucous membranes in the nose.

Foetus malformations leading to lower birth weight and birth defects are considered as very severe health effects. However, quantitative assessment of those benefits is not possible since the extrapolation and quantification of the identified health effects from animal studies to human health effects are considered too uncertain. However, qualitatively, it can be concluded that the willingness-to-pay to avoid developmental health impacts is comparatively high: In the ECHA valuation study (2014) to estimate monetary values of preventing a range of diseases and conditions associated with chemicals exposure e.g. for a very low birth weight willingness-to-pay values in the range of €128,000 to €405,000 were derived, and for major internal birth defects in the range of €128,000 to €712,000 respectively. For comparison, in this study for avoidance of cancer morbidity a central value of €410,000 was derived.

RAC has confirmed the negative health impacts due to inhalation and dermal exposure to DMAC and NEP for cases of use of DMAC / NEP with RCR > 1. The health risks are effectively zero if the compliance with the DNELs is reached. SEAC agrees that possibility for such a risk reduction demonstrates that there are potential health benefits due to the restriction proposed. If quantifiable, the risk reduction could be used as a proxy for the health benefits, however, SEAC has not identified a method for quantification.

No quantification of health benefits was provided. In the Dossier also no estimate for the total number of workers exposed and consequently no number for the share of workers exposed above the level of the DNELs was estimated. Therefore, the total number of workers who may benefit from implementation of adequate risk reduction measures is not available, and no benefit estimate based on assumptions was provided. In Annex XV report consultation no information was submitted on the number of people exposed in the different sectors.

However, for DMAC for some specific sectors a number is given for the potentially exposed workers, which may benefit from the restriction (see Table 15). For NEP no such information is available even for single sectors. However, based on comments in the Annex XV report consultation (see Table 13) for some of the mentioned industry sectors using DMAC the compliance with the DNELs might be reached already now, because of adaptations in RMMs already made due to former NMP and DMF restrictions. Specifically, it might be concluded that for the Electrical wire winding sector (comments #3609,_#3668) and for Medical membranes manufacturers no further health benefits for the exposed workers are expected due to this restriction proposed (comments #3602, #3708).

The European Man-made Fibres Association states there is a need to invest in and to adapt existing LEV systems (#3367). This is not fully plausible for SEAC since the risks are caused mainly by dermal exposure on which the impact of LEV is limited. For exposed workers health benefits may arise. However, the use of maximum number of **750 workers** which are directly exposed as an estimate would overestimate the number of benefitting workers since i) not all of the workers were exposed above DNELs and ii) since two of the producers have since ceased production (Table 15). According to the comment there are no numerous companies left on the sector, however, SEAC does not know exact number of them.

Table 15: Summary of EU use volume, number of relevant companies and number of potentially exposed workers by downstream use of DMAC described in Annex A (based on the background document for DMAC prepared by ECHA (ECHA, 2012a), inputs received through the CfE (CfE, 2020) and related follow-up communication.)

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).

Based on received comments from the consultation of the Annex XV report SEAC concludes that for the Electrical wire winding sector and for medical membranes manufacturers no further health benefits by exposed workers are expected to accrue due to this restriction (this concerns DMAC use only). Moreover, because of the low risks in the above mentioned sectors it seems very likely that the RCRs could be reduced below 1 by considering advanced exposure estimation methodology (such as tier 2 modelling and monitoring).

SEAC notes that the European Man-made Fibres Association indicates that the proposed restriction causes for its members a need to invest in and to adapt existing LEV systems such that health benefits may arise for some (unknown) fraction of 750 potentially exposed workers. SEAC does acknowledge this, but notes that the identified risks are mainly caused by dermal exposure on which LEV will have only a minor effect.

In industrial sectors using DMAC as solvent for production of agrochemicals, pharmaceuticals and fine chemicals, only very limited health benefits as well as limited RMM adaption costs (PPE, trainings) are expected. Given the observed level of derived risks (RCR around 2) it seems very likely that the RCRs could be reduced below 1 by considering advanced exposure estimation methodology (such as tier 2 modelling and monitoring).

In the production of agrochemicals, pharmaceuticals and fine chemicals, the use of DMAC as process solvent and reagent takes place in closed industrial installations. Furthermore, based

on information gathered by CfE, DMAC is re-used several times during the process as solvent in chemical synthesis before ending up in chemical waste streams (ECHA, 2012a), and recovery of DMAC from the final product is very efficient. All industrial handling of DMAC and NEP requires charging/discharging operations (PROC 8a/b) during which the exposure mainly may take place (Cefic/ BDO & Derivatives Sector Group, #3588). Given the dermal DNEL as proposed by RAC, safe charging/discharging operations (PROC 8a/b) are possible when all dermal RMMs are applied and when the workers are regularly trained in use of PPE and gloves. Therefore, in production sectors using DMAC as solvent in closed industrial processes zero or only very limited health benefits (and RMM adaption costs) are expected (#3588).

For NEP, conclusions over health benefits are not possible. No information about RMM adaptation costs to be compliant with the proposed DNELs were submitted in the consultation. Compared to DMAC, use of NEP can be considered as a niche use. In the absence of opposing information, it is likely that due to adaptions of RMM already to former NMP and DMF restrictions the economic impacts and also the health benefits of the proposed restriction are very limited.

RAC notes that measurable levels of NEP metabolites have been also measured in the urine of German children and adolescents. The source of this exposure is unclear, but it is likely that this restriction proposal would also indirectly reduce the exposure of the general public, thus also causing benefits for the general public.

SEAC acknowledges that as the conclusions here are partly based on individual comments submitted in the consultation of the Annex XV report, there might be some uncertainty involved in them. Similarly as in the case of costs, there is very little information available on NEP which increases the uncertainty of the conclusions for this substance.

3.4.4.3. Other relevant impacts

Summary of Dossier Submitter's assessment:

Concerning the **distributional impacts,** the Dossier submitter notes that 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 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.

In turn, 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 customers in form of higher prices of products, while in other sectors it might affect 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.

SEAC conclusion(s):

In general, SEAC finds the cost impacts described for the companies plausible. However, because the cost impacts and their impact on competitiveness are not further substantiated SEAC cannot evaluate impacts on competitiveness further.

SEAC agrees that an EU-restriction is expected to contribute to a harmonisation of risk management measures in companies and different industry sectors across the EU, and thus may reduce inequalities in worker protection against risks to DMAC and NEP exposures. Also the differences in prices for related consumer products attributable to different protection levels and resulting in different prevention costs may be levelled.

SEAC notes possible co-benefits of e.g. glove use to protect against dermal exposure of other hazardous substances than DMAC and NEP.

Key elements underpinning the SEAC conclusion(s):

In general, SEAC finds plausible that companies which have to adapt their operational conditions and risk management measures, may try to transfer additional costs via higher prices to their customers to some degree. If no complete transfer is possible, profitability is expected to decrease to some degree. Whether the shift of costs to customers in fact will arise, is not further substantiated in the restriction report. Similarly, it is not further substantiated whether the cost impacts would have a significant impact on relative competitiveness. Since no further evidence for these cost impacts is provided, they are not taken into account at this point of evaluation.

In a comment (3587) from European Man-made Fibres Association (CIRFS) it is stated that imports of Man-made Fibres products from Non-EU countries may increase, however, longer lead times, and disturbed supply chains have to be taken into account for decisions about increased imports.

3.4.4.4. Proportionality

Summary of Dossier Submitter's assessment:

The Dossier Submitter did not attempt to estimate the net societal welfare change of the proposed restriction via a cost-benefit analysis, rather the proportionality is assessed through comparison of the estimated costs per worker for risk reduction across dipolar aprotic solvent restriction dossiers. Namely, costs and benefits of the proposed restriction are compared to the (benchmark) costs and benefits of the NMP REACH restriction.

Cost estimates derived in the NMP dossier serve as a benchmark for the proportionality analysis. However, the comparison approach has some limitations as the Dossier Submitter does not have sufficient knowledge of all working conditions in affected companies and thus no precise cost estimates at sector level could be developed for DMAC and NEP.

According to the Dossier Submitter, 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, and for both cases inhalatory and dermal DNELs are based on developmental effects. Based on this, the Dossier submitter finds the comparative approach justified on the benefit side.

In summary, the aforementioned comparative approach does not provide a complete assessment of the proportionality of the proposed restriction. As a conservative approach, the total costs associated with implementing all measures for which cost could be quantified are computed.

SEAC conclusion(s):

SEAC observes the RAC conclusion that for some uses the RMMs and OCs implemented and recommended by the manufactures and/or importers are not sufficient to control the risk as RCRs are above one. However, the ECETOC TRA modelling used will, in some cases, result in very conservative estimates for exposure and risk estimation. Thus, the RCRs could be reduced below 1 by considering advanced exposure estimation methodology (such as tier 2 modelling and monitoring), or change of input parameters in the tier 1 modelling (e.g. duration of exposure, currently assumed to be 8 hours a day in most scenarios).

Regarding **effectiveness**, SEAC notes that RAC is of the opinion that the proposed restriction would be effective in risk reduction. It should be possible for most companies to reduce the exposure by adaption and improvement of OCs and RMMs to a level below the DNELs derived by RAC.

SEAC notes in the benefit section that **health benefits** were not quantified, but mainly qualitatively described. SEAC recognises the severe health impacts of developmental toxicity linked to not adequately controlled exposures to DMAC and NEP.

SEAC notes in the cost section above, that the cost information largely consist of qualitative information although also some general cost information is available, however, difficult to directly tie with a certain company size or calculate as a cost per employee. Information on aggregated **compliance costs** per sector is not available, however, indications of compliance costs per company in a sector are derived.

Thus, SEAC concludes that a proportionality assessment comparing quantified costs and benefits is not possible. Instead, proportionality has been analysed and assessed by a **semi-qualitative cost-benefit comparison, and by a benchmarking approach.**

The restriction is considered **likely proportional** in **electrical wire coating** sector and manufacturing **medical membranes** sector since protective measures are going to be implemented shortly or have already been carried out, and thus, zero or low adaption costs are expected. Use of DMAC in **Manufacture of chemicals and chemical products, and agrochemicals, pharmaceuticals and fine chemicals** is also considered likely proportional since measures (LEV, Training, PPE) to comply with the harmonized DNELs for NMP are considered to be also effective for the DMAC emission reduction (see Table 16) i.e., one set of measures brings in benefits both from NMP and DMAC emissions.

Proportionality could not directly be demonstrated for **Man-Made Fibres** sector and **Apparel and textile industry** since further investments in LEV seem to be required for compliance with the harmonized DNELs based on a consultation comment from industry (#3667; #3683; comment to SEAC draft final opinion). SEAC considers plausible that training and administrative risk reduction measures which can be implemented at relatively low cost are not sufficiently effective to reduce exposure (dermal, inhalation) to a safe level. OSH measures to reduce dermal exposure (PPE, training for PPE use) are already implemented (#3587). To manage the costs SEAC proposes a **transition period of 4 years** such that more costly risk reduction technologies (mainly LEV) can be implemented gradually. Moreover, SEAC considers plausible that the RAC-modified proposal for dermal DNEL could reduce pressure on further expansions of RMM and thus the costs of compliance for industry compared to the original proposal. The lower costs are primarily a consequence of the higher dermal DNEL value proposed by RAC. Taking this and the proposed transitional period for Man-Made Fibres into account, SEAC considers the restriction likely to be proportional.

For NEP use information received is very sparse. In the absence of opposing information, it is likely that due to adaptations of RMMs due to earlier NMP and DMF restrictions the economic impacts and similarly the health benefits of this restriction are limited. As such SEAC considers it likely that the restriction would be proportional. In addition, to the semi-qualitative cost-benefit comparison a **benchmark for compliance costs per worker** derived for NMP restriction is applied to inform the proportionality considerations. Due to the structural similarity between NMP and DMAC, large similarities in uses and development toxicity of both substances it is considered that a cost comparison can be done on those two substances. The cost comparison for **wire coating sector** shows that **per worker costs are significantly below NMP restriction compliance costs.** This also holds for the worst-case scenario, where all available measures are affected i.e. training, LEVs, and biomonitoring need to be implemented, and CSR needs to be updated (see Table 17). However, due to the NMP and DMF restrictions these measures are considered to be already implemented to a large degree.

Key elements underpinning the SEAC conclusion(s):

Semi-qualitative cost-benefit comparison

Given indications about the level of expected compliance costs provided in consultation to Annex XV dossier, already implemented risk management measures because of restricted uses of DMF and NMP and OSH regulation, and the timing of the costs the likely proportionality was analysed and assessed by a **semi-qualitative cost-benefit comparison.** This assessment was done per sector for the different uses of DMAC and NEP.

Comments received from European Winding Wire Association and two manufacturer of medical membranes which refer to the use of DMAC, state that process adaptations, LEV, and individual protective measures are going to be implemented shortly or have already been carried out. Thus it is expected that no additional protective measures need to be implemented, and zero or low adaption costs by these actors in manufacturing medical membranes sector and electrical wire coating sector are expected due to the proposed restriction. Thus there is indication that for these sectors the restriction is likely proportional (see Table 17).

Use of DMAC as process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals takes place in closed industrial installations. All industrial handling of DMAC and NEP requires charging/discharging operations (PROC 8a/b) during which exposure mainly may take place (Cefic/ BDO & Derivatives Sector Group, #3588). Given the dermal DNEL as proposed by RAC, safe charging/discharging operations (PROC 8a/b) are possible when all dermal RMMs are applied and when the workers are regularly trained in use of PPE and gloves. Thus, in production sectors using DMAC as solvent in industrial processes only very limited health benefits and consequently RMM adaption costs are expected and therefore proportionality is considered likely.

For the companies in Man-Made Fibre sector and in Apparel and textile industry it was indicated in different comments (#3587, #3667, #3682, comment to SEAC draft final opinion) that adaptation and expansion of existing LEVs is required because the proposed harmonized DNELs are lower than the existing national OELs for which the LEVs were developed and installed. Local exhaust ventilation is already installed in MMF companies for fibre production with DMAC, as shown to the dossier submitter during online site visits, but not considered sufficient to be compliant with the proposed DNELs. Also additional training and administrative risk reduction measures are not sufficiently effective to reduce exposure (dermal, inhalation) to a safe level. A transitional period of 4 years is proposed for Man-Made Fibre sector to allow gradual implementation which in turn would support economic feasibility of adoption of additional technical measures as indicated in comment #3587 and #3682. SEAC concludes, that although the proportionality of the original Dossier Submitter proposal could not be directly demonstrated, with RAC derived higher dermal DNEL and with a 4-year sector-specific transitional period the proposed restriction is likely to be proportional on this sector. The European Apparel and textile Confederation voiced their support for the Man-made Fibre sector 4-year transitional period in their comment (#1220, in the consultation on the SEAC draft opinion).

For the case of NEP, conclusions about proportionality are mainly based on missing contradictory information. No information about RMM adaption costs to be compliant with the proposed DNELs were submitted in the consultation. Compared to DMAC the use of NEP can be considered as a niche use. In the absence of opposing information, it is likely that due to adaptions of RMM to former NMP and DMF restrictions the economic impacts and also the health benefits of the proposed restriction are very limited, such that it is likely that the restriction would be proportional.

Table 16: Proportionality assessment per sector (RMO1)

DMAC **Sector (NACE_R2 Labels (code))**	**Adaption of RMM needed (DNEL compliance with current measures (inhalation, dermal)**	**Compliance cost per company**	**Proportionality likely/ unlikely**
Manufacture of chemicals and chemical products (C20) Manufacture of other organic basic chemicals (C2014)	Cefic BDO & Derivatives sector group of Cefic (#3588): We refer to the measures for the implementation of the NMP Directive: All necessary measures (LEV, Training, PPE) to comply with the NMP limits are also effective for the DMAC emissions. The adaptation of the conditions in the process, infrastructure and individual protective measures are being implemented or have already been carried out.	€0 No additional RMM	**Proportonality likely**
Manufacture of man-made fibres (C206) *Apparel and textile manufacturing industry*	European Man-made Fibres Association (#3587): Local exhaust ventilation is already installed in MMF companies for fibre production with DMAC because of OSH requirements, but not considered sufficient to comply with proposed DNELs. The European Apparel and Textile	**€368 000 – €736 000** Adaptation and extension of Local exhaust ventilation (LEV) might be needed within the technical limits possible to maintain a safety margin to the proposed inhalation DNEL. **Reference made to compliance costs**	**Proportionality** of the initial DS proposal: **Unlikely** 4-year transitional period proposed for economic feasibility (#3587) **Proportionality** due to higher dermal DNEL and the 4y transition period (in the RAC-SEAC proposal): **Likely** **Proportionality** of the RAC-SEAC proposal: **Likely**

(Some companies of Apparel and textile sector are also involved in production of synthetic yarns and using DMAC.)	Confederation (EURATEX) (#3662; a comment to SEAC draft final opinion): Adaptation and expansion of existing LEVs is required because the DNELs are much lower than the existing national OELs for which the LEVs were developed and installed	**of** European Man-made Fibres Association (#3587); LEV adaption costs are of similar order of magnitude	
Manufacture of medical and dental instruments and supplies (C325) • Use as solvent in the production of polysulphone membranes	Company name confidential (#3602) – medical (dialyzer) membranes for hemodialysis: Local exhaust ventilation systems (LEV) are already installed in DMAC-relevant workplaces. With regards to the currently proposed inhalation DNEL only, no need to install or adapt LEV is expected to meet this air/inhalation limit. Adequate OHS training is already required and established in line with applicable OHS regulations on a regular basis. This also covers dermal exposure and use of required PPE. This topic was also discussed in comment #3708 (company name confidential):: According to the results of the inhalation exposure measurements, no need for LEV system and training program is expected.	€0 No additional RMM	**Proportionality likely**
Manufacture of electrical equipment (C27) – Use	European Wire Winding Association	**€25,000 per year** per winding wire	**Proportionality**

as solvent in coatings (wire coaters)	(EWWA) (#3609, #3668): All necessary measures to comply with the NMP restriction DNELs are also effective for the DMAC emissions (see REACH Restriction 71, guideline for users of NMP). The adaptation of the conditions in the process, infrastructure and individual protective measures are being implemented or have already been carried out. RMM are already in place: LEV, PPE, Regular training on yearly base, special training for new workers or due to special events or changes in the process.	installation case-by-case adaption of risk management measures might be required to be compliant with dermal DNEL	**likely** Additional costs are considered affordable.
Other sectors	-	-	No evidence provided to demonstrate not proportionate

Benchmark approach

In addition, a **benchmark for compliance costs per worker** derived for NMP restriction is applied to assess the proportionality considerations. Due to the structural similarity between NMP and DMAC, large similarities in uses and development toxicity of both substances a cost comparison is possible. The cost comparison for **wire coating sector** shows that per worker costs are significantly below NMP restriction compliance costs. This holds also for the worst-case where, in the same time, training, LEV measures, and biomonitoring needs to be implemented, and CSR updated.

For NMP restriction SEAC has evaluated cost-effectiveness for Automotive and Wire coating sector only since no major costs are expected for other sectors. DMAC and NEP uses are not relevant in automotive sector, and thus for the benchmark approach only the wire coating sector can be used. In the context of worker health protection cost-effectiveness is defined as compliance costs per worker.

Starting point for cost-effectiveness analysis are the theoretical compliance costs covering the complete package of risk management measures (training, LEV), biomonitoring and CSR-update. In reality less measures or no measures at all are needed to comply with the restriction. Therefore the compliance costs are refined based on comments received in public

consultation about likely reactions of companies in the different sectors to adapt to the harmonized DNELs.

The following table shows the benchmark compliance costs for Wire coating sector from NMP restriction and theoretical compliance costs per worker for DMAC restriction. In comments from industry it was indicated that no or only very limited costs of the restriction are expected. For information also the compliance costs per worker for Man-made fibre and Medical membranes sector for DMAC restriction are shown. SEAC notes the uncertainties of a comparison of compliance costs between different sectors due to different conditions of production and operation in different sectors.

Table 17: Cost-effectiveness of different sectors for DMAC and for NMP restriction and number of potentially exposed workers per sector (Background document for DMAC/NEP restriction; ECHA, 2014a, 2014b, own calculations)

Sector	**Number of workers potentially exposed**	**Cost estimate (in million)**		**Cost estimate per year per worker**	**Qualification of costs based on Public consultation comments**
		2014	**2021**		
NMP					
Wire Coating sector	1 000	€19*	€22	**€22 000** (mainly due to investment in new production lines)	
DMAC					
Wire Coating sector	1 500 – 2 000 Remark: In comment (#3609) 4220 workers (inhalation exposure) and 3798 workers (dermal exposure) mentioned	-	-	**€511 - €3 761** (Training, LEV, Biomonitoring, CSR-update)	€0 Zero or very limited compliance costs are expected since RMM are already in place (#3609, #3668)
Man-Made Fibres sector	750	-	€5 - €10	**€1 129 - €16 209** (Training, LEV, Biomonitoring, CSR-update)	**€1 472 - €2 943** LEV extension and adaption costs (#3587)

Medical membranes sector	500 – 1 000	-	-	**€511 - €3 761** (Training, LEV, Biomonitoring, CSR-update)	€0 Two producers state no need for adaption LEV or training, and thus zero or very limited compliance costs (#3602, #3708).

*Corresponding to a transitional period of 10 years

The cost comparison for **wire coating sector** shows that per worker costs are significantly below NMP restriction compliance costs also for the worst-case where, in the same time, training, LEV measures, and biomonitoring needs to be implemented, and CSR updated. This is mainly due the restriction of NMP which has already taken place, and the adaptations in LEV, and other safety measures thereof.

3.4.5. Practicality, including enforceability

Summary of Dossier Submitter's assessment:

The Dossier Submitter notes that the practicality of implementing adequate RMM to control dermal and inhalation exposure to DMAC and NEP below the DNELs depends on the company specific workplace situation. 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 OC and RMM. The Dossier Submitter proposes an 18 months transitional period for the restriction.

The Dossier Submitter acknowledges, that enforcing a restriction by restricting uses by means of binding DNELs 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. The proposed restriction on DMAC and NEP shows a high resemblance with the restriction on NMP. The NMP guideline (developed 2019) 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 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.

RAC conclusion(s):

The proposed restriction is practical and enforceable by implementing adequate RMMs, which need to be described in the individual exposure scenarios. The implementation of adequate RMM/OCs to reduce inhalation and dermal exposure to DMAC and NEP below the DNELs depends on the specific workplace. The DNELs are binding and apply to all workplaces. The need for additional RMMs varies widely across sectors and companies and the restriction offers flexibility in the implementation of RMM/Ocs.

RAC recommends an update of the NMP guideline to include also other restricted aprotic solvents as soon as a decision on the legal implementation of the DMAC and NEP restriction is taken.

Key elements underpinning the RAC conclusion(s):

RAC took into account the FORUM advice for this restriction proposal. Contributors in the

Annex XV consultation provided somewhat contradicting information regarding the practicality of this restriction proposal.

Enforcing a restriction by restricting uses with occupational exposure by means of binding DNELs 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. The proposed restriction on DMAC and NEP shows a high resemblance with the restrictions of NMP and DMF.

The NMP guideline (developed 2019) 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.

SEAC conclusion(s):

SEAC considers that given the DNELs proposed by RAC, practicality of the restriction depends on whether risk management measures are available such that compliance with the DNELs is administratively feasible and enforceable.

Furthermore SEAC finds the restriction to be enforceable and monitorable. SEAC considers that there appears no need for additional enforcement activities than those to be performed under the "normal REACH enforcement scheme".

Setting up the restriction with DNELs as proposed here does not require any new enforcement procedures. Rather the same type of verification could be used that would be done for any other substance for which there are exposure scenarios provided. From this point of view, practicability is ensured. SEAC notes that a general guidance for aprotic solvents should be developed.

SEAC initially considered a transitional period of 18 months after entry into a force sufficient for registrants who will need to update CSAs and communicate in the supply chain the changes made through the (e)SDS. SEAC further concluded, that affected downstream users would need time to implement additional risk management measures to become compliant with the DNELs for which, in general, 18 months could be considered sufficient. However, based on the comments received, SEAC agrees that individual sectors may need a longer transition time to adjust to the proposed restriction (see sections 2.2.2 "SEAC opinion summary", and 3.5.2 "Uncertainties evaluated by SEAC").

Key elements underpinning the SEAC conclusion(s):

SEAC understands, that in principle, a downstream user is compliant with the restriction when they apply the operational conditions and risk management measures described in 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 perform his own assessment. The compliance of downstream users has to 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 CMRD (2004/37/EC), and by checking if the OC and RMM are implemented.

SEAC considers based on the information available that there is no need for additional enforcement activities than those to be performed under the "normal REACH enforcement scheme". The only difference is the level of the DNEL value, which is to be used in the risk assessment and which has to be communicated to downstream users. The level of the DNEL value itself does not imply changes in enforcement.

3.4.6. Monitorability

Summary of Dossier Submitter's assessment:

According to the Dossier Submitter, 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. Methods are available to measure DMAC and NEP in the air and their metabolites in the urine (see Background Document section 2.6.4).

RAC conclusion(s):

RAC agrees with the Dossier Submitter that monitorability is possible through enforcement by checking the RMMs and OC implemented at the individual workplace including verification of workplace exposure levels.

Key elements underpinning the RAC conclusion(s):

Enforcement authorities can check that appropriate risk management measures are implemented and that appropriate operational conditions are taken to ensure that exposure of workers is below the DNELs.

RAC recommends an update of the NMP guideline as soon as a decision on the legal implementation of the DMAC and NEP restriction is taken.

SEAC conclusion(s):

SEAC notes that for the proposed restriction commonly used procedures for measurement and monitoring can be applied. Based on the information provided in the restriction dossier, SEAC agrees that the restriction is monitorable.

Key elements underpinning the SEAC conclusion(s):

SEAC agrees that monitoring of the proposed restriction can be conducted through regular enforcement activities largely in a similar manner as in case of other restricted aprotic solvents NMP and DMF.

3.4.7. Conclusion whether the suggested restriction is the most appropriate EU-wide measure

RAC conclusion(s):

RAC agrees with the conclusions drawn by the Dossier Submitter that a restriction is the most appropriate risk management option to regulate the occupational risks arising from the use of DMAC and NEP. However, it needs to be noted that some waste management activities may remain unregulated under this restriction.

The proposed restriction is considered effective, practical and monitorable , because:

i) it reduces inhalation and dermal exposure in case these DNELs are complied with in the relevant workplaces,

ii) DNELs apply equally to all sectors and users in supply chains (however some uses especially in waste management might not be covered by a restriction),
iii) it allows for (conditional but) continued use of DMAC and NEP in processes where substitution is difficult to achieve and
iv) the risks to workers resulting from exposure to DMAC and NEP can be reduced through the implementation of technical RMMs. This offers high flexibility for sectors and downstream users at company level.

RAC notes that the proposed restriction should be accompanied by setting an BOELV for NEP and DMAC under the OSH regulation to ensure harmonised maximum inhalation exposure levels under different legislations across the EU for all exposure scenarios.

Key elements underpinning the RAC conclusion(s):

Both substances are used as solvents in an broad application field. They are interchangeable with other aprotic solvents in some uses, but these may have the same developmental toxic properties as DMAC or NEP and are therefore not recommended. There is insufficient information on possible alternatives and there risks to draw appropriate conclusions.

The wide rage of applications combined with the lack of alternatives argues against an authorisation procedure.

The current BOELV (former IOEL converted into a BOELV without new assessment) for DMAC is clearly outdated and higher than the derived systemic long-term inhalation DNEL. In addition there is no BOELV or IOELV for NEP. As a timely inclusion in the prioritisation list of the Commission is not foreseeable, the implementation of OSH limit values for NEP and DMAC would take substantially longer than implementation of binding DNELs under REACH restriction.

RAC also recognises that the similar aprotic solvents NMP and DMF have been also regulated under a REACH restriction. This might be the main reason to favour restriction also in case of DMAC and NEP as this option would be a harmonised approach for the four solvents (NMP, DMF, NEP and DMAC) that have similar uses. In addition, the restriction proposal will be able to prevent regrettable substitution of NMP and DMF by NEP and DMAC.

SEAC conclusion(s):

SEAC considers the suggested restriction the most appropriate EU-wide measure.

Key elements underpinning the SEAC conclusion(s):

SEAC considers that the proposed restriction is effective and proportionate, taking into account the RAC opinion. Furthermore, SEAC notes that RAC is of the view that some remaining uncertainties tend to lead to an overestimations of risks and human health impacts.

Given the overall considerations SEAC considers the modified proposal as proportionate and effective and hence considers it to be the most appropriate union wide measure.

3.5. SUMMARY OF UNCERTAINTIES

3.5.1. Uncertainties evaluated by RAC

Summary of Dossier Submitter's assessment:

The Dossier Submitter has listed potential uncertainties in the proposal. 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, and ii) the variation in exposure estimates because of applying or not applying additional RMM by the Dossier Submitter.

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 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 and risks.

RAC conclusion(s):

The restriction proposal presents a number of uncertainties.

The more significant uncertainties relate to the Dossier Submitter's exposure assessment. Contributions from the Annex XV consultation were not able to eliminate these uncertainties.

Overall, most of the uncertainties were addressed in the evaluation in a conservative way leading to overestimations of risks and human health impacts.

Key elements underpinning the RAC conclusion(s):

Table 10 presents the main uncertainties identified by RAC in their assessment.

The exposure modelling of the Dossier Submitter relies almost fully on a tier 1 model for occupational exposure assessment (ECETOC TRA worker module). Details are documented in Table 18 below.

The number of monitoring datasets (workplace air monitoring and biomonitoring) is very limited regarding range and quality:

- Not all uses are covered by monitoring. Especially some uses with comparably high exposure levels are not covered by monitoring.
- Some of the uses with monitoring data seem to show higher exposure values than the modelled values. This is an unusual situation and cannot be clarified satisfyingly.

The information submitted in the Annex XV consultation provides contradictory data related to the different applications of DMAC, including exposure levels, OCs/RMMs, appropriate measurement methods and the organisation of occupational health and safety in the concerned industry sectors.

In the Annex XV consultation, no contributions were received for NEP. Therefore RAC's

assesment relies fully on the information provided by the Dossier Submitter.

Table 18: Identified uncertainties in the RAC assessment

RAC assessment	Identified key uncertainties		Source of uncertainty		Consequence for risk assessment
	No.	Description of the uncertainty	Input	Metho-dology	
Hazard assessment	1	NEP: hazard assessment was based solely on animal data and critical inhalation study did not show any effects at the highest dose tested.	[X]		Possible over-estimation
	2	Because of the lack of chemical specific data, default factors used for the correction of differences in exposure conditions and cover uncertainties related to the extrapolations made.		[X]	Over-estimatio n
	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 with conservative assumptions used to estimate exposure levels.		[X]	Over-estimation
	4	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. BMR1 % can be considered rather conservative		[X]	Over-estimation
Exposure assessment	5	ECETOC TRA v3 is selected as first-tier model to estimate worker inhalation and dermal exposure. Applying higher-tier exposure tools would result in different exposure estimations, however this requires more detailed information of the working conditions, which is not available.		[X]	Over-estimation
	6	The exposure scenarios and PROCs originate from the registration dossier. The Dossier Submitter is not sure (supported by communication with industry) if all described exposure scenarios and tasks (expressed in PROCs) are still performed.	[X]		Over-estimation for some industrial sectors
	7	ECETOC TRA v3 inhalation validations indicate a low level of conservatism for PROC 5, 7, 14 and 19.		[X]	Under-estimation

RAC assessment	Identified key uncertainties		Source of uncertainty		Consequence for risk assessment
	No.	Description of the uncertainty	Input	Metho-dology	
	8	ECETOC TRA v3 inhalation validations indicate an overestimation of LEV efficiency for PROC 7, 8a, 10, 13, 14 and 19.		[X]	Under-estimation
	9	ECETOC TRA v3 validations indicate an overestimation of dermal exposure for PROC 1-3.		[X]	Over-estimation
	10	ECETOC TRA v3 validations indicate an underestimation of dermal exposure for PROC 6, 7, 10, 11, 17 and 19.		[X]	Under-estimation
	11	RMM/OCs are applied that are considered common industry standard, although these are not prescribed by all registrants in their CSRs.	[X]		Under-estimation
	12	Default (reasonable) worst-case RMM and protection factors are applied for the use of general ventilation systems, gloves and RPE.	[X]		Over-estimation
	13	A full-shift eight hour is assumed by the Dossier Submitter for all activities.	[X]		Over-estimation
	14	The modelled data for the different sites and uses remain uncertain, also due to contradicting information from the consultation.		[X]	Over- or under estimation
	15	Process temperatures indicated in the CSRs are uncerctain, resulting in uncertainty with regard to the selected volatility category.	[X]		Over-estimation
	16	The lack of representative air monitoring for most of the uses leads to uncertainty with regard to the inhalation exposure.	[X]		Over-estimation
	17	The lack of representative dermal and biomonitoring data for most of the uses leads to uncertainty with regard to the dermal exposure.	[X]		Over-estimation
Number of	18	There is limited information on the use of NEP and number of workers exposed	[X]		Over-/under-

RAC assessment	Identified key uncertainties		Source of uncertainty		Consequence for risk assessment
	No.	Description of the uncertainty	Input	Metho-dology	
workers		to NEP.			estimation
	19	The number of workers potentially exposed to DMAC is only described for a few sectors where DMAC is used.	[X]		Over-/under-estimation
Exposure scenarios	20	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]		Over-/under-estimation
	21	Limited information is available about the actual concentration of NEP in formulations. The impact of the proposed restriction on continued use of these formulations is uncertain.	[X]		Over-/under-estimation

3.5.2. Uncertainties evaluated by SEAC

Summary of Dossier Submitter's assessment:

The Dossier submitter has listed 30 potential uncertainties in the proposal. 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 ("RAC" - discussed above), ii) the variation in exposure estimates because of applying or not applying additional RMM by the Dossier Submitter ("RAC" -discussed above) and iii) the non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs (SEAC side).

The non-quantified costs of technical risk reduction measures (mainly Local exhaust ventilation) associated with implementation of additional OC and RMM to comply with the proposed DNELs will negatively affect the proportionality. For proportionality assessment a benchmark approach is applied based on dipolar aprotic solvents already restricted. However, benchmarks could only be derived based on NMP restriction, not in case of DMF restriction. Furthermore, benchmarks could only be derived for two sectors affected by the NMP restriction. The proportionality assessment indicates that the assessment is quite robust as it appears that some additional investments could be made before the conclusion on proportionality changes.

SEAC conclusion(s):

SEAC agrees that as a whole, there are large uncertainties related to the Dossier Submitter's estimation of the socio-economic impacts of the restriction, both with regard to benefits and costs. In summary, benefits are not quantified, and compliance costs per sector are neither provided. On the other hand, the compliance costs per company and per worker were partly quantified. Finally, costs of technical risk management measures were not quantified, but qualitatively taken into account.

Compliance costs linked to this restriction will only arise in sectors and companies which need to adapt their RMMs. Information on required risk management measures to comply with the proposed DNELs was partly provided in the consultation of the Annex XV dossier such that uncertainties about sector response and compliance are generally considered moderate for the use of DMAC and large for the uses of NEP. Thus uncertainties about compliance cost is considered moderate for DMAC and large for NEP.

SEAC notes that the man-made fibre sector stresses the need for a longer (4 years) transitional period. SEAC cannot judge in detail the impacts on the compliance costs, and thus on proportionality of allowing a longer transitional period. However, in the consultation of the Annex XV report, some indication about the economic feasibility of additional LEV was provided in case of a longer transitional period of 4 years would be implemented instead of 1.5 years. Thus, SEAC considers that uncertainty concerning the proportionality would be decreased on this sector if the longer transitional period was agreed upon. In sum, the uncertainties of the proportionality assessment are considered moderate for DMAC and large(r) for NEP.

Key elements underpinning the SEAC conclusion(s):

Information about the adaption of RMMs needed to comply with the proposed DNELs is provided in Consultation to Annex XVII dossier by some industry associations and companies. Therefore, for the sector Production of agrochemicals, pharmaceuticals and fine chemicals, Manufacture of man-made fibres, Manufactures of medical membranes, and Electrical wire coating sector, the remaining uncertainties are considered moderate.

For uses of NEP no information is provided in restriction dossier or via the consultation on whether RMMs are already in place. Thus uncertainties about whether the compliance is needed and if yes, what should be their magnitude are considered large.

Health benefits are not quantified. For three sectors (Man-made-fibre, Medical membranes, Electrical wire coating sector) estimates about the number of exposed workers are provided, but no quantitative information is provided in restriction dossier and in public consultation about the reduction in the number of exposed workers due to the restriction which can be used as an quantitative indication for the health benefits.

Costs of risk management measures are partly quantified: technical measures like Local exhaust ventilation were not quantified, and SEAC did a LEV cost assessment based on the NMP and DMF restriction. Since only sparse information is available about the number of exposed workers per company, conditions of production etc., the number of LEV systems needed per company on average and needed LEV design can only be very roughly estimated, the uncertainties of the LEV cost assessment is considered large. The uncertainties of the other costs items estimated by the Dossier submitter (training costs, biomonitoring costs, CSR-update costs) are considered low to moderate.

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