ECHA
EUROPEAN CHEMICALS AGENCY

How to comply with REACH Restriction 71, 76, 80 and 81; guideline for users of the aprotic solvents NMP, DMF, DMAC, and NEP

March 2026

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Version	Changes	
1.0	10.07.2019	First edition (NMP)
2.0	23.03.2026	Amendment to include guidelines for DMF, DMAC, and NEP

Acknowledgements

ECHA would like to thank the following organisations for their support and contributions to the drafting of this guideline: ALMAC group (pharmaceutical industry), BASF (chemical company), Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Bundesstelle für Chemikalien (BAuA; German Federal Institute for Occupational Safety and Health, division for chemicals), CEFIC (European Chemical Industry Council) Petrochemicals, Chemler consultancy, CIRFS European (European Man–made Fibres Association), EDENA (global network and industry voice for nonwovens and related industries), EFPIA (European Federation of Pharmaceutical Industries and Associations), Industrievereinigung Chemiefaser e.V. (IVC; German Industry Association of Man-made fibers).

Title: How to comply with REACH Restriction 71, 76, 80 and 81; guideline for users of the aprotic solvents NMP, DMF, DMAC, and NEP

Reference: ECHA-25-H-13-EN
ISBN: 978-92-9468-522-3
Cat. Number: ED-01-25-034-EN-N
DOI: 10.2823/2107178
Publication date: March 2026
Language: EN

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Table of Contents

Table of Tables

1. Introduction

1.1 What is the content of this guideline and who should follow it?

This document aims to support users of 1-methyl-2-pyrrolidone (NMP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC), 1-ethylpyrrolidin-2-one (NEP), or with mixtures containing those substances (C ≥ 0.3 %), to comply with the related restriction requirements under the REACH Regulation[1]. Moreover, this guideline may help enforcement authorities to understand what is expected to comply with the restrictions and evaluate the compliance at a site.

NMP, DMF, DMAC, and NEP are aprotic solvents and have a harmonised classification as toxic for reproduction (reproductive toxicant category 1B). In Europe, those aprotic solvents are subject to REACH Annex XVII restrictions[2]: Entry 71 for NMP[3], Entry 76 for DMF[4], Entry 80 for DMAC[5] and Entry 81 for NEP[6]. If you use one of those aprotic solvents in your workplace, you need to protect anyone who could be exposed to it. This guideline is intended to help you understand what you need to do to comply with the provisions of those restrictions but also against the background of your existing occupational safety and health (OSH) obligations.

This guideline follows the 2019 NMP restriction guideline, but now also includes DMF, DMAC, and NEP REACH restrictions from 2021 (DMF) and 2025 (NEP and DMAC).

To ensure that the scope of the guideline is clear, it is worth clarifying the meaning of some of the terms used in the document.

Use: as defined in the REACH Regulation (Article 3(24)): any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation.

User of NMP, DMF, DMAC, or NEP: in this guideline, the term user is to be understood as "end user" i.e. any actor using one of those substances or mixtures containing one of those substances in his industrial or professional activities but not supplying it further.

Worker: In this guideline, the term worker is to be understood as any person employed by an employer including trainees and apprentices but excluding domestic workers[7] as well as self-

[1] Further requirements apply under EU legislation on health and safety at work, in particular Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (the CMRD) (OJ L 158 30.4.2004, p. 50).

[2] As reprotoxic substances, they also fall under the scope of application of Directive (EU) 2004/37, and REACH Annex XVII Entry 30 and Entry 72.

[3] Commission Regulation (EU) 2018/588 amending Annex XVII of REACH as regards NMP

[4] Commission Regulation (EU) 2021/2030 amending Annex XVII of REACH as regards DMF

[5] Commission Regulation (EU) 2025/1090 amending Annex XVII of REACH as regards DMAC

[6] Commission Regulation (EU) 2025/1090 amending Annex XVII of REACH as regards NEP

[7] International Labour Organization (ILO) C189 - Domestic Workers Convention, 2011 (No. 189)

employed professionals[8].

Employer: In this guideline, the term employer is to be understood as any natural or legal person who has an employment relationship with the worker and has responsibility for the undertaking and/or establishment (see Article 3(b) of Directive 89/391/EEC (the EU OSH Framework Directive).

Supplier of NMP, DMF, DMAC, or NEP or of mixtures containing these aprotic solvents: as defined in REACH regulation (Article 3(23)): any manufacturer, importer, downstream user or distributor placing on the market NMP, DMF, DMAC, or NEP, on their own or in a mixture.

Suppliers of NMP, DMF, DMAC, or NEP can be:

- Registrants of one of those substance(s) (manufacturers or importers)
- Downstream users supplying one of those substances(s) (e.g. re-fillers)
- Distributors supplying one of those substance(s)

Suppliers of mixtures containing NMP, DMF, DMAC, or NEP can be:

- Registrants formulating and supplying mixtures containing one of those substance(s)
- Downstream users formulating and supplying mixtures containing one of those substance(s)
- Distributors supplying mixtures containing one of those substance(s).

1.2 The restrictions

Due to their hazardous properties, the uses of NMP, DMF, DMAC, and NEP have been restricted by the European Commission. The restrictions were published in the Official Journal of the European Union on 18 April 2018 (NMP), 19 November 2021 (DMF) and 2 June 2025 (DMAC and NEP). The restriction entries are listed in Annex XVII to REACH and apply to the manufacture, placing on the market, and use of NMP (Entry 71), DMF (Entry 76), DMAC (Entry 80) or NEP (Entry 81). More information on the REACH restriction dossier is available on the ECHA website under 'Registry of restriction intentions until outcome' for the individual substances NMP[9], DMF[10], and DMAC and NEP[11]. The following three tables set out the requirements of the restrictions.

[8] For practical reasons, this guideline does not address self-employed professionals and, accordingly, they are excluded from the scope of this guideline. This exclusion does not affect the applicability of the REACH restrictions discussed herein, which apply equally to self-employed professionals.

[9] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e1806abf64

[10] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18213ec9e

[11] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e1844d552a

Table 1: Paragraph 1 of the restrictions for NMP, DMF, DMAC, and NEP

NMP (Entry 71)	1. Shall not be placed on the market as a substance on its own or in mixtures in a concentration equal to or greater than 0.3 % after 9 May 2020 unless manufacturers, importers and downstream users have included in the relevant chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 14.4 mg/m^3 for exposure by inhalation and 4.8 mg/kg/day for dermal exposure.
DMF (Entry 76)	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 12 December 2023 unless manufacturers, importers and downstream users have included in the relevant chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 6 mg/m^3 for exposure by inhalation and 1.1 mg/kg/day for dermal exposure.
DMAC (Entry 80)	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 23 December 2026 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.
NEP (Entry 81)	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 23 December 2026 unless manufacturers, importers and downstream users have included in the chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 4.0 mg/m^3 for long-term exposure by inhalation and 2.4 mg/kg bw/day for long-term dermal exposure.

In practice paragraph 1 requires suppliers (as defined above) of NMP, DMF, DMAC, and NEP, or of mixtures containing those substance(s) (C ≥ 0.3% w/w), to perform a chemical safety assessment using the mandatory DNELs for workers as specified for the individual substances.

Suppliers must document this assessment in a report and communicate the results of the assessment (appropriate conditions of use and risk management measures) with the safety datasheet they provide to their customers. The mandatory DNELs need to be communicated in the safety data sheets regardless of tonnage. Suppliers of NMP must be compliant with this paragraph since 9 May 2020 onward, supplier of DMF since 12 December 2023 and suppliers of DMAC and NEP from 23 December 2026 onward.

In fact, this is the usual safety communication via the extended safety data sheet (eSDS) under REACH regulation. The only difference is that DNELs for workers set by ECHA and the EU Commission must be used.

Table 2: Paragraph 2 of the restrictions for NMP, DMF, DMAC, and NEP

NMP (Entry 71)	2. Shall not be manufactured, or used, as a substance on its own or in mixtures in a concentration equal to or greater than 0.3 % after 9 May 2020 unless manufacturers and downstream users take the appropriate risk management measures and provide the appropriate operational conditions to ensure that exposure of workers is below the DNELs specified in paragraph 1.
DMF (Entry 76)	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 12 December 2023 unless manufacturers and downstream users take the appropriate risk management measures and provide the appropriate operational conditions to ensure that exposure of workers is below the DNELs specified in paragraph 1.
DMAC (Entry 80)	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 23 December 2026 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.
NEP (Entry 81)	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 23 December 2026 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.

In practice paragraph 2 requires that suppliers (as defined above) of NMP, DMF, DMAC, or NEP, or of mixtures containing those substance(s) (C ≥ 0.3% w/w), to ensure that the workers' exposure is not above the DNELs set in the restrictions.

NMP manufacturers and users must be compliant with this paragraph from 9 May 2020, DMF manufacturers and users from 12 December 2023 and DMAC and NEP manufacturers and users from 23 December 2026.

This paragraph emphasizes the responsibility of the employer for his workers to ensure compliance via operational conditions at use. Finally, this paragraph is also the link to the general OSH S.T.O.P.-principle (check first for possible substitution, second for technical exposure control, third for organisational measure and then for personal protection equipment; see p. 22).

Table 3: Paragraph 3 of the restrictions for NMP, DMF, DMAC, and NEP

NMP (Entry 71)	3. By way of derogation from paragraphs 1 and 2, the obligations laid down therein shall apply from 9 May 2024 in relation to placing on the market for use, or use, as a solvent or reactant in the process of coating wires.
DMF (Entry 76)	3. By way of derogation from paragraphs 1 and 2, the obligations laid down therein shall apply from 12 December 2024 in relation to placing on the market for use, or use, as a solvent in direct or transfer polyurethane coating processes of textiles and paper material or the production of polyurethane membranes, and from 12 December 2025 in relation to placing on the market for use, or use, as a solvent in the dry and wet spinning processes of synthetic fibres.
DMAC (Entry 80)	3. By way of derogation from paragraphs 1 and 2, the obligations laid down therein shall apply from 23 June 2029 in relation to placing on the market for use, or use, as a solvent in the production of man-made fibres.
NEP (Entry 81)	[no derogation]

In practice paragraph 3 grants or granted more time to suppliers for specific uses to comply with paragraph 1 and 2 of the restrictions on:

- **NMP** as a solvent or reactant in the process of wire coatings at the latest since 9 May 2024.
- **DMF** as a solvent in direct or transfer polyurethane coating processes of textiles and paper material or the production of polyurethane membranes or as a solvent in the dry and wet spinning processes of synthetic fibres at the latest since 12 December 2025.
- **DMAC** as a solvent in the production of man-made fibres at the latest from 23 June 2029

For **NEP** no derogations are specified.

This guideline focuses on the compliance with paragraph 2 of the restrictions, from the user point of view (employer and worker). The situation of users of NMP, DMF, DMAC, and NEP is different from the usual situation of users of substances or mixtures under REACH because the individual DNELs are mandatory for all actors and the timeline for compliance is set by the individual restrictions.

In addition, the requirements for protecting workers from health and safety risks arising from exposure to these substances are defined in EU OSH legislation, especially the Carcinogens, Mutagens or Reprotoxic substances Directive (CMRD). In that context, Annex III of the CMRD specifies occupational exposure limit (OEL) values for NMP, DMF and DMAC (see Section 1.5).

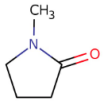
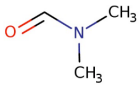
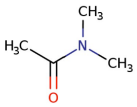
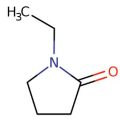
1.3 What are NMP, DMF, DMAC, and NEP?

NMP, DMF, DMAC, and NEP are organic chemical compounds. The common names, European Community (EC) numbers, Chemical Abstracts Service (CAS) registry numbers, and main physico-chemical properties are listed in Table 4.

NMP, DMF, and DMAC are manufactured in and/or imported to the European Economic Area in large volumes (≥ 10 000 tonnes per year), NEP at a lower volume of < 1 000 tonnes per year. The four substances are commonly used as solvents in various industries such as petrochemical, textiles or pharmaceutical. For more information on uses, see the information

published in ECHA's public chemicals database (ECHA Chem)[12] related to those substances and Appendix 3.

Table 4: Common names, identifiers and main properties

	NMP	DMF	DMAC	NEP
Common name	1-methyl-2-pyrrolidone	N,N-dimethyl-formamide	N,N-dimethyl-acetamide	1-ethyl-pyrrolidin-2-one
Chemical structure				
EC number	212-828-1	200-679-5	204-826-4	220-250-6
CAS number	872-50-4	68-12-2	127-19-5	2687-91-4
Molecular formula	C_5H_9NO	C_3H_7NO	C_4H_9NO	$C_6H_{11}NO$
Molecular weight (g/mol)	99.13	73.09	87.12	113.16
Boiling point at 101 325 Pa	204.1°C	152-153°C	166°C	212.5°C
Vapour pressure	32 Pa at 20°C	377 Pa at 20°C	200 Pa at 21.7°C	18 Pa at 20°C

1.4 Hazards

The four aprotic solvents NMP, DMF, DMAC, and NEP are reproductive toxicants and may damage the unborn child. In addition, NMP causes serious eye irritation, skin irritation and may cause respiratory irritation, DMF causes serious eye irritation, and DMF and DMAC are acutely toxic if inhaled and in contact with skin. The European Union has recognised these hazardous properties and provided harmonised classifications (and labelling) under the Classification, Labelling and Packaging (CLP) Regulation as presented in Table 5.

At the workplace, all four aprotic solvents can enter the body by inhaling vapours (or aerosols) of the substance, or via the skin from different ways of exposure (e.g., direct contact during use, unintended splashes or droplets, wearing contaminated personal protective equipment and touching contaminated surfaces; vapours in the workplace atmosphere can also enter the body via the skin.

[12] https://chem.echa.europa.eu/

Table 5: Harmonised classifications of NMP, DMF, DMAC, and NEP

Hazard class and category	Hazard code and statement		Concentration limits[1)]
NMP (CLP00, ATP09), index No 606-021-00-7			
Repr. 1B	H360D***	Reproductive toxicity, may damage the unborn child	0.3 % (GCL)
Eye Irrit. 2	H319	Serious eye irritation, causes serious eye irritation	10 % (GCL)
Skin Irrit. 2	H315	Skin irritation, causes skin irritation	10 % (GCL)
STOT SE 3	H335	Specific target organ toxicity – single exposure, may cause respiratory irritation	10 % (SCL)
DMF (CLP00), index No 616-001-00-X			
Repr. 1B	H360D***	Reproductive toxicity, may damage the unborn child	0.3 % (GCL)
Acute Tox. 4*	H332	Acute toxicity, harmful if inhaled	1 % (GCL)
Acute Tox. 4*	H312	Acute toxicity, harmful in contact with skin	1 % (GCL)
Eye Irrit. 2	H319	Serious eye irritation, causes serious eye irritation	10 % (GCL)
DMAC (CLP00, ATP09), index No 616-011-00-4			
Repr. 1B	H360D***	Reproductive toxicity, may damage the unborn child	0.3 % (GCL)
Acute Tox. 4*	H332	Acute toxicity, harmful if inhaled	1 % (GCL)
Acute Tox. 4*	H312	Acute toxicity, harmful in contact with skin	1 % (GCL)
NEP (ATP05), index No 616-208-00-5			
Repr. 1B	H360D	Reproductive toxicity, may damage the unborn child	0.3 % (GCL)

1) Either generic concentration limits (GCL) or specific concentration limits (SCL) apply. Below the indicated concentration limits, no respective classification has to be applied.

The *associated with Acute Tox. 4 indicates a minimum classification for this category.

The *** associated with H360D means that the Repr. 1B classification was transposed from the previous Directive[13] without any more recent examination under the CLP. However, the Repr. 1B classifications were confirmed in the restriction dossiers.

[13] The European Directive on Dangerous Substances (DSD) covering dangerous substances was introduced in 1967 to protect public health, in particular the health of workers handling dangerous substances. The directive was replaced by a new law known as the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (CLP) from 20 January 200: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32008R1272

Please also note the self-classifications by registrants, e.g. Eye Irrit. 2 for DMAC and Eye Dam. 1 for NEP.

For NMP, DMF and DMAC both following elements shall be visible on the label which is fixed to the container/packaging, for NEP only the 'Health hazard' element applies, the signal word danger is obligatory for all four aprotic solvents:

Danger

Signal word *Health hazard (GHS08)* *Exclamation mark (GHS07)*

For further information on classification, labelling and packaging requirements, consult the Guidance on labelling and packaging in accordance with Regulation (EC) 1272/2008[14].

1.5 What are DNELs and how are they applied?

Derived no-effect levels (DNELs) are the exposure levels to a substance below which no negative health effects are expected to occur in humans. They are calculated from hazard information generated and collated for substance registration under REACH and function as reference values for chemical safety assessment. More than one DNEL can exist for a substance since the DNEL is exposure route- and effect- specific. In cases where multiple routes are applicable, the combined systemic risk has to be considered in addition to the systemic risk from the individual routes. Long-term/chronic systemic[15] DNELs are calculated for a daily exposure. For workers, this means the exposure is averaged over a standard 8-hour workday.

DNELs for inhalation and dermal exposure arise from the most relevant critical adverse health effects such as reproductive (developmental) toxicity, sub-chronic toxicity, or respiratory irritation.

DNELs are typically derived by registrants, i.e. substance manufacturers and importers, as part of the REACH registration process for hazardous substances. In certain situations, DNELs may be derived by authorities (restriction procedure e.g. for NMP, NEP, DMF, DMAC) or may be recommended by ECHA's Risk Assessment Committee (authorisation procedure).

For the four aprotic solvents NMP, DMF, DMAC, and NEP, long-term systemic DNELs for inhalation and dermal exposure (see Table 6) have been derived by authorities, as part of the REACH restriction processes. These specific, mandatory DNELs relating to inhalation and dermal exposure of workers must be applied in the chemical safety assessment by any manufacturer, importer, and (downstream) user if required, using the substance according to the conditions of the restriction.

If the exposure level does not exceed these DNELs, the conditions of use are considered

[14] Guidance on labelling and packaging https://echa.europa.eu/documents/10162/2324906/clp_labelling_en.pdf

[15] *Systemic effect* means an adverse health effect when the substance is absorbed into the body, becomes distributed and acts on organs remote from the point of contact.

sufficient to adequately control the risks. If not, the operational conditions (OCs)[16] and risk management measures (RMMs)[17] need to be revised until the exposure level does not exceed the DNELs.

Usually, the chemical safety assessment is carried out by the REACH registrant. For practical reasons the exposure is often estimated by the registrants using exposure modelling tools. Information on the conditions of safe use is provided with the extended safety data sheet.

Applying the operational conditions and risk management measures described in the exposure scenario annexed to the safety data sheet should ensure that the applicable DNELs are not exceeded.

Relationship between DNELs and occupational exposure limits (OELs)

Inhalation DNELs co-exist with OELs, which can for example be European-wide binding OELs or national OELs. For NMP, DMF, and DMAC binding OELs[18] exist which are higher than the inhalation DNELs (see Table 6). Member States have the possibility to enact lower national OELs, which may be set to values lower than the binding OELs. Some Member States aligned the national OELs with the DNELs of the REACH restrictions. For NEP currently no European-wide binding OEL has been set, but some Member States have set national OELs.

DNELs and OELs do apply simultaneously to the same work activities. This may be confusing at first glance, if the values are different. However, DNEL and OEL values are derived under different EU legislation. The values are found in Section 8.1 of the safety data sheet.

For the user, it is important to note that DNELs and OELs are derived and implemented under different legal frameworks. Compliance with DNELs under REACH is achieved by implementing the operational conditions and risk management measures described in the exposure scenarios provided by the supplier(s) (see Section 2). Compliance with OELs for reprotoxic substances under occupational safety and health legislation is typically demonstrated by workplace exposure monitoring (see Section 4). In practice, the lower limit value will usually determine the operational conditions and risk management measures. However, inhalation and dermal DNELs must be considered together and may therefore drive the required operational conditions and risk management measures even where an OEL is lower.

Table 6: REACH long-term DNELs for workers and binding OELs for the four aprotic solvents

Substance	EC number	CAS number	REACH DNELs, systemic long-term		European binding OELs[1)]	
			Inhalation (mg/m³)	Dermal (mg/kg bw and day)	8-hours (mg/m³)	Short-term (mg/m³)
NMP	212-828-1	872-50-4	14.4	4.8	40 (10 ppm[2)])	80 (20 ppm)

[16] *Operational conditions (OCs)* are the conditions under which a substance is used, including parameters such as duration, frequency, and intensity of exposure. They are critical in assessing potential exposure levels.

[17] *Risk management measures (RMMs)* encompass the strategies and practices implemented to control and minimize the risks associated with exposure to a substance. RMMs may include engineering controls, personal protective equipment, and procedural changes designed to reduce exposure to acceptable levels.

[18] DIRECTIVE (EU) 2022/431 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work

Substance	EC number	CAS number	REACH DNELs, systemic long-term		European binding OELs[1)]	
			Inhalation (mg/m^3)	Dermal (mg/kg bw and day)	8-hours (mg/m^3)	Short-term (mg/m^3)
DMF	200-679-5	68-12-2	6	1.1	15 (5 ppm)	30 (10 ppm)
DMAC	204-826-4	127-19-5	13	1.8	36 (10 ppm)	72 (20 ppm)
NEP	220-250-6	2687-91-4	4	2.4	[no binding OEL]	[no binding OEL]

[1)] Note: Member States have the possibility to enact lower national OELs, which may be set to values lower than the binding OELs.
[2)] parts per million by volume in air

Remember!

→ Derived no-effect levels (DNELs) and occupational exposure limits (OELs) contribute to protect workers against adverse health effects from chemical exposure at work.

→ By law you must take steps to comply with:

- For NMP, DMF and DMAC with both the binding DNELs established under the applicable REACH restrictions, and the national limit values adopted pursuant to Directive 2004/37/EC on risks related to exposure to carcinogens, mutagens or substances toxic to reproduction (CMR) at work.
- For NEP with the binding DNELs established under the applicable REACH restriction as well as with the national limit values.

→ DNEL and OEL values are both found in Section 8.1 of the safety data sheet.

→ Adequate controls (operational conditions and risk management measures) must be in place to ensure that exposure of workers is below the value(s).

→ For products requiring exposure scenarios attached to the safety data sheet, the mandatory operational conditions and risk management measures needed to comply with the DNELs are provided within those scenarios.

→ All users - as employers – are under the obligation to assess all the risks to which workers are exposed and to put in place the resulting preventive and protective measures. The safety data sheet provides very useful information to support this activity.

→ For NMP, DMF, DMAC, and NEP keeping exposure below the DNEL should also meet the requirements of most national occupational exposure limits.

More on DNELs and occupational exposure limit values

OELs values (comparable to long-term inhalation DNELs) define the limit of the time-weighted average of the concentration of a chemical agent in the air within the breathing zone of a worker in relation to a specified reference period (typical 8-hours per day). Short term

exposure limit (STEL) values define the level below which adverse health effects are unlikely to occur over 15 minutes exposure time as long as the 8-hour average is not exceeded (see also Appendix 1). For NMP, DMF and DMAC both 8 hours and short-term binding OEL values exist (see Table 6). However, no acute (short term) DNELs were derived for the four aprotic solvents.

OELs are national, directly enforceable, limit values that must be set by Member States considering the OEL values derived within the framework of European Directives, such as Directive 2004/37/EC on risks related to exposure to carcinogens, mutagens or substances toxic to reproduction (CMR) at work.

A worker must not be exposed above the OEL. Employers are responsible for ensuring compliance with OELs and must therefore have risk management measures in place to ensure that exposure to NMP, DMF, DMAC or NEP is prevented or reduced to a minimum, at least controlled to a level below the OEL.

Suggested biomarker DNELs

For all four aprotic solvents dermal uptake is a relevant route of exposure. The OEL or the inhalation DNEL are not sufficient to account for relevant dermal uptake. To limit potential health risks from all routes of exposure, monitoring of the internal exposure by measuring the substance or its metabolites in a biological sample such as urine is usually recommended. However, there is no legal requirement in the REACH restrictions on NMP, DMF, DMAC, or NEP to perform biological monitoring. Suggested biomarker DNELs for metabolites of NMP, DMF, DMAC, and NEP and their source are summarised in Table 7 and further described in Appendix 2.

Table 7: Suggested biomarker DNELs for metabolites of NMP, DMF, DMAC, and NEP

Substance	Suggested biomarker DNELs	Source
NMP	25 mg 5-HNMP (5-hydroxy-N-methyl-2-pyrrolidone)/g creatinine (sampling at the end of shift) AND 8 mg 2-HMSI (2-hydroxy-N-methylsuccinimide)/g creatinine (sampling next morning following an 8 h work shift)	How to comply with REACH Restriction 71, guideline for users of NMP. Explanatory Note on Biological Monitoring (2019)[19]
DMF	8 mg NMF (N-methylformamide) plus HMMF (N-(hydroxymethyl)-N-methylformamide)/L urine (sampling at the end of shift) AND/OR 10 mg AMCC (N-acetyl-S-(N-methylcarbamoyl)cysteine)/L urine (sampling at the end of shift at the end of the workweek)	Committee for Risk Assessment (RAC) and the Committee for Socio-Economic Analysis (SEAC) opinion DMF (2019)[20] Kilo et al. (2017); Lamkarkach et al. (2022)
DMAC	20 mg NMAC (N-methylacetamide)/L urine corresponding to 15 mg NMAC/g creatinine (sampling at the end of shift at the end of the workweek)	RAC and SEAC opinion DMAC and NEP (2023)[21]
NEP	10 mg 5-HNEP (5-hydroxy-N-ethyl-2-pyrrolidone)/L urine corresponding to 7 mg 5-HNEP/g creatinine (sampling at the end of shift) AND 8 mg 2-HESI (2-hydroxy-N-ethylsuccinimide)/L urine corresponding to 6 mg 2-HESI/g creatinine (sampling next morning following an 8 h work shift) OR 20 mg 5-HNEP plus 2-HESI/L urine corresponding to 15 mg 5-HNEP plus 2-HESI/g creatinine (sampling next morning following an 8 h work shift at the end of the workweek)	

[19] Explanatory Note on Biological Monitoring ECHA July 2019 https://echa.europa.eu/documents/10162/17233/entry_71_exp_note_biomonitoring_en.pdf/25c684f2-243e-4321-e7c0-ba7074838ab6

[20] https://echa.europa.eu/documents/10162/b6644298-54a4-052a-9bbc-6824966d151e

[21] https://echa.europa.eu/documents/10162/847134de-5d46-355d-bbf0-650fd9f59f78

2. What you need to do to adequately control risk

When you purchase NMP, DMF, DMAC, or NEP, your supplier must provide you with an (extended) safety data sheet.[22] Information about the REACH restrictions 71, 76, 80, and 81 can be found in Section 15 of the safety data sheet. When exposure scenarios are attached to the safety data sheet, they describe the operational conditions and appropriate risk management measures to adequately control the risk for each relevant use. Downstream users are required by law to apply those risk management measures or take other appropriate action (see Section 2.3) to ensure that the level of exposure predicted in the exposure scenario is not exceeded. If you have implemented the operational conditions and risk management measures specified for the exposure scenario(s), you should be below all relevant DNELs.

There may be situations where you do not receive an updated safety data sheet e.g. because your last supply was more than 12 months before the restrictions entered into force. Or in other situations you may have received an updated safety data sheet but without any attached exposure scenarios e.g. because the aprotic solvent is part of a mixture and the safe use information has been integrated into the main body of the safety data sheet, or your supplier has registered < 10 tonnes/year. The first thing to do in these situations is to contact your supplier to understand if you can obtain the extended safety data sheet (see Section 5).

Remember that, even if you do not receive an extended safety data sheet, the conditions imposed by the REACH restrictions 71, 76, 80, and 81 are still applicable, and must be complied with. Ultimately this means that you must be able to demonstrate compliance according to your national requirements (mainly through monitoring the exposure).

The next four subsections describe what you have to do according to the requirements of REACH. You should keep in mind that you also must comply with your occupational safety and health (OSH) obligations (some aspects of this are covered in Section 2.5).

Your first step is to check whether your uses of NMP, DMF, DMAC, or NEP are described in the extended safety data sheet that you have received with your substance.

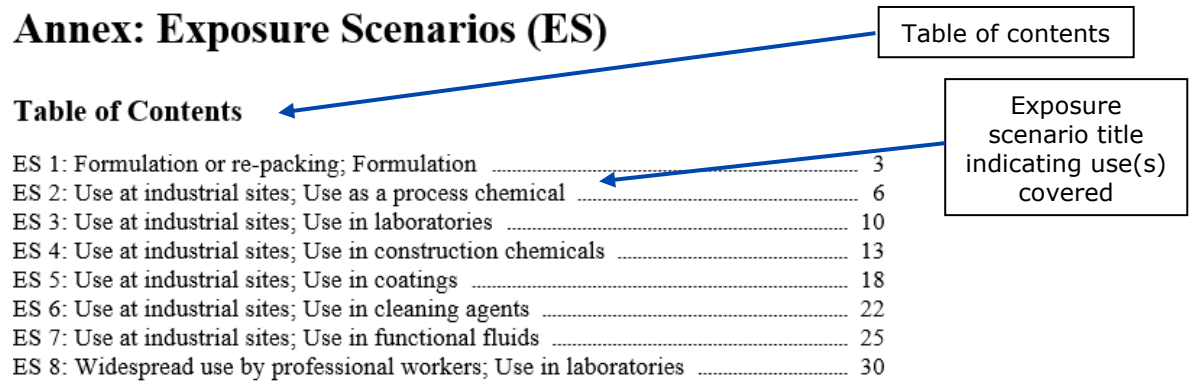
2.1 How to check if your use is covered by the exposure scenarios (ES) received

You can do this by:

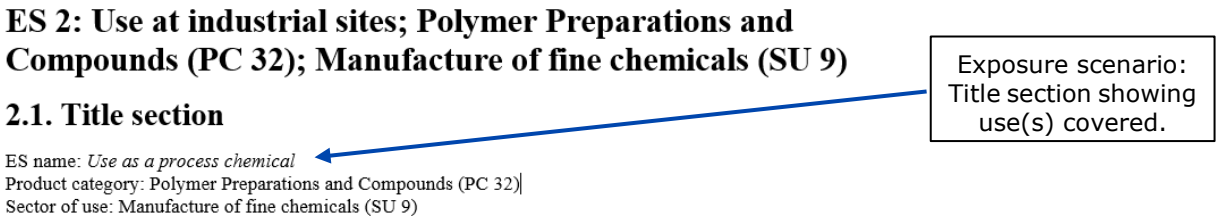
1. Checking your use(s): look at (i) the safety data sheet Section 1.2 on identified uses, and (ii) in the title section of the attached exposure scenarios. Verify that your use(s) is/are described there (bear in mind that you may have multiple uses).

[22] *Extended* means that a registrant in your supply chain has registered the substance as being manufactured or imported into Europe in a quantity greater than 10 tonnes per year, and that the safety data sheet has exposure scenarios (ES) annexed to it. The registration number can be found in Section 1 of the safety data sheet.

As a good practice, your supplier should provide a Table of Contents to the annex of exposure scenarios, so that you can easily identify the scenarios most relevant to your use(s).



If a Table of Contents is not provided, then you have to check the title section of every exposure scenario to identify the ones that match your uses.



2. Checking your activities: In the exposure scenario(s) which corresponds to your use(s), (or contributing scenario(s) which corresponds with your tasks/activities), check the title sections to make sure that all your process types / tasks are described by the process categories and environmental release categories listed there (normally written as PROC / ERC with a number e.g. PROC2 / ERC3).[23]

[23] *PROC* is an abbreviation of Process Category and describes tasks or process types from an occupational perspective. In exposure modelling, the selected PROC defines the baseline exposure estimate, while exposure reduction is achieved through operational conditions and risk management measures. *ERC* is an abbreviation of Environmental Release Category and is a way of characterising a use and its potential for release or emission to the environment. Sector of use category (SU) describes in which sector of the economy the substance is used e.g. rubber manufacturing sector, agriculture, forestry, fishery etc. PROC, ERC, SU are elements of the use descriptor system. More information on the use descriptor system can be found here: https://echa.europa.eu/documents/10162/17224/information_requirements_r12_en.pdf .

Environment	
1: *Use as a process chemical*	ERC 4
Worker	
2: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions	PROC 1
3: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions	PROC 2
4: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition	PROC 3
5: Transfer of substance or mixture (charging/discharging) at non dedicated-facilities	PROC 8a
6: Transfer of substance or mixture (charging/discharging) at dedicated facilities	PROC 8b
7: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)	PROC 9

Contributing scenario showing tasks/activities covered.

3. Checking your conditions of use: Compare the information given in the contributing scenario with the operational conditions and the risk management measures that you apply in your workplace.

2.2.6. Control of worker exposure: Transfer of substance or mixture (charging/discharging) at dedicated facilities (PROC 8b)

Product (article) characteristics
Covers concentrations up to 100 %
Liquid
Amount used (or contained in articles), frequency and duration of use/exposure
Covers use up to 8 h/day
Technical and organisational conditions and measures
Assumes that activities are undertaken with appropriate and well maintained equipment by trained personnel operating under supervision.; Ensure regular inspection, cleaning and maintenance of equipment and machines.; Clear spills immediately.; Ensure daily cleaning of the equipment.
Provide a good standard of controlled ventilation (5 to 10 air changes per hour).
Conditions and measures related to personal protection, hygiene and health evaluation
Wear chemically resistant gloves (tested to EN374) in combination with 'basic' employee training.; If skin contamination is expected to extend to other parts of the body, then these body parts should also be protected with impervious garments in a manner equivalent to those described for the hands.; For further specification, refer to section 8 of the SDS.
Use suitable eye protection.
Other conditions affecting workers exposure
Indoor use
Assumes process temperature up to 20 °C

Contributing scenario showing operational conditions and risk management measures required.

Condition of use is implemented at the user's site.

Condition of use is NOT implemented at the user's site.
Action is required by the user.

Condition of use is implemented at the user's site.

If the conditions of use in your workplace differ from the exposure scenario of your supplier, you may still be able to demonstrate that, under your conditions of use, the exposure levels (for humans and the environment) are equivalent to or lower than under the conditions described by the supplier. When assessing the exposure level (using a modelling tool), modification of one factor can be compensated by modification of another factor. If applicable, your supplier should provide information (e.g. the scaling tool/method, the parameters that can be modified and their boundaries) in the exposure scenario.

2.2 Use is covered by the exposure scenarios received

If the conclusion of your check is that your use is covered by one of the exposure scenarios received and that you have the appropriate operational conditions and risk management measures in place in the workplace, no further action under REACH is needed at this point. You should document your check and any action you have taken to guarantee the compliance with the conditions of use in the exposure scenario. Under worker protection legislation you may be required to monitor worker exposure (e.g. to verify compliance with an OEL), and this can be used to confirm compliance. If the monitoring indicates otherwise, then there are duties under REACH to inform your supplier that the operational conditions and risk management measures being communicated are inappropriate (see Section 5).

Applying the operational conditions and risk management measures described in the exposure scenario should ensure that exposure of workers is below the DNELs for both inhalation and dermal adverse effects. If you are unsure, get advice from a competent person, for example an occupational hygienist.

2.3 Use is NOT covered by the exposure scenarios received

If the conclusion of your check is that your use is not covered by any of the exposure scenarios received (your use does not match any exposure scenario, or it deviates significantly from them), then you have a number of choices.[24] Bear in mind the timeline for compliance with the restrictions, when considering the following options:

- Substitute NMP, DMF, DMAC or NEP with a different substance, for which an exposure scenario is available which covers your conditions of use[25].
- Make your use known to your supplier with the aim of making it an "identified use" and include it in the supplier's chemical safety assessment under the REACH Regulation. Your supplier will then provide you with an updated extended safety data sheet / exposure scenario.
- If your use is included, but the conditions of use (operational conditions and risk management measures) differ, implement the conditions of use described in the exposure scenario you have received. Where necessary, adjust your process or existing control measures to ensure they align with the conditions of use described in the exposure scenario.
- Find another supplier who provides NMP, DMF, DMAC or NEP with a safety data sheet and exposure scenario that covers your use.
- If none of the above options are available or applicable, prepare a downstream user chemical safety report, and inform ECHA. ECHA's Practical Guide 17[26] supports the preparation of a downstream user chemical safety report and includes an example of how to use measured data to demonstrate that the risk is adequately controlled. Remember that the conditions imposed by the REACH restrictions 71, 76, 80 and 81 are still applicable, and must be complied with. Check if any exemptions apply to you

[24] For more details, consult ECHA's Guidance for downstream users, Chapter 4.4. https://echa.europa.eu/documents/10162/23036412/du_en.pdf/9ac65ab5-e86c-405f-a44a-190ff4c36489

[25] Where technically possible, OSH legislation may require the substitution of a substance, mixture, or process with an alternative that, under its conditions of use, poses no risk or a lower risk to health or safety. This is reflected in Article 4(1) of the CMRD.

[26] ECHA's Practical Guide 17 https://echa.europa.eu/documents/10162/17250/pg17_du_csr_final_en.pdf/03aeab25-405a-45a4-9a66-5fa5c2dbfcb2

with regards to the downstream user chemical safety report i.e. if you use one of the solvents in quantities less than 1 tonne per year, or for the purposes of product and process-oriented research and development (PPORD).

2.4 Checking your use: Mixture safety data sheet

If you purchase and use NMP, DMF, DMAC or NEP in a mixture the same obligations as when you purchase one of the solvents on their own are applicable. However, it may be more difficult to identify your use and conditions of use (operational conditions and risk management measures), as the information may be incorporated into the safety data sheet itself rather than attached to it in an annex. You still have to do the checks described earlier but, in this case, you may have to look in the main body of the safety data sheet to identify the relevant information. You should check the identified uses in Section 1.2 and see if there are any attachments / annexes to the safety data sheet where the conditions of use are described. If there are no attachments, you need to look for the information on the operational conditions and risk management measures at the different sections in the main body of the safety data sheet (most likely Sections 7.3 and 8.2). If you conclude that your use is not covered, then the bullet points in Section 2.3 above will apply to you. Remember that the conditions imposed by REACH Restriction 71, 76, 80 and 81 are still applicable, and must be complied with.

Note: If the supplier of a mixture has incorporated safe use information from the exposure scenario of the ingredients into the main body of the safety data sheet, they are still legally required to provide exposure scenarios upon request, provided the manufacturer has registered the substance in quantities exceeding 10 tonnes per year.

2.5 How does the (extended) safety data sheet support your workplace risk assessment?

If you use one of the solvents in your workplace, you must conduct a comprehensive risk assessment and determine what measures and equipment need to be put in place to manage the risks. This must be done in line with the conditions of use described in the (extended) safety data sheet and at the same time complying with the provisions of the restriction. National legislation for the protection of the health and safety of workers from the risks related to chemical (including carcinogenic, mutagenic and reprotoxic) agents requires employers to carry out a workplace risk assessment. This risk assessment should document what specific preventive measures are required to reduce the risk. Pregnant workers are a particular target population / group given the adverse health effects that NMP, DMF, DMAC, or NEP have on the unborn child, and measures to avoid exposure should be taken to satisfy legislative requirements for the protection of pregnant workers.[27] Similar precautions should be considered for any other group of workers who may be at particular risk[28]. Information contained in the safety data sheet from your supplier must be taken into account in your risk assessment and you should determine if you can satisfy the conditions described in it. The assessment and the implementation of the preventive measures should be done before any new activity with any of the solvents commences, and if there is any change in existing working conditions which may affect workers' exposure. If you consider that the information in the safety data sheet is not sufficient to assess the risk to health and safety of workers arising from the use of the solvents, in particular the safety data sheet Section 8.2.1 on appropriate engineering controls, please contact your supplier (as described in Section 5).

[27] Council Directive 1992/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding.

[28] See Article 3(4) of the CMRD and Articles 9(1) and 15 of the EU OSH Framework Directive.

Under the REACH Regulation, a supplier must update a safety data sheet without delay once a restriction has been introduced[29]. You should identify it as "Revision: (date)" and provide the new version to all former recipients in the following 12 months. The receipt of a new safety data sheet from your supplier should trigger a review of your workplace arrangements for the control of exposure of your workers to NMP, DMF, DMAC, or NEP. You should identify what changes in the operational conditions and risk management measures are now described for your use(s) in the exposure scenarios, and what changes may be necessary to your existing workplace exposure control equipment and supporting management systems.

According to worker protection legislation, the hierarchy of control measures should be applied meaning that you should focus on preventing exposure of your workers (by all routes, e.g. inhalation, skin contact, oral) as a priority i.e. substitute by a safer substance or process technology[30]. Where exposure may still occur, technical or engineering controls will need to be applied to minimise risk and exposure for inhalation and dermal (direct or vapour skin contact) at source, for example by enclosing the process or tasks, e.g. with suitably designed containment and associated local exhaust ventilation[31], complemented by the provision of organisational arrangements, including reducing the number of workers exposed (or avoiding particular target populations/groups) or duration of their exposure[32]. Only when these approaches have been exhausted and if a residual risk remains, should personal protective equipment be considered. If, based on the workplace risk assessment, you have doubts about the appropriateness of the risk management measures communicated to you in the (extended) safety data sheet, you should communicate with your supplier (see Section 5).

Please remember that personal protective equipment (PPE) must be appropriate both for the individual wearer and for the intended use of the solvent. As a result, different types or styles of PPE (respiratory protective equipment[33], gloves[34] or protective clothing) may be required across your workforce. For all exposure controls introduced, their selection, installation, worker training, operation / use, and maintenance must be properly managed by you. More details on the hierarchy of control, which is also called the S.T.O.P. principle - Substitution, Technical measures, Organisational measures, Personal protection - can be found on the web site of the European Agency for Safety and Health at Work (EU-OSHA)[35],[36]. There is a tendency to adopt strategies which rely heavily on personal protective equipment when controlling dermal exposure. This is not in line with the European OSH legislation[37]. The risk management strategy for dermal exposure should follow the same philosophy as that for inhalation exposure. The hierarchy of control applies equally to all exposure routes. For dermal, technical measures such as automation, barriers, design of tools must be considered before personal

[29] See Article 31(9)(b) of REACH.

[30] See Article 4(1) of the CMRD.

[31] Correct installation and operation of an LEV system is essential to ensure exposure is controlled; for guidance see http://www.hse.gov.uk/lev/employers.htm

[32] See in particular Article 5 of the CMRD.

[33] For good practice on respiratory protective equipment, see http://www.hse.gov.uk/respiratory-protective-equipment/how-to-choose.htm

[34] For good practice on glove selection and glove management, see http://www.hse.gov.uk/skin/employ/gloves.htm

[35] EU-OSHA https://osha.europa.eu/sites/default/files/publications/documents/WEB-info-sheet-legislation-HWC-2018-19_0.pdf

[36] Refer to ECHA's Guidance for downstream users https://echa.europa.eu/documents/10162/23036412/du_en.pdf/9ac65ab5-e86c-405f-a44a-190ff4c36489

[37] According to the general rule of Article 3 of Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace: *"Personal protective equipment shall be used when the risks cannot be avoided or sufficiently limited by technical means of collective protection or by measures, methods or procedures of work organization"*.

protection. If the risk cannot be sufficiently controlled by technical/ organisational measures, then the only remaining strategy may be to rely on personal protective equipment.

Your existing exposure controls, as determined by your existing workplace risk assessment, may have been based upon previous exposure scenarios provided by your supplier(s) and considering existing national limit values (i.e. occupational exposure limit values, and in some cases, national biological limit values). In the restrictions on NMP, DMF, DMAC, and NEP harmonised DNELs at European level are derived, which are typically lower than existing national occupational limit values, which will still need to be complied with. Following the conditions described in the exposure scenario(s) for your use(s) of the solvents, should typically help you to achieve exposure lower than the national limit values. In applying these conditions, you should follow the hierarchy of control measures (see above). For NMP, DMF, and DMAC, both 8 hours and short-term binding occupational exposure limit values exist in parallel to DNELs (see Table 6 in Section 1.5 above). For NEP, national occupational exposure limit values exist in some Member States in parallel to DNELs. Adequate controls must be in place to ensure that exposure of workers is below these values.

Appendix 1 provides a flowchart to illustrate the steps, decisions and action you need to take. Further advice can be obtained from your national authority.

Remember!

→ NMP, DMF, DMAC, and NEP are reproductive toxicants, and may damage the unborn child, hence their uses are restricted under the REACH Regulation and OSH legislation in Europe. Particular attention must be paid to pregnant workers, as well as to any other group of workers at particular risk.

→ The restrictions already have or will have triggered a revision to the safety data sheet for the substances (and of mixtures containing it) provided by your supplier(s). More specifically, the operational conditions and risk management measures recommended to be put in place as exposure controls may have changed. In case you have been supplied e.g. DMAC or NEP in the last 12 months, but you have not received an updated safety data sheet, and think that you should have, please contact your supplier.

→ Review your own use(s) of NMP and DMF but especially of DMAC and NEP against the revised (extended) safety data sheet from your supplier, modify your process and/or control equipment where necessary, record your decisions and instruct your workforce.

→ Comply with the hierarchy of control measures (S.T.O.P. principle) at your workplace(es). (S.T.O.P. = check first for possible **s**ubstitution, second for **t**echnical exposure control, third for **o**rganisational measures and then for **p**ersonal protection equipment).

3. Examples of good practices to control exposure

Controlling exposure during industrial processes where NMP DMF, DMAC, or NEP are used will require that risk management measures are designed and implemented at each step (or task) where the substance is used and there is a potential for exposure. Although NMP, DMF, DMAC, and NEP are used in a wide number of sectors and settings (see Appendix 3), many activities or tasks are common across industry sectors. Table 8 below gives an overview of some generic tasks and examples of good practices for the control of inhalation and dermal exposure. It is important to note that this is not a comprehensive list and that other risk management measures may be suitable to control exposure as well. Articles 4 and 5 of the CMRD, in particular Article 5(5), outline measures to prevent or reduce the exposure of workers.

The examples and handling recommendations provided in this section are not meant to exempt employers from their responsibility to assess and manage the risks at their own site and workplaces in accordance with applicable national requirements and guidance. They are not intended to constitute a complete overview of all measures that may be necessary in individual cases. Employers are required to conduct a thorough, site-specific risk assessment that reflects the particular conditions of their own undertaking or establishment.

Table 8: Some examples of good practices to control exposure

Task	Possible PROCs	Good practices to control exposure	Example of use
Loading, unloading	8b, 9	Vapour recovery system Permanent and (semi-)closed systems such as piping and dedicated hoses (or arms) for loading and unloading trucks/containers	Formulation, chemical processes, coatings. When substance or mixture is delivered in large quantities (truck).
Storage	0 - other	Dedicated area Closed containers Integrated retention designed to retain any spillage	Most uses will include storage
Transfer	8b, 9	Permanent and (semi-)closed systems such as piping for regular transfers where possible Fume cabinet Local exhaust ventilation	Most uses will contain some transfer operations
Mixing	5	Closed systems where possible Local exhaust ventilation	Formulation, chemical processes, cleaning, coatings
Sampling	1, 2, 3, 4, 9[1)]	Closed sampling valves where possible Local exhaust ventilation	Formulation, chemical processes, coatings
Spraying	7	Automation Full enclosure	Cleaning, coatings
Wiping (roller application or brushing)	10	Fume cabinet Local exhaust ventilation	Cleaning, coatings

Task	Possible PROCs	Good practices to control exposure	Example of use
Dipping / pouring	13	Automation Closed systems where possible Full enclosure Covered dipping tanks Local exhaust ventilation	Cleaning, coatings
Laboratory activities	15	Fume cabinet	Laboratory use, quality control of samples
Maintenance	28	Clean and purge any system/equipment before maintenance	Most uses will contain some maintenance operations
[1)] Sampling activity may be included in a more general activity such as closed transfers (PROC 1 – 4) or transfer into small containers (PROC 9).			

Technical measures such as engineering controls aim at enclosing (fully or partially) and removing fumes or vapours from the tasks where NMP, DMF, DMAC or NEP are used and will help to control both inhalation and dermal exposure (both direct skin exposure and systemic absorption of vapours through the skin). Organisational measures such as special working methods (standard operating procedures, written working instructions, permits to work etc.) aim to separate the worker from harm (restrict access), reduce the exposure time (by design, ergonomic organisation, provision of appropriate personal protective equipment), and ensure workers are aware of the risk and properly trained to apply the technical measures correctly, to handle emergency measures and to use the personal protective equipment when it is required (fitting, wearing, removing and maintenance).

Where open tasks are involved, best possible and well-maintained exhaust ventilation, good housekeeping and occupational hygiene practices as well as correct use of appropriate personal protection equipment are important to control exposure. Special attention should be given to prevent surface contamination and spillage and, particularly for DMF and DMAC, to the systemic absorption of vapours through the skin.

Concrete and illustrated examples of some of the risk management measures listed in Table 8 are shown below. These examples are not exhaustive but illustrate the type of equipment that some companies have in place to control exposure for different tasks. It should be recognised that certain exposure control equipment may be specific to certain industry sectors. The examples included below have been kindly provided by some of the stakeholders mentioned in the acknowledgments.

The colour of the arrows indicates different types of risk management measures:

→ Elements for consideration from the assessment/modelling of exposure to workers under REACH.

→ Additional safety measures (not necessarily for exposure control to hazardous substances).

3.1 Charging and discharging

Bulk: Road tanker / truck or other tank container

Charging and discharging at tank farm or from a buffer tank in case of a continuous production process (PROC 8b).

<table>
<tr>
<td> 
  </td>
<td>  </td>
<td>Filling pipe

Safety rope and harness (work is 4m above ground level)

Local exhaust ventilation (LEV) pipe

Chemical resistant gloves and goggles (not visible)

Cone ensures fitting, and effectiveness of LEV

Safety shoes, working clothes</td>
</tr>
<tr>
<td>Above: Tank container at filling station (outdoor)

Below: Opening of dome</td>
<td colspan="2">Picture is showing inserting of the filling pipe & risk minimization measures.

Manual task: coupling and decoupling</td>
</tr>
<tr>
<td colspan="3">Standard personal protection equipment for the worker: gloves, goggles for manual handling with potential exposure (e.g. sampling), working clothing, safety shoes, helmet.

There are special tasks requiring additional measures e.g. loading and unloading from railcars (precautionary splash protection), maintenance etc. Requirements for additional safety measures are defined in the workplace risk assessment by the local occupational safety advisor knowing the exact working environment.

NMP: Personal sampling representing exposure during a normal shift at a tank farm/filling station operations (example from a company) measured concentrations of 0.003 – 0.12 mg/m^3. Moreover, five out of twelve results were below the limit of detection (LoD) or limit of quantitation (LoQ).

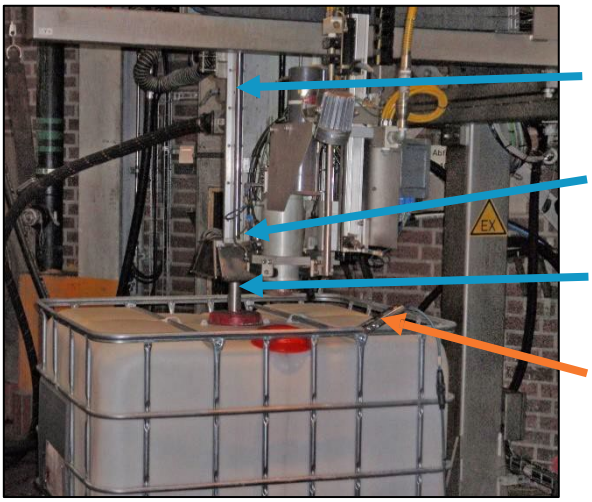
DMF/DMAC: No monitoring data is available; however, based on the physico-chemical properties of the substances, the air concentration is expected be approximately ten times higher than that of NMP.

NEP: No monitoring data is available; however, based on the physico-chemical properties of the substance, the air concentration is expected be similar to that of NMP.</td>
</tr>
</table>

3.2 Transfer operations

Standard IBC – container (**i**ntermediate **b**ulk **c**ontainer, IBC)

Semi-automatic filling of IBC (PROC 8b)

<table>
<tr><td>  </td><td>Product supply and off-gas pipes

LEV with capturing hood

Filling pipe

Electrical grounding</td></tr>
<tr><td colspan="2">The task is conducted indoor with enhanced ventilation.

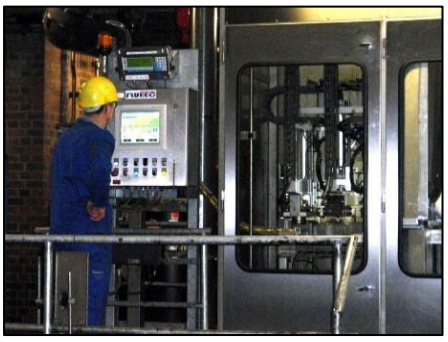
A fork lifter is used to place the IBC under the filling station. The filling pipe is inserted automatically, and the filling is done automatically. Manual tasks with potential exposure: closing of the IBC with the cap.</td></tr>
<tr><td colspan="2">Standard personal protection equipment for the worker (not shown): gloves, goggles, working clothing, safety shoes.</td></tr>
<tr><td colspan="2">NMP: Personal sampling representing inhalation exposure during a normal shift showed concentrations of 0.023 - 0.046 mg/m^3.</td></tr>
</table>

Standard Drum

Semi-automatic filling unit for drums (PROC 8b)

	Product supply LEV Filling pipe
The details of the unit are more or less identical with details of the filling unit of an automated filling line.	
Standard personal protection equipment for the worker (not shown): gloves, goggles, working clothing, safety shoes.	
NMP: Personal sampling representing exposure during a normal shift showed air concentrations of 0.003 - 0.064 mg/m^3. Comparable measurement without LEV resulted in a detectable air concentration of 0.11 mg/m^3.	

Automatic filling unit for drums (PROC 8b)

	
Loading of empty drums for automated filling	Outside control of automated filling in a closed chamber
The filling task and capping the drum with the lid is performed automatically in the closed chamber.	
Standard personal protection equipment for the worker: gloves, goggles, working clothing, safety shoes, helmet.	
Due to the full containment of the solvent filling inside a closed chamber, a potential of significant exposure towards the worker does not exist.	

3.3 Transfer into small container

Perform volume transfer in a fume cupboard

Use moveable sashes (horizontal and vertical) to shield unused areas to optimize airflow around into the fume cupboard -> minimized working area

Prefer small storage canisters (here 10 litres) -> one person can handle it safely and ergonomically without space consuming equipment and place storage canister upright again after usage -> no leakage possible

Prefer the use of drain taps with pressure compensation (liquid flow out of and air flow into the canister happen at the same time in a controlled manner -> even liquid flow)

Wear protection clothing according to the safety data sheet: shoes, Lab coat, gloves, eye/face protection

Use plastic bottles that are suitable for your application

Place drip catcher below and clean after usage -> clean and dry floor

NMP: No monitoring data available however, exposure modelling with Stoffenmanager estimates levels clearly below the limits.

Task: filling small containers for further analysis in a laboratory setting. The labels are attached to the bottles once the transfer is completed.

The task is performed in a fume cupboard specified in accordance with European Norm (EN) 14175, with the vertical sash only partially opened during the task.

Standard personal protection equipment for the worker: gloves, goggles, working clothing, safety shoes.

NMP: Personal sampling representing inhalation exposure during a normal shift showed concentrations of 0.022 - 0.27 mg/m^3.

3.4 Storage

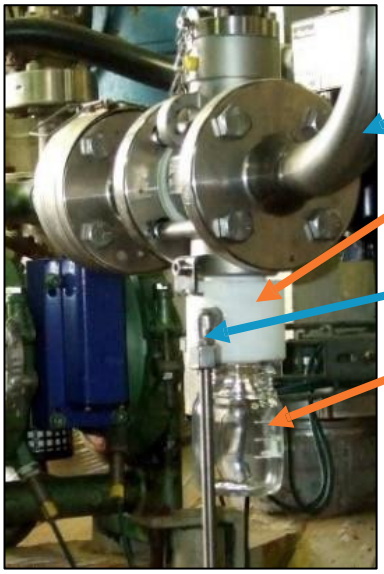
Dedicated area
Integrated retention

Container under permanent ventilation and air conditioning, equipped with flame and temperature detection

No specific PPE for workers (only handling of the closed IBCs)

3.5 Sampling

Semi-closed sampling



Product containing line

Fixed connector

Off-gas line

Sampling bottle

Standard operations like manual sampling require personal protection equipment: gloves, goggles for manual handling with potential exposure, working clothing, safety shoes, helmet (when outside the building).

NMP: Personal sampling representing exposure during a normal shift showed concentrations of 0.004 - 0.083 mg/m^3.

Sampling point

<table>
<tr>
<td> 
</td>
<td>Double block valve (1: gate valve, 2: needle valve)

Drain to slop system

Pressure: 14 bars, Temperature: 36ºC</td>
</tr>
<tr>
<td colspan="2">PPE: normal PPE (incl. goggles) and additionally gloves that are resistant to the used aprotic solvent.</td>
</tr>
</table>

3.6 Preparation for maintenance

High level description of the preparations that equipment such as filters, pumps or short piping undergo before being sent for maintenance. The first step is to obtain permit-to-work.

1. Block out up- and downstream pipework, if possible, with double-block-and-bleed valve arrangement.
2. Drain equipment of solvents to slop vessel/container, preferably connected to flare for lighter hydrocarbon fraction components. Slop is recovered and returned to the process or disposed of with certified waste disposal handler. If no flare connection is available, vent vessel/container to safe location to prevent worker exposure.
3. Preferably flush equipment with water to slop vessel/container, bio treatment plant or disposal container. Flushing is done while the equipment is still closed. Flush water is fed into the equipment via dedicated nozzles.
4. Purge with nitrogen to slop vessel/container or disposal container with vent to safe location or disposal to bio treatment plant.
5. Set spectacle blinds up- and downstream at the interfaces with equipment that is still under pressure (to avoid spillage in case of leaking valves).
6. Dismantle / open equipment for final cleaning.

7. Jet wash the pieces of equipment with high pressure water in the plant or at dedicated area.
8. Hand over to maintenance or workshop personnel to carry out maintenance task(s).

PPE:

- For open system (such as jet washing): solvent resistant gloves, chemical resistant overall and face shield.
- RPE is used during blinding (step 5).

For closed system: high shoes, flame retarding suit, gloves helmet and goggle.

3.7 Cleaning equipment

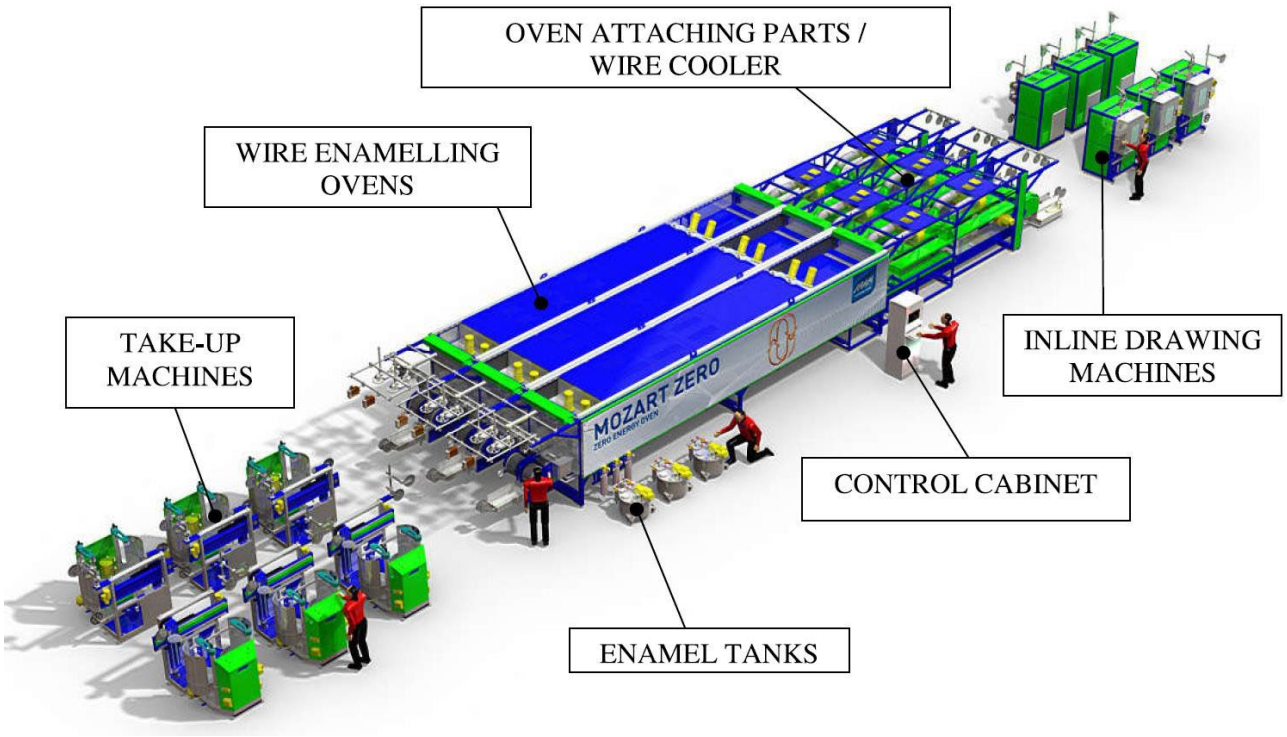
Gloves, face shield, full chemical resistant overall to be protected against potential projections during manual cleaning

PROC 28

Task: Cleaning of large industrial mixers.

3.8 Use of NMP in wire winding, sector example

For illustration, here is an example of a new type of enameling machine for serial production of wire winding (Source: MAG Maschinen- und Apparatebau AG). Wire winding operations with this type of machine can be associated with PROC 2. Occupational airborne measurement (personal sampling) have shown typical inhalation values < 1 mg/m^3 in the vicinity of the machine.

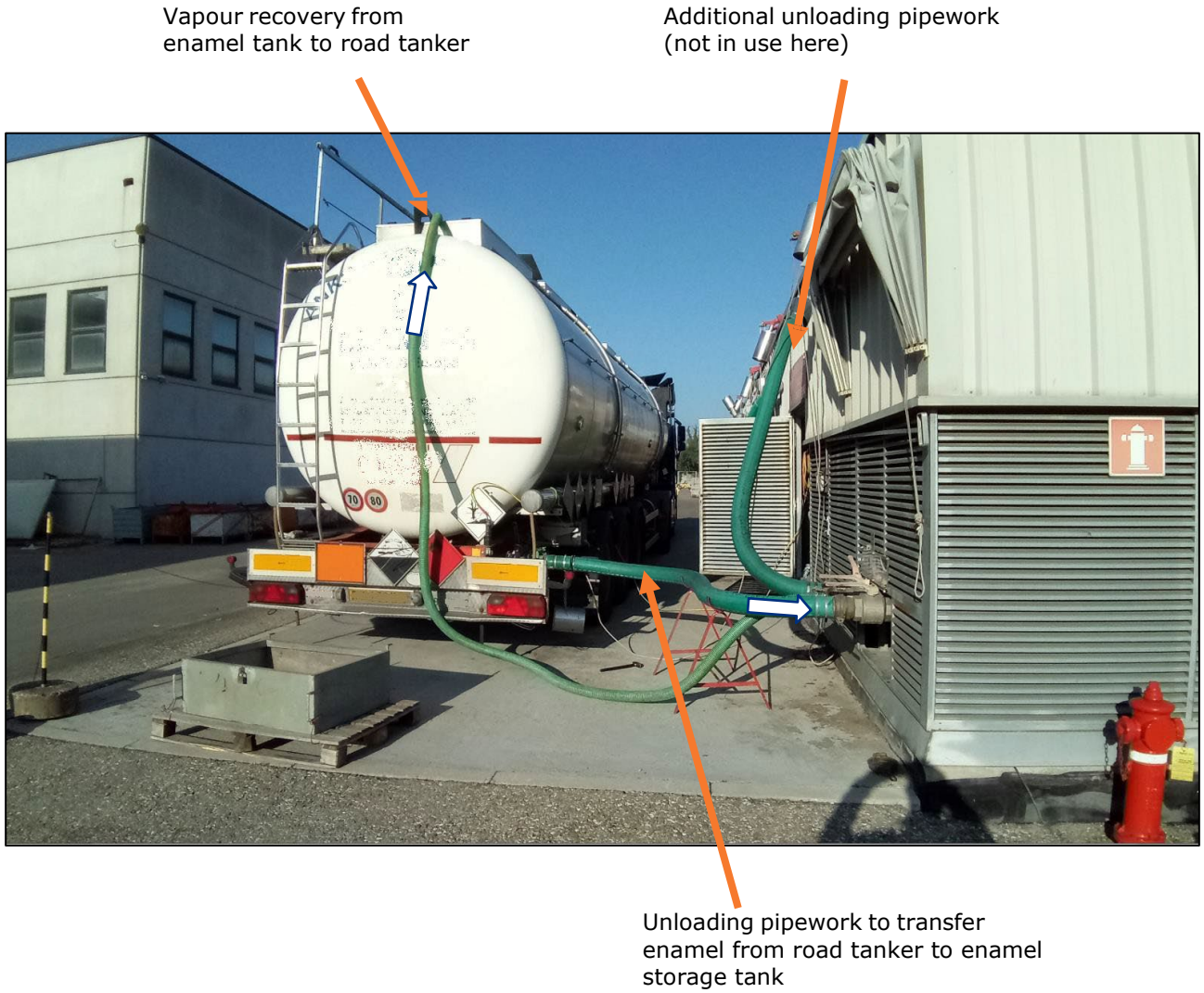


Enamel supply

Enamel is a mixture containing typically 20 – 50 % NMP. The mixture can be supplied in large quantities by road tanker or in IBCs (intermediate bulk container).

Example of unloading enamel from a road tanker to storage tanks in the enameling department. At this installation, this operation is conducted weekly and takes a maximum of one hour.

⟹ Indication of direction of flow.



Central enamel storage

The NMP containing enamel, like all other enamels, are stored in a dedicated area with control access. Here is an example of a facility where the enamel is delivered and stored in intermediate bulk containers (IBC).

The containers are connected to a closed central pipework system and enamel is pumped automatically into the enamel coating machinery. During normal production, no manual operation with enamels on the machinery is necessary.

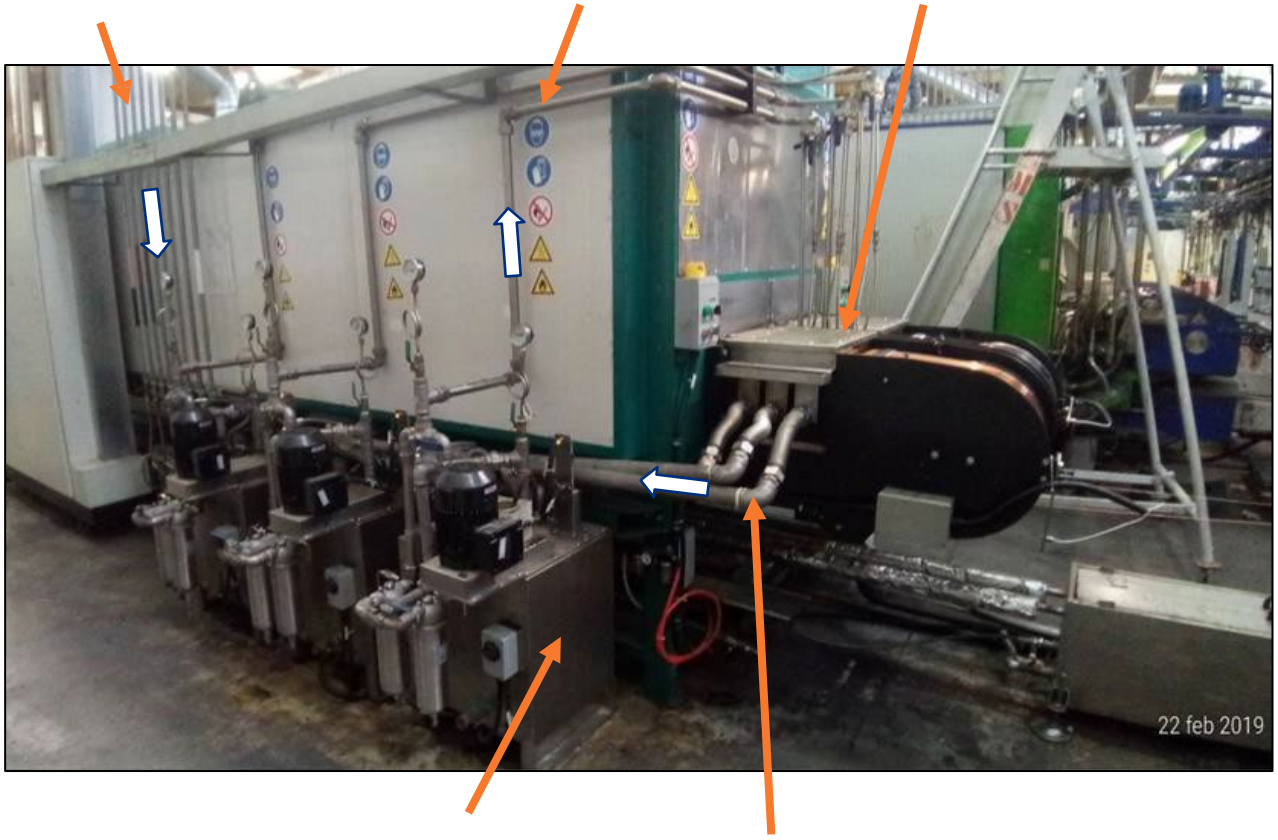
Enamel supply at enameling machine

⟹ Indication of direction of flow.

Enamel supply from enamel storage tank

Enamel supply to application unit

Enamel application unit



Enameling side tank

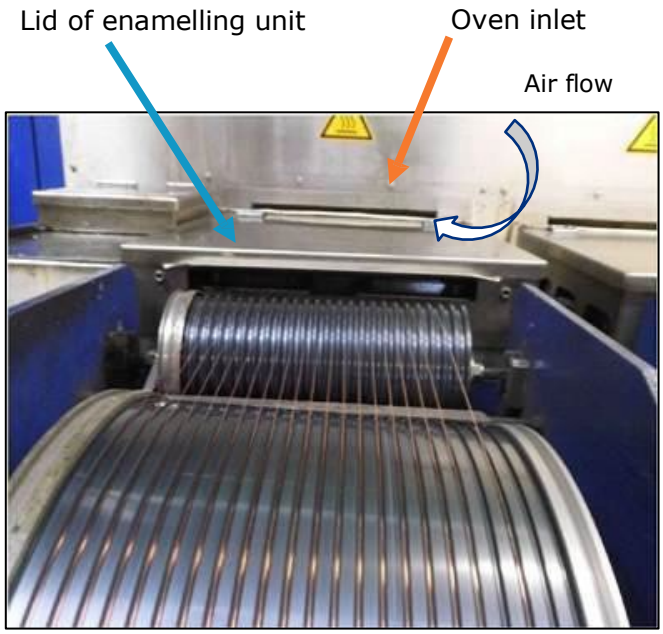
Return of excess enamel

Enamel application unit

One wire runs several times through the enameling oven (in the picture below, the same wire can be seen coiled several times). At each passage through the application unit, a thin coat of enamel is applied on the wire. The enamel is slowly and constantly extruded through a small tube; the wire is pulled through the enamel at the tip of the tube. It is then passed through a die that scrapes superfluous enamel off the wire. The wire then enters the oven for curing. The excess enamel is recovered and recirculated in a closed system (see Enamel supply at enameling machine above).

The lids of the application units are always closed during the process. The enameling chamber at the inlet of the oven is under negative pressure due the extraction system to capture emissions from the enamel supply system, and to contain any degradation products or products of combustion from entering the workplace air. The ventilation is part of the regulation system of the enameling machine and is monitored.

The combination of the die arrangement and the negative pressure from the oven extracts vapours generated during the process into the oven where they are burned off with the help of a catalyst.



Cleaning Process

Cleaning of enameling side tank

Manual cleaning of side tanks using NMP is conducted on rare occasions only in a closed room with air extraction. The work takes place on a designated table.

The operator is protected with safety glasses, chemical resistant gloves and other equipment like an apron and forearm protection. Additionally, the operator wears respiratory protection.

3.9 Additional good practice material

German Federal Institute for Occupational Safety and Health (BAuA) material on the safe filling of organic liquids (English content): https://www.baua.de/EN/Topics/Chemicals-biological-agents/Hazardous-substances/Activities-with-hazardous-substances/Organic-liquids?pos=1.

European Solvent Industry Group (ESIG) material to encourage responsible and safe handling of solvents at work: https://www.esig.org/solventswork/.

Relevant general guidance for OCs/RMMs are also available from the Health and Safety Executive (HSE): https://www.hse.gov.uk/coshh/essentials/general/index.htm

4. Monitoring and checking compliance

Under the REACH restriction, the primary obligation for NMP, DMF, DMAC, or NEP users is ensuring that the exposure of workers is below the DNELs and hence to comply with risk management measures described in the exposure scenarios attached to or incorporated into the body of the safety data sheets. Under the worker protection legislation, the S.T.O.P. (see Section 2.5) and minimisation principles need to be followed when complying with the OEL set for NMP, DMF, DMAC, or NEP to keep the exposure not only below the limit value but also as low as possible. An important aspect of the good control practice is to ensure that workers are properly trained, the process integrity is maintained and associated technical or engineering and organisational controls and personal protective equipment are appropriately used and maintained.

Under the worker protection legislation, the employer must assess all risks and take the necessary preventive and protective measures to ensure the exposure to hazardous chemicals is appropriately managed. This includes some form of measurements in line with worker protection legislation. The use of established procedures for measuring carcinogens, mutagens, or reprotoxic (CMR) substances is a legal requirement[38]. This may involve air sampling as well as biological monitoring of the worker as part of health surveillance. The workplace risk assessment should detail what kind of monitoring is necessary and how it should be performed. An equation in Appendix 2 provides a method for exposure calculation with a work shift longer than eight hours.

NMP, DMF, DMAC, or NEP users commonly verify exposure levels by workplace air monitoring according to a recognised standard (see Table 9 in Appendix 2). Air sampling is an established practice to verify that the exposure by inhalation remains below the national occupational exposure limit value. Available surveillance methodologies include the EN 689:2018+AC:2019 or national equivalent, which provides a methodological framework for monitoring exposure by inhalation. Others include the German (TRGS 402[39]) methodology.

For substances readily absorbed through the skin, like NMP, DMF, DMAC, or NEP, the evaluation of exposure by the inhalation route may underestimate the body's uptake. In such a case there may be a role for biological monitoring with a validated method that provides information on the total exposure (inhalation and skin absorption). Examples of biological monitoring methods that use urine analysis are available in Appendix 2.

Even if the aim of exposure monitoring is normally to verify compliance with an OEL, manufacturers and users of NMP, DMF, DMAC, or NEP may also use the monitoring data to demonstrate that the risk management measures communicated in the exposure scenario deliver compliance with the NMP, DMF, DMAC, or NEP restriction in their site-specific operational conditions.

In addition to the air monitoring methods mentioned above, Chapter R.14 of the ECHA Guidance on Information Requirements and Chemical Safety Assessment[40] also provides advice on exposure estimation (including use of measurements) in Section R.14.6. A few examples of air sampling and analytical techniques with the potential to fulfil the requirements for

[38] See, in particular, Article 5(5)(e) of the CMRD.

[39] German TRGS 402 BAuA - Technical Rules - TRGS 402 Identification and assessment of the risks from activities involving hazardous substances: inhalation exposure - Federal Institute for Occupational Safety and Health

[40] ECHA Guidance R.14 Occupational exposure assessment https://echa.europa.eu/documents/10162/17224/information_requirements_r14_en.pdf/bb14b581-f7ef-4587-a171-17bf4b332378

workplace exposure can be found in Appendix 2. Occupational safety and health authorities or service providers may have information available about local requirements and available methodologies.

Enforcement of the compliance with the NMP, DMF, DMAC, or NEP restrictions may be carried out by national labour inspectors and/or REACH enforcement authorities depending on the Member State. Users of NMP, DMF, DMAC, or NEP should contact their national authorities for advice on local requirements.

5. Why and when to communicate with your supplier

According to the restrictions, the DNEL values must be communicated to the users of NMP, DMF, DMAC, and NEP in the safety data sheet and the users need to implement the appropriate risk management measures and provide the appropriate operational conditions to ensure that exposure of workers is below these DNELs.

Every downstream user has an important role to play in the implementation of the restrictions. By being in active contact with your suppliers, you can make sure they are aware of your uses and can provide you with the necessary information on time.

There are specific situations where it is important that you contact your supply chain. For instance:

- Once a restriction has been imposed, suppliers need to add the restriction information into their safety data sheet without undue delay. They also need to send the updated document to customers they have supplied to during the last 12 months preceding the update of the safety data sheet. If you have not yet received an updated document especially for the latest restrictions on DMAC and NEP, contact your supplier and clarify when you can expect an updated safety data sheet.

- There may be situations where you have received an updated safety data sheet but without any attached exposure scenarios e.g. because your supplier has registered < 10 tonnes/year. If in doubt, contact your supplier to clarify this point.

- If you have information showing that the conditions of use described in the safety data sheet are inappropriate, you need to inform your supplier. For example, you have air sampling (static or personal) results showing that the exposure levels at the workplace are above the DNEL for inhalation although the operational conditions and risk management measures in place correspond to those described in the extended safety data sheet for the use. This is important information to share with your suppliers, so that they can review the recommendations given in the extended safety data sheet.
- You may source the solvents from several suppliers. If you notice that the operational conditions and risk management measures described in the extended safety data sheets for the same use differ from one supplier to another, it is recommended to contact your suppliers. In this way, the suppliers can explain the reason for the difference or even come to an agreed set of operational conditions and risk management measures for the use.
- Is the information in the safety data sheet applicable to your own use? If the way you use the solvents is not described or is different from what is described in the extended safety data sheet, it is important to clarify the situation with your supplier.
    - If your use or conditions of use are not covered by any of the exposure scenarios received from your suppliers, one of your options is to ask your supplier to include your use / conditions of use in their chemical safety report and to provide you with an exposure scenario for it (see Section 2.4). You need to

make sufficient information available to your supplier to enable them to make such an assessment. Your sector organisation may have developed a sector use map[41] as a convenient means of supplying an overview of the relevant uses and associated conditions of use specifically for your sector.

- If the risk management measures described contradict the hierarchy of control measures or it is difficult to know if you have implemented all RMMs with the right efficiency required for safe use (for example, efficiency for the ventilation or the gloves), contact your supplier to clarify the situation.
- If you use a mixture containing any of the solvents, it is likely that no exposure scenario is attached to the safety data sheet you receive from your supplier. It may be difficult to recognise if exposure scenario information has been integrated into the main body of the document. If in doubt, contact your supplier to clarify this point.

- You can also contact your suppliers regarding potential alternatives. The suppliers of the solvents may be aware of alternative substances or technologies for some uses that could be relevant for your process.

[41] The use map is a concept developed to improve the quality of the information on use and conditions of use communicated from downstream users to suppliers and the efficiency of this communication process. See https://echa.europa.eu/csr-es-roadmap/use-maps/concept

6. References and further reading

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Further reading

Interim Guidance for National Labour Inspectors on how to use Occupational Exposure Limits (OELs), Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs) when assessing effective control of exposure to Chemicals in the workplace; SLIC WG Chemex,

2015. https://ec.europa.eu/social/BlobServlet?docId=15614&langId=en

Guidance for National Labour Inspectors on the interaction of the Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation (REACH) (Regulation (EC) No.1907/2006), the Chemical Agents Directive (CAD) and the Carcinogens and Mutagens Directive (CMD); SLIC, 2013. http://ec.europa.eu/social/BlobServlet?docId=11812&langId=en

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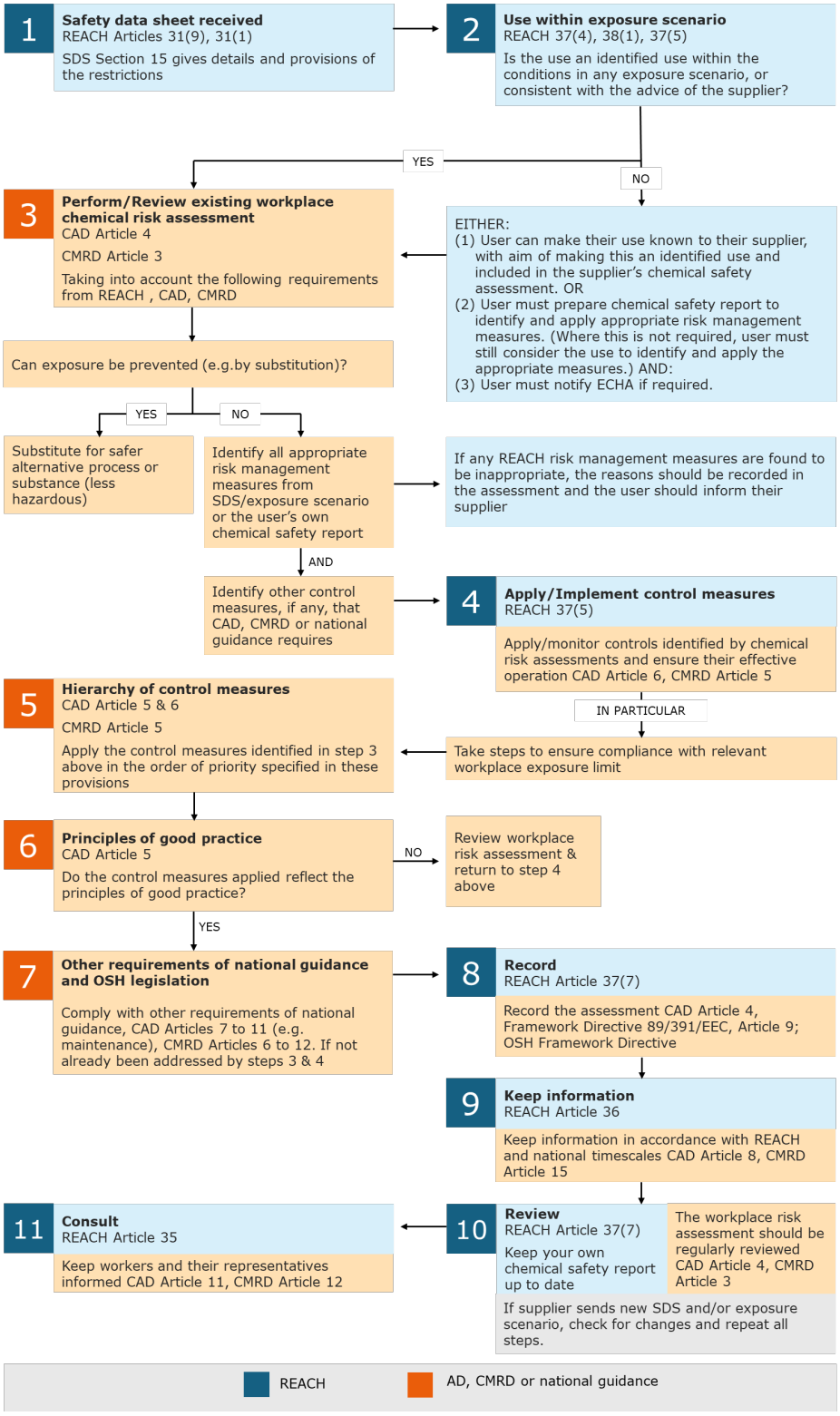
Appendix 1. Flowchart to illustrate REACH and CAD/CMRD interaction



Flowchart adapted from the Senior Labour Inspectors' Committee's Guidance for National Labour Inspectors on the interaction of REACH and the Chemical Agents Directive (CAD), November 2013 (see link in Section 6).

Appendix 2. Potential analytical methods

The sampling and analysis methods used to compare exposure concentrations with a limit value should fulfil certain requirements in terms of uncertainty and measuring range among other parameters.

The standard EN 482 "Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents" provides requirements for methods for sampling and analysis used to compare exposure concentrations with a limit value. In terms of measuring ranges the method should be able to measure 0.1 to 2 times the occupational exposure limit for an 8-hour time-weighted average (TWA).

The methods included in Table 9 have validation data that show compliance with the requirements of the standard EN 482 for the different systemic inhalation DNEL values.

The list of workplace air monitoring methods is not exhaustive and includes only validated methods with a sufficient measurement range to demonstrate compliance with the systemic inhalation DNEL for the relevant substance.

Table 9: Potential analytical methods for workplace exposure (air) monitoring

Method/Reference	Analytical technique and sampling media	Limit of quantification LoQ and (sampling volume and/or time)
NMP		
MAK Commission Method 1 N-Alkyl-2-pyrrolidones (Breuer, Ehmann et al. 2002)	GC/NPD Silica gel sorbent tube	0.1 mg/m^3 (40 L, 2 hours)
MAK Commission Method 2 N-Alkyl-2-pyrrolidones (Rosenberger and Breuer 2002)	GC/MS Silica gel sorbent tube	0.15 mg/m^3 (40 L, 2 hours)
DMF		
DGUV Method 213-574 Method for the determination of carboxylic acid amides (Krämer 2002)	GC/FID Charcoal sorbent tube	0.13 mg/m^3 (120 L, 2 hours)
OSHA Method 66 N,N-Dimethylformamide (DMF)[42]	GC/NPD Charcoal sorbent tube	0.045 mg/m^3 (10 L, 50 minutes)
DMAC		
DGUV Method 213-574 Method for the determination of carboxylic acid amides (in Krämer, 2012)	GC/FID Charcoal sorbent tube	0.1 mg/m^3 (120 L, 2 hours)

[42] https://www.osha.gov/sites/default/files/methods/osha-66.pdf

Method/Reference	Analytical technique and sampling media	Limit of quantification LoQ and (sampling volume and/or time)
INRS Method M-97 N,N-Diméthylacétamide[43]	GC/NPD XAD resin sorbent tube	0.25 mg/m^3 (18 L, 2 hours)
NEP		
MAK Commission Method 1 N-Alkyl-2-pyrrolidones (Breuer, Ehmann et al. 2002)	GC/NPD Silica gel sorbent tube	0.1 mg/m^3 (40 L, 2 hours)
MAK Commission Method 2 N-Alkyl-2-pyrrolidones (Rosenberger and Breuer 2002)	GC/MS Silica gel sorbent tube	0.3 mg/m^3 (40 L, 2 hours)
Abbreviations: FID: Flame Ionisation Detector; GC: Gas Chromatography; MS: mass spectrometry; NPD: Nitrogen Phosphorus Detector		

Exposure calculation with a work shift longer than 8h

It is not uncommon that a worker has a work-shift longer than 8 hours in a day. Calculation methods exist whereby the exposure of a worker in any 24-hour period can be treated as equivalent to a single uniform exposure for 8-hours, the 8-hour time-weighted average (TWA) exposure. The general formula to calculate the daily exposure is given by:

$$\frac{C_1T_1 + C_2T_2 + \ldots C_nT_n}{8}$$

where C1 is the occupational exposure and T1 is the associated exposure time in hours in any 24-hour period. This approach can also be applied to give the same protection to extended work shift workers that is given to usual work shift ones. The European standard EN 689 Annex G Workplace exposure - Measurement of exposure by inhalation to chemical agents - Strategy for testing compliance with occupational exposure limit values provides some examples of applications of the calculation method[44]; other methods exist at national level[45].

Biological monitoring

Biological monitoring is the measurement and assessment of hazardous substances or their metabolites in tissues, secretions, excreta or expired air, or any combination of these, in exposed workers. Measurements reflect combined (systemic) exposure resulting from substance absorption through all routes: inhalation, dermal, and oral.

NMP, DMF, DMAC, and NEP are readily absorbed through both inhalation and the skin. As a result, dermal exposure significantly contributes to the internal dose. Systemic absorption of vapours through the skin is particularly relevant for DMF and DMAC due to their relatively high vapour pressures, or in situations where highly effective respiratory protective equipment (RPE) is required for processes involving high air concentrations. Consequently, biological

[43] https://www.inrs.fr/publications/bdd/metropol/fiche.html?refINRS=METROPOL_97

[44] EN 689:2018+AC:2019

[45] Health and Safety Executive, EH40/2005, 2018 Calculation methods, p.33

monitoring can serve as a valuable complement to air monitoring. However, there is no legal requirement in the REACH restrictions on NMP, DMF, DMAC or NEP to perform biological monitoring.

In the following sections, biomonitoring methods referred to in the restrictions on NMP, DMF, DMAC, and NEP are summarised. A table with the suggested biomarker DNELs is presented in Section 1.5, Table 7. Compliance with suggested biomarker DNELs indicates that the systemic long-term risk from inhalation, dermal, and oral exposure is well-controlled.

General instructions for handling and storage of urine samples:

Urine samples should be collected in sealable 500 mL bottles, e.g., polypropylene, and stored in a deep freezer at a maximum temperature of –20°C until processing. Samples can be preserved under these conditions for at least six months. If an external analytical laboratory is used, ensure that the samples remain within the specified temperature limit during transport (see e.g. Bader, Rosenberger et al. (2002), Käfferlein and Angerer (2002); Schettgen (2002)).

Suggested biomonitoring approach for NMP

NMP is well absorbed following inhalation (40 – 60 %) and dermal (≤100 % depending on conditions) exposure[46].

An approach to biomonitoring of NMP was published by ECHA in July 2019 'How to comply with REACH Restriction 71, guideline for users of NMP: Explanatory Note on Biological Monitoring'[47]. According to this explanatory note, NMP is excreted in urine as free, non-metabolised NMP but also as metabolites, 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP), N-methylsuccinimide (MSI), 2-hydroxy-N-methylsuccinimide (2-HMSI) and 2-pyrrolidone (2-P). 5- HNMP and 2-HMSI are the major urinary metabolites. Due to comparatively short half-life of NMP (~4 h), the low concentrations in urine and possible risk of contamination, 5-HNMP and 2- HMSI are preferred markers of exposure. Biological half-lives of 5-HNMP and 2-HMSI after inhalation exposure are 6 to 8 h and 16 to 28 h, respectively (SCOEL 2016). Delayed elimination of NMP following dermal-only exposure to NMP vapor was reported, with peak times for free NMP, 5-HNMP and 2-HMSI being delayed by approximately 4 hours (Bader, Wrbitzky et al. 2007, Bader, Wrbitzky et al. 2008). The delayed peak maximum and the long biological half-life makes urinary 2-HMSI especially suitable marker for the NMP exposure. However, both 5-HNMP and 2-HMSI may be chosen for the monitoring of exposure (SCOEL, 2016). Currently 5-HNMP is the one which is most often used in commercial laboratories in Europe.

The study of Bader et al. (2007) provides relevant information to correlate concentrations of NMP in air with the concentration of the metabolites 5-HNMP and 2-HMSI in urine. In this study volunteers were exposed 2 x 4 h to 10, 40, 72, or 80 mg NMP/m3 under resting conditions and under workload. In the following Table 10 the concentration of 5-HNMP and 2-HMSI in urine are presented.

[46] Background document to RAC and SEC Opinion on 1-methylpyrrolidin-2-one (NMP) https://echa.europa.eu/documents/10162/149a1347-47b5-ab07-058d-eb80611521c8

[47] https://echa.europa.eu/documents/10162/17233/entry_71_exp_note_biomonitoring_en.pdf/25c684f2-243e-4321-e7c0-ba7074838ab6

Table 10: Concentrations of NMP metabolites in urine[48]

Metabolite	Exposure	Median peak concentrations of metabolites in urine (mg/g creatinine)			
		10 mg/m³	40 mg/m³	72 mg/m³	80 mg/m³
5-HNMP	Resting	16	57	113	106
	Workload	21	81	133	161
2-HMSI	Resting	5.4	18.7	29.6	30.6
	Workload	5.8	21.2	36.2	43.0

The following biomarker DNELs for **NMP** were suggested in the above-mentioned ECHA Explanatory Note on Biological Monitoring for NMP based on the data by Bader et al. (2007):

> **25 mg 5-HNMP (5-hydroxy-N-methyl-2-pyrrolidone)/g creatinine (sampling end of shift) AND**
>
> **8 mg 2-HMSI (2-hydroxy-N-methylsuccinimide)/g creatinine (sampling next morning following an 8 h work shift).**

The optimum sampling time for 5-HNMP is 2 to 4 h after the end of the work-shift, and for the longer half-life metabolite 2-HMSI, the sampling time is 16 h after the exposure (on the morning after an 8 h work shift). In both cases the measured urinary concentration is recommended to be corrected for urinary creatinine to compensate for diuretic variations (SCOEL, 2016). It should be noted that because of the longer half-time of 2-HMSI, some accumulation during the work week may occur. This may result in higher levels in the end of the work week when compared to the samples taken in the second morning of the work week.

Main uncertainties related to the biomonitoring approach are related to the sampling time. Because of the short half-life of the 5-HNMP the sample is recommended to be taken 2 to 4 hours after the work-shift. If another sampling time is used, the biomarker given above does not apply. It is also noteworthy, that in the case of significant dermal exposure peak urinary levels may be delayed (SCOEL, 2016). As discussed above, in these cases 2-HMSI might be a better marker than 5-HNMP because of the longer half-time.

Analytical measurement systems exist to determine the biomarkers for NMP (see Table 11). The limit of quantification (LoQ) of the analytical method should be less than reference level. According to OECD "Occupational Biomonitoring Guidance Document" (OECD 2022) ideally the LoQ is 10 % of the Occupational Biomonitoring Level.

Table 11: Potential analytical methods for biological monitoring for NMP

Method/type of sampling	Analytical technique	Limit of quantification LoQ	Reference
Urine, spot sample	GC/MS	3 mg 5-HNMP/L[1)]	Bader, Rosenberger et al. (2002)

[48] As measured in the study by Bader et al. (2007)

Method/type of sampling	Analytical technique	Limit of quantification LoQ	Reference
		3 mg 2-HMSI/L[1, 2)]	
Urine, spot sample	GC/MS	60 µg 5-HNMP/L[1)] 15 µg 2-HMSI/L[1)]	Schindler, Koslitz et al. (2012)
Urine, spot sample	GC/MS	69 µg 5-HNMP/L[1)] 45 µg 2-HMSI/L[1)]	Meier, Schindler et al. (2013)

[1)] Limit of quantification (LoQ) converted from limit of detection (LoD) based on LoQ ~ 3 x LoD

[2)] The LoQ is less than 10 % of the biomarker DNEL for this metabolite; more sensitive methods are available and might be selected

Abbreviations: GC/MS: Gas Chromatography – Mass Spectrometry

Suggested biomonitoring approach for DMF

Liquid DMF, similar to the other aprotic solvents, is readily absorbed via the skin and the skin may serve as a reservoir for prolonged absorption (Wang, Chang et al. 2009). Furthermore, due to the high vapour pressure of DMF, dermal absorption can occur directly from DMF vapours in air as demonstrated in a study with human volunteers with inhalation absorption via the lungs of ca. 60% and absorption of the vapour via the dermal route of ca. 40% (Nomiyama, Nakashima et al. 2001).

DMF is metabolised in the liver to N-(hydroxymethyl)-N-methylformamide (HMMF) which is demethylated to N-methylformamide (NMF). Further oxidation can lead to formamide. The combined assessment of HMMF and NMF in urine is routinely used as a biological marker for occupational DMF exposure. During analysis of the metabolites by gas chromatography (GC), HMMF undergoes thermal decomposition to NMP. Subsequently, the combined amounts of the originally excreted NMF and the NMF generated from HMMF are detected as total NMF. Those metabolites are excreted very fast with a half-life of approximately 4 hours (Seitz, Kilo et al. 2018).

N-Acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) was identified as another main metabolite, which is not entirely excreted before the beginning of the next day's shift and generally accumulates during a work week (Seitz, Kilo et al. 2018).

RAC noted in its opinion on DMF[49] that at least three different biomonitoring approaches have been reported in the literature, focusing on different metabolites, with different half-lives, and therefore covering different exposure periods (Kilo, Göen et al. 2016, Seitz, Kilo et al. 2018).

For 220 workers in the acrylic fibre industry a significant linear relationship was observed between DMF in air and NMF as well as between DMF in air and AMCC in post-shift urine samples (Seitz, Kilo et al. 2018). Workers were exposed to median of DMF concentration in the air during the whole shift of 3.19 mg/m^3 (range < 0.15 – 46.9 mg/m^3) and showed median concentration for total NMF of 4.80 mg/L (range 0.20 – 50.6 mg/L) and for AMCC of 4.75 mg/g

[49] https://echa.europa.eu/documents/10162/b6644298-54a4-052a-9bbc-6824966d151e

creatinine (range 0.06 – 49.6 mg/g creatinine). Excluding workers who had been using breathing masks on the day of the study led to even tighter correlations.

No statistically significant differences in parameters for liver effects (such as liver enzyme activities, main parameter of alcohol-induced strain on the liver, and a liver independent strain parameter of alcohol consumption) were identified in 220 DMF-exposed workers (mean 6.2 mg DMF/m^3; SD 7.6 mg/m^3) compared to 175 controls in a cross-sectional study. Metabolite concentrations in the urine of workers were 7.75 mg NMF/L (SD 8.82 mg/L) and 9.42 mg AMCC/g creatinine (SD 10.4 mg/g creatinine), (Kilo, Göen et al. 2016).

RAC noted in its opinion that the systemic long-term inhalation DNEL of 6 mg/m^3 would correspond to a biomarker DNEL of 8 mg total NMF/L urine based on equations provided by Seitz, Kilo et al. (2018).

RAC further noted that the urinary concentration of the DMF-metabolite AMCC is a biomarker for the assessment of cumulative whole-body exposure to DMF over a workweek and could be complementary to measuring NMF. However, RAC did not suggest a biomarker DNEL for this metabolite. In the recent publication by Lamkarkach, Meslin et al. (2022), a biomonitoring value of 10 mg AMCC/L urine or g creatinine was suggested based on four biomonitoring studies that provided NOAEL for effects on liver enzymes between 9.42 and 25.4 mg AMCC/g creatinine. The authors of the study considered this value as conservative. The study of Kilo, Göen et al. (2016) reported AMCC concentrations of 9.42 and 10.4 mg/g creatinine for the two cohorts of workers with no effects on liver enzymes.

The following biomarker DNELs for **DMF** were suggested based on the RAC and SEAC opinion on DMF[50] and the publication by Kilo et al. (2016), Seitz et al. (2018) and Lamkarkach et al. (2022):

8 mg NMF (N-methylformamide) plus HMMF (N-hydroxymethyl-N-methylformamide)/L urine (sampling end of shift)

and/or

10 mg AMCC (N-acetyl-S-(N-methylcarbamoyl)cysteine)/L urine (sampling end of shift at the end of the workweek)

Since NMF and HMMF are excreted very fast with a half-life of approximately 4 hours and do not accumulate, total NMF determined in urine samples taken at the end of shift reflects the daily DMF exposure (Seitz, Kilo et al. 2018). An adjustment to creatinine has not improved the relation between NMF and air DMF (Seitz et al., 2018) or affected the urinary NMF-concentration in relation to dehydration/sweating (Miyauchi, Tsuda et al. 2014).

AMCC is not entirely excreted before the beginning of the next day's shift and generally accumulates during a work week. Thus, the determination of AMCC in urine samples at the end of the work week is thought to reflect the weekly exposure to DMF. After cessation of exposure, the urinary AMCC elimination decreased with a half-life of around 23 h (Seitz et al., 2018).

Analytical measurement systems exist to determine the biomarkers for DMF (see Table 12).

[50] https://echa.europa.eu/documents/10162/b6644298-54a4-052a-9bbc-6824966d151e

Table 12: Potential analytical methods for biological monitoring for DMF

Method/type of sampling	Analytical technique	Limit of quantification LoQ	Reference
Urine, spot sample	GC/NPD or GC/TSD	3.0 mg total NMF/L urine[2)] 1.5 mg AMCC/L urine	Käfferlein and Angerer (2002)
Urine, spot sample	GC/MS[1)]	0.3 mg total NMF/L urine	Will, Göen et al. (2002)
Urine, spot sample	HPLC/MS (SPE–LC–MS/MS; online solid-phase extraction followed by liquid chromatography with tandem mass spectrometry	15 µg AMCC/L urine	Schettgen (2002) Seitz, Kilo et al. (2018)

[1)] A temperature of 250°C or above is recommended to obtain complete degradation of HMMF into NMF to measure total NMF in urine

[2)] The LoQ is less than 10 % of the biomarker DNEL; a more sensitive method is available and might be selected

Abbreviations: GC: Gas Chromatography; HPLC: high-performance liquid chromatography; MS: mass spectrometry; NPD: Nitrogen Phosphorous Detector; TSD: Thermionic specific detector

Suggested biomonitoring approach for DMAC

Similarly to DMF, DMAC vapour is significantly absorbed through the skin (Nomiyama, Omae et al. 2000). DMAC is oxidised in the liver to N-hydroxymethyl-N-methylacetamide (HMMA) and demethylated to N-methylacetamide (NMAC). HMMA, similar to HMMF, undergoes thermal decomposition to NMAC during analysis of the metabolites by gas chromatography (GC) (Kawai, Mizunuma et al. 1997). The urinary half-life of NMAC was determined with 9.0 ± 1.4 hours and 5.6 ± 1.3 hours via skin and lung, respectively (Nomiyama et al., 2000).

In the RAC and SEAC opinion on DMAC and NEP[51] it is suggested that 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, Rhyne Jr et al. 1995, Nomiyama, Omae et al. 2000).

In the background document to the RAC and SEAC opinion on DMAC and NEP[52] it is described that the interpolation of the systemic long-term inhalation DNEL of 13 mg DMAC/m^3 leads to 23 mg NMAC/L urine, assuming the non-linear relationship as used by Walter, Drexler et al. (2020). Another interpolation of the systemic long-term inhalation DNEL of 13 mg DMAC/m^3 leads to a mean value of 25 mg NMAC/g creatinine assuming a linear relationship between the log-transformed DMAC concentration (in ppm) and log-transformed NMAC concentration (in mg NMAC/g creatinine) as observed by Spies et al. (1995). In addition, Nomiyama, Omae et

[51] https://echa.europa.eu/documents/10162/847134de-5d46-355d-bbf0-650fd9f59f78
[52] https://echa.europa.eu/documents/10162/75a0c497-69e0-1c74-689d-667bd49e47b9

al. (2000) exposed twelve healthy male volunteers for 4 hours to 6.1 ppm (22.1 mg/m^3)[53] for dermal (whole body with respiratory mask) and for inhalation exposure (nose-only). The mean NMAC value after DMAC exposure was 11.2 mg NMAC/g creatinine (6.9 - 20.1 mg/g).

The following biomarker for **DMAC** was suggested in the RAC and SEAC opinion on DMAC and NEP using the factors suggested by Spies et al. (1995) and Nomiyama et al. (2000) to account for inter- and intra-individual variation:

> **20 mg NMAC (N-methylacetamide)/L urine corresponding to 15 mg NMAC/g creatinine (sampling end of shift at the end of the workweek).**

Considering the observed biological half-lives of urinary NMAC of 9.0 hours and 5.6 hours via skin and lung, respectively, urine samples should be taken at the end of shift at the end of the workweek.

The creatinine-adjusted method was found a more adequate method than adjustment for urinary volume or specific gravity (see background document to the RAC/SEAC opinion).

Analytical measurement systems exist to determine the biomarkers for DMAC (see Table 13).

Table 13: Potential analytical methods for biological monitoring for DMAC

Method/type of sampling	Analytical technique	Limit of quantification LoQ	Reference
Urine, spot samples (workers)	GC/MS[1)]	0.3 mg total NMAC/L	Will, Göen et al. (2002)
Urine, pooled samples (workers)	GC/MS[1)]	0.16 mg total NMAC/L	Yamamoto, Matsumoto et al. (2018)
[1)] A temperature of 250°C or above is recommended to obtain complete degradation of HMMF into NMF to measure total NMF in urine Abbreviations: GC: Gas Chromatography; MS: mass spectrometry			

Suggested biomonitoring approach for NEP

NEP is rapidly metabolized in the liver by gradual oxidation of the pyrrolidone ring. Independent of the exposure route, 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy-N-ethylsuccinimide (2-HESI) are the main metabolites (David, Gerofke et al. 2021). Elimination half-lives were calculated in humans after oral exposure and were determined to be 7 hours for 5-HNEP and 22 to 27 hours for 2-HESI (Koch, Bader et al. 2014).

No human studies are available for NEP to provide a measured correlation between NEP air levels and urinary metabolite levels for deriving a biomarker DNEL. Therefore, the urinary mass balance approach as described by David et al. (2021) as part of the European Human Biomonitoring Initiative was used by the dossier submitter of the restriction on DMAC and NEP and supported by RAC to provide a rough estimate of a biomarker DNEL. In this publication human biomonitoring guidance values were derived for the general population for urinary NEP metabolites 5-HNEP and 2-HESI combined (10 and 15 mg/L for children and adults,

[53] 1 ppm DMAC = 3.624 mg DMAC/m^3 (at 20ºC and 1013 hPa); see background document to the RAC and SEAC opinion on DMAC and NEP

respectively). Since the human biomonitoring guidance values were derived based on animal toxicity data, the level of confidence of the human biomonitoring guidance values was therefore considered medium/low (David et al., 2021). Corresponding to the systemic long-term inhalation DNEL of 4 mg NEP/m^3, the submitter of the restriction on DMAC and NEP calculated in the background document to the RAC and SEAC opinion a value of 20 mg/L for the sum of urinary NEP metabolites 5-HNEP and 2-HESI[54]. Other factors included in the calculation were the ratio of the averaged molecular weight of the metabolites and the molecular weight of NEP of 1.2, a urinary excretion factor (96 hours) for both metabolites of 0.507 (based on Koch et al., 2014), and a daily urinary flow rate (adjusted to the body weight) for adults of 0.02 L/kg bw/day.

The following biomarkers for **NEP** were suggested in the RAC and SEAC opinion on DMAC and NEP based on the mass balance approach:

> **10 mg 5-HNEP (5-hydroxy-N-ethyl-2-pyrrolidone)/L urine corresponding to 7 mg 5-HNEP/g creatinine measured (sampling end of shift) *AND***
>
> **8 mg 2-HESI (2-hydroxy-N-ethylsuccinimide)/L urine corresponding to 6 mg 2-HESI/g creatinine) (sampling next morning following an 8 h work shift).**
>
> ***OR***
>
> **20 mg 5-HNEP plus 2-HESI/L urine corresponding to 15 mg 5-HNEP plus 2-HESI/g creatinine (sampling next morning following an 8 h work shift at the end of the workweek)**

The most appropriate sampling time for 5-HNEP plus 2-HESI was proposed to be on the morning following an 8 h work shift, 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. In case high inhalation exposure is expected, 5-HNEP can be measured from post-shift samples to capture recent exposure.

The level of confidence of the biomarker DNEL has to be considered as medium to low since the human biomonitoring guidance values (David et al., 2021) were derived based on animal toxicity data as limited human toxicological data on NEP is available.

Analytical measurement systems exist to determine the biomarkers for DMAC (see Table 14).

Table 14: Potential analytical methods for biological monitoring for NEP

Method/type of sampling	Analytical technique	Limit of quantification LoQ	Reference
Urine, spot sample (workers)	GC/MS	45 µg 5-HNEP/L urine[1)] 15 µg 2-HESI/L urine[1)]	Schindler, Koslitz et al. (2012)
[1)] Limit of quantification (LoQ) converted from limit of detection (LoD) based on LoQ ~ 3 x LoD Abbreviations: GC: Gas Chromatography; MS: Mass Spectrometry			

[54] https://echa.europa.eu/documents/10162/75a0c497-69e0-1c74-689d-667bd49e47b9

Appendix 3. Typical uses of the substances

NMP, DMF, DMAC, and NEP are used predominantly as a solvent in the industrial production of other chemicals and in the industrial production of articles. In most uses, the solvents have to be removed during the production process and therefore are not part of the final products or recycled or disposed of as waste.

Table 15: Overview of typical uses of NMP, DMF, DMAC, and NEP[55]

Use description	NMP	DMF	DMAC	NEP
Process solvent in the industrial manufacture of other chemicals				
High volume chemicals *Typical processes:* *Extraction.*	Extraction processes to produce chemicals of importance like Butadiene, Acetylene, and Aromatics.			
Oil and gas products *Typical processes:* *Extraction.*	Extraction processes for the cleaning of oil and gas products and emissions from their production. Examples for processes requiring NMP are desulfuration, removal of carbon dioxide (CO_2), COS (carbonyl sulphide) and hydrogen sulfide (H_2S).	Extraction agent in petrochemical industry.		Extraction agent in petrochemical industry.

[55] From: Background document to the restriction dossiers and industry sources

Use description	NMP	DMF	DMAC	NEP
Other chemicals *Typical processes:* *Mainly closed systems. Elevated process temperatures possible.*	Solvent for chemical synthesis in the manufacture of other chemicals. This includes for example the production of bulk and fine chemicals, pharmaceuticals, and agrochemicals.	Solvent for chemical synthesis of fine chemicals, pharmaceutical active ingredients, crop protection ingredients and polymers.	Solvent for chemical synthesis in the manufacture of other chemicals. This includes for example the production of fine chemicals, pharmaceuticals, and agrochemicals.	Solvent for chemical synthesis in the manufacture of other chemicals. This includes for example the production of fine chemicals, pharmaceuticals, and agrochemicals.
Process solvent in the industrial production of articles				
Batteries *Typical processes:* *Mainly closed systems. Elevated process temperatures possible.*	NMP is used both in lithium-ion batteries as in other hybrid batteries using nickel, manganese, or cobalt lithiated oxides. In lithium-ion batteries it is used in the production of the cathode. In addition, NMP is used as a cleaning agent for process equipment.			
Microprocessors & semiconductor *Typical processes:* *Clean room environment. High level of containment and automation.*	Solvent in the electronics industry and for the production of printed circuit boards. In semiconductors, NMP is used as a carrier solvent in dedicated formulations and coating formulations, and as a manufacturing process aid for wafer cleaning and stripping.			Solvent in the electronics industry.
Membranes *Typical processes:* *Chemical industry standard*	Process solvent in the production of drinking water filtration, or dialysis.	Process solvent in the production of osmosis, ultrafiltration, or nanofiltration membranes.	Process solvent for the production of filters and membranes.	

Use description	NMP	DMF	DMAC	NEP
Man-made-fibres *Typical processes:* *Mainly closed systems. Elevated process temperatures possible.*	Process solvent in the production of polymer-based clothing/fibres e.g. for helmets, bullet proofed jackets etc.	Process solvent in the production of polyurethane coated e.g. textiles, artificial leather, membranes.	Spinning solvent in the production of fibres e.g. acrylic and polyurethanepolyurea copolymer and meta-aramid fibres.	
Winding wire *Typical processes:* *Metalworking industry. Mainly closed systems. Elevated process temperatures possible.*	Solvent in special enamels in the production of coated/insulated wire for coils.		Solvent in coatings e.g. polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation.	
Other coated articles *Typical processes:* *Mainly closed systems. Elevated process temperatures possible.* *For NMP different types of processes and tasks.*	Solvent in a wide range of different coatings.	Solvent for coating processes on the manufacture of non-metallic mineral products.		
Industrial cleaning operations				
Cleaning in place (CIP) *Typical processes:* *Closed systems. Elevated process temperatures possible.*	Used as a solvent for cleaning tanks and vessels.			Used as a solvent for cleaning tanks and vessels.
Industrial paint stripping *Typical processes:* *Closed systems or equipped with adequate ventilation.*	Used as a solvent for removing paint from aluminium, light alloys, iron, and steel.			Used as a solvent for removing paint from aluminium, light alloys, iron, and steel.

Use description	NMP	DMF	DMAC	NEP
Elevated process temperatures possible.				
Equipment cleaning *Typical processes:* *Manual operations.*	Used as cleaning solvent for industrial machinery and tools.			Used as cleaning solvent for industrial machinery and tools.

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