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/[reference code to be added after the adoption of the SEAC opinion]

13 March 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 opinion adopted by RAC 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**.

ADOPTION OF THE OPINION OF SEAC

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

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 **[date of adoption of the opinion]**. **[**The deadline for the opinion of SEAC was in accordance with Article 71(3) of the REACH Regulation extended by **[number of days]** by the ECHA decision **[number and date]]**[Error! Bookmark not defined.].

[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.**] [**No comments were received from interested parties during the consultation in accordance with Article[s 69(6) and][Error! Bookmark not defined.] 71(1)**]**[Error! Bookmark not defined.].

The opinion of SEAC was adopted **by [consensus**.**][a simple majority]**[Error! Bookmark not defined.] of all members having the right to vote. [The minority position[s], including their grounds, are made available in a separate document which has been published at the same time as the opinion**.]**[Error! Bookmark not defined.].

Contents

Tables

Figures

1. OPINION OF RAC AND SEAC[1]

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] Do not delete any of the headings in this document under any circumstances. This is important to keep in mind for the combination of the RAC and SEAC opinion towards the end of the opinion-making process.

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: Similarly to the restrictions on NMP (Annex XVII – entry 71) and DMF (Annex XVII – entry 76), to enable biomonitoring, RAC recommends to derive DNELs (biomarker) since DMAC and NEP can be readily absorbed via exposed skin (see p. 15 and 16). RAC notes that biomonitoring is not needed for REACH enforcement.

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.

Derived No Effect Levels (DNEL) that are lower than those used in the Chemical Safety Reports of the registration dossiers of DMAC and NEP are derived by the Dossier Submitter for both substances using the benchmark dose (BMD) approach. The Dossier Submitter proposed the following DNELs for workers:

[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 %.

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)

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. Applications of DMAC and NEP are traded freely and are used in all Member States of the EU. Action at EU level would ensure a 'level playing field' for all producers, importers and users of DMAC and NEP and products containing these substances. In addition, the 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 to be justified as proposed by the Dossier Submitter. 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, even taking into account the higher DNEL value derived by RAC, risk characterisation ratios (RCR) above one are estimated for many of the uses that are described by the Dossier Submitter. **Therefore, RAC concluded 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 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.

RAC further recommends to derive corresponding BOELVs for NEP and DMAC under OSH regulation to ensure a harmonised maximum inhalation exposure level under different legislations across the EU and covering of all possible exposure scenarios including e.g. waste management activities.

2.2.2. SEAC opinion summary

Text

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 the 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 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:

- 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 **3**), 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 3: 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 4 and Table 5.

Table 4: 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 5: 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 6 and Table 7 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 6: 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[3] 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/m^3 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	According to the Dossier Submitter this use is covered by the exposure scenario 'Use as solvent in the production of man-made fibres'.				

[3] 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)		
of films or 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 50th 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 7).

Table 7: 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/m^3)	Post shift urine concentrations of 5-HNEP and 2-HESI (mg/g creatinine)
		Inhalation (mg/m^3)	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		

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)		
Cleaning agents	Low	2.83 – 14.14	0.82 – 2.57		Max. 17 (5-HNEP) Max. 4.63 (2-HESI) n = 2 (Koslitz et al., 2014)
	Medium	14.14	0.82		
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[4] 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[5].

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

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

[5] 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

professional uses of DMAC and NEP, especially when it concerns processes under elevated 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 8 for DMAC and in

Table **9** 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 8: 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[6] 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**				

[6] 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)[7] 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**				

[7] [7] 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[8]											
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**				

[8] 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 9: 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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

[Text]

Key elements underpinning the SEAC conclusion:

[Text]

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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 reduce the number of workers at risk to zero at some costs for industry.

Costs: A precise estimate of the total costs incurred by each sector cannot be provided by the Dossier Submitter. Estimated costs relate to the costs of implementing additional RMM 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, is not assessed.

For the 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:

[Text added by ECHA-S]

SEAC conclusion(s):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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:

[Text added by ECHA-S]

SEAC conclusion(s):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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 OC and appropriate RMM 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 OC and implement additional RMM. 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 effect profitability. Competitors who have already the proposed RMM in place may have a competitive advantage and could take over market shares from companies affected by the restriction.

SEAC conclusion(s):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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 cost and benefits of the two existing REACH restrictions: NMP and DMF.

Cost estimates derived in the NMP and DMF dossiers 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.

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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 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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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):

Text

Key elements underpinning the SEAC conclusion(s):

Text

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 10 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 10: Identified uncertainties in the RAC assessments

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 uncertain, 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 non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs (SEAC side).

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

SEAC conclusion(s):

Text

Key elements underpinning the SEAC conclusion(s):

Text

4. REFERENCES

References cited in the Background Document and in the present opinion:

Antoniou, E. E., Gelbke, H. P., Ballach, J., Zeegers, M. P., & Schrage, A. (2021). The Association Between Dimethylacetamide Exposure and Liver Toxicity: A Large Retrospective Analysis in Workers From Four European Factories. J Occup Environ Med, 63(12), e893-e898. 10.1097/JOM.0000000000002397

BASF. (2005). Prenatal Developmental Toxicity Study in Wistar Rats Dermal Application N-Ethyl-2-pyrrolidone (Project No.: 34R0033/04006).

BASF. (2006). Repeated Dose 90-day Oral Toxicity study in Wistar rats; Administration in the diet N-Ethyl-2-pyrrolidon (Project No. 50S0033/04072).

BASF. (2007a). Prenatal Developmental Toxicity Study in Himalayan Rabbits. Oral Administration (Gavage) N-Ethyl-2-pyrrolidone (Project No.: 40R0033/04058).

BASF. (2007b). Supplementary Prenatal Developmental Toxicity Study in Himalayan Rabbits Oral Administration (Gavage) N-Ethyl-2-pyrrolidone (Project No.: 40R0033/04075).

BASF. (2010). Prenatal Developmental Toxicity Study in Himalayan Rabbits Dermal Application N-Ethyl-2-pyrrolidone (Project No.: 44R0033/04110).

BASF. (2011). Subacute 28-day inhalation lung toxicity in Wistar rats liquid aerosol with vapor fraction N-Ethyl-2-pyrrolidone (Project No.: 40I0033/04I021).

BASF. (2013). 90-day inhalation study in Wistar rats vapor exposure N-Ethyl-2-pyrrolidone (Project No.: 50I0033/04I036).

Cocker J, Mason HJ, Warren ND, Cotton RJ (2011) Creatinine adjustment of biological monitoring results. Occupational Medicine 61(5):349-353 doi:10.1093/occmed/kqr084

DuPont. (1997). Dimethylacetamide (DMAC): developmental toxicity Study in Sprague-Dawley Rats (OTS0554045-1).

ECHA. (2012). Guidance on information requirements and chemical safety asse–sment - Chapter R.8: Characterisation of dose [concentration]-response for human health. In (Vol. 2.1). Helsinki.

ECHA. (2014). Opinion on an Annex XV dossier proposing restrictions on 1-Methyl-2-pyrrolidone (NMP). In Committee for Risk Assessment (RAC) & Committee for Socio-economic Analysis (SEAC) (Eds.). Helsinki: European Chemicals Agency.

ECHA. (2016). Guidance on Information Requirements and Chemical Safety Assessment Chapter R.14: Occupational exposure assessment. In. Helsinki: European Chemicals Agency.

ECHA. (2017). Guidance on Information Requirements and Chemical Safety Asse–sment - Chapter R.7c: Endpoint specific guidance. In (Vol. 3.0). Helsinki.

EFSA. (2017). Update: use of the benchmark dose approach in risk assessment. EFSA Journal, 15, 4658. 10.2903/j.efsa.2017.4658

Horn, H. J. (1961). Toxicology of dimethylacetamide. Toxicol Appl Pharmacol, 3, 12-24. 10.1016/0041-008x(61)90003-5

Kennedy G.L. (1990). Biological monitoring in the American chemical industry. In Fiserova-Bergerova V & Ogata M (Eds.), Biological monitoring of exposure to industrial chemicals (pp. 63–67). Cincinnati: ACGIH.

Klimisch, H. J., & Hellwig, J. (2000). Developmental toxicity of dimethylacetamide in rabbits following inhalation exposure. Hum Exp Toxicol, 19(12), 676-683. 10.1191/096032700668432103

Malley, L. A., Slone Jr, T. W., Makovec, G. T., Elliott, G. S., & Kennedy Jr, G. L. (1995). Chronic toxicity/oncogenicity of dimethylacetamide in rats and mice following inhalation exposure. Fundamental and Applied Toxicology, 28(1), 80-93. http://dx.doi.org/10.1006/faat.1995.1149

Monsanto. (1980). A TWENTY-FOUR MONTH ORAL TOXICITY/CARCINOGENICITY STUDY IN RATS OF N,N-DIMETHYLACETAMIDE ADMINISTERED VIA THE DRINKING WATER (PROJECT NO. 75-1267).

Monsanto. (1990). A TWENTY-FOUR MONTH ORAL TOXICITY/CARCINOGENICITY STUDY IN RATS OF N,N-DIMETHYLACEDAMIDE ADMINISTERED IN DISTILLED WATER (OTS0539235).

Monsanto. (1993). Running Title: DMAC Biomonitoring. MONITORING ACRYLIC FIBER WORKERS FOR LIVER TOXICITY AND EXPOSURE TO DIMETHYLACETAMIDE: 1. ASSESSING EXPOSURE TO DIMETHYLACETAMIDE BY AIR AND BIOLOGICAL MONITORING (OTS0558186).

Nomiyama, T., Omae, K., Ishizuka, C., Yamauchi, T., Kawasumi, Y., Yamada, K., Endoh, H., & Sakurai, H. (2000). Dermal absorption of N,N-dimethylacetamide in human volunteers. International Archives of Occupational and Environmental Health, 73(2), 121-126. http://dx.doi.org/10.1007/s004200050017

Okuda, H., Takeuchi, T., Senoh, H., Arito, H., Nagano, K., Yamamoto, S., & Matsushima, T. (2006). Developmental toxicity induced by inhalation exposure of pregnant rats to N,N-dimethylacetamide. Journal of Occupational Health, 48(3), 154-160. http://dx.doi.org/10.1539/joh.48.154

RAC-SCOEL. (2016). Joint Opinion to resolve differences in scientific opinion as regards exposure levels for N-Methyl-2-Pyrrolidone. In.

Saillenfait, A. M., Gallissot, F., & Sabaté, J. P. (2007). Developmental toxic effects of N-ethyl-2-pyrrolidone administered orally to rats. Journal of Applied Toxicology, 27(5), 491-497. 10.1002/jat.1237

Schmied-Tobies, M. I. H., Murawski, A., Rucic, E., Schwedler, G., Bury, D., Kasper-Sonnenberg, M., Koslitz, S., Koch, H. M., Brüning, T., & Kolossa-Gehring, M. (2021). Alkyl pyrrolidone solvents N–methyl–2–pyrrolidone (NMP) and N–ethyl–2–pyrrolidone (NEP) in urine of children and adolescents in Germany – human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V). *Environmental International*, *146*. http://dx.doi.org/10.1016/j.envint.2020.106221

Spies, G. J., Rhyne Jr, R. H., Evans, R. A., Wetzel, K. E., Ragland, D. T., Turney, H. G., Leet, T. L., & Oglesby, J. L. (1995a). Monitoring acrylic fiber workers for liver toxicity and exposure to dimethylacetamide 1. Assessing exposure to dimethylacetamide by air and biological monitoring. Journal of Occupational and Environmental Medicine, 37(9), 1093-1101. http://dx.doi.org/10.1097/00043764-199509000-00010

Spies, G. J., Rhyne Jr, R. H., Evans, R. A., Wetzel, K. E., Ragland, D. T., Turney, H. G., Leet, T. L., & Oglesby, J. L. (1995b). Monitoring acrylic fiber workers for liver toxicity and exposure to dimethylacetamide 2. Serum clinical chemistry results of dimethylacetamide- exposed workers. Journal of Occupational and Environmental Medicine, 37(9), 1102-1107. http://dx.doi.org/10.1097/00043764-199509000-00011

Walter, D., Drexler, H., Hartwig, A., & MAK Commission. (2020). N,N-Dimethylacetamide – Addendum for re-evaluation of the BAT value. Assessment Values in Biological Material – Translation of the German version from 2020. In MAK Collect Occup Health Saf. (Vol. Oct;5(3):Doc058.). https://doi.org/10.34865/bb12719e5_3ad

Additional references:

Antoniou EE, Gelbke HP, Jochen B, Zeegers MP, Schrage A. (2022). The Association Between Dimethylacetamide Exposure and Liver Toxicity: A Large Retrospective Analysis in Workers From Four European Factories. J Occup Environ Med. 64(8):e524-e526. doi: 10.1097/JOM.0000000000002589.

Bader M, Wrbitzky R, Blaszkewicz M, van Thriel C. (2007). Human experimental exposure study on the uptake and urinary elimination of N-methyl-2-pyrrolidone (NMP) during simulated workplace conditions. Arch Toxicol. 81(5):335-46. doi: 10.1007/s00204-006-0161-6.

Brüning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jäckh R, Leibold E, Pallapies D, Rettenmeier AW, Schlüter G, Stropp G, Sucker K, Triebig G, Westphal G, van Thriel C. (2014). Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol 88: 1855–1879

David M, Gerofke A, Lange R, Kolossa-Gehring M, Apel P. (2021) The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) for the aprotic solvents N-methyl-2-pyrrolidone (NMP) and N-ethyl-2-pyrrolidone (NEP). Int J Hyg Environ Health. Sep;238:113856. doi: 10.1016/j.ijheh.2021.113856.

Ding x, Dahl AR. (2003). Olfactory mucosa: composition, enzymatic localization and metabolism. In: Doty R (ed) Handbook of olfaction and gustation. Marcek Dekker, New york, pp 51–73

Ding x, Kaminsky lS. (2003). Human extrahepatic cytochromes p450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annu Rev Pharmacol Toxicol 43:149–173

EFSA (2010). Scientific Opinion on Lead in Food. EFSA Journal 2010; 8(4):1570. doi: 10.2903/j.efsa.2010.1570

Frederick cB, Bush Ml, lomax lg, Black KA, Finch l, Kimbell JS, Morgan KT, Subramaniam RR, Morris JB, ultman JS. (1998). Application of a hybrid computational fluid dynamics andphysiologically based Inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. Toxicol Appl Pharmacol 152:211–231