ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

Annexes

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

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

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

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

CONTACT DETAILS OF THE DOSSIER SUBMITTER:

Bureau REACH, National Institute for Public Health and the Environment (RIVM)

Antonie van Leeuwenhoeklaan 9

3721 MA Bilthoven, the Netherlands

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LIST OF ABBREVIATIONS

Acronym	Explanation
2BE	2-butoxyethanol
2-HESI	2-hydroxy-N-ethylsuccinimide
2ME	2-methoxyethanol
2-MeTHF	2-methyltetrahydrofuran
5-HNEP	5-hydroxy-N-ethyl-2-pyrrolidone
AC	Acetamide
ACGIH	American Conference of Governmental Industrial Hygienists
ACN	Acetonitrile
ACS	American Chemical Society
ALT	Alanine aminotransferase
AMD	N,N-dimethyl lactamide
AP	Alkaline Phosphatase
API	Active Pharmaceutical Ingredients
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BAT	Biological Tolerance Value
BEI	Biological Exposure Index
BLV	Biological Limit Value
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
BPR	Biocidal Products Regulation
BSP	Bromsulphthalein
BUN	Blood Urea Nitrogen
BW	Body weight
CA	Cellulose Acetate
CAD	Chemical Agents Directive
Cefic	European Chemical Industry Council
CES	Critical Effect Size
CfE	Call for Evidence
CI	Confidence interval
CLP	Classification, Labelling and Packaging
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DFG	Deutsche Forschungsgemeinschaft
DMA	Dimethylamine
DMAC	N,N-dimethylacetamide
DMEU	1,3 dimethyl-2-imidazolidinone
DMF	N,N-dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one
DMPA	Dimethylolpropanoic acid; 2,2-bis(hydroxymethyl)propionic acid

DMPU	1,3-dimethyl3,4,5,6-tetrahydro-2 (1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
DNEL	Derived No-Effect Level
DU CSR	Downstream User Chemical Safety Report
EHS	Environmental, Health and Safety
EtOH	Ethanol
EU	European Union
EWWA	European Winding Wire Association
FD	Framework Directive
FOB	Functional Observational Battery
FSH	Follicular Stimulating Hormone
GBL	Gamma-butyrolactone
GCI	Green Chemistry Institute
GD	Gestation Day
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
GM	Geometric Mean
GO	Graphene oxide
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
GTP	Glutamyltranspeptidase
HMPA	Hexamethylphosphoramide
IVC	Association of the German, Austrian and Swiss man-Made Fibres Industries
LD50	Median (50%) Lethal Dose
LDH	Lactate Dehydrogenase
LEV	Local Exhaust Ventilation
LH	Luteinizing Hormone
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LoD	Limit of Detection
LOQ	Limit Of Quantification
MAK	Maximum Workplace Concentration
MEK	Methyl ethyl ketone
MF	Microfiltration
MI	Methylimidazole
MIBK	Methyl isobutyl ketone
NBP	N-butyl pyrrolidone
NEP	1-ethylpyrrolidin-2-one
NF	Nanofiltration
NIPS	Non-solvent Induced Phase Separation
NMAC	N-methylacetamide
NMP	N-Methyl-2-Pyrrolidone
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level

OC	Operational Conditions
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OR	Odds Ratio
OSH	Occupational Safety and Health
PA	Polyamide
PAI	Polyamide-imide
PAN	Polyacrylonitrile
PBI	Polybenzimidazole
PCE	Power Conversion Efficiency
PDMS	Polydimethylsiloxane
PEG	Polyethylene Glycol
PEI	Polyesterimide
PES	Poly(ethersulphone)
PI	Polyimides
PoD	Point of Departure
PP	Polypropylene
PPPR	Plant Protection Products Regulation
PPSU	Poly(phenylsulphone)
PPTA	Poly(p-phenylene terephthalamide
PROC	Process
PS	Polystyrene
PSA	Polysulfonamide
PTFE	Polytetrafluoro-ethylene
PUD	Polyurethane Dispersion
PV	Photovoltaics
PVDF	Poly(vinylidene-fluoride
RCR	Risk Characterisation Ratio
rGO	reduced Graphene oxide
RMM	Risk Management Measures
RPE	Respiratory Protective Equipment
SCOEL	Scientific Committee on Occupational Exposure Limit Values
SKB	SmithKline Beecham
SPOS	Solid-Phase Organic Synthesis
SPPS	Solid-Phase Peptide Synthesis
SVHC	Substance of Very High Concern
TEGDA	Triethylene glycol diacetate
TG	Test Guideline
THF	Tetrahydrofuran
TIPS	Temperature Induced Phase Separation
TLV	Threshold Limit Value
TPU	Thermoplastic elastomer polyurethane
TRA	Targeted Risk Assessment
TWA	Time-Weighted Average

UF	Ultrafiltration
ULN	Upper Limit Normal

Annex A: Manufacture and uses

A.1. Manufacture, import and export

A.1.1. DMAC

N,N-dimethylacetamide (DMAC) is manufactured in the European Union (EU) and imported into the EU. A total of fourteen registration dossiers are currently active for DMAC. The total tonnage band of the full registration is between 10 000 and 100 000 tonnes per year. Registrants are located in Germany, the Netherlands, Ireland, Portugal, Hungary, Spain, Belgium, France and Northern Ireland (ECHA, 2021b). A total manufacturing volume of between 10 000 and 100 000 tonnes per year is also estimated based on aggregated information from chemical safety reports (CSRs). In addition, >1 000 tonnes are imported annually. No clear information on trends in manufacture and import is available. The estimated aggregated tonnage band is consistent with information obtained by ECHA in 2010 during the consultation on the Annex XV Substance of Very High Concern (SVHC) dossier. Submitted information points to a total manufacturing volume of DMAC in the EU in the range of 15 000 to 20 000 tonnes, a total import volume of DMAC on its own of between 1 000 and 2 000 tonnes and a total export volume of between 3 000 and 4 000 tonnes (ECHA, 2012a). DMAC was to some extent imported in mixtures, mainly for the production of fibres, and in articles as residual content (<3%) in fibres and films (ECHA, 2012a). Based on obtained data, the total annual consumption of DMAC in the EU as process chemical (solvent) and for the formulation of mixtures was estimated at 11 000 to 19 000 tonnes per year in 2010 (ECHA, 2012a). No clear information on trends in manufacturing and import volumes is available to the Dossier Submitter. The estimation may therefore be regarded as an appropriate indication for 2022.

DMAC is manufactured by the reaction of dimethylamine (DMA) and acetic acid in closed systems. The reaction takes place at elevated temperature and pressure and the substance is purified by distillation (ECHA, 2012a).

A.1.2. NEP

1-ethylpyrrolidin-2-one (NEP) is manufactured in the EU and imported into the EU. A total of five registration dossiers are currently active for NEP. The total tonnage band of the full registration is 100 to 1 000 tonnes per year. Registrants are located in Germany, the Netherlands, Ireland, Spain and Lithuania (ECHA, 2021a). Based on aggregated information from CSRs, a total manufacturing volume of between 1 000 and 10 000 tonnes per year is estimated by the Dossier Submitter. No clear information on trends in manufacture and import is available. Detailed information on the manufacturing process of NEP is also not available.

A.2. Uses

This section presents an overview of the main uses of DMAC and NEP in industrial and professional settings. Data presented in this chapter is based on information from the ECHA background document for DMAC (ECHA, 2012a), which draws on information obtained in the respective stakeholder consultation, non-confidential information from the registration dossiers and the Call for Evidence (CfE) conducted following the inclusion of this Annex XV restriction report in ECHA's Registry of Intentions.

In the EU, both DMAC and NEP are used as a solvent in various production processes and in a wide variety of applications in industrial and professional settings, which are further described below. For DMAC, there are no indications of consumer uses in the registration

dossiers. For NEP, several consumer uses have been identified based on a registration dossier, although other registrants advise against consumer use. Reported consumer uses include anti-freeze products, coating products, lubricants and greases, adhesives and sealants, air care products, surface treatment products for non-metal surfaces, inks and toners, leather treatment products, polishes and waxes as well as washing and cleaning products (ECHA, 2021a). Upon queries of the Dossier Submitter, the relevant registrant stated consumer uses to be obsolete or incorrect and reported an intention to update their registration dossier.

In 2019, a market survey, initiated by the German competent authority for REACH, aimed to identify paint removers available to consumers in Germany. One of the identified products, a graffiti remover offered through a web shop until the end of 2021, contained up to 20% of NEP according to the safety data sheet (SDS). As of 2022, this product is not available anymore. However, internet searches by the Dossier Submitter revealed the availability of graffiti removers containing between 50% and 100% of NEP in online web shops.

In the CfE conducted in support of the preparation of this Annex XV restriction report on DMAC and NEP, the German competent authority for REACH stated that – according to the Mintel Global New Product Database – NEP is used in nine cosmetic products in the European region. These products (seven nail polish products, one cleansing milk, and two make-up products; identified through a search on 24 February 2020) were introduced to the market between 2007 and 2017 (CfE, 2020). As risks to human health following use in cosmetic products are excluded from the scope of REACH Restriction under Article 67.2, this information on consumer uses of NEP in cosmetics is not deemed of relevance to this restriction report.

The online Nordic Products Register[1] (SPIN database; accessed in December 2021), which contains data about the substances in preparations in Nordic countries (Sweden, Finland, Norway and Denmark), indicates that DMAC and NEP may have been used in consumer formulations between 2000 and 2019. Precise information on consumer uses, specific product formulations and the size of the market could however not be obtained. The total number of reported preparations and the reported tonnages are displayed in Figure 1 and Figure 2.

Due to harmonised classification as Repr. 1B in Annex VI of the Classification, Labelling and Packaging (CLP) Regulation and following the provisions of Entry 30 of REACH Annex XVII, DMAC and NEP are prohibited for placing on the market for supply to the general public in concentrations greater than or equal to 0.3% by weight. The restriction applies to the substances themselves, in another substance (e.g. as impurity) and in mixtures. Based on this legal provision and concentration limit, no risks related to consumer use are anticipated by the Dossier Submitter. Mixtures for consumer use containing concentrations above 0.3% of DMAC or NEP, that could pose a risk to consumers, are outside the scope of this restriction proposal and should be removed from the market by national inspectorates and enforcement. The Dossier Submitter has no indication of potential risks in relation to the use of DMAC and NEP in consumer product formulations at concentrations below 0.3%.

[1] *SPIN: Substances in preparations in Nordic countries: www.spin2000.net/spinmyphp/*

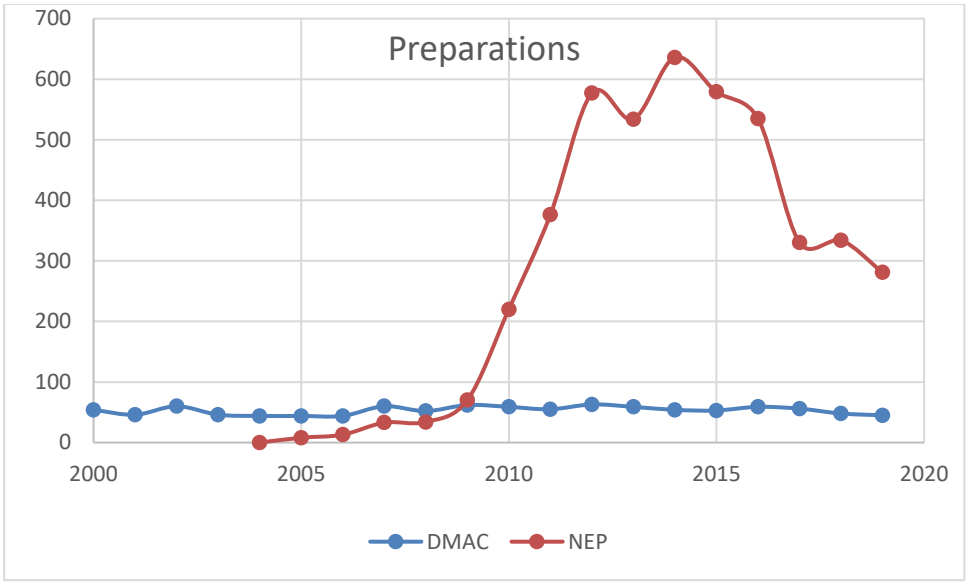

Figure 1: Number of preparations with DMAC and NEP in Sweden, Finland, Norway and Denmark from 2000 to 2019.

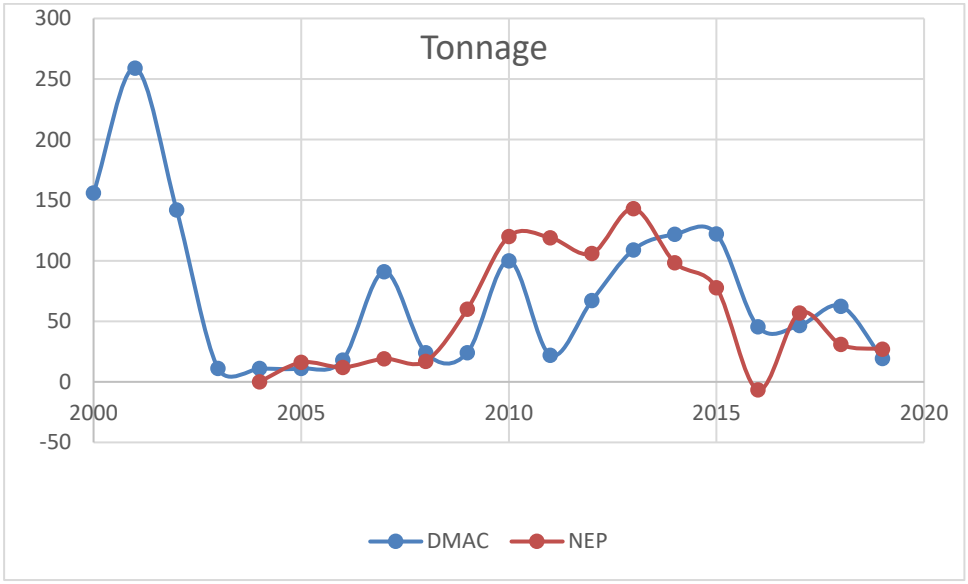

Figure 2: Reported tonnage of DMAC and NEP in Sweden, Finland, Norway and Denmark from 2000 to 2019.

With respect to articles, the Dossier Submitter notes that DMAC and NEP may be used as solvent in the manufacture of certain articles. Consequently, residual amounts of DMAC and NEP may be present in articles placed on the market for purchase by the general public. Information on typical residual concentrations in consumer articles or articles for professional users and on possible consumer exposure is not available for most uses. A recent query directed at the Dutch Food and Product Safety Inspectorate (personal communication, May 2021) showed no records of chemical analyses of residues in articles and in productformulations. In addition, a search in the EU Safety Gate[2] rapid alert system for angerous non-food products (conducted in May 2021) resulted in no findings for DMAC and NEP.

[2] *https://ec.europa.eu/safety-gate-alerts/screen/webReport*

A.2.1. DMAC

According to information in the background document for DMAC prepared by ECHA (ECHA, 2012a), inputs received through the CfE (CfE, 2020) and related follow-up communication, the main uses for DMAC in Europe are:

- Process solvent and reagent (65-70% of tonnage) in the production of:
  - Agrochemicals;
  - Human and veterinary pharmaceuticals, including excipient (carrier ingredient);
  - Fine chemicals;
- Process solvent for spinning of fibres of various polymers (20-25% of tonnage) including:
  - Acrylic fibre;
  - Polyurethanepolyurea copolymer fibres (elastane, Spandex);
  - Meta-aramid fibres;
- Solvent in coatings used for electrical wire insulation (3-5% of tonnage), e.g. polyamide-imide (PAI) enamels (varnishes);
- Process solvent in the production of polysulphone membranes (<1% of tonnage); and
- Other uses (<3.5% of tonnage), e.g.
  - Laboratory uses;
  - Petrochemical applications; and
  - Cellulose fibres.

A.2.1.1. Process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals

DMAC is a dipolar aprotic solvent with high solving power for high molecular weight polymers. The solvent is miscible with - and can be used for - a wide range of organic and inorganic compounds. The polar nature of DMAC enables it to act as a combined solvent and reaction catalyst in many reactions. Furthermore, its boiling point (166ºC) allows reactions to be carried out at much higher temperatures than would be achievable in many organic solvents, without the need to operate under pressure. DMAC is reported to be used to some extent as intermediate for chemical synthesis (ECHA, 2012a).

- Agrochemicals (e.g. fertilizers, pesticides)

Agrochemical use of DMAC refers to its use in the chemical synthesis of active ingredients in industrial installations or small-scale industrial laboratory use for quality assurance purposes. Because DMAC is a Reprotoxic 1B substance, there is no use of DMAC in agrochemical formulations (#21A in ECHA, 2012d).

- Pharmaceutical use (e.g. in antibiotics, novel contrast media and veterinary medicines)

DMAC is used as a solvent within pharmaceutical research and development laboratories, pilot manufacturing plants and commercial manufacturing plants (#1 in ECHA, 2012d). The main use of DMAC in the pharmaceutical industry is as process solvent, e.g. in the chemical synthesis of active ingredients. The use is regulated under pharmaceutical regulation with limitations for residual DMAC concentrations in pharmaceuticals (EMA, 2021). DMAC is also used as solvent in the manufacturing process of a contrast media for diagnostic imaging (CfE, 2020). In addition, DMAC is used as excipient (carrier ingredient) in human and veterinary pharmaceuticals due to its polar, aprotic characteristics (ECHA, 2012a).

In the production of veterinary medicines, DMAC is used in three different steps of the process (CfE, 2020), i.e.:

- During the synthesis of the active substance;
- During manufacturing of the excipient; and
- As excipient itself.

Many veterinary medicinal products contain DMAC as excipient mainly in injectable and transcutaneous forms.

- Fine chemicals

There is some small-scale laboratory use for quality assurance of DMAC itself or laboratory research use at industrial sites or at universities (#21A in ECHA, 2012d).

The total number of companies in the EU involved in the use of DMAC as process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals was estimated at between 100 and 1 000 in 2010 (ECHA, 2011a). ECHA's background document reported that there was no conclusive data but at least tens of sites could be concluded to be using DMAC in the synthesis of other substances (ECHA, 2012a). The use of DMAC as process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals is generally understood to be limited to a small number of users consuming high DMAC volumes in closed industrial installations (ECHA, 2012a). This information from 2012 is still valid according to the lead registrant.

In follow-up communications to the CfE, stakeholders reported that DMAC is recovered during the production process. Recovery from the final product is reported be very efficient and DMAC is reported to be re-used several times as solvent in chemical synthesis before ending up in chemical waste streams.

A.2.1.2. Process solvent for spinning of fibres of various polymers

The second largest application area of DMAC is as spinning solvent in the production of fibres of various polymers. The use of DMAC is of particular relevance for the production of continuous filament fibres and to a lesser extent for the production of non-continous fibres – whereby continuous filament fibres are suitable for weaving, knitting and carpet production. Non-continous fibres can be spun into yarns or used as fillings (ECHA, 2012a).

According to information reported in the background document for DMAC prepared by ECHA (ECHA, 2012a), the CfE (CfE, 2020) and related follow-up communication, the main types of fibres produced with DMAC are:

- Acrylic and polyurethanepolyurea copolymer (Spandex) fibres; and
- Meta-aramid fibres.

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

During fibre production, DMAC acts as the solvent in the polymerization reaction and helps with transfering the polymer through the spinning process to produce very fine fibres. To some extent, DMAC is also used in mixtures applied with the purpose of adding specific additives or other polymers to the fibre spinning process. When DMAC is used, solidification is achieved either by precipitation in a chemical bath where the spinneret is submerged – so called wet spinning – or by evaporating the solvent in a stream of air or inert gas, named dry spinning (ECHA, 2012a).

In the production of acrylic and Spandex fibres, DMAC (on its own) is reported to be used as a solvent in relation to polyacrylonitrile and polyurethane (CfE, 2020). DMAC is reported to be predominantly used in the wet spinning process. As of 2022, 100% of acrylic fibres produced in the EU are produced by wet spinning production lines, while the global share of wet spinning processes is slightly lower at 90% (industry consultation).

The Association of the German, Austrian and Swiss man-Made Fibres Industries (IVC) reports an annual use of around 1 900 tonnes of DMAC as of 2020 by six fibre producers located in the EU (CfE, 2020). Two production sites in Germany have however ceased production in 2021 and 2022. The total annual use volume of the man-made fibre industry has thus likely decreased. DMAC is recovered and recycled several times in this process, with recovery rates exceeding 99%. The consumption of DMAC (0.5-1% per cycle) is due to solvent losses caused by the acid hydrolysis during recovery, environmental releases, solvent residues in produced fibres and DMAC being disposed of as waste from the process. Recovery is reported to be achieved by installations comprising a distillation unit, a squeezing column unit and a DMAC stripping unit (ECHA, 2012a). Reported recovery rates were confirmed in follow-up communications to the CfE.

The fibres are further processed (transfer and filling operations, rewinding and beaming, spinning of yearn, and knitting or weaving) in order to produce the fabric, which will consequently be dyed and/or washed). Typically, DMAC is present as a residue at significant concentration only in the first steps of fibre processing. Raw fibres may contain up to 3% of residual DMAC, but according to industry the typical DMAC content of raw fibres is between 0.1 and 0.5%. The greige fabric, i.e. the unbleached or undyed fabric, normally contains DMAC at levels below 0.1%. This concentration will be further reduced during dying and washing. No detectable or very low level of residual DMAC is reported to be present in final textiles (e.g. in baby diapers, residues are reportedly at parts per billion, i.e. ppb, levels). Employed processing techniques are reported to have an influence on the residual content of DMAC. Spun dyed fibres, which are dyed during fibre production are, for example, found to contain higher residues than fibres dyed using convential processes due to a comparatively lower use of water and other chemicals (ECHA, 2012a).

As a result of the residual concentrations of DMAC in fibres, occupational exposure may not only occur during fibre production but also during further processing of fibres. Inhalation exposures of equal magnitude of those relating to fibre production cannot be excluded (ECHA, 2012a).

Up to 2021, six companies in the EU were involved in the use of DMAC as process solvent for spinning of fibres of various polymers with about 750 potentially exposed workers (CfE, 2020). In 2021 and 2022, two of the six companies closed (one for the production of acrylic fibres[3] and one for the production of Spandex[4]) affecting about 350 employees of which an unknown proportion was potentially exposed (industry consultation). As of 2012, 100 to 1 000 companies were estimated to be involved in the processing of raw fibres, while over 1 000 were estimated to produce textiles (ECHA, 2012a).

While clothing textiles are the major application area for the aforementioned fibres, the fibres are to some extent also used for technical applications. Examples are:

- Fibreglass/meta-aramid nonwoven (felt) fabrics used for aerospace composites;
- Surface tissue made of polyacrylonitril used in fibre reinforced plastics (e.g. for truck cabins);
- Meta-aramid fibres in different systems where typical properties of textiles should be adapted to high ambient temperatures, e.g. filters for hot gas filtration and fire protective clothing; and

[3] *https://wip-kunststoffe.de/wip/nachrichten/969351-dralon-lingen-wird-geschlossen/*

[4] *https://www.the-spin-off.com/news/stories/The-Materials-Asahi-Kasei-to-close-its-European-production-site-16096*

- Paper made from synthetic meta-aramid polymer in two physical forms, i.e. short fibres (floc) and microscopic fibrous binder particles (fibrids). The paper is widely used in two major end uses including (i) insulation for electrical equipment applications in liquid and dry transformers, motors, and generators and (ii) structural composites (ECHA, 2012a).

Given their high resistance to high temperature, chemical degradation, and abrasion, meta-aramid fibres are furthermore used for military suits (used by Special Forces and pilots) and protective clothing in industrial settings to protect workers against electrical shock in addition to their use in protective clothing for firemen (industry consultation).

Examples of meta-aramid fibres, which are more commonly known by their trade names are the original Nomex® (DuPont) fibre and subsequently developed commercially available fibres, such as Conex® (Teijin), Apyeil® (Unitika), and Fenilon® (Russia), some of which may now no longer be available (Horrocks, 2016). Meta-oriented aromatic polyamides can be processed into meta-aramid fibres or films on solution in polar aprotic solvents, e.g., hexamethylphosphoramide (HMPA), N-methyl-2-pyrrolidone (NMP), DMAC, and N,N-dimethylformamide (DMF) (Bandyopadhyay et al., 2015; Vu, 2018) . DMAC is reported to be the sole solvent used in the EU-27 (industry consultation).

Acrylic fibres are also used as precursor fibres for the production of carbon fibres used, for example, in wind energy plants or the construction of carbon-concrete for light-weighted bridges (ECHA, 2012a). More than 90% of commercial carbon fibres are made from acrylic precursor fibres that are produced through wet spinning (Khayyam et al., 2020). Solvents reported to be used in the wet spinning of acrylic precursor fibres are DMF, zinc chloride, sodium thiocyanate, DMAC and dimethyl sulfoxide (DMSO) (Huang, 2009; Nunna et al., 2019). The wet-spinning solvent is one of the parameters affecting the physical and thermochemical properties of precursor fibers along with the copolymer structure, the dope solid content, the temperature of dope and the coagulation bath, the solvent/non-solvent ratio of the coagulation bath, the jet stretch, and the steam drawing ratio (Fakhrhoseini et al., 2018).

A.2.1.3. Solvent in coatings e.g. polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation

The use of DMAC as solvent in coatings is related to the production of PAI enamels for electrical wire insulation (2% of DMAC use in Europe), but manufactures of DMAC have indicated that the substance is used for other coatings as well (ECHA, 2012a). PAI enamel (varnish) is a special coating application applied in a closed system and under controlled conditions. DMAC in the PAI enamels is anticipated to be decomposed at the elevated temperatures at which the application of the enamels in industrial settings takes place (industry consultation). According to the European Winding Wire Association (EWWA), the maximum concentration of DMAC in varnishes is 15%.

PAI-based enamel is one of the most important insulating enamels in electrical engineering and widely used for enamels on wires used for various electrical parts, e.g. electrical motors, generators and transformers. These electrical parts are used for a wide range of applications in vehicles, electrical appliances, electrical tools, and in relation to electricity production. Applications vary widely in size and range from small motors in watches to motors for high-speed trains as well as small transformers in cellphone battery recorders to transformers employed in power plants. Wire diameters and enamel application rates vary accordingly (industry consultation).

Approximately 15 companies, with 2 000 to 2 500 employees, are active within the European winding wire industry. Of those employees, between 1 500 and 2 000 are estimated to potentially be exposed to DMAC (CfE, 2020).

A.2.1.4. Process solvent in the production of polysulphone membranes

In the EU, DMAC is used by the medical device industry as a solvent for the production of filters and membranes which are then used in dialysis treatment (used for renal replacement therapy) and other lifesaving extracorporeal therapies (CfE, 2020; ECHA, 2012a). DMAC-based membranes produced in the EU are reported to be used for the regular treatment of over 100 000 patients in the EU and 500 000 patients worldwide (CfE, 2020). Residual DMAC is present at concentrations below 0.01% in membranes for medical devices used by downstream users (#4 in ECHA, 2012d).

The substance serves as solvent in the spinning solution consisting of polysulphone and poly-N-vinylpyrrolidone (PVP), in a continuous wet spinning process, which is the state-of-art process for hollow fibre production (ECHA, 2012a). In addition, DMAC can be used as a solvent for polyethersulphone membrane production through the precipitation bath process (#3 in ECHA, 2012d). The membrane forming polymer (e.g. polyethersulphone) and several process aids (e.g. pore-forming agents) are physically dissolved in DMAC as the only solvent or the main component in a solvent mixture. The viscous polymer solution is continually precipitated as a thin, liquid film in a non-solvent (precipitation bath) whereby the solid membrane forms with the desired structure and pore size distribution. When the miscibility gap of the polymeric solution is exceeded, the polymer precipitates, thereby forming a solid, highly porous, sponge-like structured membrane. These membranes are used in pharmaceutical and food applications (#3 in ECHA, 2012d). It is however unclear if the use of DMAC as solvent for polyethersulphone membrane production by the precipitation bath process still occurs in Europe. Upon contact, the company that described the use of DMAC in this process now states that all their polyethersulphone membranes do not need DMAC in their production process by the end of the third quarter in 2022 (industry consultation).

Approximately six companies with an estimated 500 to 1 000 employees use DMAC in the production of medical membranes within Europe (CfE, 2020).

A.2.1.5. Other uses

The background document for DMAC prepared by ECHA in 2012 (ECHA, 2012a) describes the following other applications (probably accounting for <3.5% of tonnage):

- Solvent in paint strippers (<1%): Although the 2012 background document (ECHA, 2012a) mentions SDSs indicating DMAC in concentrations in the range of 0.1% to 5%, there is currently no indication of DMAC being used in paint strippers in commercial products.
- Petrochemical applications
- Laboratory use (0.3%-0.6%): There is some small laboratory use for quality assurance of DMAC itself or laboratory research use at industrial sites or at universities (CfE, 2020).
- Filling and packaging for scientific research and development
- Adhesives
- Plastic and anti-set off agents in polymer moulding and casting
- Potentially in sealants, putty, paints and lubricants in metal working fluids,
- Production of cellulose fibres such as cellophane
- A minor use in ink removers, < 0.01 tonnes in eraser pens, has been reported to be ceased from mid-2012 onwards.

A.2.2. NEP

NEP is used as industrial solvent (Koch et al., 2014), catalyst and cationic surfactant (ECHA, 2011b; Saillenfait et al., 2007). NEP is used in many applications as substitute for the structural analogue NMP, e. g. for surface coatings, in cleaning agents for metals, glass and plastics, in washing agents and in paint strippers (Saillenfait et al., 2016; Schmied-Tobies et al., 2021; Umweltbundesamtes, 2015). It is used in varnishes in a spraying department of an automobile plant (Koslitz et al., 2014). It is reported to be used as solvent or co-solvent in the manufacture of pesticides. The presence of NEP in 30 commercial liquid pesticides could not be demonstrated (Li et al., 2018). Other uses include applications in the pharmaceutical and electronics industries (Saillenfait et al., 2016). The use of NMP and NEP in cosmetic products has been banned in 2019 (Schmied-Tobies et al., 2021). The possible use of NEP in consumer products has been mentioned above in Section A.2.

One registration dossier indicates the following additional industrial or professional uses for NEP:

- Water treatment chemicals
- Oil field drilling and production operations
- Binders and release agents
- Polymer processing
- Agrochemicals
- Road and construction applications

The registrant indicated that these additional industrial or professional uses have been abandoned for NEP. However, this has not been reflected in an updated registration dossier by April 2022.

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

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

Further enquiries directed at the relevant chapter of the European Chemical Industry Council (CEFIC), the 1,4 butanediol Derivatives Sector Group, resulted in additional information on the use of NEP in coatings. An increase of the use of NEP in coatings was observed in the last ten years after the classification of NMP as reprotoxic. However, the use of NEP in coatings has either already been phased out by companies or is expected to be phased out. Specialised coatings might still contain NEP although in very low concentration (<0.1%) (industry consultation).

A.3. Uses advised against by the registrants

A.3.1. DMAC

No uses advised against

A.3.2. NEP

Consumer use is advised against by some, but not all, registrants.

Annex B: Information on hazard and risk

B.1. Identity of the substance(s) and physical and chemical properties

Described in the main report

B.2. Manufacture and uses (summary)

The following uses of DMAC (Table 1) and NEP (Table 2) are identified for the risk assessment.

Table 1: DMAC use overview

Use	Resulting life cycle stage				Process Category (PROC)
	Manufacture	Formulation	End use		
			Industrial	Professional	
Manufacturing	x		x		1, 2, 3
Formulation		x	x		3, 4, 5
Charging and discharging			x		8a, 8b, 9
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals			x		1, 2, 3, 4
Use as solvent in the production of man-made fibres			x		1, 2, 3, 4, 13, 14, 19, 21
Use as solvent in coatings			x		7, 10, 13
Use as solvent in the production of films			x		1, 2, 3, 4
Use as laboratory chemical			x	x	15
Use of DMAC in other applications			x	x	-

Table 2: NEP use overview

Use	Resulting life cycle stage	Process Category (PROC)

	Manufacture	Formulation	End use		
			Industrial	Professional	
Manufacturing	x		x		1, 2, 3, 4
Formulation and (re)packing		x	x	x[##]	1, 2, 3, 4, 5, 14
Charging and discharging			x	x	8a, 8b, 9
Use in industrial chemical processes			x		1, 2, 3, 4
Use as solvent in coatings			x	x	7, 10, 11, 13, 19
Use as laboratory chemical			x	x	15
Use as binder and release agent			x	x	6, 7, 10, 11, 13, 14
Use in cleaning agents[#]			x	x	7, 10, 11, 13
Use in oil field drilling and production operations			x	x[##]	1, 2, 3, 4, 8a, 8b
Use in agrochemicals				x	1, 2, 4, 8a, 8b, 11, 13
Use in functional fluids			x	x	1, 2, 3, 4, 8a, 8b, 9, 20
Use in road and construction applications				x	8a, 8b, 9, 10, 11, 13
Polymer processing			x	x	1, 2, 3, 4, 5, 6, 8a, 8b, 9, 13, 14, 21
Water treatment chemicals			x		1, 2, 3, 4, 8a, 8b, 13

B.3. Classification and labelling

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

Described in the main report.

B.3.2. Classification and labelling in classification and labelling inventory/ Industry's self classification(s) and labelling

All notifiers used the harmonised classification given in section B.3.1, according to the Classification and Labelling Inventory.

B.4. Environmental fate properties

Not relevant for this proposal

B.5. Human health hazard assessment

B.5.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

B.5.1.1. DMAC

The information on toxicokinetics were adapted from the OECD SIDS (OECD, 2001) and summary in the CSR prepared by the lead registrant. The toxicokinetic properties of DMAC were studied in rodents (rats and mice), primates and humans.

Absorption
DMAC is readily absorbed into the mammalian system following oral, dermal and inhalation exposure. Oral absorption after a single gavage treatment with radiolabelled DMAC was quantified in rats (Kennedy, 1986; Monsanto, 1974; reliability not assignable, performed at Industrial Bio-test Labs). The oral absorption was above 80% indicating nearly quantitative absorption. The percentage of dermal and inhalation absorption has not explicitly been determined in animals or humans. The molecular weight below 100, the log P of -0.77 and the vapour pressure of 2 hPa are in favour of a higher potential of inhalative than dermal absorption. A skin permeability constant of 10.7 ± 1.9 mg/cm²/h was determined *in vitro* using human skin (Ursin et al., 1995) and observations indicative for rapid dermal absorption (not quantified) were seen in rabbits after occlusive dermal exposure to DMAC (Finlay et al., 2001). Rapid absorption upon inhalation was indicated in rats and mice as peak plasma concentrations were reached <2h within initial exposure (Hundley et al., 1994).

Two male volunteers were exposed to DMAC vapour (10 ppm, 2×3 h) a) via inhalation and dermal route in an exposure chamber (most part of the body naked) or b) only via the dermal route (breathing of normal air outside the chamber via mask; (Maxfield et al., 1975)). The highest urine concentration of N-methylacetamide (NMAC, 45-100 ppm) was found in a). In b) the values were in the range of 6 to 23 ppm. The difference in the amount of NMAC excreted following exposure with and without the mask in a) and b) indicated that more DMAC vapour was absorbed through the lungs than through the skins. 70% and 30% of the DMAC metabolite NMAC excreted were attributed to absorption through the lungs and skin, respectively. The results show that dermal absorption contributes significantly to the overall amount of systemically available DMAC following vapour exposure. In this same study DMAC liquid (375 mg) was applied to the skin of four male volunteers once daily for five consecutive days and urine samples were collected twice daily for ten days starting from the first exposure (Maxfield et al., 1975). The absorbed dose varied from 38 to 197 mg (10-53%). The highest concentrations of NMAC were found in the urine sampled in the afternoon and a significant correlation between estimated dose and urinary NMAC concentration was found. The estimated dose DMAC recovered as NMAC in the urine was 2 to 10%.

In another study twelve male volunteers were exposed to DMAC vapour (6.1 ± 1.3 ppm for 4 h) via the dermal route (inside a whole-body-type exposure chamber while 90% of their skin was naked and inhalation of fresh air via a respirator) or inhalation route (exposed to DMAC vapour via a respirator) (Nomiyama et al., 2000). Dermal and respiratory absorption were calculated as the area under the curve of urinary concentrations of NMAC. The individual dermal absorption rates defined as dermal absorption over dermal plus respiratory absorption

fluctuated widely between 12.9% and 73.3%. Mean dermal absorption was estimated to be 40.4% of total urinary NMAC. DMAC vapour was significantly absorbed through the skin.

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

Metabolism, Distribution & Excretion
Three male rats were exposed to 5 ppm of ^{14}C-DMAC for 12 hour. DMAC was found in the urine (41% of total recovered ^{14}C), and in the faeces and expired air (14% and 15% of total ^{14}C, respectively). At the end of the post-exposure period, the carcass and tissues contained about 22% of the total ^{14}C. Fat and muscles were major sites of retention (Monsanto, 1982b). Male Crl:CD BR rats and male Crl:CD-1(ICR)BR mice were exposed (whole body) to 50, 150, 300 and 500 ppm DMAC with single exposures (1, 3 or 6 hour) or repeated exposures (6 hour for ten times). DMAC plasma half-life in rats ranged from 0.6 to 1.5 hour and persisted in plasma for at least 24h after the 150, 300 and 500 ppm exposure. Regardless of exposure level, repeated DMAC exposures resulted in plasma profiles of DMAC and NMAC similar to those from a single exposure (Hundley et al., 1994).

Pregnant Sprague-Dawley rats (n=12) were gavaged once with 500 mg DMAC/kg bw at gestation day (GD) 15 (BASF, 2001). Similarly, two pregnant monkeys (*Macaca fascicularis*) were gavaged once with 500 mg DMAC/kg bw on GD 100 or GD 105 (BASF, 2000). The maximum DMAC concentration was reached 1-2 h and 2-8 h after gavage in rats and monkeys, respectively. In both species, high concentrations of DMAC were already found 0.5 h after treatment (70% and 40% of Cmax in rats and monkeys, respectively). In both species, DMAC excretion was the highest during the first 12 hours after gavage; NMAC concentrations increased in the second half of the post-treatment period (12-24 h) and were the highest at termination (24 h after treatment). Maternal and foetal DMAC and NMAC levels were comparable 24 h after gavage (very similar DMAC and NMAC concentrations were noted in amniotic fluid and maternal plasma in rats, and in maternal and foetal serum in monkeys).
There are some human data on excretion of DMAC in which urine samples from 5 workers were examined for 4 consecutive weeks (Kennedy Jr & Pruett, 1989). Airborne DMAC appeared to account for the greatest amount of urinary NMAC detected at the exposure concentrations encountered (0.5 to 2 ppm). A relationship of 10 ppm urinary NMAC for each 1 ppm DMAC inhaled was observed.

A study with twelve healthy male volunteers was conducted (Nomiyama et al., 2000). They were exposed twice to DMAC for 4 h at intervals of 96 h or above to 6.1 ppm for dermal (whole body with respiratory mask) and for inhalation exposure (nose-only). Biological half-lives of urinary NMAC were 9 h and 5.6 h via skin and lung respectively.

B.5.1.2. NEP

A single toxicokinetic study is available with NEP in Sprague Dawley rats and in humans. Further information on toxicokinetics were adapted from the summary in the CSR prepared by the lead registrant. This information was mainly derived based on toxicology studies.

Absorption

NEP is bioavailable via all routes (oral, dermal, inhalation) as demonstrated by effects in the acute inhalation toxicity study (aerosol 5.1 mg/l), in the 90 -day oral repeated dose toxicity study with rats and in the oral and dermal teratogenicity studies in rats and rabbits.

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

Metabolism & Excretion
In a human study, 20.9 mg NEP was orally dosed to three male volunteers (Koch et al., 2014). These volunteers collected all their urine samples over a period of 4 days post dose. In these samples, the NEP metabolites 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy-N-ethylsuccinimide (2-HESI) were identified and quantified and determined their urinary elimination kinetics and their metabolic conversion factors. NEP is rapidly biotransformed by hydroxylation to 5-HNEP, which is further oxidized to N-ethylsuccinimide; this intermediate is further hydroxylated to 2-HESI. This is expected to be the main metabolism pathway. After 4 days, 50.7% of the dose was recovered as these two metabolites in urine (29.1% as 5-HNEP and 21.6% as 2-HESI). Maximum concentrations (mean of the three individuals) for 5-HNEP occurred approximately 7 h and for 2-HESI approximately 18 h post dose (based upon mg/L values). Within the first 24 h after exposure, 33.3% of the oral NEP dose was excreted as the two metabolites (26.4% as 5-HNEP and 6.9% as 2-HESI) in the urine. On day two, another 10.5% of the dose was excreted, with 2-HESI being the major metabolite (8.2%) and 5-HNEP representing only a minor share (2.3%). Elimination half-times, determined mathematically from the mg/L and creatinine-adjusted concentrations over time via the rate constant k (halftime = ln(2)/k) were approximately 7 h for 5-HNEP and 22-27 h for 2-HESI, depending on whether mg/L or creatinine-adjusted concentrations were used for calculation. The range of elimination half-times for 5-HNEP (5.5–8.5 h) was rather small both between the individuals and the underlying concentration dimension. The range for 2-HESI was considerably larger (17.4–29.9 h). While the elimination of 5-HNEP was basically finished 72h post dose, significant amounts of 2-HESI were still eliminated after 96h. All the potential metabolites named above are at least slightly more water soluble than the parent chemical and have a molecular weight lower than 500 Dalton. Therefore, NEP and its metabolites are expected to be excreted predominantly via the urine. Excretion via urine is proven by orange or reddish discoloured urine, which was observed in all substance-treated rabbits in the oral teratogenicity study. This is most likely due to the excreted test compound or its metabolites.

As described by Schindler et al. (2012) trace levels of both 5-HNEP and 2-HESI could already be detected in the pre-dose sample of volunteer 1 originating from a suspected background exposure of the general population to NEP. However, these pre-dose levels of 5-HNEP (0.070 mg/L) and 2-HESI (0.077 mg/L) were considerably lower than the levels observed after the controlled dosage of this study. The pre-dose metabolite levels of volunteers 2 and 3 were below the limit of detection (LoD) of the analytical method. Thus, the background exposure to NEP did not interfere with the study design to investigate elimination kinetics and metabolic conversion factors.

In general, the elimination half times of NEP are in rather good accordance to the known elimination half times of the analogous NMP metabolites determined from three individuals after oral exposure to 100 mg NMP of ~4 h for 5-HNMP and of ~17 h for 2-HMSI (Akesson & Jönsson, 1997). The primary hydroxylated metabolites of both N-alkyl pyrrolidones are eliminated much faster than the later-stage succinimide metabolites. However, the data on NEP compared to the previously published data on NMP indicate that the elimination half times of the NEP metabolites seem to be somewhat longer than elimination half times of the NMP metabolites.

Bury et al. (2019) investigated the metabolism and excretion of NEP after repeated oral dosing in pregnant and non-pregnant Sprague Dawley rats. The rats received a daily dose of NEP by gavage of 50 mg/kg bw/day (assumed to cause maternal toxicity, but not developmental toxicity) for 14 days and in case of the pregnant rats this was from GD 6-19. The toxicokinetics were also investigated after single dosing in non-pregnant rats only (Bury et al., 2019). Similar to in humans, NEP metabolized quickly to 2-HESI and 5-HNEP. The half-life of NEP was estimated to be 1-2 hours. After a single oral dose of 50 mg/kg bw of NEP to non-pregnant female rats, Tmax for NEP (1 h) and its metabolites 5-HNEP (4 h) and 2-HESI (8 h) were similar to those of NMP (1 h) and its respective metabolites 5-HNMP (4 h) and 2-HMSI (6–12 h) after a single oral dose of 125 mg NMP/kg bw (Carnerup et al., 2005). The mean renal conversion factors (Fue) for 5-HNEP in rats after single oral dosages were similar to those in humans (1.0- and 1.4-fold higher as investigated by (Koch et al., 2014)) at the two lower doses investigated (5 and 50 mg/kg/day), but 1.7- to 1.8-fold higher at 250 mg/kg/day. Conversely, Fue for 2-HESI was generally lower in rats compared to humans (0.28- to 0.38-fold at the lower doses and 0.13- to 0.16-fold at 250 mg/kg/day). According to the authors, similar interspecies differences have been previously reported when comparing human and rodent data for the metabolism of NMP.

Effect of pregnancy
There were marked differences between non-pregnant and pregnant rats at late gestation (Bury et al., 2019). After repeated administration, elimination of NEP from plasma was slower in pregnant rats compared to non-pregnant rats with Area Under the Curves (AUCs) and T1/2 twice as high in pregnant rats. Plasma NEP (median concentrations) ratios between pregnant and nonpregnant rats (repeated dose) were 1.07 (1 h), 1.67 (4 h), 21.2 (8 h), and 643 (16 h). Metabolism was also affected. Here, the plasma 5-HNEP (median concentrations) ratios between pregnant and non-pregnant rats (repeated dose) were 0.38 (1 h), 0.51 (4 h), 0.93 (8 h), and 13.3 (16 h). In case of 2-HESI, the ratios were 6.52 (1 h), 1.50 (4 h), 0.70 (8 h), and 10.2 (16 h). This outcome might be related to reduced hepatic levels of several cytochrome P450 (CYP) enzymes in rats during pregnancy, including CYP2E1.
The placental transfer of NEP on GD 19 was rapid. Both NEP and 5-HNEP in foetal plasma and amniotic fluid (at the end of pregnancy) were similar to those in maternal plasma already 1 h after dosage. The kinetic profiles of NEP and 5-HNEP were comparable in the mothers and the foetuses. However, significant lower concentrations of 2-HESI were found in foetal plasma compared to the dams. This suggests a lower placental transfer or lower metabolic capacity of the cytochrome P450 oxidase system in the foetus.

B.5.2. Repeated dosed toxicity

Information on DMAC and NEP was obtained from a literature search, the registration dossiers, previous CLH proposals on DMAC (ECHA, 2013) and NEP (ECHA, 2011c) and the OECD SIDS for DMAC (OECD, 2001). Effects described in tables are significant, unless stated otherwise. Effect levels not specified with data are indicated as 'not specified.

B.5.2.1 Animal data

B.5.2.1.1 DMAC

A summary of the studies and the adverse effects are found in Table 3 below:

Table 3: Summary of studies informing on effects after repeated exposure to DMAC

Species, strain, number and sex/group	Study type, duration, dose levels	NOAEC/NOAEL, relevant findings, remarks	Reliability	Reference
Inhalation				
Rat Crl: CD BR 87 m 87 f OECD guideline 453 GLP	Combined chronic toxicity and carcinogenicity study 2 years 0, 25, 100, 350 ppm (0, 90, 360, 1260 mg/m^3, whole body, vapour) 6h/day, 5d/week	<u>Males</u> NOAEC: 25 ppm (90 mg/m^3) 100 ppm: BW ↓ (-5%, n.s.), BW gain ↓ (-8%, n.s.), rel. liver weight ↑ (22%, n.s.), rel. kidney weight ↑ (25%, n.s.), hepatic focal cystic degeneration ↑ (44% vs. 26% in control), accumulation of pigments in Kupffer cells ↑ (8% vs. 2% in control, n.s.), hepatic peliosis ↑ (11% vs. 5% in control, n.s.), severe chronic progressive nephropathy (19% vs. 15% in control, n.s.) 350 ppm: BW ↓ (-10%, n.s.), BW gain ↓ (-16%, n.s.), rel. liver weight ↑ (34%), rel. kidney weight ↑ (70%), hepatic focal cystic degeneration ↑ (50% vs. 26% in control), accumulation of pigments in Kupffer cells ↑ (34% vs. 2% in control), biliary hyperplasia (79% vs. 57% in control), hepatic peliosis ↑ (13% vs. 5% in control), severe chronic progressive nephropathy ↑ (32% vs. 15% in control) <u>Females</u> NOAEC: 100 ppm (360 mg/m^3) 350 ppm: BW ↓ (-11%), BW gain ↓ (-17%, n.s.), rel. liver weight ↑ (10%, n.s.), rel. kidney weight ↑ (21%), accumulation of pigments in Kupffer cells ↑ (20% vs. 3% in control) No increase in tumor incidences observed in both males and females.	1	DuPont (1994); Malley et al. (1995)
Rat F344/DuCrlCrlk 50 m 50 f OECD guideline 451 with deviations GLP	Carcinogenicity study 104 weeks 0, 18, 90, 450 ppm (0, 65, 324, 1620 mg/m^3, whole body, vapour) 6h/day, 5d/week	<u>Males</u> NOAEC: 18 ppm (65 mg/m^3) 90 ppm: cholesterol ↑ (45%), blood triglycerides ↑ (44%), blood phospholipids ↑ (37%), gamma-GTP ↑ (183%), BUN ↑ (24%), abs. liver weight ↑ (10%), rel. liver weight ↑ (14%), adipose liver degeneration ↑ (not specified), brown pigment renal proximal tubule ↑ (16% vs. 4% in control, n.s.), moderate chronic progressive nephropathy ↑ (54% vs. 24% in control), severe chronic progressive nephropathy ↑ (4% vs. 2% in control)	2	Anonymous (2013a)

		450 ppm: BW ↓ (-16%), BW gain ↓ (-22%), blood cholesterol ↑ (100%), blood triglycerides ↑ (200%), blood phospholipids ↑ (182%), gamma-GTP ↑ (530%), BUN ↑ (55%), abs. liver weight ↑ (10%), rel. liver weight ↑ (32%), adipose liver degeneration ↑ (not specified), eosinophilic foci liver ↑ (58% vs. 24% in control), hepatocellular adenoma ↑ (18% vs. 2% in control), hepatocellular carcinoma ↑ (8% vs. 0% in control), brown pigment renal proximal tubule ↑ (32% vs. 4% in control), cysts kidney ↑ (12% vs. 0% in control), moderate chronic progressive nephropathy ↑ (68% vs. 24% in control), severe chronic progressive nephropathy ↑ (18% vs. 2% in control) <u>Females</u> NOAEC: 18 ppm (65 mg/m^3) 90 ppm: cholesterol ↑ (20%), blood triglycerides ↑ (60%), blood phospholipids ↑ (16%), gamma-GTP ↑ (33%), abs. liver weight ↑ (14%), rel. liver weight ↑ (9%), adipose liver degeneration ↑ (not specified), brown pigment renal proximal tubule ↑ (30% vs. 10% in control) 450 ppm: BW gain ↓ (-22%), blood cholesterol ↑ (71%), blood triglycerides ↑ (83%), blood phospholipids ↑ (53%), gamma-GTP ↑ (100%), abs. liver weight ↑ (15%), rel. liver weight ↑ (27%), adipose liver degeneration ↑ (not specified), small clear cell foci liver ↑ (10% vs. 0% in control), brown pigment renal proximal tubule ↑ (46% vs. 10% in control)		
Rat Sprague-Dawley 10 m 10 f Equivalent to OECD guideline 412 with limited endpoints and exposure time, and limited details on effect sizes GLP: not specified	Subacute study 2 weeks (with 2-wk recovery for 5 rats/sex/dose) 0, 100, 288, 622 ppm (0, 360, 1040, 2240 mg/m^3, whole body, vapour) 6h/day, 5d/week (10 exposures)	NOAEC (local): <100 ppm (<360 mg/m^3) NOAEC (systemic): 100 ppm (360 mg/m^3) 100 ppm: nasal irritation 288 ppm: blood cholesterol ↑, leukocytes ↓ (f), rel. liver weight ↑ (m/f: 21/22%), hepatocellular hypertrophy, testicular atrophy, nasal irritation 622 ppm (4-day exposure): BW loss (-28%), mortality ↑, clinical signs, blood cholesterol ↑, GOT ↑, BUN ↑ (m), GPT ↑ (males), leukocytes and	3	DuPont (1983c); Kelly et al. (1984)

		platelet counts ↓, neutrophils ↑, rel. liver weight ↑ (62/52%), rel. kidney weight ↑ (50/58%), rel. spleen and thymus weight ↓, hepatocellular hypertrophy and necrosis ↑, lymphocytic depletion in thymus and spleen, hypocellularity in bone marrow, local inflammation of the stomach and intestine, testicular atrophy, nasal irritation		
Rat Crl: CD BR 13 m (9 in control group) No guideline study GLP: no	Subacute study 2 weeks 0, 52, 150, 300, 480 ppm (0, 190, 540, 1080, 1730 mg/m^3, whole body, vapour) 6h/day, 5d/week (10 exposures)	NOAEC: 300 ppm (1080 mg/m^3) 480 ppm: BW ↓ (-12%) No gross pathologic changes that could be related to DMAC exposure. No effect on testis weight, testis histopathology or sperm counts.	3	Valentine et al. (1997)
Rat Crl: CD(SD)BR 15 m No guideline study GLP: not specified	Subacute study 2 weeks (with 2-wk recovery for 5 rats/dose) 0, 10, 30, 100, 300 ppm (0, 36, 110, 360, 1080 mg/m^3, nose only, vapour) 3, 6 or 12h/day, 5d/week (10 exposures)	NOAEC: 100 ppm (360 mg/m^3) 300 ppm: BW ↓ (≥6h, -6%), blood cholesterol ↑ (≥3h, 58%), blood protein ↑ (12h, 13%), hepatocellular hypertrophy with margination of hepatocellular cytoplasmic contents and hepatic cellular cytoplasmic lipid-like vacuolation (12h)	3	Kinney et al. (1993)
Mouse Crl:CD-1 BR 78 m 78 f OECD guideline 453 GLP	Combined chronic toxicity and carcinogenicity study 18 months 0, 25, 100, 350 ppm (0, 90, 360, 1260 mg/m^3, whole body, vapour) 6h/day, 5d/week	<u>Males</u> NOAEC: 25 ppm (90 mg/m^3) 100 ppm: individual hepatocellular necrosis ↑ (19% vs. 14% in control, n.s.), accumulation of pigments in Kupffer cells ↑ (27% vs. 9% in control) 350 ppm: centrilobular hepatocellular hypertrophy ↑ (25% vs. 0% in control), individual hepatocellular necrosis ↑ (25% vs. 14% in control, n.s.), accumulation of pigments in Kupffer cells ↑ (46% vs. 9% in control), <u>Females</u> NOAEC: 100 ppm (360 mg/m^3) 350 ppm: rel. liver weight ↑ (17%), individual hepatocellular necrosis ↑ (15% vs. 2% in control), accumulation of pigments in Kupffer cells ↑ (40% vs. 22% in control, n.s.), diffuse, bilateral retinal atrophy ↑ (34.5% vs. 6.6% in control)	1	DuPont (1994); Malley et al. (1995)

		No increase in tumor incidences observed in both males and females.		
Mouse B6D2F1/Crlj 50 m 50 f OECD guideline 451 with deviations GLP	Carcinogenicity study 104 weeks 0, 12, 60, 300 ppm (0, 43, 216, 1080 mg/m^3, whole body, vapour) 6h/day, 5d/week	<u>Males</u> NOAEC: 60 ppm (216 mg/m^3) 300 ppm: BW ↓ (-9%), BW gain ↓ (-22%), AST ↑ (560%), ALT ↑ (250%), LDH ↑ (390%), rel. liver weight ↑ (34%), liver nodules ↑ (50% vs. 34% in control, n.s.), eosinophilic foci liver ↑ (20% vs. 2% in control), hepatocellular adenoma ↑ (56% vs. 20% in control), BUN ↑ (109%), kidney deformity ↑ (20% vs. 2% in control, n.s.), renal papillary necrosis ↑ (20% vs. 0% in control), kidney scarring ↑ (42% vs. 18% in control) <u>Females</u> NOAEC: 60 ppm (216 mg/m^3) 300 ppm: AST ↑ (160%), ALT ↑ (580%), rel. liver weight ↑ (65%), liver nodules ↑ (68% vs. 10% in control, n.s.), eosinophilic foci liver ↑ (48% vs. 2% in control), hepatocellular adenoma ↑ (70% vs. 4% in control), hepatocellular carcinoma ↑ (16% vs. 0% in control), renal papillary necrosis ↑ (36% vs. 20% in control, n.s.)	2	Anonymous (2013b)
Mouse (young adult) Crl:CD-1(ICR)BR) 10 m No guideline study GLP: no	Subacute study 2 weeks (with 2-wk recovery for 5 mice/dose) 0, 30, 100, 310, 490, 700 ppm (0, 110, 360, 1120, 1760, 2520 mg/m^3, whole body, vapour) 6h/day, 5d/week (10 exposures)	NOAEC: 100 ppm (360 mg/m^3) 310 ppm: rel. testes weight ↓ (-15%, n.s.), testicular lesions (2/5 vs. 0/5 in control) 490/700 ppm: clinical signs, mortality (dead or killed in extremis; 490 ppm: 2/10; 700 ppm: 8/10), BW ↓ (700 ppm: -15% at day 3), BW gain ↓ (700 ppm only), effects on red blood cell parameters and platelet counts, rel. liver weight ↑ (490 ppm: 23%), rel. testes (490 ppm: -30%) and lung weight ↓ (490 ppm: -10%), histopathological changes in liver, bone marrow, lymphoid organs and adrenal glands (all reversible), testicular lesions (490/700 ppm: 3/6, 9/9 vs. 0/5 in control), minimal to mild bilateral degeneration and atrophy of seminiferous tubules in mice (490 ppm: 3/5 vs. 0/5 in controls)	3	Valentine et al. (1997)
Mouse (young pubescent) Crl: CD BR 12 m (9 in control group)	Subacute study 2 weeks 0, 52, 150, 300, 480 ppm (0, 190, 540, 1080,	NOAEC: 300 ppm (1080 mg/m^3) 480 ppm: abs. testes weight ↓ (-21%), minimal to mild bilateral degeneration and atrophy of	3	Valentine et al. (1997)

No guideline study GLP: no	1730 mg/m^3, whole body, vapour) 6h/day, 5d/week (10 exposures)	seminiferous tubules (3/9 vs 0/9 in controls)		
Oral				
Rat Long-Evans 70 m 70 f OECD guideline 453 GLP: no	Combined chronic toxicity and carcinogenicity study 2 years 0, 100, 300, 1000 mg/kg bw/day (drinking water, daily, ad libitum)	<u>Males</u> LOAEL: 100 mg/kg bw/day 100 mg/kg bw/day: rel. liver weight ↑ (23%) 300 mg/kg bw/day: BW ↓ (-11%), rel. liver weight ↑ (28%), incidence of adverse liver effects ↑ (central lobular hypertrophy 40% vs. 0% in control; hepatocellular vacuolization 77% vs. 41% in control; necrosis 24% vs. 11% in control; intracytoplasmic brown pigment 4% vs. 0% in control) 1000 mg/kg bw/day: BW ↓ (-20%), blood clotting time ↓ (-15%), erythrocyte counts ↑ (13%), ALP ↓ (-30%, n.s.), rel. liver weight ↑ (46%), rel. testis weight ↓ (-23%), incidence of adverse liver effects ↑ (central lobular hypertrophy 74% vs. 0% in control; hepatocellular vacuolization 83% vs. 41% in control; necrosis 29% vs. 11% in control; intracytoplasmic brown pigment 42% vs. 0% in control), testicular maturation arrest/degeneration/atrophy ↑ (90% vs. 70% in control), decreased secretory product/atrophy prostate gland ↑ (19% vs. 7% in control), splenic atrophy ↑ (21% vs. 4% in control) <u>Females</u> NOAEL: 100 mg/kg bw/day 300 mg/kg bw/day: rel. liver weight ↑ (17%), incidence of adverse liver effects ↑ (central lobular hypertrophy 38% vs. 0% in control; hepatocellular vacuolization 70% vs. 41% in control; intracytoplasmic brown pigment 3% vs. 0% in control), ovarian cysts ↑ (34% vs. 27% in control 1000 mg/kg bw/day: BW ↓ (-17%), rel. liver weight ↑ (26%), incidence of adverse liver effects ↑ (central lobular hypertrophy 75% vs. 0% in control; hepatocellular vacuolization 83% vs. 41% in control; necrosis 17% vs. 6% in	1	Monsanto (1980, 1990, 1993)

		control; intracytoplasmic brown pigment 16% vs. 0% in control), ovarian cysts ↑ (46% vs. 27% in control No increase in tumor incidences observed in both males and females. Only statistical analyses performed for histopathology data on testes.		
Rat CD 6 m 6 f No Guideline study GLP: no	Semi-chronic study 90 days 0, 1000 ppm (diet; nominal 60 mg/kg bw/day)	NOAEL: 60 mg/kg bw/day Only one dose tested and only effect observed was slight leukocytosis and slight anemia.	3	Kennedy and Sherman (1986)
Rat Sprague-Dawley 10 m 10 f OECD guideline 407 (with deviations; a.o. no histopathology performed) GLP: no	Subacute study 4 weeks 0, 290, 590, 1170, 2350 mg/kg bw/day (gavage, water), 5d/week	LOAEL: 290 mg/kg bw/day (as derived in registration dossier, cannot be verified without histopathology) ≥290 mg/kg bw/day: ALP ↓ (m), abs. heart weight ↓ (m), total lipids ↑, abs./rel. adrenal weight ↓ (f), thin/filamentary uterine horns (290/590 mg/kg bw/day: 20/30% vs. 0% in control) ≥590 mg/kg bw/day: ALP ↓ (f), blood clotting time ↑ (m), abs. heart weight ↓ (f), rel. heart weight ↓, abs. spleen weight ↓, rel. liver weight ↑, rel. kidney weight ↑ (m) ≥1170 mg/kg bw/day: reduced general condition, ruffled coat, BW ↓ (m/f: -21/-14%), serum creatinine ↑, lymphocytes ↓, neutrophil granulocytes ↑, blood clotting time ↑ (f), rel. kidney weight ↑ (f), abs. ovary weight, abs./rel. uterus weight, abs./rel. testes weight, atrophy of testes and uterus, thin uterine horns 2350 mg/kg bw/day: ruffled coat, diarrhea, excitation and tremor, BW gain ↓, mortality ↑ (m/f: 90/70%), yellow discoloration of liver and kidney, local effects in stomach	3	BASF (1975b)
Dermal				
No reliable studies found.				
m: male, f: female, ↑: increased, ↓: reduced, abs.: absolute, ALP: alkaline phosphatase, ALT/GPT: alanine aminotransferase, AST/GOT: aspartate aminotransferase, BSP: bromsulphthalein, BW: body weight, BUN: blood urea nitrogen, gamma-GTP: gamma glutamyltranspeptidase, LDH: lactate dehydrogenase, n.s.: not statistically significant, rel.: relative				

Inhalation – Rats

DuPont (1994); Malley et al. (1995)

In a combined chronic toxicity and carcinogenicity study by Malley et al. (1995) (according to GLP and OECD 453 with minor deviations), 87 male and 87 female Crl: CD BR rats/group were exposed to 0, 25, 100, 350 ppm DMAC (0, 90, 360, 1260 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 2 years. Interim sacrifice was conducted after 12 months (10 rats/dose/sex) for evaluation of toxic effects. For exclusive measurement of liver cell proliferation further interim sacrifices (5 rats/dose/sex) were performed 0.5, 3, and 12 months after initiation of the study.
No treatment-related effects were found in: clinical signs, survival, hematology, ophthalmology, liver cell proliferation, urinalysis and neoplastic effects. In males and females at 100 and 350 ppm, a slight (mostly not statistically significant) decrease in body weight (up to 11%) and body weight gain (up to 17%) was observed.
As to histopathological changes, treatment-related effects were only observed at the terminal sacrifice, not at the interim sacrifice. In both sexes, hepatotoxicity was seen, not always statistically significant (n.s.) (pair-wise comparisons) but mostly with a clear dose response (see Table 4). In males, statistically significant increases were observed in focal cystic degeneration at 100 and 350 ppm, and in hepatic peliosis, hepatic accumulation of pigments (lipofuscin/hemosiderin) and biliary hyperplasia at 350 ppm, albeit that no dose-response was seen for the latter effect. A statistically significant increase in hepatic accumulation of pigments (lipofuscin/hemosiderin) was also observed in females at 350 ppm. The mechanism responsible for the pigment accumulation was not clear (no evidence of hepatocellular necrosis or increased apoptosis, no hematological evidence of damage to red blood cells, iron contamination in DMAC administered unlikely given 99.96% purity). The relative liver weight in males showed a clear dose response and effect over time (12 months: 6% at 100 ppm and 10% at 350 ppm; 24 months: 22% at 100 ppm and 34% at 350 ppm), with the 34% at 350 ppm reaching statistical significance. In females the relative liver weight was statistically significantly increased after 12 months of treatment (100/350 ppm: 23/28%), but no longer after 24 months (100/350 ppm: 1/10%). According to the study pathologists, these liver weight changes most likely represent enzyme induction associated with metabolism of DMAC, whereas the histopathological changes (generally of minimal severity) collectively taken are suggestive of slight hepatotoxicity. Relative weight of kidneys was increased after 24 months, in males at 100 ppm (25%, n.s.) and 350 ppm (70%), and in females at 350 ppm (21%). The majority of male and female rats in all groups, including controls, showed chronic progressive nephropathy (CPN), a spontaneous age-related disease in rats (with a distinct male predisposition) for which the weight of evidence suggests no human counterpart. In males but not females, DMAC increased the severity of the CPN (19/32% at 100/350 ppm vs. 15% in control, n.s. at 100 ppm). Secondary to the effects of kidney disfunction, lesions in a number of other tissues/organs were observed (including e.g. heart, spleen, stomach, seminal vesicles, testes, epididymides).
Conclusions: In this 2-year inhalation study in rats, the liver was the primary target organ, with adverse effects detected in males at 100 ppm (360 mg/m^3) and in females at 350 ppm (1260 mg/m^3). The NOAEC was 25 ppm (90 mg/m^3) in males and 100 ppm (360 mg/m^3) in females.

Table 4: Effects in rats after chronic inhalation exposure to DMAC for 2 years; means ± standard deviation, incidence of total shown in between brackets

Parameter	0 ppm	25 ppm	100 ppm	350 ppm
Rel. liver weight (%) in males after 12 months	2.86 ± 0.53	2.92 ± 0.32	3.03 ± 0.40	3.15 ± 0.33
Rel. liver weight (%) in males after 24 months	2.95 ± 0.23	3.01 ± 0.41	3.59 ± 1.34	3.95 ± 0.84*
Rel. liver weight (%) in females after 12 months	2.68 ± 0.23	2.97 ± 0.38	3.30 ± 0.47*	3.42 ± 0.32*

Rel. liver weight (%) in females after 24 months	3.47 ± 0.32	3.28 ± 0.42	3.51 ± 0.39	3.83 ± 0.49
Incidence (%) hepatic focal cystic degeneration in males	26 (17/65)	38 (24/63)	44* (28/63)	50* (31/62)
Incidence (%) biliary hyperplasia in males	57 (37/65)	73 (46/63)	67 (42/63)	79* (49/62)
Incidence (%) accumulation of pigments (lipofuscin and hemosiderin) in Kupffer cells in males	2 (1/65)	6 (4/63)	8 (5/63)	34* (21/62)
Incidence (%) accumulation of pigments (lipofuscin and hemosiderin) in Kupffer cells in females	3 (2/62)	3 (2/62)	13 (8/62)	20* (13/64)
Incidence (%) hepatic peliosis in males	5 (3/65)	3 (2/63)	11 (7/63)	13* (8/62)
Rel. kidney weight (%) in males after 24 months	0.76 ± 0.06	0.83 ± 0.26	0.95 ± 0.34	1.29 ± 0.73*
Rel. kidney weight (%) in females after 24 months	0.66 ± 0.12	0.75 ± 0.11	0.69 ± 0.10	0.80 ± 0.15*
Incidence (%) chronic progressive nephropathy in males after 24 months	94 (61/65)	98 (62/63)	98 (62/63)	100 (62/62)
Incidence (%) chronic progressive nephropathy in females after 24 months	84 (52/62)	84 (52/62)	81 (50/62)	84 (54/64)
Incidence (%) severe chronic progressive nephropathy in males after 24 months	15 (9/61)	15 (9/62)	19 (12/62)	32* (20/62)

*statistically significant ($p < 0.05$) vs. control

Anonymous (2013a)

In an inhalation carcinogenicity study (OECD guideline 451 with restrictions: inadequate air change rate during exposure), groups of 50 male and 50 female F344 rats/group were exposed to 0, 18, 90 and 450 ppm DMAC (ca. 0, 65, 324 and 1620 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 2 years.

No treatment related effects were observed on the viability of the animals. Reduced body weight (-16%) and body weight gain (-22%) were observed in males at 450 ppm. In females, body weight gain was reduced (-22%) at 450 ppm. At 450 ppm, males showed a decreasing trend in food consumption throughout the study course, while this trend was seen in female animals only until week 7 with gradual recovery thereafter. Relevant significant changes in clinical chemistry parameters indicating liver toxicity were observed for both sexes at 90 and 450 ppm and this increase was dose-dependent. These included: cholesterol (males 45/100%, females 20/71%), triglycerides (males 44/200%, females 60/83%), phospholipids (males 37/182%, females 16/53%), and gamma-glutamyltranspeptidase (gamma-GTP; males 183/530%, females 33/100%). Significantly increased liver weights at 90 and 450 ppm in both males (14/32%) and females (9/27%) correlated with adverse non-neoplastic lesions at histopathology in liver described as adipose liver degeneration (not specified). Kidney toxicity was observed in males at 90 and 450 ppm, with significantly elevated levels of blood urea nitrogen (BUN; 24/55%), and significantly increased incidence of moderate (54/68% vs. 24% in control) or severe chronic progressive nephropathy (4/18% vs. 2% in control). No

significantly increased incidence of chronic progressive nephropathy was observed in females. Incidence of accumulation of renal tubular brown pigment was significantly increased at 90 and 450 ppm in females (30/46% vs. 10% in control) and in males (16/32% vs. 4% in control, n.s. at 90 ppm). Increased incidence of hepatocellular adenoma (18% vs. 2% in control) and carcinoma (8% vs. 0% in control) was observed in male rats at 450 ppm. In female rats, no increase in tumor incidence was observed. The incidence of tumors in males at the highest dose level was found only in the presence of overt toxic effects. Therefore, the maximum tolerated dose (MTD) is considered to be exceeded at this dose level and the tumor findings are of questionable relevance. In addition, during the exposure period, the air change rate was inadequately low (6 changes/h instead of at least 10 changes/h). This raises some concern on the reliability of the study as it may have resulted in higher dermal, oral and inhalation exposure of the animals in comparison to exposure conditions with the recommended air change rate.
The NOAEC was 18 ppm (65 mg/m^3) in male and female rats.

DuPont (1983c); Kelly et al. (1984)
In a subacute inhalation study (similar to OECD guideline 412, but with 2-week instead of 4-week exposure, and with limited endpoints tested/details reported), 10 male and 10 female Sprague-Dawley rats/group were exposed to 0, 100, 288 or 622 ppm DMAC (0, 360, 1040, 2240 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 2 weeks. Rats were sacrificed after 10 exposures (5 rats/sex/dose) or after a 2-week recovery period (other half of each group). The high exposure concentration was terminated after 4 days of treatment, with 3 rats dead and 2 in extremis. During the 4-day exposure period the 622-ppm group showed severe weight loss (-28%). Histological examination of this group immediately after the exposure period showed liver hypertrophy and necrosis, lymphocytic depletion in the thymus and spleen, hypocellularity in the bone marrow and inflammation of the stomach and small intestine. The stomach and intestinal effects are likely due to ingestion of DMAC from the fur. In the 288-ppm group, liver hypertrophy was observed immediately after the 10th exposure. After a two-week recovery period the liver hypertrophy was still evident in the 622 and 288 ppm rats along with testicular atrophy. No histological liver or testicular changes were seen in the 100-ppm group. Histological evidence of nasal irritation was seen in the 288 and 100 ppm group immediately after exposure and two weeks later. These nasal effects were seen to a lesser extent in the rats exposed to 622 ppm DMAC.
Clinical lab measurements and organ weight analyses were supportive of the histological findings in the liver, spleen and thymus. Liver enzymes (glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT)) were increased in the 622-ppm group and there was a dose-dependent increase in blood cholesterol levels in all test groups immediately after exposure. Relative liver weights were increased in the 622 (male/female: 62/52%) and 288 (22/21%) ppm groups and remained increased two weeks later. Relative kidney weights were increased at 622 ppm (50/58%) in both sexes. Spleen weights were decreased in the 622-ppm group, thymus weights were decreased in the 622 and 288 ppm groups. Immediately after exposure leukocytes and platelets were decreased in the 622 ppm males and females; two weeks later the 622 ppm group leukocytes and platelets remained low, and the 288 and 100 ppm females also had low leukocyte counts.
The NOAEC for local effects (nasal irritation) was <100 ppm (360 mg/m^3) and the NOAEC for systemic effects was 100 ppm (360 mg/m^3).

Valentine et al. (1997)
In a subacute study targeted at testes effects, 13 male Crl: CD-BR rats/group (control n=9) were exposed to 0, 52, 150, 300 or 480 ppm DMAC (0, 190, 540, 1080, 1730 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week, for 2 weeks and sacrificed after the last exposure. Examinations included clinical signs, body weight, gross pathology, and testes weight and histopathology. No clinical signs were detected, and histopathological examinations revealed no effects on the testes, nor were testis weight or sperm count

affected. The only effect observed was a slight decrease in body weight (-12%) at 480 ppm. So, 480 ppm (1730 mg/m^3) was a marginal LOAEC in this limited study.

Kinney et al. (1993)
In a subacute inhalation study targeted at effects on nasal passages, liver, testes and epididymides, 15 male Crl: CD(SD) BR rats/dose and time were exposed to 0, 10, 30, 100 or 300 ppm DMAC (0, 36, 110, 360, 1080 mg/m^3, nose only) for 3, 6 or 12 h per day, 5 days per week, for 2 weeks. Five rats/dose and time were kept for a 2-week recovery period. Examinations included clinical signs, body weight, some clinical chemistry parameters, gross pathology, liver and testes weight, and histopathology of liver, testes, epididymides and nasal passages. No clinical signs and effects on organ weights (liver and testes) were observed and also no effects at necropsy. Body weight was slightly decreased (<10%) at 300 ppm only, with 6 and 12h/day exposures. Significantly increased serum levels of cholesterol (58%) were observed at 300 ppm (all exposure durations). Total protein (13%) was increased at 300 ppm with 12h/day exposure times only. These increases were no longer seen after the 2-week recovery period. Histopathology revealed changes in the liver but only at the 300-ppm level and exposure for 12h/day. Liver changes consisted of hepatocellular hypertrophy together with margination of hepatocellular cytoplasmic contents and hepatic cellular cytoplasmic lipid-like vacuolation. These changes were present in all of the rats examined in this group (graded as between slight to moderate in severity). These changes persisted after the recovery period but with decreased incidence and severity. No treatment related changes were seen in the testes, epididymides and nasal passages. In contrast to other subacute studies (whole body inhalation exposure including dermal absorption) the inhalation route was investigated by nose-only exposure in this study. The toxicological relevance of altered clinical chemistry parameters is questionable without effects in histopathology.
The NOAEC in this limited study was 100 ppm (360 mg/m^3).

Additional data from other studies - Rats
In a semi-chronic toxicity study (Horn, 1961) with limitations (limited number of animals and parameters investigated; limited documentation), 5 rats (sex and strain unspecified)/group were exposed to 0, 40, 64.4, 103 or 195 ppm DMAC (corresponding to 0, 140, 230, 370, 700 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 6 months. Exposed animals appeared to show some evidence of lung irritation, but changes in the lung were difficult to evaluate because of pneumonia which was also observed in controls. Rats at 195 ppm presented an unkempt appearance with red-tinged discharge around the eyes, and gained less weight than controls (no further details). Granular cytoplasm was observed in liver lobules in 1/5 animals at 64.4 ppm, hepatocellular degeneration was noted at 103 ppm (significant in 3/5 rats, mild in 2/5 rats), and hepatocellular cholangitis, periangitis and focal necrosis occurred in all animals at 195 ppm.
In a fertility study and a one-generation study (see section B.5.3.1 Toxicity for Sexual function and fertility), inhalation exposure to DMAC resulted in some slight increases in relative liver weight. In the fertility study (Monsanto, 1982a; Wang et al., 1989), 12 male Sprague-Dawley rats/group were exposed to 0, 40, 120 or 400 ppm DMAC (0, 140, 430, 1400 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week for 15 weeks. No statistically significant differences in clinical chemistry parameters (protein, ALP, GPT) were noted. Relative liver weights were significantly increased at 120 ppm (12%) and 400 ppm (22%). Histopathology revealed no effects in any of the three studied organs (liver, testes, kidney).
In the one-generation study (Ferenz & Kennedy Jr, 1986), 10 male and 20 female Crl: CD rats/group were exposed to 0, 30, 100, 300 ppm DMAC (0, 110, 360, 1080 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week for 10 weeks (prebreeding). This was followed by treatment for 6 h per day, 7 days per week for 7-8 weeks (breeding, gestation and lactation). In parent animals (F0), relative liver weights were increased at 300 ppm in males (18%) and females (16%). After a 20-day recovery period, the relative liver weights were still slightly, but not statistically significantly, increased. Histopathology was not performed.

In a prenatal developmental toxicity study (similar to OECD TG 414; (Okuda et al., 2006); see section B.5.3.2 Toxicity for Development), 10 female (pregnant) Crj:CD(SD)IGS rats/group were exposed to vapour of DMAC (purity >99.9%) at concentrations of 0, 100, 300, 450 or 600 ppm DMAC (equivalent to 0, 360, 1080, 1620 or 2160 mg/m^3, whole body) for 6 h per day, from GD 6 to 19. In dams no clinical signs or increased liver enzymes (AST, ALT or LDH) were noted. Decreased body weight at ≥450 ppm (450/600 ppm: -7/-14%) and increased liver weight at ≥300 ppm were observed (300/450/600 ppm: 13/12/19%), accompanied by swelling of centrilobular hepatocytes without the occurrence of hepatocellular necrosis at ≥300 ppm (40/100/70% vs. 0% in control), which was statistically significant at ≥450 ppm.

The data from these studies support that liver is the target organ in rats after repeated inhalation dosing of DMAC.

Inhalation - Mice

DuPont (1994); Malley et al. (1995)
In a combined chronic toxicity and carcinogenicity study by Malley et al. (1995; according to GLP and OECD 453 with minor deviations: no clinical chemistry and no urinalysis; tabulated details of results not presented), 78 male and 78 female CD-1 mice/group were exposed to 0, 25, 100, 350 ppm DMAC (0, 90, 360, 1260 mg/m^3, whole body, vapour) for 6h per day, 5 days per week, for 18 months. Interim sacrifice (5 mice/dose/sex) was performed 0.5, 3, and 12 months after initiation of the study for assessment of liver cell proliferation.
No treatment-related effects were found concerning the parameters body weight, hematology, ophthalmology, liver cell proliferation, necropsy and neoplastic effects. Aside from increased incidences of diarrhea in males (at 100 and 350 ppm) and ruffled fur in females (at 350 ppm) there were no clinical signs. Survival was not affected in males, but slightly decreased in females at 350 ppm (66% vs. 80% in controls). Liver effects were observed in both sexes, consisting of a 17% increase in relative liver weight in female mice at 350 ppm, increased incidences of accumulation of pigments in Kupffer cells in males at 100 and 350 ppm (27/46% vs. 9% in control) and in females at 350 ppm (40% vs. 22% in control; n.s.), and an increase in individual hepatocellular necrosis (apoptosis) in males (100/350 ppm: 19/25% vs. 14% in control; n.s.) and females (350 ppm: 15% vs. 2% in control). Centrilobular hepatocellular hypertrophy was additionally significantly increased at 350 ppm in males (25% vs. 0% in control), but not in females. The mechanism responsible for the lipofuscin/hemosiderin pigment accumulation was not clear (no hematological evidence of damage to red blood cells, iron contamination in DMAC administered unlikely given 99.96% purity, occurrence of apoptosis but only few mice affected). The study pathologists considered the the liver weight change in females and the hypertrophy in males most likely the result of enzyme induction associated with metabolism of DMAC, but the pigment accumulation (generally of minimal severity) collectively with the apoptosis (minimal to mild) suggestive of slight hepatotoxicity. In females there were some statistically significant increases in relative kidney weight, but the changes were small (<10%) and not dose-dependent, and without kidney histopathology. High-dose females showed an increased incidence of diffuse, bilateral retinal atrophy (34.5% vs. 6.6% in controls).
In this 18-month inhalation study in mice the liver was the primary target organ, with adverse effects detected in males at 100 ppm (360 mg/m^3) and in females at 350 ppm (1260 mg/m^3). The NOAEC was 25 ppm (90 mg/m^3) in males and 100 ppm (360 mg/m^3) in females.

Anonymous (2013b)
In an inhalation carcinogenicity study (comparable to OECD Guideline 451 with acceptable restrictions: uncommon sensitive mouse strain used, inadequate air change rate during exposure, in male animals), 50 male and 50 female B6D2F1 mice/group were exposed to 0,

12, 60 and 300 ppm DMAC (ca. 0, 43, 216 and 1080 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 2 years.
No treatment related effects were observed on the viability of the animals. In male animals, body weight (-9%) and body weight gain (-22%) were statistically significantly reduced at 300 ppm. No relevant effects on body weight or body weight gain were observed in female animals. At 300 ppm, food consumption showed an increasing trend early at administration for both sexes and also at late phases for females. Clinical chemistry parameters, such as aspartate aminotransferase (AST; males/females: 560/160%), alanine aminotransferase (ALT; 250/580%), were significantly increased at 300 ppm in both sexes, which can be linked to hepatic toxicity, but this was not dose-dependent. Hepatic toxicity at 300 ppm consisted of increased relative liver weight (34/65%) and increased incidences of liver nodules (50% vs. 34% in controls, n.s.; 68% vs. 10% in controls, n.s.) and liver eosinophilic foci (20% vs. 2% in control; 48% vs. 2% in control). In males, significantly increased BUN levels were observed at 300 ppm by 109%. This was accompanied by increased incidences of renal papillary necrosis and kidney deformity at 300 ppm (20% vs. 0% and 20% vs. 2% in control, respectively), plus kidney scarring (42% vs. 18% in controls). In females, kidney toxicity only consisted of an increased incidence (not statistically significantly) of renal papillary necrosis at 300 ppm (36% vs. 20% in controls). Significantly increased incidences of hepatocellular adenoma (56% vs. 20% in control; 70% vs. 4% in control) occurred at 300 ppm in both sexes, whereas hepatocellular carcinoma were increased at 300 ppm in females (16% vs. 0% in control). The authors considered the highest dose to exceed the MTD. During the exposure period the air change rate was inadequately low (6 changes/h instead of at least 10 changes/h). This raises concerns on the reliability of the study as it may have resulted in higher dermal, oral and inhalation exposure of the animals in comparison to exposure conditions with the recommended air change rate.
The NOAEC was 60 ppm (216 mg/m^3) in male and female mice.

Valentine et al. (1997)
In a subacute study, 10 male Crl:CD-1(ICR)BR) mice (35 days old)/group were exposed to 0, 30, 100, 310, 490, 700 ppm DMAC (0, 110, 360, 1120, 1760, 2520 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week, for 2 weeks and sacrificed after the last exposure (5 mice/group) or after a 2-week recovery period (5 mice/group). In a supplemental experiment with older mice (61 days old) and targeted at testes effects, 12 mice/group (control n=9) were exposed to 0, 52, 150, 300 or 480 ppm DMAC (0, 190, 540, 1080, 1730 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week, for 2 weeks and sacrificed after the last exposure. Examinations included clinical signs, body weight, gross pathology, and testes weight and histopathology.
In the main study, no effects were detected at 100 ppm. Exposure to 490 and 700 ppm was not well tolerated in pubescent mice, with clinical signs including a.o. lethargy and tremors, mortality (2/10 at 490 ppm and 8/10 at 700 ppm), decreased body weight (700 ppm: -15% at day 3), and effects on red blood cell parameters and platelet counts. In addition, relative weight of liver was increased (23%) and of lung decreased (-10%) at 490 ppm, with no recovery seen after the 2-week recovery period for the liver. Relative weights of testes were affected at 310 ppm (-15%, n.s.) and irreversibly at 490 ppm (-30%), and with testicular lesions (310/490/700 ppm: 2/5, 3/6, 9/9 vs. 0/5 in control), usually associated with decreased number of sperm and increased germinal epithelium in epididymis in mice. Minimal to mild bilateral degeneration and atrophy of seminiferous tubules in mice (3/5 vs. 0/5 in controls) was observed at 490 ppm. At 490 and 700 ppm, histopathology showed hepatocellular hypertrophy, minimal to mild hepatocellular necrosis, lymphoid atrophy and/or necrosis, bone marrow hypocellularity, minimal adrenal cortical necrosis, and testicular lesions, which were no longer seen after the 2-week recovery period.
In the supplemental experiment, no clinical signs were detected, and survival and body weights were not affected. Effects on the testes were only seen at 480 ppm, with a decrease in absolute weight (-21%) and minimal to mild bilateral degeneration and atrophy of

seminiferous tubules in mice (3/9 vs. 0/9 in controls); sperm counts were not significantly affected.
The NOAEC was 100 ppm (360 mg/m^3) in pubescent mice and 300 ppm (1080 mg/m^3) in young adult mice.

Additional data from other studies - Dogs
In a semi-chronic toxicity study (Horn, 1961) with limitations (limited number of animals and parameters investigated; limited documentation), 2 male dogs (strain unspecified)/group were exposed to 0, 40, 64.4, 103 or 195 ppm DMAC (corresponding to 0, 140, 230, 370, 700 mg/m^3, whole body, vapour) for 6h/day, 5 days/week, for 6 months. Exposed animals showed some evidence of lung irritation, but only slightly greater than that seen in control animals. Dogs at 103 and 195 ppm had periportal liver cell degeneration and increased bromsulphthalein (BSP) retention. At 195 ppm, additionally an increase in alkaline phosphatase (ALP) was seen.
The Dossier Submitter assigned no NOAEC due to the limitation of the study.

Oral

Monsanto (1980, 1990, 1993)
In a combined chronic toxicity and carcinogenicity study (comparable to OECD guideline 453 but with some restrictions, e.g. no details about the test substance; problems in analytical methodology of DMAC in drinking water), 70 male and 70 female Long-Evans rats/group were treated with 0, 100, 300 or 1000 mg DMAC/kg bw/day via drinking water for 24 months. At the end of 6 or 12 months of treatment, 10 animals/sex/group were randomly selected and sacrificed for examinations; at the end of 24 months on test, all of the survivors were killed. The dosing in this study was most probably based on a subacute pilot study (Anonymous, 1976), in which 6 male and 6 female Long-Evans rats/group were exposed to 0, 125, 250, 500, 1000 mg DMAC/kg bw/day via drinking water (ab libitum) for 31 days, and where no treatment-related effects were observed at any dose tested regarding clinical signs, body weight (gain), water and food consumption, necropsy data.
No relevant clinical signs were observed, except alopecia in high dose rats. Body weight was significantly reduced in males at ≥300 mg/kg bw/day (300/1000 mg/kg bw/day: -11/-20%) and in females at 1000 mg/kg bw/day (-17%). No effects were detected on food and water consumption. The toxicological relevance of effects in hematology and clinical chemistry (males: decreased blood clotting time (-15%), increased erythrocyte count (13%), decreased ALP (-30%); no significant changes in females) was questionable. Urinalysis and ophthalmology parameters were unremarkable. At all time points (6, 12 and 24 months of treatment), relative liver weights were significantly increased at all doses in males (by 23 to 46% at 24 months) and at ≥300 mg/kg bw/day in females (by 17 to 26% at 24 months). Relative testes weight was reduced only at 24 months at 1000 mg/kg bw/day (-23%). When analysed in 1979, no gross or microscopic lesions were observed in tissues/organs of the high dose and control animals, aside from some splenic hemosiderosis in high dose females considered of unclear significance. No microscopic examination of the low and mid dose animals was therefore performed. However, re-analyses in 1990 and 1993 concerned histopathology of control and treatment groups of all animals. Upon re-analysis, it appeared that 24 months of DMAC treatment at 300 and 1000 mg/kg bw/day did result in some treatment-related findings. These included minimal to moderate central lobular liver hypertrophy (males: 40/74% vs. 0% in control; females: 38/75 vs. 0% in control), liver cell vacuolization (males: 77/83% vs. 41% in control; females: 70/83 vs. 41% in control), necrosis (males: 24/29% vs. 11% in control; females: 7/17% vs. 6% in control), and intracytoplasmic brown pigmentation in either reticuloendothelial cells and/or hepatocytes (males: 4/42% vs. 0% in control; females: 3/16% vs. 0% in control). In males in the highest dose tested, also minimal to severe maturation arrest/atrophy/degeneration of the germinal epithelium in the testes was seen (90% vs. 70% in control), with secondary effects on the

prostate (decreased secretory product/atrophy: 19% vs. 7% in control). An increase in lymphoid cell depletion/atrophy of the spleen (21% vs. 4% in control) was observed in males at 1000 mg/kg bw/day, but primarily in those that died unscheduled deaths. In females the hemosiderosis was no longer seen, but instead an increase in (minimal to moderate) ovarian cysts (34/46% vs. 27% in control) was observed. No increase in the incidences of tumors were detected in any organ.
Although at the low dose (100 mg/kg bw/day) no histopathological lesions in the liver were observed, the increase in relative liver weight in male rats was such (23%) that the LOAEL in this study is set at 100 mg/kg bw/day.

Kennedy and Sherman (1986)
In a repeated dose toxicity oral study (not according to an OECD guideline; only one dose, insufficient documentation; incomplete histopathology), 6 male and 6 female CD rats/group received 0 or 1000 ppm DMAC in their diet (equivalent to 60 mg DMAC/kg bw/day) for 90 days. Examinations included clinical signs, body weight, food consumption, some hematology and clinical chemistry parameters, gross examination, weight and microscopic pathology of the main organs (adrenal, brain, kidney, liver, lung, spleen and testes). No toxic effects were detected except for a slight leukocytosis (increased leucocyte count; male/female: 28/16%) and slight anemia (decreased erythrocyte count; -17/-20%). Without any further effects, the toxicological relevance of the hematology findings is questionable.
The NOAEL in this limited study was 60 mg/kg bw/day, the only dose tested.

BASF (1975b)
In a subacute oral study (comparable to OECD guideline 407 but with limited documentation and no functional observational battery (FOB) and histopathology performed), 10 male and 10 female Sprague-Dawley rats/group were gavaged with 0, 290, 590, 1170 or 2350 mg DMAC (in water)/kg bw/day, for 5 days per week for 4 weeks. No detailed data is available in online registration dossier.
Clinical signs like ruffled coat and reduced general condition were seen at 1170 mg/kg bw/day, as well as significant decrease of body weight compared to controls (male/female: -21/-14%), and atrophy of testes and uterus. Lethal effects were observed at the high dose level of 2350 mg/kg bw/day (90/70%), with animals displaying ruffled coat, diarrhea, excitation, tremor, reduced body weight gain, yellow discoloration of liver and kidney, atrophy of testes and uterus, and local effects in the stomach. The two lower dose levels were less toxic, but still showed some of the clinical chemistry parameters and organ weight changes that were also affected at the two higher doses. These included increases in total serum lipids (in males and females ≥290 mg/kg bw/day), thin/filamentary uterine horns (290/590 mg/kg bw/day: 20/30% vs. 0% in control), relative liver weight (in both sexes ≥590 mg/kg bw/day) and relative kidney weight (in males at ≥590 mg/kg bw/day and females at ≥1170 mg/kg bw/day), and decreases in ALP (in males at ≥290 mg/kg bw/day and females at ≥590 mg/kg bw/day), absolute and relative heart weight (at ≥590 mg/kg bw/day in both sexes but with absolute heart weight also decreased in males at 290 mg/kg bw/day), absolute spleen weight (in both sexes at ≥590 mg/kg bw/day), and in absolute and relative adrenal weight (in females at ≥290 mg/kg bw/day). Reduced absolute and relative testicular weight, reduced absolute and relative weight of uterus and decreased absolute ovary weight were observed at ≥1170 mg/kg bw/day.
A LOAEL of 290 mg/kg bw/day was derived in the registration dossier, but needs verification by histopathology.

<u>Dermal</u>
No reliable repeated dose toxicity studies for DMAC were found for the dermal route.

Additional data from other studies-Dogs

In a semi-chronic dermal toxicity study (Horn, 1961) with limitation (strain unspecified; limited number of animals and parameters investigated; limited documentation), 1 male and 1 female dog per group (2 lowest doses) or 2 male dogs per group (2 highest doses) received 0, 0.10, 0.32, 1.0, 4.0 mL DMAC/kg bw/day (0, 94, 300, 940, 3760 mg/kg bw/day) to the clipped skin (open; 5 days/weeks; washing after 5 h exposure/day) for 6 months. Dogs at the 2 highest doses showed progressive impairment of health, with weight loss, clinical signs, and dogs dying after 15-16 days (at 3760 mg/kg bw/day) or sacrificed moribund after 6 weeks (at 940 mg/kg bw/day). These animals also showed skin irritation, skin lesions and liver damage (fatty degeneration), but kidneys (the only other organ examined in this study) were unremarkable. At a dose level of 300 mg/kg bw/day, one dog lost 2.1 kg of body weight over the first 2 months of treatment, but recovered 1.3 kg of this loss over the rest of the study. This animal also showed transient increases in ALP and BSP retention. No effects on body weight or ALP/BSP were observed in the other dog at 300 mg/kg bw/day, but this dog developed an ulcer. Both dogs at 300 mg/kg bw/day showed marked scaliness of the skin. Upon histopathology, the livers at the two lowest doses showed slightly reticulated cytoplasm, while the skin showed only some slight thickening and/or inflammatory reaction. The author concluded that 0.1 mL/kg bw/day appears a safe level with respect to liver damage. The same appears so for local skin effects.

B.5.2.1.2 NEP

A summary of the studies and the adverse effects are found in Table 5 below:

Table 5: Summary of studies informing on effects after repeated exposure to NEP

Species, strain, number, sex/group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Inhalation				
Rat Wistar 10 m 10 f OECD 413 EU Method B.29 (EC 440/2008) EPA OPPTS 870.3465 GLP: yes	90-day RDT 0, 30, 60, 200 mg/m^3 (nose/head only, vapour) 6h/day, 5d/week (total 65 exposures)	NOAEC local: 60 mg/m^3 NOAEC systemic: 200 mg/m^3 200 mg/m^3: degeneration and/or regeneration of olfactory epithelium	1	BASF (2013a)
Rat Wistar 10 m 5 f OECD 412 EU Method B.8 (EC 440/2008) GLP: yes	28-day RDT 0, 80, 200, 400 mg/m^3 (nose/head only, aerosol with vapour) 6h/day, 5d/week	NOAEC local: 80 mg/m^3 NOAEC systemic: 400 mg/m^3 200 mg/m^3: salivation, nose irritation, degeneration/regeneration of olfactory epithelium 400 mg/m^3: salivation, nose irritation, degeneration/regeneration of olfactory epithelium, epithelial alteration of cuboidal cells in larynx (f)	1	BASF (2011)
Oral				

Rat Wistar 10 m 10 f OECD 408 (EC 59/2001) GLP: yes	90-day RDT 0, 100, 300, 1000 mg/kg bw/day (feed)	NOAEL: 100 mg/kg bw/day 300 mg/kg bw/day: food consumption ↓ (up to -13.2/-7.5% in m/f), BW gain ↓ (-18.8/-23.5% in m/f), BW ↓ (up to - 8.7% in m/f), grip strength forelimbs ↓ (m: 33%) and motor activity (f: -30%), rel. liver weight ↑ (+13/7% in m/f), centrilobular hypertrophy of hepatocytes (m), rel. kidney weight ↑ (m: 14%), increased basophilic tubules and accumulation of hyaline droplets (m) 1000 mg/kg bw/day: food consumption ↓ (up to -21.1/-21.3% in m/f), BW gain ↓ (-39.1/52.6% in m/f), BW ↓ (up to -17.6/-18.3% in m/f), grip strength forelimbs ↓ (m: 40.1%), motor activity ↓ (f: -30%), rel. liver weight ↑ (+53/29% in m/f), abs. liver weight ↑ (m: 26%), centrilobular hypertrophy of hepatocytes (m/f), rel. kidney weight ↑ (+32/22% in m/f), increased basophilic tubules and accumulation of hyaline droplets (m), abnormal sperm heads ↑ (not specified)	1	BASF (2006)
Rat Sprague-Dawley 5 m 5 f OECD 407 GLP: not specified	28-day RDT 0, 5, 50, 250 mg/kg bw/day (gavage)	NOAEL: 250 mg/kg bw/day	2	Saillenfait et al. (2016)
Dermal – no relevant studies				
m: male, f: female, ↑: increased, ↓: reduced, abs.: absolute, BW: body weight, n.s.: not statistically significant, rel.: relative				

Inhalation

BASF (2013a)

In an inhalation study over 90 days (65 exposures) according to Good Laboratory Practice (GLP) and OECD guideline 413, 10 male and 10 female rats per dose group were exposed to NEP vapour for 6h/day on 5 consecutive days/week at concentrations of 0, 30, 60, and 200 mg/m^3 of the test item via nose/head-only inhalation exposure. On each exposure day a clinical examination was performed before, during and after exposure. Detailed clinical observation was performed at the beginning, midterm and end of the study. Ophthalmology was performed before the beginning of the exposure in all test groups and at the end of the end of the exposure in the control and high concentration group animals. Body weights and food consumption of the animals were determined weekly. At the end of the exposure period, functional observation battery and motor activity tests were performed. Against the end of the exposure period, urine was collected in all animals and analysed according to the guideline. On the day after the last exposure, blood was sampled and examined for a range of hematology and clinical chemical parameters as indicated in the guideline. After blood sampling the animals were sacrificed and subjected to necropsy (including macroscopic examination of the major internal organs and collection of organ weight data). In addition, sperm motility and total sperm head count (testis and caudal epididymides) were assessed. Selected tissues were processed histopathologically and were evaluated by light microscopy according to the OECD guideline.

The inhalation exposure did not lead to any exposure-related clinical signs of toxicity nor were there any effects on clinical chemistry, hematology, urine and sperm parameters. The target organ was the nasal cavity. Histological examination revealed signs of grade 1-3 (minimal-

moderate) degeneration and regeneration of the olfactory epithelium in the nasal cavity (levels I-IV) at the highest tested concentration of 200 mg/m^3 (Table 6). Body weight gain was slightly reduced (not specified) on some days during the exposure period at all exposure concentrations, but these changes were transient and not-dose related, and body weights were not significantly different between test groups and controls. Some additional changes in relative and/or absolute liver and ovary weights were observed at 60 and 200 mg/m^3, but these were either small, or not dose-related, or not statistically significant. Therefore, under the current test conditions, the NOAEC for local effects in the nasal cavity was at the mid concentration of 60 mg/m^3 and the NOAEC for systemic toxicity was at the high concentration of 200 mg/m^3.

Table 6: Histological findings in nasal cavity upon exposure to NEP

	Male animals				**Female animals**			
Test group concentration (mg/m^3)	0	1 (30)	2 (60)	3 (200)	0	1 (30)	2 (60)	3 (200)
Organs examined	10	10	10	10	10	10	10	10
Nasal cavity (level I)								
Degeneration/regeneration, olfactory epithelium								3
Grade 1								2
Grade 2								1
Nasal cavity (level II)								
Degeneration/regeneration, olfactory epithelium				7				7
Grade 1				5				4
Grade 2				2				2
Grade 3								1
Nasal cavity (level III)								
Degeneration/regeneration, olfactory epithelium				8				10
Grade 1				4				4
Grade 2				3				4
Grade 3				1				2
Nasal cavity (level IV)								
Degeneration/regeneration, olfactory epithelium				10				10
Grade 1				3				5
Grade 2				4				4
Grade 3				3				1

BASF (2011)

In a 28-day study according to GLP and OECD guideline 412, 10 male and 5 female rats per dose group received doses of 0, 80, 200, and 400 mg/m^3 NEP as a liquid aerosol with vapour fraction via nose/head-only inhalation exposure for 4 weeks on 5 consecutive days per week and 6h/day. A concurrent control group was exposed to air. On each exposure day a clinical examination was performed before, during and after exposure. Body weights and food consumption of the animals were determined weekly. On the day after the last exposure, blood was sampled and examined for a range of hematology and clinical chemical parameters as indicated in the guideline. After blood sampling the animals were sacrificed and subjected to necropsy (including macroscopic examination of the major internal organs and collection of organ weight data). Selected tissues were processed histopathologically and were evaluated by light microscopy. Histological examinations were performed in respiratory tract, liver and testes according to standardized methods.

During the exposure period the animals of the control group and low concentration (80 mg/m³) showed no clinical signs and findings different from control. During the exposure period several animals of the intermediate and high concentration (200 and 400 mg/m³) showed abnormal clinical signs including salivation, red encrusted nose, nose discharge,

lacrimation of eyes. These signs were only observed directly after the daily exposure period and fully reversible before the start of next exposure. On the post-exposure observation day all animals were free of clinical signs. No treatment-related changes among clinical chemistry parameters, food consumption, or hematology were measured. Some transient decreases in body weight gain were observed in males at 400 mg/m^3 on study days 4 and 8 and in females at 200 mg/m^3 on study day 3, but overall, body weights were not significantly different between test groups and controls. Histopathologically, only the respiratory tract was affected, with degeneration and/or regeneration of the olfactory epithelium in the nasal cavity of animals of the mid and high dose group which was regarded to be treatment related. Furthermore, all female and 7 male animals of the high dose group showed minimal focal epithelial alteration of cuboidal cells in the larynx at the base of epiglottis (level I), as compared to 1/5 females and 5/10 males in the control group. In females, a treatment-related effect cannot be ruled out. Under the test conditions of this 28 day-study, the NOAEC for local effects in the nasal cavity was 80 mg/m^3 while the NOAEC for systemic effects was 400 mg/m^3.

Oral

BASF (2006)
In a subchronic oral study according to GLP and OECD guideline 408, NEP was administered to groups of 10 male and 10 female Wistar rats at doses of 0, 100, 300 or 1000 mg/kg bw/day in feed over a period of three months. Dietary concentrations of NEP for each group and sex were adjusted weekly, based on body weight and food consumption measurements from the previous week. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. An FOB and measurement of motor activity was carried out. Vaginal smears for estrus cycle determination of all female animals were prepared and evaluated each day during the last 4 weeks of the study. Clinicochemical, hematological examinations and urinalyses were performed towards the end of the administration period. Ophthalmological examinations were performed before and towards the end of the administration period. All animals were assessed by gross pathology, followed by histopathological examinations. Additionally, sperm parameters were determined immediately after necropsy and organ weight determination.
NEP caused substance-related effects at 300 and 1000 mg/kg bw/day in both sexes of rats and at 100 mg/kg bw/day in males. Food consumption in both sexes was statistically significantly decreased during the whole study period at 1000 mg/m^3 (up to -21.1% in males and -23.3% in females) and on several days over the study period at 300 mg/kg bw/day (up to -13.2% in males and -7.5% in females). In both sexes body weight was significantly decreased at concentrations of 1000 mg/m^3 from day 7-91 (-17.6% in males and -18.3% in females at sacrifice) and 300 mg/m^3 (up to -8.7% in both sexes). Body weight gain was statistically significantly decreased during the whole study period in both sexes at 300 (up to -18.8% in males and -23.5% in females) and 1000 mg/kg bw/day (up to -39.1% in males and -52.6% in females). Grip strength of the forelimbs was significantly decreased in males at 300 and 1000 mg/kg bw/day (-33% and 40.1%, respectively) and overall motor activity was decreased in females at 1000 mg/kg bw/day (-30%). Relative liver weight was increased at 100 (+7% in males), 300 (+13% in males; +7% in females) and 1000 mg/kg bw/day (+53% in males; +29% in females). Absolute liver weight was increased at 1000 mg/kg bw/day in males (+26%). Relative kidney weight was increased in males at 100 and 300 mg/kg bw/day (+9/14%, respectively) and in both sexes at 1000 mg/kg bw/day (+32% in males; +22% in females). Histomorphologically, centrilobular hypertrophy of hepatocytes could be correlated to the increased liver weights in both sexes at the high dose and in males at the low and mid doses, with a dose-dependent increase in severity seen in males. The kidneys of male rats in all treated groups showed an increase of basophilic tubules and accumulation of hyaline droplets, confirmed immunohistochemically as alpha 2µ globuline.

These findings are considered not relevant to humans as they are due to a male rat specific mechanism. Beyond the findings above, there were some effects on clinical chemistry and hematology parameters, mainly observed at 1000 mg/kg/day. Additionally, sperm examination showed an increased number of sperms with abnormal heads in males receiving 1000 mg/kg bw/day (11.4% vs. 2.0% in controls; 8 males with >4% abnormal sperm vs. 0 in controls). This was not associated with any weight changes or (histo)pathological changes in the testis, nor did administration of 1000 mg/kg bw/day affect the number of homogenization resistant spermatids, epididymal sperm count and sperm motility. Since the liver hypertrophy is probably more adaptive than adverse and there are no other effects on hepatotoxic biomarkers such as AST, ALT, ALP and bilirubin, the overall NOAEL under the conditions of this study was 100 mg/kg bw/day.

Saillenfait et al. (2016)
In a 4-week repeated dose study according to GLP and OECD guideline 407, NEP diluted in distilled water was orally administered by gavage to male and female Sprague-Dawley rats at doses of 0 (vehicle control), 5, 50, and 250 mg/kg/day for 28 consecutive days. The parameters assessed in males and females included clinical observations, body and organ weight, haematology, clinical chemistry, urinalysis, liver cytochrome P450, and histopathology of thymus, spleen, liver, kidneys, and right epididymis and testis (males). Nevertheless, due to technical problems with the metabolic cages, reliable urine samples for accurate urinalysis were only obtained for a few animals in the female study. Therefore, a second study was conducted in female rats with an identical protocol, except for haematology and clinical chemistry which were not further evaluated.
Transient decreases in body weight and body weight gain of the males were observed during the first days of treatment at 50 and 250 mg/kg/day. Growth was normal thereafter but the body weight at the high dose remained slightly lower (8-9%) than in controls. There was a marked increase in urine volume at the beginning of treatment in males and female rats at doses of 50 and 250 mg/kg/day. No biologically significant differences were observed in hematological and clinical chemistry values (including hepatoxicity biomarkers) in males and females at necropsy. There was a significant increase in relative kidney weight ratio in females at doses of 50 and 250 mg/kg bw/day, but only in the first study. Histological examination revealed a minimal increase in hyaline droplets in the renal tubules of the kidneys of one male rat at the mid dose and four males at the high dose, likely due to accumulation of alpha 2µ globuline (as shown by immunochemistry). Additionally, minimal or slight hepatocellular centrilobular hypertrophy was seen in the liver of all males at 250 mg/kg/day, presumably related to a moderate liver enzyme induction (1.7-fold increase in total P450 concentration and 2.3-fold increase inCYP2E1 activity). CYP2E1 activity was also slightly increased in females at 250 mg/kg bw/day (1.6-fold), but without liver pathology. Minimal tubular degeneration was noted in the testis of a single male at 250 mg/kg bw/day. The results of this study demonstrate that NEP results in mild renal and hepatic effects in male, but not female, rats at 250 mg/kg bw/day. As the renal effects can be considered male rat specific, and the liver hypertrophy is probably more adaptive than adverse, the NOAEL in this study is 250 mg/kg bw/day, the highest dose tested. It is noted that this dose was probably too low to detect adverse effects, given that hardly any toxicity was seen at a dose of 500 mg/kg bw/day in a 14-day range-finding study. In addition, adverse effects in the previously conducted 90-day study started from >300 mg/kg bw/day.

Additional information from other studies - rabbits
In some, but not all, oral developmental toxicity studies, described in detail in section B.5.3.2 Toxicity for development, effects on the liver and kidney were observed. Two developmental toxicity studies in rabbits (performed according to GLP and to OECD 414 guidelines; (BASF, 2007a, 2007b) showed an increase in relative liver and kidney weight and enzymatic activity in pregnant animals after exposure to 200/220 mg/kg bw/day. This could indicate mild liver damage, but no histopathological analysis was performed. In combination, the two studies

provide a NOAEL for maternal toxicity (conservatively set) of 60 mg/kg bw/day, based on indications for (mild) liver toxicity at 200/220 mg/kg bw/day. When integrating these rabbit studies with the rat studies described above, the overall NOAEL for repeated dose (liver) effects is 100 mg/kg bw/day.

Dermal

No relevant studies with NEP.

B.5.2.2 Human data

B.5.2.2.1 DMAC

Human evidence from case reports demonstrates there is a clear relationship between liver impairment and DMAC exposure in humans occupationally exposed. However, exposure levels were reported as ranges with high uncertainty or not reported at all.

Inhalation and dermal
Gong et al. (2016) reported a rare case (42-year-old male worker) suffering from severe acute toxic hepatitis with short term recurrence induced by renewed contact with DMAC. A field test indicated the 8h time weighted average concentration in the factory was 12.6 mg/m^3, i.e. lower than the national standard in China of 20 mg/m^3. However, 15-min peak exposures ranged up to 45 mg/m^3. Six other workers were investigated from the same worksite of which 2 females had abnormal hepatic function. 1 month of rest at home restored the liver function. Corsi (1971) reported abnormal liver function in 14 individuals from an investigated group of 41 workers that were exposed to DMAC for 2-10 years.

Spies et al. (1995a, 1995b) investigated hepatotoxicity through clinical chemistry parameters but did not observe significant toxic effects in workers of an acrylic fibre manufacturing facility. Exposure was measured over a 1-year period by full-shift (12h) personal air monitoring of DMAC and biological monitoring of DMAC, NMAC and acetamide. 93 of 127 male workers, in 7 job classifications (1 job from the solution preparation department, 6 jobs from the spinning department), with potential exposure to DMAC were monitored on the second consecutive workday, after at least 3 days off, for the first 10 months of the study and on both the first and second days during the final 2 months of the study. Post-shift urinary NMAC levels were significantly correlated with DMAC levels. An air level of 6.7 ppm (24 mg/m^3; threshold limit value (TLV)) 12h time-weighted average (TWA; equivalent to 10 ppm (36 mg/m^3) 8h TWA) corresponded to a urine NMAC level of 62 mg NMAC/g creatinine in a post-shift spot urine sample obtained after the second consecutive workday. A level of 35 mg NMAC/g creatinine in post-shift spot urine sample was recommended as a biomonitoring index (Spies et al., 1995a). Evidence of liver toxicity in the workers was assessed by serum total bilirubin, AST, ALT, alkaline phosphatase and gamma-GTP at least once during the study period for all 127 exposed workers and 217 workers with no previous or current exposure to DMAC. Workers were classified as high exposed if one or more biomonitoring results exceeded triggers of 60 mg NMAC/g creatinine or 136 mg DMAC equivalent/g creatinine. Exposures were classified as unspecified if biomonitoring results did not exceed either trigger. The geometric mean concentration of DMAC in air over the study period was 1.9 ppm 12h-TWA in the high exposure group (21 workers, 96 air measurements; arithmetic mean estimated at 3 ppm 12h-TWA) and 1.3 ppm 12h-TWA in the unspecified exposure group (106 workers, 294 air measurements). No significant DMAC exposure-related trends in serum chemistries were detected. Existing liver disease during the study period was not found to be a confounder; neither was age for total bilirubin, ALT and alkaline phosphatase and alcohol for all but gamma-GTP. The authors concluded that brief TLV exposures and chronic low level exposures (1.9 ppm or 6.9 mg/m^3 12h-TWA, equivalent to 10.3 mg/m^3 8h-TWA) do not cause

hepatotoxic clinical chemistry responses. No conclusions regarding hepatoxic effects of long-term exposure to the TLV could be made (Spies et al., 1995b).

Jung et al. (2007) reported an indication for increased hepatic injury in monitored workers. In a study with 1045 workers exposed to DMAC from January 2001 to July 2004 in two plants producing polyurethane elastic fibres, DMAC as solvent was used and is described. A pre-placement health examination, post-placement health examinations every 10 days for the next three months, and semi-annual periodic health examinations thereafter were performed; pre-placement health examination included hepatic function tests, AST, ALT, and gamma-GTP, and tests for viral hepatitis; urine NMAC (marker for DMAC exposure) were tested at the semi-annual periodic health examinations. Urine sampling was conducted only during the period 2003-2004. Correlation between DMAC exposure and hepatotoxic effects was not clear (exposure was related to the biological exposure index of 30 mg NMAC/g creatinine, but urine sampling was conducted only during the second half of the monitoring period; there were no data about inhalation exposure concentration or dermal exposure; low number of urine samples). Data on biological exposure index are not suitable for quantitative estimation of DMAC exposure. There were some indications for DMAC-induced hepatic injuries in 38 out of 1045 monitored workers but there was no sufficient quantitative data on exposure (Jung et al., 2007).

The relationship between the incidence of hepatic injury among new employees in a cohort of elastane fibre workers and exposure to DMAC was studied by Lee et al. (2006). Elastane fibre workers exposed to DMAC were monitored for hepatic injury. Four hundred and forty (440) new workers employed from 1 January 2002 to 31 July 2004 were included as study subjects. DMAC exposure estimates were based on urinary NMAC concentrations. Each new worker completed a preplacement health examination (serum hepatic function tests such as ALT, AST, and gamma-GTP levels, and serological tests for viral hepatitis B and C). No relevant effects were detected at this pre-placement examination. The new workers were monitored with follow up hepatic function tests every 10 days for 3 months, and all DMAC exposed workers had a periodic health examination every 6 months. Urinary NMAC measurement was added to the biannual regular health examination from 2003 (comment: no data from 2001). There were 28 cases of DMAC induced hepatic injury. Incidence rates were 7 (cut-off exposure classification >30 mg NMAC/g creatinine) or 10 times (cut-off exposure classification >20 mg NMAC/g creatinine) higher in high exposure groups than in low exposure groups. Odds ratios for DMAC-induced liver injury of 3.70 (95% CI 1.33-10.26; $p<0.05$) and 4.67 (95% CI 1.66-13.15; $p<0.01$) were determined for >20 mg or >30 mg NMAC/g creatinine. Fewer DMAC induced hepatic injuries occurred among workers employed for a longer period; workers whose exposure duration was more than 7 months showed no hepatic injury in either the high or low exposure groups. The results showed some indication for increased hepatic injury in workers employed with DMAC exposure, but there was not sufficient evidence to conclude on a dose dependency of these effects (Lee et al., 2006).

In a retrospective study by Wang and Chen (2020), 60 factory workers of a DMAC plant (47 males and 13 females, aged 21-51) were included for a 2-year treatment (January 2017 to January 2019) with a combination of Chinese drugs (reduced glutathione, polyene phosphatidylcholine, glycyrrhizin compound, Hugan tablets and ornithine aspartate). Serum levels of ALT, AST, LDH, gamma-GTP, ALP, bilirubin and ammonia were measured before and after drug treatment. Livers were examined via ultrasonic and CT imaging. Workers were exposed to DMAC via dermal, inhalation or other means, and included in this study only when they had normal liver function before working with DMAC (exposure levels not specified), and had levels of ALT and AST in this study considered unhealthy of >50 U/l and >40 U/l, respectively. 58.3% of workers had no obvious clinical symptoms after DMAC exposure, while 41.7% felt fatigue and weakness, and 21.7% felt upper abdominal discomfort and loss of appetite. About 8.3% of workers suffered from mild yellow staining of skin and sclera. Fatty

liver and intrahepatic calcifications were found in 41.7% and 28.3% of workers, respectively. Enzymatic levels of 490.88±72.51 U/l and 210.88±29.44 U/l were measured for ALT and AST, respectively. Values of ALT and AST were significantly reduced upon drug treatment in 61.7% and 71.7% of workers, respectively. A relation between ALT concentration (before drug treatment) and hospitalization time was found. On the other hand, smoking did not affect hospitalization time. According to the authors, DMAC-induced hepatoxicity could thus be treated via timely monitoring and suitable treatments.

In another retrospective study in workers from four European man-made fibres factories conducted for Industrievereinigung Chemiefaser e.V. (Antoniou et al., 2021), enzyme levels (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT)) combined with data on indications for liver injuries (hepatocellular, mixed and cholestatic) were analysed. Exposure to DMAC was determined via area sampling with permanently installed, continuous measuring systems or with discontinuous sampling procedures during a work shift (the position of the sampler was fixed next to the workstation in the breathing area where the worker worked most of the time). From this, the 50th (median) and 90th (as the higher representation of exposure of each year) percentile (median) of the DMAC exposure distribution was determined based on 8h TWA measurements of all air exposures (in ppm) for each year. This resulted in in eight exposure groups (median: 0.00-0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00, 2.01-2.50, 2.51-3.00, 3.01-4.00 and 4.01-6.00 ppm; published as supplementary material to the article). Exposure data were mostly from the fibre production area (the highest exposure) from the four factories, but also included other areas from one factory (polymerisation, dispersions, solvent recovery, cutter and baler, pack-room and laboratory). See Table 7 for more details. Although the results for all enzymes measured were presented, the analysis was conducted on ALT and AP levels only, as GGT and AST levels were considered of less specificity for liver disease. Levels of ALT were compared to ALT levels considered normal values (40 IU/l) and defined as upper limit normal (ULN) in three groups: ≥2× ULN (indication for possibly elevated ALT), ≥3× ULN (possibly elevated ALT) and ≥5× ULN (clearly elevated ALT). Out of 1844 observations for ALT enzyme levels, 29 (1.5%), 4 (0.2%) and 1 (0.05%; not specified in which exposure group) were identified as ≥2×, ≥3× and ≥5× ULN, respectively (see Table 8). An (inverse) association between DMAC exposure and ALT enzyme levels was noted. Liver injuries, as defined on the basis of biochemical criteria using ALT and AP levels, included 2 (0.1%; 1 observation in 0.51-1.00 and 1 in 3.01-4.00 ppm exposure group) observations of (indicative) hepatocellular injury, 5 (0.3%; 3, 1 and 1 observations in 0.00-0.50, 0.51-1.00 and 1.51-2.00 ppm exposure groups, respectively) observations of mixed injuries and 0 observations of cholestatic injuries. According to the authors, no indication of a relationship between DMAC exposure and elevated levels of ALT and/or increased observations of liver injuries were noted even at DMAC levels equal to or above current OELs. It was remarked by the authors that their study did not contain data on confounders such as alcohol or drug use amongst workers. However, confounding was considered not to have played a major role in the analysis, as a null effect was observed.

Table 7: Description of worker populations and data from different man-made fibres companies

	Company A	**Company B**	**Company C**	**Company D**
No. of observations included in this study (No. of workers and measurements)	959 (ALT) + 951(AP) (150, on average 6 measurements per persoon)	100 (ALT) (62 workers and on average 2 measurements per person)	513 (ALT) (at least 10/exp. group)**	272 (ALT) (at least 10/exp. group)**
Working area	Fibre production and others*	Fibre production	Fibre production	Fibre production
DMAC exposure area	Calculated median	Calculated	Calculated median	Calculated median

measurement (8h-TWA)	and 90th percentiles	median and 90th percentiles	and 90th percentiles	and 90th percentiles
Liver tests	ALT, AP, AST, GGT	ALT, AST, GGT	ALT, AST, GGT	ALT, AST, GGT
Year of DMAC and liver measurement/follow-up	2012-2019	2016-2020	1977, 1980-1990, 1992,1994, 1998-2006, 2008, 2011-2014, 2016-2019	1992-2001, 2003-2007, 2010-2011, 2013, 2015, 2017-2019
Type of anonymized liver enzyme data	Individual data	Individual data	DMAC exposure groups	DMAC exposure groups

* others: polymerization, dispersions, solvent recovery, cutter and baler, pack-room, laboratory, ** Matching no. of workers and observations not possible due to data protection policy

Table 8: Observations of elevated levels of liver enzyme alanine aminotransferase per 50th perctile exposure group in man-made fibre workers

DMAC exposure group (50th percentile, ppm)	Observations (N)		
	Total	ALT ≥2× ULN*	ALT ≥3× ULN*
0.00-0.51	499	4	0
0.51-1.00	209	2	0
1.01-1.50	299	8	1
1.51-2.00	320	7	2
2.01-2.50	253	6	0
2.51-3.00	120	1	0
3.01-4.00	68	1	1
4.01-6.00	75	0	0

*ULN=40 IU/L; ALT: alanine aminotransferase

In a clinical study 8 male volunteers (20-32 years old, mean body weight 75 kg) were exposed to 10 ppm DMAC (36 mg/m^3, whole body, vapour) for 6h per day on 5 consecutive days. Measured parameters were behavior, porphyrin excretion in urine (24-h samples every day), urine analysis, blood sampling (before and after study period) for hematology and clinical chemistry. The study resulted in a porphyrin excretion in a normal human range and pre- and post-exposure values for hematology, clinical chemistry and urinanalysis within normal limits. No toxic effects were reported after exposure to 10 ppm DMAC for 5 days (DuPont, 1974).

A few other studies investigating exposure or toxicokinetics of DMAC in humans did not investigate and/or report systemic toxic effects (Antoniou et al., 2021; Borm et al., 1987; Kennedy Jr & Pruett, 1989; Maxfield et al., 1975; Nomiyama et al., 2000; Perbellini et al., 2003; Princivalle et al., 2010). Some of these studies investigated the relationship of external exposure to DMAC with internal/urinary metabolite concentrations. The reported average exposure levels by Borm et al. (1987) ranged from 6.1 to 22.2 ppm (22 to 79.9 mg/m^3), no correlation between DMAC air concentrations and urinary samples was found, concluding a large portion of exposure must have been via the dermal route. The DMAC air concentration in the study by Kennedy Jr and Pruett (1989) was lower, 1.8-7.2 mg/m^3 and they did find a relationship between air (1 ppm) and urinary NMAC (10 ppm). Although no toxic effects were observed in any of these studies, this was also not the focus of the studies.

A summary of epidemiology studies describing liver effects related to (mostly inhalation) exposure to DMAC and possibly relevant to derive effects levels in humans can be found in Table 9.

Table 9: Summary of epidemiology studies with workers exposed to DMAC

Type of data/report	Exposure concentrations (if applicable)	Relevant information about the study	Study observations	Dossier Submitter observations	Reference
Case report	12.6 mg/m^3 (8h TWA) Up to 45 mg/m^3 (15 min peak exposures) Occupational exposure in a polymide film factory	7 workers exposed to DMAC for 3 to 6 months	42-year-old male worker suffered from severe acute toxic hepatitis upon exposure for approximately 6 months. Six other workers were assessed upon this case. In 2 female workers, abnormal liver function (increased direct and total bilirubin, and increased AST and ALT levels) was noted. Liver function restored upon 1 month of rest at home.	No dose-response or effects levels can be established.	Gong et al. (2016)
Cohort study	Air concentrations not reported Occupational exposure	41 workers exposed to DMAC 2-10 year	Abnormal liver function 14/41 workers. Association was found between impaired liver function and duration of exposure to DMAC.	No dose-response or effects levels can be established.	Corsi (1971)
Cohort study	Unspecified exposure group (106 workers): 1.3 ± 2.1 ppm (12h TWA; 4.7 mg/m^3) High exposure group (21 workers): 1.9 ± 2.6 ppm (12h TWA; 7.2 mg/m^3) Occupational exposure in an acrylic fibre manuafacturing facility	127 male works exposed to DMAC in 12-hour shifts 217 male in-plant controls (no previous or current exposure to DMAC). 1-year study period and follow up Biomonitoring of NMAC in urine samples. Evidence of liver toxicity was assessed by serum clinical chemistry tests (serum levels of total bilirubin, AST, ALT, ALP, and gamma-GTP)	Biomonitoring results of 21 of 217 workers did exceed one of the biomonoitoring trigger values of 60 mg NMAC/g creatinine or 136 mg DMAC equivalent/g creatinine, and formed the high-exposure group. The other 106 workers formed the unspecified-exposure group. Unspecified exposure group (106 workers): 13.5 ± 2.3 mg NMAC/g creatinine High exposure group (21 workers): 26.7 ± 2.7 mg NMAC/g creatinine No significant DMAC exposure-related trends in hepatic serum clinical chemistry results were detected..	A no-effect level of 7.2 mg/m^3 for a 12h TWA (equivalent to a 8h TWA of 10.8 mg/m^3) could be deduced.	Spies et al. (1995a, 1995b)
Cohort study	Air concentrations not reported Occupational exposure in two plants producing polyurethane elastic fibres	1045 workers exposed to DMAC from January 2001 to July 2004 (3.5 years) Biomonitoring of NMAC in urine samples during 2003-2004. Hepatic function tests, serum clinical chemistry tests (AST, ALT, and	Median concentration (in department with 21 cases linked to liver injury) was 25.1 mg NMAC/g creatinine (range 4.6-196; 228 samples). Median concentration (not linked to liver injury) was 11.8 mg NMAC/g creatinine (range 0.1-133.9; 1056 samples).	No dose-response or effects levels can be established.	Jung et al. (2007)

		gamma-GTP), and tests for viral hepatitis.	Median concentrations between groups not statistically significantly different. Hepatic injuries in 38 of 1045 monitored workers. Data on biological exposure index are not suitable for quantitative estimation of DMAC exposure.		
Cohort study	Air concentrations not reported Occupational exposure in a plant producing elastane fibres	440 new workers followed from January 2002 to July 2004 (2.5 years) Biomonitoring of NMAC in urine samples. Serum clinical chemistry tests (AST, ALT, and gamma-GTP) and serological tests for viral hepatitis B and C. Hepatic injury defined as: ALT activity >2 upper limit normal activity or ratio serum ALT/ALP ≥5.	There were 28 cases of DMAC-induced hepatic injury. OR for DMAC-induced liver injury was 3.70 (95% CI 1.33-10.26; p<0.05) for >20 mg NMAC/g creatinine. OR for DMAC-induced liver injury was 4.67 (95% CI 1.66-13.15; p<0.01) for >30 mg NMAC/g creatinine. No hepatic injury in workers exposed >7 months in high or low exposure groups. Incidence rates were 7 (cut-off exposure classification >30 mg NMAC/g creatinine) or 10 times (cut-off exposure classification >20 mg NMAC/g creatinine) higher in high-exposure groups than in low-exposure groups. Fewer DMAC induced hepatic injuries occurred among workers employed for a longer period.	No dose-response or effects levels can be established.	Lee et al. (2006)
Cohort study	Air concentrations not reported Occupational exposure in a DMAC-plant	60 workers (47 males, 13 females, aged 21-51) from January 2017 to January 2019 (2 years). Workers were treated with a combination of Chinese drugs (reduced glutathione, polyene phosphatidylcholine, glycyrrhizin compound, Hugan tablets and ornithine aspartate). Ultrasonic and CT imaging of livers, serum clinical chemistry tests (AST, ALT, LDH, bilirubin, ammonia and gamma-GTP).	58.3% of workers had no obvious clinical symptoms after DMAC exposure. 41.7% felt fatigue and weakness, and 21.7% felt upper abdominal discomfort and loss of appetite. About 8.3% of workers suffered from mild yellow staining of skin and sclera. Fatty liver and intrahepatic calcifications were found in 41.7% and 28.3% of workers, respectively. Enzymatic levels of 490.88±72.51 U/l and 210.88±29.44 U/l were measured for ALT and AST,	No dose-response or effects levels can be established.	Wang and Chen (2020)

		Unealthy liver function (determined before start of study) was >50 U/l and >40U/l for ALT and AST (respectively)	respectively. Values of ALT and AST were significantly reduced upon drug treatment in 61.7% and 71.7% of workers, respectively.		
Cohort study	50th and 90th percentiles of the DMAC exposure distribution determined as representation of exposure to DMAC for each year (8 h TWA), resulting in eight exposure groups (based on 50th percentile): 0.00-0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00, 2.01-2.50, 2.51-3.00, 3.01-4.00 and 4.01-6.00 ppm Occupational exposure in five man-made fibre factories	2795 exposure-outcome observations (1977-2020) Liver function was based on ALT levels; normal levels 40 IU/L defined as upper limit normal (ULN). Three defined levels: ≥2× ULN (indication for possibly elevated ALT), ≥3× ULN (possibly elevated ALT) and ≥5× ULN (clearly elevated ALT)	Out of 1844 observations: 29 (1.5%), 4 (0.2%) and 1 (0.05%) were identified as ≥2×, ≥3× and ≥5× ULN, respectively. An (inverse) association between DMAC exposure and ALT enzyme levels was noted. Liver injuries included 2 (0.1%) observations of (indicative) hepatocellular injury and 5 (0.3%) observations of mixed injuries.	A no-effect level of 21.7 mg/m^3 for a 8h TWA could be deduced	Antoniou et al. (2021)
Clinical study	36 mg/m^3 whole-body, 6 h/day, 5 days	8 male volunteers Endpoints studied: behavior, porphyrin excretion in urine (24-h samples every day), urine analysis, blood sampling (before and after study period) for hematology and clinical chemistry	No (toxic) effects observed.	A no-effect level of 36 mg/m^3 for short-term exposure.	DuPont (1974)

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, gamma-GTP: gamma glutamyltranspeptidase, LDH: lactate dehydrogenase, OR: odds ratio, TLV: threshold limit value level

Dermal

Baum (1997) presented 2 case reports where 2 females suffered from hepatic injury after being accidentally exposed to high concentrations of DMAC (unclear how much and how long), mainly via the dermal route. The two females, 25 and 39 years of age, also had clinical signs of jaundice, icterus and dark urine. Clinical chemistry revealed liver effects in both females with altered liver functions and severe effects observed in the older woman. The liver biopsy of this female revealed toxic hepatitis.

Intravenous

In a clinical observation case study 17 patients with malignant tumors were treated with DMAC in a phase 1 study to discover its potential antitumor activity (Weiss et al., 1962). After repeated i.v. application of DMAC 15 patients survived long enough for effect evaluation; only 2 gave any evidence of objective remission of disease. DMAC was applied as a 10% solution at dose levels from 100-610 mg/kg bw/day up to 5 days. Within 24 h after application, severe vomiting occurred, and seven patients experienced liver toxicity (measured as serum GOT; old term for AST). DMAC exposure resulted in influence on the central nervous system (≥400 mg/kg bw abnormal mental status: depression, lethargy, disorientation, confusion, visual and auditory hallucinations). The signs appeared with delay (indicating an effect of DMAC-

metabolites), were accompanied by slowed EEG signals and were reversible at the end of the therapy. The study was too limited to eliminate DMAC as an effective chemotherapeutic agent for human malignancy. The authors discussed a potential in the field of neuropsychiatry for hallucinogenic effects of DMAC.

B.5.2.2.2 NEP

No relevant studies.

B.5.2.2.3 Conclusion

No relevant human data is available for NEP. For DMAC several case reports and cohort and clinical studies are available. Some of these studies indicate that liver effects after DMAC exposure found in animals are also relevant to humans. However, as no concentrations of DMAC in the air were reported, no dose-response information could be retrieved from these studies. In other studies, in which DMAC air concentrations were reported, no evidence for liver effects was seen. From these studies it appears that short-term exposures at the level of the OEL (10 ppm (36 mg/m^3) 8h TWA) are not (liver) toxic (DuPont, 1974; Spies et al., 1995a, 1995b). For chronic exposure, an overall no-effect level of 6 ppm (21.7 mg/m^3; 50th percentile) 8h TWA can be deduced from the Antoniou et al. (2021) study. This study is given preference over the Spies et al. (1995a, 1995b) study (no-effect level 1.9 ppm (6.9 mg/m^3) 12h TWA, equivalent to 10.3 mg/m^3 8h TWA), given that it concerns more recent data from more workers, over more years and from work associated with the highest DMAC exposure.

B.5.3. Toxicity for reproduction

DMAC and NEP are both classified as Repr. 1B; H360D and may damage the unborn child.

The information for DMAC and NEP on this endpoint was gathered from the registration dossiers, OECD SIDS for DMAC (OECD, 2001), previous CLH proposals for DMAC (ECHA, 2013) and NEP (ECHA, 2011c) and study reports that were available. Effects described in tables are significant, unless stated otherwise. Effect levels not specified with study data are indicated as 'not specified'.

B.5.3.1. Toxicity for sexual function and fertility

B.5.3.1.1 DMAC

A summary of the studies and the adverse effects on sexual function and fertility are found in Table 10 below:

Table 10: Summary of studies informing on effects on reproductive performance after exposure to DMAC

Species, strain, number and sex/group	Study type, duration, dose levels	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Inhalation				
Rat Crl: CD® 10 m 20 f OECD guideline 415 with	1-generation reproduction toxicity study 10-18 weeks 0, 30, 100, 300 ppm (0, 110, 360, 1080 mg/m^3, whole body, vapour)	NOAEC reproductive toxicity/fertility: 300 ppm (1080 mg/m^3) NOAEC pup toxicity: 100 ppm (360 mg/m^3) No statistically significant differences in reproductive indices at any dose tested.	2	DuPont (1983b); Ferenz and Kennedy Jr (1986)

restrictions (limited endpoints) GLP: not specified	Prebreeding: 6h/day, 5d/week (10 weeks) Breeding, gestation, lactation: 6h/day, 7d/week (7-8 weeks) Males: 63 exposures Females: 89-104 exposures	F1: 300 ppm: BW PND 21 ↓ (-7-13%), rel. liver weight ↑ (7-11%)		
Rat Sprague-Dawley 12 m No guideline study GLP: not specified	Male fertility study 15 weeks 0, 40, 120, 400 ppm (0, 140, 430, 1400 mg/m^3, whole body, vapour) 6h/day, 5d/week (69 exposures)	NOAEC reproductive toxicity/fertility: 400 ppm (1400 mg/m^3) NOAEC foetal toxicity: 400 ppm (1400 mg/m^3) No statistically significant differences in reproductive indices at any dose tested.	2	Monsanto (1982a); Wang et al. (1989)
m: male, f: female, ↑: increased, ↓: reduced, abs.: absolute, FSH: follicular stimulating hormone, LH: luteinizing hormone, n.s.: not statistically significant, PND: postnatal day, rel.: relative				

Inhalation

DuPont (1983b); Ferenz and Kennedy Jr (1986)
In a one-generation reproduction toxicity study in rats (OECD guideline 415 with limited endpoints), 10 male and 20 female Crl: CD rats/group were exposed to 0, 30, 100, 300 ppm DMAC (0, 110, 360, 1080 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week for 10 weeks (prebreeding). This was followed by treatment for 6 h per day, 7 days per week, 7-8 weeks (breeding, gestation and lactation). Mating started when rats were 100 days old (each male was placed in a cage with two females). The exposure period ended upon completion of the breeding period (males) or at 21 days postpartum (females). In parent animals (F0), relative liver weights were increased at 300 ppm in males (18%) and females (16%). After a 20-day recovery period, the relative liver weights were still slightly, but not statistically significantly, increased. Enlarged testes were noted at 30 ppm (20% vs. 0% in control), but not in other dose groups. Testes weight was unaffected, as was ovarian weight. Histopathology was not performed. No statistically significant differences in mating, fertility, gestation, viability and lactation indices were found at any dose tested, nor was gestation length affected. Pups in treated groups were not different from control pups with respect to clinical signs, physical appearance, developmental parameters (age of pinna detachment, hair growth and eye opening) and gross pathological findings. On PND 1, 4 and 21, body weights of pups from rats exposed to 300 ppm were slightly lower than those of controls, but not always statistically significantly. At PND 21, the decrease was statistically significant for male pups from litters where both parents were exposed to 300 ppm (decrease 7%) and for male and female pups from litters where only the dams were exposed to 300 ppm (decrease 13%). In these pups the relative liver weights (7-11%) were increased, probably related to the decrease in body weight. As DMAC produced no effects on the reproductive performance of rats at any dose tested, the NOAEC for fertility was 300 ppm (1080 mg/m^3), the highest dose tested. It is noted that the high dose chosen for this study was too low, given that little to no general toxicity was observed. The NOAEC for pup toxicity was 100 ppm (360 mg/m^3), based on a slight decrease in pup body weight at 300 ppm.

Monsanto (1982a); Wang et al. (1989)
In a fertility study, 12 male Sprague-Dawley rats/group were exposed to 0, 40, 120 or 400 ppm DMAC (0, 140, 430, 1400 mg/m^3, whole body, vapour) for 6 h per day, 5 days per week for 15 weeks. After 43 exposures (64 days), 1 male was cohoused with 2 unexposed females. The study was terminated for males at week 15 after 69 exposures (no post exposure observation period), and females were sacrificed at GD 20. Relative liver weights were significantly increased at 120 ppm (12%) and 400 ppm (22%), in the absence of macro- or microscopic lesions (see B.5.2 Repeated Dose Toxicity). Testes weights were similar in all

groups. Reproductive data indicated no treatment-related effects in males on copulation and mating efficiency or on efficiency in effecting pregnancy. No treatment-related effects on pre- or post-implantation loss, number of live and dead fetuses and foetal weight were seen. External examination of the fetuses was generally unremarkable.
The NOAEC for male fertility and for foetotoxicity was 400 ppm (1400 mg/m^3), the highest dose tested. Again, this dose appears too low as high dose, given the limited toxicity observed at this dose.

Additional information from other studies
In some, but not all, 2-week inhalation studies described in detail in section B.5.2 Repeated Dose Toxicity, effects on the testis were observed. In rats, these included testicular atrophy at 288 but not at 100 ppm DMAC in one study (DuPont, 1983c; Kelly et al., 1984), whereas no testis effects were seen in two other rat studies at similar (300 ppm; (Kinney et al., 1993)) or even higher DMAC doses (480 ppm; (Valentine et al., 1997)). In prebuscent mice, testicular lesions associated with decreased number of sperm and increased germinal epithelium in epididymis were seen from 310 ppm (NOAEC 100 ppm), with additionally minimal to mild bilateral degeneration and atrophy of seminiferous tubules observed at 490 ppm. In young adult mice, effects on the testes occurred at 480 ppm (decreased absolute weight, minimal to mild bilateral degeneration, atrophy of seminiferous tubules in mice; NOAEC 300 ppm) (Valentine et al., 1997). In the long-term inhalation studies with mice, however, no treatment-related effects on the reproductive organs were noted up to highest doses tested of 300/350 ppm (see B.5.2). This was also the case in the long-term inhalation studies with rats (up to 350/450 ppm, see B.5.2).

In an experimental study 10 male B6C3F1 mice/group were exposed to 0, 20 or 700 ppm (0, 70, 2500 mg/m^3, whole body, vapour) for 7h/day, 5 days/week, for 6 weeks (Fairhurst et al., 1992; NIOSH, 1980). No clinical signs of toxicity and no effects on body weight gain were observed. Sperm was examined 5 weeks after the end of exposure. No significant differences in frequency of abnormal sperm between the exposed groups and controls were observed.

Oral

No reproduction toxicity studies for DMAC to derive reliable NOAELs/LOAELs via oral route were found.

Information from other studies
In oral repeated dose toxicity studies described in detail in section B.5.2, effects on the reproductive organs were mostly observed at relatively high doses, i.e. at 1000 mg/kg bw/day in a 2-yr rat study (ovarian cysts, small testes/testis atrophy and decreased secretory product/atrophy prostate gland; (Monsanto, 1980, 1990, 1993)) and from 1170 mg/kg bw/day in a 4-week rat study (decreased weights of testes, uterus and ovary; (BASF, 1975b)). In the latter study, thin/filamentary uterine horns were additionally noted at lower doses of 290 and 590 mg/kg bw/day.

Dermal

A study report with on a dermal one-generation study in rats exists. This study was carried out during the 1970's by Industrial Bio-Test Laboratories, a lab known to have provided fraudulent reports to sponsors during this period. In absence of independent verification of the study report in question, these data are not considered further here.

Other routes

In an experimental study, 8 male Sprague-Dawley rats/group were exposed (intraperitoneal injection) to 0 or 862 mg DMAC/kg bw/week for 8 or 11 weeks (Khera et al., 2020). Male rats were mated with an equal number of untreated female rats after 8 or 11 weeks to assess fertility. After 8 weeks, significant reduced absolute testes (-11%) and epididymis (-27%) weight, decreased sperm concentration (-74%) and motility (-65%), increased number of apoptotic cells in seminiferous tubules (1100%) and significant decreased number of pups (-62%) per animal were noted. No pups were conceived at all after 11 weeks of exposure, demonstrating infertility of males. No change in serum levels of follicular stimulating hormone (FSH), luteinizing hormone (LH) or testosterone were measured.

B.5.3.1.2 NEP

There are no reproductive toxicity studies available with NEP focussing on reproduction and fertility.

Information from other studies
In the repeated dose toxicity studies described in detail in section B.5.2, no treatment-related effects on the reproductive organs were observed in a 28-day oral study (highest dose 250 mg/kg bw/day), a 28-day inhalation study (highest dose 400 mg/m^3) and a 90-day inhalation study (highest dose 200 mg/m^3). In the latter study sperm motility and total sperm head count were also not affected. In a 90-day oral study, sperm analysis revealed an increased number of sperms with abnormal heads in males at the highest dose (2.0, 2.2, 2.8 and 11.4% in controls, 100, 300 and 1000 mg/kg bw/day groups, respectively; males with >4% abnormal sperm: 0, 1, 2, 8 in controls, low, mid and high dose, respectively), indicative of disrupted sperm maturation at very high dosages. There were however no histopathological changes in the testis, and the number of homogenization resistant spermatids, epididymal sperm count and sperm motility were not affected.

B.5.3.2. Toxicity for development

B.5.3.2.1 DMAC

Most of the DMAC study summaries were adapted from the CLH proposal submitted in 2013 (RAC opinion adopted in 2014) and from the CSR of the lead registrant, accompanied with extra or adjusted information directly derived from original study reports or publications.
A summary of the studies and the adverse effects on development are found in Table 11 below:

Table 11: Summary of studies informing developmental toxicity after exposure to DMAC

Species, strain, number and sex/group	Study type, duration, dose levels	NOAEC/NOAEL, relevant findings, remarks	Reliability	Reference
Inhalation				
Rat Crj:CD(SD)IGS 10 f (pregnant) Similar to OECD TG 414 GLP: not specified	Prenatal developmental toxicity study GD 6-19 0, 100, 300, 450, 600 ppm (0, 360, 1080, 1620, 2160 mg/m^3, whole body, vapour), 6h/day	NOAEC (maternal and development): 100 ppm (360 mg/m^3) <u>Maternal</u> 300 ppm: rel. liver weight ↑ (13%), swelling of centrilobular hepatocytes ↑ (40% vs. 0% in control, n.s.) 450 ppm: uncorrected BW ↓ (-7%), rel. liver weight ↑ (12%), swelling of	2	Okuda et al. (2006)

		centrilobular hepatocytes ↑ (100% vs. 0% in control) 600 ppm: uncorrected BW ↓ (-14%), rel. liver weight ↑ (19%), swelling of centrilobular hepatocytes ↑ (70% vs. 0% in control) <u>Foetal</u> 300 ppm: BW ↓ (m/f: -10/-8%), fetuses with ventricular septal defect ↑ (3.2% and in 2/10 litters vs. 0% in control, n.s.) 450 ppm: BW ↓ (m/f: -20/-21%), fetuses with ventricular septal defect ↑ (11% and in 6/10 litters vs. 0% in control), fetuses with persistent truncus arteriosus ↑ (3.2% and in 2/10 litters vs. 0% in control, n.s), fetuses with fused cervical arch ↑ (5.9% and in 2/10 litters vs. 0% in control) 600 ppm: intrauterine deaths ↑ (3.4 vs. 1.1 in control, n.s.), BW ↓ (m/f: -35/-33%), live male fetuses ↓ (4.0 fetuses/litter vs. 7.4 in control), fetuses with anasarca ↑ (4% and in 3/9 litters vs. 0% in control), fetuses with cleft palate ↑ (1% and in 1/9 litter vs. 0% in control, n.s.), fetuses with ventricular septal defect ↑ (45% and in 8/8 litters vs. 0% in control), fetuses with persistent truncus arteriosus ↑ (24% and in 7/8 litters vs. 0% in control), fetuses with malpositioned subclavian branch ↑ (8.2% and in 3/8 litters vs. 0% in control), fetuses with retro-oesophagal subclavian ↑ (6.1% and in 3/8 litters vs. 0% in control), fetuses with exoccupital ↑ (8% and in 4/9 litters vs. 0% in control), fetuses with fused cervical arch ↑ (4% and in 2/9 litters vs. 0% in control, n.s.), fetuses with fused rib ↑ (4% and in 2/9 litters vs. 0% in control, n.s.)		
Rat Crl: CD 25 f (pregnant) Similar to OECD TG 414 GLP: not specified	Prenatal developmental toxicity study GD 6-15 0, 32, 100, 282 ppm (0, 115, 360, 1015 mg/m^3, whole body, vapour) 6h/day	NOAEC (maternal): 282 ppm (1015 mg/m^3) NOAEC (developmental): 100 ppm (360 mg/m^3) 282 ppm: foetal BW ↓ (-6%) No adverse effects in dams. No effects on resorption, death fetuses and the incidence of variations and malformations were observed.	2	DuPont (1983a); Solomon et al. (1991)
Rabbit Himalayan 15 f (pregnant) Similar to OECD TG 414 GLP: yes	Prenatal developmental toxicity study GD 7-19 0, 200, 700, 2000 mg/m^3 (whole body, vapour) 6h/day	NOAEC (maternal): 700 mg/m^3 NOAEC (developmental): 200 mg/m^3 <u>Maternal</u> 2000 mg/m^3: placental weight ↓ (-18%) <u>Foetal</u> 700 mg/m^3: BW ↓ (-7%), fetuses with acrania or microphthalmia ↑ (each 1.1% and in 1/14 litter vs. 0% in control, n.s.), fetuses with skeletal malformations ↑ (3.2%	2	BASF (1989); Klimisch and Hellwig (2000)

		and in 3/14 litters vs. 0% in control, n.s.), fetuses with: malformation vertebral column, sternebrae or cleft sternum ↑ (each 1.1% and in 1/14 litter vs. 0% in control, n.s.), fetuses with separated origin of carotids ↑ (44% and in 13/14 litters vs. 42% and in 12/13 litters in control, n.s.), fetuses with skeletal variations ↑ (18% and in 7/14 litters vs. 11% and in 4/13 litters in control, n.s.), fetuses with accessory ribs ↑ (11% and in 6/14 litters vs. 0% in control), fetuses with fused sternebrae ↑ (6.3% and in 3/14 litters vs. 3.0% and in 2/13 litters in control, n.s.), fetuses with: accessory thoracic vertebra or 12th rib shortened ↑ (each 1.1% and in 1/14 litter vs. 0% in control, n.s.) 2000 mg/m^3: BW ↓ (-13%), fetuses with open eye ↑ (2.6% and in 1/14 litter vs. 0% in control, n.s.), fetuses with cleft palate ↑ (2.6% and in 1/14 litter vs. 0% in control, n.s.), fetuses with soft tissue malformations ↑ (10% and in 7/14 litters vs. 6.1% and in 3/13 litters in control, n.s.), fetuses with septal defects ↑ (5.1% and in 4/14 litters vs. 3.0% and in 2/13 litters in control, n.s.), fetuses with: malformation great vessels, truncus arteriosus communis, spleen hypoplasia or spleen agenesis ↑ (each 1.3% and in 1/14 litter vs. 0% in control, n.s.), fetuses with separated origin of carotids ↑ (85% and in 14/14 litters vs. 42% and in 12/13 litters in control), fetuses with skeletal malformations ↑ (2.6% and in 2/14 litters vs. 0% in control, n.s.), fetuses with: malformation sternebrae or fused ribs ↑ (each 1.3% and in 1/14 litter vs. 0% in control, n.s.), fetuses with skeletal variations ↑ (56% and in 11/14 litters vs. 11% and in 4/13 litters in control), fetuses with accessory ribs ↑ (37% and in 10/14 litters vs. 0% in control), fetuses with fused sternebrae ↑ (33% and in 9/14 litters vs. 3.0% and in 2/13 litters in control), fetuses with irregular shape sternebrae ↑ (7.7% and in 6/14 litters vs. 3.0% and in 2/13 litters in control, n.s.), fetuses with accessory thoracic vertebra ↑ (3.8% and in 1/14 litter vs. 0% in control, n.s.), fetuses with accessory: lumbar vertebra or sternebrae ↑ (each 1.3% and in 1/14 litter vs. 0% in control, n.s.)		
Oral				
Rat Crl: CD(SD)BR 25 mated females 24-25 litters OECD guideline 414 GLP: yes	Prenatal developmental toxicity study GD 7-21 0, 20, 65, 150, 400 mg/kg bw/day (gavage)	NOAEL (maternal): 150 mg/kg bw/day NOAEL (developmental): 65 mg/kg bw/day <u>Maternal:</u> 400 mg/kg bw/day: corrected BW ↓ (excluding product of conception; -7%), corrected BW gain ↓ (-74%), food consumption ↓ (-13%), rel. kidney weight ↑ (17%), rel. liver weight ↑ (9%), mitotic	1	DuPont (1997)

		figures in liver ↑ (16% vs. 0% in control), placentas with white or tan outer edges ↑ (56% vs. 4% in control) <u>Foetal:</u> 150 mg/kg bw/day: BW ↓ (-4%), Small and non-significant increase in malformations resembling the clear increase in malformations observed at 400 mg/kg bw/day. 400 mg/kg bw/day: live fetuses ↓ (10.4 per litter vs. 14.1 in control), early/late resorptions ↑ (2.8/0.3 resorptions/litter vs. 0.4/0 in control), BW ↓ (-34%), fetuses with malformations ↑ (sum-incidence 69% affected per litter in 24/24 litters vs. 0.6% in 2/24 litters in control), fetuses with distended brain ventricle ↑ (11% and in 8/24 litters vs. 0% in control), fetuses with synotia ↑ (6% and in 7/24 litters vs. 0% in control), fetuses with anasarca ↑ (11.2% and in 8/24 litters vs. 0.3% and in 1/24 litter in control), fetuses with micrognathia ↑ (0.8% and in 1/24 litter vs. 0% in control), fetuses with naris atresia ↑ (13.2% and in 10/24 litters vs. 0% in control), fetuses with malformations heart and greater vessels ↑ (55% and in 24/24 litters vs. 0% in control), fetuses with fused ribs ↑ (2% and in 2/24 litters vs. 0% in control), fetuses with absent vertebra ↑ (0.8% and in 2/24 litters vs. 0% in control), fetuses with hemivertebrae ↑ (1.6% and in 3/24 litters vs. 0% in control), fetuses with variations ↑ (sum-incidence 97.8% affected per litter in 20/24 litters vs. 51.8% in 24/24 litters in control), fetuses with patent ductus arteriosus ↑ (4% and in 6/24 litters vs. 0% in control), fetuses with retarded ossification sternebrae ↑ (25.6% and in 17/24 litters vs. 3.3% and in 7/24 litters in control)		
Rat COBS CD 22-25 pregnant females Similar to OECD guideline 414 GLP: no	Prenatal developmental toxicity study GD 6-19 0, 65, 160, 400 mg/kg bw/day (gavage)	NOAEL (maternal): 160 mg/kg bw/day NOAEL (developmental): 65 mg/kg bw/day <u>Maternal:</u> 400 mg/kg bw/day: corrected BW gain ↓ (-18%) <u>Foetal:</u> 160 mg/kg bw/day: fetuses with 25 presacral vertebrae (variation) ↑ (8.1% and in 5/23 litters vs. 2.8% and in 2/22 litters, n.s.) 400 mg/kg bw/day: post-implantation loss ↑ (2.6 per dam vs. 1.2 in control), BW ↓ (-34%), fetuses with malformations ↑ (16.8% and in 21/24 litters vs. 0.3% and in 1/22 litter in control), fetuses with: cleft palate ↑ (1.0% and in 3/24 litters vs. 0% in control, n.s.), anasarca ↑ (1.7% and in 2/24 litters vs.	2 (viral infection)	Johannsen et al. (1987)

		0% in control, n.s.), heart/vessel anomalies ↑ (22.6% and in 18/24 litters vs. 0% in control, n.s.), vertebral anomaly ↑ (2.1% and in 3/24 litters vs. 0% in control, n.s.), rib anomaly ↑ (2.1% and in 2/24 litters vs. 0% in control, n.s.), variations, fetuses with: 25 presacral vertebrae ↑ (12.3% and in 10/24 litters vs. 2.8% and in 2/22 litters in control, n.s.), 14th rudimentary/full rib ↑ (6.8/7.5% and in 3/24 litters vs. 3.4/0.7% and in 5/22 litters in control, n.s.), unossified sternebrae No. 5-6 ↑ (87.7% and in 23/24 litters vs. 29.0% and in 15/22 litters in control, n.s.), unossified sternebrae No. 1-4 ↑ (19.9% and in 13/24 litters vs. 0.7% and in 1/22 litter in control, n.s.), reduced skull ossification ↑ (9.6% and in 7/24 litters vs. 0% in control, n.s.), reduced vertebrae ossification (20.5% and in 13/24 litters vs. 0% in control, n.s.), major vessel variations ↑ (6.2% and in 6/24 litters vs. 0% in control)		
Rat Sprague-Dawley 18-24 pregnant females Similar to OECD guideline 414 GLP: no	Prenatal developmental toxicity study GD 6-15 0, 113, 340, 1020 µl/kg bw/day (0, 106, 320, 960 mg/kg bw/day; actual dose received, gavage)	NOAEL (maternal and developmental): 106 mg/kg bw/day <u>Maternal:</u> 320 mg/kg bw/day: uncorrected BW ↓ (-7%), BW gain ↓ (-21%), vaginal bleeding (19% vs. 0% in control), placental weight ↓ (-18%) 960 mg/kg bw/day: uncorrected BW ↓ (-25%), BW gain ↓ (-79%), vaginal bleeding (25% vs. 0% in control) <u>Foetal:</u> 320 mg/kg bw/day: dead implants ↑ (11.4% vs. 5.7% in control), BW ↓ (-18%), fetuses with external malformations ↑ (6.8% and in 7/24 litters vs. 0.7% and in 1/22 litter in control), fetuses with anasarca ↑ (3.5% and in 6/24 litters vs. 0% in control), fetuses with aplasia of tail ↑ (1.2% and in 2/24 litters vs. 0% in control), fetuses with atresia ↑ (0.6% and in 1/24 litter vs. 0% in control), fetuses with malformed vertebrae ↑ (8.8% and in 7/24 litters vs. 2.1% and in 2/22 litters in control), fetuses with hydroureter ↑ (1.1% and in 1/24 litter vs. 0% in control) 960 mg/kg bw/day: complete resorption	2	BASF (1976b)
Mouse NMRI 22-24 pregnant females Similar to OECD guideline 414 GLP: no	Prenatal developmental toxicity study GD 6-15 0, 256, 427, 1280 µl/kg bw/day (0, 240, 400, 1200 mg/kg bw/day, actual dose received, gavage)	NOAEL (maternal and developmental): 240 mg/kg bw/day <u>Maternal:</u> 400 mg/kg bw/day: placental weight ↓ (-12%) 1200 mg/kg bw/day: diarrhea (10% of animals), uncorrected BW ↓ (-11%), volume amniotic fluid in uterus ↑ (84% of animals vs. 0% in control), placental weight ↓ (-25%)	2	BASF (1976c)

		Foetal: 400 mg/kg bw/day: BW ↓ (-8%), external malformations, fetuses with: exencephaly ↑ (2.5% and in 5/24 litters vs. 0% in control), no eye lid closure ↑ (1.7% and in 3/24 litters vs. 0% in control), visceral malformation: fetuses with cleft palate ↑ (4.8% and in 3/24 litters vs. 1.4% and in 1/23 litter in control), skeletal malformation: fetuses with fused ribs ↑ (4.1% and in 6/24 litters vs. 0% in control) 1200 mg/kg bw/day: post-implantation loss (41% of implants vs. 19% in control), BW ↓ (-36%), external formations, exencephaly ↑ (31.9% and in 17/19 litters vs. 0% in control), no eye lid closure ↑ (10.6% and in 12/19 litters vs. 0.4% and in 1/23 litter in control), oligodactylia ↑ (18.4% and in 11/19 litters vs. 0% in control), syndactylia ↑ (3.5% and in 5/19 litters vs. 0% in control), brachygnatia or macroglossia ↑ (each 1.4% and in 2/19 litters vs. 0% in control), visceral malformation: fetuses with cleft palate ↑ (53.3% and in 11/19 litters vs. 2.7% and in 2/23 litters in control), skeletal malformations, fetuses with: fused ribs ↑ (82.3% and in 19/19 litters vs. 0% in control), synotosis of processus spinalis ↑ (18.8% and in 11/19 litters vs. 0% in control)		
Mouse NMRI >20 pregnant females No guideline followed GLP: no	Prenatal developmental toxicity study GD 6-15 0, 427, 640, 1280, 3200 µl/kg bw/day (0, 400, 600, 1200, 3000 mg/kg bw, actual dose received, gavage) Single application on one of the gestation days	NOAEL (maternal): 1200 mg/kg bw NOAEL (foetal): 400 mg/kg bw NOAELs not used for DNEL derivation, due to limitations of this study (e.g. single dose). Foetal: 400 mg/kg bw: fetuses with exencephaly ↑ (dosed GD 9; 1.0% vs. 0.4% in control) 600 mg/kg bw: BW ↓ (dosed GD 9-12; not specified), fetuses with abnormalities ↑ (dosed GD 8/9: sum-incidence 2.5/12.2% vs. 1.4% in control), fetuses with exencephaly ↑ (dosed GD 8/9: 0.6/2.2% vs. 0% in control) 1200 mg/kg bw: BW ↓ (dosed GD 6, 9-12; not specified), fetuses with abnormalities ↑ (dosed GD 7/8/9: sum-incidence 2.7/17.1/61.5% vs. 1.9/0/2.5% in control), fetuses with cleft palate ↑ (dosed GD 6: 2.5% vs. 0% in control), fetuses with kinked tail ↑ (dosed GD 7: 1.6% vs. 0% in control), fetuses with exencephaly ↑ (dosed GD 7/8/9: 1.6/19.1/6.4% vs. 0.5/0/0% in control), fetuses with scoliosis ↑ (dosed GD 9: 0.5% vs. 0% in control) 3000 mg/kg bw: implantations ↓ (dosed GD 12; 9.9 per dam vs. 12.8 in control), live	3	BASF (1975a)

		fetuses ↓ (52-77% vs. 88-96% in control), BW ↓ (dosed GD 6-15; not specified), fetuses with abnormalities ↑ (dosed GD 7/8/9: sum-incidence 13.1/100/65.2% vs. 3.2/0/0.8% in control), fetuses with fused ribs ↑ (dosed GD 6: 8.6% vs. 0% in control), fetuses with exencephaly ↑ (dosed GD 7: 3.6% vs. 0% in control), fetuses with brachygnathia inferior ↑ (dosed GD 7: 1.8% vs. 0% in control), fetuses with head malformations, macroglossia, anophthalmia, exophthalmia ↑ (each 1.2% vs. 0% in control). Other malformations noted, but incidence not specified (dosed GD #): exencephaly (GD 6, 8, 9), micrognatia (GD 6, 8), anophthalmia (GD 6), hydrocephalus (GD 6), cleft palate (GD 6, 8), spina bifida (GD 8), kyphosis (GD 8), oligodactylia (GD 8, 9), short tail (GD 8), split jaws (GD 8), syndactylia (GD 9), polydactylia (GD 9), accessory toes (GD 9) No tables with results of incidence (external, visceral, skeletal examination) were provided.		
Rabbit Russian 10-11 pregnant females Similar to OECD guideline 414 GLP: no	Prenatal developmental toxicity study GD 6-18 0, 100, 300, 500 µl/kg bw/day (0, 94, 280, 470 mg/kg bw/day, actual dose received, gavage)	NOAEL (maternal): 280 mg/kg bw/day NOAEL (developmental): 94 mg/kg bw/day <u>Maternal:</u> 470 mg/kg bw/day: expression of pain and tremor, clinical signs, hepatic lobule (1 animal), mortality (18% of animals), uncorrected BW ↓ (GD 18/28: -13/-17%) <u>Foetal:</u> 280 mg/kg bw/day: resorptions ↑ (35.4% per dam vs. 16.7% in control, n.s.), BW ↓ (-11%), fetuses with malformations ↑ (13% and in 3/9 litters vs. 0% in control, n.s.), fetuses with: cleft palate ↑ (10.3% and in 2/9 litters vs. 0% in control), fused ribs or microphthalmia ↑ (each 2.6% and in 1/9 litter vs. 0% in control) 470 mg/kg bw/day: complete resorption	2	BASF (1976a); Merkle and Zeller (1980)
Rabbit Russian 10 pregnant females Similar to OECD guideline 414 GLP: no	Prenatal developmental toxicity study GD 6-18 0, 100, 300, 900 µl/kg bw/day (0, 94, 280, 850 mg/kg bw/day, actual dose received, gavage)	NOAEL (maternal): 280 mg/kg bw/day NOAEL (developmental): 94 mg/kg bw/day <u>Maternal:</u> 850 mg/kg bw/day: sedation and ataxia, BW ↓, food consumption ↓, diarrhea, mortality ↑ (100% vs. 0% in control), pale yellowish parenchymatous organs, pronounced hepatic lobules <u>Foetal:</u> 280 mg/kg bw/day: implantation loss ↑ (45.4% of implants vs. 11.5% in control, n.s.), BW ↓ (-6%), fetuses with malformations ↑ (5% and in 2/10 litters vs. 0% in control), fetuses with: exencephaly	2	BASF (1974)

		and renal cyst ↑ (3.3% and in 1/10 litter vs. 0% in control), cleft palate ↑ (1.6% and in 1/10 litter vs. 0% in control)		
Dermal – No reliable studies available				
m: male, f: female, ↑: increased, ↓: reduced, abs.: absolute, BW: body weight, GD: gestation day, n.s.: not statistically significant, rel.: relative				

Inhalation

Okuda et al. (2006)

In a prenatal developmental toxicity study (similar to OECD TG 414 and well documented study but with less pregnant dams than required), 10 female (pregnant) Crj:CD(SD)IGS rats/group were exposed to vapour of DMAC (purity >99.9%) at concentrations of 0, 100, 300, 450 or 600 ppm DMAC (equivalent to 0, 360, 1080, 1620 or 2160 mg/m^3, whole body) for 6 h per day, from GD 6 to 19. Dams were weighed regularly and were monitored for clinical signs. On day 20 of gestation all dams were necropsied. On the day of necropsy liver enzymes (AST, ALT, LDH) were measured in dams and liver was sectioned for histopathology. The uterus was opened and the numbers of live and dead fetuses (including resorptions) and implantations were recorded. Foetal weights and sex were determined, and the fetuses were examined externally for malformations. One half of the fetuses was examined for visceral malformations after fixation with Bouin's solution (Nishimura's technique). The other half were examined for skeletal malformations after staining with Alizarin red S.

No clinical signs or increased liver enzymes (AST, ALT or LDH) were observed (Table 12), but maternal body weight was decreased at ≥450 ppm (450/600 ppm: -7/-14%). No maternal body weight gain data or weight data corrected for gravid uterine weight were reported. Maternal liver effects were observed at ≥300 ppm, as noted by significantly increased relative liver weights (300/450/600 ppm: 13/12/19%). In addition, swelling of centrilobular hepatocytes without the occurrence of hepatocellular necrosis was noted at ≥300 ppm (40/100/70% vs. 0% in control), which was statistically significant at ≥450 ppm.

Table 12: Body weights, blood chemistry, organ weight and histopathology of pregnant rats exposed to DMAC or clean air as control.

	Maternal exposure concentration (ppm)				
	0	100	300	450	600
No. of pregnant rats examined	10	10	10	10	10
Body weight (g)					
GD 6	263 ± 7	260 ± 7	262 ± 15	261 ± 8	259 ± 10
GD 13	301 ± 11	299 ± 14	295 ± 17	290 ± 10	280 ± 14**
GD 20	383 ± 21	379 ± 23	368 ± 26	356 ± 16*	330 ± 30**
Blood biochemistry					
AST (IU/l)	49 ± 9	49 ± 6	50 ± 12	50 ± 8	49 ± 7
ALT (IU/l)	33 ± 6	35 ± 6	34 ± 6	32 ± 6	33 ± 7
LDH (IU/l)	192 ± 122	130 ± 26	127 ± 40	137 ± 36	138 ± 47
Organ weight					
Absolute liver weight (g)	14.3 ± 1.2	14.6 ± 1.3	15.5 ± 1.5	14.9 ± 1.3	14.5 ± 1.3
Relative liver weight (%)	3.73 ± 0.20	3.86 ± 0.29	4.22 ± 0.24**	4.19 ± 0.31**	4.43 ± 0.21**
Histopathology					
No. of rats bearing swelling of centrilobular hepatocytes	0	0	4	10##	7##

All values, except histopathology, are expressed as mean ± S.D. Relative liver weight: liver weight/body weight measured at time of necropsy. * and **: Significantly different from the control group at $p \leq 0.05$ and $p \leq 0.01$ by Dunnett's test, respectively.
: Significantly different from the control group at $p \leq 0.01$ by Chi-square test.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase.

The number of male live fetuses was decreased at 600 ppm (4.0 fetuses/litter vs. 7.4 in control), but not of female live fetuses and no clear effect at lower concentrations were observed. The number of intrauterine deaths was increased at 600 ppm (3.4 fetuses/litter vs. 1.1 in control), but was not statistically significant different compared to the control. Foetal body weight was decreased at ≥300 ppm in males (-10/-20/-35%) and females (-8/-21/-33%). The number of fetuses with anasarca, as an external malformation, increased at 600 ppm (4 fetuses (4%) in 3/8 litters vs. 0% in control); one of these foetuses also had cleft palate. Visceral examinations showed a dose-dependent increased incidence of malformations (Table 13), such as: malpositioned subclavian branch and retroesophageal subclavian artery. Persistent truncus arteriosus, which was classified as a serious congenital heart disease affecting postnatal survival, was accompanied by an increased incidence of ventricular septal defects. Visceral malformations were observed at 300 ppm (ventricular septal defect) and above. Skeletal malformations were increased at 600 ppm (Table 14), in particular increased incidence of fused exoccipital and cervical arch.

The maternal and developmental NOAEC was 100 ppm (360 mg/m^3) based on increased liver weights and hepatocellular swelling for maternal toxicity and decreased foetal body weights and increased incidence of ventricular septal defects for foetal effects at 300 ppm. The limited number of pregnant dams reduces the sensitivity of this study and therefore increases the uncertainty of the derived NOAEC.

Table 13: Visceral (cardiovascular) malformations in rat fetuses after inhalation exposure to DMAC from day 6-19 (Okuda et al., 2006) (no. of fetuses and no. of litters respectively)

Visceral malformation	0	100 ppm	300 ppm	450 ppm	600 ppm
Ventricular septal defect	0/68 (10) (0%)	0/65 (10) (0%)	2/63 (2/10) (3.2%)	7/63 (6/10) (11%)	22/49 (8/8) (45%)
Persistent truncus arteriosus	0/68 (10) (0%)	0/65 (10) (0%)	0/63 (10) (0%)	2/63 (2/10) (3.2%)	12/49 (7/8) (24%)
Malpositioned subclavian branch	0/68 (10) (0%)	0/65 (10) (0%)	0/63 (10) (0%)	0/63 (10) (0%)	4/49 (3/8) (8.2%)
Retroesophagal subclavian	0/68 (10) (0%)	0/65 (10) (0%)	0/63 (10) (0%)	0/63 (10) (0%)	3/49 (3/8) (6.1%)
Total	0/68 (0/10) (0%)	0/65 (0/10) (0%)	2/63 (2/10) (3.2%)	7/63 (6/10) (11%)	23/49 (8/8) (47%)

Table 14: Skeletal malformations in rat fetuses after inhalation exposure to DMAC from day 6-19 (Okuda et al., 2006) (no. of fetuses and no of litters respectively)

Skeletal malformation	0	100 ppm	300 ppm	450 ppm	600 ppm
Fused exoccipital	0/73 (10) (0%)	0/72 (10) (0%)	0/67 (10) (0%)	0/68 (10) (0%)	4/50 (4/9) (8%)
Fused cervical arch	0/73 (10) (0%)	0/72 (10) (0%)	0/67 (10) (0%)	4/68 (2/10) (5.9%)	2/50 (2/9) (4%)
Fused rib	0/73 (10) (0%)	0/72 (10) (0%)	0/67 (10) (0%)	0/68 (10) (0%)	2/50 (2/9) (4%)
Total	0/73 (0/10) (0%)	0/72 (0/10) (0%)	0/67 (0/10) (0%)	4/68 (2/10) (5.9%)	6/50 (6/9) (12%)

DuPont (1983a); Solomon et al. (1991)

In a prenatal developmental toxicity study (similar to OECD TG 414), 25 female pregnant Crl: CD rats/group were exposed to 0, 32, 100 or 282 ppm DMAC (equivalent to 0, 115, 360 or 1015 mg/m^3, whole body, vapour, purity >99.9%) for 6 h per day from GD 6 to 15. On GD 21 all animals were killed and submitted to gross macroscopy. The numbers of corpora lutea

and implantations, resorptions (early, late) were recorded. The number of fetuses, their body weights and sex were determined. External examinations for malformations were done on fetuses. One half of the fetuses were examined for visceral abnormalities (this included stunted and externally malformed fetuses). The heads of these fetuses were fixed in Bouin's solution and examined. Skeletal examination was done on all fetuses.
The only significant adverse effect observed in the dams in this study was a decreased (uncorrected) maternal body weight gain (days 6-8 and days 6-15) at 282 ppm which showed a significant dose-response trend (32/100/282 ppm: -4/-7/-15% at GD 6-15). Decreased maternal body weight gain was also observed from GD 6 to 21 upon correction (body weight excluding products of conception; -8/-6/-10%), although not statistically significant. No effects on (corrected) maternal body weight on GD 21 and on absolute liver weight were observed in dams in any dose group. Decreased foetal body weight (-6%) was noted at 282 ppm, but no increased incidences of resorption, death fetuses, external, visceral or skeletal variations and malformations were found.
The NOAEC (maternal toxicity) was 282 ppm (1015 mg/m^3), the highest dose tested, as no adverse effects were noted. The NOAEC (developmental toxicity) was 100 ppm (360 mg/m^3) based on a slight decrease in foetal body weight at 282 ppm (1015 mg/m^3).

BASF (1989); Klimisch and Hellwig (2000)
In a prenatal developmental toxicity study (similar to OECD TG 414; with restrictions e.g. less pregnant females per group than required and exposure restricted to GD 7 to 19) groups of 15 pregnant Himalayan rabbits were exposed to 0, 200, 700 or 2000 mg/m^3 (whole body, vapour) and 5 rabbits per satellite group (for hepatotoxicity) to 0 or 2000 mg/m^3 (whole body, vapour) for 6h/day on GD 7 to 19. On GD 29 all animals were killed, and fetuses were examined externally. Dams were observed for clinical signs and maternal body weights were recorded. At termination the weights of the uterus were measured, the numbers of corpora lutea and implantations were counted. The numbers of fetuses, foetal weight and sex were determined. External examination for malformations was done. Trunks of the fetuses were fixed in ethanol and processed for staining. The heads of the fetuses were fixed in Bouin's solution and evaluated according to Wilson's technique.
Placental weight (700/2000 mg/m^3: -15/-18%) was statistically significantly decreased at ≥700 mg/m^3, but was considered a substrance-realted effects only at 2000 mg/m^3. No other signs of maternal toxicity (body weight (gain), gross pathology and histopathological changes in liver) were found. Foetal body weight (200/700/2000 mg/m^3: -9/-7/-13%) was statistically significantly reduced at all doses compared to the control group. No effects on preimplantation loss, resorptions and death fetuses were observed (see Table 15). The unexpectedly low number of implants and live fetuses in the control group complicated a decision whether the reduced foetal body weight at the two lower doses was related to the substance or not. However, the reduced foetal body weight and placental weight in the highest dose group were considered as treatment-related toxicity. The incidence of soft tissue malformations (see Table 16) was slightly higher at 2000 mg/m^3 (total incidence: 10% in 7/14 litters vs. 6.1% in 3/13 litters in the control group, n.s.). The increase was not statistically significant, possibly due to the control incidence (6.1%) being higher than the historical control incidence (1.3%). The soft tissue malformations included septal defects (4 cases), truncus arteriosus communis, malformations of great vessels, and agnesis/hypoplasia of spleen (each 1 case). When looking at these individual findings, it is noted that these were mostly above the historical control incidences for these findings. An increased incidence of separated origin on the carotids (classified as a soft tissue variation) was observed at 2000 mg/m^3 (85% of fetuses in 14/14 litters vs. 42% in 12/13 litters in control). Increased incidence of some skeletal variations (

Table 17) were observed at ≥700 mg/m^3, such as accessory ribs (700/2000 mg/m^3: 11% in 6/14 litters/37% in 10/14 litters vs. 0% in the control group) and fused sternebrae (6.3% in 3/14 litters (n.s.)/33% in 9/14 litters vs. 3% in 2/13 litters in the control group).
The NOAEC for maternal toxicity is 700 mg/m^3, based on decreased placental weight at 2000 mg/m^3. The NOAEC for developmental toxicity is 200 mg/m^3 based on skeletal variations and in particular the increase in accessory ribs at 700 mg/m^3.

Table 15: Developmental toxicity in rabbits after inhalation of DMAC

Parameter	Control	200 mg/m^3	700 mg/m^3	2000 mg/m^3
% Pre-implantation loss	18.0	9.1	7.1	7.4
Number of implants per dam	6.0	6.9	7.5	6.7
Number of live fetuses per dam	4.7	6.5	6.7	5.6
% living fetuses per dam	76.9	94.0	86.7	82.1
Number of dead implants per dam	1.3	0.4	0.8	1.1
% Post-implantation loss	23.1	6.0	13.3	17.9

Table 16: Summary of foetal soft tissue malformations in rabbits after inhalation of DMAC

Fetal soft tissue malformation	*Test group 0 (0.0 mg/l)*	*Test group 1 (0.2 mg/l)*	*Test group 2 (0.7 mg/l)*	*Test group 3 (2.0 mg/l)*	*Historical control data*
Litters evaluated	13	13	14	14	44
Fetuses evaluated	66	86	95	78	223
Microphthalmia					
Fetal incidence	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	–
Litter incidence	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	–
Truncus arteriosus communis					
Fetal incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)
Litter incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.3)
Malformation of great vessels					
Fetal incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	–
Litter incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	–
Septal defect					
Fetal incidence	2 (3.0)	0 (0.0)	2 (2.1)	4 (5.1)	–
Litter incidence	2 (15)	0 (0.0)	2 (14)	4 (29)	–
Hypoplasia of lungs					
Fetal incidence	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	–
Litter incidence	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	–
Hernia diaphragmatica					
Fetal incidence	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	–
Litter incidence	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	–
Agnesis of spleen					
Fetal incidence	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.3)	–
Litter incidence	0 (0.0)	1 (7.7)	0 (0.0)	1 (7.1)	–
Hypoplasia of spleen					
Fetal incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	–
Litter incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	–
Agenesis of gallbladder					
Fetal incidence	2 (3.0)	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.9)
Litter incidence	1 (7.7)	2 (15)	0 (0.0)	0 (0.0)	2 (4.5)
Total fetal soft tissue malformations					
Fetal incidence	4 (6.1)	2 (2.3)	3 (3.2)	8 (10)	3 (1.3)
Litter incidence	3 (23)	2 (15)	3 (21)	7 (50)	3 (6.8)

Figures in parentheses indicate percent.

Table 17: Summary of foetal skeletal variations in rabbits after inhalation of DMAC

Skeletal variation	*Test group 0 (0.0 mg/l)*	*Test group 1 (0.2 mg/l)*	*Test group 2 (0.7 mg/l)*	*Test group 3 (2.0 mg/l)*	*Historical control data*
Litters evaluated	13	13	14	14	44
Fetuses evaluated	66	86	95	78	223
Accessory thoracic vertebra					
Fetal incidence	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.8)	–
Litter incidence	0 (0.0)	0 (0.0)	1 (7.1)	1 (7.1)	–
Accessory lumbar vertebra					
Fetal incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	–
Litter incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	–
Sternebrae fused					
Fetal incidence	2 (3.0)	3 (3.5)	6 (6.3)	26[b] (33)	–
Litter incidence	2 (15)	2 (15)	3 (21)	9[a] (64)	–
Sternebra(e) of irregular shape					
Fetal incidence	2 (3.0)	3 (3.5)	2 (2.1)	6 (7.7)	9 (4.0)
Litter incidence	2 (15)	3 (23)	2 (14)	6 (43)	8 (18)
Accessory sternebra					
Fetal incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	–
Litter incidence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	–
Accessory rib(s)					
Fetal incidence	0 (0.0)	1 (1.2)	10[b] (11)	29[b] (37)	2 (0.9)
Litter incidence	0 (0.0)	1 (7.7)	6[a] (43)	10[b] (71)	2 (4.5)
Twelfth rib(s) shortened					
Fetal incidence	0 (0.0)	1 (1.2)	1 (1.1)	0 (0.0)	5 (2.2)
Litter incidence	0 (0.0)	1 (7.7)	1 (7.1)	0 (0.0)	4 (9.1)
Rudimentary cervical rib(s)					
Fetal incidence	3 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	–
Litter incidence	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	–
Total fetal skeletal variations					
Fetal incidence	7 (11)	7 (8.1)	17 (18)	44[b] (56)	19 (9.0)
Litter incidence	4 (31)	6 (46)	7 (50)	11[a] (79)	17 (39)

Figures in parentheses indicate percent; significantly different from control: [a]$P < 0.05$; [b]$P < 0.01$.

Additional information from other studies

Some additional data are available from a one-generation study (Ferenz & Kennedy Jr, 1986) and a male fertility study (Monsanto, 1982a; Wang et al., 1989), described in detail in section B.5.3.1. Toxicity for Sexual function and fertility. In the one-generation study, pups in treated groups were not different from control pups with respect to clinical signs, physical appearance, developmental parameters (age of pinna detachment, hair growth and eye opening) and gross pathological findings. On PND 1, 4 and 21, body weights of pups from rats exposed to 300 ppm were slightly lower than those of controls, but not always statistically significantly. At PND 21, the decrease was statistically significant for male pups from litters where both parents were exposed to 300 ppm (decrease 7%) and for male and female pups from litters where only the dams were exposed to 300 ppm (decrease 13%). In these pups the relative liver weights were increased, probably related to the decrease in body weight. The NOAEC for pup toxicity was 100 ppm (360 mg/m^3), based on a slight decrease in pup body weight at 300 ppm.

In the male fertility study no treatment-related effects on pre- or post-implantation loss, number of live and dead fetuses and foetal weight were seen (Monsanto, 1982a; Wang et al., 1989). External examination of the fetuses was generally unremarkable. The NOAEC for developmental toxicity was 400 ppm (1400 mg/m^3), the highest dose tested.

<u>Oral</u>

The toxicity studies where DMAC was administered orally are considered supportive information for the derivation of a worker (inhalation/dermal) DNEL. The study summaries were adapted from the CLH report (2014) and the CSR by the lead registrant.

DuPont (1997)

In a prenatal developmental toxicity study (OECD TG 414) 24-25 pregnant Crl: CD®(SD)BR rats/group received 0, 20, 65, 150 or 400 mg DMAC/kg bw/day via gavage at GD 7-21. The study was terminated at GD 22. In dams there were no treatment related clinical signs and

no mortality. Maternal body weight (both in- and excluding products of conception) was statistically significantly reduced (-15/-7%, respectively) at 400 mg/kg bw/day on GD 22. Maternal body weight gain over GD 7 to 22 was statistically significantly reduced at 400 mg/kg bw/day (in/-excluding products of conception: -52/-74%). At other doses no effects on maternal body weight (gain) were observed, aside from a slightly reduced corrected maternal body weight gain at 150 mg/kg bw/day (-14%, n.s.). Food consumption was statistically significantly reduced at 400 mg/kg bw/day (-13%). Clinical chemistry data revealed no treatment related effects. Organ weights showed statistically significant increases in relative kidney (17%) and liver (9%) weights in the 400 mg/kg bw/day dose group. At necropsy no treatment related effects were detected, but placentas in the highest dose group had white or tan outer edges (56% vs. 4% in control), and mitotic figures in liver possibly related to metabolism of the substance were noted (incidence: 16% vs. 0% in control). However, the increased mitotic figures in liver were considered not to be adverse since no degeneration or inflammation was found.
At 400 mg/kg bw/day, early and late resorptions (Table 18) were significantly increased resulting in a significantly reduced number of live fetuses (-26%). Foetal body weight was statistically significantly reduced at ≥150 mg/kg bw/day (150/400 mg/kg bw/day: -4/-34%). The incidence of foetal malformations and variations was significantly increased at the high dose level (Table 19). However, at 150 mg/kg bw/day four affected fetuses from one litter revealed distended brain ventricles and one fetus was found with naris atresia, heart and vessel malformations, cleft palate, macroglossia, micrognathia, and synotia (Table 19). The observed malformations have similarity with the specific malformations at the high dose level and may represent the bottom end of the dose response curve for malformations. At 400 mg/kg bw/day (Table 19), developmental toxicity was evident with a significantly increased incidence of total malformations (synotia, anasarca, micrognathia, naris atresia, malformations of the heart and great heart vessels, distended lateral brain ventricles, fused ribs, absent vertebrae and hemivertebrae), and variations (97.8% sum-incidence of fetuses affected per litter in 20/24 litters vs. 51.8% in 24/24 litters in control; patent ductus arteriosus, retarded ossification sternebra). The NOAEL for maternal toxicity is 150 mg/kg bw/day based on decreased corrected body weight gain and macroscopic changes of the placenta at 400 mg/kg bw/day. The NOAEL for developmental toxicity is 65 mg/kg bw/day based on the observation of non-significant increases of malformations at 150 mg/kg bw/day. These malformations resemble the clear increase observed at 400 mg/kg bw/day.

Table 18: Developmental toxicity in rats after oral exposure to DMAC via gavage at GD 7-21 (dose in mg/kg bw/day)

Parameter	**0**	**20**	**65**	**150**	**400**
Early resorptions/litter	0.4	0.6	0.6	0.5	2.8*
Late resorptions/litter	0	0	0	0	0.3*
Live fetuses/litter	14.1 (100%)	13.6 (96%)	14.1 (102%)	14.5 (103%)	10.4* (74%)
Mean foetal weight	4.88	5.03	4.99	4.69*	3.22*

*: statistically significant, p≤0.05

Table 19: Incidence of foetal malformations in rats after oral exposure to DMAC via gavage at GD 7-21

INCIDENCE OF FETAL MALFORMATIONS[a]

GROUP:	I	II	III	IV	V
DAILY DOSE (mg/kg):	0	20	65	150	400
EXTERNAL					
No. Examined[b]	338[24]	327[24]	339[24]	362[25]	250[24]
No. Affected	1[1]	0[0]	1[1]	1[1]	69[17]
Mean percent affected	0.3	0.0	0.3	0.3	31.3
per litter (S.E.)	(0.28)		(0.35)	(0.31)	(6.49)
(S.D.)	(1.36)		(1.70)	(1.54)	(31.77)
Anus - Absent	...[c]	...	...	...	1(1)
Ear - Synotia	...	...	...	1(1)	15(7)*
Entire Body - Anasarca	1(1)	...	1(1)	...	28(8)*
Head - Micrognathia	...	...	...	1(1)	2(1)*
Limb - Short	1(1)	...	...	...	...
Paw - Adactyly	1(1)	...	...	...	...
Palate - Cleft	...	...	...	1(1)	...
Snout - Naris Atresia	...	...	...	1(1)	33(10)*
Tail					
- Absent	...	...	...	...	1(1)
- Vestigial	...	...	...	...	1(1)
VISCERAL					
No. Examined	184[24]	172[24]	177[24]	190[25]	206[24]
No. Affected	0[0]	0[0]	1[1]	1[1]	113[24]
Mean percent affected	0.0	0.0	0.6	0.5	57.3
per litter (S.E.)			(0.60)	(0.50)	(5.51)
(S.D.)			(2.92)	(2.50)	(26.98)
Heart &/or Greater Vessels					
- Malformation	...	...	1(1)	1(1)	113(24)*
HEAD					
No. Examined	183[24]	171[24]	177[24]	190[25]	206[24]
No. Affected	0[0]	0[0]	0[0]	5[2]	82[18]

INCIDENCE OF FETAL MALFORMATIONS*

GROUP:	I	II	III	IV	V
DAILY DOSE (mg/kg):	0	20	65	150	400
HEAD (CONT.)					
Mean percent affected	0.0	0.0	0.0	4.5	38.1
per litter (S.E.)				(4.01)	(6.72)
(S.D.)				(20.05)	(32.93)
Brain – Distended Lateral Ventricles[d]	...	...	...	4(1)	23(8)*
Severe	...	...	...	...	1(1)
Moderate	...	...	...	2(1)	15(7)
Slight	...	...	...	2(1)	7(2)
Mandible - Micrognathia	...	...	...	1(1)	...
Nares - Naris Atresia	...	...	...	1(1)	70(18)*
Palate - Cleft	...	...	...	1(1)	...
Tongue - Large	...	...	...	1(1)	...
SKELETAL					
No. Examined	338[24]	327[24]	339[24]	362[25]	250[24]
No. Affected	1[1]	0[0]	0[0]	0[0]	13[7]
Mean percent affected	0.3	0.0	0.0	0.0	5.1
per litter (S.E.)	(0.28)				(2.18)
(S.D.)	(1.36)				(10.68)
Rib - Fused	...	...	...	...	5(2)*
Sternebra - Non-fused	1(1)	...	...	...	2(2)
Vertebra					
- Absent	...	...	...	...	2(2)*
- Fused	...	...	...	...	2(1)
- Hemi	...	...	...	...	4(3)*
TOTAL NUMBER AFFECTED	2(2)	0(0)	1(1)	5(2)	167(24)
MEAN PERCENT AFFECTED	0.6	0.0	0.3	2.6	69.0
PER LITTER(S.E.)	(0.38)		(0.35)	(2.29)	(5.41)
(S.D.)	(1.88)		(1.70)	(11.47)	(26.50)

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[a] Individual fetal alterations are presented in Appendix I.

[b] Number examined and affected, including the number affected with the listed malformations, are expressed as Fetuses [Litters] or Fetuses (Litters).

[c] For ease of reading, zeros have been replaced with ellipses for the listed malformations.

[d] Statistical analyses were performed on the combined data. The data broken down by severity are presented for information only.

* Significant trend (Jonckheere's test); $p \leq 0.05$.

Note: Statistical analyses are only conducted on the individual endpoints. The overall total and totals by exam are presented for information only.

Johannsen et al. (1987)
In a prenatal developmental toxicity study (similar to OECD TG 414, limitation: possibly viral infection present, but without apparent effect on health of dams) groups of 22-25 pregnant COBS CD rats were dosed with DMAC (purity 99.72%) at 0, 65, 160, 400 mg/kg bw/day by gavage on GD 6-19. No treatment-related clinical signs were observed, aside from red/swollen conjunctivae with associated swelling of the neck characteristic of viral infection (noted in all groups, including the control group). Mean maternal body weight gain on GD 0 to 20 was statistically significantly reduced at 400 mg/kg bw/day, both without and with correction for gravid uterine weight (-23%/-18%). At 160 mg/kg bw/day, a small decrease in corrected maternal body weight gain was seen (-14%, n.s.). Data on maternal body weight were not reported. Examinations at Caesarean section revealed a slight increase in post-implantation loss at 400 mg/kg bw (2.6 per dam vs. 1.2 in control). This was probably due to a relatively high incidence of early resorptions and a statistically significant increase in the number of late resorptions, as number of implantations was not but number of viable fetuses was decreased. At 400 mg/kg bw/day, mean foetal body weight was decreased (-34%) and examinations for external, visceral and skeletal malformations/abnormalities showed increased occurrence of combined malformations/abnormalities (16.8% in 21/24 litters vs. 0.3% in 1/22 litter in control). Incidence of heart/vessel malformations were increased (22.6% in 18/24 litters vs. 0% in control; e.g. truncus arteriosus, no ductus arteriosus), and to a lesser extent: cleft palate, anasarca, vertebral and rib anomalies. No significant compound related malformations were found at lower dose levels. The occurrence of 25 presacral vertebrae (160/400 mg/kg bw/day: 8.1/12.3% in 5/23 or 10/24 litters vs. 0.3/2.8% in 1/22 or 2/22 litters in control; classified as variations) was increased at ≥160 mg/kg bw/day when compared to control data. Other variations were only observed at 400 mg/kg bw/day and included: 14th rudimentary/full rib, unossified sternebrae (No. 5-6 and No. 1-4), reduced skull and vertebrae ossification and major vessel variations. The NOAEL for maternal toxicity is 160 mg/kg bw based on (corrected) reduced body weight gain at 400 mg/kg bw/day, and the NOAEL for developmental toxicity is 65 mg/kg bw/day based on 25 presacral vertebrae variation in fetuses at 160 mg/kg bw/day.

BASF (1976b)
In a prenatal developmental toxicity study (similar to OECD TG 414, limited documentation), 18-24 pregnant Sprague-Dawley rats/group were given oral doses of DMAC of 0, 106, 320 or 960 mg/kg bw/day (0, 113, 340, 1020 µl/kg bw/day) via gavage at GD 6-15. Each dose level had its own control group. On day 20 all dams were killed, and fetuses were examined externally. The numbers of implantation sites, resorptions (early, mid-late, late) were recorded, as were the numbers of live and dead fetuses, foetal weights and foetal sex. One third of the fetuses were examined for visceral abnormalities (according to Wilson). The remaining fetuses were examined skeletally. Visceral and skeletal malformations were not reported separately (incidences summed).
Maternal body weight on GD 20 and maternal body weight gain on GD 6 to 20 were decreased at 960 mg/kg bw/day (-25%/-79%) and also slightly at 320 mg/kg bw/day (-7%/-21%). No statistics and no correction for gravid uterine weight were performed on the maternal body weight data. Vaginal bleeding occurred at 320 and 960 mg/kg bw/day (19%/25% vs. 0% in control). The number of dead fetuses and runts increased at 320 mg/kg bw/day (Table 20). At 960 mg/kg bw/day, all embryos died (Table 20), mostly in the mid-late period (no live fetuses in this group). At 320 mg/kg bw/day, foetal body weight (-18%) and placental weight (-18%) were decreased, and at external examination of fetuses, increased numbers of external malformations were found (Table 20). External malformations included: anasarca (3.5% in 6/24 litters vs. 0% in control), aplasia of the tale (1.2% in 2/24 litters vs. 0% in control), and atresia (0.6% in 1/24 litters vs. 0% in control). Skeletal and visceral examination revealed an increased incidence of malformations of vertebrae (split/aplastic; 8.8% in 7/24 litters vs. 2.1% in 2/22 litters in control) and hydroureter (1.1% in 1/24 litter

vs. 0% in control) at 320 mg/kg bw/day. The maternal toxicity (vaginal bleeding, reduced placental weight) at the mid dose could be secondary to foetal toxicity. As this is not clear, both the maternal and developmental NOAEL are 106 mg/kg bw/day, based on reduced placental weight and vaginal bleeding in dams, and increased incidence of dead fetuses, reduced foetal body weight and runts and of malformations (external, skeletal and visceral) in fetuses at 320 mg/kg bw/day.

Table 20: Developmental toxicity in rat after oral application of DMAC

Parameter	Control 1	106 mg/kg bw/day	Control 2	320 mg/kg bw/day	Control 3	960 mg/kg bw/day
Number of litters	18	18	22	24	23	20
Implants per litter	12.8	12.4	13.4	12.4	12.6	11.1
% dead implants	3.0	6.2	5.7	11.4*	8.9	100**
% living fetuses related to implantations	97.0	93.7	94.3	88.6	91.1	Complete resorption
No. of male/female fetuses	111/112	103/97	135/144	138/126	141/124	0/0
Living fetuses per litter	12.4	11.7	12.7	11.0	11.5	-
Foetal weight in g	3.71±0.29	4.10±0.29[1]	3.84±0.29	3.14±0.38*	3.27±0.25	-
Foetal length in cm	3.60±0.12	3.72±0.12[1]	3.84±0.13	3.47±0.23	3.65±0.15	-
Placental weight in g	0.52±0.08	0.52±0.08	0.57±0.08	0.47±0.07*	0.53±0.07	-
% fetuses with malformations	0	0.5	0.7	6.8*	4.9	-
No. of runts	1	1	1	50	0	-

*: statistically significant, p≤0.05; **: statistically significant, p≤0.01
1: significantly increased compared to the concurrent untreated control (no toxicological relevance)
Means ± standard deviation given (not available for all parameters)

BASF (1976c)
In a prenatal developmental toxicity study (similar to OECD Guideline 414, limited documentation) groups of 22-24 pregnant NMRI mice were gavaged at GD 6-15 with 240, 400 or 1200 mg DMAC/kg bw/day (0, 256, 427, 1280 µl/kg bw/day). Each dose level had its own control group. The study was terminated at GD 18. Test concentrations were chosen based on an acute toxicity test that has been conducted prior to this study resulting in a LD50 of about 6400 µl/kg bw. Chosen test concentrations were equivalent to 1/5, 1/15 and 1/25 of the LD50. Oral application of the test substance diluted in water was performed with a cannula and an application volume of 200 µl/animal/day, leading to a total application frequency of ten times. Control animals were included and received water. All fetuses were observed for external malformations. One out of three of all fetuses were observed for soft tissue examinations. Two out of three of all fetuses were observed for skeletal effects. The dose of 1200 mg/kg bw/day resulted in a toxic reaction to maternal mice; body weight (-11%) was reduced on GD 18 and 10% of animals had diarrhea. No maternal body weight gain data or weight data corrected for gravid uterine weight were reported. In addition, volume of amniotic fluid in uterus was increased (84% of animals vs. 0% in control). 1200 mg/kg bw/day led to embryo lethality; embryos and fetuses died during the entire gestation period and implantation loss were reported to be 41% (vs. 19% in control; Table 21). Reduced

foetal body weight (400/1200 mg/kg bw/day: -8/-36%; Table 21), placental weight (400/1200 mg/kg bw/day: -12/-25%) and increased incidence of malformations and number of runts (Table 21) were observed at ≥400 mg/kg bw/day. At 400 and 1200 mg/kg bw/day, external malformations (exencephaly: 2.5% of fetuses in 5/24 litters and 31.9% in 17/19 litters vs. 0% in control, respectively; no eye lid closure: 1.7% in 3/24 litters vs. 0% in control and 10.6% in 12/19 litters vs. 0.4% in 1/23 litter in control, respectively), visceral malformations (cleft palate: 4.8% in 3/24 litters vs. 1.4% in 1/23 litter in control and 53.3% in 11/19 litters vs. 2.7% in 2/23 litters in control, respectively), and skeletal malformations (fused ribs: 4.1% in 6/24 litters and 82.3% in 19/19 litters vs. 0% in control, respectively) were noted. In addition, oligodactylia, syndactylia, brachygnatia, macroglossia and synotosis of processus spinalis were observed in fetuses at 1200 mg/kg bw/day. The NOAEL for maternal toxicity is 240 mg/kg bw/day, based on decreased placental weight. The NOAEL for developmental toxicity is also 240 mg/kg bw/day, based on a slight decrease in foetal body weight and an increase in foetal malformations (external, skeletal and visceral) at 400 mg/kg bw/day.

Table 21: Developmental toxicity in mice after oral application of DMAC via gavage

Parameter	Control 1	240 mg/kg bw/day	Control 2	400 mg/kg bw/day	Control 3	1200 mg/kg bw/day
Numbers of litters	23	22	22	24	23	19
Implants per litter	13.8	13.2	11.1	12.3	12.3	12.6
% dead implants	13.2	17.2	12.9	14.6	19.1	41.0*
No. of living fetuses	276	240	210	252	229	141
No. of male/female fetuses	162/114	152/88	119/91	127/125	121/108	86/55
Living fetuses per litter	12.0	10.9	9.1	10.5	10.0	7.42
Foetal weight in g	1.04 ± 0.15	1.01 ± 0.13*	1.11 ± 0.13	1.03 ± 0.13*	1.17 ± 0.13	0.75 ± 0.14*
Foetal length in cm	2.20 ± 0.15	2.22 ± 0.12	2.25 ± 0.11	2.20 ± 0.14	2.28 ± 0.12	1.91 ± 0.19
Placental weight in g	0.08 ± 0.01	0.07 ± 0.01*	0.08 ± 0.01	0.07 ± 0.01*	0.08 ± 0.01	0.06 ± 0.01*
% fetuses with malformations	5.4	1.2	1.0	5.9	0.9	77.3*
No. of runts	22	23	6	23	3	97

*: statistically significant, p≤0.05

BASF (1975a)

In an experimental study, pregnant Albino SPF NMRI mice (>20/group) were treated 0, 400, 600, 1200, 3000 mg/kg bw (0, 427, 640, 1280, 3200 µl/kg bw) as single dose by gavage on a single day from GD 6 to 15 and the study ended on GD 18. Each dose level had its own control group. On GD 18 all dams were killed, and fetuses were examined for external abnormalities. The aim of this study was to determine the dose level inducing no developmental and maternal effects after single oral application for each GD. The numbers of implantation sites, resorptions (early, late) were recorded, as were the numbers of live and dead fetuses, foetal weights and foetal sex. One third of the fetuses were examined for visceral abnormalities. The remaining fetuses were examined skeletally. Visceral and skeletal malformations were not reported separately (incidences summed). No tables with results were provided in the report submitted. The results below are reported for the range of GDs

at which DMAC was applied for which the effect was observed. In none of the groups signs of maternal clinical signs were observed.
At 3000 mg/kg bw, the number of implantations (9.9 per dam vs. 12.8 in control) was reduced of dams treated on GD 12 and the number of live fetuses was decreased (52-77% vs. 88-96% in control) on all treated gestation days. Foetal body weight (not specified) was reduced at 600 (treated on GD 9-12), 1200 (treated on GD 6, 9-12) and 3000 mg/kg bw (treated on GD 6, 9-12). Increased incidences of total foetal malformations were noted at 600 (treated on GD 8/9: 2.5/12.2% of fetuses vs. 1.4% in control), 1200 (treated on GD 7/8/9: 2.7/17.1/61.5% vs. 1.9/0/2.5% in control) and 3000 mg/kg bw (treated on GD 7/8/9: 13.1/100/65.2% vs. 3.2/0/0.8% in control). At ≥600 mg/kg bw, malformations observed in multiple dose groups included exencephaly (dosed 600 mg/kg bw on GD 8/9: 0.6/2.2% vs. 0% in control; dosed 1200 mg/kg bw on GD 7/8/9: 1.6/19.1/6.4% vs. 0.5/0/0% in control; dosed 3000 mg/kg bw on GD 7: 3.6% vs. 0% in control, incidence not specified for GD 6, 8 or 9) and cleft palate (dosed 1200 mg/kg bw on GD 6: 2.5% vs. 0% in control; dosed 3000 mg/kg bw on GD 6 or 8: incidence not specified). Incidence was not always specified for every dose group and GD and other malformations were only observed in one dose group.
As this is a study aiming to determine the susceptible days for inducing maternal and developmental effects and seen its limitation to exposure on a single day, this study cannot be used to derive a NOAEL/LOAEL. Therefore, this study is not included in the summary table (Table 9) in the main report.

BASF (1976a); Merkle and Zeller (1980)
In a prenatal development toxicity (similar to OECD TG 414) Russian rabbits (10-11/group) were exposed to 0, 94, 280, 470 mg DMAC/kg bw/day (0, 100, 300, 500 µl/kg bw/day) by gavage (substance diluted in bi-distilled water, 10 ml/day) at GD 6 to 18. All animals were sacrificed on GD 28. All fetuses were observed for external malformations and received two-plane x-ray. Skeletal evaluations were based on x-ray results. The heads of the fetuses were fixed in Bouin'scher solution. Using the method proposed by Wilson (1965), approximately 3 -4 weeks after fixation, ca. 8-10 transverse cross sections were made and evaluated from each head.
Clinical signs (expression of pain and tremor) were observed at 470 mg/kg bw/day in dams, as well as increased mortality (18% of animals died). Furthermore, reduced maternal body weight was observed at 470 mg/kg bw/day on GD 18 and GD 28 (-13% and -17%, respectively), which correlated with reduced food consumption. Over GD 0 to 18, dams at all doses lost weight. Weight loss was also seen over GD 0 to 28 in dams at the high dose, whereas in dams at the low and mid dose the weight gain was reduced. No correction for gravid uterine weight was performed on the maternal body weight data. No histopathological changes were observed at 280 mg/kg bw/day, but at 470 mg/kg bw/day a pronounced hepatic lobule was noted in one maternal animal after sectioning. Number of implants per dam was not affected at any dose level but resorption was increased at 280 mg/kg bw/day and complete resorption was noted at 470 mg/kg bw/day (Table 22). Foetal body weight was decreased at 280 mg/kg bw/day (-19%) and the incidence of total malformations increased (Table 22; 13% of fetuses in 3/9 litters vs. 0% in control, n.s.). Malformations noted were: cleft palate (10.3% in 2/9 litters), microphthalmia and fused ribs (each 2.6% in 1/9 litter).
The NOAEL (maternal toxicity) is 280 mg/kg bw/day based on clinical signs of toxicity, weight loss and mortality at 470 mg/kg bw/day. The NOAEL (developmental toxicity) is 94 mg/kg bw/day based on reduced foetal body weight and increased resorptions and foetal malformations (external and skeletal) at 280 mg/kg bw/day.

Table 22: Developmental toxicity in rabbits after oral application of DMAC

Parameter	Untreated control	94 mg/kg bw/day	280 mg/kg bw/day	470 mg/kg bw/day
Pregnant rabbits	10/12	11/11	10/10	11/12
Corpora lutea/dam	7.8	8.5	7.9	N.A.

Implantations/dam	6.4	6.8	6.5	6.8
% living fetuses per implantations per dam	83.3	88.2	64.6	Complete implantation loss
Total dead fetuses	2	-	-	-
% resorptions per pregnant dam	16.7	11.8	35.4	100**
Foetal weight in g	32.9 ± 5.2	32.3 ± 3.3	26.1 ± 5.0*	N.A.
Total runts	0	1	0	N.A.
No. of malformed fetuses	0/54	0/65	5/39	N.A.
Litters with malformed fetuses	0	0	3	N.A.
% living fetuses/litter with variations and retardations	83.7	65.7	86.1	N.A.

Means ± standard deviation; *: statistically significant, p≤0.05; **: statistically significant, p≤0.05

BASF (1974)
In an early prenatal developmental study (similar to OECD TG 414) groups of 10 pregnant New Zealand White rabbits were given oral gavage doses of 94, 280 or 850 mg DMAC/kg bw/day (0, 100, 300 or 900 µl/kg bw/day) GD 6 to 18. All dams were killed at GD 29 and fetuses were examined for external abnormalities. The numbers of implantation sites, resorptions (early, late) were recorded, as were the numbers of live and dead fetuses, foetal weights and foetal sex. The soft tissues of the fetuses were examined, and skeletal tissues were stained and examined.
At 850 mg/kg bw/day marked maternal toxicity occurred; reduced food consumption, weight loss and clinical signs were observed (sedation, ataxia and diarrhea). All dams died before test end at this dose level (no live fetuses in this group). No maternal toxicity was noted at lower dose levels. Upon histopathological examination, pale yellowish parenchymatous organs and pronounced hepatic lobules were observed at 850 mg/kg bw/day in dams. At 280 mg/kg bw/day, an increased post-implantation loss (45% versus 11.5% in control) was seen and foetal body weight was slightly reduced (-6%). An increase in variations was also observed, as was the incidence of malformed fetuses (5% of fetuses in 2/10 litters vs. 0% in control) and included: cleft palate (1.6% of fetuses in 1/10 litter), renal cyst and exencephaly (both observed in 3.3% of fetuses in 1/10 litter).
The NOAEL (maternal) is 280 mg/kg bw/day based on clinical signs of toxicity, weight loss and mortality at 850 mg/kg bw/day, and the NOAEL (developmental toxicity) is 94 mg/kg bw/day based onincreased post-implantation loss, foetal malformations (visceral and external) and variations.

Dermal

Multiple dermal studies were identified where the effect of DMAC was evaluated after dermal application. These studies were carried out during the 1970's by Industrial Bio-Test Laboratories, a lab known to have provided fraudulent reports to sponsors during this period. In absence of independent verification of the study report in question, these data are not considered further here.

B.5.3.2.2 NEP

Table 23: Summary of studies informing developmental toxicity after exposure to NEP

Species, strain, number, sex/group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Inhalation – No studies				

Oral				
Rat Sprague-Dawley 24-25 time mated 19-24 pregnant OECD 414 GLP: yes	Prenatal developmental toxicity study GD 6-20 0, 50, 250, 500, 750 mg/kg bw/day (gavage)	NOAEL (maternal): 750 mg/kg bw day NOAEL (foetal): 50 mg/kg bw/day <u>Foetal</u>: 250 mg/kg bw/day: BW ↓ (-7%), fetuses with skeletal variations: supernumerary ribs ↑ (32.2% vs. 17.9% in control), 500 mg/kg bw/day: BW ↓ (-28%), fetuses with malformations ↑ (7% vs. 0.4% in control), litters with malformations ↑ (47.8% vs. 5.3% in control), fetuses with external malformations ↑ (2.8% vs. 0% in control), litters with external malformations ↑ (30.4% vs. 0% in control), fetuses with skeletal malformations ↑ (6.3% vs. 0% in control), litters with skeletal malformations ↑ (39.1% vs. 0% in control), fetuses with skeletal variations ↑ (80.3% vs. 17.9% in control), litters with skeletal variations ↑ (100% vs. 73.7% in control). 750 mg/kg bw/day: BW ↓ (-42%), resorption rate ↑ (83%),fetusses with malformations ↑ (41% vs. 0.4% in control), litters with malformations ↑ (47.8% vs. 5.3% in control), fetuses with external malformations ↑ (25.6% vs. 0% in control), litters with external malformations ↑ (55.6% vs. 0% in control), fetuses with visceral malformations ↑ (25.0% vs. 0.7% in control), litters with visceral malmormations ↑ (50.0% vs. 5.3% in control), fetuses with skeletal malformations ↑ (26.3% vs. 0% in control), litters with skeletal variations ↑ (57.1% vs. 0% in control), fetuses with skeletal variations ↑ (94.7% vs. 17.9% in control), litters with skeletal variations ↑ (100% vs. 73.3% in control), malformations/variations included edema, cardiovascular defects, fused cervical arches, incomplete ossifaction, 14th supernumerary ribs.	1	Saillenfait et al. (2007)
Rabbit Himalayan 25 m (not exposed) 25 f OECD 414 GLP: yes	Prenatal developmental toxicity study GD 6-28 0, 20, 60, 200, 220 mg/kg bw/day (gavage) Repeated using 0 and 220 mg/kg bw/day (gavage)	NOAEL (maternal): 60 mg/kg bw day NOAEL (foetal): 60 mg/kg bw/day Maternal: 200 mg/kg bw/day: relative liver weight ↑ (16%), relative kidney weight ↑ (7%), alanine transferase ↑ (1.41±0.78 vs. 0.96±0.57 µkat/l in controls), γ-glutamyltransferase activity ↓ (118±45 vs. 83±19 in controls), inorganic phosphate ↑ (1.44±0.13 vs. 1.31±0.14 mmol/l in controls), calcium ↓ (3.21±0.18 vs. 3.04±0.20 mmol/l in controls). 220 mg/kg bw/day: absolute liver weight ↑ (13%), relative liver weight ↑ (16%),	1	BASF (2007a, 2007b)

		clotted time ↓ (17.2±1.4 vs. 17.8±0.8 in controls), alkaline phosphatase activity ↓ (0.54±0.11 vs. 0.64±0.15 µkat/l), alanine transferase ↑ (1.09±0.44 vs. 0.82±0.21 µkat/l in controls), γ-glutamyltransferase activity ↓ (109±23 vs. 76±22 in controls), inorganic phosphate ↑ (1.23±0.14 vs. 1.12±0.15 mmol/l in controls), urea ↑ (5.02±0.64 vs. 4.57±0.54 mmol/l in controls), triglycerides ↑ (0.43±0.08 vs. 0.32±0.08 mmol/l in controls), cholesterol ↑ (0.19±0.07 vs. 0.13±0.06 mmol/l in controls), albumin ↓ (29.79±3.28 vs. 31.85±3.14 g/l in controls), magnesium ↓ (0.92±0.09 vs. 0.98±0.10 mmol/l in controls). <u>Foetal:</u> 200 mg/kg bw/day: litters with malformations ↑ (48% vs. 17% in control), litters with skeletal malformations ↑ (35% vs. 8.7% in control). 220 mg/kg bw/day: foetal BW ↓ (-15%), fetuses with malformations ↑[1] (15% vs. 6.0% in control), litters with malformations ↑ (67% vs. 31% in control), fetuses with external malformations ↑[1] (1.4% vs. 0.0% in control), fetuses with visceral malformations ↑[1] (12% vs. 4.0% in control), litters with visceral malformations ↑ (54% vs. 24% in control), fetuses with visceral variations ↑[1] (17% vs.3.3 in control), litters with visceral variations (50% vs. 20% in control), fetuses with skeletal malformations ↑[1] (6.9% vs. 2.7% in control), fetuses with skeletal variations ↑[1] (81% vs. 62% in control).		
Dermal				
Rat Wistar 25 m 25 f GLP: yes	Prenatal developmental toxicity study GD 6-19 0, 200, 400, 800 mg/kg bw/day 6h/day	NOAEL (maternal): 800 mg/kg bw day NOAEL (foetal): 400 mg/kg bw/day <u>Foetal:</u> 800 mg/kg bw day: BW ↓ (-11%), foetuses with skeletal variations ↑: incomplete ossification of basisphenoid ↑ (26% vs. 7.7% in control), unilateral ossification of sternebra ↑ (8.3% vs. 0.8% in control) and supernumerary 14th rib ↑ (16.6% vs. 4.4% in control).	1	BASF (2005)
Rabbit Himalayan 25 f OECD 414 EU Method B.31 EPA OPPTS 870.3700 GLP: yes	Prenatal developmental toxicity study GD 6-28 0, 100, 300, 1000 mg/kg bw/day 6h/day (semi-occlusive)	NOAEL (maternal): 1000 mg/kg bw day NOAEL (foetal): 300 mg/kg bw/day <u>Foetal:</u> 1000 mg/kg bw day: fetuses with cardiovascular malformations altogether ↑ (3.5% vs. 0% in control), absent subclavian (0.7% vs. 0% in control), ventricular septum defect (1,4% vs. 0% in	1	BASF (2010)

		control), dextrocardia (2.1% vs. 0% in control).		

*minus the gravid uterus weight
[1]no statistical analysis reported

m: male, f: female, ↑: increased, ↓: reduced, abs.: absolute, BW: body weight, GD: gestation day, n.s.: not statistically significant, rel.: relative

Inhalation
No studies available

Oral – NEP

Saillenfait et al. (2007)
NEP (purity 99%, impurities not given) was administered daily by gavage on GD 6-20 to 19-24 pregnant Sprague-Dawley rats per group. Based on a dose-range finding study, the dose levels were 0, 50, 250, 500 and 750 mg/kg/d. All females were observed daily for clinical signs of toxicity. Maternal food consumption and body weights were measured every 3 days from GD 6. Animals were killed on GD 21 and ovary, uterine content and fetuses were examined for external anomalies. The number of pregnant dams at euthanasia was respectively 20, 19, 23, 24 and 23. Half of the fetuses were examined for visceral changes and half for skeletal anomalies. This study was consistent with OECD guideline 414 except that the age of the dams is not given in the publication. However, the weight of the dams when supplied was consistent with Sprague-Dawley females aged 8 to 9 weeks, which is in agreement with OECD 414 requirement to use young adult animals.
No clinical signs were reported except that urine of dams given NEP was bright yellow. Maternal body weight gain was significantly reduced at all doses on GD 6-9 as well as on GD 15-18 from 250 mg/kg bw/day onward, on GD 18-21 from 500 mg/kg bw/day and on GD 12-15 at the highest dose (see Table 24). After correction for gravid uterine weight, no significant effect on corrected maternal body weight was noted and therefore the reduction in weight gain during gestation was probably mainly due to post-implantation loss (see Table 25). Decrease in weight gain was accompanied by a significant decrease of food consumption in all groups on GD 6-9 as well as in the 500 and 750 mg/kg bw/day groups on GD 9-12. During late gestation, significantly decreased food consumption was observed only at the highest dose on GD 15-18 and 18-21.

Table 24: Maternal parameters upon oral exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)				
	0	*50*	*250*	*500*	*750*
Body weight changes GD 6-9	13±2	**2±7****	**0±8 ****	**-4±5 ****	**-4±6 ****
GD 9-12	19±6	19±5	18±7	19±5	15±6
GD12-15	18±9	20±7	20±8	16±5	**8±6****
GD15-18	41±11	39±8	**34±10***	**28±8****	**13±6****
GD18-21	47±13	43±8	41±12	**37±11****	**12±10****
GD 0-21	170±36	154±25	**142±31* (-17%)**	**128±28** (-25%)**	**74±22** (-56%)**
Corrected weight gain[a]	66±23	60±26 (-9%)	52±16 (-21%)	55±13 (-17%)	58±12 (-11%)
Corrected weight GD 21[b]	292	287 (-2%)	279 (-5%)	282 (-3%)	283 (-3%)
Food consumption: *GD 6-9*	24±2	**19±4****	**18±3 ****	**17±2 ****	**15±3 ****
GD 9-12	26±2	25±3	25±3	**24±2****	**22±3****
GD12-15	26±3	26±4	27±3	26±2	25±2
GD15-18	28±4	29±74	28±4	27±3	**25±2***
GD18-21	26±4	26±4	25±3	24±2	**24±3***
GD0-21	26±2	25±3	24±2	**24±2* (-8%)**	**22±2** (-15%)**

[a] body weight gain during GD0-21 minus gravid uterine weight
[b] body weight at GD 0 plus gain during GD0-21 minus gravid uterine weight. Calculated based on results given in the publication, no statistical analysis performed
* p<0.05, **p<0.01

The number of implantation sites was similar across groups. A significant dose-related increase in post-implantation loss was observed at the two highest doses (20.8 and 88.3% respectively vs. 9.1% in control) (Table 25). It consisted mainly of an increase in resorptions at these two dose levels (19.9 and 83.2% respectively vs. 9.1% in control), as well as a small non significant increase in dead fetuses per litter at the highest dose (5.1%). A dose-related increase in late resorptions was observed from 500 mg/kg bw/day onward (12.8 and 16.9% respectively vs. 0.5% in control), whereas early resorptions were significantly induced only at 750 mg/kg bw/day (66.2% vs. 8.7% in control). A significant and dose-related decrease in foetal weight was also observed at 250 mg/kg and higher doses (-7, -28 and -42% respectively). This decrease was greater than the corresponding decrease of corrected maternal weight.

Table 25: Gestational parameters upon oral exposure to NEP (adoted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)				
	0	*50*	*250*	*500*	*750*
% post-implantat° loss / litter	9.1±22.5	3.7±5.9	5.6±11.4	**20.8±25.9 ***	**88.3±22.9 ****
% dead fetuses / litter	0.0±0.0	0.0±0.0	0.0±0.0	0.9±2.3	5.1±8.8
% resorptions / litter	9.1±22.5	3.7±5.9	5.6±11.4	**19.9±26.0 ***	**83.2±25.2 ****
% early resorptions / litter[a]	8.7±22.2	3.7±5.8	5.6±11.4	7.1±11.1	**66.2±34.0****
% late resorptions / litter[a]	0.5±2.0	0.0±0.0	0.0±0.0	**12.8±22.9***	**16.9±25.6****
Fetal body weight (g)	5.58±0.26	5.61±0.33	**5.19±0.37 **** **(-7%)**	**3.99±0.19 **** **(-28%)**	**3.19±0.40 **** **(-42%)**

* p<0.05, **p<0.01

The incidence of malformations in foetuses and in litters was increased at the two highest doses (Table 26), and statistically significantly so for external and skeletal malformations at 500 and 750 mg/kg/d and for visceral malformations at 750 mg/kg/d. External malformations essentially consisted of edema and anal atrasia associated with the absence of tail. Visceral

evaluation revealed heart and great vessels malformations. Skeletal malformations primarily involved the axial skeleton. The most common were fused cervical arches. Skeletal variations were significantly increased from 250 mg/kg/d onward and consisted mainly of retarded ossification of the skull bones and sternebrae and supernumerary ribs. All reported malformations were rare malformations and exceeded the historical control data from the same laboratory.

Table 26: Malformations and variations upon oral exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)				
	0	*50*	*250*	*500*	*750*
% foetus with any malformations	0.4%	0.8%	0.3%	**7.0%****	**41.0%****
% litters with any malformations	5.3%	10.5%	4.3%	**47.8%****	**88.9%****
% foetus with external malformations	0%	0%	0.3%	**2.8%***	**25.6****
% litters with external malformations	0%	0%	4.3%	**30.4%***	**55.6%****
Oedema[a]	0	0	0	1.0% (13%)	26% (55%)
Mand. micrognatia and cleft palate[a]	0	0	0	0.3% (4%)	0
Anal atresia and absent tail[a]	0	0	0	1.4% (17%)	0
% foetus with visceral malformations	0.7%	1.7%	0%	4.9%	**25.0****
% litters with visceral malformations	5.3%	10.5%	0%	22.7%	**50.0%***
Cardiovascular malformations[a]*:*	0	0	0	4.2% (18%)	25% (50%)
Truncus arteriosus persistent[a]	0	0	0	1.4% (9%)	15% (25%)
Aorta, transposed[a]	0	0	0	0.7% (4%)	0
Aorta, origin abnormalities[a]	0	0	0	1.4% (4%)	0
Pulmonary artery, narrowed[a]	0	0	0	0.7% (4%)	5% (12%)
Interventricular septum defect, isolated[a]	0	0	0	0	5% (12%)
% foetus with skeletal malformations	0%	0%	0%	**6.3%****	**26.3%****
% litters with skeletal malformations	0%	0%	0%	**39.1%****	**57.1%****
Mandible, small and split palatine[a]	0	0	0	0.7% (4%)	0
Cervical arches malformations[a]	0	0	0	4.9% (30%)	21% (43%)
Atlas and exoccipital, fused[a]	0	0	0	1.4% (9%)	0
Cervical arches, fused[a]	0	0	0	3.5% (22%)	16% (29%)
Cervical and first thoracic arches, fused[a]	0	0	0	0	5.3% (14%)
Absent[a]	0	0	0	1.4% (9%)	0
Ribs, thor., lumbar and sacral verteb., absent[a]	0	0	0	0.7% (4%)	0
Thoracic vertebral centra, absent[a]	0	0	0	0.7% (4%)	0
Ribs, fused[a]	0	0	0	0.7% (4%)	5.3% (14%)
% foetus with skeletal variations	17.9%	23.1%	**32.2%****	**80.3%****	**94.7%****
% litters with skeletal variations	73.7%	73.7%	78.3%	**100%***	100%
Frontal and parietals, incomplete ossification[a]	0	0	2	28% (74%)	47% (86%)
Supraoccipital, incomplete or bipartite ossif.[a]	0	0	0	18% (56%)	58% (100)
Sternebrae : incompl. ossif. or unossif.[a]	0	1	6	18% (65%)	42% (71%)
Ribs: 14th supernumerary all[a]	6	12	41	44% (83%)	74% (71%)
14th supernumerary long[a]	1	0	4	22% (39%)	58% (71%)
14th supernumerary short[a]	5	12	37	22% (70%)	16% (10%)

* $p<0.05$, **$p<0.01$
[a] % of fetuses (litters) affected

Overall this study shows that NEP induces foetotoxic effects arising as post-implantation loss and reduction of foetal growth and teratogenic effects arising as external, visceral and skeletal malformations and skeletal variations in rats by oral route. These effects occur in the presence of slight, transient maternal toxicity. When correcting the significantly decreased maternal body weight change to take into account the post-implantation loss from 500 mg/kg/d onward and the reduction of foetal weight from 250 mg/kg/d onward, corrected maternal body weight gain and corrected maternal body weight on GD 21 were not significantly affected at any dose. This is also supported by the absence of reduction of maternal food consumption during

late gestation at 250 mg/kg/d and 500 mg/kg/d when foetal growth occurs. Malformations induced by NEP are rare malformations observed above historical controls and with a statistical significance.
In conclusion, the NOAEL for developmental toxicity is 50 mg/kg bw/day based on an increase in skeletal variations and a reduced foetal weight. The NOAEL for maternal toxicity is 750 mg/kg bw/day, given the absence of adverse effects.

BASF (2007a, 2007b)
NEP was tested for its prenatal developmental toxicity in two studies in Himalayan rabbits performed according to GLP and to OECD 414 guidelines. NEP was administered as an aqueous solution to 25 inseminated female Himalayan rabbits/group by stomach tube at doses of 0, 20, 60 and 200 mg/kg bw on day 6-28 post insemination. The study was repeated using dose levels of 0 and 220 mg/kg bw/day. All females were observed daily for clinical signs of toxicity. Maternal food consumption was measured daily and body weights every 2 or 3 days. Animals were killed on GD 29 (postinsemination). Blood was taken from all surviving females and maternal blood and serum parameters were evaluated. Gross pathology was performed and ovary, uterine content and fetuses were examined for external anomalies. Maternal liver, spleen and kidneys were also weighted. Corpora lutea were determined and number and distribution of implantation sites were determined. Fetuses were examined for external and visceral changes and for skeletal anomalies.
In the first study (BASF, 2007a) 22-23 females/group had implantation sites at terminal sacrifice. Maternal parameters are summarized in Table 27. One low dose group animal had to be sacrificed after abortion on day 29 post insemination (PI) and one high dose group animal died prematurely on GD 23 after gavage error. Orange or reddish discolored urine was recorded in all high-dose females from GD 8 and one mid-dose dam from GD 27. This finding reflects the systemic availability of NEP but is not considered to reflect an adverse toxic effect. No other significant clinical sign was reported.

A slight loss of weight in high dose females was noted on GD 6 when gavage was started and the consequent slight difference (not significant) between high dose and control animals was maintained until the terminal sacrifice (up to -3%). This was reflected by a statistically significant decrease of weight gain in high dose females between GD 6-9, but the weight gain over the entire gavage period was not statistically significantly affected (it was significantly affected over the whole gestation period GD 0-29). Similarly, the maternal corrected body weight was not statistically different between groups. Statistically significant decreases of daily food consumption compared to controls were observed on GD 6 to 17 in the high dose group. Increases in food consumption were also noted on some days between GD 22 to 27 in the mid-dose group.

Table 27: Maternal parameters upon oral exposure to NEP (adopted from CLH report (ECHA, 2011c))

		Dose (mg/kg/day)			
	GD	0	20	60	200
Body weight:	GD0	2456±180	2451±198	2480±224	2467±184
	GD6	2545±205	2526±189	2566±245	2540±193 (-0.2%)
	GD29	2800±197	2790±180	2822±168	2713±181 (-3%)
Body weight changes:	0-6	88.7±45.88	75.7±47.70	85.8±60.08	73.0±42.73 (-18%)
	6-29	236.5±85.83	246.1±98.79	240.3±105.39	173.2±88.57 (-27%)
	0-29	343.6±82.49	339.9±133.80	341.7±100.45	**246.0±106.66** (-28%)**
Corrected weight gain[a]		-86.4±86.79	-66.3±96.96	-75.9±105.90	-104.6±118.03 (-27%)
Corrected weight GD29[b]		2458.5±169.13	2476.3±137.97	2490.2±223.54	2435.7±129.35 (-1%)
Food consumption[c]:	0-6	122.9±2.24	120.4±5.30	124.0±2.95	124.3±4.79 (+1%)
	6-29	96.8±12.33	98.5±10.41	100.1±6.71	82.9±7.27 (-14%)
	0-29	101.6±15.75	102.6±13.29	104.6±11.83	91.5±18.27 (-10%)

* p<0.05, **p<0.01
[a] weight of the carcass at GD29 after removal of the gravid uterus minus day 6 body weight
[b] weight of the carcass at GD29 after removal of the gravid uterus (grams).
[c] Mean per day and per animal. No statistical analysis reported for food consumption calculated over several days.

Absolute maternal weights of the liver, spleen and kidneys were not significantly affected but an increase in relative liver (p<0.01) and kidney (p<0.05) weights were observed at the high dose (+16 and +7% respectively). Analysis of blood parameters revealed an increase of enzymatic activities of the alanine transferase from the mid-dose (0.96±0.57 µ kat/l in controls vs 1.17±0.47* at mid-dose and 1.41±0.78** at the high dose) and of the γ-glutamyl transferase at the high dose (83±19 nkat/l in controls vs 118±45** at the high dose). The levels of calcium (3.04±0.20 mmol/l in controls vs 3.15±0.25* at mid-dose and 3.21±0.18** at the high dose) and inorganic phosphate (1.31±0.14 mmol/l in controls vs 1.44±0.13** at the high dose) were also increased from the mid-dose or at the high dose.
The authors considered that the slight increase in alanine aminotransferase activity in the high dose group is indicative of mild liver damage, because liver weights in this group were increased correspondingly. The elevated γ-glutamyltransferase activities was also assessed as being treatment-related, being a consequence of microsomal enzyme induction in the liver. Although the slight increases in calcium and inorganic phosphate were not particular marked, the author considered these findings to be test substance-related, too, albeit difficult to interpret in their pathogenesis, due to the isolated occurrence of both effects and due to the low magnitude of change. Gross pathology revealed no substance-related observations in the dams. Microscopic examination was not performed, so it is not known whether microscopic lesions were present in the organs.
There were no significant substance-related influences on the gestational parameters including the highest dose level (200 mg/kg bw/day). Conception rate, mean number of corpora lutea, total implantations, resorptions and live fetuses, foetal sex ratio or the values calculated for the pre- and post-implantation losses were unaffected by the treatment. No substance-related differences to the control were recorded for placental and foetal body weights in any of the substance-treated groups, the latter being reduced by only 4% at 200 mg/kg bw/d.

External malformations were reported in one foetus at mid dose (spina bifida) and in one foetus at high dose (meningocele). These findings have never been reported in historical controls of the laboratory (from 9 studies). Three incidences of encephalocele (0.26% of litter

and 0.039% of foetuses) and 1 incidence of meningocele (0.09% of litter and 0.013% of foetuses) are reported in the literature in 1136 litters of Himalayan rabbits (Viertel 2003). These malformations are therefore considered as rare. There was no increase of external variations in the treated animals (data not shown in Table 28).
No significant increase in visceral malformations is observed. It is noted that 2 foetuses (1.6% vs. 0.6% in control) have a cardiovascular malformation (ventricular septum defect) at high dose. One control foetus also has this defect and the incidence at high dose is in the range of historical controls of the laboratory (range of foetal incidence: 0 – 2.3%) and it may not be related to treatment. There was no visceral variation attributed to treatment (data not shown in Table 28).
The incidence of litters with foetuses having skeletal malformations was statistically increased at the high dose. Statistical analysis of the foetal incidence was not performed. Both litter (35% vs. 8.7% in control) and foetal (6.3% vs. 1.3% in control) incidences for skeletal malformations were above historical control range (0 to 17.4% of litters and 0 to 2.8% of foetuses affected in historical controls). Skeletal malformations affected sternebrae, vertebral column, ribs and/or skull bones. In particular, the incidence of foetuses per litter with misshapen cervical vertebra was statistically significant at high dose (data not shown in the table). The vast majority of the noted skeletal variations appeared without a dose response. Increases in misshapen sacral vertebra and supernumerary 13th rib were however observed at the high dose above historical controls (misshapen sacral vertebra: 0 to 1.3% of foetuses and 0 to 8% of litters affected; supernumerary 13th rib: 2.5% to 12.7% of foetuses and 16.0% to 52.2% of litters affected) and were both statistically significant when incidence of affected foetuses by litter was considered (data not shown in the Table 28).

Table 28: Foetal and litter incidence of malformations and variations after oral exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)				Historical controls[b]
	0	20	60	200	
% foetus with any malformations[c]	2.6%	3.0%	1.4%	9.5%	4.16%
% litters with any malformations	17%	18%	9.1%	48%*	20.98%
% foetus with external malformations[c]	0%	0%	0.7%	0.8%	0.2% (0-0.8%)
% litters with external malformations	0%	0%	4.5%	4.3%	0.5% (0-5.0%)
% foetus with visceral malformations[c]	1.3%	2.2%	0.7%	3.2%	2.9% (0.6-4.9%)
% litters with visceral malformations	8.7%	14%	4.5%	17%	15.6% (4.0-24.0%)

Cardiovascular malformations[a]*:*	0.6%	0	0	1.6%	-
Ventricular septum defect	0.6%	0	0	1.6%	0.7% (0-2.3%)
% foetus with skeletal malformations [c]	1.3%	0.7%	0.7%	6.3%	1.5% (0-2.8%)
% litters with skeletal malformations	8.7%	4.5%	4.5%	35%*	8.8% (0-17.4%)
Severely malformed skull bones	0	0	0	0.8%	0
Misshapen cervical vertebra	0	0	0	2.4%	0.08% (0-0.7%)
Cervical hemivertebra	0	0	0	0.8%	0.08% (0-0.7%)
Small cervical arch	0	0	0	0.8%	0
Absent lumbar vertebra	0	0.7%	0	0.8%	0.2% (0-0.7%)
Splayed lumbar arch	0	0	0.7%	0	0
Misshapen lumbar vertebra	0.6%	0	0	0.8%	0.2% (0-0.7%)
Sternebrae severely fused	0	0	0.7%	0	0.08% (0-0.7%)
Branched rib	0	0.7%	0	0	0
% foetus with skeletal variations [c]	66%	82%	79%	73%	68.4% (57.2-82.8%)
% litters with skeletal variations	91%	100%	100%	96%	97.6% (82.4-100%)
Misshapen sacral vertebra	0	1.5%	0.7%	4.0%	0.2% (0-1.3%)
Supernumerary rib (13th); cartilage not present	5.2%	3.0%	5.8%	17%	6.3% (2.5-12.7%)

* $p<0.05$,
[a] incidence of foetuses with cardiovascular malformations, i.e. ventricular septum defect.
[b] mean fetal incidence (range) in historical control data from 9 studies performed in the same laboratory from 2003 to 2006.
[c] no statistical analysis for this parameter

In the second study using dose levels of 0 and 220 mg/kg bw/day (BASF, 2007b), 24-25 females had implantation sites at scheduled necropsy. A similar level of maternal toxicity was seen as after administration of 200 mg/kg bw/day in the first study. According to the summary of the CLH report in 2011, NEP induced a slight maternal toxicity with transient significant effects on food consumption (-19% for GD 6-29 and -15% for GD 0-29) and body weight gain (-38% for GD 6-29 and -91.7% for GD 0-29), in particular at the beginning of treatment. The corrected maternal body weight was not affected (-1%).

Absolute and relative maternal weights of the liver were significantly increased in treated females ($p<0.01$) (+13 and +16% respectively). Analysis of blood parameters revealed a decrease in the clotted time (17.8±0.8 in controls vs 17.2±1.4* in treated dams) and in the enzymatic activity of the alkaline phosphatase (0.64±0.15 µkat/l in controls vs 0.54±0.11* in treated dams) and an increase of enzymatic activities of the alanine transferase (0.82±0.21 µkat/l in controls vs 1.09±0.44* in treated dams) and of theγ-glutamyl transferase (76±22 nkat/l in controls vs 109±23** in treated dams). The levels of inorganic phosphate (1.12±0.15 mmol/l in controls vs 1.23±0.14* in treated dams), urea (4.57±0.54 mmol/l in controls vs 5.02±0.64* in treated dams), triglycerides (0.32±0.08 mmol/l in controls vs 0.43±0.08** in treated dams) and cholesterol (0.13±0.06 mmol/l in controls vs 0.19±0.07** in treated dams) were also increased. Albumin (31.85±3.14 g/l in controls vs 29.79±3.28* in treated dams) and magnesium (0.98±0.10 mmol/l in controls vs 0.92±0.09* in treated dams) were significantly decreased. As for the first study, the authors considered that the higher γ-glutamyltransferase activity as well as the increased triglyceride and cholesterol values are due to a microsomal induction of the phase II enzymes in the hepatocytes. Even the lower albumin values as well as the shortened prothrombin time in the dose group are hints of a changed liver cell metabolism according to this enzyme induction. A slightly higher serum alanine-aminotransferase activity in the serum of the treated rabbits was considered an indication of a mild liver damage. Gross pathology revealed no substance-related observations in the dams. In the absence of microscopic examinations, it is not known whether microscopic lesions were present in the organs.

A significantly lowered foetal weight was observed after administration of 220 mg/kg bw/day (about -15%). NEP had no significant effect on post-implantation loss but NEP induced a statistically significant increased incidence of litteres with foetuses with total and visceral malformations at 220 mg/kg bw/day (67% vs. 32% in control and 54% vs. 24% in control, respectively, see Table 29). External malformations were reported in two foetuses from two litters in the test group. They showed severe multiple malformations (gastroschisis, cleft palate, meningocele, misshapen head, malrotated fore- and hindlimbs, forelimbs micromelia and ectrodactily in one fetus, acephaly, thoracogastroschisis, absent claw, forelimb paw hyperflexion in the other). These findings are rare as only 1 foetus (0.08% of foetuses) was reported to have multiple external malformations and 1 malrotated limb in historical controls of the laboratory (from 9 studies). There was no significant increase of external variations in the treated animals (data not shown in Table 29).
A statistically significant increase in visceral malformations was observed in the test group and they exceed historical control data. The two foetuses with multiple external malformations also showed multiple severe visceral malformations. When considering each type of malformation one by one, the incidences of small spleen and of absent gallbladder in the test group were slightly above the historical control upper range but were not statistically significant. The incidence of absent subclavian was above historical controls and was statistically significantly above incidence in controls when considering the incidence of foetuses per litter (data not shown in Table 29). When considering the incidence of the different malformations of the cardiovascular system altogether, it is observed that 2 foetuses were affected in controls vs 7 in the test group (no statistical analysis and no historical control data available for this calculated value). A statistical increase in the incidence of visceral variations was also noted but the incidence was in the historical control range.
The incidence of foetuses per litter with skeletal malformations was statistically increased in treated group and exceeded the historical control upper range (data not shown in Table 29). Malformations affect different foetal components and these findings did not form a distinct malformation pattern. Skeletal variations were also increased (statistically significant when considering incidence of foetuses per litter, data not shown in the table). In particular, the incidence of incomplete ossification of cervical centrum, extra ossification site between cervical arches, fused sternebra, misshapen sacral vertebra and supernumerary rib (13th) were above historical controls and statistically significant when considering incidence of foetuses per litter (data not shown in the Table 29).

Table 29: Foetal incidence of malformations and variations after oral exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)		*Historical controls*[a]
	0	*220*	
% foetus with any malformations[b]	6.0%	15%	3.74% (1.27-7.64%)
% litters with any malformations	32%	**67%***	19.21% (8.0-28.0%)
% foetus with external malformations[b]	0%	1.4%	0.2% (0-0.8%)
% litters with external malformations	0%	8.3%	0.5% (0-5.0%)

% foetus with visceral malformations [b]	4.0%	12%	2.6% (0.6-4.9%)
% litters with visceral malformations	24%	**54%***	13.8% (4.0-21.7%)
Small spleen	0	1.4%	0.8% (0-0.8%)
Absent gallbladder	2.0%	4.9%	1.5% (0-2.8%)
Cardiovascular malformations [b,c]	1.4%	4.9%	-
Absent subclavian [f]	0	2.1%	0.08% (0-0.6%)
Persistent truncus arteriosus [e]	0	0.7%	0
Ventricular septum defect [f]	0.7% (4%)	0	0.6% (0-2.3%)
% foetus with visceral variations [b]	3.3%	17%	15.3% (5.6-28.1%)
% litters with visceral variations	20%	**50%***	47.3% (11.8-78.3%)
% foetus with skeletal malformations [b]	2.7%	6.9%	1.3% (0-2.8%)
% litters with skeletal malformations	16%	38%	7.9% (0-17.4%)
Small hyoid	0	0.7%	0
Severely malformed vertebra, sternum and/or ribs	0	0.7%	0
Misshapen cervical vertebra	0.7%	0	0
Cervical hemivertebra	0.7%	0	0
Fused cervical arch	0	0.7%	0
Misshapen thoracic vertebra	0	0.7%	0.08% (0-0.7%)
Absent lumbar vertebra	0	0.7%	0.2% (0-0.7%)
Misshapen lumbar vertebra	0.7%	1.4%	0.2% (0-0.7%)
Sternebrae severely fused	0.7%	1.4%	0.08% (0-0.6%)
Malpositioned and bipartite sternebra	0	0.7%	0
Small forepaw phalang [h]	0	0.7%	0
% foetus with skeletal variations [b]	62%	81%	68.8% (57.2-82.8%)
% litters with skeletal variations	100%	100%	96.6% (82.4-100%)
Incomplete ossify. of cervical centrum	1.3%	15%	2.6% (0-4.9%)
Extra ossif. site between cervical arches	0	3.5%	0.08% (0-.08%)
Fused sternebra	5.3%	13%	5.6% (2.8-10.7%)
Misshapen sacral vertebra	1.3%	4.9%	0
Supernumerary rib (13th); cartilage not present	13%	29%	5.4% (2.5-11.7%)

* $p<0.05$,
[a] mean fetal incidence (range) in historical control data from 9 studies performed in the same laboratory from 2003 to 2006.
[b] no statistical analysis for this parameter
[c] incidence of foetuses with cardiovascular malformations, i.e. absent subclavian, persistent truncus arteriosus, ventricular septum defect and mishappen heart altogether.
[d] do not include one additional foetus in the test group with multiple visceral malformations including absent subclavian and one with multiple visceral malformations including malpositioned subclavian branch.
[e] do not include one foetus in controls and two additional foetuses in the test group with multiple visceral malformations including persistent truncus arteriosus
[f] do not include one additional foetus in controls and two foetuses in the test group with multiple visceral malformations including ventricular septum defect.
[g] do not include one additional foetus in the test group with multiple skeletal malformations including small forepaw and hindpaw phalanges.

Integrating both studies, the overall NOAEL for maternal toxicity is conservatively set at 60 mg/kg bw/day, based on indications for (mild) liver toxicity at 200/220 mg/kg bw/day. The NOAEL for foetal toxicity is also 60 mg/kg bw/day, based on an increase in skeletal and visceral malformations at 200/220 mg/kg bw/day.

Dermal - NEP

BASF (2005)
In a prenatal developmental study, performed according to GLP and OECD 414 guideline, NEP was applied dermally (6 hours/day) as an aqueous solution (33.3%) to 25 artifically inseminated female Wistar rats/group on GD 6-19. Rats were dosed 200, 400 and 800 mg/kg bw/day onto the intact shaven dorsal skin using a semi-occlusive dressing. All females were observed daily for clinical signs of toxicity. Maternal food consumption was measured daily and body weights every 2 or 3 days. Animals were killed on GD 20 (post-insemination). Gross pathology was performed and ovary, uterine content and fetuses were examined for external anomalies. Corpora lutea and the number and distribution of implantation sites were determined. Fetuses were examined for external and visceral changes and for skeletal anomalies.

Vaginal hemorrhage was occasionally observed between GD 13 to 15 (in 3, 1, 4 and 7 dams at 0, 200, 400 and 800 mg/kg) without clear relation to treatment. The skin was free from any notable findings. Maternal parameters are summarized in Table 30. Over the whole gavage period, food consumption was 10% lower in the high dose group than in controls (no statistical analysis reported for cumulative food consumption). The body weight change was significantly lower in the high-dose animals than in controls (-22%) and corrected body weight gain was significantly decreased at mid- and high doses during the gestation period (-21 and -43% respectively). Similarly, the maternal body weight was significantly lower than controls at GD 6-8 in the mid-dose group and at GD 6-8, 8-10 and 17-19 in the high-dose group. At GD 20, both the maternal weight and the maternal corrected weight were significantly decreased in the high dose group, but the decrease was only small (-5%).

Table 30. Maternal parameters upon dermal exposure to NEP (adopted from CLH report (ECHA, 2011c))

		Dose (mg/kg/day)			
	GD	0	200	400	800
Body weight:	GD0	163.7±6.62	162.8±7.88	161.1±6.69	164.9±9.07
	GD6	192.6±9.08	191.9±8.31	191.2±7.42	194.1±9.45
	GD20	266.3±16.11	267.7±15.14	258.2±17.76 (-3%)	**252.5±19.00*** (-5%)
Body weight changes:	0-6	29.0±5.32	29.2±3.79	30.0±3.69	29.3±4.16
	6-19	64.7±10.84	65.2±10.84	58.5±10.89 (-10%)	**50.7±12.33**** (-22%)
	0-19	102.7±14.99	105.0±12.59	97.1±15.56 (-5%)	**87.6±14.11**** (-15%)
Corrected weight gain[a]		29.4±6.82	27.5±6.18	**23.3±7.47*** (-21%)	**16.7±7.85**** (-43%)
Corrected weight GD29[b]		222.0±12.0	219.4±11.67	214.4±11.14 (-4%)	**210.8±13.05**** (-5%)
Food consumption[c]:	0-6	15.5±2.45	15.9±2.03	16.5±1.84	16.0±2.44
	6-19	20.0±1.86	20.3±1.73	19.2±2.34	18.1±3.70 (-10%)
	0-19	18.8±2.93	19.1±2.75	18.5±2.48	17.7±3.26 (-6%)

* p<0.05, **p<0.01
[a] weight of the carcass at GD29 after removal of the gravid uterus minus day 6 body weight
[b] weight of the carcass at GD29 after removal of the gravid uterus (grams).
[c] Mean per day and per animal. No statistical analysis reported for food consumption calculated over several days.

No significant effect was observed on reproductive parameters and in particular on post-implantation loss. However, foetal body weight was significantly decreased (-11%) in the high dose group. Treatment with NEP did not result in external or visceral malformations. Skeletal malformations were observed in one mid-dose foetus (malpositioned bipartite sternebra) and one high-dose foetus (misshapen lumbar vertebra), but also in one control foetus (misshapen lumbar vertebra). The incidences of total external, visceral and skeletal variations were also not increased following treatment with NEP. The majority of the noted skeletal variations appeared without a dose response. For some individual skeletal variations however,

significant increases were observed: for incomplete ossification of basisphenoid at the high dose, for unossified sternebra at all doses but no dose-response and within historical control, for unilateral ossification of sternebra at the low and hogh dose but no dose-response, and for supernumerary 14th at the high dose.

Although some effects on maternal food consumption and weight/weight gain were seen at the mid and/or high dose, the corrected maternal weight at GD 20 was only slightly decreased (up to 5%). This is not considered adverse, and hence the NOAEL for maternal toxicity is 800 mg/kg bw/day. A decreased foetal weight (-11%) and an increased incidence of some skeletal variations were observed at 800 mg/kg bw/day. Although these occurred in the presence of slight maternal toxicity, it is noted that the decrease in foetal weight was greater than the corresponding decrease of corrected maternal weight. Therefore the NOAEL for developmental toxicity is considered to be 400 mg/kg bw/day.

BASF (2010)
A prenatal developmental study was performed in rabbits by dermal route (according to GLP and OECD 414 guideline). NEP was applied as an aqueous preparation to 3 groups of 25 inseminated female Himalayan rabbits at doses of 100, 300 and 1000 mg/kg bw/day, onto the intact shaven dorsal skin using a semi-occlusive dressing, on GD 6-28 for 6 hours/day. Deionized water was used as vehicle. All females were observed daily for clinical signs of toxicity. Maternal food consumption was measured daily and body weights every 2 or 3 days. Animals were killed on GD 29 (post-insemination). Gross pathology was performed and ovary, uterine content and fetuses were examined for external anomalies. Corpora lutea were determined and number and distribution of implantation sites were determined. Fetuses were examined for external, visceral and skeletal anomalies.

One low dose group animal died prematurely (cause of death not given) and one mid dose group animal had to be sacrificed after abortion on day 29 post insemination (PI). Orange or reddish discolored urine was recorded in all high-dose females from GD 8. This finding reflects the systemic availability of NEP but is not considered to reflect an adverse toxic effect. No other significant clinical sign was reported. The skin was free from any notable findings.
Statistically significant decreases of daily food consumption were observed from GD 6 to 17 in the high dose group compared to controls. Increases in food consumption were also noted at the end of the gestation and were significant at GD 27-28. Over the whole gavage period, food consumption was 17% lower in the high dose group than in controls (no statistical analysis reported). A loss of body weight was noted in high-dose females on GD 6-9 when gavage was started but there was no statistical difference between the body weight of control and treated animals during the administration period. The consequent body weight difference with controls was maintained approximately stable until the terminal sacrifice (2%). A statistically significant decrease of weight gain was also observed in high-dose females on GD 6-9 but it did not attain statistical significance over the whole administration period (-21%). No significant effect on the corrected weight gain was observed and corrected maternal weight was similar across groups.

Main reproductive parameters are summarised in Table 31. 21-24 pregnant rabbits per group had implantation sites. No significant effect was observed on reproductive parameters and in particular on post-implantation loss. Foetal weight was slightly, but not statistically significantly, decreased by 6%.

Table 31. Gestational parameters upon dermal exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)			
	0	*100*	*300*	*1000*
% post-implantat° loss/ litter	5.8±10.71	5.2±9.79	8.9±13.11	9.6±14.48
% dead fetuses / litter	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
% resorptions / litter	5.8±10.71	5.2±9.79	8.9±13.11	9.6±14.48
% early resorptions/ litter	4.6±9.08	3.1±7.31	6.8±11.02	5.5±13.58
% late resorptions / litter	1.2±3.87	2.1±7.47	2.1±5.32	4.0±6.37
Fetal body weight (g)	39.1±2.49	37.9±5.18	39.4±3.97	36.8±3.89 (-6%)

* $p<0.05$, ** $p<0.01$

Malformations and variations in the foetuses are reported in Table 32. External malformations were reported in one foetus at the high dose (cleft palate). Cleft palate has been reported in historical controls of the laboratory (from 24 studies) with a foetal incidence of 0.06% (range: 0-0.6%) and although rare, this malformation is therefore observed with an incidence within the historical control range. There was no increase of external variations in the treated animals (data not shown in Table 32). No significant increase in overall or individual incidences of visceral malformations were observed. Several malformations of the cardiovascular system are however reported in treated animals. In particular, absent subclavian is observed in one mid-dose and one high-dose foetus, whereas it has not been reported in historical controls despite the large size of the database (24 studies). Membranous ventricular septum defect and dextrocardia also exceed historical control range at the high dose, although it is noted that the three foetuses with dextrocardia are in the same litter. There was no visceral variation attributed to treatment (data not shown in Table 32). No significant increase in overall or individual incidences of skeletal malformations and no dose response are observed. The vast majority of the noted skeletal variations appeared without a dose response. Only the increase in incidence of supernumerary 13th rib (cartilage not present) was observed at the high dose above historical controls (2.5 to 13.9% of foetuses and 8.0 to 52.2% of litters affected) and was statistically significant when litter incidence and incidence of affected foetuses by litter were considered (data not shown in Table 32).

Table 32. Foetal incidence of malformations and variations upon dermal exposure to NEP (adopted from CLH report (ECHA, 2011c))

	Dose (mg/kg/day)				Historical controls[b]
	0	100	300	1000	
% foetus with any malformations [c]	1.9%	6.5%	5.2%	4.9%	4.07% (1.27-7.64%)
% litters with any malformations	13%	29%	24%	22%*	23.40% (8.00-43.48%)
% foetus with external malformations [c]	0%	0%	0%	0.7%	0.3% (0-2.6%)
% litters with external malformations	0%	0%	0%	4.3%	2.0% (0-20.0%)
% foetus with visceral malformations [c]	0.6%	3.9%	4.5%	3.5%	2.6% (0-7.2%)
% litters with visceral malformations	4.3%	13%	19%	13%	15.5% (0-43.5%)
Cardiovascular malformations[a]:	0	1.3%	0.7%	3.5%	-
Absent subclavian	0	0	0.7%	0.7%	0
Ventricular septum defect	0	0.6%	0	1.4%	0.06% (0-0.7%)
Dextrocardia	0	0	0	2.1%	0
% foetus with skeletal malformations [c]	1.3%	2.6%	0.7%	0.7%	1.9% (0.6-3.1%)
% litters with skeletal malformations	8.7%	17%	4.8%	4.3%	12.8% (4.0-21.7%)
% foetus with skeletal variations [c]	65%	62%	61%	69%	60.9% (51.5-77.8%)
% litters with skeletal variations	100%	96%	95%	100%	96.6% (80.0-100%)
Supernumerary rib (13th); cartilage not present	7.7%	0.6%	12%	16%	6.9% (2.5-13.9%)

* $p<0.05$,
[a] incidence of foetuses with cardiovascular malformations, i.e. absent subclavian, aortic arch atresia, ventricular septum defect (membranous) and dextrocardia altogether.
[b] mean fetal incidence (range) in historical control data from 24 studies performed in the same laboratory from 2003 to 2009.
[c] no statistical analysis for this parameter

Overall, NEP by dermal route in rabbits induced limited non-adverse maternal effects at 1000 mg/kg/d at the beginning of substance administration (GD 6-9) as evidenced by a loss of maternal body weight gain and statistically significant decreases in maternal food consumption. Over the whole gestation period, no significant difference in maternal corrected body weight was noted. In this study, NEP had no significant effect on post-implantation loss, foetal weight and incidence of external or skeletal malformations. A few rare cardiovascular malformations were however observed and in particular the incidence of absent subclavian, membranous ventricular septum defect and dextrocardia were above historical control range in the high dose foetuses. Similar cardiovascular effects were also observed in the oral study. Therefore the NOAEL for maternal toxicity is set at 1000 mg/kg bw/day in absence of adverse effects, the NOAEL for foetal toxicity is set at 300 mg/kg bw/day based on cardiovascular malformations.

B.5.4. Other effects

Not relevant for this proposal

B.5.5. Derivation of DNEL(s)/DMEL(s)

BMD analysis
As alternative for the NOAEL approach, the benchmark dose (BMD) approach is used to determine the Point of Departure (PoD) for setting DNEL levels. The BMD approach is a scientifically more advanced method (ECHA, 2012b; EFSA, 2017) in comparison with the NOAEL approach. In the BMD approach, the complete set of dose-response data are used to estimate the shape of the dose-response relationship of endpoints.

The BMD approach interpolates between applied dose levels, and derives the BMD, which is a dose level associated with a predefined response (critical effect size (CES) or benchmark response (BMR)). Therefore the effect size associated with a BMD is known by definition (i.e. the BMR). In the BMD approach, the uncertainty in the dose-response is translated into uncertainty about the (true) BMD. Therefore, the BMD is reported by its (90%) confidence interval (CI), which ranges from the lower to the upper confidence limits, the BMDL and BMDU respectively.

The BMDL is usually used as the reference point for the derivation of a health based guidance value (e.g. a DNEL). In principle, based on the BMD analyses regarding various endpoints, the lowest BMDL should be used as PoD. However in some cases, the data is so poor that the dose-response relationship cannot be well defined and the estimated BMD confidence interval is very wide with a relative low BMDL. In general, the BMDL confidence intervals grow wider with smaller BMRs, therefore inspection of the confidence interval of the $BMDL_1$ is warranted as not all data sets might be adequate to allow the calculation of such a small increase in incidence with sufficient precision. As a default a BMDL will not be considered as PoD when the 90% CI BMDU/BMDL is ≥10, presented in italics in the overview tables. However, the effect is still considered as a (qualitative) indicator of an effect occurring in the particular organ or system.

Methods
The Dossier Submitter used a tiered approach in determining the PoDs. BMD analyses for all endpoints in all studies was considered too unpractical and laborious. First, key studies were determined (see summary tables in the main report section 1.1.4.5. and 1.1.4.8.) for repeated dose and developmental toxicity for DMAC and NEP based on the Klimisch score and observed NOAE(C)L/LOAE(C)Ls. Second, BMD analyses were performed on the key studies focussing on the observed critical effects in the key study or associated endpoints observed in key studies for the same substance with a different exposure route or species. For both DMAC and NEP, liver effects (relative liver weight and histopathology) are considered the most sensitive endpoint for systemic toxicity after repeated exposure. For NEP, degeneration/regeneration of the olfactory epithelium was considered the most sensitive local effect after repeated exposure. For developmental toxicity, reduced foetal weight, increased malformations and variations (external, skeletal and visceral) were endpoints included in the BMD analyses for both DMAC and NEP. For NEP, post-implantation loss was additionally included.

As noted above, BMD analyses is a scientifically more advanced method in comparison with the NOAEL to determine a dose response relationship. Due to their severity, the malformations (external, skeletal and visceral) were included in all BMD analyses on developmental toxicity studies, regardless of whether or not a significant increase was reported in the study summaries at the LOAEL or LOAEC dose. For NEP, post-implantation was included for the same reason.

Next to the endpoints described above, specific critical effects noted in the key studies were included when deemed biologically relevant.

With BMD analyses it is possible to combine data sets for a defined endpoint which differ in a specific aspect, such as sex, species or exposure duration, but are similar otherwise. In such a combined analysis covariates are used to account for the differences in data sets and the precision of the estimated BMD(s) is improved, i.e. a smaller BMD confidence interval is obtained. Only data sets of key studies were combined to limit the time needed for the BMD calculations.

The software package PROAST (versions 70.2 and 70.3) was used for the BMD analysis (https://www.rivm.nl/en/proast). To account for the model uncertainly in the BMD analysis,

the Model Averaging approach was applied with 1000 bootstrap runs. The Model Averaging approach takes both model uncertainty and uncertainty due to sampling errors into consideration. For fitting continuous dose-response data, a group of models, i.e. the exponential, hill, inverse exponential, and log-normal models, were used for the BMD analysis. For quantal data, a suit of eight models (two stage, log-logistic, Weibull, log-probit, gamma, logistic, exponential latent variable model and Hill latent variable model) was used.

Detailed results of the BMD analyses are described in Appendix I.

Benchmark responses
The REACH Guidance R8 (ECHA, 2012b) refers to a BMR of 5% as, on average, comparable to a NOAEL. If other BMD indicators are used, e.g. a BMD_{10}, it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed. The more recent EFSA guidance (EFSA, 2017) on the BMD approach discriminates two types of data. For quantal data various studies estimated that the median of the upper bounds of extra risk at the NOAEL was close to 10%, suggesting that the $BMDL_{10}$ may be an appropriate default. For continuous data, a re-analysis of a large number of NTP studies showed that the $BMDL_{05}$ was, on average, close to the NOAEL derived from the same data. The EFSA Scientific Committee noted that these default BMRs may be modified based on statistical or biological considerations.

The Dossier Submitter considers for systemic effects the following BMRs: 10% change in organ or body weight and 10% extra risk in observed histopathology (Table 33). The Dossier Submitter considers changes in body weight (decrease) and relative organ weight (more specifically, the liver) to be adverse >10% change without the need for an additional assessment factor. It is recognized that changes in relative liver weight in absence of histopathological liver damage and relevant clinical chemistry changes can be considered more adaptive in nature than adverse. However such interpretation is difficult within a BMD analyses with different BMDLs for liver effects therefore a BMR of 10% change in relative liver weight is taken as adverse. For liver histopathology the default 10% extra risk is considered appropriate.

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

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

Table 33: Specifications of the BMR per endpoint used in BMD analyses in this dossier

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

DNEL derivation approach

The derivation of DNELs by the Dossier Submitter in the current dossier was performed according to ECHA guidance on the characterisation of the dose-response for human health described in REACH Guidance Chapter R.8 (ECHA, 2012b). The DNELs are limited to the inhalation and dermal route as it is expected that oral exposure is not relevant for workers if normal hygienic measures are in place. Point of departures (PoDs) from key repeated dose studies and reproduction toxicity studies were determined using the BMD approach for systemic, and where relevant, local effects.

Inter- and intraspecies differences

Default assessment factors as given in ECHA Guidance R.8.4.3.1 will be applied. For interspecies extrapolation these concern default allometric scaling factors for rat to human (4), mouse to human (7), and rabbit to human (2.4) extrapolation. No allometric scaling factors are required for inhalation exposure. In addition, the default factor of 2.5 for remaining differences in toxicodynamics and -kinetics between animals and humans will be applied. For intraspecies extrapolation, the default factor for workers (5) will be applied.

Dose descriptor modification

The exposure in experimental studies may differ from the human exposure situation and thus needs correction. For inhalation exposure, the ECHA guidance describes for instance a correction for the number of hours exposure per day in an experimental study (usually 6 h) and during the work shift (usually 8 h/day) and for the volume of air inhaled in rest (6.7 m^3) versus the volume of air while performing light activity during an 8 hour working day (10 m^3). For dermal exposure, a correction may be necessary for the number of exposure days per week in an experimental study (usually 7 days in a dermal and oral study) and the number of working days per week (5 as default).

Study duration corrections

These might be needed to extrapolate from a sub-chronic to chronic duration. By default a factor two is taken. A factor of one may be considered if it concerns local effects which are not driven by duration. In case the PoD is derived from a prenatal developmental toxicity study no correction is made for exposure duration or on the dose description concerning daily exposure. No correction is required from a daily exposure to a five days per week exposure, because in combination with a correction for the limited exposure during GD period (generally 15 days during a gestation period of 21 days in the rat) would approximate a correction factor of 1, i.e. 5/7 x 21/15 = 1).

Route to route extrapolation

Route-specific studies will be used to derive worker DNELs for the corresponding routes, when available. When unavailable, route-to-route extrapolation will be used.

DNEL derivation - DMAC

Repeated dose toxicity

The inhalation chronic toxicity and carcinogenicity studies of Malley et al. (1995) in rats and mice were used to derive a systemic long-term inhalation DNEL. As PoD a $BMDL_{10}$ of 65 mg/m^3 is taken, based on hepatic Kupffer cell pigmentation in male mice (see 1.1.4.9 in main report). This PoD is corrected for exposure duration (6 to 8 h) and breathing volume activity (6.7 to 10 m^3). Subsequently, the following assessment factors are applied: an interspecies remaining differences factor of 2.5 (default) and an intraspecies factor of 5 (default worker). This leads to a systemic long-term inhalation DNEL for workers of 2.6 mg/m^3.

Two cohort studies are available for exposure to DMAC via inhalation in workers of which no-effect levels of 10.8 or 21.7 mg/m^3 (8-h TWA equivalent), based on liver function, can be derived (Antoniou et al., 2021; Spies et al., 1995a, 1995b). The study by Antoniou et al.

(2021) is given preference over the Spies et al. (1995a, 1995b) studies, given that it concerns more recent data from more workers, over more years and from work associated with the highest DMAC exposure. No assessment factor is used considering the size of the study and the availability of other human studies. This leads to a systemic long-term inhalation DNEL for workers of 22 mg/m^3.

For a systemic long-term dermal DNEL based on BMD modelling, the oral chronic toxicity and carcinogenicity study from Monsanto (1980, 1990, 1993) in rats was used. The PoD taken is the $BMDL_{10}$ of 19 mg/kg bw/day for increased relative liver weight in male rats (see 1.1.4.9 in main report). Following route-to-route extrapolation by correcting for differences in absorption between the oral and dermal route, the oral $BMDL_{10}$ is converted to a dermal $BMDL_{10}$. Given that for DMAC 100% is assumed for both oral and dermal absorption, the dermal $BMDL_{10}$ is identical to the oral $BMDL_{10,}$ i.e. 19 mg/kg bw/day. After correction for exposure duration (7 to 5 days) and application of an allometric scaling factor of 4 (default rat), an interspecies remaining differences factor of 2.5 (default), and an intraspecies factor of 5 (default worker), a systemic long-term dermal DNEL for workers of 0.53 mg/ kg bw/day can be derived.

There are no human data available on dermal repeated dose toxicity and therefore the animal DNEL of 0.53 mg/kg bw/day is applied.

Developmental toxicity
The rat and rabbit inhalation developmental toxicity studies of Okuda et al. (2006) and Klimisch and Hellwig (2000) were used to derive a developmental toxicity inhalation DNEL based on BMD modelling. As PoD the $BMDL_1$ and $BMDL_{10}$ of 320 mg/m^3 is taken based on skeletal malformations and visceral variations, respectively, in rabbits (see 1.1.4.9 in main report). This PoD is corrected for exposure time (6 to 8 h) and breathing volume activity (6.7 to 10 m^3). No additional correction for exposure duration (7 to 5 days) is suggested for developmental toxicity as it is unknown what the most sensitive period for DMAC-induced developmental adverse effects is or whether such a period exists at all. Subsequently, the following assessment factors are applied: an interspecies remaining differences factor 2.5 (default) and an intraspecies factor of 5 (default worker). This leads to a systemic long-term inhalation DNEL for workers of 13 mg/m^3.

The oral prenatal developmental toxicity study in rat from DuPont (1997) was used to determine a developmental toxicity dermal DNEL based on BMD modelling. As PoD a $BMDL_1$ of 92 mg/kg bw/day is taken based on foetal head malformations in rats (see 1.1.4.9 in main report). No correction for exposure duration (7 to 5 days) is suggested, as earlier discussed. Following route-to-route extrapolation by correcting for differences in absorption between the oral and dermal route, the oral $BMDL_1$ is converted to a dermal $BMDL_1$. Given that for DMAC 100% is assumed for both oral and dermal absorption, the dermal $BMDL_1$ is identical to the oral $BMDL_{1,}$ i.e. 92 mg/kg bw/day. Subsequently, the following assessment factors are applied: an allometric scaling factor of 4 (default rat), an interspecies remaining differences factor 2.5 (default) and an intraspecies factor of 5 (default worker). This leads to a systemic long-term dermal DNEL for workers of 1.8 mg/kg bw/day.

There are no human data available on developmental toxicity and therefore the animal DNEL of 13 mg/m^3 and 1.8 mg/kg bw/day are applied.

Biological limit value DMAC
Urinary excretion of NMAC could serve as biological limit value (BLV) for DMAC, as indicated by studies describing post-shift spot urine sampling for biological monitoring of workers for occupational DMAC exposure (Nomiyama et al., 2000; Perbellini et al., 2003; Spies et al., 1995a). Post-shift urinary NMAC levels were significantly correlated with DMAC levels in

workers of an acrylic fibre manufacturing facility (Spies et al., 1995a). No metabolic saturation and plateau in urinary levels of NMAC were observed at the threshold limit value (10 ppm or 36 mg/m^3, 8-h TWA) or higher air levels of DMAC, respectively. In another study, mean urinary NMAC was assumed to be about 30 mg NMAC/g creatinine after exposure to 10 ppm (36 mg/m^3) DMAC vapour 8 h/day for 5 days, as calculated from half-life data of NMAC in healthy volunteers (Nomiyama et al., 2000). In this study the creatinine-adjusted method was a more adequate method than the other two adjustment methods tested (NMAC concentration adjusted for urinary volume or specific gravity). For more information regarding human toxicokinetic and repeated dose toxicity data see B.5.1.1. DMAC and B.5.2.1.1 DMAC The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a biological exposure index (BEI) of 30 mg NMAC/g creatinine in post-shift urine after a workweek, based on a threshold limit value (TLV)-TWA of 10 ppm (36 mg/m^3; (ACGIH, 2011)). The ACGIH noted that the recommended BEI could be exceeded at the TLV-TWA and that it is uncertain at which air exposure level of DMAC saturation becomes significant. Recently, the Deutsche Forschungsgemeinschaft (DFG) proposed a Biological Agent Tolerance (BAT) value of 25 mg NMAC/L urine sampled at end of shift or after several shift (long-term exposure), based on a DMAC air concentration of 5 ppm (18 mg/m^3) and a non-linear relationship between air concentration of DMAC and urinary NMAC (Walter et al., 2020). The UK's Health and Safety Executive (HSE) issued a biological monitoring guidance value for DMAC of a biological of 100 mmol NMAC/mol creatinine collected post-shift, corresponding to 65 mg NMAC/g creatinine (conversion factor: 1 mmol/mol=0.646 mg/g (HSL)). The UK occupational exposure standard for DMAC is 10 ppm and no further information was found on the derivation of the biological monitoring guidance value.

DNEL derivation – NEP

Repeated dose toxicity (local effects)

The inhalation toxicity studies of BASF (2011, 2013a) in rats were used to derive a local acute inhalation DNEL and a systemic long-term inhalation DNEL. As PoD for local inhalation effects, a $BMDL_{10}$ of 57 mg/m^3 is taken, based on the occurrence of degeneration/regeneration of the olfactory epithelium in a 28-d rat study (see 1.1.4.9 in main report). An interspecies remaining differences factor of 2.5 (default) and an intraspecies factor of 5 (default worker)) are applied. Since local effects are not primarily driven by exposure time but by exposure concentration, no correction for exposure duration is needed. This is confirmed for NEP as the $BMDL_{10}$ value for the same effects in the 90-day study is equal or above the $BMDL_{10}$ in the 28-day study. This leads to a local acute inhalation DNEL for workers of 4.6 mg/m^3.

Repeated dose toxicity (systemic effects)

For the systemic long-term inhalation DNEL, the PoD is 200 mg/m^3, the highest tested dose in the 90-day inhalation study, where no systemic effects were observed. This PoD is corrected for exposure duration (6 to 8 h) and breathing volume during activity (6.7 to 10 m^3). Subsequently, the following assessment factors are applied: an interspecies remaining differences factor of 2.5 (default), an intraspecies factor of 5 (default worker), and a factor 2 for exposure duration (sub-chronic to chronic). This leads to a systemic long-term inhalation DNEL for workers of 4 mg/m^3.

For a systemic long-term dermal DNEL based on BMD modelling, the oral sub-chronic toxicity study from BASF (2006) in rats was used. The PoD taken is the $BMDL_{10}$ of 170 mg/kg bw/day for increased relative liver weight (see 1.1.4.9 in main report). Following route-to-route extrapolation by correcting for differences in absorption between the oral and dermal route, the oral $BMDL_{10}$ is converted to a dermal $BMDL_{10}$. Given that for NEP 100% is assumed for both oral and dermal absorption, the dermal $BMDL_{10}$ is identical to the oral $BMDL_{10}$. i.e. 170 mg/kg bw/day. After correction for exposure duration (7 to 5 days) and application of an allometric scaling factor of 4 (default rat), an interspecies remaining differences factor of 2.5 (default), an intraspecies factor of 5 (default worker), and a factor 2 for exposure duration

(sub-chronic to chronic), a systemic long-term dermal DNEL for workers of 2.4 mg/ kg bw/day can be derived.

Developmental toxicity
The oral developmental toxicity studies of Saillenfait et al. (2007) in rats and BASF (2007a, 2007b) in rabbits are used to derive a developmental toxicity inhalation DNEL via rout-to-route extrapolation based on BMD modelling. The PoD taken is the $BMDL_1$ of 38 mg/kg bw/day for foetal cardiovascular malformations in rabbits (see 1.1.4.9 in main report). Following route-to-route extrapolation the oral dose is converted into an inhalatory dose, in accordance with REACH Guidance R.8 (ECHA, 2012b), using the following formula:

$$inhalation\ dose\ (mg/m^3) = \frac{\frac{oral\ dose\ (mg/kg)}{2.4\ (AS)} \times 70\ (kg\ bw)}{10\ (\mathrm{m^3/person})}$$

No further correction for differences in absorption is needed as for NEP 100% is assumed for both oral and inhalatory absorption. No additional correction for exposure duration (7 to 5 days) is suggested for developmental toxicity as it is unknown what the most sensitive period for NEP-induced developmental adverse effects is or whether such a period exists at all. An interspecies remaining differences factor 2.5 (default) and an intraspecies factor of 5 (default worker) are applied. This leads to a systemic long-term inhalation DNEL for workers of 8.9 mg/m^3.

The dermal prenatal developmental toxicity studies in rat from (BASF, 2005) and in rabbits from (BASF, 2010) were used to determine a developmental toxicity dermal DNEL based on BMD modelling. As PoD taken is the $BMDL_5$ of 330 mg/kg bw/day based on decreased foetal body weight in rats (see 1.1.4.9 in main report). A correction factor for exposure duration (6 to 8 h) is applied. No correction for exposure duration (7 to 5 days) for developmental toxicity is suggested, as discussed above. An allometric scaling factor of 4 (default rat), an interspecies remaining differences factor of 2.5 (default) and an intraspecies factor of 5 (default worker) are applied. This leads to a systemic long-term dermal DNEL for workers of 5.0 mg/kg bw/day.

B.6. Human health hazard assessment of physicochemical properties

Not relevant for this proposal

B.7. Environmental hazard assessment

Not relevant for this proposal

B.8. PBT and vPvB assessment

Not relevant for this proposal

B.9 Exposure assessment

B.9.1 General discussion on releases and exposure

Scope of the exposure assessment

- DMAC and NEP are no longer expected to be present in consumer products above the legal limit of 0.3% w/w as both substances are classified as repro cat 1B. The use of NEP in cleaning agents and in coatings by consumers is however still registered at ECHA by one registrant. At the same time consumer uses are indicated as uses advised against by other registrants. No consumer uses are included in this dossier for the reasons stated in the Summary of the main report.
- Indirect exposure of humans via the environment is considered to be outside the scope of this dossier. The focus of this dossier is on occupational exposure.

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

- First the exposure assessments as presented in the various registration dossiers are evaluated. The Dossier Submitter does not attempt to recalculate the exposure estimations using other tools than applied by the registrants. In order to recalculate the worker exposure with other (higher-tier) tools, a more detailed description of the worker tasks and worker environment is required, which is not available to the Dossier Submitter. The ESs and contributing scenarios as presented by the registrants in their CSRs are taken as starting point for this restriction proposal. For a few scenarios a Tier 2 exposure model (Advanced REACH Tool) is used by some registrants. To the Dossier Submitter it is not clear if these specific scenarios are representative for downstream use applications further down the supply chain. Therefore, instead ECETOC Targeted Risk Assessment (TRA) is used to estimate a more reasonable worst-case exposure concentration for these situations.
- Operational conditions (OC) and risk management measures (RMM) as applied by the registrant are evaluated. In some contributing scenarios, the Dossier Submitter deviates from the OC and RMM applied by the registrant for various reasons:
    - Applying RMM and OC that are considered common industry standard, e.g. the use of Local Exhaust Ventilation (LEV) for processes where exposure can occur, although these RMM/OCs may not be prescribed by all registrants in their CSRs. This may lead to an underestimation of exposure in some particular working situations.
    - For consistency reasons. The Dossier Submitter applies default (reasonable worst-case) protection factors for the use of gloves and respiratory protective equipment (RPE) in industrial and professional settings, assuming a basic level of training, and does not apply a broader range of protection factors as some registrants do. In most cases it is believed that this results in an overestimation of exposure when in practice a higher reduction can be reached, e.g. by more specific training and supervision.
    - The Dossier Submitter does not apply LEV, gloves or RPE for PROC1 (Process), PROC2 and PROC3 activities. These activities take place in closed continuous or batch processes, with limited manual interventions, including closed sampling. Because of the available level of containment in which these processes take place no additional LEV is considered of relevance.
    - As a reasonable worst-case exposure estimate no improved general ventilation is applied, because it cannot be excluded that activities take place in less well-ventilated areas. Therefore, only indoor use with basic ventilation is applied as a worst-case assumption.
    - When applying risk management measures the use of LEV is preferred over the use of RPE by the Dossier Submitter. Only in workplace situations where exposure cannot so easily be controlled by LEV, like spraying in a professional setting, or for maintenance work, the use of RPE is applied.
- No account is taken by the Dossier Submitter for possible consecutive tasks or processes for a worker when a specific process is time limited. It is acknowledged that exposure for a worker may be underestimated if he/she continues work in other processes, however as

no information is available on the daily activities of workers for all exposure scenarios and all contributing scenarios, such correction is impossible to make. In this restriction report all exposure estimates are performed by applying an exposure duration of eight hours.

- Similar exposure scenarios in different CSRs with the same contributing scenarios are only included once in this dossier. This applies to the use of DMAC and NEP in charging and discharging activities, formulation activities and the use as a laboratory chemical.
- When registrants prescribe different RMM and OC for the same exposure scenario this is evaluated by the Dossier Submitter. When it is considered possible that different RMM and OC can be applied in workplace situations (e.g. the use of LEV or RPE, processes at elevated temperatures), this is taken into account by performing multiple exposure estimates.

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

All model exposure estimates and inhalation measurement results in this registration dossier are presented in mg/m^3. When results are provided in ppm (e.g. using ECETOC TRA v3.1 or in published articles) these values are recalculated at 25 ºC and 1 atmosphere using the molecular weight of DMAC (87.12 g/mol) or NEP (113.16 g/mol), applying the formula: mg/m^3 = (ppm x molecular weight) / 24.45 (https://www.cdc.gov/niosh/docs/2004-101/calc.html).

Urine biological monitoring results in literature studies are generally presented in mg/g creatinine for the DMAC metabolite NMAC or the NEP metabolites 5-hydroxy-N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy- N-ethylsuccinimide (2-HESI). When results are provided in other units (ppm, mg/L, mmol/mol etc) these are (when possible) converted to mg/g creatinine using conversion factors described in Table 34.

Table 34: Conversion factors between biological monitoring urine unitse units

Concentration value	Conversion value	Reference
1 mmol/mol creatinine	0.646 mg/g creatine[#]	HSL, 2018
1 mg/L or 1 ppm	1 mg/g creatinine	ECHA, 2011
1 mmol NMAC/l	78 mg/L	Kawai (1997)

[#] Molecular mass NMAC = 73.09, Molecular mass creatinine: 113.12, 1 mmol/mol creatinine = 73.09 / 113.12 = 0.646 mg/g creatinine

General remarks on the applied worker exposure models

The lead-registrant uses EasyTRA (v4.1.0 and v4.2.0) to determine inhalation and dermal exposure of workers to DMAC and NEP in various exposure scenarios and process categories (PROCs). EasyTRA uses algorithms on the basis of the latest versions of the ECHA REACH Guidance Chapters R.12 (as of 2015) and R.14 (as of 2016). The Tier 1 exposure assessments (reduced number of parameters, conservative results) refer to ECETOC TRA v3.1 (2012) for the worker exposure assessment. Other registrants use ECETOC TRA v2.0 for the exposure assessment. For Tier 2 assessments the Advanced REACH Tool (ART) v1.5 is used by some registrants for a limited number of contributing scenarios as higher-tier worker exposure tool. Measurements are used by some registrants as Tier 3 exposure assessment method.

The Dossier Submitter only uses ECETOC TRA v3.1 for the exposure assessment. ECETOC TRA v3.1 generates inhalation exposure in ppm and dermal exposure in mg/kg/bw day. The

combined internal body burden is determined by converting the inhalation exposure (ppm to mg/m^3) to an internal exposure by assuming that a worker inhales 10 m^3 during a work shift of 8 hours, assuming 100% absorption via inhalation and a body weight of 70 kg, and adding that to the dermal exposure, assuming 100% absorption by the dermal route. Input parameters are defaults as given in ECHA guidance (ECHA, 2016a).

Most activities are considered to take place at or around room temperature. For these processes the ECETOC TRA low fugacity category (≥0.01-<500 Pa) is selected based on a vapour pressure of 200 Pascal for DMAC and 18 Pascal for NEP at 20 °C. However some contributing scenarios are described to take place at elevated temperatures. For these exposure assessments a medium or high fugacity category is selected based on vapour pressure references at elevated temperatures (see Table 35).

Table 35: Vapour pressure references for DMAC and NEP and relation to ECETOC TRA v3.1 fugacity categories

Substance	Fugacity category (ECETOC TRA v3.1)	Vapour pressure (Pa)	Temperature (°C)	Reference
DMAC	Low (≥0.01-<500 Pa)	200	20	GESTIS-database
	Medium (≥500 - ≤10,000 Pa)	652	40	GESTIS-database
	High (>10,000 Pa)	-	*180*[#]	REACH online dossier
NEP	Low (≥0.01-<500 Pa)	18	20	GESTIS-database
	Low (≥0.01-<500 Pa)	28	25	GESTIS-database
	Low (≥0.01-<500 Pa)	50	32	Health Canada (Canada, 2017)
	Low (≥0.01-<500 Pa)	165	50	GESTIS-database

[#] DMAC is manufactured by the reaction of acetic acid and dimethylamine in closed systems at elevated temperature (180 °C, REACH online registration dossier information) and pressure. However this process temperature is above the boiling point temperature of DMAC of 165 °C (GESTIS-database). The exact temperature of DMAC to which workers can be exposed is not clear. Also the corresponding vapour pressure at that temperature is not known. For these situations the high fugacity category is selected assuming a vapour pressure >10,000 Pa.

Because of their respective vapour pressures of 200 Pa (DMAC) and 18 Pa (NEP), both substances fall within the ECETOC TRA v3.1 low fugacity category (≥0.01-<500 Pa). This means that when using ECETOC TRA v3.1 to calculate the exposure for the same process category with the same conditions of use will result in the same exposure estimate in ppm. In reality, however, exposure to DMAC, will probably be higher under the same conditions of use than exposure to NEP due to its higher vapour pressure.

When applying exposure models one should always keep in mind that exposure models are a simplification of the actual work situation. Tier 1 exposure models like ECETOC TRA v3.1 should offer a conservative exposure estimate. According to the ECHA guidance Chapter R.14 (ECHA, 2016a) in general the 90th percentile value, representing the reasonable worst case exposure level of a distribution within a generally suitable dataset (i.e. a dataset corresponding to the conditions described in a contributing scenario), should be used as the exposure value for the risk characterisation. Under particular conditions other percentiles may be applicable as well. A justification should be provided in the CSR. For instance, the use of the 75th percentile may be justified when the data set reflects worst-case situations only (e.g. data sets taken in companies suspected of being non-compliant). ECETOC TRA v3.1. presents the 75th percentile of the exposure distribution (ECETOC, 2012). In recent years ECETOC TRA has been validated by different research groups. In these studies the contributing scenario (PROCs) estimates are compared with exposure measurements results. Based on the available validation studies contributing scenarios (PROCs) are identified where the initial inhalation exposure concentration might be underestimated or the effect of LEV might be overestimated (Schlueter & Tischer, 2020). For liquids they indicate a low level of conservatism for PROC5, PROC7, PROC14 and PROC19 contributing scenarios. An overestimation of the efficiency of LEV in actual workplaces is reported to occur for PROC7, PROC8a, PROC10, PROC13, PROC14, PROC19 contributing scenarios. ECETOC recently

started a systematic review of worker inhalation exposure estimates of the TRA tool. However, results are not yet available, and the implementation will take some time. The dermal exposure model was validated in 2017 (Marquart et al., 2017). The authors conclude that in 80% of the exposure cases the model estimate is higher than the 75th percentile of the measured values. The validation results indicate that the model overestimates dermal exposure for situations where contact with the substance is expected to be very limited (PROC1-3), with a 75th percentile of measured concentrations for PROC3 <0.001 mg/kg bw/day. For situations where high exposure values were found the model tends to underestimate exposure. PROCs with the highest initial exposure values in ECETOC TRA v3.1. are PROC6, PROC7, PROC10, PROC11, PROC17 and PROC19. In the same study the reduction effect of gloves is evaluated by analyzing 11 datasets with measurements inside and outside of gloves. The average reduction per data set ranges between 80.5-99.99%, with six of the data sets having a reduction of >95% and an overall average reduction factor of 34 (± 97% reduction).

Despite these limitations in the exposure model ECECTOC TRA v3.1 is applied by the Dossier Submitter because of the limited input parameters required and the direct connection with the REACH use descriptor system (PROCs). Applying higher-tier occupational exposure models like Stoffenmanager® or the Advanced REACH Tool requires more contextual information on the processes performed and the relevant OC/RMM. This information is not available to the Dossier Submitter. The results of the model validation studies are used to evaluate the exposure estimates and to support the conclusions in the risk assessment.

B.9.1.1 Summary of the existing legal requirements

Worker legislation

EU legislation on the protection of health and safety of workers working with chemical agents is spread over several pieces of legislation. First, Framework Directive 89/391/EEC[5], further referred to as FD, lays down general duties for employers and workers concerning health and safety at work. Second, the Chemical Agents Directive (CAD, 98/24/EC)[6] and the Directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD, 2004/37/EC)[7] further elaborate and expand the general duties in the Framework Directive. Even though DMAC and NEP are not classified as carcinogenic or mutagenic substances, the CMD may be of interest. According to the CMD (article 18a) no later than in the first quarter of 2019 the European Commission shall, taking into account the latest developments in scientific knowledge, assess the option of amending the scope of Directive 2004/37/EC to include reprotoxic substances. On that basis, the Commission shall present, if appropriate, and after consulting management and labour, a legislative proposal. At the moment a proposal to regulate reprotoxic substances under Directive 2004/37/EC has been published.[8] Third, some specific legislation pertaining to young workers and pregnant workers

[5] *Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (consolidated version 11-12-2008).*

[6] *Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (consolidated version 26-07-2019).*

[7] *Council Directive 2004/37/EC of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (consolidated version 26-07-2019).*

[8] *Texts adopted - Protection of workers from the risks relating to exposure to carcinogens, mutagens and reprotoxins at work ***I - Thursday, 17 February 2022 (europa.eu)*

applies. In this section, the implications of these three bodies of legislation for DMAC and NEP will be considered.

Occupational Safety and Health (OSH) Legislation

Duty of care

The basic duty of employers is the duty to ensure the safety and health of workers in every aspect related to the work (article 5 FD). Within the context of his responsibilities, the employer shall take the measures necessary for the safety and health protection of workers, including prevention of occupational risks and provision of information and training, as well as provision of the necessary organization and means. The employer shall be alert to the need to adjust these measures to take account of changing circumstances and aim to improve existing situations (article 6 FD). This duty of care is not explicitly incorporated in the CAD and CMD. Still, it is clear from the objective of these Directives that they do in fact install a general duty upon the employer to protect workers "from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents" (article 1 CAD).

The CAD applies not only to classified substances, but also to any chemical agent which, whilst not meeting the criteria for classification as hazardous in accordance with the CLP Regulation may, because of its physicochemical, chemical or toxicological properties and the way it is used or is present in the workplace, present a risk to the safety and health of workers, including any chemical agent that is assigned an occupational exposure limit value (article 2 CAD). The wordings of the CAD, notably "any chemical", make it abundantly clear that DMAC and NEP fall within the scope of this Directive (as well as of the FD). The employer therefore has to take measures or, more generally, deploy a health and safety policy pertaining to the risk of working with DMAC and NEP.

Risk assessment

The health and safety policy of the employer, as well as specific safety measures, are to be grounded upon a thorough assessment of the risks (art. 6(3) and 9(1) FD; art. 4 CAD). The employer shall assess any risk to the safety and health of workers arising from the presence of hazardous chemical agents, taking into consideration their hazardous properties. The employer shall consider:

- their hazardous properties;
- information on safety and health that shall be provided by the supplier;
- the level, type and duration of exposure;
- the circumstances of work involving such agents, including their amount;
- any occupational exposure limit values or biological limit values established on the territory of the Member State in question;
- the effect of preventive measures taken or to be taken;
- where available, the conclusions to be drawn from any health surveillance already undertaken.

One of the main sources to assist the employer in assessing the risks, is "information on safety and health that shall be provided by the supplier, (e.g. the relevant SDS in accordance with Regulation (EC) No 1907/2006 of the European Parliament and of the Council (art. 4 CAD). It may be inferred from the wordings of article 4 that the employer must actively gather information concerning classification as well as Risk Management Measures. Also, article 4 of the CAD refers to information resulting from "health surveillance". Health surveillance is particularly interesting for tracing slowly developing or hidden ailments, such as sensibilisation or damage to genetic material.

Risk management measures

In carrying out his obligation to ensure the health and safety of workers in any activity involving hazardous chemical agents the employer shall take the necessary preventive

measures (art. 5 CAD, in conjunction with art. 6 FD). As a general principle, any risks to the health and safety of workers at work involving hazardous chemical agents "shall be eliminated or reduced to a minimum" (art. 5(2) and 6(1) CAD). In case the risk assessment reveals a risk, the specific protection and prevention measures listed in Article 6 of the CAD apply. Article 6 CAD lists a hierarchy of prevention measures, which states a preference for substitution of hazardous agents by less hazardous alternatives. The CMD also prescribes 'replacement' as the preferred preventive measure "in so far as is technically possible" (art. 4 CMD). Even if the CMD does not, as yet, address reprotoxic substances, it may apply to DMAC and NEP in the near future due to the intended amendment of the Directive. The wording "in so far as is technically possible" implies that socio-economic considerations may not, in principle, be taken into account.

Where the nature of the activity does not permit risk to be eliminated by substitution, the employer should reduce the risk to a minimum by means of specific preventive or protective measures, such as (article 5 and 6 CAD):

- the design and organisation of systems of work at the workplace;
- the provision of suitable equipment for work with chemical agents and maintenance procedures which ensure the health and safety of workers at work (work equipment and protective systems must comply with the relevant Community provisions, in particular with Directive 94/9/EC on equipment and protective systems intended for use in potentially explosive atmospheres);
- reducing to a minimum the number of workers exposed or likely to be exposed,
- reducing to a minimum the duration and intensity of exposure;
- appropriate hygiene measures;
- reducing the quantity of chemical agents present at the workplace to the minimum required for the type of work concerned;
- suitable working procedures including arrangements for the safe handling, storage and transport within the workplace of hazardous chemical agents and waste containing such chemical agents.
- design of appropriate work processes and engineering controls and use of adequate equipment and materials, so as to avoid or minimise the release of hazardous chemical agents which may present a risk to workers' safety and health at the place of work;
- application of collective protection measures at the source of the risk, such as adequate ventilation and appropriate organizational measures;
- where exposure cannot be prevented by other means, application of individual protection measures including personal protective equipment.

In the realm of Occupational Safety and Health (OSH) legislation, the use of personal protective equipment, which is a common Risk Management Measure in various CSRs, is to be considered the ultimum remedium, a control measure that may only be called upon if all other technical or organisational measures are insufficient to ensure safe exposure.

Another obligation resulting from the workers' Directives is that the employer shall provide workers with information on the outcome of the risk assessment, the presence of hazardous chemical agents as well as any information from SDSs.

All the above measures "shall be accompanied by health surveillance [..] if it is appropriate to the nature of the risk" (article 6 CAD). Health surveillance is deemed appropriate (article 10 CAD, also article 14 CMD) where

- the exposure of the worker to a hazardous chemical agent is such that an identifiable disease or adverse health effect may be related to the exposure
- there is a likelihood that the disease or effect may occur under the particular conditions of the worker's work, and

- the technique of investigation is of low risk to workers.

Furthermore, there shall be valid techniques for detecting indications of the disease or effect. Annex II to the CMD supplies practical recommendations for the health surveillance of workers.

Occupational exposure
At any rate, the exposure to hazardous substances should be kept below the occupational exposure limit. "In any event, where an occupational exposure limit value effectively established on the territory of a Member State has been exceeded, the employer shall immediately take steps, taking into account the nature of that limit, to remedy the situation by carrying out preventive and protective measures." (art. 6(5) CAD). Also, the employer shall establish procedures (action plans) which can be put into effect when an accident, incident or emergency related to the presence of hazardous chemicals agents at the workplace occurs and shall ensure that this information is available (art. 7 CAD in conjunction with art. 8 FD). As indicated in section B 5.10, the current SCOEL OEL value differs from the DNELs obtained by some registrants using the REACH methodology.

Skin notation
The SCOEL[9] has agreed that there is a need to assign a skin notation if dermal absorption could contribute substantially to the total body burden and consequently to concern regarding possible health effects. 'Substantial contribution' to the total body burden will be, in general, in the order of 10% or more of the uptake from respiratory exposure at the 8-hour Time Weighted Average (TWA). It should be noted that a skin notation relates specifically to dermal absorption of the material (whether as solid, liquid or gas). It does not relate to, and further, is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation.

Safety signs
In some cases, particularly when risks cannot be avoided or reduced, the employer is obliged to put safety and/or health signs in place. The signs should be in accordance with the requirements listed in the Annexes to Directive 92/58/EEC.[10] Specifically, Annex III of this Directive demands that containers used at work for chemical substances or mixtures classified as hazardous according to the criteria for any physical or health hazard class in accordance with Regulation (EC) No 1272/2008, and containers used for the storage of such hazardous substances or mixtures, together with the visible pipes containing or transporting such hazardous substances and mixtures, must be labelled with the relevant hazard pictogram in accordance with that Regulation.

Applicability to DMAC and NEP
It is clear that all of the aforementioned obligations in the worker protection legislation fully apply to any use of DMAC and NEP in practice, as can also be deducted from Article 2 of REACH which states that the REACH Regulation applies without prejudice to, among others, the Directives 98/24/EC and 2004/37/EC. It may be also concluded, from the wordings of Article 6 CAD and Article 4 CMD, that substitution of DMAC and NEP for less hazardous substances should be the first measure to be considered. As long as DMAC and NEP are not, however, listed in Annex XIV or XVII of REACH, it may be questioned whether the substitution on the basis of the workers protection Directive is to be considered 'reasonable'. The CAD does leave latitude for the use of DMAC and NEP, as long as the employer minimizes the

[9] *SCOEL, 2017. Methodology for derivation of occupational exposure limits of chemical agents. The general decision-making framework of the Scientific Committee on Occupational Exposure Limits (SCOEL).*

[10] *Council Directive 92/58/EEC of 24 June 1992 on the minimum requirements for the provision of safety and/or health signs at work (consolidated version 26-07-2019).*

remaining risks in accordance with Article 5 and 6 CAD. This implies, however, that the Risk Management Measures described in any CSR pertaining to the safe use of DMAC and NEP should also be in line with these Articles and also that the registrant may not content himself with achieving an RCR <1.

However, it is also clear from rulings by the European Court of Justice that measures on the basis of workers' protection Directives are subject to the notion of "reasonably practicable".[11] Even if the 13th recital to the Framework Directive states that "the improvement of workers' safety, hygiene and health at work is an objective which should not be subordinated to purely economic considerations", this does not imply that all measures to minimize risks are to be deemed 'reasonable'. Economic as well as organizational and technical considerations may, under circumstances, be taken into account (as is the case in many national OSH legislations).

OSH legislation might be more stringent should reprotoxic substances cat 1 and 2, in the near future, be woven into the Carcinogens and Mutagens Directive 2004/37/EC. This will probably put more pressure on 'replacement' of DMAC and NEP "in so far as is technically possible" (art. 4 CMD). In this respect, designation of DMAC and NEP to Annex XVII might be helpful in clarifying what uses of DMAC and NEP could, 'technically' speaking, be replaced. This does not, however, relieve the individual employer to fulfil his individual duty to investigate the technical possibilities for replacement. Still, as the revision of CMD is pending, it is not justified to speculate any further in this respect.

Protection of young people at work and pregnant workers
In view of the classification as reproductive toxic 1B, specific attention should be paid to the protection of young people at work as well as pregnant workers. This may also be deduced from Article 15 FD, which states that "Particularly sensitive risk groups must be protected against the dangers which specifically affect them."

Young People at Work
The legal requirements protecting young people at work are scattered over various bodies of EU legislation, but are also assembled in Directive 94/33/EC on the protection of young people at work[12]. Young people, within the meaning of the Directive, are workers under 18 years of age.

Even if the Directive is not an individual Directive within the Framework of Directive 89/391/EEC, as it is not geared to occupational health and safety only, Article 15 FD is mentioned in the recital, thereby placing Directive 94/33/EC within the realm of health and safety. Particularly, Article 7 of the Directive states that Member States shall ensure that young people are protected from any specific risks to their safety, health and development, notably from work "involving harmful exposure to agents which are toxic, carcinogenic, cause heritable genetic damage, or harm to the unborn child or which in any other way chronically affect human health". The Annex to the Directive specifies various hazards, such as H360 (may damage the unborn child).

The heading of Article 7 clearly runs "Vulnerability of young people - Prohibition of work", and Article 7(2) explicitly prohibits work involving harmful exposure to agents. This leaves open the question which exposure should be considered "harmful". From the perspective of REACH, any exposure under the DNEL is to be deemed "not harmful". So if, by adequate Risk Management Measures, exposure will stay under the DNEL, it is not forbidden for young workers to handle DMAC and NEP. If, however, exposure to harmful conditions may not be

[11] *ECJ, June 14 2007, C-127/05, nr. 58 (Commission vs. United Kingdom).*

[12] *Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work (Consolidated version 26-07-2019).*

precluded, working with DMAC and NEP is prohibited. As a minimum, the employer should take the specific legislation into account when performing a risk assessment as meant in art. 4 CAD (in conjunction with art. 9 FD).

Pregnant & breast feeding at work
Pregnant workers and workers who have recently given birth or are breastfeeding are among the specific groups of workers referred to in Article 15 of the Framework Directive. Their protection is regulated in Directive 92/85/EEC.[13]

Most prominent in this Directive is the obligation imposed upon the employer, in Article 4(1), to assess the nature, degree and duration of exposure to substances carrying specific risk of workers who are pregnant, have recently given birth or are breastfeeding and shall inform these workers of the results of the assessment and of all measures to be taken concerning health and safety at work.[14] This obligation reflects art. 9(1) FD, which states that the employer shall be in possession of an assessment of the risks to safety and health at work, including those facing groups of workers exposed to particular risks; Annexes I and II of Directive 92/85/EEC list various specific risks, among others working with substances labelled for germ cell mutagenicity (H340 and H341), carcinogenicity (H350 and H351), reproductive toxicity or the additional category for effects on or via lactation (H360-H362) and specific target organ toxicity after single exposure (H370 and H371).

If it is determined that the workers are or may be exposed to the aforementioned risks, the employer is to take the necessary measures to ensure that, by temporarily adjusting the working conditions and/or the working hours of the worker concerned, the exposure of that worker to such risks is avoided. If the adjustment of her working conditions and/or working hours is not technically and/or objectively feasible, or cannot reasonably be required on duly substantiated grounds, the employer shall take the necessary measures to move the worker concerned to another job. If this is not technically and/or objectively feasible or cannot reasonably be required on duly substantiated grounds, the worker concerned shall be granted leave in accordance with national legislation and/or national practice for the whole of the period necessary to protect her safety or health (art. 5 (1-3)).

As DMAC and NEP fall within the category of agents presented within Annex I of this directive, all the above does apply to DMAC and NEP using industries. This means that pregnant or breastfeeding workers may not work with DMAC and NEP, and should be moved to another job or even be granted leave.

Plant Protection Product and Biocidal Product legislation
In the DMAC Annex XIV background document DMAC is reported to be used to some extent as intermediate for synthesis of some substances, among others agrochemicals (fertilisers, pesticides, etc.). It can be questioned whether the risks in these applications are to be addressed via REACH or by the dedicated Plant Protection Products Regulation (PPPR, 1107/2009/EC[15]) or by the Biocidal Products Regulation (BPR, 528/2012/EC[16]).

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[13] 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 (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC) (consolidated version 26-7-2019).

[14] In Article 3, it is stated that the Commission shall draw up guidelines on the assessment of the chemical, physical and biological agents and industrial processes considered hazardous for the safety or health of pregnant workers, workers who recently gave birth and breast feeding workers. COM/2000/0466 def.

[15] Regulation 1107/2009/EC concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (consolidated version 27-03-2021)

[16] Regulation 528/2012/EC concerning the making available on the market and use of biocidal products (consolidated version 20-11-2019)

The PPPR has its own authorisation mechanism of authorisation requirements for active substances, synergists and safeners as well as a negative listing of unacceptable co-formulants in Annex III of that directive. The BPR has its own authorisation mechanism for active ingredients. Both a positive and a negative listing of active substances of biocidal products exists resulting from this authorisation obligation. BPR has no specific requirements for co-formulants except for those co-formulants that are substances of concern. Substances of concern are defined as 'any substance, other than the active substance, which has an inherent capacity to cause an adverse effect, immediately or in the more distant future, on humans, in particular vulnerable groups, animals or the environment and is present or is produced in a biocidal product in sufficient concentrations to present risks of such effects' (BPR). When a co-formulant is flagged as substances of concern, a risk assessment will be obligatory both via BPR as via REACH (duplication).

At this moment both the PPPR and the BPR do not limit the use of DMAC and NEP and according to the registration dossier DMAC and NEP are still used in agrochemical synthesis and formulation.

When it comes to restrictions under REACH, plant protection products and biocidal products are not exempted from the scope of Title VIII of REACH. A REACH restriction could thus cover different substances used in plant protection and biocidal applications (active substances, co-formulants, safeners and synergists). As the risk assessment in part B shows risks for this use application, we see no reason to exempt these uses from this restriction proposal.

Pharmaceuticals
The Annex XIV background document for DMAC mentions the use of DMAC as excipient (carrier ingredient) in human and veterinary pharmaceuticals. Applications relate to pharmaceuticals like antibiotics and novel contrast media. No use of NEP in the production of pharmaceuticals has been described by the registrants.

The safe use of substances in medicinal products are assessed under the dedicated legislation for medicinal products (Medicinal Products Directives for human products and veterinary products; Directive 2001/83/EC[17] and 2019/6[18]) and are exempted for registration in REACH. However, the formulation process of medicinal product itself are not reviewed via the dedicated legislation and registration of this part of the process is obligatory under REACH. The use of DMAC as excipient is included in the registration dossier and risks are calculated for this use in part B of this report. As medicinal products are not excluded from the scope of Title VIII (restrictions), medicinal products could in principle be addressed with a restriction proposal. However, as the medicinal product legislation has its own review for the safe use of the end products itself, and no information on potential risks in this end-use is available via REACH, we suggest only to include the formulation process of pharmaceuticals within the restriction.

Cosmetics
DMAC and NEP are listed in Annex II of Regulation 1223/2009 in the list of substances prohibited in cosmetic products.[19]

[17] *Directive 2001/83/EC on the Community code relating to medicinal products for human use. (consolidated version 26-7-2019).*

[18] *Regulation 2019/6 on veterinary medicinal products (consolidated version 07-01-2019).*

[19] *Regulation 1223/2009 on cosmetic products (consolidated version 03-12-2020).*

B.9.1.2 Summary of the effectiveness of the implemented operational conditions and risk management measures

The implemented operational conditions and risk management measures (RMM) by the Dossier Submitter are the use of closed systems (enclosure) and dedicated systems (PROCs 1-2-3-8b), a limit on the DMAC or NEP concentration in the mixture, the use of local exhaust ventilation (LEV), dilution (outdoor activities) and the use of gloves. The use of closed systems (enclosure) is incorporated in the initial exposure concentration estimation for the relevant contributing scenarios (PROCs) in ECETOC TRA v3.1. No additional reduction score is applied by the Dossier Submitter.

The effectiveness of LEV depends on the process during which it is applied. Its effectiveness for inhalation exposure reduction in ECETOC TRA v3.1 is 80-90% for professional use and 90-95% for industrial uses. Such effectiveness levels can only be achieved when the LEV is selected or designed for the specific process and applied properly. For outdoor uses a dilution factor is applied (30% exposure reduction) (ECETOC, 2012). Although good- or enhanced ventilation can be applied in ECETOC TRA (30-70% exposure reduction), as a worst-case exposure estimate no improved general ventilation is applied by the Dossier Submitter, because it cannot be excluded that activities take place in less well-ventilated areas. Therefore, only indoor use with basic ventilation is applied as a worst-case assumption.

The effectiveness of gloves in ECETOC TRA v3.1 ranges from 80% (APF5) to 95% (APF20). For industrial settings a default of 90% reduction (APF10) is applied by the Dossier Submitter, corresponding to the ECETOC TRA v3.1 description of 'chemically resistant gloves (tested to EN374) in combination with 'basic' employee training'. For professional settings a default of 80% reduction (APF5) is applied by the Dossier Submitter, corresponding to the ECETOC TRA v3.1 description of 'suitable gloves tested to EN374'. The reduction effect of gloves has been evaluated by analyzing 11 datasets with measurements inside and outside of gloves (Marquart et al., 2017). The average reduction per data set ranges between 80.5-99.99%, with six of the data sets having a reduction of >95% and an overall average reduction factor of 34 (± 97% reduction).

The effectiveness of limiting the exposure duration and limiting the concentration (weight fraction) of DMAC and NEP in the mixture are accounted for by applying the ECETOC TRA v3.1 categorical adjustment. For example, in a categorical approach a PROC wherein the substance is used at a maximum concentration of 25%, the exposure estimate is multiplied by factor 0.6.

The use of respiratory protective equipment (RPE) is applied only for maintenance activities and professional spraying scenarios. A default protection factor of 90% (APF10) is applied by the Dossier Submitter.

Next to the applied RMM described above, other operational conditions and RMM may apply to the uses of DMAC and NEP, which are not described. Operational conditions as post-cleaning of materials with water before contacting the materials, avoiding spray processes, avoiding heating processes, among other may reduce the exposure potential. The use of whole body protection may also be applied as personal protective equipment if other RMM are not practical. ECETOC guidance on their Targeted Risk Assessment tool (TR093, TR107, TR114, TR124, TR131) (ECETOC, 2004, 2009, 2012, 2014, 2018) and ECHA guidance (ECHA, 2012c) Chapter R.13 on risk management measures and operational conditions provide information on how effective such RMM can be.

In Table 36 the ECECTOC TRA v3.1 exposures modifying factors are presented that are applied by the Dossier Submitter in the exposure estimation.

Table 36: ECETOC TRA v3.1 exposure estimation input parameters and corresponding exposure modifying factors

Input parameter	Specific OC / RMM	Exposure modifying factor
Concentration (weight fraction)	> 0.25 – 1	1
	0.05 – 0.25	0.6
	0.01 – 0.05	0.2
	< 0.01	0.1
Duration (maximum hours per day)	>4 – 8	1
	>1 – 4	0.6
	0.25 – 1	0.2
	<0.25	0.1
Ventilation*	Indoors	1
	Indoors with LEV	0.05 - 0.2
	Indoors with good general ventilation	0.7
	Indoors with enhanced general ventilation	0.3
	Outdoors	0.7
Dermal protection	No gloves	1
	Chemically resistant gloves according to EN 374 (APF 5)	0.2
	Chemically resistant gloves according to EN 374 with basic activity training (APF 10)	0.1
	Chemically resistant gloves according to EN 374 with specific activity training (APF 20) **	0.05
Respiratory protection	No respirator	1
	Respirator with APF 10	0.1
	Respirator with APF 20**	0.05

** A combination of indoor use, LEV and (good or enhanced) general ventilation is also possible. In that case the exposure modifying factors are multiplied. The dossier submitter only assumed indoor use with basic ventilation as a worst-case assumption. Good or enhanced ventilation was not applied by the Dossier Submitter in this dossier.*

*** Not applied by the Dossier Submitter in this dossier.*

In the tables below an overview is given of the exposure scenarios and life cycle stages of DMAC and NEP. For DMAC the structure as described in the Background Document for N,N-Dimethylacetamide (ECHA, 2012a) is followed. For NEP the life cycle is based on the registrants' CSRs and the use information as available in the ECHA public database.

Remarks on the table of uses

- The registrants' CSRs does not include a separate exposure scenario for manual maintenance and cleaning. A separate exposure scenario is included by the Dossier Submitter to cover manual maintenance activities. ECETOC TRA v3.1 does not provide exposure estimates for this PROC. Users are advised to adopt the values of an alternative PROC such as PROC8a (ECETOC, 2018). Therefore the Dossier Submitter applies PROC8a input parameters to estimate exposure during maintenance and cleaning.
- For NEP no separate exposure scenario for charging and discharging activities is included in the registrants' CSRs. However, in line with DMAC, a separate exposure scenario is included by the Dossier Submitter for charging and discharging activities reflected b,y contributing scenarios PROC8a, PROC8b and PROC9. Other ESs frequently include charging and discharging activities as well. These are considered to be adequately covered by this general exposure scenario for charging and discharging activities and are not repeated.
- For NEP some registrants' CSRs include a separate exposure scenario for distribution in an industrial setting. However, in this dossier distribution is not described separately. The various contributing scenarios of distribution (PROC1-4, PROC8a-9, PROC15) are

considered to be adequately covered by the exposure scenario manufacturing, formulations and (re)packing, charging and discharging and use as laboratory chemical.

- For the use of NEP as binders and release agents, for the use of NEP in cleaning agents and for use in coatings, some registrants' CSRs include (in addition to the lead registrant's CSR) production/formulation (PROC1-5), charging/discharging (PROC8a-9) and use as laboratory chemical (PROC15) steps. These contributing scenarios are considered to be covered by the exposure scenario manufacturing, formulations and (re)packing, charging and discharging and use as laboratory chemical. For these exposure scenario the lead registrant's CSR is followed.
- The use of DMAC and NEP as laboratory chemical is described in a separate exposure scenario.Some CSRs include a laboratory step in other exposure scenario as well. For NEP a PROC10 scenario for laboratory use is described. This is not considered in this restriction report. In this dossier the use of DMAC and NEP as laboratory chemical is considered to be covered in the exposure scenario use as laboratory chemical and reflected by process category PROC15.
- According to the ECHA background document for N,N-Dimethylacetamide (DMAC) (ECHA, 2012a) DMAC is used in the formulation of paint stripper products by producers of cleaning products for the industrial sector. Paint strippers or paint removers are used (by metal industry, but also professional users) in conjunction with other solvents (mainly dichloromethane) for removal of paints/varnishes. The paint strippers are applied (depending on the type) on the item by dipping or manually with a brush or bristle. The paint is afterwards removed with a scraper. According to information from SDSs, DMAC in commercial products is in the range of 0.1-5%. According to comments received during consultation, some registrants seem to consider to advise against this use in their registration dossiers (ECHA, 2012a). No industrial or professional end use of paint strippers is included in the registrants' CSRs. Also no use advised against is found in the registrants' CSRs. Therefore this exposure scenario is not included in this dossier and no exposure calculations are performed for this scenario.
- Potential other uses of DMAC are identified (ECHA, 2012a). These include use of DMAC in petrochemical applications, filling / packaging for scientific research and development, adhesives, plastic / anti-set off agents in polymer moulding/casting, and potentially in sealants, putty, paints, lubricants in metal working fluids, and the production of cellulose fibres such as cellophane. At the moment it is not clear if DMAC is still used for these applications. If so, many of these uses can be considered to be covered by other exposure scenarios already included in this dossier, e.g. transfer of chemicals (e.g. filling / packaging), the use of DMAC as solvent for the application of mixtures or articles (e.g. use in adhesives), use in coatings (e.g. putty and paints) or for the production of man-made fibres (e.g. production of cellulose fibres). No substantial information is available with respect to process descriptions / operational conditions or potential for exposure for these uses. Therefore this exposure scenario is not included in this dossier and no exposure calculations are performed for this scenario.

Table 37: DMAC Exposure scenario overview

Number	Short description of exposure scenario	Resulting life cycle stage			Process Category (PROC)	Environmental Release Category (ERC)
		Manufacture	Formulation	End use		

				Industrial	Professional		
9.2	Manufacturing	x		x		1, 2, 3	1
9.3	Formulation		x	x		3, 4, 5	2
9.4	Charging and discharging			x		8a, 8b, 9	2
9.5	Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals			x		1, 2, 3, 4	4
9.6	Use as solvent in the production of man-made fibres			x		1, 2, 3, 4, 13, 14, 19, 21	4, 12a
9.7	Use as solvent in coatings			x		7, 10, 13	4
9.8	Use as solvent in the production of films			x		1, 2, 3, 4	4
9.9	Manual maintenance (cleaning and repair) of machinery			x		28 (8a)	
9.10	Use as laboratory chemical			x	x	15	4, 8a, 6a

Table 38: NEP Exposure scenario overview

Number	Short description of exposure scenario	Resulting life cycle stage				Process Category (PROC)	Environmental Release Category (ERC)
		Manufacture	Formulation	End use			
				Industrial	Professional		
9.2	Manufacturing	x		x		1, 2, 3, 4	1, 4, 6a
9.3	Formulation and (re)packing		x	x	x[##]	1, 2, 3, 4, 5, 14	2, 3, 8a
9.4	Charging and discharging			x	x	8a, 8b, 9	2
9.5	Use in industrial chemical processes			x		1, 2, 3, 4	4
9.7	Use as solvent in coatings [#]			x	x	7, 10, 11, 13, 19	4, 8a, 8c, 8d, 8f
9.9	Manual maintenance (cleaning and repair) of machinery			x	x	28 (8a)	
9.10	Use as laboratory chemical			x	x	15	4, 8a
9.11	Use as binder and release agent			x	x	6, 7, 10, 11, 13, 14	5, 8a-f
9.12	Use in cleaning agents			x	x	7, 10, 11, 13	4, 8a, 8d

9.13	Use in oil field drilling and production operations			x	x[#]	1, 2, 3, 4, 8a, 8b	4, 8d
9.14	Use in agrochemicals				x	1, 2, 4, 8a, 8b, 11, 13	8a, 8d
9.15	Use in functional fluids			x	x	1, 2, 3, 4, 8a, 8b, 9, 20	7, 9a-b
9.16	Use in road and construction applications				x	8a, 8b, 9, 10, 11, 13	8f
9.17	Polymer processing			x	x	1, 2, 3, 4, 5, 6, 8a, 8b, 9, 13, 14, 21	6d, 8a, 8c, 8d, 8f
9.18	Water treatment chemicals			x		1, 2, 3, 4, 8a, 8b, 13	4

[#] Exposure scenario's in a professional setting have been described for these scenario's. The Dossier Submitter considered these to be only relevant for the industrial setting.

NB: Exposure scenarios 9.13 to 9.18 are described by one registrant only. The registrant indicates (personal communication) that once they update their CSR these uses will no longer be included in the CSR. As the updated CSR is not yet available and these uses are still mentioned at the ECHA website, the Dossier Submitter decides to include these exposure scenario in the restriction report.

B.9.2 Manufacturing

Manufacturing describes the process of the manufacturing of DMAC and NEP itself. The manufacturing of other chemicals or mixtures and formulation steps are described under other exposure scenarios like formulation and use as solvent in various applications. The use of DMAC and NEP as laboratory chemicals and laboratory analysis, charging and discharging activities and manual maintenance are also described in separate exposure scenarios.

DMAC

DMAC is manufactured by the reaction of acetic acid and dimethylamine in closed systems at elevated temperature (180 °C, REACH online registration dossier information) and pressure. The substance is purified by distillation. According to information provided by registrants DMAC is manufactured within a high integrity contained system where little potential for exposure exists. The end product is transferred into vessels/large containers at dedicated automated facilities. Sampling is undertaken using closed loop systems. Exposure may take place during automated filling, maintenance and laboratory analysis with a higher likelihood for worker exposure during maintenance and laboratory analysis. Automated filling of the product minimizes worker exposure during filling. In addition, the use of gloves reduces the potential for incidental dermal contact. Exposures to DMAC are likely to be highest during maintenance operations, in particular in the absence of adequate PPE (ECHA, 2011a, 2012a).

The manufacturing process of DMAC is described by the registrants with contributing scenarios PROC1, PROC2 and PROC3. These PROCs include closed sampling activities. An eight hour exposure duration is considered with no additional RMM in place except for the level of containment already included in PROC1-3 situations. A low fugacity category is applied based on the DMAC vapour pressure of 200 Pascal. As the manufacturing process is said to take place at elevated temperatures also exposure estimations at elevated temperatures are performed. The exact temperatures of DMAC to which workers can be exposed are not known to the Dossier Submitter. Based on the mentioned reaction temperature of 180 °C a high fugacity category is selected for the manufacturing contributing scenarios.

NEP

The manufacturing process of NEP is described by the registrants with contributing scenarios PROC1, PROC2, PROC3 and PROC4. These PROCs include closed sampling activities. An eight

hour exposure duration is considered. Registrants differ in the prescribed RMM, e.g. one registrant prescribes LEV for PROC3. In line with the exposure assessment approach the Dossier Submitter does not apply additional RMM like LEV for processes with a high level of containment already included (e.g. PROC1-3 situations). For PROC4 – where opportunity for exposure arises – LEV (90%) and the use of gloves (APF10, 90%) are applied. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. As the manufacturing process is said to take place at elevated temperatures also exposure estimations at elevated temperatures are performed. The exact temperatures of NEP to which workers can be exposed are not known to the Dossier Submitter. It can be assumed that the vapour pressure at elevated temperatures is within the ECETOC TRA v3.1 medium fugacity category.

B.9.2.1 Occupational exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the manufacturing of DMAC and NEP. These estimated inhalation concentrations for DMAC, based on the identified contributing scenarios, are in the range of 0.036-10.69 mg/m^3 (low fugacity) and 0.036-178.16 mg/m^3 (high fugacity). Measurement data from industry during manufacturing activities indicate that the 8-hour time weighted average exposure is <2.49 mg/m^3. These results indicate that the model estimations are on the conservative side, especially for the exposure estimations at elevated temperatures.

Table 39: Calculated exposures for manufacturing of DMAC using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
1	8	1	Indoors	No	No	0.036	0.034	0.039
2	8	1	Indoors	No	No	3.56	1.37	1.88
3	8	1	Indoors	No	No	10.69	0.69	2.22
Exposure estimates at elevated temperatures (high fugacity category)								
1	8	1	Indoors	No	No	0.036	0.034	0.039
2	8	1	Indoors	No	No	89.08	1.37	14.10
3	8	1	Indoors	No	No	178.16	0.69	26.14

The (OECD, 2001) summarises measurement data of Monsanto collected in the period of 1992-1994 for the manufacturing of DMAC and estimates a central tendency value of 1.06 mg/m^3 during manufacturing with a high end inhalation exposure estimation of 2.49 mg/m^3. No indication is given on the temperature of the process. Based on inhalation measurement results of DuPont for manufacturing personnel a value of 0.14 mg/m^3 is presented (NB: from the report it is not clear if the central tendency concentration value or the high-end value is given). Potential dermal dose rate is estimated (assumingly using the EASE exposure model) to be in the range of 1,300-1,900 mg/day (18.6-27.1 mg/kg bw/day) with no dermal protection assumed and a concentration weight factor of 1.

Table 40: Measured DMAC inhalation exposure concentrations during DMAC manufacturing contributing scenarios

Study	Concentration (mg/m^3)	Min (mg/m^3)	Max (mg/m^3)	90-percentile (mg/m^3)	Potential dermal dose rate (mg/day)	Task description
(OECD, 2001)	1.06		2.49		1,300-3,900	Manufacturing - Field operators

(OECD, 2001)	0.14				1,300-3,900	Manufacturing

Table 41: Calculated exposures for manufacturing of NEP using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m^3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
Exposure estimates at elevated temperatures (medium fugacity category)								
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	23.14	1.37	4.68
3	8	1	Indoors	No	No	46.28	0.69	7.30
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	9.26	0.69	2.01

B.9.3 Formulation

B.9.3.1 General information

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

Exposure may occur during formulation of DMAC (in batch formulation processes workers may have multiple and/or significant contact with DMAC), transfers of DMAC or of mixtures containing DMAC to and from large containers using either dedicated or non-dedicated facilities (ECHA, 2012a). According to comments by an industry association (EUROPACABLE) and one of the companies using DMAC in coatings, at all 4 sites involved in the formulation of enamel mixtures the process is carried out in closed systems (sealed circuits). Limited and short time exposure could occur during maintenance / filter sockets change and sampling operations. During these operations PPEs (inhalation and skin) and adequate ventilation would be employed as standard practice (ECHA, 2012d).

The formulation of mixtures may take place in batch formulation processes, usually with a high level of containment where limited opportunity for exposure arises. The possible use of DMAC and NEP as laboratory chemical and laboratory analysis, charging and discharging activities and manual maintenance are described in separate exposure scenarios.

B.9.3.2 Exposure estimation

DMAC

The use of DMAC for the formulation of preparations is reflected by contributing scenarios PROC3, PROC4, PROC5. According to the registrant PROC5 is used to describe the formulation

of preparations only because it is possible for this PROC to define a safe use by risk minimization requirements (goggles, gloves) being obligatory in any chemical plant at any time when handling a chemical substance. They indicate that in practice there is neither significant contact to DMAC at any stage of use (PROC5). The registrant indicates that any significant dermal exposure can be excluded due to mandatory use of chemical resistant gloves. Automated filling and workers wearing gloves (butyl) and goggles can be regarded as common industry standard for large scale industrial installations (BASF, 2012).

An eight hour exposure duration is considered for all contributing scenarios and a DMAC weight fraction of 1 (100%). A low fugacity category is applied based on the DMAC vapour pressure of 200 Pascal. LEV is not prescribed by all registrants for PROC5 and different exposure reduction factors for gloves are applied (80-90%). For PROC5 therefore exposure is estimated with and without the use of LEV. For the use of gloves the exposure reduction factor of 90% (APF10) is applied based on the use of gloves with good activity training as can be expected in industrial settings.

NEP
The use of NEP in formulation steps is reflected by the registrants by contributing scenarios PROC1, PROC2, PROC3, PROC4, PROC5 and PROC14. An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%). For PROC4, PROC5 and PROC14 – where opportunity for exposure arises – LEV (90%) and the use of gloves (APF10, 90%) are applied. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. For PROC5 a scenario at elevated temperature (medium fugacity) is described.

NB: For NEP an exposure scenario in a professional setting is also described by the registrants. According to ECHA Guidance document R.12 (ECHA, 2015) "a use in the formulation stage corresponds to specific activities meant to produce a mixture to be put on the market. This means that during formulation, the substance is transferred and mixed with other substances. It corresponds to activities taking place at industrial sites. Mixing activities during end use are not to be reported under this formulation stage. Manufacturers' or importers' own formulation should be reported under this life cycle stage." Therefore no exposure scenario for a professional setting was included by the Dossier Submitter.

B.9.3.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the formulation of mixtures containing DMAC and NEP.

Table 42: Calculated exposures for formulation of mixtures containing DMAC using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
3	8	1	Indoors	No	No	10.69	0.69	2.22
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	0.69	0.94
5	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	1.37	1.63
5	8	1	Indoors	No	Yes (90%)	17.82	1.37	3.92

DMAC inhalation exposure for contributing scenarios PROC3, PROC4, PROC8a and PROC8b have been measured at BASF. 8-hour inhalation exposure concentrations, covering multiple PROCs, are reported to be below <0.07-<0.22 mg/m³ (not detectable in 6 different measurements over a period of 2 years) (BASF, 2012).

Table 43: Measured DMAC inhalation exposure concentrations during the formulation of mixtures containing DMAC

Study	Concentration (mg/m³)	Min (mg/m³)	Max (mg/m³)	90-percentile (mg/m³)	Task description
(BASF, 2012)	<0.07-<0.22				Including sampling of product, PROC3, PROC4, PROC8a and PROC8b

Table 44: Calculated exposures for formulation of mixtures containing NEP using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
5	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	1.37	1.70
14	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.34	0.67
Exposure estimates at elevated temperatures (medium fugacity category)								

B.9.4 Charging and discharging

B.9.4.1 General information

Charging and discharging of DMAC and NEP concerns a generic exposure scenario describing the transfer and distribution processes of DMAC or NEP and mixtures containing DMAC or NEP. After manufacturing the end product is transferred into vessels/large containers at dedicated automated facilities. Automated filling of the product minimises worker exposure during filling. In addition, the use of gloves is common during these activities, which reduces the potential for incidental dermal contact (ECHA, 2012a). After transfer at the manufacturing sites DMAC and NEP are transported to downstream users where bulk transfer from IBC's, tankers or drums into the reactor or blenders takes place using closed pipelines or by using pumps. These processes are normally contained and/or equipped with LEV (ECHA, 2011a).

B.9.4.2 Exposure estimation

The charging and discharging of DMAC and NEP is reflected by contributing scenarios PROC8a, PROC8b and PROC9. For DMAC only industrial settings are considered by the registrants, for NEP both industrial and professional settings.

DMAC

According to one of the registrants in practice there is neither significant contact to DMAC at any stage of use nor a significant opportunity for such a contact at sampling or charging or discharging (PROC8a and PROC8b). The registrant indicates that any significant dermal exposure can be excluded due to mandatory use of chemical resistant gloves. Automated filling and workers wearing gloves (butyl) and goggles can be regarded as common industry standard for large scale industrial installations (BASF, 2012).

An eight hour exposure duration is considered for all contributing scenarios and a DMAC weight fraction of 1 (100%). A low fugacity category is applied by most registrants, although also transfer activities up to 40 °C are applied in the calculation applying a medium fugacity. LEV was not prescribed by all registrants for PROC8b (room temperature activities) and different exposure reduction factors for gloves were applied (80-90%). Calculations by the dossier submitter are performed for both low and medium fugacity scenarios. For PROC8b (room temperature scenarios) exposure is estimated with and without the use of LEV. For the use of gloves the exposure reduction factor of 90% (APF10) is applied based on the use of gloves with good activity training as can be expected in industrial settings.

NEP

An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%, industrial use) and 0.05-0.25 (5-25%, professional use). For all contributing scenarios the use of gloves (APF5-10 80-90%) is applied. LEV was not prescribed by all registrants for charging and discharging activities. Calculations by the dossier submitter are performed for activities with and without the use of LEV (80-95%). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.4.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the charging and discharging of DMAC and NEP.

Table 45: Calculated exposures for charging and discharging of DMAC using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate long-term inhalation (mg/m3)	Exposure estimate long-term dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
8a	8	1	Indoors with LEV (90%)	No	Yes (90%)	3.56	1.37	1.88
8b	8	1	Indoors with LEV (95%)	No	Yes (90%)	0.89	1.37	1.50
8b	8	1	Indoors	No	Yes (90%)	17.82	1.37	3.92
9	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	0.69	0.94
Exposure estimates at elevated temperatures (medium fugacity category)								
8a	8	1	Indoors with LEV (90%)	No	Yes (90%)	17.82	1.37	3.92
8b	8	1	Indoors with LEV (95%)	No	Yes (90%)	4.45	1.37	2.01
9	8	1	Indoors with LEV (90%)	No	Yes (90%)	17.82	0.69	3.23

The OECD presents measurement data of DuPont (OECD, 2001). Inhalation exposure concentrations during tank car and tank wagon loading (1-8 hours a day) were reported to be 5.27 mg/m^3 and 1.21 mg/m^3 for drum loading (NB: from the report it is not clear if the

central tendency concentration value or the high-end value is given). Potential dermal dose rate was estimated (assumingly using the EASE exposure model) to be in the range of 1,300-1,900 mg/day (18.6-27.1 mg/kg bw/day) with no dermal protection assumed and a concentration weight factor of 1.

DMAC inhalation exposure concentrations in a PROC3, PROC4, PROC8a and PROC8b scenario have been measured at BASF. Shift inhalation exposure concentrations were reported to be below <0.07-<0.22 mg/m³ (not detectable in 6 different measurements over a period of 2 years) (BASF, 2012).

Table 46: Measured DMAC inhalation exposure concentrations during DMAC charging and discharging contributing scenarios

Study	Concentration (mg/m³)	Min (mg/m³)	Max (mg/m³)	Task description
(OECD, 2001)	5.27			Tank car and tank wagon loading personnel
(OECD, 2001)	1.21			Drum loading personnel
(BASF, 2012)	<0.07-<0.22			PROC3, PROC4, PROC8a and PROC8b scenarios

Table 47: Calculated exposures for charging and discharging of NEP using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
Industrial setting								
8a	8	1	Indoors with LEV (90%)	No	Yes (90%)	4.63	1.37	2.03
8a	8	1	Indoors	No	Yes (90%)	46.28	1.37	7.98
8b	8	1	Indoors with LEV (95%)	No	Yes (90%)	1.16	1.37	1.54
8b	8	1	Indoors	No	Yes (90%)	23.14	1.37	4.68
9	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
9	8	1	Indoors	No	Yes (90%)	23.14	0.69	3.99
Professional setting								
8a	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	13.88	1.65	3.63
8a	8	<0.25	Indoors	No	Yes (80%)	69.42	1.65	11.56
8b	8	<0.25	Indoors with LEV (90%)	No	Yes (80%)	2.78	1.65	2.04
8b	8	<0.25	Indoors	No	Yes (80%)	27.77	1.65	5.61
9	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	5.55	0.82	1.62
9	8	<0.25	Indoors	No	Yes (80%)	27.77	0.82	4.79

B.9.5 Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals

B.9.5.1 General information

DMAC is used as excipient (carrier ingredient) in human and veterinary pharmaceuticals due to its polar, aprotic characteristics. Applications relate to the manufacture of pharmaceuticals (e.g. antibiotics and novel contrast media), agrochemicals (fertilizers, pesticides etc.), and

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

For NEP an exposure scenario "Use in industrial chemical processes" is described. That exposure scenario and included contributing scenarios is considered to be in line with the DMAC exposure scenario "Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals" and is therefore included here.

The possible use of DMAC and NEP as laboratory chemical and laboratory analysis, charging and discharging activities and manual maintenance (including equipment cleaning) are described in separate exposure scenarios.

B.9.5.2 Exposure estimation

The use of DMAC and NEP as solvent in industrial settings is reflected by contributing scenarios PROC1, PROC2, PROC3 and PROC4.

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

An eight hour exposure duration is considered for all contributing scenarios and a DMAC weight fraction of 1 (100%). A low fugacity category is applied based on the DMAC vapour pressure of 200 Pascal. LEV was not prescribed by all registrants for PROC4, therefore for this scenario exposure is estimated with and without the use of LEV. For the use of gloves the exposure reduction factor of 90% (APF10) is applied based on the use of gloves with good activity training as can be expected in industrial settings.

NEP
An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%). For contributing scenario PROC4 the use of gloves (APF10 90%) and LEV (90%) is applied in the exposure assessment. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.5.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of DMAC and NEP as a solvent in the production of agrochemicals, pharmaceuticals and fine chemicals.

Table 48: Calculated exposures for the use of DMAC as a solvent using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m^3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
1	8	1	Indoors	No	No	0.036	0.034	0.039
2	8	1	Indoors	No	No	3.56	1.37	1.88
3	8	1	Indoors	No	No	10.69	0.69	2.22
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	0.69	0.94
4	8	1	Indoors	No	Yes (90%)	17.82	0.69	3.23

Table 49: Calculated exposures for the use of NEP as a solvent using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02

B.9.6 Use as solvent in the production of man-made fibres

B.9.6.1 General information

DMAC is used in the production of man-made fibres made of polymers such as acrylic, polyurethane-polyurea copolymer (elastane) and meta-aramid fibres. It acts as the solvent in the polymerization reaction and helps transfer the polymer through the spinning process to produce very fine fibres. To some extent, DMAC is also used in mixtures applied to add specific additives or other polymers into the fibre spinning process (ECHA, 2012a). In the spinning process fluid polymer filaments emerge from the holes in a spinneret, and gradually solidify. When DMAC is used, solidification is achieved either by precipitation in a chemical bath where the spinneret is submerged – so called wet spinning - or by evaporating the solvent in a stream of air or inert gas, named dry spinning. DMAC is recovered and recycled several times in this process. The consumption of DMAC (0.5-1% per cycle) is due to solvent losses caused by the acid hydrolysis during recovery, environmental releases, residuals of solvent remaining in the fibres and DMAC disposed of as waste from the process. Recovery is reported to be achieved by installations comprising a distillation unit, a squeezing column unit and a DMAC stripping unit. The fibres are further processed (transfer and filling operations, rewinding and beaming, spinning of yearn, and knitting/weaving in order to produce the fabric, which will consequently be dyed and/or washed), with DMAC typically being present as a residue at significant concentration only in the first steps of the fibre processing (raw

fibres may contain up to 3% of residual DMAC, but according to industry typical DMAC content is between 0.1 and 0.5%). The greige fabric,- i.e. the fabric before it's bleached / dyed- normally contains DMAC levels below 0.1%, which will further be reduced during dying/washing. No detectable or very low level of residual DMAC are reported to be present in final textiles (e.g. in baby diapers, residues are reportedly at ppb levels) (ECHA, 2012a).

The use of DMAC as laboratory chemical and laboratory analysis, charging and discharging activities and manual maintenance (including equipment cleaning) are described in separate exposure scenarios.

B.9.6.2 Exposure estimation

The use of DMAC as solvent in the production of man-made fibres in an industrial setting is reflected by contributing scenarios PROC1, PROC2, PROC3 and PROC4. Specific activities like extrusion and the handling of treated objects are reflected by contributing scenarios PROC14 and PROC13 respectively. PROC19 is relevant for manual activities involving hand contact. For the reprocessing of fibres no adequate process category is available. Occupational exposure to DMAC may occur during its use in industrial situations as a solvent during fibre production or during the further processing of fibres, both due to inhalation or dermal contact. It was stated by industry that the process is well controlled, with most of the modules involved in the process being closed, and others, such as spinning, practically enclosed / equipped with LEV. Only some process steps would bear risk of exposure, such as start/stop of the spinning line, maintenance operations, or cleaning. However, according to the comments provided, during such steps all necessary risk management measures would be taken and strict protocols followed in order to minimise exposure of workers to DMAC. Workers would be generally required to wear appropriate gloves, protective clothing, eye protection and respiratory protection where direct contact with DMAC is possible. Employers may take additional precautions to minimise the exposure of pregnant women, including temporary change of workplace.

As regards fibre processing, inhalation exposures of equal magnitude of those relating to fibre production cannot be excluded. Industry stakeholders have commented that DMAC is bound to the polymer, and that extensive heat is required to release DMAC and that after the first steps of processing the residues would be negligible (ECHA, 2012a).

An eight hour exposure duration is considered for all contributing scenarios. A DMAC weight fraction of 1 (>25-100%) is applied for all contributing scenarios except for the processing of fibres were a DMAC concentration of 1-5% is considered. Both low and medium fugacity categories are applied by registrants and even operating temperatures up to 300 °C are indicated in closed spinning columns. Calculations by the dossier submitter are performed for both low and medium fugacity scenarios. For the use of gloves the exposure reduction factor of 90% (APF10) is applied based on the use of gloves with good activity training as can be expected in industrial settings. The processing of fibres cannot be estimated with ECETOC TRA v3.1. Industry measurement results are used instead for the exposure estimation.

B.9.6.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of DMAC as a solvent in the production of man-made fibres. These estimated inhalation concentrations based on the identified contributing scenarios are in the range of 0.036-35.63 mg/m^3. Published measurement results in literature and measurement data reported by registrants in the CSRs indicate that the inhalation exposure estimations might not be conservative enough. Measured inhalation concentrations (although sometimes based on

stationary air measurements) above 10 ppm (36 mg/m^3; EU indicative OEL) have been reported (Antoniou et al., 2021; Duarte, 2015).

Table 50: Calculated exposures for the use of DMAC as a solvent using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
1	8	1	Indoors	No	No	0.036	0.034	0.039
2	8	1	Indoors	No	No	3.56	1.37	1.88
3	8	1	Indoors	No	No	10.69	0.69	2.22
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	0.69	0.94
13	8	1	Indoors with LEV (90%)	No	Yes (90%)	3.56	1.37	1.88
14	8	1	Indoors with LEV (90%)	No	Yes (90%)	1.78	0.34	0.60
19	8	1	Indoors with LEV (90%)	No	Yes (90%)	3.56	14.14	14.65
Exposure estimates at elevated temperatures (medium fugacity category)								
1	8	1	Indoors	No	No	0.036	0.034	0.039
2	8	1	Indoors	No	No	17.82	1.37	3.92
3	8	1	Indoors	No	No	35.63	0.69	5.78
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	7.13	0.69	1.70
13	8	1	Indoors with LEV (90%)	No	Yes (90%)	17.82	1.37	3.92
14	8	1	Indoors with LEV (90%)	No	Yes (90%)	17.82	0.34	2.89
19	8	1	Indoors with LEV (90%)	No	Yes (90%)	17.82	14.14	16.69

Published measurement data are available over a broad time period both for the primary fibre production and the secondary fibre processing. Measurement data are described below, sorted by publication date of the studies. The data are summarized in Table 51 and Table 52.

Primary fibre production

Kennedy and Pruett measured DMAC concentrations in five workers for four consecutive weeks (Kennedy Jr & Pruett, 1989). Activities were performed in an area where fibres containing DMAC were being processed. The work area was equipped with an exhaust fan. Weekly inhalation exposure concentrations ranged from 1.8-12.29 mg/m^3 with a geometric mean week value of 3.96 mg/m^3. In addition to air monitoring also post-shift urine samples were collected. Weekly mean NMAC urine values ranging between 8-21 ppm were observed with daily urine NMAC values ranging from 1-42 ppm.

Inhalation exposure measurements were performed and biological monitoring urine samples collected under personnel of the dope preparation and spinning departments of an acrylic fibre manufacturing facility (Spies et al., 1995a). Measurements were performed each month during the course of one year. In total 419 DMAC inhalation measurements were performed with a geometric mean exposure of 5.17 mg/m^3 for a 12-hour shift exposure. This corresponds to an 8-hour geometric mean exposure of 7.75 mg/m^3. The authors indicate that exposure levels >36 mg/m^3 are possible. Employees from seven job classes were recruited for biological monitoring (dope preparation, jet room operator, spinning operator, senior spinning operator, relief operator, dye room operator, and utility). According to the authors biological monitoring was targeted toward those job classes for which previous air monitoring had suggested a higher potential for DMAC exposure. Employees worked 12-hour shifts. Clear differences were obtained between pre-shift and post-shift samples, with a geometric mean NMAC concentration for pre-shift samples of 1.7 mg MMAC/g creatine (first day of measurements), 8.9 mg MMAC/g creatine (second day pre-shift) and for post-shift samples of 15.4 and 16.1

mg MMAC/g creatine on day one and day two respectively, with a reported 80-percentile value of 35 mg MMAC/g creatinine.

Biological monitoring urine samples results from 27 workers exposed to a mixed vapor of DMF and DMAC in a synthetic fibre plant were presented (Kawai et al., 1997). Concentrations up to 1,000 µmol/L or 78 mg NMAC/L were found, although the majority of the measurements was below 300 µmol/L (23.4 mg NMAC/L).

OECD presents measurement results from the 1992-1994 period of North American workers involved in spinning acrylic fibre (OECD, 2001). These workers were exposed to arithmetic mean DMAC concentrations of 9.3 mg/m^3 during dope preparation, 7.02 mg/m^3 during spinning and <0.36 mg/m^3 during ring spinning or open-end spinning. Maximum exposures up to 51.35 mg/m^3 have been reported. The estimated intakes by dermal exposure (assuming no dermal protection) were in the range of 650–3,900 mg/day. One company though commented (ECHA, 2012d) that this estimated dose had relied on an unlikely scenario (not reasonable to assume no dermal protection) and extremely conservative estimate (contact with saturated aqueous solution for 8 hours). It is also noted that dermal absorption of DMAC via gas phase is known to contribute to the overall exposure, as DMAC can stick to the skin (especially if it is wet) and, having a high boiling point, continues being absorbed by the skin both during and after work, unless a shower and change of clothing at the end of the shift take place (e.g. see urinary analysis study for DMAC and its metabolite by Perbellini et al. (Perbellini et al., 2003).

Perbellini et al. present the results of a biological monitoring study involving 223 workers in a synthetic acrylic fibre factory (Perbellini et al., 2003). The task of most workers was to check the automatic production of fibres. Every day, two groups of six workers started up two or three spinning machines (an operation taking about 30 minutes), which would then work continuously for about 15 days except for occasional unscheduled stoppages. Environmental (stationary) DMAC concentrations indicated constant exposure levels with median values not exceeding 5.34 mg/m^3. For short time periods (less than five minutes) exposures could reach 18-36 mg/m^3. In addition to air monitoring also end of shift urine samples were collected. Average post-shift urine NMAC concentrations were 20.5 mg/g creatinine (range 1.5-173.6 mg/g creatinine) with higher levels for operators involved in the start-up of machinery. An increase over consecutive days of urine NMAC concentrations was detected.

Lee et al. describe cases of hepatic injury among new elastine fibre workers in Korea (Lee et al., 2006). Urinary NMAC data were obtained from new workers and workers longer employed who worked in the 19 departments of the 440 new workers. DMAC exposure was based on the 967 urinary NMAC results from January 2003 to July 2004. Results were divided into two groups. One group where DMAC induced hepatic injuries (DIHI) occurred and one group in which there were no DIHI. The median urinary NMAC level of 503 samples from the eight departments in which 28 DIHI cases had occurred was 19.6 mg/g creatinine (range 2.2–196.5). The concentration of the 464 urinary NMAC results from the other 11 departments was 5.2 mg/g creatinine (range 0.1–79.2).

Jung et al. present biological monitoring data of workers in a factory producing polyurethane elastic fibres where DMAC is used to dissolve the urethane oligomer-polymer mixture (Jung et al., 2007). The median of urinary NMAC results of DMAC induced hepatic injury (DIHI) group (228 samples from the department of 21 DIHI cases, department of packing, exchanging spinneret, and visual inspection in three productive units) were 25.1 mg/g creatinine (range 4.6–196.5). The median of urinary NMAC results in the other group (n=1,056) was 11.8 mg/g creatinine (range 0.1–133.9).

Duarte divided 81 workers of an acrylic fibre production plant into four inhalation exposure groups, based on exposure data collected by industry in the period of 2013-2014 (no reference indicated) (Duarte, 2015). The exposure groups were a) not exposed (n=12), b) <7.13 mg/m^3 (n=23), c) 7.13-36 mg/m^3 (n=23) and >36 mg/m^3 (n=23). Group D workers have the same daily average exposure as group C workers, but are incidentally exposed to short-term exposures (15 minutes, 1-2 times per week) >36 mg/m^3. In addition to air monitoring results also biological monitoring urine samples were collected post-shift (the exact day of the week was not indicated). There is a clear increase of DMAC and NMAC urinary levels with increasing inhalation DMAC exposure. There is a huge difference between working areas, with dope preparation and spinning showing the highest urinary NMAC levels, 69.89 and 45.35 mg/g creatinine respectively. Tow-to-tow area activities resulted in urinary NMAC levels of 6.60 mg/g creatinine. Employees working in other areas (solvent recovery, cut and bailing, open-end-spinning, pilot plant and laboratory) have urinary NMAC levels clearly below 6.5 mg/g creatinine.

DGUV presents an overview of stationary DMAC inhalation exposure measurements (n≈250) collected in the period of 2000-2011 with a measurement duration >6 hours during different activities related to the production of fibres and textiles (DGUV, 2012). 90-percentile DMAC inhalation values are reported to be in the range of 0.15 mg/m^3 (half-comb, carded yarn spinning, fleece production) to 9.8 mg/m^3 for weaving activities. The 90-percentile average value for personal measurements was reported to be 4 mg/m^3 (without LEV) and 0.68 mg/m^3 for the measurements were LEV was reported to be present.

The Dutch Labour Inspectorate published a report with regard to exposure to DMAC and PFOA at a Dutch Teflon producing company (SZW, 2017b). The highest measured inhalation DMAC value in 1992 was reported to be 13.18 mg/m^3 with an average exposure concentration of 8.55 mg/m^3. No further details on RMM/OC or number of measurements are available.

Results of biological monitoring data collected in 2017 in polyvinyl chloride workers in Turkey are presented (Tutkun et al., 2019). 109 DMAC exposed workers participated in the study. Urinary DMAC levels were determined. Operators were divided into two groups, based on previous urinary DMAC levels. Group 2 with urinary DMAC levels of 1-3 mg/L (1-3 mg/g creatinine) and group 3 with urinary DMAC levels of >3 mg/L (>3 mg/g creatinine). Average urinary DMAC levels were 2.43 mg/L (2.43 mg/g creatinine) and 3.17 mg/L (3.17 mg/g creatinine) for group 2 and group 3 respectively.

8-hour time weighted average (90-percentile values) area (static) air measurement results of DMAC exposure are presented for four EU fibre producing companies (Antoniou et al., 2021). Data were collected over a broad time period, two companies provided data from the period >2012. Two other companies provided data form 1977 and 1992 forward up to 2019. Area sampling for the DMAc exposure measurements was performed either with permanently installed, continuous measuring systems or with discontinuous sampling procedures during a work shift. The more than 1,800 measurement results cover all areas (including polymerization, spinning, washdraw, dispersions, solvent recovery) and have been divided into 90-percentile exposure classes for all years of exposure, ranging from 0.00 - 3.6 to ≥32.10 mg/m^3 (0 - ≥9.1 ppm). These are stratified into categories:
- 0.00 – 3.6 mg/m^3: 220 measurements
- >3.6 - 7.2 mg/m^3: 214 measurements
- >7.2 - 10.8 mg/m^3: 311 measurements
- >10.8 - 14.4 mg/m^3: 455 measurements
- >14.4 - 18 mg/m^3: 377 measurements
- >18 – 21.6 mg/m^3: 91 measurements
- >21.6 – 25.2 mg/m^3: 81 measurements
- >32.10 mg/m^3: 95 measurements

Secondary fibre processing

Exposure to DMAC during the whole work shift by personal air measurements for eight workers on five consecutive days was monitored (Borm et al., 1988). Measurements were performed in a plant where prefabricated synthetic product was handled and mechanically processed. DMAC was not directly used as such in this area, the exposure concentration was attributed to DMAC slowly diffusing from the synthetic product during mechanical processing and handling. The individual (personal) time-weighted average concentration of DMAC ranged from 2.49-184 mg/m^3 with an overall geometric mean exposure of 21.38 mg/m^3. The average concentration between the workers over the five days ranged from 21.38-78.39 mg/m^3. The authors state that workers were continuously exposed to DMAC vapours (inhalation and skin) and frequently had skin contact with the product. Biological monitoring spot urine samples were collected from eight exposed workers and four referents each day just before and immediately after work during the 5-day workshift. In addition the exposed workers were asked to provide an urine sample on the Monday morning following the weekend. The urine NMAC concentration of exposed workers was 25.2 ± 14.3 mg NMAC/L. This was higher than the NMAC concentration of the control group which was 1.25 ± 0.39 mg NMAC/L. A half-life of 16 hours (± 2 hours) was derived. During the workweek a build up of the concentration was noticeable. Post-shift concentrations in urine ranged from 7.07-200.4 µmol/mmol creatinine.

OECD indicates that inhalation exposure to DMAC due to escaping vapours is possible during secondary spinning (OECD, 2001). Confirmation at fibre customers (textile converters) has shown that exposure levels in e.g. Ring Spinning or Open-End Spinning systems are <0.36 mg/m^3. In tow processing at the carding machines exposure levels are reported to be <18 mg/m^3. According to the authors dermal exposure from hand contact with acrylic fibres containing DMAC does not occur with dry skin. If the skin is sweaty, the maximum daily potential is approximately 10 µg/kg (0.7 mg/day).

Table 51: Measured DMAC inhalation exposure concentrations during the use of DMAC in the production of man-made fibres

Study	GM* Concentration (mg/m^3)	Min (mg/m^3)	Max (mg/m^3)	90-percentile (mg/m^3)	Potential dermal dose rate (mg/day)	Remarks
Primary fibre production						
(Kennedy Jr & Pruett, 1989)	3.96	1.82	12.29			
(Spies et al., 1995a)	7.75					
(OECD, 2001)	<0.36 – 9.3		51.35		650-3,900	
(Perbellini et al., 2003)	5.34		36			
(Duarte, 2015)	<7.13 - 36		>36			
(DGUV, 2012)	<LOQ – 5			0.15 – 9.8		Stationary
(DGUV, 2012)	<LOQ – 0.2			0.68 – 4		Personal (with and without LEV)
(SZW, 2017b)	8.55		13.18			

Study	GM* Concentration (mg/m³)	Min (mg/m³)	Max (mg/m³)	90-percentile (mg/m³)	Potential dermal dose rate (mg/day)	Remarks
(Antoniou et al., 2021)				3.6 - >32.10		
Secondary fibre processing						
(Borm et al., 1988)	21.38	2.49	184			
(OECD, 2001)	<17.82				0.7	

* Geometric mean

Table 52: Biological monitoring - post-shift urine concentrations in mg NMAC/g creatinine (unless otherwise indicated)

Study	Job-title	GM* (mg NMAC/g creatinine)	Range (mg NMAC/g creatinine)	Remarks
Primary fibre production				
(Kennedy Jr & Pruett, 1989)	Operator (n=3)	11.78 (mg/L urine)	7 – 20 (mg/L urine)	
(Kennedy Jr & Pruett, 1989)	Non-DMAC operator (n=1)	17.75 (mg/L urine)	13-26 (mg/L urine)	
(Spies et al., 1995a)	Operator (n=55)	1.7	2.4	First day, before shift
(Spies et al., 1995a)	Operator (n=54)	15.4	2.7	First day, end of shift
(Spies et al., 1995a)	Operator (n=57)	8.9	3.1	Second day, before shift
(Spies et al., 1995a)	Operator (n=335)	16.1	2.5	Second day, end of shift
(Spies et al., 1995a)	Operator (n=98)	26.7	2.7	High exposure group
(Spies et al., 1995a)	Operator (n=295)	13.5	2.3	Unspecified exposure group
(Spies et al., 1995a)	Operator	35 (80-percentile)		
(Kawai et al., 1997)	Operators		<78 (mg/L urine)	
(Perbellini et al., 2003)	All operators (post-shift, n=223).	20.5	1.5-173.6	The task of most workers was to check the automatic production of fibres. Every day, two groups of six workers started up two or three spinning machines (duration about 30 minutes), which would then work continuously for about 15

Study	Job-title	GM* (mg NMAC/g creatinine)	Range (mg NMAC/g creatinine)	Remarks
				days except for occasional unscheduled stoppages.
(Perbellini et al., 2003)	Starting up of machinery (pre-shift, n=35)	7.3	1.5-30.6	During machine startup Operations (duration about 30 minutes), some workers had to immerse their hands (protected by gloves) in a water/DMAC solution (50%) at a temperature of 50 °C. 17 workers (belonging to the 2nd, 4th, and 6th teams) were supplied with an active charcoal mask. Workers in the 1st, 3rd, and 5th teams did not use a mask.
(Perbellini et al., 2003)	Starting up of machinery (halfway through the shift, n=35)	7.8	1.5-26.5	
(Perbellini et al., 2003)	Starting up of machinery (post-shift, n=35)	14.2	5.6-44.6	
(Perbellini et al., 2003)	Starting up of machinery (n=18)	12.8	6.6-24.3	Post-shift. Without mask
(Perbellini et al., 2003)	Starting up of machinery (n=17)	15.7	5.6-44.6	Post-shift. With mask
(Perbellini et al., 2003)	Starting up of machinery (n=18)	12.6	6.4-24-3	Post-shift. No immersion of hands
(Perbellini et al., 2003)	Starting up of machinery (n=16)	14.5	5.6-44.6	Post-shift. Immersion of hands
(Perbellini et al., 2003)	Starting up of machinery (n=17)	2.5	1.5-10.3	First day after two days rest, pre-shift.
(Perbellini et al., 2003)	Starting up of machinery (n=14)	10.8	2.7-21.9	First day, post-shift. With end of shift shower and change of clothing.
(Perbellini et al., 2003)	Starting up of machinery (n=13)	4.7	1.5-11.7	Second day (16 hours later), pre-shift.
(Perbellini et al., 2003)	Starting up of machinery (n=14)	17.6	7.1-28-2	Second day, post-shift. With end of shift shower and change of clothing.
(Perbellini et al., 2003)	Starting up of machinery (n=13)	4.9	2.7-7.1	Third day (24 hours later), pre-shift.
(Lee et al., 2006)	DMAC induced hepatic injuries (DIHI) group (503 samples)	19.6	2.2-196.5	
(Lee et al., 2006)	Non-DIHI group (464 samples)	5.2	0.1-79.2	
(Jung et al., 2007)	DMAC induced hepatic injury group (packing, exchanging spinneret, visual inspection) (n=21 cases / 228 samples)	25.1	4.6-196.5	

Study	Job-title	GM* (mg NMAC/g creatinine)	Range (mg NMAC/g creatinine)	Remarks
(Jung et al., 2007)	Other workers not part of DIHI group (n=1,056 samples)	11.8	0.1-133.9	
(Duarte, 2015)	Group A	<LOQ		Control group (no DMAC exposure)
(Duarte, 2015)	Group B	2.93 (0.26 mg DMAC/L)		Expected inhalation exposure <7.2 mg/m^3
(Duarte, 2015)	Group C	18.35 (0.60 mg DMAC/L)		Expected inhalation exposure 7.2-36 mg/m^3
(Duarte, 2015)	Group D	40.04 (2.91 mg DMAC/L)		Expected inhalation exposure >36 mg/m^3
(Duarte, 2015)	Dope preparation (n=5)	69.89		Dissolve polymer in DMAC
(Duarte, 2015)	Spinning (n=20)	45.35		Fibre is subjected to: coagulation, extrusion, washing, dyeing, drying and crimping.
(Duarte, 2015)	Tow-to-top (n=4) ##	6.60		Continuous filaments from cut and bailing area are subjected to opening, carding, spinning and packaging.
(Duarte, 2015)	Other	<6.45		All other work areas: solvent recovery, cut and bailing, open-end-spinning, pilot plant and laboratory.
(Tutkun et al., 2019)	Control group (101)	0.06 (mg DMAC/L urine)		
(Tutkun et al., 2019)	Group 2	2.43 (mg DMAC/L urine)		Operators whose previous urinary DMAC levels were between 1-3 mg/L.
(Tutkun et al., 2019)	Group 3	3.17 (mg DMAC/L urine)		Operators whose previous urinary DMAC levels were between >3 mg/L.
Secondary fibre processing				
Study	**Job-title**	**GM* (mg/g creatinine)**	**Range (mg/g creatinine)**	
(Borm et al., 1988)	Operator A (n=3)	41.42	11.69-129.5	
(Borm et al., 1988)	Cleaner (n=1)	50.21	36.37-73.45	
(Borm et al., 1988)	Operator B (n=2)	54.65	32.24-101.6	
(Borm et al., 1988)	Inspection (n=2)#	8.71	<LOD – 14.6	

* Geometric mean

These workers worked 4 hours per day instead of the others who worked 8 hours per day.

DMAC is not used, but residual levels of DMAC are present in fibres (≈0.01%)

B.9.7 Use as solvent in coatings

B.9.7.1 General information

Approximately 3-5% of DMAC in the EU is used as solvent in coatings for industrial use. The only use which has been described in detail (during consultations with industry) is the use of the DMAC in the production of PAI enamels (varnishes) used for electrical wire insulation, but manufacturers of DMAC have indicated that it is used for other coatings as well. Some coatings may be applied in industrial settings by spraying, roller application/brushing or dipping, as indicated in some registration dossier(s).

The use of DMAC in the enamelling process is comparable to the use of NMP and is described in more detail in the guidance for users of NMP document (ECHA, 2019). The enamel is slowly and constantly extruded through a small tube, the wire is pulled through the enamel at the tip of the tube.. This specific application of the enamel to the wire is considered to be a PROC10 application by the dossier submitter whilst new type of enamelling machines are more associated with PROC2 scenarios. Applied DMAC in the PAI enamels is anticipated to be decomposed at the elevated temperatures at which the application of the enamels in industrial settings takes place. The average concentration of DMAC in the enamel is 10% (ECHA, 2012a). It is unclear if NEP is used in the wire coating sector as contradicting information was received from registrants and the EWWA sector. As a conservative approach the Dossier Submitter included the use of NEP in the enamelling process by including PROC2 and PROC10 scenarios.

NEP is used in coatings like paints, ink, toners and adhesives. It was found in varnishing of hard plastic components in an automobile plant (Koslitz et al., 2014).

The use of DMAC and NEP as laboratory chemical and laboratory analysis, charging and discharging activities and manual maintenance (including equipment cleaning) are described in separate exposure scenarios. The production of coatings is described in exposure scenario formulation.

B.9.7.2 Exposure estimation

The use of DMAC and NEP as solvent during the application of industrial coatings is reflected in the registrants' CSRs by contributing scenarios PROC7, PROC10 and PROC13. In addition PROC2 for new type of enamel machines is included for both DMAC and NEP. For NEP also professional use is described, reflected by contributing scenarios PROC10, PROC11, PROC13 and PROC19.

DMAC
In general, the exposure of DMAC used in coatings may occur during the application of coatings by spraying, roller application/brushing or dipping. These coating applications were mentioned to be automated; therefore no worker exposure would be associated with the respective registered processes such as industrial spraying / roller / brushing and pouring (ECHA, 2012a).

Specifically for the use of DMAC in enamels, industry explained that the enamel application for copper wires for the electronics sector is a specific process where enamels are directly applied on the running wire in the ovens in a closed system. All plants in Europe were mentioned to be fitted with recycling ovens and catalyst systems, where DMAC is evaporated and mineralized (ECHA, 2012a).

An eight hour exposure duration and a DMAC weight fraction of 0.05-0.25 (5-25%) are selected for all contributing scenarios. For all contributing scenarios except for PROC2 the use of gloves (APF10 90%) and LEV (90-95%) is applied in the exposure assessment. A low fugacity category is applied, based on the DMAC vapour pressure of 200 Pascal. For PROC2 and PROC10 (the application of DMAC in the wire-coating process) in addition a medium fugacity category is applied, as this process is reported to take place at elevated temperatures.

NEP
An eight hour exposure duration is selected for all contributing scenarios. NEP is assumed to be present in a weight fraction in the range of 0.05-0.25 (5-25%) in coatings like paints, ink, toners and adhesives. The use of gloves (APF5-10 80-90%) and LEV (80-95%) are applied in the exposure assessment, except for PROC2. For spraying activities in a professional setting (PROC11) in addition the use of a respirator (APF10, 90%) is selected. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. For PROC2, PROC10 and PROC13 two contributing scenario are estimated. The first scenario with a low fugacity category. The second scenario with a medium fugacity category, based on a reported activity temperature up to 130 °C (PROC13).

B.9.7.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of DMAC and NEP as a solvent in the application of industrial and professional coatings. The estimated inhalation concentrations for DMAC, based on the identified contributing scenarios, are in the range of 2.14-10.69 mg/m^3.

Table 53: Calculated exposures for the use of DMAC as a solvent in industrial coatings using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
2	8	<0.25	Indoors	No	No	2.14	0.82	1.13
7	8	<0.25	Indoors with LEV (95%)	No	Yes (90%)	10.69	2.57	4.10
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.14	1.65	1.95
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.14	0.82	1.13
Exposure estimates at elevated temperatures (medium fugacity category)								
2	8	<0.25	Indoors	No	No	10.69	0.82	2.35
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	10.69	1.65	3.17

Very little information is available in the open literature on the inhalation exposure during surface coating. DGUV presents an overview of 24 stationary exposure measurements collected in 9 companies in the period of 2000-2011 (DGUV, 2012). It presents stationary DMAC inhalation exposure measurement results with a measurement duration >6 hours during surface coating. The 90-percentile inhalation exposure value during surface coating is reported to be 3.22 mg/m^3.

In a response to the Comments Document on ECHA's Draft 4th Recommendation for N,N-Dimethylacetamide a French company, and repeated by the trade organization Europacable, comments that in 2010 and 2011 both short term and shift exposures showed that exposure was each time less than 10% of the OEL (without taking into account the personal protective

equipment effect) (#12 and #20 in ECHA, 2012d). The comment does not state which limit value is intended, the French OEL of 7.2 mg/m³ or the more general European value of 36 mg/m³. No further reference or details with regard to RMM and OC are given.

Table 54: Measured DMAC inhalation exposure concentrations during the use of DMAC as solvent in the production of industrial coatings

Study	GM* Concentration (mg/m³)	Min (mg/m³)	Max (mg/m³)	90-percentile (mg/m³)	Potential dermal dose rate (mg/day)	Remarks
(DGUV, 2012)	<LOQ#			3.22		Stationary
(ECHA, 2012d)	<0.72-3.6					

* Geometric mean

The number of measurements below the limit of quantification (LOQ) is higher than the number of measurements above the LOQ. Therefore the authors did not present the geometric mean (GM) concentration.

Table 55: Calculated exposures for the use of NEP as a solvent in coatings using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
Industrial setting								
2	8	<0.25	Indoors	No	No	2.78	0.82	1.22
7	8	<0.25	Indoors with LEV (95%)	No	Yes (90%)	13.88	2.57	4.56
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	1.65	2.04
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	0.82	1.22
Exposure estimates at elevated temperatures (medium fugacity category)								
2	8	<0.25	Indoors	No	No	13.88	0.82	2.81
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	13.88	1.65	3.63
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	13.88	0.82	2.81
Professional setting								
10	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	13.88	3.29	5.28
11	8	<0.25	Indoors with LEV (80%)	Yes (90%)	Yes (80%)	5.55	12.86	13.65
13	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	5.55	1.65	2.44
19	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	13.88	16.97	18.96

Exposure to NEP was demonstrated during varnishing of hard plastic components in an automobile plant (Koslitz et al., 2014). Two specific biomarkers of exposure, 5-hydroxy- N-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy- N-ethylsuccinimide (2-HESI), were analyzed in urine samples of 14 workers. For this purpose, pre-shift, post-shift and next day pre-shift urine samples were collected midweek. Twelve workers performed regular work tasks (loading, wiping and packing), whereas two workers performed special work tasks including cleaning the sprayer system with organic solvents containing N-alkyl-2-pyrrolidones (mainly NMP). Spot urine samples of nine non-exposed persons of the same plant served as controls. Median post-shift urinary levels of workers with regular work tasks (5-HNEP: 0.18 mg/g creatinine; 2-HESI: 0.18 mg/g creatinine) were ~6-fold higher compared to the controls (0.02-0.03 mg/g creatinine). Maximum levels were 17.00 mg/g creatinine (5-HNEP) and 4.63 mg/g creatinine (2-HESI) in workers with special cleaning tasks. NB: the varnishes and

solvents contained NMP (known due to compulsory labeling) but no information was available whether they also contained NEP.

Table 56: Biological monitoring - urine 5-HNEP and 2-HESI concentrations in mg/g creatinine

Study	Job-title	Median (mg/g creatinine)	Range (mg/g creatinine)	Remarks
(Koslitz et al., 2014)	Controls (n=9)	0.02 (5-HNEP) 0.03 (2-HESI)	<LOD-0.46 (5-HNEP) <LOD-0.63 (2-HESI)	Post-shift
	Regular work tasks (n=12)	0.10 (5-HNEP) 0.18 (5-HNEP) 0.11 (5-HNEP) 0.12 (2-HESI) 0.18 (2-HESI) 0.17 (2-HESI)	0.02-2.86 (5-HNEP) 0.06-2.56 (5-HNEP) 0.01-3.47 (5-HNEP) 0.04-3.46 (2-HESI) 0.03-2.40 (2-HESI) 0.04-4.52 (2-HESI)	Pre-shift Post-shift Pre-shift 2 Pre-shift Post-shift Pre-shift 2
	Special cleaning tasks (n=2)		0.27-0.60 (5-HNEP) 0.83-1.10 (5-HNEP) 2.52-17.00 (5-HNEP) 1.10-1.23 (2-HESI) 0.84-0.98 (2-HESI) 1.95-4.63 (2-HESI)	Pre-shift Post-shift Pre-shift 2 Pre-shift Post-shift Pre-shift 2

B.9.8 Use as solvent in the production of films

B.9.8.1 General information

DMAC is considered to be a good solvent for polyimide resins used in film production. It is also reported as the "ideal" solvent for the production of dialyser membranes, based on polysulphones. DMAC is used in the EU by the medical device industry as a solvent for production of filters and membranes, which then are used in dialysis treatment and other lifesaving extracorporeal therapies. DMAC serves as solvent in the spinning solution consisting of polysulphone and poly-N-vinylpyrrolidone, in a continuous wet spinning process, as it is the state of art for hollow fibre production. Residual DMAC is present in membranes (below 0.01% in membranes for medical devices) used by downstream users (ECHA, 2012a).

Industry stated that residual DMAC is removed during processing from some of the films by downstream users, which takes place at temperatures between 90 and 180 °C. The released DMAC is removed from the waste stream typically by incineration. It was also stated that in other films DMAC remains contained through the life cycle even if the films are processed at temperatures up to 400 °C (DMAC has strong affinity to polymer, therefore even at extreme temperatures only an insignificant amount could be released). With any theoretical leaching during the waste stage claimed to be not an issue, as the waste will be handled properly, and DMAC is biodegradable and does not bioaccumulate.

B.9.8.2 Exposure estimation

The use of DMAC as solvent in the production of films is considered to be covered by the exposure scenario 'Use as solvent in the production of man-made fibres'.

B.9.8.2.1 Workers exposure

Communication with industry indicates that the inhalation exposure estimates might not be conservative enough and that exposure can be underestimated.

Gong et al. presents inhalation exposure measurement results in a polyimide film factory in China (Gong et al., 2016). Nine personal air samples were collected during the production process in which 4,4-diaminodiphenyl and pyromellitic anhydride were employed as raw materials, with DMAC as the solvent. After combining them to synthetize polyamide acid, defoaming and stretching process were involved to generate the end-products. The production equipment mainly included reactor, vacuum degassing vessel, filter, hopper, casting and winding machines, along with hot air systems. The employee (shift leader and operator) worked fixed 12-hours schedules in two shifts. The daily tasks consisted of routing inspection on equipment and production process, solvent extraction and recovery as well as reactor operation at the resin synthesis area, during which time direct exposure to DMAC could occur. Though the workshop was equipped with a local ventilation system, the employees indicated that it did not always function properly. A distinct pungent odor was noticeable during the exposure measurements. Long-sleeved coveralls and gauze masks were provided to the workers. The 8-hour time-weighted average DMAC concentration was reported to be 12.8 mg/m^3. However, the 15-minute short-term exposure concentrations at the inspection site of film transition, solvent extraction area and the reactor were reported to be 45.0, <6.6 and 10.90 mg/m^3, respectively.

Table 57: Measured DMAC inhalation exposure concentrations during the use of DMAC in the production of films

Study	GM* Concentration (mg/m^3)	Min (mg/m^3)	Max (mg/m^3)	90-percentile (mg/m^3)	Potential dermal dose rate (mg/day)
(Gong et al., 2016)	12.8	6.6	45		

* Geometric mean

B.9.9 Manual maintenance (cleaning and repair) of machinery

B.9.9.1 General information

Manual maintenance of machinery takes place at different stages of the life-cycle of DMAC and NEP. Depending on the life-cycle stage these activities occur more or less frequently, in indoor or outdoor situations and with varying duration of exposure.

During manufacture exposures to DMAC are likely to be highest during maintenance operations, in particular in the absence of adequate PPE (ECHA, 2011a, 2012a).

B.9.9.2 Exposure estimation

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

DMAC
An eight hour exposure duration is considered for both contributing scenarios and a DMAC weight fraction of 1 (100%). For indoor maintenance activities the use of gloves (APF10 90%), LEV (90%) and RPE (APF10, 90%) are applied in the exposure assessment, based on industry common practice. For outdoor activities instead of LEV a ventilation (dilution) factor of 30%

is applied (ECETOC, 2012). A low fugacity category is applied based on the DMAC vapour pressure of 200 Pascal.
NB: The Dossier Submitter remarks that the use of RPE during the whole eight hour working shift should not be recommended. It is believed that in practice however the actual exposure duration will be shorter than the eight hours applied here in the exposure assessment. Also in some downstream user applications the concentration of DMAC will be less than 100%.

NEP
An eight hour exposure duration is considered for both contributing scenarios with a NEP weight fraction of 1 (100%) for industrial settings and 0.25 (25%) for professional settings. For indoor maintenance activities the use of gloves (APF5-10 80-90%), LEV (80-90%) and RPE (APF10, 90%) are applied in the exposure assessment. For outdoor activities instead of LEV a ventilation (dilution) factor of 30% is applied (ECETOC, 2012). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.9.2.1 Workers exposure

Below the ECETOC TRA v3.1 calculated exposures are given for exposure to DMAC and NEP during manual maintenance activities.

Table 58: Calculated DMAC exposures during manual maintenance activities using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
28[#]	8	1	Indoors with LEV (90%)	Yes (90%)	Yes (90%)	0.36	1.37	1.42
28[#]	8	1	Outdoors (30%)	Yes (90%)	Yes (90%)	2.49	1.37	1.73

[#] PROC28 applying ECETOC TRA v3.1 PROC8a input parameters

DMAC concentrations were measured in five workers for four consecutive weeks, including one machine repair man (Kennedy Jr & Pruett, 1989). Weekly inhalation exposure concentrations ranged from 0.89-8.66 mg/m^3 with a geometric mean week value of 3.51 mg/m^3. In addition to air monitoring also post-shift urine samples were collected. Weekly mean DMAC values in urine of 9.19 mg/L urine were observed with daily values ranging from 8-11 mg/L urine.

The OECD summarized measurement data of DuPont for maintenance personnel associated with the manufacture and processing of DMAC and estimates a task inhalation exposure concentration of <3.5 mg/m^3 (task duration 0.25-1 hour) (NB: from the report it is not clear if the central tendency concentration value or the high-end value is given) (OECD, 2001). Potential dermal dose rate was estimated (assumingly using the EASE exposure model) to be in the range of 1,300-1,900 mg/day (18,6-27,1 mg/kg bw/day) with no dermal protection assumed and a concentration weight factor of 1.

81 workers of an acrylic fibre production plant were divided into four exposure groups, based on exposure data collected by industry data in the period of 2013-2014 (no reference indicated) (Duarte, 2015). Biological monitoring urine samples were collected post-shift (the exact day of the week was not indicated). Mechanical maintenance area activities resulted in urinary NMAC levels of 6.45 mg/g creatinine.

Table 59: Measured DMAC inhalation exposure concentrations during manual maintenance activities

Study	Concentration (mg/m^3)	Min (mg/m^3)	Max (mg/m^3)	Task description
(Kennedy Jr & Pruett, 1989)	3.51	0.89	8.66	Machine repairman (n=1 / 20 samples)
(OECD, 2001)	3.5			Maintenance personnel

Table 60: Biological monitoring - post-shift urine concentrations in mg NMAC/g creatinine (unless otherwise indicated)

Study	Job-title	GM* (mg NMAC/g creatinine)	Range (mg NMAC/g creatinine)	Remarks
(Kennedy Jr & Pruett, 1989)	Machine repairman (n=1)	9.19 (mg/L urine)	8-11 (mg/L urine)	
(Duarte, 2015)	Mechanic Maintenance (n=2)	6.45		Maintenance of equipment in contact with DMAC

* Geometric mean

Table 61: Calculated NEP exposures during manual maintenance activities using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
Industrial setting								
28#	8	1	Indoors with LEV (90%)	Yes (90%)	Yes (90%)	0.46	1.37	1.44
28#	8	1	Outdoors (30%)	Yes (90%)	Yes (90%)	3.24	1.37	1.83
Professional setting								
28#	8	<0.25	Indoors with LEV (80%)	Yes (90%)	Yes (80%)	1.39	1.65	1.84
28#	8	<0.25	Outdoors (30%)	Yes (90%)	Yes (80%)	4.86	1.65	2.34

PROC28 applying ECETOC TRA v3.1 PROC8a input parameters

B.9.10 Use as laboratory chemical

B.9.10.1 General information

DMAC and NEP are used as laboratory chemicals in research and development activities. During manufacturing and use quality analysis takes place in laboratory settings.

DMAC
In the production of fibres linear density analysis are performed. Further down the supply chain DMAC is used as laboratory chemical in a wide range of applications.

B.9.10.2 Exposure estimation

The use of DMAC and NEP as laboratory chemicals is reflected by contributing scenario PROC15. Within a laboratory setting risk management measures like LEV or a fume cupboard can be considered to be available. The use of LEV would be anticipated to reduce inhalation exposure by at least 50% and handling within a fume cupboard would reduce exposure by at least a factor of 10 (90%). Similarly the use of appropriate gloves would be expected to significantly reduce the extent of dermal exposure (ECHA, 2011a).

DMAC
An eight hour exposure duration is considered for both industrial and professional contributing scenarios and a DMAC weight fraction of 1 (100%). The use of gloves (APF5-10 80-90%) and LEV (80-90%) are applied in the exposure assessment. A low fugacity category is applied based on the DMAC vapour pressure of 200 Pascal. However some analyses are reported to take place at elevated temperatures. Depending on this higher temperature a medium or high fugacity should be selected for situations were exposure to DMAC at elevated temperatures occurs. Applying a medium or high fugacity category for PROC15 with the same RMM would result in inhalation exposure estimates that are 2-10 times higher than the exposure estimates for the low fugacity category.

NEP
An eight hour exposure duration is considered for both industrial and professional contributing scenarios and a NEP weight fraction of 1 (100%). The use of gloves (APF5-10 80-90%) and LEV (80-90%) are applied in the exposure assessment. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.10.2.1 Workers exposure

Below the ECETOC TRA v3.1 calculated exposures are given for the use of DMAC and NEP as laboratory chemical.

Table 62: Calculated exposures for the use of DMAC as laboratory chemical using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
15	8	1	Indoors with LEV (90%) – Industrial setting	No	Yes (90%)	1.78	0.034	0.29
15	8	1	Indoors with LEV (80%) – professional setting	No	Yes (80%)	3.56	0.068	0.58

81 workers of an acrylic fibre production plant were divided into four inhalation exposure groups, based on exposure data collected by industry in the period of 2013-2014 (no reference indicated) (Duarte, 2015). In addition to air monitoring results also biological monitoring urine samples were collected post-shift (the exact day of the week was not indicated). Employees working in the laboratory have urinary NMAC levels clearly below 5 mg/g creatinine.

Table 63: Biological monitoring - post-shift urine concentrations in mg NMAC/g creatinine (unless otherwise indicated)

Study	Job-title	GM* (mg NMAC/g creatinine)	Range (mg NMAC/g creatinine)	Remarks
(Duarte, 2015)	Laboratory (n=7)	<5		Laboratory

* Geometric mean

Table 64: Calculated exposures for the use of NEP as laboratory chemical using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
15	8	1	Indoors with LEV (90%) – Industrial setting	No	Yes (90%)	2.31	0.034	0.36
15	8	1	Indoors with LEV (80%) – professional setting	No	Yes (80%)	4.63	0.068	0.73

B.9.11 NEP - Use as binder and release agent

B.9.11.1 General information

This exposure scenario describes the industrial and professional use of NEP as binder and release agent.

B.9.11.2 Exposure estimation

The use of NEP as binder and release agent is reflected by contributing scenario PROC6, PROC7, PROC10, PROC13 and PROC14 for industrial settings and contributing scenarios PROC10, PROC11 and PROC13 for professional settings.

NEP
An eight hour exposure duration is considered for both industrial and professional contributing scenarios. The binders and release agents are mixtures in which NEP is reported to be present in a weight fraction in the range of 0.05-0.25 (5-25%). The use of gloves (APF5-10 80-90%) and LEV (80-95%) are applied in the exposure assessment. For spraying activities in a professional setting (PROC11) additionally the use of a respirator (APF10, 90%) is selected. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.11.2.1 Workers exposure

Below the ECETOC TRA v3.1 calculated exposures are given for the use of NEP as binder and release agent.

Table 65: Calculated exposures for the use of NEP as binder and release agent using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
Industrial setting								
6	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	1.39	1.65	1.84
7	8	<0.25	Indoors with LEV (95%)	No	Yes (90%)	13.88	2.57	4.56
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	1.65	2.04
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	0.82	1.22
14	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	1.39	0.21	0.40
Professional setting								
10	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	13.88	3.29	5.28
11	8	<0.25	Indoors with LEV (80%)	Yes (90%)	Yes (80%)	5.55	12.86	13.65
13	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	5.55	1.65	2.44

B.9.12 NEP - Use in cleaning agents

B.9.12.1 General information

This exposure scenario describes the industrial and professional use of NEP in cleaning agents. BASF describes in its sales folder for solvents that NMP and NEP have been employed as an ingredient in paint removers, cleaners and degreasers because of its solvent power for plastics, resins, oils and grease (BASF, 2016). NEP has also been used as an alternative for NMP in paint and varnish strippers and graffiti removers (Brushia, 2019), which is confirmed by the data in various SDSs that indicate NEP concentrations up to 100%. Among the applications are the use in the electronic industry, in the medical sector and in the automotive sector (cleaning diesel intake part).

B.9.12.2 Exposure estimation

The use of NEP in cleaning agents is reflected by contributing scenario PROC7, PROC10 and PROC13 for industrial settings and contributing scenarios PROC10, PROC11 and PROC13 for professional settings.

An eight hour exposure duration is considered for both industrial and professional contributing scenarios. NEP used in cleaning agents is assumed to be present in a weight fraction in the range of 0.05-0.25 (5-25%). The use of gloves (APF5-10 80-90%) and LEV (80-95%) are applied in the exposure assessment. For spraying activities in a professional setting (PROC11) in addition the use of a respirator (APF10, 90%) is selected. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. For PROC13 also a scenario with a medium fugacity category is estimated, based on a reported activity temperature up to 130 °C.

B.9.12.2.1 Workers exposure

Below the ECETOC TRA v3.1 calculated exposures are given for the use of NEP in cleaning agents.

Table 66: Calculated exposures for the use of NEP in cleaning agents using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
Industrial setting								
7	8	<0.25	Indoors with LEV (95%)	No	Yes (90%)	13.88	2.57	4.56
10	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	1.65	2.04
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	0.82	1.22
Exposure estimates at elevated temperatures (medium fugacity category)[#]								
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	13.88	0.82	2.81
Professional setting								
10	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	13.88	3.29	5.28
11	8	<0.25	Indoors with LEV (80%)	Yes (90%)	Yes (80%)	5.55	12.86	13.65
13	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	5.55	1.65	2.44

[#] Operating temperature up to 130 °C

B.9.13 Use of NEP in oil field drilling and production operations

B.9.13.1 General information

The use of NEP in oil field drilling and production operations (industrial as well as professional setting) is described by one registrant. For this dossier only industrial use is considered to be relevant. No specific information has been found by the Dossier Submitter on this application.

B.9.13.2 Exposure estimation

The use of NEP in oil field drilling is reflected by contributing scenario PROC1-4, PROC8a and PROC8b. The charging and discharging activities (PROC8a and PROC8b) are described in the exposure scenario charging and discharging.

An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. For PROC4 – where opportunity for exposure arises – LEV (90%) and the use of gloves (APF10, 90%) are applied.

B.9.13.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in oil field drilling and production operations.

Table 67: Calculated exposures for use of NEP in oil field drilling and production operations using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate long-term inhalation (mg/m3)	Exposure estimate long-term dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02

B.9.14 Use of NEP in agrochemicals

B.9.14.1 General information

The professional use of NEP in agrochemicals is described by one registrant. The use of NMP in agrochemicals has been described as the application as Co-formulant in herbicide, pesticide and fungicide formulations (Hunt & Dale, 2018) and the chemical similarity suggests that for NEP this may be the same. One of the SDSs for NEP (>99.5% NEP) indicates the use for the production of refined oil, lithium ion batteries, pharmaceuticals, pesticides among others. However, actual information on the application of NEP is lacking.

B.9.14.2 Exposure estimation

The use of NEP in agrochemicals is described by contributing scenario's PROC1, PROC2, PROC4, PROC8a, PROC8b, PROC11 and PROC13. The manufacturing and formulation activities (PROC1, PROC2 and PROC4) and the charging and discharging activities (PROC8a and PROC8b) are described in separate exposure scenario elsewhere in this dossier. A mixing step is mentioned by the registrants. Therefore in addition contributing scenario PROC5 is added to the exposure assessment.

An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%). The use of gloves (APF5 80%) is applied for those situations were exposure arises (PROC5, PROC11 and PROC13). For spraying activities (PROC11) in addition the use of a respirator (APF10, 90%) is selected. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.14.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in agrochemicals.

Table 68: Calculated exposures for use of NEP in agrochemicals using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
5	8	1	Indoors	No	Yes (80%)	46.28	2.74	9.35
11	8	1	Indoors	Yes (90%)	Yes (80%)	46.28	21.43	28.04
13	8	1	Indoors	No	Yes (80%)	46.28	2.74	9.35

B.9.15 Use of NEP in functional fluids

B.9.15.1 General information

The industrial and professional use of NEP in functional fluids is described by one registrant. The use of NMP in functional fluids has been described as the application in cable oils, transfer oils, hydraulic fluids in industrial equipment, coolants, insulators, refrigerants (Hunt & Dale, 2018) and the chemical similarity suggests that for NEP this may be the same. However, actual information on the application of NEP is lacking.

B.9.15.2 Exposure estimation

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

An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1 (100%, industrial use) and 0.05-0.25 (5-25%, professional use). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal. For PROC4 LEV (90%) is applied. The use of gloves (APF5-10, 80-90%) is applied for PROC4 and PROC20.

B.9.15.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in functional fluids.

Table 69: Calculated exposures for use of NEP in functional fluids using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate (mg/kg combined bw/day)
Industrial setting								
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
Professional setting								
20	8	<0.25	Indoors	No	Yes (80%)	13.88	0.21	2.19

B.9.16 Use of NEP in road and construction applications

B.9.16.1 General information

The professional use of NEP in road and construction applications is described by one registrant. The use of NMP in road and construction applications has been described as the application in solvents, cleaners/strippers, adhesives/binders, de-fluxing and waterproofing (Hunt & Dale, 2018) and the chemical similarity suggests that for NEP this may be the same. The information in various SDSs confirms the use of NEP for the use sector building and construction (SU19) for some of the adhesives, coatings and putties. Three products (SDS > 2015) were identified for sealing of cement or concrete products and containing up to 7% NEP.

B.9.16.2 Exposure estimation

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

An eight hour exposure duration is considered for all contributing scenarios and a NEP weight fraction of 1. Activities are assumed to be carried out outdoors for which a dilution factor of 30% is applied (ECETOC, 2012).The use of gloves (APF5 80%) is applied in the exposure assessment. For spraying activities (PROC11) in addition the use of a respirator (APF10, 90%) is selected. A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.16.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in road and construction applications.

Table 70: Calculated exposures for use of NEP in road and construction applications using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
10	8	1	Outdoors (30%)	No	Yes (80%)	80.99	5.49	17.06
11	8	1	Outdoors (30%)	Yes (90%)	Yes (80%)	32.40	21.43	26.06
13	8	1	Outdoors (30%)	No	Yes (80%)	32.40	2.74	7.37

B.9.17 Use of NEP in polymer processing

B.9.17.1 General information

The industrial and professional use of NEP in polymer processing is described by one registrant. NEP is mainly used in water-based polyurethane dispersions (PUDs). In the production of PUDs often NMP and NEP are being used (Chemicals, 2022; Farmer et al., 2020).

B.9.17.2 Exposure estimation

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

An eight hour exposure duration is considered for all contributing scenarios. NEP used in polymer processing is assumed to be present in a weight fraction of 1 (100%) for the PROC1-5 contributing scenarios and in the range of 0.05-0.25 (5-25%) for the other scenarios. The use of LEV (80-90%) and gloves (APF5-10 80-90%) are applied for contributing scenarios where opportunity for exposure arises (PROC4-6, PROC13, PROC14 and PROC21). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.17.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in polymer processing.

Table 71: Calculated exposures for use of NEP in polymer processing using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
Industrial setting								
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
5	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	1.37	1.70
6	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	1.39	1.65	1.84
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	0.82	1.22
14	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	1.39	0.21	0.40
21[#]	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	-	-	-
Professional setting								
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	23.14	1.37	4.68
14	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	5.55	0.41	1.21
21[#]	8	<0.25	Indoors with LEV (80%)	No	Yes (80%)	-	-	-

[#] With ECETOC TRA for PROC21 only exposure to dust (solids) can be estimated

B.9.18 Use of NEP in water treatment chemicals

B.9.18.1 General information

The industrial use of NEP in water treatment chemicals is described by one registrant. No information has been found on the application by the Dossier Submitter.

B.9.18.2 Exposure estimation

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

An eight hour exposure duration is considered for all contributing scenarios. NEP used in water treatment chemicals is assumed to be present in a weight fraction of 1 (100%) for the PROC1-4 contributing scenarios and in the range of 0.05-0.25 (5-25%) for PROC13. The use of LEV (90%) and gloves (APF10 90%) are applied for contributing scenarios where opportunity for exposure arises (PROC4 and PROC13). A low fugacity category is applied based on the NEP vapour pressure of 18 Pascal.

B.9.18.2.1 Workers exposure

Below the ECECTOC TRA v3.1 calculated exposure concentrations are given for the use of NEP in water treatment chemicals.

Table 72: Calculated exposures for use of NEP in water treatment chemicals using ECECTOC TRA v3.1

PROC	Duration (max. hours/day)	Concentration (weight fraction)	Use of ventilation	Respiratory protection	Gloves protection (factor)	Exposure estimate inhalation long-term (mg/m3)	Exposure estimate dermal long-term (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day)
Industrial setting								
1	8	1	Indoors	No	No	0.046	0.034	0.041
2	8	1	Indoors	No	No	4.63	1.37	2.03
3	8	1	Indoors	No	No	13.88	0.69	2.67
4	8	1	Indoors with LEV (90%)	No	Yes (90%)	2.31	0.69	1.02
13	8	<0.25	Indoors with LEV (90%)	No	Yes (90%)	2.78	0.82	1.22

B.10. Risk characterisation

The risk characterisation is performed using the estimated exposure concentrations (based on ECETOC TRA v3.1) and comparing these results with the DNELs (Table 73) derived in this dossier by the Dossier Submitter. The resulting risk characterisation ratios (RCRs) for each industrial and professional use are described in this chapter.

- The derived RCRs are subsequently evaluated carefully using information on available exposure measurements and results from exposure model validation studies. Exposure models are a simplification of the actual work situation. Tier 1 exposure models like ECETOC TRA v3.1 should offer a conservative exposure estimate, preferably the 90th percentile value, representing the reasonable worst case exposure level of a distribution within a generally suitable dataset (i.e. a dataset corresponding to the conditions described in a contributing scenario), should be used as the exposure value for the risk characterisation (ECHA, 2016a). ECETOC TRA v3.1. presents the 75th percentile of the exposure distribution (ECETOC, 2012). It is assumed that exposure monitoring data provide a more realistic view of the exposure to DMAC or NEP at the workplace, although it is acknowledged by the Dossier Submitter that the number of studies is limited and do not reflect all workplaces within a sector. For exposure scenario where measurement results were available these measurement results were thoroughly evaluated. If the measurement results were found to be reliable and reflective of the assessed ES, the measurement results were used to adjust or support the initially derived RCRs.
- In recent years ECETOC TRA has been validated by different research groups. In these studies the contributing scenario (PROCs) estimates have been compared with exposure measurements results. Based on the available validation studies contributing scenarios (PROCs) were identified where the initial inhalation or dermal exposure concentration might be underestimated or the effect of LEV might be overestimated (Marquart et al., 2017; Schlueter & Tischer, 2020). Results of these validation studies are used by the Dossier Submitter to evaluate the derived RCRs. The main conclusions are presented below
    - For inhalation exposure a low level of conservatism was found for PROC5, PROC7, PROC14 and PROC19 contributing scenarios. An overestimation of the efficiency of LEV in actual workplaces is reported to occur for PROC7, PROC8a, PROC10, PROC13, PROC14, PROC19 contributing scenarios (Schlueter & Tischer, 2020).
    - For dermal exposure the validation results indicate that the model overestimates dermal exposure for situations where contact with the substance is expected to be

very limited (PROC1-3), with a 75th percentile of measured concentrations for PROC3 <0.001 mg/kg bw/day. For situations where high exposure values were found the model tended to underestimate exposure. PROCs with the highest initial exposure values in ECETOC TRA v3.1. are PROC6, PROC7, PROC10, PROC11, PROC17 and PROC19. The reduction effect of gloves was also evaluated by analyzing 11 datasets with measurements inside and outside of gloves. The average reduction per data set ranged between 80.5-99.99%, with six of the data sets having a reduction of >95% and an overall average reduction factor of 34 (± 97% reduction) (Marquart et al., 2017).

- The registrants used a higher DNEL in their registration dossiers. In these dossiers no RCRs >1 were found. To the Dossier Submitter it is not clear if all OC/RMM available in daily practice were taken into account in the registrants' exposure assessments. This might not have been necessary for exposure scenario where the RCR already was <1 by applying only a limited set of OC/RMM, resulting in a more worst-case exposure scenario. It is anticipated by the Dossier Submitter that for some processes the registrant could have applied OC/RMM used in practice, resulting in lower exposure estimates. Since specific workplace information is not available to the Dossier Submitter no refinements have been considered in the exposure estimations and derived RCRs.

The RCRs are given for the individual routes of exposure (inhalation and dermal) and are added together to present the risk for the combined exposure. Risks for the use of DMAC are identified for most PROCs described for the various uses in an industrial setting, indicated by RCRs >1. In general, from a risk perspective, dermal exposure is the critical exposure route for DMAC. Risks for the use of NEP are identified for many PROCs, indicated by RCRs >1. In general, from a risk perspective, inhalation exposure is the critical exposure route for NEP.

Table 73: DNELs for DMAC and NEP to be used in the calculation of RCRs

	DMAC	NEP
Inhalation DNEL (mg/m^3)	13	4
Dermal DNEL (mg/kg bw/day)	0.53	2.4

B.10.1. Manufacturing

B.10.1.1. Human health

B.10.1.1.1. Workers

DMAC

The calculated RCRs for the manufacturing processes of DMAC (PROC1-PROC3) are presented in Table 74.

Table 74: Manufacturing of DMAC for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
1	<0.01	0.064	0.067
2	0.27	2.58	2.86
3	0.82	1.30	2.12
High fugacity category			
1	<0.01	0.064	0.067
2	6.85	2.58	9.44
3	13.70	1.30	15.01

Conclusion

Manufacturing processes (PROC2 and PROC3) can lead to exposures above the DNELs, resulting in calculated combined RCRs of 2.12-2.86 for activities at room temperature. For activities at elevated temperature the combined RCRs increase to 9.44-15.01 mainly due to an increase in inhalation exposure. As the RCRs are above 1 a risk has been identified, even though the processes take place in closed system. Calculations for PROC1 showed combined RCR far below 1 (RCR=0.067) for activities at room temperature as well as activities at elevated temperate. Inhalation 8-hour average measurement results during manufacturing are reported to be <2.49 mg/m^3 (RCR=<0.20) indicating that the model estimations (especially for activities at elevated temperatures) are on the conservative side. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. Therefore no risk via inhalation and dermal exposure is identified.

NEP

The calculated RCRs for the manufacturing processes of NEP (PROC1-PROC4) are presented in
Table 75.

Table 75: Manufacturing of NEP for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86
Medium fugacity category			
1	0.012	0.014	0.026
2	5.79	0.57	6.36
3	11.57	0.29	11.86
4	2.31	0.29	2.60

Conclusion

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

B.10.2. Formulation

B.10.2.1. Human health

B.10.2.1.1. Workers

DMAC

The calculated RCRs for the formulation of DMAC (PROC3-PROC5) are presented in Table 76.

Table 76: Formulation of DMAC for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
3	0.82	1.30	2.12
4	0.14	1.29	1.43
5	0.14	2.59	2.72
5 (no LEV)	1.37	2.59	3.96

Conclusion

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

NEP

The calculated RCRs for the formulation of NEP (PROC1-PROC5 and PROC14) are presented in Table 77.

Table 77: Formulation of NEP for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86
5	0.58	0.57	1.15
5 (medium fugacity)	5.79	0.57	6.36
14	0.58	0.14	0.72

Conclusion

Formulation processes (PROC2, PROC3 and PROC5) at room temperature can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.15-3.76. For activities at elevated temperature (PROC5) the combined RCR increases to 6.36 due to an increase in inhalation exposure. As the RCRs are above 1 a risk has been identified. Calculations for PROC1, PROC4 and PROC14 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3

situations. In addition for PROC5 activities for liquids, ECETOC TRA validation studies (Schlueter & Tischer, 2020) indicate a low level of conservatism. For PROC2, PROC3 and PROC5 activities a risk is identified, mainly due to inhalation exposure, which cannot be excluded by model validation study results.

B.10.3. Charging and discharging

B.10.3.1. Human health

B.10.3.1.1. Workers

DMAC

The calculated RCRs for charging and discharging activities with DMAC (PROC8a, PROC8b and PROC9) are presented in
Table 78.

Table 78: Charging and discharging of DMAC for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
8a	0.27	2.59	2.86
8b	0.069	2.59	2.66
8b (no LEV)	1.37	2.59	3.96
9	0.14	1.29	1.43
Medium fugacity category			
8a	1.37	2.59	3.96
8b	0.34	2.59	2.93
9	1.37	1.29	2.66

Conclusion

Charging and discharging processes at room temperature as well as at elevated temperatures can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.43-3.96. As the RCRs are above 1 a risk is identified. Measurement results during charging and discharging show a wide variation in exposure, with measurement results reported to be below 5.27 mg/m3 (RCR=0.41). It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a contributing scenarios. Together with the identified risk via dermal exposure the identified risks for these activities remain.

NEP

The calculated RCRs for charging and discharging activities with NEP in an industrial and professional setting (PROC8a, PROC8b and PROC9) are presented in
Table 79.

Table 79: Charging and discharging of NEP for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
8a (with LEV)	1.16	0.57	1.73
8a (no LEV)	11.57	0.57	12.14
8b (with LEV)	0.29	0.57	0.86
8b (no LEV)	5.79	0.57	6.36

9 (with LEV)	0.58	0.29	0.86
9 (no LEV)	5.79	0.29	6.07
8a (professional use) (with LEV)	3.47	0.69	4.16
8a (professional use) (no LEV)	17.36	0.69	18.04
8b (professional use) (with LEV)	0.69	0.69	1.38
8b (professional use) (no LEV)	6.94	0.69	7.63
9 (professional use) (with LEV)	1.39	0.34	1.73
9 (professional use) (no LEV)	6.94	0.34	7.29

Conclusion

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

B.10.4. Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals

B.10.4.1. Human health

B.10.4.1.1. Workers

DMAC

The calculated RCRs for the use of DMAC as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals (PROC1-PROC4) are presented in Table 80.

Table 80: Use of DMAC as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	<0.01	0.064	0.067
2	0.27	2.58	2.86
3	0.82	1.30	2.12
4	0.14	1.29	1.43
4 (no LEV)	1.37	1.29	2.66

Conclusion

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

NEP
The calculated RCRs for the use of NEP as solvent in industrial processes (PROC1-PROC4) are presented in Table 81.

Table 81: Use of NEP as solvent in industrial processes – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86

Conclusion

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

B.10.5. Use as solvent in the production of man-made fibres and films

B.10.5.1. Human health

B.10.5.1.1. Workers

The calculated RCRs for the use of DMAC as solvent in the production of man-made fibres and films (PROC1-PROC4, PROC13, PROC14, PROC19 and reprocessing of fibres) are presented in Table 82.

Table 82: Use of DMAC as solvent in the production of man-made fibres for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
1	<0.01	0.064	0.067
2	0.27	2.58	2.86
3	0.82	1.30	2.12
4	0.14	1.29	1.43
13	0.27	2.59	2.86
14	0.14	0.65	0.78
19	0.27	26.68	26.96
Reprocessing of fibres	0.72	-	-
Medium fugacity category			
1	<0.01	0.064	0,067
2	1.37	2.58	3.96
3	2.74	1.30	4.04
4	0.55	1.29	1.84

13	1.37	2.59	3.96
14	1.37	0.65	2.02
19	1.37	26.68	28.06

Conclusion

The use of DMAC in the production of man-made fibres and films can lead to exposures above the DNELs, resulting in calculated combined RCRs of 0.067-26.96 for activities at room temperature. For activities at elevated temperature the combined RCRs increase to 0.067-28.06 mainly due to an increase in inhalation exposure. Especially for PROC19 a very high dermal exposure was estimated with a RCR of 26.68. As the RCRs are above 1 a risk has been identified. Inhalation 8-hour average measurement results from industry during the production of man-made fibres indicate that the DNEL can be exceeded. Calculations for PROC1 showed combined RCR far below 1 (RCR=0.067) for activities at room temperature as well as activities at elevated temperate. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. Therefore no risk via inhalation and dermal exposure is identified for PROC1-PROC3 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC13, PROC14 and PROC19 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC19 situations(Marquart et al., 2017). Therefore the identified risk for PROC4, PROC13, PROC14, PROC19 activities remains. For the reprocessing of fibres no adequate PROC is available. The inhalation RCR of 0.72 is based on the data reported in a CSR and reflects the 95-percentile value for the reprocessing of fibres based on air monitoring results of continuous monitoring analyzers. Dermal exposure estimates for the reprocessing of fibres are not available. Therefore a risk can not be excluded.

B.10.6. Use as solvent in coatings

B.10.6.1. Human health

B.10.6.1.1. Workers

DMAC

The calculated RCRs for the use of DMAC as solvent in coatings (PROC2, PROC7, PROC10 and PROC13) are presented in Table 83.

Table 83: Use of DMAC as solvent in coatings for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
2	0.16	1.55	1.72
7	0.82	4.85	5.67
10	0.16	3.11	3.27
13	0.16	1.55	1.72
Medium fugacity category			
2	0.82	1.55	2.37
10	0.82	3.11	3.93

Conclusion

The use of DMAC in coatings can lead to exposure above the DNELs, resulting in combined RCRs of 1.72-5.67 for activities at room temperature. For activities at elevated temperature (PROC2 and PROC10) the combined RCR increases from 1.72 to 3.93, due to an increase in inhalation exposure. As the RCRs are above 1 a risk has been identified. Inhalation 8-hour average measurement results during the use of DMAC in coatings are reported to be <3.6 mg/m^3 (RCR <0.28), which is in the same order of magnitude as the exposure model results. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC2 situations. Therefore no identified risk via inhalation and dermal exposure is foreseen for PROC2 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7 and PROC10 situations (Marquart et al., 2017). Therefore the identified risk remains.

NEP

The calculated RCRs for the use of NEP as solvent in coatings (PROC7, PROC10 and PROC13) are presented in Table 84.

Table 84: Use of NEP as solvent in coatings for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
Low fugacity category			
2	0.69	0.34	1.04
7	3.47	1.07	4.54
10	0.69	0.69	1.38
13	0.69	0.34	1.04
Medium fugacity category			
2	3.47	0.34	3.81
10	3.47	0.69	4.16
13	3.47	0.34	3.81
10 (professional use)	3.47	1.37	4.84
11 (professional use)	1.39	5.36	6.75
13 (professional use)	1.39	0.69	2.07
19 (professional use)	3.47	7.07	10.54

Conclusion

The use of NEP in coatings in both an industrial (PROC2, PROC7, PROC10 and PROC13) and a professional setting (PROC10, PROC11, PROC13 and PROC19) can lead to exposure above the DNELs, resulting in combined RCRs of 1.04-4.54 (industrial setting) and 2.07-10.54 for professional setting. For activities at elevated temperature (PROC2, PROC10 and PROC13, industrial setting) the combined RCR increases from 1.04 to 4.16, due to an increase in inhalation exposure. As the RCRs are above 1 a risk has been identified. No inhalation exposure measurements are available. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC2 situations. Therefore no identified risk via inhalation and dermal exposure is foreseen for PROC2 situations. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7 and PROC10 situations (Marquart et al., 2017). Therefore the identified risks for these activities remain.

B.10.7. Manual maintenance (cleaning and repair) of machinery

B.10.7.1. Human health

B.10.7.1.1. Workers

DMAC

The calculated RCRs for the exposure to DMAC during maintenance of machinery (PROC28, indoors and outdoors) are presented in Table 85.

Table 85: Exposure to DMAC during manual maintenance of machinery for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
28 (indoors)	0.027	2.59	2.61
28 (outdoors)	0.19	2.59	2.78

Conclusion

Manual maintenance of machinery can lead to exposure above the DNELs, resulting in combined RCRs of 2.61-2.78. As the RCRs are above 1 a risk has been identified. Inhalation 8-hour average measurement results from industry during the maintenance and cleaning activities indicate that the exposure concentration outside the respirator can highly exceed the DNEL. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report an overestimation of the efficiency of LEV in actual workplaces for PROC8a (used for the calculation of PROC28) contributing scenarios. Together with the identified risk via dermal exposure the identified risks for these activities remain.

NEP

The calculated RCRs for the exposure to NEP during maintenance of machinery (PROC28, indoors and outdoors) are presented in Table 86.

Table 86: Exposure to NEP during manual maintenance of machinery for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
28 (indoors)	0.12	0.57	0.69
28 (outdoors)	0.81	0.57	1.38
28 (professional use, indoors)	0.35	0.69	1.03
28 (professional use, outdoors)	1.21	0.69	1.90

Conclusion

Manual maintenance of machinery can lead to exposure above the DNELs, resulting in combined RCRs of 1.38 (industrial setting, outdoor) and 1.03-1.90 (professional setting, indoors and outdoors). As the RCRs are above 1 a risk has been identified for these scenarios. Calculations for PROC28 (industrial setting, indoors) show a combined RCR below 1 (RCR<0.69). Therefore for this activity no risk via inhalation or dermal exposure is identified, provided RPE is worn during the activities. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020)

report an overestimation of the efficiency of LEV in actual workplaces for PROC8a (used for the calculation of PROC28) contributing scenarios. For outdoor activities and for maintenance in a professional setting the identified risks for these activities remain. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

B.10.8. Use as laboratory chemical

B.10.8.1. Human health

B.10.8.1.1. Workers

DMAC

The calculated RCRs for the use of DMAC as laboratory chemical (PROC15, industrial and professional use) are presented in Table 87.

Table 87: Use of DMAC as laboratory chemical for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
15 (industrial use)	0.14	0.064	0.20
15 (professional use)	0.27	0.13	0.40

Conclusion

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

NEP

The calculated RCRs for the use of NEP as laboratory chemical (PROC15, industrial and professional use) are presented in Table 88.

Table 88: Use of NEP as laboratory chemical for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
15 (industrial use)	0.58	0.014	0.59
15 (professional use)	1.16	0.028	1.19

Conclusion

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

B.10.9. Use of NEP as binder and release agent

B.10.9.1. Human health

B.10.9.1.1. Workers

The calculated RCRs for the industrial and professional use of NEP as binder and release agent (PROC6, PROC7, PROC10, PROC11, PROC13, PROC14 are presented in Table 89.

Table 89: Use of NEP as binder & release agent for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
6	0.35	0.69	1.03
7	3.47	1.07	4.54
10	0.69	0.69	1.38
13	0.69	0.34	1.04
14	0.35	0.086	0.43
10 (professional use)	3.47	1.37	4.84
11 (professional use)	1.39	5.36	6.75
13 (professional use)	1.39	0.69	2.07

Conclusion

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

B.10.10. Use of NEP in cleaning agents

B.10.10.1. Human health

B.10.10.1.1. Workers

The calculated RCRs for the industrial and professional use of NEP in cleaning agents (PROC7, PROC10, PROC11, PROC13) are presented in Table 90.

Table 90: Use of NEP in cleaning agents for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
7	3.47	1.07	4.54
10	0.69	0.69	1.38

13	0.69	0.34	1.04
13 (medium fugacity)	3.47	0.34	3.81
10 (professional use)	3.47	1.37	4.84
11 (professional use)	1.39	5.36	6.75
13 (professional use)	1.39	0.69	2.07

Conclusion

The use of NEP as cleaning agent in both an industrial (PROC7, PROC10, PROC13) and a professional (PROC10, PROC11, PROC13) setting can lead to exposure above the DNELs, resulting in combined RCRs of 1.04-4.54 (industrial setting) and 2.07-6.75 (professional setting). For activities at elevated temperature (PROC13, industrial setting) the combined RCR increases from 1.04 to 3.81, due to an increase in inhalation exposure. As the RCRs are above 1 a risk has been identified for these scenarios. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC7 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC7, PROC10 and PROC13 contributing scenarios. In addition ECETOC TRA tended to underestimate dermal exposure for PROC7, PROC10 and PROC11 situations (Marquart et al., 2017). Therefore a combined risk via inhalation and dermal exposure is identified for all PROCs.

B.10.11. Use of NEP in oil field drilling and production operations

B.10.11.1. Human health

B.10.11.1.1. Workers

The calculated RCRs for the use of NEP in oil field drilling and production operations (PROC1-PROC4) are presented in Table 91.

Table 91: Use of NEP in oil field drilling and production operations for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86

Conclusion

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

B.10.12. Use of NEP in agrochemicals

B.10.12.1. Human health

B.10.12.1.1. Workers

The calculated RCRs for the professional use of NEP in agrochemicals (PROC5, PROC11 and PROC13) are presented in Table 92.

Table 92: Use of NEP in agrochemicals for professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
5	11.57	1.14	12.71
11	11.57	8.93	20.50
13	11.57	1.14	12.71

Conclusion

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

B.10.13. Use of NEP in functional fluids

B.10.13.1. Human health

B.10.13.1.1. Workers

The calculated RCRs for the industrial and professional use of NEP in functional fluids (PROC1-PROC4 and PROC20) are presented in Table 93.

Table 93: Use of NEP in functional fluids for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86
20 (professional use)	3.47	0.086	3.56

Conclusion

The use of NEP in functional fluids can lead to exposures above the DNELs for PROC2, PROC3 and PROC20 activities, resulting in calculated combined RCRs of 1.73-3.76. As the RCRs are

above 1 a risk has been identified for these scenarios. No inhalation exposure measurements are available. Calculations for PROC1 and PROC4 show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations. However, for PROC2, PROC3 and PROC20 a risk is identified, mainly due to inhalation exposure. These risks cannot be excluded by inhalation measurement results or inhalation exposure model validation study results.

B.10.14. Use of NEP in road and construction application

B.10.14.1. Human health

B.10.14.1.1. Workers

The calculated RCRs for the professional use of NEP in road and construction application (PROC10, PROC11 and PROC13) are presented in Table 94.

Table 94: Use of NEP in road and construction application for professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
10	20.25	2.29	22.53
11	8.10	8.93	17.03
13	8.10	1.14	9.24

Conclusion

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

B.10.15. Use of NEP in polymer processing

B.10.15.1. Human health

B.10.15.1.1. Workers

The calculated RCRs for the industrial and professional use of NEP in polymer processing (PROC1-PROC6, PROC13, PROC14 and PROC21) are presented in Table 95.

Table 95: Use of NEP in polymer processing for industrial and professional use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86

5	0.58	0.57	1.15
6	0.35	0.69	1.03
13	0.69	0.34	1.04
14	0.35	0.086	0.43
21	-	-	-
1 (professional use)	0.012	0.014	0.026
2 (professional use)	5.79	0.57	6.36
14 (professional use)	1.39	0.17	1.56
21 (professional use)	-	-	-

Conclusion

The industrial and professional use of NEP in polymer processing can lead to exposures above the DNELs, resulting in calculated combined RCRs of 1.03-3.76 (PROC2, PROC3, PROC5, PROC6, PROC13, industrial setting) and RCRs of 1.56-6.36 (PROC2 and PROC14). As the RCRs for these scenarios are above 1 a risk has been identified. Calculations for PROC1, PROC4 and PROC14 (industrial) show combined RCRs below 1 (RCR<0.86). Therefore for these PROCs no risk via inhalation or dermal exposure is identified. No inhalation exposure measurements are available. It should be noted that ECETOC TRA validation studies (Schlueter & Tischer, 2020) report a low level of conservatism for PROC5 and PROC14 contributing scenarios and an overestimation of the efficiency of LEV in actual workplaces for PROC13 and PROC14. Validation study results (Marquart et al., 2017) indicate that dermal exposure is overestimated for PROC1-PROC3 situations and underestimated for PROC6 situations. For PROC2, PROC3, PROC5, PROC6 and PROC13 (industrial setting) and for PROC2 and PROC14 (professional setting) a risk is identified, mainly due to inhalation exposure, which cannot be excluded by model validation study results. The registrant included contributing scenario PROC21, which is "the low energy manipulation and handling of substances bound in/on materials or articles" resulting in the release of dust. The registrant did not include an exposure estimate in the CSR. With ECETOC TRA v3.1 it is not possible to calculate possible exposure to NEP as a result of handling articles.

B.10.16. Use of NEP in water treatment chemicals

B.10.16.1. Human health

B.10.16.1.1. Workers

The calculated RCRs for the use of NEP in water treatment chemicals (PROC1-PROC4 and PROC13) are presented in Table 96.

Table 96: Use of NEP in water treatment chemicals for industrial use – calculated RCR values

Process Category (PROC)	RCRs		
	Inhalation	Dermal	Combined
1	0.012	0.014	0.026
2	1.16	0.57	1.73
3	3.47	0.29	3.76
4	0.58	0.29	0.86
13	0.69	0.34	1.04

Conclusion

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

Annex C: Impact Assessment

C.1. Risk Management Options

Described in the main report

C.2. Alternatives

C.2.1. Description of the use and function of the restricted substance(s)

The aim of this section on alternatives is to provide information for the analysis of whether the equivalent function provided by the substance can be obtained by other substances or techniques and for assessing the net impact of the proposed restriction to the human health and the environment. This will facilitate in defining a proportionate restriction that is targeted to the identified risk (Dubourg, 2021; ECHA, 2008).

C.2.1.1. DMAC

DMAC is a dipolar, aprotic solvent with high solving power. The solvent can be used for a wide range of organic and inorganic compounds and is miscible in water, ethers, esters, ketones and aromatic compounds. The combination of properties explains the importance of the use of DMAC in several applications. DMAC as such is mainly used to enhance a chemical reaction driven by its solvent characteristics as part of the process to make a product. Next to DMAC, many organic solvents are available as potential alternative, but the characteristics of these solvents are not exactly equal to DMAC. The availability of technically feasible alternatives will differ per application.

Information on the available alternatives was collected from the CSRs, chapter 4 of the Annex XV SVHC dossier for DMAC and public comments on this SVHC dossier, from communication with ECHA, industries and the literature. The CSRs did not provide any information on potential alternatives. The Annex XV SVHC dossier indicated that no information on actual replacement of DMAC with alternative solvents was obtained and that the efforts by industry in reducing the use of the substance have rather focused on improving the recovery rate of DMAC. A number of dipolar aprotic solvents mentioned as potential alternative, but these solvents carry essentially the same health hazards as DMAC. The dossier further indicated that two polar aprotic solvents, DMSO and DMI, could potentially be used as alternatives for some applications of DMAC, such as in the production of pharmaceuticals and other chemicals, but these were not suggested as solvents for manufacturing of textile fibres of the types for which DMAC was used. Comments from industry on the annex XV SVHC dossier for DMAC indicated that, according to industry, there were no general alternatives to DMAC available. They indicated that substitution to other dipolar aprotic solvents would not be a real improvement regarding their toxicological properties. DMSO cannot be considered as a general substitute for DMAC because of the different characteristics and the penetrant sulphur containing decomposition products such as methyl-mercaptan that are toxic by inhalation and cause additional efforts in the off-gas treatment, whereas acetone and acetonitrile have very different properties (e.g. solubilization properties) and are non-recommendable due to their flammability. The alternatives identified are discussed per use category (see A.2.1).

Dipolar aprotic solvents, such as DMAC, are produced globally in hundred thousand tonnes per year and have been applied in many production processes throughout the chemical industry (McCoy, 2019). They are being used in a range of molecular separations such as aromatic/aliphatic separation and the carboxylic acid separation from water (Brouwer &

Schuur, 2020). Furthermore, aprotic solvents to date are the most commonly used solvents for membrane preparation by non-solvent separation (Wang et al., 2019). The main uses for DMAC in Europe as mentioned in A.2.1 are:

- Process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals (65-70% of tonnage)
  - Agrochemicals
  - Human and veterinary pharmaceuticals, including excipient (carrier ingredient);
  - Fine chemicals
- Process solvent for spinning of fibres of various polymers including acrylic, polyurethanepolyurea copolymer (elastane, Spandex) and poly(m-phenylene isophthalamide) (PMIA, meta-aramid) (20-25% of tonnage);
- Solvent in coatings e.g. polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation (3-5% of tonnage);
- Process solvent in the production of polysulphone membranes (<2% of tonnage);
- Other uses (<2.5% of tonnage);
  - Laboratory uses,
  - Petrochemical applications,
  - Cellulose fibres

The use categories in the previous Annex XV SVHC dossier for DMAC are roughly similar with the current ones. It may be assumed that the additional two uses mentioned in the Annex XV SVHC dossier, the use in paint and ink removers, have been substituted or are used in very low amounts. The Annex XV SVHC dossier mentions the use of DMAC as excipient (carrier ingredient) in human and veterinary pharmaceuticals and the applications relate to pharmaceuticals like antibiotics and novel contrast media.

In identifying the alternatives to DMAC, the various applications have been clustered according to the processes of relevance in relation to the use of DMAC. Thus, facilitating the understanding the reason why DMAC has been applied and the production processes that need to be adapted. Following this line, all applications related to polymers, coatings, resins, paints, films, enamels, varnishes, membranes and fibres are dealt with together.

Phase inversion or phase separation. For the first group of applications (polymers, coatings, resins, paint, films, enamels, varnish, membranes) the preparation of a dope solution for dope and casting and the process of phase inversion or phase separation is of relevance. The process starts with dissolving a polymer in a solution and subsequently removal of the solvent and casting of the polymer takes place. Phase inversion can be applied by different techniques of which non-solvent induced phase separation (NIPS) and temperature induced phase separation (TIPS) are most widely used.

Spinning. Spinning is generally applied for producing fibres but can also be used for the production of certain membranes (electro spinning) and coatings, and for the production of perovskite films to be used in solar cells (spin-coating of PbI2 solution). There are many types of spinning methods. Two main types of spinning can be distinguished, namely melt spinning and solution spinning. The first is of little relevance for this dossier as no solvent is being used. In solution spinning four types are distinguished: dry spinning, wet spinning, gel spinning and electrospinning. In the process to produce fibres a solution is pumped through a spinneret and the solvent is removed by evaporation (dry-spinning process) or by extracting with a solvent (wet-spinning process). Currently, dry spinning is the most applied spinning technique. Wet spinning is often applied for heavier denier yarn, whereas electrospinning is used for the very small diameter yarn (nm's). Both in the process of phase inversion as in spinning DMAC may be used.

In the search for alternatives, graphene dispersion/exfoliation and production of perovskite solar cells were identified as possible applications where DMAC is used, although these two

applications are still in a very early stage of commercial production. These applications will be discussed here shortly as well.

C.2.1.2. NEP

NEP shares a number of physical-chemical properties with NMP and is considered as an alternative for NMP. Therefore, it is considered to be applied in similar applications although limited information seems to be available (Ashland, 2016; Fernandes, 2015; Koch et al., 2014; Silberzahn, 2013; Ulrich et al., 2018). Chapter A.2.2 identifies a small number of uses for NEP on basis of the literature. It further indicates that the registration dossiers indicate the following industrial or professional uses for NEP: water treatment chemicals, oil field drilling and production operations, binders and release agents, polymer processing, agrochemicals, and road and construction applications. No further detailed information was found or received about these uses and it is unclear if currently NEP is used in these applications. Very limited information is available about NEP volumes, exposed workers and uses and no information was received during the CfE.

About 100 retrieved SDSs confirmed the use in solvents, cleaners and strippers, paint and graffity removers, lubricants, adhesives and binders, coatings and putties. Concentrations of NEP used in these applications range from <0.5% in putties to 100% in relation to, amongst others, cleaners and paint removers. For adhesives generally NEP concentrations less than 10% are applied. The data in the retrieved SDSs indicate that coatings may contain up to 1%, whereas specific coating products such as dispersions, thickeners and fixatives may contain up to 12.5% NEP. Two of the identified products contained between 50 and 100% NEP. For putties less than 0.5% NEP is generally applied.

Chapter A.2.2 indicates an increase in the use of NEP in coatings after the classification of NMP as reprotoxic based on information from CEFIC. This information also indicates that NEP is expected to be phased out and that only specialized coatings may still contain NEP in very low concentrations (<0.1%). From current and previous safety datasheets it became also clear that NMP has been replaced by NEP in a number of applications, but that considerably higher concentrations may be present than the 0.1% mentioned by CEFIC. The replacement of NMP by NEP would suggest that the alternatives to NMP would also be feasible as alternatives to NEP.

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

C.2.2. Identification of potential alternative substances and techniques fulfilling the function

C.2.2.1. DMAC

Process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals

Chapter A.2.1 indicates that 65-70% of the DMAC tonnage is used as a process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals. The applications relate to pharmaceuticals (e.g. antibiotics and novel contrast media), agrochemicals (fertilisers, pesticides etc.), and fine chemicals (ECHA, 2012a). According to

comments by the industry during the SVHC consultation (ECHA, 2012a)*: 'Agrochemical use of DMAC is exclusively chemical synthesis of active ingredients in industrial installations or small-scale industrial laboratory use for quality assurance. There is no use of DMAC in agrochemical formulation as DMAC is a CMR cat. 1b substance and thus its use in agrochemical formulations is prohibited according to Regulation 1107/2009.'* Further information on the use of DMAc or its alternatives in the production of agrochemicals is very limited.

Ashcroft et al. (2015) investigated the use of various solvents in pharmaceutical/fine chemicals batch operations in which high quality, consistent quality and high yields are key characteristics on the basis of articles published in Organic Process Research & Development between 1997 and 2012. Acetonitrile (ACN), DMF, DMSO, NMP and DMAC were among the top five dipolar aprotic solvents used, with DMAC covering about 10%.

Process solvents used in the pharmaceutical industry have been under scrutiny since the 1990s. Solvents account for between 80 and 90% of the mass used in typical pharmaceutical/ fine chemicals (non-polymer) batch chemical operations where sequential steps of organic synthesis reactions generate a considerable amount of waste per kg of the final product (Constable et al., 2007; Slater & Savelski, 2009). As the solvents account for a considerable amount of the overall costs, efforts were undertaken to increase recovery (Joshi & Adhikari, 2019). Other reasons for a critical look at solvent use had to do with the hazardousness of the substances in general and with remaining impurities of the solvents in the final products. The latter is covered by the classification of solvents within the guideline for residual solvents by (Agency, 2021), which contain internationally coordinated guidelines and limit values. DMAC is classified as a class two solvent, which means it should be limited in pharmaceutical products because of its inherent toxicity.

The hazardousness of the solvents in general has also been reason for several pharmaceutical companies to develop guidelines for solvent selection with the aim to replace hazardous solvents by less hazardous ones. First solvent selection guide for the pharmaceutical industry was published by SmithKline Beecham (SKB) in 1999 and focused on the 35 most commonly used solvents by SKB (Curzons et al., 1999). Comparable solvent selection guides were developed by other pharmaceutical companies such as AstraZeneca, Bristol-Myers Squibb, Pfizer, GSK and Sanofi. In an analysis of the various guides Byrne et al. (2016) concluded that for certain substances the different selection guides generated different results although many of the dipolar aprotic, chlorinated, hydrocarbon and ether solvents were considered as undesirable among which DMAC. Thus, cooperative efforts were undertaken by six European pharmaceutical companies which lead to the CHEM21 selection guide (Prat et al., 2016), whereas the comparable efforts were undertaken in the US by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (Roundtable, 2011; Slater & Savelski, 2009). The aim of these guides was to support developments in reducing the amount of solvents used and substituting hazardous for less hazardous solvents taking into account environmental health, safety and sustainability issues (Slater & Savelski, 2009). Prat et al. (2016) concluded: *'The carbonate solvents show a remarkable range of polarity, dimethyl carbonate being a potential replacement for MEK [methyl ethyl ketone], ethyl acetate, MIBK [Methyl isobutyl ketone], butyl acetate and most other ketones and glycol ethers. Cyclic carbonates such as ethylene and propylene carbonate are much more polar and could replace undesirable aprotic dipolar solvents such as DMF.'* Although DMAC was evaluated in the survey, no specific examples of potential substitutes have been mentioned in the study. The authors indicate that the selection guide provide a first step and that it is necessary to extend the selection with further developing work e.g. a check on reaction compatibility is necessary before any scale-up.

For a proper analysis of the possibility for substitution it is necessary to know the kind of reactions for which dipolar aprotic solvents and especially DMAC is being used. Solvents are

usually used at any step of the synthesis pathway of an active substance or excipients, and sometimes during the drug product formulation process (Grodowska & Parczewski, 2010). Ashcroft et al. (2015) who carried out an investigation on dipolar aprotic solvents found that nearly 50% of DMF/DMAC/NMP/DMSO usage could be attributed to nucleophilic substitution reactions (mostly SNAr and SN2 reactions). An example of such reaction are the Halex reactions where a chlorine is replaced by a fluorine, with for instance KF, NaF, CsF as a nucleophilic source of fluorine and using a dipolar aprotic solvent. Ashcroft et al. (2015) provide examples where in different processes DMF has been substituted by acetone, ethanol (EtOH) and 2-methyltetrahydrofuran (2-MeTHF). They indicate that although the kinetics of these substitution reactions are often faster in dipolar aprotic solvents, alternative solvents can also be used and reaction speed may be increased in sealed systems under a small positive pressure. In their study nearly 10% of DMF/DMAC/DMSO and NMP use was associated with amide formation reactions and referring to another study they conclude that greener substitutes can nearly always be found for the preparation of pharmaceutically relevant molecules.

Dipolar aprotic solvents (DMF, DMAC, NMP) are also frequently used in the preparation of peptides by means of solid-phase organic synthesis (SPOS), or more specifically solid-phase peptide synthesis (SPPS) (Bryan et al., 2018; Lawrenson, 2018; Wegner et al., 2021). The use of dipolar aprotic solvents in oligonucleotide synthesis is mentioned by Bryan et al. (2018). In SPPS a resin, often polyethylene glycol (PEG) or polystyrene (PS), is used to carry out the actual synthesis (Varnava & Sarojini, 2019). The solvents are normally used in large amounts for washing, deprotection, and coupling steps in SPPS. The resin must be washed between the procedures to remove excess reagents and by-products, which result in considerable solvent loss, considerable process energy consumption and thus accompanying overall costs of the manufacturing process (Lawrenson, 2018; Wegner et al., 2021). SPOS typically offers many advantages over conventional solution-phase synthesis (Lawrenson, 2018). Although in various studies the use of DMF is mentioned, use of DMAC should also not be excluded.

Bryan et al. (2018) describe five alternative solvents for the use in used in solid phase peptide synthesis (SPPS) and oligonucleotide synthesis, their applications and indicate the limitations of their use: N-formyl morpholine (CAS number 4394-85-8), Dimethylisosorbide (CAS number 5306-85-4), Propylene carbonate (CAS number 108-32-7), Dihydrolevoglucosenone (Cyrene; CAS number 53716-82-8) and N-Butylpyrrolidinone (NBP; CAS number 3470-98-2). However, Wegner et al. (2021) indicate that there is no gold standard solvent that can replace the dipolar aprotic solvents use in all SPPS processes and that each resin and peptide sequence have to be evaluated on its own. Challenges mentioned include unacceptable resin swelling, insolubility of raw materials and lower yields and purities of the peptide.

Ashcroft et al. (2015) have analysed the solvent usage trends and observe that substitution of the dipolar aprotic solvents goes relatively slowly and provide some reasons why that is the case. Only 2-MeTHF (CAS-number 96-47-9) has been increased considerably between 1997 and 2012. Ashcroft et al. (2015) also notice large reductions in use of DMF, n-hexane, diisopropyl ether, DMAC, DMSO and a complete elimination of diethyl ether and dioxane. They provide examples of substitution of dipolar aprotic solvents, mainly for DMF. The results indicate the possibility to replace the solvents in most cases. Bryan et al. (2018) showed that dichloromethane and 1,2-dichloroethane use has remained fairly consistent in process chemistry over a 16-year period. They conclude that, finding drop-in replacements for dichloromethane and 1,2-dichloroethane is even more challenging than for dipolar aprotic solvents, which were also presented.

The literature contains several potential substitutes for the use of hazardous solvents in the pharmaceutical industry such as water as a process solvent, ionic liquids and supercritical fluids and even solvent-free processes (Cue & Zhang, 2009; Grodowska & Parczewski, 2010).

There are a few examples where hazardous solvents have been replaced by less hazardous ones, thus providing a basis where technical feasibility has been proven. Such examples are the substitution of DMF by ethanol and 2-methylTHF (Ashcroft et al., 2015), methylene chloride by ethyl acetate and 2-methylTHF (De Palma, 2006), and the substitution of tetrahydrofuran (THF) by ethanol (Cue & Zhang, 2009). No concrete examples have been found where DMAC has been replaced by a substitute and no cost data on substitution has been provided. Potential alternatives should be checked for significant process and safety issues, e.g. the reaction in solution, the effect on particle size of the API and the impact manufacturing costs by the ease of isolation (Cue & Zhang, 2009) and significant efforts will be required to phase in the potential substitutes.

Summarizing, alternatives mentioned in the literature include ethanol (CAS number 64-17-5), cyclic carbonates such as ethylene carbonate (CAS number 96-49-1) and propylene carbonate (CAS number 108-32-7), N-formyl morpholine (CAS number 4394-85-8), Dimethylisosorbide (CAS number 5306-85-4), Propylene carbonate (CAS number 108-32-7), Dihydrolevoglucosenone (Cyrene; CAS number 53716-82-8) and N-Butylpyrrolidinone (NBP; CAS number 3470-98-2) and 2-MeTHF (CAS-number: 96-47-9). In contrast to other dipolar aprotic solvents, no concrete examples have been found for the substitution of DMAC, but the literature data suggest that such replacement should be technical feasible.

Fibres

Quite a number of artificial fibres are produced by using DMAC. The use of DMAC in the production of acrylic and modacrylic fibres, polyurethane fibres and meta-Aramid fibres (Nomex) is well-known (SZW, 2017a; US-EPA, 1982). The fibres can be produced by dry spinning, wet spinning, melt spinning and reaction spinning (US-EPA, 1982). Currently, 95% of the fibres is produced by dry spinning (Linel, 2021; LyondellBasell, 2013), whereas in the past wet spinning was more applied (US EPA, 1982). For heavier yarns wet spinning is still preferable (Linel, 2021; US-EPA, 1982). Solvents being used may be different for the various types of spinning. Fibres may be used in solid paper or pressboard (Nomex), tow (Nomex), nonwoven and woven fabric, and yarn and can be applied in the textile and construction industries.

The production of fibres made from **polyacrylonitrile (PAN)**, such as acryl (e.g. Orlon) and modacryl, is extensively described in US-EPA (1982), which list the various solvents being used by the various producers in dry and wet spinning. Sodium thiocyanate (NaSCN), zinc chloride (ZnCl2), DMF and DMAC are mentioned as solvents for the acrylic fibres and DMF, DMAC and acetone are mentioned for the modacrylic fibres (US-EPA, 1982). Beckman et al. (2021) indicates that acrylonitrile is successfull into polyacrylonitrile fibres using the solvents DMF, DMAC, DMSO, propylene carbonate, or aqueous sodium thiocyanate in a 45 to 55% solution.

Polyeruthane fibres (Spandex) is being used in a broad range of products (Linel, 2021). Commercial producers and recyclers of spandex mention DMAC and DMF as solvents (e.g. (MFC Progretti srl, 2022)). DMAC has been used in the Lycra factory of DuPont in the Netherlands in the period between 1964 and 2004. DMAC was used in the polymerization process (chain extension reaction) as well as during spinning (SZW, 2017a).

BASF (2013b) claims to have a solvent free production of thermoplastic elastomer polyurethane (TPU) as well as a solvent free process for the melt spinning of the fibres. LyondellBasell (2013) indicates that spandex can be produced in a non-solvent process melt-spun process, but that only a limited amount is produced by this method. It is not known to which amount melt spinning is currently being applied in practice.

The use of DMAC in the production of **aramids** is mentioned in the Annex XV SVHC dossier (ECHA, 2011a) and by Mera and Takata (2000), Abe and Yabuki (2012) and Trigo-López et

al. (2018) in their reviews on aramids. The low temperature solution polymerization method, which is generally used commercially, utilizes a combination of NMP as a solvent and CaCl2 in the production of p-aramids and DMAC for the production of m-aramids (Trigo-López et al., 2018). Besides this production method, some high temperature synthesis methods are known as well as some alternative synthesis methods of which limited information is provided (Trigo-López et al., 2018). Interfacial polymerization, a low temperature solution polymerization production method, was used for production of the m-aramid Conex in which THF is used in the preliminary oligomerization and subsequent dissolving the polymer in NMP/CaCl2 (Abe & Yabuki, 2012; Mera & Takata, 2000). Recently, environment friendly aramids have been produced using ionic liquids instead of polar aprotic solvents such as NMP, DMAc and DMF and some other more environment friendly methods have been described as well. However, it is not clear whether these procedures have already been successfully157d (Mera & Takata, 2000; Trigo-López et al., 2018).

Current commercial wet and dry spinning of m-aramid both utilizes DMAC or DMF, whereas for p-aramid generally NMP is applied (Trigo-López et al., 2018). Electrospinning using DMAC is being described for m-Aramid and polysulfonamide (PSA), whereas for polyurethane (TPU) DMF was used (Chen et al., 2009). Wenhua et al. (2016) mentions electrospinning of TPU by a DMF/THF volume percentage of 3:1. Moreland (2010), Abe and Yabuki (2012) and Trigo-López et al. (2018) describe that the poly(p-phenylene terephthalamide) (PPTA) is dissolved in concentrated sulfuric acid to prepare a dope for the dry-jet spinning of the p-aramid fibres.

DMAC has experimentally been applied in the electrospinning of gelatin successful used for tissue engineering and regenerative medicine. Besides DMAC other organic solvents used were DMF, DMI, DMSO, NMP and HFP (Aoki et al., 2015).

Coatings and enamel

Coatings are generally the deposition of one or more polymeric layers on different kinds of material. There may be different coating processes used in industry such as dip coating and spin coating. Both in the preparation of the dope solution as in the spinning process solvents may be used. Wire coating may be considered as a dip coating where the base material is dipped into the varnish and where the excess varnish is squeezed with pinch rollers. Aprotic solvents, such as NMP, DMAC, DMF and DMSO, are used for the most solvent resistant polymers: polyamideimides (PAI) and polyimides (PI). (IST, 1995) offers their PI wire enamel with NMP as a solvent or as NMP in combination with aromatic hydrocarbons or DMAC.

Coatings have been applied in a number of applications. Poly(vinylidene-fluoride) (PVDF) films are for instance used in applications such as hydrophobic coatings in architecture, membranes for microfiltration, gas separation or water desalination, and as ferroelectric memories for data storage. PVDF has a very limited solubility in common organic solvents. PVDF is generally dissolved in polar solvents such as DMF, DMSO, NMP or DMAC. Ultra-thin films of PVDF can be realized by spin-coating (Li et al., 2013).

In the production of artificial PU synthetic leather DMF is used as a solvent at multiple process steps. Layers of polymeric material are added to a woven fabric to meet strength and aesthetic criteria. Because of regulatory concerns about DMF some manufacturers are switching to using DMAC. Alternative solvents meeting the technical performance criteria and with better human health and environmental hazard performance –identified are cyrene, dimethyl isosorbide, γ-valerolactone, cyclopentyl methyl ether, and glycofurol (Ramphal et al., 2019).

In producing enamelled wire a thin polymer film is applied to a wire in a number of layers. The polymer is applied dissolved in a solution after which the solvents are evaporated in an enameling oven (EGTEI, 2005). Besides the solvent, catalysts and other components may be added to the solution to influence the application and performance properties of the enamel depending on the final use of the coating (Anton et al., 2008). In the process of wire coating

different coats can be applied (basecoat and overcoat) and different polymers can be used such as PAI, PI, polyesterimide (PEI) and PVDF. Main polymers applied for enamels are polyesterimides, polyurethanes, polyesters, and polyesteramideimides (Anton et al., 2008). PEI-based enamel is one of the most important insulating enamels in electrical engineering (Biondi, 2008). The solvents being used depend on the polymer. Most wire enamel resins are dissolved in a mixture of cresol isomers and aromatic hydrocarbons, whereas polyesterimide, poly(amide-imides) and polyimides use highly polar solvents (e.g., DMF, DMAC, NMP, etc.) as solvent (Biondi, 2008; Mesaki & Goda, 2001). DMAC has been mentioned for PAI, PI and PVDF enamels.

Anton et al. (2008) mention a number of alternative wire enamel technologies instead of using solvents, but indicate that only limited amount of these technologies survived because of technical or economic considerations. Some technologies have survived for very special applications, for instance the extrusion process or powder coating. Alternatives solvents seem also to be available. In 2004 BASF (BASF, 2004) proposed propylene carbonate as an alternative solvent for wire coatings made from polyester imides (PIs) that traditionally were produced with cresol as the solvent. It is not known to what extent PC has been commercialized. Recently, cyrene has been successfully applied in the production of PAIs, which are used in a wide range of applications including the production of electrical wire insulation (wire enamel) (Deswarte & McElroy, 2019). It is not clear whether this concerns experimental or commercial production.

Wire coating can be applied by different wire enamel technologies, but according to Anton et al. (2008) only high solid wire enamels are universally applied. A number of other technologies lack the technical performance needed (e.g. hot melt resins, dispersions and water borne wire enamels), whereas others (e.g. mild solvent-–based wire enamels) did not fulfil economic feasibility because of the price of the raw materials. Concerning the solvents, various alternatives seem to be available. However, the specific properties needed depend on the enamel applied and on the enamelling conditions and thus on the polymer, the solvent and the process parameters. The Japanese UBE Group offers a complete PI varnish product line in a water, or low environmental impact organic solvent, based system. This varnish is the base for polyimide coated films to be used on e.g. wire coating. However, although the product concerns low impact systems the producer suggests concentration adjustment by means of DMAC or NMP.

Membranes

Polymeric membranes are being used in many separation techniques such as reverse osmosis, nanofiltration, ultrafiltration, and microfiltration. These separation techniques may be applied in water purification and gas separation, but also in medical and biological applications including dialysis, drug release, and cell culture (Marino et al., 2018; Yadav et al., 2021). Generally applied polymers are polyamide (PA), cellulose acetate (CA), PVDF, polypropylene (PP), polytetrafluoro-ethylene (PTFE), polysulphone (PSF or PSU), poly(ethersulphone) (PES or PESU), and poly(phenylsulphone) (PPSU) (Kahrs & Schwellenbach, 2020; Marino et al., 2018; Russo et al., 2021; Wang et al., 2019). All these polymers require strong polar solvents for membrane processing. Experimentally DMAC have been applied to polybenzimidazole (PBI), PSF, PVDF, PAN and polydimethylsiloxane (PDMS), whereas PI was dissolved in DMF instead of DMAC because of brittleness using DMAC (Fei et al., 2019). The application of polymeric membranes is related with the fact that they are relatively simple to apply, their low energy consumption, the ease of control and scale-up, their flexibility and environmental friendliness (Yadav et al., 2021). Polymeric membranes can be produced by melt extrusion, controlled stretching, electrospinning and track etching, but phase inversion is most widely used (Dong et al., 2021; Kim et al., 2016; Yadav et al., 2021) and among phase inversion non-solvent induced phase separation is most applied.

Most of the polymers mentioned need strong solvents with strong polarity for processing the membranes such as NMP, DMF and DMAC (Dong et al., 2021; Marino et al., 2018; Wang et al., 2019; Yadav et al., 2021). Others being mentioned include dioxane (Kahrs & Schwellenbach, 2020) and other petroleum-based solvents solely or in blends (Dong et al., 2021). For sulphone-based membranes, DMF, NMP and DMAC are currently among the most used solvents (Marino et al., 2018; Wang et al., 2019). The solvents dominate the mixing rate and may thus affect the membrane structure and the performance, but also additives may be of influence by changing characteristics such as swelling capacity and permeability (Fei et al., 2019; Marino et al., 2018).

During the last five years considerable attention has been paid to the development of more sustainable production processes of polymeric membranes. Especially the use of the solvents and the release of large amounts of solvent containing wastewater has got considerable attention, initially by a better process control and retrieval of the solvents, but also by looking for substitutes (Wang et al., 2019). The search for substitutes focus in first part to the similarity in solubility parameters compared to the current aprotic solvents (Marino et al., 2018). The Hansen solubility parameters, and the polymer-solvent distance, represent an indicator of system stability from a thermodynamic point of view (Marino et al., 2018). Furthermore, factors that have to be considered for controlling the membrane morphology are the process conditions and the composition of the initial polymer solution as they have a major impact on the thermodynamics and kinetics of the membrane formation process. In this context, different membrane-forming polymers, different solvents and various non-solvent or polymeric additives can be used to alter the fundamental progress of phase inversion (Kahrs & Schwellenbach, 2020).

Numerous environment friendly or so-called green solvents potentially available as alternatives for membrane fabrication comprise tributyl O-acetyl citrate, triethylene glycol diacetate (TEGDA), Methyl-5-(dimethylamino)-2-methyl-5-oxopentanoate (PolarClean), Cyrene, and organic carbonates e.g. ethylene, methyl lactate, triethylphosphate, ionic liquids, ϒ-valerolactone, and others (Dong et al., 2021; Yadav et al., 2021). However, most of these alternatives have been investigated in relatively few studies and have not yet been tested on a larger scale. According to the physical characteristics methyl lactate should be able to dissolve PEI membranes, but experiments failed to support this. Membranes prepared with methyl lactate have exhibited several defects (Dong et al., 2021). It is reported that the majority of companies producing membranes still use traditional organic solvents, such as NMP and DMAC (Marino et al., 2018). However, there are also a few studies that report the successful preparation of membranes for water desalination and reclamation by ultrafiltration (UF) and nanofiltration (NF) with conventional polymers, including PSF, PES, and CA and the preparation of microfiltration (MF) and UF membranes, from PES and PVDF using PolarClean (Russo et al., 2021; Wang et al., 2019).

Dong et al. (2021) indicate that with the development of more 'green' solvents, overcoming their limitations and actual replacement of the traditional solvents will become more feasible. They indicate however, that prices of these 'green' solvents are generally higher and that the biodegradability of the solvents may result in eutrophication. The review indicates that much literature is available on 'green' polymers and solvents, but that studies on scaling up to commercial scale are very limited. They conclude that more studies should be dedicated to the casting techniques in order to introduce green solvents in the commercial production of membranes. The authors indicate that for a successful introduction the alternatives should be phase-in alternatives requesting limited capital investment, they should be affordable and the supply should be guaranteed (Dong et al., 2021).

The available data suggest that the aprotic solvents are still being used in a majority of the membrane production facilities, but that several potential alternatives are on the way and have been successfully used to produce membranes on lab scale. It is not clear whether these

solvents are already applied in commercial production. During the industry consultation (Sartorius) it has been confirmed that other production methods can be applied without the need of DMAC. It was confirmed that only 5% the PESU ultrafiltration membranes still need DMAC, but will be changed at the end of 2022.

Graphene dispersions

The use of DMAC has been mentioned as a solvent in various scientific papers on the preparation of graphene dispersions using graphene oxide (GO) or reduced graphene oxide (rGO). Graphene has a wide range of applications in biomedicine, energy storage, as nanocomposites, but also in nanoelectronics and thermal applications (Backes et al., 2020; Liang et al., 2018; Manzetti & Gabriel, 2019).

One of the challenges of graphene is its hydrophobicity and the resulting aggregation, which hinders the production of graphene in a large scale at low cost or in high purity (Perumal, 2019). This has led to much work on the use of aprotic solvent liquid-phase exfoliation of graphite to produce graphene dispersions without aggregation (Rodgers et al., 2015). However, the high costs of these solvents and their toxicity has led to a search for alternatives (Coleman, 2009; Kulyk et al., 2021). One alternative to aprotic solvents, such as DMF, NMP and DMAC, is the use of surfactants in aqueous solutions to stabilize graphene in solution without reaggregation (Backes et al., 2020; Shabafrooz et al., 2018).

Up till now limited studies have specifically been dedicated to more environment friendly solvents for the exfoliation of graphene (Pan et al., 2018; Paolucci et al., 2020; Salavagione et al., 2017). Whereas the studies of (Pan et al., 2018; Salavagione et al., 2017) were dedicated to cyrene, that of (Paolucci et al., 2020) was dedicated to Polarclean. Although the results with alternatives demonstrate that the challenges posed by graphene can be overcome the cost effectiveness of the modifications and processes is still unclear (Johnson et al., 2015; Kulyk et al., 2021).

Most commercial graphene dispersions on the market use NMP or water as a solvent, although some use ethanol or DMAC. The data presented indicate that the work on exfoliation of graphene is still ongoing and that besides DMAC there are several solvents that can be utilized in the Liquid-Phase Exfoliation of graphene.

Solar cells

The solar cell market is divided between the crystalline silicium photovoltaics (PV) with a 95% market share and the thin film PVs with a 5% market share currently. Among the thin film PV technologies is the perovskite based solar cells which are considered to be the most promising competitor of the current silicon based solar cells as the cost of producing them is low and the power conversion efficiency is relatively high (Rezaee et al., 2021; Vidal et al., 2021). The perovskite based solar cells are still under development and have not yet been put on the market.

Between the first development of perovskite in 2009 and 2021, the power conversion efficiency (PCE) of perovskite solar cells increased from about 3.5% to 22-23%, which is rapid compared to the development in other types of solar cells. The method brings considerable advantages compared to the production methods of other solar cells in terms of costs and manufacturing, which together with the impressive rate of increase of the PCE, leads to high expectations for commercial production (Bagher, 2015; Park, 2021; Rezaee et al., 2021). Polar aprotic solvents play an essential role in the deposition of the perovskite and thus in the quality of the final perovskite thin films produced.

Bagher (2015) report the use of NMP, Doolin et al. (2021) refers mainly to DMF and to a lesser extent to gamma-butyrolactone (GBL), DMSO, NMP and DMAC, whereas Park (2021) mention NMP, DMSO, GBL, DMAC and 1,3-dimethyl3,4,5,6-tetrahydro-2 (1H)-pyrimidinone

(DMPU) as a solvent and Rezaee et al. (2021) DMF, DMSO, GBL and NMP as most widely used and HMPA, DMI, DMAC, ACN, 2-methoxyethanol (2ME) and 2-butoxyethanol (2BE) to a lesser extent. Search for alternatives was carried out by Gardner et al. (2016) who got good results on perovskite formation for GBL and combinations of GBL with other solvents, whereas Wu et al. (2021) used combinations of ACN and other solvents and reached power conversion efficiencies above 20%. The results show that in laboratory setting alternatives for the DMAC are available.

Photoresist stripper

In the SVHC Annex XV dossier the use of DMAC as a solvent in paint strippers (paint removers) and ink removers is being mentioned (ECHA, 2012a). In Lee (1993) and in OECD (2001) DMAC has been mentioned as solvent in the production of photo-resist stripping compounds for the semiconductor industry. Alternatives mentioned in Lee (1993) comprise NMP, DMSO, DMF and sulfolane, mixtures of these substances or mixtures of these substances with organic amines. An internet search for SDSs for resist removers showed the presence of DMAC in only one product. Most products contained NMP. The data suggest only limited use of DMAC and sufficient alternatives being present.

C.2.2.2. NEP

Use in agrochemicals

The use of NMP in agrochemicals has been described in Hunt and Dale (2018) as the application as co-formulant in herbicide, pesticide and fungicide formulations and the chemical similarity suggest that for NEP this may be the same. One of the safety datasheets for NEP (>99.5% NEP) indicates the use to produce refined oil, lithium-ion batteries, pharmaceuticals, pesticides among others. A few SDSs for pure NEP mention the application as industrial additive and the use in industrial synthesis. However, actual information on the application of NEP and the amounts and on alternatives in these applications is lacking.

Ashcroft et al. (2015) investigated the use of various solvents in pharmaceutical/fine chemicals batch operations on basis of articles published in Organic Process Research & Development between 1997 and 2012. Acetonitrile (ACN), DMF, DMSO, NMP and DMAC were among the top five dipolar aprotic solvents used, with DMAC covering about 10%, while NEP was not mentioned in any of the 388 papers studied. Application of NEP can thus be assumed to be limited and sufficient alternatives seem to be available.

The use of NMP and NEP for peptide synthesis is described in the BASF sales leaflet for solvents for Chemical Synthesis (BASF, 2016). This application is also mentioned in Kerkel et al. (2021), which mentions the use of N-butyl pyrrolidone (NBP) as a substitute for DMF, NMP or NEP in solid-phase peptide syntheses.

Cleaning agent

BASF describes in its sales folder for solvents that NMP and NEP have been employed as an ingredient in paint removers, cleaners and degreasers because of their solvent power for plastics, resins, oils and grease (BASF, 2016). NEP has also been used as an alternative for NMP in paint and varnish strippers and graffiti removers (Brushia, 2019), which is confirmed by the data in various SDSs that show NEP concentrations up to 100%. Among the applications are the use in electronic industry, the medical sector and in the automotive sector (cleaning diesel intake part).

Silberzahn (2013) describes the development of NMP and NEP-free alternatives for coating removers or cleaners used for stripping coatings from aluminum long before the labeling of NMP as reprotoxic/SVHC in 2011. The paper indicates that the use of alternatives may require

technical changes and also may lead to higher energy consumption in case higher reaction temperature needed, but there are also a number of technical advantages in the removal process. There are also alternatives available that function at a similar temperature as NMP and NEP. Silberzahn (2013) indicates that only for some very specific cases, such as cleaning application systems for polyurethane coatings within a very short timeframe during an ongoing production process, still NMP and/or NEP is needed.

Oil field drilling and production operations

No information has been found on this application, neither on the presence of alternatives.

Use in functional fluids

The use of NMP in functional fluids has been described in Hunt and Dale (2018) as the application in cable oils, transfer oils, hydraulic fluids in industrial equipment, coolants, insulators, refrigerants and the chemical similarity suggest that for NEP this may be the same. However, actual information on the application of NEP and on alternatives is lacking.

Road and Construction applications

The use of NMP in road and construction applications has been described in Hunt and Dale (2018) as the application in solvents, cleaners/strippers, adhesives/binders, de-fluxing and waterproofing and the chemical similarity suggest that for NEP this may be the same. The information in various SDSs for some of the adhesives, coatings and putties confirm the use of NEP for the use sector "building and construction" (SU19). Three products were identified for sealing of cement or concrete products and containing up to 7% NEP. No information on alternatives for building and construction in general has been found.

Binders and release agents/Polymer processing

The uses in adhesives, coatings, putties and resins have been described here. The SDSs showed that quite a number of these products contain polyurethane and to a lesser extent other polymers such as polyester.

NEP is mainly used in water-based polyurethane dispersions (PUDs). Chemicals (2022) indicate that in the production of water-based PUDs often NMP and NEP are being used. These PUDs are often marketed as an environment friendly alternative for solvent based polyurethanes. Initially, NEP and DMSO were both assumed to be alternatives to NMP in the preparation of PUDs after the classification of NMP as SVHC. However, it was concluded that NEP was too expensive and insufficiently studied. Ketones, such as acetone or MEK were also considered as possible alternatives (Fernandes, 2015).

The use of NMP and NEP in the preparation of PUDs is confirmed by Farmer et al. (2020) who investigated the application of NMP replacement solvents under the EU Horizon 2020 programme. They indicate that according to industrial PUD producers dimethylolpropanoic acid; 2,2-bis(hydroxymethyl)propionic acid (DMPA), which is essential for obtaining water dispersible polymers, is difficult to dissolve in current PUD formulations. Farmer et al. (2020) further explain the advantages of using NMP and/or NEP for the water borne PUDs. They conclude in their study Resolve that none of the solvents developed in ReSolve are viable alternatives to lactam type solvents, such as NMP and NEP, although various solvents, such as dipropylene glycol dimethyl ether, have been mentioned in the literature as potential alternatives. They recommended follow-up studies with confidential hydroxymethylfurfural solvents in the PUD synthesis under industrially relevant conditions. A UK coating company launched a new range of polyurethane and polyurethane/acrylic dispersions in 2014 that was claimed free of pyrrolidone solvents. The dispersions were claimed to be non-toxic, but the constituents were not disclosed (Incorez, 2021).

McKeen (2006) mentions the use of NEP for the dissolving of PAI resins used in wire coating. They list some commercial PAI resins suitable for coating applications, a few of which containing NEP. Among the other PAI resins, ethanol/toluene is mentioned as solvent.

The use of NEP and GBL have been mentioned as a replacement for NMP in the preparation of PAI resins that was applied in the production of piston coatings, but it was recognized that these solvents pose challenges in terms of occupational health and safety. The retrieved safety datasheets showed that NEP is also applied in practice. One of the data sheets concern an anti-friction coating with NEP concentrations between 32 and 40% NEP. Experiments with three alternative solvents, such as DMPU, 1,3 dimethyl-2-imidazolidinone (DMEU), and 1-methylimidazole (MI), that were compared with PAI resins that were produced using NMP-, NEP- and/or GBL showed 1-methylimidazole to meet the required conditions (Rasheva, 2013). An excellent heat-resistent PAI binder resin that conforms to REACH regulations and does not include restricted substances is commercialized by ShowaDenko. The website indicates that the performance is similar to conventional PAI resin and that it does not contain any Annex XIV or Annex XVII substances. The substitutes used instead of NMP/NEP have not been released (Showa Denko Materials Co., 2021).

NEP has also been used in the manufacturing of PES hollow fibre membranes. PES membranes experimentally produced by NIPS using a more environmentally friendly, green solvent N,N-dimethyl lactamide (AMD) were compared with membranes produced using NEP (Uebele et al., 2021). The authors concluded that AMD is a promising solvent that provide membrane properties competitive with the NEP produced ones.

Use in water treatment chemicals

No information has been found on the application, neither on the presence of alternatives.

Leather finishing agents

Three SDSs concerned leather finishing agents, two containing up to 2.5%, but one containing between 30 and 40% NEP. No information on alternatives has been found, but the limited number of products suggest that in most other agents, other substances are used.

C.2.3. Risk reduction, technical and economic feasibility, and availability of alternatives

C.2.3.1. DMAC

During the last 5-10 years several scientific publications have been published concerning the replacement of the regular aprotic dipolar solvents being used in various separation techniques (Brouwer & Schuur, 2020), the production processes of membranes using NIPS techniques (Figoli et al., 2014), films and coatings, e.g. for the production of perovskite films to be used in solar cells (Doolin et al., 2021; Gardner et al., 2016; McDowell & Bazan, 2017; Park, 2021; Vidal et al., 2021), and the solid phase organic synthesis (SPOS/SPPS) (Lawrenson, 2018), because of their toxicity (McCoy, 2019). Some publications have referred to environmental, health and safety (EHS) considerations applied by large chemical and pharmaceutical firms, such as Sanofi-Aventis, GSK, AstraZeneca and Pfizer, and used a comparable ranking in the selection of safer alternatives (Byrne et al., 2016; Doolin et al., 2021; Wu et al., 2021) or used an alternative EHS assessment (Byrne et al., 2016).

A large part remained in the stage of selecting the proper physical and chemical characteristics or in applying the alternatives in an experimental set-up and it is indicated by several authors

that tailor made solutions have to be applied to come to a successful substitution. Technical equally good alternatives for DMAC in some major applications (solvent in coatings used for wire insulation and process solvent in the production of membranes) seems still to be limited. For other applications (like spinning of fibres, graphene dispersion and cleaners) alternatives are already available and may have been implemented. Table 97 provides an overview of the conclusions for the different uses.

Table 97: Overview of the availability of alternatives for different uses.

Use category	Alternative available	Comment
Uses mentioned in chapter B.2.		
Process solvent and reagent in the production of agrochemicals, pharmaceuticals and fine chemicals	Likely	
Process solvent for spinning of fibres of various polymers including acrylic, polyurethane polyurea copolymer (Elastane, Spandex) and poly(m-phenylene isophthalamide) (PMIA, meta-aramid)	Likely	Use of DMAC mentioned for acrylic and modacrylic fibres, polyurethane fibres and meta-Aramid fibres. DMAC seems to have been phased out for a number of processes in the EEA.
Solvent in coatings e.g. polyamide-imide (PAI) enamels (varnishes) used for electrical wire insulation	Possibly	DMAC possibly used for different kinds of polymers among which PAI enamels.
Process solvent in the production of polysulphone membranes	Possibly	Not only applied for polysulphone membranes, but also for other polymers. Quite some research into potential alternatives for aprotic solvents. Some producers already changed to alternatives., but not clear whether applicable to all polymers and processes
Other uses		
Laboratory uses, Petrochemical applications, Cellulose fibres	Information lacking	
New identified uses		
graphene dispersion/exfoliation	Likely	Mainly experimental application. Alternatives on the market. Economic feasibility of newly developed alternatives still unclear
production of perovskite solar cell	Likely	Experimental stage, promising future product
metal–organic framework (MOF) synthesis	Information lacking	
Old uses		
photoresist stripper	Yes, alternatives available	Very limited use

Likely = substitution seems to be possible for the whole sector
Possibly = substitution on experimental basis of in a part of the sector, but still challenges to come to a general implementation

C.2.3.2. NEP

Data on NEP application is rather scarce, specifically compared to DMAC. The data available from the registration dossiers and from SDSs provided some information although mainly qualitative (Table 98). From the retrieved data the use in cleaners, graffiti and paint removers, in binders and release agents and in polymer processing are the most obvious and suggest that NEP can be substituted in most applications. The information on alternatives for these applications is also limited, but suggest that substitutes are available among which NBP, acetone or MEK, dipropylene glycol dimethyl ether, hydroxymethylfurfural solvents, ethanol/toluene and 1-methylimidazole. For the cleaners, the polyurethane and polyurethane/acrylic dispersions and the PAI resins commercial products not containing NEP are on the market.

Table 98: Overview of the availability of alternatives for different uses of NEP.

Use category	Alternative available	Comment
Uses mentioned in chapter B.2.		
Use in agrochemicals	Likely, but information lacking	use in industrial synthesis, among which pesticides and pharmaceuticals mentioned in SDSs
Cleaning agent	Likely	Graffity and paint removers, detergents, application in medical and electronic industry, application in automotive sector
Oil field drilling and production operations	Information lacking	
Use in functional fluids	Information lacking	
Road and Construction applications	Likely, but information lacking	See two categories below
Binders and release agents	Likely	Adhesives, coatings and putties (some of which with polyester)
Polymer processing	Likely	Application mainly for production of PUDs, and to lesser extent for PAI and PES
Use in water treatment chemicals	Information lacking	
New identified use		
leather finishing agent	Likely	Limited number of products

Likely = substitution seems to be possible for the whole sector
Possibly = substitution on experimental basis of in a part of the sector, but still challenges to come to a general implementation

Alternatives mentioned in the literature for DMAC include ethanol (CAS number 64-17-5), cyclic carbonates such as ethylene carbonate (CAS number 96-49-1) and propylene carbonate (CAS 108-32-7), N-formyl morpholine (CAS number 4394-85-8), dimethylisosorbide (CAS number 5306-85-4), propylene carbonate (CAS number 108-32-7), dihydrolevoglucosenone (Cyrene) (CAS number 53716-82-8), NBP (CAS number 3470-98-2) and 2-MeTHF (CAS number 96-47-9), Polarclean (CAS number 1174627-68-9), GBL (CAS number 96-48-0), DMSO (CAS number 67-68-5), DMPU (CAS number 7226-23-5), HMPA (CAS number 680-31-

9), DMI (CAS number 80-73-9), 2ME (CAS number 109-86-4), 2BE (CAS number 111-76-2) and sulfolane (CAS number 126-33-0) amongst others.

Some of the substitutes are not recommendable from a public health or environmental health perspective such as hexamethylphosphoramide (Muta. 1B, Carc. 1B) and 2-methoxyethanol (Repr. 1B). Other substitutes have other aspects that are not recommendable such as DMSO (penetrant smell and toxic degradation products) and acetone and acetonitrile (flammability). Quite a number of the alternatives do not have a harmonized classification, but rely on a notified classification under the REACH registration such as N-formyl morpholine, polarclean, cyrene, γ-valerolactone, cyclopentyl methyl ether, and glycofurol. Dimethyl isosorbide has not been classified at all. These substances are regularly mentioned in the literature as being more human and environment-friendly than the dipolar aprotic solvents.

The information on alternatives for NEP is limited, but suggest that substitutes are available among which NBP, acetone or MEK, dipropylene glycol dimethyl ether, hydroxymethylfurfural solvents, ethanol/toluene and 1-methylimidazole. A number of these substances are more human and environment friendly than NEP. The marketing of NEP-free products also suggests the possibility of replacement by substitutes.

Although substitution seems to be possible for most application from a technical perspective, as indicated by alternatives used in experimental conditions or alternative production processes, information on the economic feasibility of substitution is very limited. There are a number of examples for the substitution of aprotic solvents in the preparation of pharmaceuticals and in membrane and fibre production that suggest that these may be overcome as well.

C.3. Restriction scenario(s)

As described in section 2.2 in the main report, Restricion option 2 (Binding DNELs: the restriction will prescribe binding DNELs that should be used in CSAs.) will be further assessed for both DMAC and NEP. The following chapters will describe the anticipated response per industry sector (if applicable). The Dossier Submitter assessed which additional OC and RMM could be implemented, next to those already described by most registrants, to reduce the exposure below the DNELs for DMAC and NEP based on the exposure scenarios provided by the Registrants. The suggested OC and RMM are an indication of possible exposure reduction measures. When a limitation in the duration of the task is prescribed to assure that exposure is below the DNEL it is important that, the daily aggregate (*of combined*) exposure should not exceed the DNEL. For NEP, task duration reduction can only be implemented if the inhalation exposure concentration does not exceed the local acute inhalation DNEL of 4.6 mg/m^3 at any given time during the work activity. Practically this implies that prescribing task duration reduction is not suitable for risk reduction in most cases for NEP.

It is anticipated that registrants of DMAC and NEP will update their registration dossiers with additional OC and/or RMM for the various exposure scenarios and use first tier exposure models to estimate inhalation and dermal exposures. The working conditions can vary between sectors and within sectors at workplace level. The details of those workplaces are not in complete view to the Dossier Submitter hence making it difficult to describe measures or combinations of measures to reduce exposure sufficiently. The use of a lower concentration (weight fraction) is indicative of further refinement of the exposure scenario rather than an actual RMM as the Dossier Submitter assumes DMAC or NEP concentrations used in formulations are not higher than technically needed.

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

C.3.1. DMAC

Manufacturing
No risk is identified.

Formulation
A risk is identified via inhalation for PROC5 activities without the use of LEV as not all registrants prescribe the use of LEV for PROC5. It is anticipated that LEV or other OC/RMM will be prescribed in all CSRs for PROC5 to reduce the inhalation exposure concentration below the proposed DNEL with very limited impact on the downstream users.

A risk is identified via dermal exposure for PROC4 and PROC5 formulation activities. A stricter glove regime (with specific activity training) (PROC4) together with other OC/RMM such as task duration reduction (PROC5) is anticipated to reduce the dermal exposure below the proposed DNEL. Limited impact of these additional OC/RMM are foreseen for formulators. Organizational or technical changes might be needed if the above requirements cannot be met, however detailed information on the exact working conditions are not available for the Dossier Submitter.

Charging and discharging
A risk is identified via inhalation for PROC8b activities without the use of LEV as not all registrants prescribe the use of LEV for PROC8b at room temperature. It is anticipated that LEV or other OC/RMM will be prescribed in all CSRs for PROC8b to reduce the inhalation exposure concentration below the proposed DNEL with limited impact on the downstream users. For PROC8a and PROC9 at elevated temperatures a high efficiency (95% reduction) LEV would reduce the the inhalation exposure concentration below the proposed DNEL.

A risk is identified via dermal exposure for all PROCs related to charging and discharging. For PROC9 a stricter glove regime (with specific activity training) could be prescribed to reduce the dermal exposure below the proposed DNEL. For PROC8a and PROC8b a stricter glove regime (with specific activity training) together with other OC/RMM such as task duration reduction or a lower concentration (weight fraction) could reduce the dermal exposure below the DNEL. Limited impact of these additional OC/RMM are foreseen for downstream users as it is expected that either this activity isn't performed a full 8-hour shift or lower concentrations are used. Organizational changes might be needed if the above requirements cannot be met, however detailed information on the exact working conditions are not available for the Dossier Submitter.

Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals
A risk is identified via inhalation for PROC4 activities without the use of LEV as not all registrants prescribe the use of LEV for PROC4. It is anticipated that LEV or other OC/RMM will be prescribed in all CSRs for PROC4 to reduce the inhalation exposure concentration below the proposed DNEL with very limited impact on the downstream users.

A risk is identified via dermal exposure for PROC4, a stricter glove regime (with specific activity training) could be prescribed to reduce the dermal exposure below the proposed DNEL. Limited impact of additional OC/RMM are foreseen for downstream users.

Use as solvent in the production of man-made fibres

A risk is identified via inhalation for this exposure scenario for PROC2, PROC3, PROC13, PROC14 and PROC19 at elevated temperatures and as indicated by measurement results from industry during the production of man-made fibres. The measurement data also shows that exposures can differ between companies. In the CfE it was stated by the man-made fibres sector that the proposed DNEL (as part of a range from 10-15 mg/m^3) might be reached after investments (not further specified). Another company responded in the CfE that additional technical risk reduction measures could be implemented to achieve DMAC workplace exposure levels in the same range of 10-15 mg/m^3. Indeed, measurement data in some registration dossiers show P90 stationary air measurements for most processes to be below the proposed DNEL with the exception for stationary measurements at the spinning process. This indicates that, at least for some companies, the proposed inhalation DNEL is already achieved or can be achieved with the use of additional RMM in those processes where the opportunity for high exposures arises. For other companies additional exposure reduction investments might be necessary to comply with the proposed DNEL.

In addition to the production of man-made fibres for the textile industry and as precursor to carbon fibres, DMAC is used as solvent in the production of hollow fibres used in medical membranes in a similar wet spinning process. Exposure conditions are expected to be similar to the textile and carbon precursor fibre process. Major sites are situated in France and Germany, with the production site in Germany being older. The current OEL in France is 7.2 mg/m^3, therefore it is anticipated that the proposed inhalation DNEL is already technically feasible for relatively new medical membrane assembly lines using hollow fibres. For older production sites outside France additional exposure reduction investments might be necessary to comply with the proposed DNEL.

A risk is identified via dermal exposure for PROC4, PROC13 and especially PROC19. For PROC4, a stricter glove regime (with specific activity training) could be prescribed to reduce the dermal exposure below the proposed DNEL. For PROC13, a stricter glove regime (with specific activity training) together with other OC/RMM such as task duration reduction could reduce the dermal exposure below the DNEL.

The identified risk related to PROC19 is unlikely to be controlled by additional exposure reduction measures. However, the Dossier Submitter only performed a tier I assessment for the dermal exposure for this particular PROC as it does not know the exact working conditions related to this PROC19. Information in the registration dossier about PROC19 indicate these activities are related to maintenance and troubleshooting. Biomonitoring data in some registration dossiers indicate the possibility to reduce the combined exposure in working areas that include PROC19 activities to levels below the proposed BLV with appropriate OC/RMM. However, the data is not specific enough to exclude the identified risk to PROC19 from dermal exposure.

Overall, depending on the type of production process and age of the production lines, additional OC/RMM are foreseen for downstream users. Technical measures are assumed to be feasible by the Dossier Submitter as demonstrated by exposure measurements in some of the registration dossiers. With appropriate OC and RMM, dermal exposure can be reduced below the proposed DNEL. This might be possible for PROC19 activities, although this could not be fully assessed. Biomonitoring data in some registration dossiers show that biomonitoring is used within this sector to evaluate the effectiveness of implemented RMM in general and to further investigate trends and/or high individual results for combined exposures. It is expected that most companies in this sector will implement biomonitoring schemes to evaluate and demonstrate the effectiveness of implemented OC and RMM for those activities with the potential highest exposures.

Use as solvent in coatings
A risk is identified via dermal exposure for all PROCs in this exposure scenario. For PROC7 and PROC10 a stricter glove regime (with specific activity training) together with other OC/RMM such as task duration reduction or a lower concentration (weight fraction) could reduce the dermal exposure below the DNEL. For PROC13 a stricter glove regime (with specific activity training) could be prescribed to reduce the dermal exposure below the proposed DNEL.

Impacts for the wire-coating industry are limited as this sector is in a transition to newer enamel production lines (with associated exposures similar to PROC2 instead of PROC10) due to the NMP restriction. As the NMP restriction will apply from 9th of May 2024 for this sector, it is anticipated that the proposed DNELs has no impact related to the use of DMAC as solvent in the wire coating automated process. However, other activities using DMAC in the production facility, such as charging and discharging or maintenance work, could be impacted by the proposed DNELs.

Little is known about the impact on other sectors than the wire-coating industry, as no information could be found on the specific industrial use of DMAC in coatings for these applications. The registration dossiers indicate the concentration of DMAC in spraying (PROC7) activities to be in the lower end of the 5-25% range used by the Dossier Submitter resulting in a lower expected exposure. Therefore, a limited impact of the proposed DNELs for this activity is anticipated.

Manual maintenance (cleaning and repair) of machinery
A risk is identified via dermal exposure for this exposure scenario. For PROC28 a stricter glove regime (with specific activity training) together with other OC/RMM such as task duration reduction or a lower concentration (weight fraction) could reduce the dermal exposure below the DNEL.

Limited impact of these additional OC/RMM are foreseen as manual maintenance is usually not performed for a full 8-hour shift. Organizational or technical changes might be needed if the above requirements cannot be met, however detailed information on the exact working conditions are not available for the Dossier Submitter

Use as laboratory chemical *(industrial and professional use)*
No risk is identified.

C.3.2. NEP

C.3.2.1. Industrial use of NEP

Manufacturing
A risk is identified via inhalation for PROC2 and PROC3 activities especially at elevated temperatures. For PROC4 a risk is identified only at elevated temperatures. Implementation of LEV for PROC2-4 at room temperature could reduce the inhalation exposure concentration below the DNEL. At elevated temperatures a more dedicated LEV (95% reduction), applied at those points where emissions can occur, could reduce the inhalation exposure concentration for PROC3. For PROC4 this should be combined with other OC/RMM such as enhanced general ventilation to reduce the inhalation exposure concentration below the DNEL.

Limited impact of these additional OC/RMM are foreseen as the manufacturing process is usually well contained and the modelled exposures might be an overestimate; however, no air measurements were available to the Dossier Submitter to evaluate this.

Formulation
A risk is identified via inhalation or combined exposure for PROC2, PROC3 and PROC5 activities. Implementation of LEV for PROC2 and PROC3 could reduce the inhalation exposure concentration below the DNEL. For PROC5 a more dedicated LEV (95%) or a stricter glove regime (with specific activity training) could reduce the combined exposure at room temperature. At elevated temperatures a more dedicated LEV (95%) in combination with enhanced general ventilation could reduce the inhalation exposure concentration below the proposed DNEL.

Limited impact of these additional OC/RMM are foreseen for formulators as some registrants already prescribe some of the anticipated RMM. However, as not all registrants currently prescribe these RMM, it cannot be excluded that some downstream users need to implement additional RMM or OC, although the exact number of affected downstream users is not known to the Dossier Submitter.

Charging and discharging
A risk is identified via inhalation for PROC8a and, in case no LEV is applied, for PROC8b and PROC9 as not all registrants prescribe the use of LEV. It is anticipated that LEV or other OC/RMM, such as increased general ventilation, will be prescribed in all CSRs to reduce inhalatory exposure concentration below the proposed DNEL.

Limited impact of these additional OC/RMM are foreseen for downstream users as some registrants already prescribe some of the anticipated RMM. However, as not all registrants currently prescribe these RMM, it cannot be excluded that some downstream users need to implement additional RMM or OC, although the exact number of affected downstream users is not known to the Dossier Submitter.

Use as solvent in industrial processes
A risk is identified via inhalation for PROC2 and PROC3 activities. Implementation of LEV for PROC2 and PROC3 could reduce the inhalation exposure concentration below the DNEL.

Limited impact of these additional OC/RMM are foreseen for formulators as some registrants already prescribe some of the anticipated RMM. However, as not all registrants currently prescribe these RMM, it cannot be excluded that some downstream users need to implement additional RMM or OC, although the exact number of affected downstream users is not known to the Dossier Submitter.

Use as solvent in coatings
A risk is identified via inhalation and dermal exposure for PROC7 (at room temperature) and via inhalation exposure for PROC2, PROC10 and PROC 13 (at elevated temperatures). For PROC10 and PROC13 there is a risk identified from combined exposure.

At elevated temperatures additional LEV could be applied in case of PROC2; for PROC10 and PROC13 other OC/RMM such a more dedicated LEV (95% reduction), applied at those points where emissions can occur, and enhanced general ventilation could be implemented to reduce the inhalatory exposure concentration below the DNEL. For PROC10 and PROC13 at room temperature, OC/RMM such as a lower concentration (weight fraction) or a stricter glove regime (with specific activity training) could reduce the combined exposure.

The impact of these additional OC/RMM for the use of NEP as solvent in coatings could be limited, except for PROC7 and PROC13 (at elevated temperatures). According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC7. Although this leads to lower exposure, additional OC/RMM might still be needed to reduce the inhalatory exposure. On the other hand, other registration dossiers did not limit the concentration of NEP for PROC7. If NEP is used in high

concentrations for PROC7 activities, it is unlikely this use can continue with the proposed DNELs without considerable technical investments or the use of RPE. However detailed information on the concentration of NEP in these products, and their market share, is not available for the Dossier Submitter. The proposed inhalatory DNEL can have a substantial impact for PROC13 activities at elevated temperatures as various measures might be needed to reduce the inhalation exposure concentration, however detailed information on the exact working conditions or the specific sector of use is not available for the Dossier Submitter.

Limited impact is foreseen for PROC2 and PROC10 (at elevated temperatures) activities as these relate to the wire-coating industry where enamel formulations without NEP are available.

Manual maintenance (cleaning and repair) of machinery
A risk is identified via combined exposure for outdoor activities. OC/RMM such as a lower concentration (weight fraction) or task duration reduction could reduce the combined exposure.

Limited impact of these additional OC/RMM are foreseen as manual maintenance is usually not performed for the full 8-hour shift. Organizational or technical changes might be needed if the above requirements cannot be met, however detailed information on the exact working conditions are not available for the Dossier Submitter.

Use as laboratory chemical
No risk is identified.

Binder and release agent
A risk is identified via dermal and inhalation exposure for PROC7. For all other PROCs, a risk is identified via combined exposure. A stricter glove regime (with specific activity training) together with other OC/RMM such as enhanced general ventilation, task duration reduction and/or a lower concentration could reduce the combined exposure for all PROCs.

The impact of these additional OC/RMM for the use of NEP in binder and release agents could be limited, except for PROC7. According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC7. Although this leads to lower exposure, additional OC/RMM might still be needed to reduce the combined exposure. On the other hand, other registration dossiers did not limit the concentration of NEP for PROC7. If NEP is used in high concentrations for PROC7 activities it is unlikely this use can continue with the proposed DNELs without considerable technical investments or the use of RPE. However detailed information on the concentration of NEP in these products, and their market share, is not available for the Dossier Submitter.

Cleaning agents
A risk is identified via dermal and inhalation exposure for PROC7. For PROC13 a risk is identified via inhalation at elevated temperatures, for all other PROCs, a risk is identified via combined exposure. A stricter glove regime (with specific activity training) together with other OC/RMM such as enhanced general ventilation and/or a lower concentration could reduce the inhalation concentration and combined exposure for all PROCs.

The impact of these additional OC/RMM for the use of NEP cleaning agent could be limited, except for PROC7 and PROC13 (at elevated temperatures). According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC7. Although this leads to lower exposure, additional OC/RMM might still be needed to reduce the combined exposure. On the other hand, other registration dossiers did not limit the concentration of NEP for PROC7. If NEP is used in high concentrations

for PROC7 activities it is unlikely this use can continue with the proposed DNELs without considerable technical investments or the use of RPE. However detailed information on the concentration of NEP in these products, and their market share, is not available for the Dossier Submitter. The proposed inhalatory DNEL can have a substantial impact for PROC13 activities at elevated temperatures as various measures might be needed to reduce the inhalation exposure concentration, however detailed information on the exact working conditions or the specific sector of use is not available for the Dossier Submitter.

Oil field drilling and production operations; Functional fluids; Polymer processing and Water treatment.
Current small-scale use, and associated risks, of NEP in these sectors cannot be excluded by the Dossier Submitter at this moment. Any still existing use of NEP in these activities is expected to be substituted soon as the registrant indicated these uses will not be included in the next update of the registration dossier. Therefore, the Dossier Submitter expects no impact of the proposed DNELs for these sectors.

C.3.2.2. Professional use of NEP

Charging and discharging
A risk is identified mainly via inhalation for all PROCs. Implementing LEV at those points where emissions can occur together with other OC/RMM such as enhance general ventilation, a lower concentration (weight fraction) and/or task duration reduction could reduce the combined exposure. For PROC8a RPE might be needed in addition to the OC/RMM described above.

Substantial impacts cannot be excluded for the professional use of NEP as not all downstream users may have dedicated facilities with LEV installed for the transfer of NEP. Alternatively RPE could be used although this is recommended only for incidental, short- time, activities and not for 8-hour shifts.

Use as solvent in coatings
A risk is identified via inhalation and dermal exposure for all PROCs. According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC10, PROC11 and PROC19 indicating lower expected exposures. Still, additional OC/RMM might be needed to reduce the dermal exposure in PROC19 below the proposed DNEL. On the other hand, other registration dossiers did not limit the concentration of NEP for PROC10, PROC11 and PROC19. If NEP is used in high concentrations for these activities, it is unlikely this use can continue with the proposed DNELs without considerable technical investments to reduce the exposures. For PROC13, OC/RMM a lower concentration (weight fraction) could reduce the combined exposure.

Detailed information on the concentration of NEP used in coatings is not available for the Dossier Submitter, although the relevant chapter of the CEFIC, the 1,4 butanediol Derivatives Sector Group, indicated that the use of NEP in coatings has either already been phased out by companies or is expected to be phased out. Specialised coatings might still contain NEP although in very low concentration (<0.1%). Additional research on NEP uses in SDSs indicate the use of NEP in coatings with concentrations mostly within a range from <0.5% to 10%. There are however also products available with NEP concentrations >50-100%.

The use of NEP as solvent in coating at low concentrations is expected to continue when inhalatory concentrations are estimated using higher tiered models with more specified working conditions or workplace measurements. Use of NEP as solvent in coatings at higher concentration is unlikely to continue without considerable technical investments to reduce the exposures.

Manual maintenance (cleaning and repair) of machinery
A risk is identified via the combined exposure indoors and outdoors. As RPE is prescribed it is recommended to limit this activity only for incidental, short- time, activities and not for 8-hour shifts thereby lowering the combined exposure below the DNELs for indoor activities. For outdoors a risk is identified via inhalation and although this activity could be time-limited, the inhalation concentration still exceeds the acute local inhalation DNEL. A more efficient RPE (95% efficiency) could reduce the inhalatory exposure concentration below the proposed DNEL.

Limited impact of additional OC/RMM are foreseen for downstream users as manual maintenance is usually not performed for the full 8-hour shift and outdoor activities could continue with a more efficient RPE (95%). Organizational or technical changes might be needed if the above requirements cannot be met, however detailed information on the exact working conditions are not available for the Dossier Submitter

Use as laboratory chemical
A risk is identified via inhalation exposure. OC/RMM such as enhanced ventilation/higher LEV efficiency could reduce the inhalatory exposure below the DNEL.

Limited impact of additional OC/RMM are foreseen for downstream users as use of NEP in small scale laboratory is usually performed within a fume hood with a higher ventilation efficiency.

Binder and release agent
A risk is identified for all PROCs mostly via inhalatory and dermal exposures. According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC10 and PROC11 indicating lower expected exposures. Still, additional OC/RMM might be needed to reduce the dermal exposure in PROC11 below the proposed DNEL. On the other hand, other registration dossiers did not limit the concentration of NEP for PROC10 and PROC11. If NEP is used in high concentrations for these activities, it is unlikely this use can continue with the proposed DNELs without considerable technical investments to reduce the exposures, especially for PROC11 where RPE is already included as RMM. For PROC13, a lower concentration (weight fraction) could reduce inhalatory exposure concentration.

The use of NEP as binder and release agent at low concentrations is expected to continue when inhalatory concentrations are estimated using higher tiered models with more specified working conditions or workplace measurements. Use of NEP as binder and release agent at higher concentration is unlikely to continue without considerable technical investments to reduce the exposures. Although detailed information on the concentration of NEP in these products, and their market share, is not available for the Dossier Submitter, the impact of the proposed restriction is assumed to be minor.

Cleaning agents
A risk is identified for all PROCs mostly via inhalatory and dermal exposures. According to one registration dossier the concentration of NEP is limited to the lower end of the 5-25% range used by the Dossier Submitter for PROC10 and PROC11 indicating lower expected exposures. Still, additional OC/RMM might be needed to reduce the dermal exposure in PROC11 below the proposed DNEL. On the other hand, other registration dossiers used NEP in the concentrations indicated by the Dossier Submitter for PROC10 and PROC11. If NEP is used in the higher concentration range for these activities, it is unlikely this use can continue with the proposed DNELs without considerable technical investments to reduce the exposures, especially for PROC11 where RPE is already included as RMM. For PROC13, a lower concentration (weight fraction) could reduce inhalatory exposure concentration.

Although the concentration of NEP should be limited according to the registration dossiers, it appears some products are currently on the market with a higher NEP concentration up to even 100% NEP for graffiti removers. The use of NEP as cleaning agent at low concentrations is expected to continue when inhalatory concentrations are estimated using higher tiered models with more specified working conditions or workplace measurements. Use of NEP as cleaning agent at higher concentration is unlikely to continue without considerable technical investments to reduce the exposures. Although detailed information on the concentration of NEP in these products, and their market share, is not available for the Dossier Submitter, the impact of the proposed restriction is assumed to be minor.

Use as excipient in agrochemicals; Functional fluids; Road and construction applications and Polymer processing
Current small-scale use, and associated risks, of NEP in these sectors cannot be excluded by the Dossier Submitter at this moment. Any still existing use of NEP in these activities is expected to be substituted soon as the registrant indicated these uses will not be included in the next update of the registration dossier. Therefore, the Dossier Submitter expects no impact of the proposed DNELs for these sectors.

C.4. Economic impacts

Described in the main report

C.4.1. Human health and environmental impacts

C.4.1.1. Human health impacts

Described in the main report

C.4.1.2. Environmental impacts

Not relevant for this dossier

C.5. Risk reduction capacity

Described in the main report

C.6. Other impacts, practicability and monitorability

Described in the main report

Annex D: Assumptions, uncertainties and sensitivities

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

D.1 Identification of key uncertainties

Based on the examination of every part of the previous assessment, a list of identified key uncertainties is compiled. Both uncertainties associated with the assessment inputs (e.g. data, estimates, other evidence) and uncertainties related to the methodologies (e.g. statistical methods, calculations or models, reasoning, expert judgement) applied to the scientific assessment are considered. In addition, uncertainties are assessed as standard or non-standard. Standard uncertainties are considered explicitly or implicitly addressed by the provisions of a standardised procedure or standardised assessment element. Normally, standard uncertainties do not need to be re-evaluated in each assessment that follows the defined standard procedure because they should have been assessed when the standard procedure was established. If this is not the case, the uncertainty is a non-standard uncertainty. As they are not addressed by any standardised assessment procedures, the identified non-standard uncertainties must be analysed in a case-specific way. This is done in the subsequent steps of the uncertainty analysis. Table 99 summarises the identified uncertainties.

Table 99: Identified uncertainties in the assessment.

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
Section 1.1.4 and B.5., Hazard assessment	1	Study reliability, e.g. key study of Klimisch score 2. Studies of Klimisch score 1 could provide more reliable data.	[X]		S
	2	Differences in exposure conditions, e.g. higher respiratory volume human at the workplace versus rat in rest. This is corrected with default values.		[X]	S

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	3	Route-to-route extrapolation, e.g. oral-to-dermal route and oral-to-inhalation route. Data of relevant exposure routes not always available. Extrapolation used to estimate exposure levels.		[X]	S
	4	Assessment factors, e.g. inter- and intraspecies differences. Individual differences and species differences. This is corrected with default values based on expert judgement.		[X]	S
	5	BMD analysis, e.g. setting of BMR at 1, 5 or 10% increased risk or change. The BMR can be set at a different level based on expert judgement.		[X]	NS
Section 1.1.5 and B.9, Exposure assessment	6	In line with the registrants' CSRs ECETOC TRA v3 is selected as first-tier model to estimate worker inhalatory and dermal exposure. Applying higher-tier exposure tools might result in more specific exposure scenario's with different exposure estimations, however this requires more detailed information of the working conditions, which is not available to the Dossier Submitter.		[X]	S
	7	The exposure scenario and selected PROCs originate from the registration dossier. The Dossier Submitter is not sure if all described exposure scenarios and tasks (expressed in PROCs) are still performed. This concern is supported by communication with industry in which they indicate that some exposure scenarios will not be included in the updated CSR.	[X]		S

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	8	ECETOC TRA v3 inhalation validation results indicate a low level of conservatism for PROC5, PROC7, PROC14 and PROC19 activities, possibly resulting in an underestimation of exposure via inhalation.		[X]	S
	9	ECETOC TRA v3 inhalation validation results indicate an overestimation of the efficiency of LEV for PROC7, PROC8a, PROC10, PROC13, PROC14, PROC19 activities, possibly resulting in an underestimation of exposure via inhalation.		[X]	S
	10	ECETOC TRA v3 validation results indicate an overestimation of dermal exposure for PROC1-PROC3 activities.		[X]	S
	11	ECETOC TRA v3 validation results indicate an underestimation of dermal exposure for PROC6, PROC7, PROC10, PROC11, PROC17 and PROC19 activities.		[X]	S
	12	RMM/OC are applied that are considered common industry standard, although these are not prescribed by all registrants in their CSRs. This may result in an underestimation of exposure in some particular working situations.	[X]		NS
	13	Default (reasonable) worst-case RMM and protection factors are applied for the use of general ventilation systems, gloves and RPE. A broader range of protection factors is applied by some registrants. Applying default factors is believed to result in an overestimation of exposure when in practice a higher reduction can be reached.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	14	For PROC1-PROC3 activities LEV, gloves or RPE are not applied by the dossier submitter, resulting in an overestimation of exposure when in practice these RMM are applied.	[X]		NS
	15	A full-shift eight hour is assumed by the dossier submitter for all activities, possibly resulting in an overestimation of exposure when in practice activities are performed during a shorter period and no other activities with the substance are performed.	[X]		NS
	16	Although the Dossier Submitter modelled identical processes with multiple variations of OC and RMM and provided information on the input data for the exposure modelling, resulting in exposure modifying factors, the representativeness of the modelled data for the different sites and uses remains uncertain.		[X]	S
	17	Process temperatures indicated in the CSRs might not correspond well with the actual temperature of the product to which the worker is exposed, resulting in some uncertainty with regard to the correctness of the selected volatility category.	[X]		NS
	18	The lack of representative measured air concentrations (personal sampling) for each (sub-) sector leads to some uncertainty with regard to the inhalation exposure.	[X]		S
Section 1.1.6 and B.10 Risk assessment	19	The conclusion on risks is sometimes based on the combined RCRs although the most sensitive endpoint may differ between the inhalation and dermal route.		[X]	S
Section 1.3 and A.1-A.3 Baseline	20	There is limited information on the use of NEP and number of workers exposed to NEP.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	21	The number of workers potentially exposed to DMAC is only described for a few sectors where DMAC is used.	[X]		NS
Section 2.3 and C.3 Restriction scenario	22	No details of working conditions at workplace level are available for DMAC and NEP, therefore it is not known, at a workplace level, which measures, or combination of measures, are needed to reduce exposure sufficiently.	[X]		NS
	23	Limited information is available about the actual concentration of NEP in formulations used in industrial and professional settings. The impact of the proposed restriction on the continued use of these formulations is uncertain.	[X]		NS
Section 2.4 Economic impacts	24	Not all anticipated OC or RMM could be monitised; e.g. increased ventilation or LEVs and task duration reduction.	[X]		NS
	25	The duration of the specific activity training for a stricter gloves regime, as well as the group size per training are based on judgement.	[X]		NS
	26	The time investment for occupational hygienists and number of measurements per worker in biomonitoring campaigns is based on expert judgement.	[X]		NS
	27	The time investment for preparing a DU CSR is based on expert judgement.	[X]		NS
Section 2.7 Proportionality	28	Proportionality is assessed based on only a partial quantification of the costs.	[X]		NS
	29	Only one (NMP) of the two other restrictions on dipolar aprotic solvents had sufficient information to derive a benchmark. Benchmarks could only be derived for two sectors affected by the NMP restriction.	[X]		NS

Section of the Restriction Report	Identified key uncertainties		Source of uncertainty		Standard (S) vs. non-standard (NS) uncertainties
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology	
	30	A discount rate of 4% is used.		[X]	NS

The described uncertainties about the hazard assessment (No. 1-4) represents a standard uncertainty because it is explicitly provided for by the standardised procedure used for deriving DNELs as set out in the REACH Guidance Chapter R.8 (ECHA, 2012b). Default assessment factors are applied that address the uncertainties for inter- and intraspecies differences and exposure duration as well as differences in exposure routes and other exposure conditions.

The described uncertainty about the exposure assessment (No. 6) represents a standard uncertainty because it is explicitly provided for by the pragmatic work flow as described in REACH Guidance Chapter R.14 (ECHA, 2016a). First applying a Tier-1 model, in line with the registrants, is a common practice in REACH worker exposure assessment. This results overall in more generic exposure scenarios applying default exposure parameters and taking into account the fact that more detailed information on the working conditions is not available.

The described uncertainty about the exposure assessment (No. 7) represents a standard uncertainty because it is implicitly provided for by the standardized procedure used for assessing use scenarios of substances through the supply chain. As long as certain uses are still included in the registrants' registration dossiers the Dossier Submitter is of the opinion that it cannot be excluded that DMAC and NEP are used in these applications and therefore an exposure scenario is included in this dossier.

The described uncertainties about the exposure assessment (No. 8-11) represent a standard uncertainty because it is implicitly provided for by the standardized procedure used for assessing worker exposure with ECETOC TRA. ECETOC TRA validation study results for both inhalation and dermal exposure, describing possible under- or overestimation of exposure, are described (Marquart et al., 2017; Schlueter & Tischer, 2020) and taken into account when determining whether or not there is a risk for a certain process category.

The described uncertainty about the exposure assessment (No. 16) represents a standard uncertainty because it is implicitly provided for by the standardized procedure used for assessing use scenarios of substances through the supply chain. The representativeness of the modelled data for all the different sites and uses of DMAC and NEP remains uncertain. Applying ECETOC TRA, with default reasonable worst-case exposure parameters, results in more generic exposure scenarios that are considered to cover a wide range of workplace situations further down the supply chain.

The described uncertainty about the exposure assessment (No. 18) represents a standard uncertainty because it is explicitly provided for by the standardized procedure used for the exposure estimation (ECHA, 2016a). Available measurement data are evaluated and where possible used to refine the exposure estimations. When no measurement data are available ECETOC TRA exposure estimations are used as a starting point. These exposure estimations are subsequently evaluated using ECETOC TRA validation study results for both inhalation and dermal exposure, describing possible under- or overestimation of exposure (Marquart et

al., 2017; Schlueter & Tischer, 2020). The evaluation of the modelled exposure estimates results in a reasonable worst-case exposure estimate that can be used for the risk assessment.

The described uncertainties about the risk assessment (No. 19) represent a standard uncertainty because it is explicitly provided for by the standardised procedure used for deriving RCRs as set out in the REACH Guidance Part E: Risk Characterisation (ECHA, 2016b). The formula to describe the overall combined risk is recommended to use as a default, conservative, approach when the toxicity profile is similar for the different exposure routes and the difference in the ratio between the DNELs for the target organ (the liver in this case) is not too large. For DMAC this ratio is below two. For NEP liver toxicity at higher inhalation exposure concentrations cannot be excluded.

D.2. Sensitivity analysis

The following step in the uncertainty analysis aims to evaluate the relative importance of different sources of uncertainty. For each identified uncertainty, first, sensitivity analysis is used to apply different possible inputs and/or methodological choices to the assessment and compare the outcomes to the results of the initial assessment. Then, influence analysis further considers the effects that the analysed sensitivities could exert on the overall outcomes and conclusions of the Annex XV restriction report, both individually and collectively.

D.2.1. Uncertainty 5: Setting of the BMR

Uncertainty about the most appropriate BMR per endpoint can be expected to affect the derived DNELs as with a different BMR the PoD value, and hence the DNEL, changes. The Dossier Submitter did not analyse all relevant endpoints with multiple endpoint specific BMR values as this was considered too laborious. Instead, relative liver weight, body weight and foetal body weight are assessed with a BMR of 5% and 10% change and all malformations are assessed with a BMR of 1% and 10% extra risk in appendix I. The Dossier Submitter deviated from the default BMR values for continuous data (5% change) suggested by EFSA (EFSA, 2017) for relative liver weight and body weight (10%). For quantal data the Dossier Submitter uses a BMR of 1% extra risk for malformations and post-implantation loss instead of the default 10%.

The impact of a different BMR value on the PoD may differ between the analysed endpoints. This impact depends on the specific dose-response curve for that endpoint and on the quality of the underlying data. In case of a steep dose-response curve, the change in the BMR value has a less profound impact on the PoD compared to a shallower dose-response curve. The underlying data may not be sufficiently informative to derive a PoD related to a different BMR which is too small or too large, i.e. when extrapolation outside the dose range occurs or when the required BMR falls within the experimental noise. In such cases an additional assessment factor may be required, e.g. to extrapolate from a measurable risk to a lower, acceptable risk.

A complete overview of the differences in PoD, per endpoint, substance and exposure route, due to deviating from the default BMRs can be found in Appendix I. Its influence on the corresponding DNELs will be assessed in the sections below.

D.2.2. Uncertainty 12: RMM/OC are applied that are considered common industry standard, although not prescribed by all registrants

Uncertainty about the applied RMM/OC can be expected to affect the exposure estimation outcomes as derived by the Dossier Submitter. The Dossier Submitter uses a standardized exposure assessment approach and applies the use of LEV as risk management measure for processes where exposure is likely to occur. The specific impact of selecting LEV depends on the process category and is in the range of 80-95% reduction of exposure. When these RMM are not applied by industry the actual exposure concentrations therefore can be 80-95% above the estimated concentrations by the Dossier Submitter. Its influence on the exposure concentrations will be assessed in the sections below.

D.2.3. Uncertainty 13: Default RMM and protection factors are applied, although registrants use a broader range of protection factors

Uncertainty about the applied RMM/OC can be expected to affect the exposure estimation outcomes as derived by the Dossier Submitter. The Dossier Submitter uses a standardized exposure assessment approach and for certain process categories applies default (reasonable) worst-case RMM and protection factors for the use of general ventilation systems, gloves and RPE. A broader range of protection factors is applied by some registrants. In addition, sometimes the Dossier Submitter applies RMM while the registrant does not and vice versa. To test how other RMM affect the estimated exposure, the impact of applying these RMM is presented in Table 100 together with the default RMM applied by the Dossier Submitter. Its influence on the exposure concentrations will be assessed in the sections below.

Table 100: Sensitivity analysis for the application of default RMM and applied protection factors.

RMM	- RMM not applied or lower reduction factor	Default RMM by Dossier Submitter	+ RMM applied or higher reduction factor
General ventilation	-	No advanced general ventilation – only basic ventilation	30-70% reduction of exposure
Gloves (industrial use)	80% reduction of exposure	90% reduction	95% reduction of exposure
Gloves (professional use)	-	80% reduction	90-97% reduction of exposure
RPE	-	No RPE	90-95% reduction of exposure
	No RPE	90% reduction	95% reduction of exposure

D.2.4. Uncertainty 14: RMM are not applied for PROC1-PROC3 activities, although registrants sometimes apply RMM for these activities

Uncertainty about RMM not applied by the Dossier Submitter can be expected to affect the exposure estimation outcomes as derived by the Dossier Submitter. The Dossier Submitter

uses a standardized exposure assessment approach and for PROC1-3 applies no RMM like general ventilation, LEV, gloves or RPE. Registrants sometimes apply RMM for these activities, especially for PROC2 and PROC3 activities. To test how the application of RMM affects the estimated exposure, the impact of applying these RMM is presented in Table 101 together with the default RMM applied by the Dossier Submitter. Its influence on the exposure concentrations will be assessed in the sections below.

Table 101: Sensitivity analysis for the application of additional RMM by registrants for PROC1-PROC3 activities.

RMM	**Default RMM by Dossier Submitter**	**+ RMM applied**
General ventilation	No advanced general ventilation – only basic ventilation	30% reduction of exposure
Local exhaust ventilation	No local exhaust ventilation	90% reduction of exposure
Gloves	No gloves	80% reduction of exposure
RPE	No RPE	-

D.2.5. Uncertainty 15: An eight-hour task duration is assumed, although registrants sometimes apply a shorter task duration

Uncertainty about the applied task duration reduction can be expected to affect the exposure estimation outcomes as derived by the Dossier Submitter. The Dossier Submitter uses a standardized exposure assessment approach and assumes a full-shift eight-hour task duration. Registrants sometimes apply a shorter task duration. To test how the application of a reduced task duration affects the estimated exposure, the impact of applying this operational condition is presented in Table 102 together with the default RMM applied by the Dossier Submitter. Its influence on the exposure concentrations will be assessed in the sections below.

Table 102: Sensitivity analysis for the application of a reduced task duration as Operational Condition by registrants.

Operational condition	**Default selection by dossier submitter**	**+ Operational condition applied**
Task duration reduction	No task duration reduction	40-80% reduction of the eight-hour average exposure

D.2.6. Uncertainty 17: The process temperature might not correspond well with the actual temperature of the product to which the worker is exposed

Uncertainty about the process temperature and the corresponding volatility category can be expected to affect the inhalation exposure estimation outcomes as derived by the Dossier Submitter. The Dossier Submitter uses information on process temperatures provided in the registration dossiers and background documents as input for the inhalation exposure assessment. However the actual temperature of the product to which the worker is exposed

can be different than the process temperature. As temperature affects the vapour pressure of the substance, this might result in a higher or lower ECETOC TRA volatility category. For DMAC low, medium and high volatility categories are applied for the inhalation exposure estimation. For NEP only low and medium volatility categories are selected. To test how the selection of a higher volatility category affects the inhalation exposure estimate, the impact of the volatility category on inhalation exposure is presented in Table 103 together with the default category applied by the Dossier Submitter. Its influence on the inhalation exposure concentrations will be assessed in the sections below.

Table 103: Sensitivity analysis for the selection of different volatility categories.

Substance	Low volatility category	Medium volatility category	High volatility category
DMAC	Default category based on vapour pressure at 25 °C	Factor 2-10 higher exposure compared to low volatility category	Factor 5-50 higher exposure compared to low volatility category and factor 2-6 higher exposure compared to medium volatility category.
NEP	Default category based on vapour pressure at 25 °C	Factor 2-10 higher exposure compared to low volatility category	-

D.2.7. Uncertainty 20: Limited information on the use of NEP and number of workers exposed to NEP

Uncertainty about the use of NEP and the number of workers exposed to NEP can be expected to affect the impact assessment of the proposed restriction. It remains unclear how industrial and professional use is affected by the proposed restriction and how the proposed restriction reduces the worker population at risk in absolute numbers. In addition, no information is available on the number of workers exposed to NEP, or companies working with NEP. Due to the lack of information, it remains uncertain if, and how many, downstream users would need to implement additional LEV or would substitute NEP for alternative solvents. The Dossier Submitter has no available data and cannot make an expert judgement, to justify a central estimate with an upper or lower bound for these uncertainties. The influence on the impact assessment will be assessed in the sections below.

D.2.8. Uncertainty 21: The number of workers potentially exposed to DMAC is only described for a few sectors where DMAC is used

Uncertainty about the number of workers potentially exposed to DMAC can be expected to affect the impact assessment of the proposed restriction. It remains unclear how the proposed restriction reduces the worker population at risk in absolute numbers. The Dossier Submitter has no available data and cannot make an expert judgement, to justify a central estimate with an upper or lower bound for the other sectors. Its influence on the impact assessment will be assessed in the sections below.

D.2.9. Uncertainty 22: No details of working conditions at workplace level are available for DMAC and NEP, therefore it is not known, at a workplace level, which measures, or combination of measures, are needed to reduce exposure sufficiently.

Uncertainty about the measures, or combination of measures, that are needed to reduce the exposure at workplace level can be expected to affect the impact assessment and proportionality of the proposed restriction by changing the estimation of the total cost per worker. As conservative approach the Dossier Submitter provides a cost estimate for all measures combined which corresponds to an upper bound (only for those measures that are quantified) implying that there is some risk of overestimation. Its influence on the proportionality will be assessed in the sections below.

D.2.10. Uncertainty 23: Limited information is available about the actual concentration of NEP in formulations used in different sectors.

Uncertainty about the concentration of NEP in formulations used in industrial and professional setting can be expected to affect the impact assessment of the proposed restriction (see also uncertainty 20). It remains unclear how industrial and professional use is affected by the proposed restriction as the extent to which additional OC and RMM need to be implemented depends on the concentration of NEP on these formulations. According to the available information from SDSs there is a wide range in used concentrations. However, the Dossier Submitter cannot make an expert judgement for a central estimate with an upper or lower bound for the share of different concentration ranges of NEP in formulations per sector. Its influence on the impact assessment will be assessed in the sections below.

D.2.11. Uncertainty 24: Not all anticipated OC or RMM could be monitised; e.g. increased ventilation or LEVs and task duration reduction.

Uncertainty about the costs of OC or RMM can be expected to affect the impact assessment of the proposed restriction by changing the estimation of the cost per worker to reduce exposure levels below the proposed DNELs. As described in section 2.4.1. of the Annex XV restriction report an estimation was not possible given the wide variety of (site-specific) parameters that need to be considered when designing an effective system and the resulting lack of generic cost estimates. The Dossier Submitter has no available data, or can make an expert judgement, to justify a central estimate with an upper or lower bound for the costs associated with the implementation of LEV.

The related costs of a reduction of the time that a worker is tasked with an activity with a significant exposure potential could not be assessed as this requires detailed information of the company processes at the individual workplace. The Dossier Submitter has no available data and cannot make an expert judgement, to justify a central estimate with an upper or lower bound for the costs associated with task duration reduction. The influence on the impact assessment will be assessed in the sections below.

D.2.12. Uncertainty 25: The duration of the specific activity training for a stricter gloves regime, as well as the group size per training are based on judgement.

Uncertainty about the costs of the specific activity training for a stricter gloves regime can be

expected to affect the impact assessment of the proposed restriction by changing the estimation of the cost per worker to reduce exposure levels below the proposed DNELs. The duration of the specific activity training is based on expert judgement by the Dossier Submitter. In the Annex XV restriction report a lower and upper bound for the time investment for workers and trainer is already included to provide a minimum and maximum value. The group size is set at 20 participants, however, could be higher or lower depending on company specifics such as on-site facility capacities and the number of workers performing specific tasks. To test how the group size affects the average cost estimate, a range of 50%, i.e. 10 and 30 participants, is used as lower and upper bound in Table 104. The influence on the impact assessment will be assessed in the sections below.

Table 104: Sensitivity analysis for the cost estimate per worker per training for the implementation of a stricter glove regime (with specific activity training by changing the group size.

Sector	**Average cost estimate (€/worker)**		
	Group size 10	Group size 20	Group size 30
Formulation	280	250	230
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	250	220	210
Use as solvent in the production of man-made fibres	170	140	130
Use as solvent in coatings (wire coaters)	140	110	100
Use as solvent in the production of polysulphone membranes	160	130	120
Use as solvent in coatings (other)	170	130	120
Binder and release agent	170	130	120
Cleaning agents	180	140	130

D.2.13. Uncertainty 26: The time investment for occupational hygienists and number of measurements per worker in biomonitoring campaigns is based on expert judgement.

Uncertainty about the time investment for occupational hygienist as well as the number of measurements per worker per year for the biomonitoring campaign can be expected to affect the impact assessment of the proposed restriction by changing the estimation of the cost per worker to reduce exposure levels below the proposed DNELs. The estimates are made based on expert judgement and are tested using a range of 50%, i.e. 4.5 and 13.5 working days per measurement round, as a lower and upper bound for the time investment. For the number of measurements per worker per year a lower bound of once every year and an upper bound of three times a year is used. The results are presented in Table 105. The influence on the impact assessment will be assessed in the sections below.

Table 105: Sensitivity analysis for the cost estimate for a biomonitoring campaign per worker per year by changing the time investment needed for occupational hygienist and the number of measurements per worker per year.

Sector	**Average cost estimate (€/worker/year)**					
	Time investment (total days per measurement round)			Number of measurement rounds per worker per year		
	-50%	9	+50%	-50%	2	+50%
Formulation	370	490	620	300	490	690
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	360	480	610	290	480	680
Use as solvent in the production of man-made fibres	330	450	580	260	450	640
Use as solvent in coatings (wire coaters)	310	440	570	250	440	630
Use as solvent in the production of polysulphone membranes	320	450	570	260	450	640
Use as solvent in coatings (other)	320	450	580	260	450	640

D.2.14. Uncertainty 27: The time investment for preparing a DU CSR is based on expert judgement.

Uncertainty about the time investment for occupational hygienist to prepare a DU CSR can be expected to affect the impact assessment of the proposed restriction by changing the estimation of the cost per worker to reduce exposure levels below the proposed DNELs. The estimates are made based on expert judgement and are tested using a range of 50% as a lower and upper bound for the number of exposure scenarios to be included and the time investment needed preparation and site visit, time per exposure scenario and time for risk characterisation and reporting. The results are presented in Table 106. The influence on the impact assessment will be assessed in the sections below.

Table 106: Sensitivity analysis for the cost estimates for the preparation and update of a DU CSR (excluding measurement costs) by changing the time investment needed for occupational hygienist and the number of exposure scenarios per CSR.

Cost description	**Cost estimate (€)**					
	Time investment (total days per DU CSR)			Number of exposure scenarios per DU CSR		
	-50%	6	+50%	-50%	4	+50%

Preparation of a DU CSR based on higher tier models or measurement campaign	1 300	2 700	4 000	1 800	2 700	3 600

D.2.15. Uncertainty 28: Proportionality is assessed based on only a partial quantification of the costs.

Uncertainty about the quantification of all costs can be expected to affect the impact assessment of the proposed restriction option by changing the proportionality assessment. As described above (see uncertainty 24), not all anticipated OC or RMM could be monitised and the Dossier Submitter has no details of working conditions at workplace level to indicate which measures, or combination of measures, are needed to reduce exposure sufficiently (see uncertainty 22). Therefore, the Dossier Submitter is unable to make an informed estimate about the share of the quantified costs in relation to the total costs. Its influence on the proportionality assessment will be assessed in the sections below.

D.2.16. Uncertainty 29: Only one (NMP) other restriction had sufficient information to derive a benchmark.

Uncertainty about the representativeness of the benchmark can be expected to affect the impact assessment of the proposed restriction by changing the proportionality assessment. Two benchmark figures could be derived based on the NMP restriction which provides limited information for the comparative approach. The Dossier Submitter has no other available data to estimate other benchmarks and nor does it provide lower or upper bounds for the estimated benchmarks. The information used for the derivation of the benchmark originates from the SEAC opinion on NMP (ECHA, 2014b). Some of the used information was provided by producers (e.g. wire coating) themselves. The Dossier Submitter therefore sees no reason to adjust this input other than for inflation correction.

D.2.17. Uncertainty 30: A discount rate of 4% is used.

Uncertainty about the discount rate can be expected to affect the impact assessment of the proposed restriction by changing the proportionality assessment. The ECHA Guidance on Socio-Economic Analysis (ECHA, 2008) recommends a discount rate of 4% and this value was used as point estimate in the impact assessment. The recent edition of the EU Better Regulation Toolbox (European Commission, 2021) suggests using a discount rate of 3%, providing a lower bound compared to the point estimate used in the impact assessment. This lower bound is used to test how the outcome of the cost estimates, expressed as present value over a 15-year period, may vary depending on the choice for the discount rate. The results are presented in Table 107. The influence on the proportionality assessment will be assessed in the sections below.

Table 107: Sensitivity analysis for the cost estimates, i.e. cost per exposed worker, of the proposed restriction in PV over a 15-year period by changing the discount rate.

Sector	**Cost description (€/worker) (average)**			
	Implementation of a stricter glove regime	**Biomonitoring campaign**	**DU CSR**	**All measures combined**
	Discount rate	Discount rate	Discount rate	Discount rate

	4%	3%	4%	3%	4%	3%	4%	3%
Formulation	790	830	5 700	6 100	24	32	6 500	6 900
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	710	750	5 600	6 000	24	32	6 300	6 700
Use as solvent in the production of man-made fibres	450	470	5 200	5 600	21	29	5 700	6 100
Use as solvent in coatings (wire coaters)	350	360	5 100	5 400	24	31	5 400	5 800
Use as solvent in the production of polysulphone membranes	410	430	5 200	5 500	24	32	5 600	6 000
Use as solvent in coatings (other)	430	460	5 200	5 500	24	32	5 700	6 000
Binder and release agent	430	460	-		24	32	460	490
Cleaning agents	460	480	-		24	32	480	510

D.3. Influence analysis

The influence analysis further considers the effects that the analysed sensitivities could exert on the overall outcomes and conclusions of the Annex XV restriction report, both individually and collectively.

D.3.1. Uncertainty 5: Setting of the BMR

The influence of setting different BMRs for DMAC is reflected in Table 108. Using the default BMR values would result in a five times lower dermal DNEL compared to the proposed dermal DNEL. This would affect the possibility to implement additional OC and RMM to reduce the dermal exposure below the lower DNEL and influences the possibility of continued industrial use of DMAC. In the latter case, it is more likely the restriction will not be proportional.

Table 108: DNEL derivation for DMAC for workers using the default BMR values as suggested by EFSA (EFSA, 2017) for continuous and quantal data. Highlighted in yellow are the changes from the original table.

DNEL (endpoint)	BMDL, species	Type of study	BMR and type of effect	Correction for differences in	Corrected BMDL	Assessment factors	Resulting DNEL	Reference

				exposure conditions				
Inhalation								
Repeated dose toxicity	65 mg/m³, mouse	Combined chronic toxicity and carcinogenicity study – life time	10% increased incidence of hepatic Kupffer cell pigmentation	6/8 6.7/10	32.7 mg/m³	1 – (AS) 2.5 – (RD) 5 – (IS) Total: 12.5	2.6 mg/m³	DuPont (1994); Malley et al. (1995)
Repeated dose toxicity	21.7 mg/m³, human (workers)	Retrospective epidemiological study	No effect level based on blood liver function test (ALT levels)	-	-	-	22 mg/m³	Antoniou et al. (2021)
Developmental toxicity	320 mg/m³ rabbit	PNDT – GD 7-19	10% increased incidence of visceral variations	6/8 6.7/10	161 mg/m³	1 – (AS) 2.5 – (RD) 5 – (IS) Total: 12.5	13 mg/m³	BASF (1989); Klimisch and Hellwig (2000)
Dermal								
Repeated dose toxicity	3.8 mg/kg bw/day, rat	Combined chronic toxicity and carcinogenicity study, oral drinking water– 2 years	5% increased relative liver weight	7/5 100% uptake assumed	26.6 mg/kg bw/day	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	0.11 mg/kg bw/day	Monsanto (1980, 1990, 1993)
Developmental toxicity	120 mg/kg bw/day, rat	PNDT oral gavage– GD 7-21	5% decreased foetal body weight	100% uptake assumed	120 mg/kg bw/day	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	2.4 mg/kg bw/day	DuPont (1997)
AS: allometric scaling, GD: gestational day, IS: intraspecies factor, PNDT: prenatal developmental toxicity study, RD: remaining (toxicokinetic/dynamic) differences, ALT: alanine aminotransferase								

The influence of setting different BMRs for NEP is reflected in Table 109. Using the default BMR values would result in a two times lower dermal DNEL compared to the proposed dermal DNEL and a dermal risk would be identified for most uses of NEP. Subsequent implementation of a (stricter) gloves regime is needed to reduce dermal exposure to this lower dermal DNEL. This is unlikely to affect the conclusion on proportionality as implementation of (stricter) gloves regime is considered proportional, however, in combination with the implementation of LEV it could negatively affect the proportionality.

Table 109: DNEL derivation for NEP for workers using the default BMR values as suggested by EFSA (EFSA, 2017) for continuous and quantal data. Highlighted in yellow are the changes from the original table.

DNEL (endpoint)	BMDL, species	Type of study	BMR and type of effect	Correction for differences in exposure conditions	Corrected BMDL	Asessment factors	Resulting DNEL	Reference
Inhalation								
Local toxicity	57 mg/m^3, rat	28-day RDT, inhalation	10% increased degeneration/regeneration of olfactory epithelium		57	2.5 – (RD) 5 – (IS) Total: 12.5	4.6 mg/m^3	BASF (2011)
Repeated dose toxicity	200 mg/m^3, rat	90-day RDT, inhalation	no systemic effects at highest dose (200 mg/m^3)	6/8 6.7/10	101	2.5 – (RD) 5 – (IS) 2 – (ED) Total: 25	4.0 mg/m^3	BASF (2013a)
Developmental toxicity	82 mg/kg bw/day, rabbit	PNDT, oral-gavage GD 6-28	10% increased skeletal variations	70/10	574	2.4 – (AS) 2.5 – (RD) 5 – (IS) Total: 30	19 mg/m^3	BASF (2007b)
Dermal								
Repeated dose toxicity	80 mg/kg bw/day, rat	90-day RDT, oral-feed	5% increased relative liver weight	7/5 100% uptake assumed	112	4 – (AS) 2.5 – (RD) 5 – (IS) 2 – (ED) Total: 100	1.1 mg/kg bw/day	BASF (2006)
Developmental toxicity	330 mg/kg bw/day, rat	PNDT, dermal GD 6-19	5% decreased foetal body weight	6/8 100% uptake assumed	248	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	5.0 mg/kg bw/day	BASF (2005)
AS: allometric scaling, GD: gestational day, IS: intraspecies factor, PNDT: prenatal developmental toxicity study, RD: remaining (toxicokinetic/dynamic) differences, ED: exposure duration, RDT: repeated dose toxicity								

D.3.2. Uncertainty 12: RMM/OC are applied that are considered common industry standard, although not prescribed by all registrants

Applying default common industry standards like LEV has an impact on the exposure assessment, particularly for those activities where the registrants do not apply LEV. In that case the actual exposure concentrations can be 80-95% above the estimated concentrations by the Dossier Submitter. The Dossier Submitter however believes that LEV is a common industry practice that is applied for most situations where exposure is likely to occur. This is confirmed by information received from industry via the CfE. For many activities the RMM applied by the Dossier Submitter are similar with those applied by most registrants. The influence of applying default common industry standards like LEV on the exposure estimations is therefore considered to be minor for most of the workplaces, however, for some exposure scenarios the Dossier Submitter estimated the exposure with and without the use of LEV to provide an estimation of the exposure, and subsequent risk, in case registrants do not apply LEV and common industry standards are not applied.

D.3.3. Uncertainty 13: Default RMM and protection factors are applied, although registrants use a broader range of protection factors

Applying default RMM and protection factors has an impact on the exposure assessment, particularly for those activities where the registrants apply lower or higher reduction factors. In that case the exposure can be under- or overestimated. For many activities the RMM and protection factors applied by the Dossier Submitter are similar with those applied by most registrants. Where RMM or protection factors deviate, the Dossier Submitter applies default (reasonable) worst-case reduction factors that are expected to be achieved in industrial or professional settings. The influence of applying default RMM and protection factors on the exposure estimations is considered minor and does not impact the conclusion on the exposure assessment.

D.3.4. Uncertainty 14: RMM are not applied for PROC1-PROC3 activities, although registrants sometimes apply RMM for these activities

Applying no RMM like general ventilation, LEV, gloves or RPE for PROC1-3 activities has an impact on the exposure assessment. This is especially true for PROC2 and PROC3 activities where registrants sometimes apply one or more of these RMM, resulting in a lower estimated exposure. For DMAC in many cases the registrant also does not apply RMM for PROC1-3 activities. For NEP the registrants often apply some RMM for PROC2 and PROC3 activities, resulting in a lower exposure. The Dossier Submitter assumes that PROC1-3 activities (based on the general description given in REACH Guidance document R.14, (ECHA, 2016a)) take place in closed continuous or batch processes, with limited manual interventions, including closed sampling. Because of the available level of containment in which these processes take place no additional LEV, gloves or RPE are considered relevant. This is considered a (reasonable) worst-case approach that reflects processes performed in closed systems where addition RMM are not likely. The availability of advanced general ventilation systems (resulting is a reduction of exposure concentrations) is considered to be possible and applied by some NEP registrants. The Dossier Submitter applies only indoor use with basic ventilation as a reasonable worst-case exposure estimate, because it cannot be excluded that activities take place in less well-ventilated areas. The influence on the exposure estimations is considered minor and does not impact the conclusion on the exposure assessment.

D.3.5. Uncertainty 15: An eight-hour task duration is assumed, although registrants sometimes apply a shorter task duration

Applying no task duration reduction has an impact on the exposure assessment, especially for situations where registrants do apply a reduced task duration. For most activities a task duration of eight hours is applied by both the Dossier Submitter and the registrants. In a few situations the registrants apply a shorter task duration (<1 or <4 hours), resulting in a lower estimated daily exposed dose. The Dossier Submitter does not account for possible consecutive tasks or processes for a worker when a specific process is time limited. It is acknowledged that exposure for a worker may be underestimated if he/she continues work in other processes, however as no information is available on the daily activities of workers for all exposure scenarios and all contributing scenarios, such correction is impossible to make. In this restriction report all exposure estimates are performed by applying an exposure duration of eight hours. The influence of applying no task duration reduction on the exposure estimations is considered minor and does not impact the conclusion on the exposure assessment.

D.3.6. Uncertainty 17: The process temperature might not correspond well with the actual temperature of the product to which the worker is exposed

Applying different volatility categories has an impact on the exposure assessment. When a medium or high volatility category is selected (e.g. based on information of the process temperature) this results in an estimated exposure that is 2-50 times higher than the estimated exposure applying the low volatility category. For most activities that are performed at elevated temperatures there is sufficient information to correctly select the relevant volatility class and the same classes are applied by the Dossier Submitter and the registrants.

Only for the manufacturing of DMAC there is uncertainty in the selected volatility category. The selected high volatility category results in very high estimated exposures. Exposure measurement results demonstrate a lower exposure, indicating that the temperature of the product to which the worker is exposed corresponds better to a low or medium volatility category. The influence of applying different volatility categories on the exposure estimations is in general considered to be minor and does not impact the conclusion on the exposure assessment except for the manufacturing of DMAC, where the influence is considered high. In this scenario, inhalation measurement results are preferred above the modelled estimates and thus does not impact the conclusion on the exposure assessment.

D.3.7. Uncertainty 20 & 21: Limited information on the use of NEP and number of workers exposed to NEP or DMAC.

The absence of the number of workers exposed to NEP or DMAC has an impact on the health impact assessment as no estimate could be provided for expected health benefits of the proposed restriction in terms of number workers for which their health risks are reduced to an acceptable level. Although relevant information, it does not influence the outcome of proportionality assessment as a comparative approach is taken where costs are expressed as costs per worker for exposure reduction. A change in the number of workers exposed above the DNELs would change the absolute costs of the restriction, however, the total risk reduction would change in the same manner and the proportionality would remain the same. The influence of limited use information of NEP is discussed in together with uncertainty 23 below.

D.3.8. Uncertainty 22: No details of working conditions at workplace level are available for DMAC and NEP, therefore it is not known, at a workplace level, which measures, or combination of measures, are needed to reduce exposure sufficiently.

The influence of using an upper bound (only for those measures that are quantified) cost estimate in the proportionality assessment is limited as this does not affect the conclusion on proportionality.

D.3.9. Uncertainty 23: Limited information is available about the actual concentration of NEP in formulations used in different sectors.

The absence of information on the use of NEP and concentration of NEP in formulations has a minor influence on the cost estimate. Especially for formulations with a high concentration of NEP it is anticipated that its use will be discontinued, and NEP will be substituted. The Dossier Submitter did not receive indications of NEP having a critical function in these formulation for which no alternative would be available. On the contrary, information from SDSs for professional use indicates a generic product purposes for which less hazardous alternatives are available. Substitution costs are not estimated but expected to be minor.

D.3.10. Uncertainty 24 & 28: Not all anticipated OC or RMM could be monitised; e.g. increased ventilation or LEVs and task duration reduction. Proportionality is assessed based on only a partial quantification of the costs.

The absence of cost estimates for the implementation of LEVs and implementation of task duration reduction influences the proportionality assessment as not all anticipated costs could be included. Associated costs could be substantial and might change the conclusion on proportionality; this uncertainty is regarded as the most important factor influencing the proportionality assessment.

D.3.11. Uncertainty 25: The duration of the specific activity training for a stricter gloves regime, as well as the group size per training are based on judgement.

A change in group size has a minor impact on the cost estimate (present value over 15-year period) for a stricter glove regime used in the proportionality assessment and does not influence the conclusion on proportionality.

D.3.12. Uncertainty 26: The time investment for occupational hygienists and number of measurements per worker in biomonitoring campaigns is based on expert judgement.

Changes in the time investment for occupational hygienists and the number of measurements in biomonitoring campaigns have an impact on the cost estimate (present value over 15-year period) (Table 110) but does not influence the conclusion on proportionality.

Table 110: Influence of upper boundaries of time investment for occupational hygienists and number of measurements per worker in biomonitoring campaign on the average cost estimate (present value over a 15-year period) used in the proportionality assessment.

Sector	**Cost description (€/worker)**	
	Average	+50% time investment & +50% number of measurement rounds
Formulation	5 700	10 000
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	5 600	9 900
Use as solvent in the production of man-made fibres	5 200	9 500
Use as solvent in coatings (wire coaters)	5 100	9 400
Use as solvent in the production of polysulphone membranes	5 200	9 500
Use as solvent in coatings (other)	5 200	9 500

D.3.13. Uncertainty 27: The time investment for preparing a DU CSR is based on expert judgement.

Applying the upper boundaries for the number of exposure scenario and the time investment from the sensitivity analyses leads to a twice as high cost estimate for the preparation of a DU CSR. However, this does not influence the conclusion on proportionality mainly because the costs of the preparation of a DU CSR are marginal compared to the other cost estimates.

D.3.14. Uncertainty 29: Only one (NMP) other restriction had sufficient information to derive a benchmark.

The conclusion on proportionality is based on a benchmark derived for the wire coating sector in the NMP restriction dossier and opinion development. A different value for this benchmark value could influence the conclusion of the proportionality assessment, however the Dossier Submitter does not have arguments to deviate from the used benchmark.

D.3.15. Uncertainty 30: A discount rate of 4% is used.

A change in discount rate has a minor impact on the cost estimate (present value over 15-year period) for the combination of measures used in the proportionality assessment and does not influence the conclusion on proportionality. In addition, the cost figures used to derive the benchmark value for the wire-coating sector affected by the NMP restriction has been calculated using a 4% discount rate. In order to use this benchmark value in the comparative proportionality assessment, the costs estimated for the proposed restriction should use a 4% discount rate as well.

D.4. Collective influence of uncertainties on the restriction proposal

In order to gain an impression of the joint influence of the quantified uncertainties described above this part of the analysis will implement best-case assumptions for all uncertainties and compare the resulting conclusions on the proposed restriction with the other extreme scenario of implementing only worst-case assumptions for all uncertainties. This best-case and worst-case analysis will thus demonstrate how far all the elements together may shift the conclusion in one or the other direction.

For the non-quantified uncertainties, the performed analysis of sensitivities and influences helps to allocate relative priorities to uncertainties for the benefit of better coordination of the subsequent analysis of uncertainties. The assignment of priority levels to uncertainties accounts for two factors, the relative magnitude of the uncertainty itself and the relative impact on the results of the Annex XV restriction report:

- Priority 1: Uncertainties of largest magnitude and highest potential impact on the results
- Priority 2: Uncertainties of comparatively small magnitude but comparatively high potential impact on the results
- Priority 3: Uncertainties of comparatively large magnitude but comparatively low potential impact on the results
- Priority 4: Uncertainties of smallest magnitude and lowest potential impact on the results

D.4.1. Hazard assessment

The uncertainty described for the hazard assessment, setting the BMR value, affects the risk and impact assessment for DMAC and NEP. For DMAC, it also affects the proportionality assessment. Its effect is independent on the other described uncertainties and therefore is not further assessed in the collective influence of uncertainties.

D.4.2. Exposure assessment

The collective influence of the exposure assessment uncertainties on the conclusions of this restriction report is described below. The standard uncertainty related to the applied worker exposure model is accounted for in the risk assessment by comparing modelled estimated inhalation concentrations with inhalation measurement data and by considering the exposure model validation study results.

The non-standard uncertainties of the exposure assessment are described in detail in D.2. Sensitivity analysis and D.3. Influence analysis The influence of applying default RMM/OC and default protection factors on the exposure estimations is in general considered minor. This is mainly because for most activities the RMM/OC applied by the Dossier Submitter are similar to those applied by the registrants. Because of the large variety in activities and exposure parameters, these uncertainties are not separately quantified any further by applying the best-case and worst-case approach. Instead, three main categories of uncertainties are identified that are described qualitatively below and subsequently prioritized in Table 111.

- Compensation (uncertainties 12-15): The Dossier Submitter deviates from the RMM applied by the registrant, however this does not result in a significantly different estimated exposure. For instance when the Dossier Submitter applies LEV and the registrant does not, this does not automatically result in a different exposure estimate, because the registrant might apply other RMM/OC like enhanced ventilation, a shorter task duration or the use of RPE and thereby arrive more or less at the same exposure estimate as the Dossier Submitter. In that case one RMM is compensated with another RMM. The difference in exposure estimation outcomes through compensating RMM/OC is less than a factor two.
- Deviation (uncertainties 12-15): The Dossier Submitter deviates from the RMM applied by the registrant and this is not compensated for by other RMM/OC applied by the registrant. For many activities the RMM applied by the Dossier Submitter are similar to those applied by most registrants. Where the Dossier Submitter deviates it usually concerns one exposure parameter, e.g. the application of LEV where the registrant does not or vice versa. The difference in exposure estimation outcomes as a result of applying or not applying one additional RMM depends on the specific activity and is between a factor 5-20. In this restriction report this results mainly in an overestimation of exposure by the Dossier Submitter.
- Volatility category (uncertainty 17): The Dossier Submitter applies a volatility category based on the information on process temperatures provided in the registration dossiers and background documents, provided by industry or literature, as input for the inhalation exposure assessment. Actual process temperatures may differ from the process temperature of the selected volatility category. Especially for manufacturing of DMAC and NEP the selected volatility category by the Dossier Submitter is expected to be conservative, resulting in a higher estimated exposure. The difference in exposure estimation outcomes as a result of applying a higher or lower volatility category depends on the specific activity and is between a factor 2-10 (medium instead of low volatility) or a factor 5-50 (high instead of low volatility). In the manufacturing exposure scenario for DMAC, inhalation measurement results are preferred above the modelled estimates and therefore the impact of the selected volatility category on the exposure assessment is

reduced.

In Table 111, the main categories of identified non-standard uncertainties as described above are assigned priority levels according to their potential to change the conclusions of the exposure assessment.

Table 111: Prioritisation of main categories of identified uncertainties

Identified uncertainties		Priority [1-4]
12-15	Compensation of one RMM with other RMM	3
12-15	Deviation of RMM	1
17	Volatility category	3

D.4.3. Impact assessment

D.4.3.1. Assessment of quantified uncertainties

The outcome on the cost estimate for all measures combined using the best and worst-case assumptions described in the sensitivity assessment is stated in Table 112. The average value is given for the central estimate whereas the lower or higher value of the calculated range is given for the best-case and worst-case estimate, respectively. The discount rate is kept at 4% (see section D.3.10.)

It should be noted that by using the cost estimate for all measures combined in the proportionality assessment, this already reflects the upper boundary of the quantified costs. In addition, lower costs are expected if part of the time investments are undertaken by in-house occupational hygienists assuming that existing staff members have sufficient spare capacity. The table below therefore overestimates the best-case value.

Table 112: Collective influence of uncertainties on the cost estimate, i.e. cost per exposed worker, of all measures combined for the proposed restriction in present value over a 15-year period

Sector	Cost description (€/worker) (min-max)		
	Best-case (min)	**Central estimate (average)**	**Worst-case (max)**
Formulation	2 500	6 500	15 000
Use as solvent in the production of agrochemicals, pharmaceuticals and fine chemicals	2 400	6 300	15 000
Use as solvent in the production of man-made fibres	1 900	5 700	14 000

Use as solvent in coatings (wire coaters)	1 700	5 400	14 000
Use as solvent in the production of polysulphone membranes	1 800	5 600	14 000
Use as solvent in coatings (other)	1 900	5 700	14 000
Binder and release agent	180	460	900
Cleaning agents	190	480	900

D.4.3.2. Assessment of non-quantified uncertainties

In Table 113, the non-quantified uncertainties are assigned different priority levels according to their potential to change the conclusions of the impact assessment.

Table 113: Prioritisation of identified non-quantified uncertainties

Identified uncertainties		**Priority [1-4]**
20	Limited information on the use of NEP and number of workers exposed to NEP	3
21	The number of workers potentially exposed to DMAC is only described for a few sectors where DMAC is used	3
22	No details of working conditions at workplace level are available for DMAC and NEP, therefore it is not known, at a workplace level, which measures, or combination of measures, are needed to reduce exposure sufficiently.	4
23	Limited information is available about the actual concentration of NEP in formulations used in different sectors.	3
24	Not all anticipated OC or RMM could be monitised; e.g. increased ventilation or LEVs and task duration reduction.	1
28	Proportionality is assessed based on only a partial quantification of the costs.	1
29	Only one (NMP) other restriction had sufficient information to derive a benchmark.	3

D.5. Conclusion about uncertainties

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

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

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

The non-quantified costs associated with implementation of additional OC and RMM to comply with the proposed DNELs would negatively affect the proportionality. The proportionality assessment in the main restriction report however indicates that some additional investments achieving compliance would not affect the conclusion on proportionality.

Annex E: Stakeholder information

A call for evidence was launched in preparation of the Annex XV restriction report on 18th of December 2019. The deadline for providing input was on the 13th of March 2020. The text of the call for evidence is provided below. Several targeted follow up information requests were sent because of the information provided in the call for evidence for further clarification or additional questions. In addition, two separate meetings were held with the man-made fibre (IVC) sector and with wire coating sector (EWWA).

E.1. Call for Evidence specific information requests

Introduction

Following the Commission's Regulatory Management Option Analysis (RMOA) Conclusion Document on DMAC, DMF and NMP (https://echa.europa.eu/documents/10162/12a07361-9d62-65cf-48e9-5cd6b461cc9a), Bureau REACH of the Netherlands is preparing an Annex XV restriction dossier on the use of N,N-dimethylacetamide (DMAC, CAS 127-19-5, EC 204-826-4) and 1- ethylpyrrolidin-2-one (NEP, CAS 2687-91-4, EC 220-250-6).

DMAC and NEP are REACH registered aprotic solvents, both with an EU harmonised classification in Annex VI of CLP as Repro Cat 1B, that appear to be used by the same sectors, namely as solvent for production of other chemicals (pharmaceuticals, agrochemicals and fine chemicals); for production of synthetic fibres, textiles and artificial leather; industrial coatings; films, paint strippers and cleaners. Since December 2011 DMAC is listed as a Substance of Very High Concern (SVHC) on the Candidate list for Annex XIV.

Elements of an Annex XV assessment

The elements that need to be considered during the preparation of a restriction proposal are set out in Annex XV of REACH and further elaboration in ECHA Guidance documents.

These can be summarised, as follows:

- A characterisation of exposure and resulting risks to human health from a use of a substance, including via food and water;
- A characterisation of exposure and resulting risks to the environment and wildlife from a use of a substance;
- A justification that risks are not adequately controlled and occur on a Union-wide basis;
- An analysis of the availability and technical performance of alternatives;
- A socio-economic analysis (e.g. costs and benefits to society) that would arise from a restriction.

Objective

The objective of this call for evidence is to gather (updated) information from relevant stakeholders for the preparation of an Annex XV restriction dossier on DMAC and NEP. In 2011, ECHA prepared an Annex XV SVHC dossier for identification of DMAC as SVHC and industry provided input in consultations. The results of this previous consultation will be used in conjunction with the registration information (the comments received are summarised in https://www.echa.europa.eu/documents/10162/95105cf0-affb-4fd7- b9bb-c6923e793dd8).

For DMAC, this call for evidence invites stakeholders to indicate any changes in uses, quantities, expected trends and worker exposure measurements or, where appropriate, to reaffirm the information provided in the registration dossiers and in the ECHA background document referenced above.

For NEP, information will be taken from the registration dossiers, and the call for evidence invites stakeholders to update (where appropriate) their registration dossiers and/or provide information on uses, quantities, expected trends and worker exposure measurements.

In addition, information is requested on additional exposure reduction measures and their effectiveness and costs; estimates of the number of workers involved in the different sectors and information on alternatives to the use of DMAC and NEP (hazard and risk profile of alternatives, their technical characteristics and substitutability for the restricted substances and their costs).

Stakeholders are also invited to point out any specific areas of interest/concern in case of a restriction e.g. possibilities to curtail exposure via technical measures, potential for additional use of PPEs (Personal Protective Equipment) and/or organisational/administrative measures.

Evidence and information to be collected

The objective of this call is to gather information or comments on:

1. For DMAC and/or NEP, information on the (company and/or sector level) quantities in use for the different sectors of activity and the trends in the last ten years as well as the foreseen future market demands expected for these substances.

2. For DMAC and/or NEP, information on the number of companies working with DMAC and/or NEP, the number of workers employed potentially exposed to DMAC and/or NEP, and worker exposure measurements for your specific sector and, where possible, indicate if the numbers are likely to increase or decrease in the near future.

3. The option for mandatory DNELs, similar to the (proposed) restrictions of NMP and DMF, is currently being explored. Acknowledging that the DNELs proposed by the Netherlands may be modified by the RAC as part of the opinion forming on any submitted proposal, we provide two indicative ranges of possible mandatory DNELs for DMAC and NEP, both for inhalation and dermal effects:

DMAC	*Indicative DNEL range A*	*Indicative DNEL range B*	*Current DNELs*[*]
Inhalation Systemic effects - Long-term	1-5 mg/m3 TWA	10-15 mg/m3 TWA	23-36 mg/m3 TWA
Dermal Systemic effects - Long-term	1-5 mg/kg bw/day	5-10 mg/kg bw/day	11-13.6 mg/kg bw/day

[*]Based on the registration dossiers of DMAC

NEP	*Indicative DNEL range A*	*Indicative DNEL range B*	*Current DNELs*[*]
Inhalation Systemic effects - Long-term	0.5-2 mg/m3 TWA	4-7 mg/m3 TWA	16.75 mg/m3 TWA
Dermal Systemic effects - Long-term	0.3-1.2 mg/kg bw/day	2-3 mg/kg bw/day	4 mg/kg bw/day

[*]Based on the registration dossiers of NEP

In case of a mandatory DNEL in either range A or B, do you consider the introduction of additional engineering or organisational measures to reduce exposures such as closed systems, increased automation, etc. as technically and economically feasible? Do you consider a need for any other additional measure(s) to manage the proper use of the solvents?

Additionally, provide specific information on the economic impacts of the introduction of such engineering measures or any other measures you may have in your specific sector of activity. You may also provide reasons why certain measures would not be applicable for your sector of activity.

4. In case you consider that exposure reduction is practically non-feasible for your specific sector of activity, what would be your anticipated response to a proposed restriction? Furthermore, what would be the economic impact for your own business and other actors in your sector and supply chain if DMAC and/or NEP is restricted as proposed in the EU?

5. Information on the suitability and availabilities of alternatives (including other substances or other technologies) for any industrial and professional use of DMAC or NEP. In case there are no available alternatives, it would be useful to receive information on the possible technical or economic difficulties for substitution (e.g. related to qualification of alternatives for safety critical uses), prices of alternative substances or technologies and other relevant information on substitution costs.

6. In case you are aware of other administrative or regulatory changes (national or other) affecting the use of DMAC and/or NEP in the near future e.g. introduction of new Best Available Technique reference documents (BREFs) under the IPPC Directive (1996/61/EC), please provide that information.

Additional relevant information for the preparation of an Annex XV restriction dossier is also welcome. General information on the exposure for these two substances will be taken from the available registration dossiers. Therefore, if outdated and particularly on OCs (Operational Conditions) or RMMs (Risk Management Measures) currently in place in the different sectors, these should also be updated.

Who should participate in the call for evidence?

This call for evidence is intended for interested parties such as companies (manufacturers, suppliers, distributors, importers etc.), trade associations, scientific bodies and any other stakeholders or Member States holding relevant information. Information can be submitted confidentially and will be treated as such by ECHA and the Dossier Submitter.

The information provided will be used to determine if any derogations would be necessary in the event that a restriction was proposed. However, derogations cannot be proposed without adequate information on risk and socio-economic information, including alternatives. If a derogation is not proposed in the initial restriction proposal then it will be incumbent on relevant stakeholders to provide a full justification based on a comprehensive information on risk, socio-economic elements and alternatives, during the opinion-making process.

ECHA invites interested parties to respond to the call for evidence by 13 March 2020.

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