Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Background document

to the Opinion on the Annex XV dossier proposing restrictions on 1-methyl-2-pyrrolidone (NMP)

ECHA/RAC/RES-O-0000005316-76-01/F

ECHA/SEAC/RES-O-0000005316-76-02/F

EC Number	CAS Number
212-828-1	872-50-4

25 November 2014

The confidential information in this Background Document has been deleted (marked with XXXX throughout the document).

The assessments by RAC and SEAC are presented in the boxes.

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BACKGROUND DOCUMENT TO RAC AND SEAC OPINIONS ON
1-METHYLPYRROLIDIN-2-ONE (NMP)

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A. Proposal

A.1 Proposed restriction(s)

A.1.1 The identity of the substance(s)

- Substance name: N-methylpyrrolidone
- IUPAC name: 1-methylpyrrolidin-2-one
- EC number: 212-828-1
- CAS number: 872-50-4
- Structural formula: C5H9NO

A.1.2 Scope and conditions of restriction(s)

Proposed restriction:
NMP may only be manufactured and used if it can be guaranteed that under normal operating conditions the exposure (as 8-hr TWA (time-weighted average) will remain below 5 mg/m^3. Peak exposures (15 min. STEL (short-term exposure limit)) must remain below 10 mg/m^3 and must be compensated by lower exposures during the same day in order to remain below the 8-hr TWA value. To give industry sufficient time to adjust their equipment, the restriction entries into force 60 months after inclusion in Annex XVII.

Further NMP may only be manufactured and used if dermal exposure is avoided with protective clothing and gloves, which comply with the requirements of Council Directive 89/686/ECC or other measures.

The exposure level (both inhalation and dermal) must be guaranteed by the use of preventative measures that are applied in the order of the so-called "hierarchy of control", an established concept referred to in the Chemical Agents Directive (Directive 98/24/EC), i.e. substitution, enclosure, increased local exhaust ventilation, increased general ventilation, change in operational conditions and if needed personal protective equipment.

The proposed exposure limits takes into account the use of respiratory and dermal protective equipment, other preventative measures are however preferred (as indicated in the Chemical Agents Directive).

Manufacturers and industrial and professional users of NMP must be able to demonstrate at the request of the local authorities that they comply with the above restrictions. This can be done by maintaining an exposure monitoring program in accordance with the BOHS / NVAA[1] Standard or national equivalent.

Table A.01: *Proposed restriction.*

Column 1. **Designation of substance**	***Column 2.*** **Conditions of restriction**
XX. N-methylpyrrolidone (NMP) • EC number: 212-828-1 • CAS number: 872-50-4	Shall not be manufactured and used by professional or industrial worker after [xx.yy.zzzz], unless: • the 8-hour time-weighted average exposure will remain below 5 mg/m^3 and the 15 min peak exposure remains below 10 mg/m^3. and • dermal exposure is avoided by preventative measures.

[1] *Testing Compliance with Occupational Exposure Limits for Airborne Substances. BOHS / NVAA, 2011*
http://www.bohs.org/StandardCopyPage.aspx?id=97&terms=testing%20compliance

Taking into account modification of the RMO3 proposed by RAC and comments provided by Forum, the following wording is proposed by RAC and SEAC:

Column 1. **Designation of substance**	***Column 2.*** **Conditions of restriction**
XX. N-methylpyrrolidone (NMP) IUPAC name: 1-methylpyrrolidin-2-one EC number: 212-828-1 CAS number: 872-50-4	• Manufacturers, importers and downstream users of the substance on its own or in mixtures in a concentration equal or greater than 0.3% shall use in their chemical safety assessment and safety data sheets by [xx.yy.zzz] a Derived No Effect Level (DNEL) value for workers inhalation of 10 mg/m^3 and a DNEL for workers dermal exposure of 4.8 mg/kg/day.

A.2 Targeting

This Background Document is targeted to the use of NMP in industrial settings and by professionals. The use in consumer applications is excluded from this document because:

- The use of NMP in consumer articles is already declining probably due to the current classification with the specific concentration limit of 5% and the inclusion of NMP in the REACH Candidate list (date of inclusion 20-06-2011)
- On March 1th 2013, a reclassification proposal for NMP was submitted by the Netherlands. With this, the Netherlands proposes to lower the specific concentration limit for classification as reprotoxic category 1B from 5% to 0.3%. If adopted, the lower concentration limit of the reclassification proposal will restrict the use of NMP in consumer applications completely by means of entry 30 of REACH Annex XVII. The use of NMP in concentrations below <0.3% will have no functionality in the present consumer applications
- In the update of November 2012, the lead registrant does not include the consumer use of NMP. Remaining consumer use is therefore, expected to be minimal but cannot be excluded. Although consumer exposure and risk cannot be excluded, there is not enough information for preparing a restriction dossier for consumer use. As mentioned before, the Dossier Submitter assumes that due to lowering the specific concentration limit for reprotoxic category 1B, the use of NMP in consumer applications will be restricted in the near future.

A.3 Summary of the justification

A.3.1 Identified hazard and risk

The hazard and risk of NMP was assessed using information on the hazard from the registration dossiers and the OECD SIDS dossier on NMP and the exposure information obtained from the registration dossier, literature studies and monitoring data.

NMP is classified as a skin, eye and possible respiratory irritant and is classified reprotoxic category 1B based on developmental toxicity. NMP has been studied extensively in the past decades showing a rather complete dataset of toxicological studies. The focus of the Background Document was on the repeated dose toxicity endpoints and the developmental toxicity endpoint. A number of studies in mice, rats, rabbits and one in dogs were available for evaluation by the Dossier Submitter.

In the repeated dose studies often the reduction in body weight (gain) and generic toxicological effects on liver, kidney and thymus weights and histopathology were the most critical. At higher doses these effects worsened and were accompanied by effects on the testes and spleen. There was no specific target organ identified at low to mid doses. In the prenatal developmental toxicity studies and 2-generation studies effects on maternal body weights and foetus weights were most critical. Notably, the body weight changes of the dams occurred at lower concentrations than observed in general animals. At higher concentrations, clear effects on the foetuses were observed such as variations and malformations, reduced litters, stillborn and resorptions amongst other.

Despite effects observed on testes and spermatogenesis (slicht effects) no reduction in fertility was observed in any of the reproduction toxicity studies.

Since the population of interest in the risk assessment of NMP are the workers, it was decided by the Dossier Submitter to derive DNELs for workers in general, and the pregnant workers specifically, because of the developmental toxic effects of NMP. The point of departures selected for the pregnant workers are based on prenatal developmental toxicity studies and 2-generation toxicity studies, whereas for the general workers the repeated dose studies and carcinogenicity studies (only repeated dose related effects) were considered. Oral exposure was not considered relevant for the worker population and therefore DNELs were derived for the inhalation and dermal route only.

The PODs ultimately used for DNEL derivation for workers are 500 mg/m^3 (NOAEC; reduced body weight gain in rats) and 826 mg/kg bw/d (NOAEL; ¼ mortality in rabbits) for the inhalation and dermal route, respectively. The PODs ultimately used for DNEL derivation for general workers are 247 mg/m^3 (NOAEC; reduced fetal body weight in rats) and 237 mg/kg bw/d (NOAEL; reduced live foetuses and fetal body weight in rats) for the inhalation and dermal route, respectively. Corrections on the POD for inhalation were required to account for hours exposed per day and per week. Assessment factors were used to derive the DNELs. Assessment factors were applied to account for interspecies differences (allometric scaling and remaining differences), intraspecies differences and the exposure duration, according to ECHA guidance, chapter R8. The intraspecies differences for pregnant workers differed from the worker intraspecies factor of 5 (ECHA guidance, default value). Instead, the default value of 10 was adopted which is used to account for intraspecies differences in the general population, since the critical effects concerned the unborn child, whom are not covered by the worker intraspecies differences factor. Based on the PODs and the AFs, the DNELs derived are 10 mg/m^3 and 4.6 mg/kg bw/d for the inhalation and dermal route, respectively. The DNELs derived for pregnant workers are 5 mg/m^3 and 2.4 mg/kg bw/d for the inhalation and dermal route, respectively

The registrant estimated exposure to NMP at the workplace using the EasyTRA tool; the EasyTRA tool is based on the principles of the ECETOC TRA tool. Similarly, it uses the same default values for each PROC to determine the exposure to NMP during that process taking into account any RMMs and OCs assigned to the process. According to the information obtained from the registrant, the most common RRMs applied are LEV, gloves and reduction in exposure time and/or concentrations of NMP used in the process. Detailed information on RMMs typically applied in workplaces where NMP is used is not available to the Dossier Submitter.

The exposure was calculated for the following industrial uses: manufacture, importers and suppliers, chemical industry processes (generic use for synthesis processes), formulators (generic use for production of mixtures and articles), coaters, cleaners, laboratory use, functional fluids, and use in construction industry. Professional uses considered are: importers and suppliers, formulators, coaters, laboratory use, agrochemical use and use in functional fluids. Charging and discharging of NMP is a generic process applied in both industrial and professional settings.

In general, exposures resulting from high energy processes (e.g. under elevated temperatures and processes requiring intensive manual applications) and from open processes are relatively high, despite of RMMs taken into account. In industrial settings, processes can be more enclosed and RMM options are better compared to processes and RMM options available in professional settings. Moreover, most open and high energy processes are not supported anymore by the lead registrant as it was indicated that such uses, e.g. professional cleaning with NMP, will diminish in a few years. Therefore, the exposure levels that were calculated by the registrant did not differ much between the industrial and professional uses.

The exposure levels ranged from 0.04 to 20.65 mg/m^3 for the inhalation exposure for industrial uses. Dermal exposure ranged from 0.03 to 5.49 mg/kg bw/d for industrial uses, where it is noted that RMMs are taken into account. The exposure levels ranged from 2.97 to 20.65 mg/m^3 for the inhalation exposure for professional uses. Dermal exposure ranged from 0.14 to 5.38 mg/kg bw/d for professional uses, where it is noted that RMMs are taken into account.

By combining the derived DNELs with the exposure estimates risk characterisation ratios (RCRs) were obtained. The RCRs were in most cases for workers and pregnant workers >1 indicating that there is a risk. We made a qualitative appraisal of the RCR as for some exposure estimates additional RMMs were possible.

It is therefore concluded that risks are not sufficiently controlled for a number of industrial and professional uses, especially when it concerns processes under elevated temperatures, open processes, and processes that require manual activities and additional placement of RMMs are not possible.

A.3.2 Justification that action is required on a Community-wide basis

NMP is widely used all over Europe in many applications, like in petrochemical processing, in wire coating production, in electronics and semi-conductor industry and in membrane production. Exposure can be expected for workers by using this substance in the different professional and industrial settings. It is likely that this occupational exposure results in unacceptable risk, for the general worker population and for pregnant workers specifically. Action on a Community-wide basis is required to prevent unacceptable risks from NMP. Applications of NMP are traded freely and are used in all Member States. Action at EU level would ensure a 'level playing field' for all producers, importers and users of NMP and NMP containing products.

NMP has been included in the REACH Candidate list. Therefore, measures for this substance are already taken on a Community-wide basis. Logically, additional measures should also be taken on a EU-wide basis.

A.3.3 Justification that the proposed restriction is the most appropriate Community-wide measure

NMP is a high production volume substance manufactured over 18,000 tonnes per year in Europe and is used in many different industrial and professional settings. NMP is an aprotic and medium polar organic solvent. NMP is completely miscible with water. This combination of properties explains the importance of the use of NMP. NMP is mainly used to enhance a chemical reaction driven by its solvent characteristics as part of the process to make a product. NMP is classified as toxic for the reproduction (Repr. 1B). As demonstrated in chapter B, risks for workers are identified in almost all applications of NMP. Next to NMP, many organic solvents are available as potential alternatives but the characteristics of these solvents are not exactly equal to those of NMP. The availability of technical feasible alternatives differs per use application.

In view of the Dossier Submitter, banning the manufacture and use of NMP in all or in some specific applications is not the right way forward. It is foreseen that either NMP is replaced by another equally hazardous substance or that industry will cease and/or relocate its activities outside Europe. The demonstrated risks (RCR's up to 5) in our view do not justify a major change to many supply chains. NMP is a so-called threshold substance, which means that – at least in principle – NMP can be used without causing a risk for human health. The aim of this restriction proposal is to adequately control the manufacture and use of NMP.

REACH provides the authorities with two possible instruments to regulate the risks caused by a substance: authorisation and restriction. Both authorisation and restriction could in our view result in the same level of risk reduction. The main disadvantage of the authorisation process is that it is costly and time-consuming both for industry as for authorities. Besides that, it gives large uncertainty to industry regarding the continuation of their business because an authorisation request will only be given for a limited period of time.

Outside the scope of REACH, it is an option to adjust the EU-wide Occupational Exposure Limit (OEL) to control the risks at the workplace. In 2007, the Scientific Committee on Occupational Exposure Limits (SCOEL) has published an indicative OEL of 40 mg/m^3 (8-hour TWA). This OEL is not binding. The IOEL of the SCOEL obligates member states to establish national exposure limits. When Member States establish a national exposure limit value, they must take into account the IOEL, national legislation and practice. The levels of the national exposure limits may differ due to divergence in assessment methods and differing assessments on (expert judgment of) the actual risks of the chemicals. For example, where the IOEL is health based, member states can also take into account issues around technical and economic feasibility. There is no special argumentation required when a Member State uses a higher exposure limit than the IOEL recommended by SCOEL but there is the obligation for the Member State to inform the Commission and other Member

States thereof in order for the Commission to be able to undertake the appropriate action. For NMP, the national OELs vary between 20 and 200 mg/m^3. In view of the Dossier Submitter, the indicative OEL of 40 mg/m^3 does not provide sufficient protection to the worker population (see chapter B), following the REACH guidance. In principle, one could refer the issue back to SCOEL and ask them to provide a new OEL. However, the SCOEL has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. In the case the SCOEL would change the indicative OEL value to the more protective level as indicated in this Background Document, harmonised implementation of such new the indicative OEL by all Member States is still not guaranteed. Finally, the OEL by definition only protects workers from the risks following inhalatory exposure, while the restriction proposal also shows risks following dermal exposure, for which additional risks management measures are needed. Risk reduction for NMP cannot be guaranteed via this route.

In view of the Dossier Submitter, a restriction in terms of the a mandatory harmonised DNEL combined with an obligation to wear protective cloathing is the most appropriate Community wide measure as such a restriction is effective in reduding all risks of NMP against acceptable costs for industry and society. Besides, such a restriction is foreseen to be practical for all users of NMP.

In conclusion, it is the aim of this restriction to adequately control the manufacture and of NMP by setting a limit of 5 mg/m^3 to the 8-hour TWA exposure and the obligation to wear protective clothing and gloves.

B. Information on hazard and risk

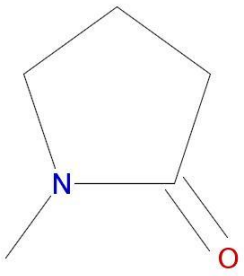
B.1 Identity of the substance(s) and physical and chemical properties

B.1.1 Name and other identifiers of the substance(s)

N-methylpyrrolidone (NMP) is the most common identifier of the substance.

Substance name: 1-methyl-2-pyrrolidone
IUPAC name: 1-methylpyrrolidin-2-one
EC number: 212-828-1
CAS number: 872-50-4 (deleted CAS numbers from CAS inventory: 53774-35-9; 57762-46-6; 26138-58-9)
Molecular formula: C5H9NO
Submission number: DF011163-70
Dossier UUID: IUC5-006c8c9e-2cbc-4b5f-bbb9-f5c8cf0de674

Synonyms are:
N-Methylpyrrolidon, 2-Pyrrolidinone, 1-methyl- (7CI, 8CI, 9CI), 1-Methyl-5-pyrrolidinone, N-Methyl-2-pyrrolidone, 1-Methylpyrrolidinone, Pyrol-M, N-Methyl-.alpha.-pyrrolidinone, N-Methyl-.gamma.-butyrolactam, 1-Methylazacyclopentan-2-one, M-Pyrol



B.1.2 Composition of the substance(s)

Data obtained from the public registration on the ECHA website (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances; date of access August 8 2012).

N-methylpyrrolidone: ≥ 80 % (w/w)

B.1.3 Physicochemical properties

NMP belongs to the chemical class of dipolar aprotic solvents having high dielectric constants and high dipolar moments. Data in table B.01 was obtained from the public registration on the ECHA website (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances; date of access August 8, 2012).

Table B.01: *Physicochemical properties of NMP.*

Property	Value	Remarks
Molecular weight	99.13 g/mol	
Physical state at 20°C and 101.3 kPa	Liquid	Clear and colourless

Property	Value	Remarks
Melting/freezing point	-24.2 °C	At 1013 hPa
Boiling point	±204 °C	At 1013 hPa
Vapour pressure	0.32 hPa	At 20 °C
Surface tension	Not surface active	Based on chemical structure, no surface activity is predicted
Water solubility	miscible	1000 g/L at 20 °C
Partition coefficient n-octanol/water (log value)	-0.46	At 25 °C
Flash point	91 °C	At 1013 hPa
Flammability	Combustible liquid. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water	Derived from flash point.
Explosive properties	Non explosive	
Self-ignition temperature	245 °C	At 1013 hPa
Oxidising properties	No oxidizing properties	The substance is incapable of reacting exothermically with combustible materials on the basis of the chemical structure.
Granulometry	Not relevant	
Stability in organic solvents and identity of relevant degradation products	Not applicable	Stability of substance is not considered as critical.
Dissociation constant	Not applicable	Substance does not contain any ionic structure
Viscosity	1.661 mPa/s at 25 °C	Value used for CSA: 1.7 mPa/s 20 °C

The calculated conversion factor from ppm to mg/m^3 is 1 ppm = 4.123 mg/m^3 (at 20°C and 1013 hPa).

B.1.4 Justification for grouping

Not relevant for this proposal.

B.2 Manufacture and uses

N-methylpyrrolidone (NMP) is a high production volume substance manufactured over 18,000 tonnes per year in Europe and is used in industrial and professional settings and NMP may be present in some consumer products. According to the registrations for NMP (November 2012), the substance is manufactured in Europe and uses are described as: use in industrial chemical processes, charging and discharging of substances and mixtures, formulation of preparations, use in laboratories, use in construction chemicals, use in coating, use in cleaning agents, use in functional fluids, and used in agrochemicals. In industrial settings, NMP may be used under elevated temperatures up to 180 °C. The registration dossier of the lead registrant (November 2012) does not include any consumer use of NMP. One registrant has notified a consumer use in his registration dossier, i.e. use in printing ink.

Information provided by the registrants on the uses is limited, providing little to no data on use amounts and detailed use or process descriptions. The data presented in this chapter is based on the information obtained from the Annex XV SVHC dossier, supplemented with data from registrations (including confidential data), input obtained during the public consultation of the SVHC dossier and a targeted stakeholder consultation carried out between November 2012 and January 2013 by the Dossier Submitter. The Background Document was based on the initial submission by the Dossier Submitter and supplemented with data received during the public

consultation of the Annex XV restriction dossier. An overview of the manufacture and uses including the sources mentioned is given below in sections B.2.1 and B.2.2.

B.2.1 Manufacture, import and export of NMP

According to the public registration of NMP, the tonnage band of NMP is 10,000 to 100,000 tonnes per annum. The public registration of NMP lists 24 registrants and suppliers from across Europe and includes 29 registration numbers. From data collected for an OECD SIDS (2007), it appears that there are three European manufacturing sites of NMP[2], with a further three in the USA and four in the Asia-Pacific region. There are no known natural sources of NMP.

The European production volume of NMP in 2003 was reported to be 30,000 to 50,000 tonnes, out of a total global production of 100,000 to 150,000 tonnes. European production had reportedly reduced to 20,000 to 30,000 tonnes by 2005 (OECD SIDS, 2007).

Table B.02: *Global and EU NMP production sites and capacity (source OECD SIDS 2007).*

Geographical region	Number of production sites	Capacity (t/a) [year]
Europe	3	30.000 – 50.000 [2003] 20.000 – 30.000 [2005]
USA	3	60.000 – 80.000 [2003]
Asia	4	10.000 – 20.000 [2003]
Global	10	100.000 – 150.000 [2003]

This indicates that Europe accounted for about one third of global capacity in 2003. It is likely that Europe's global share of capacity has reduced in recent years, as Asian chemical production capacity and demand has increased. Recent NMP-specific figures are not publicly available. Several companies indicated that they have ceased use of NMP in recent years, particularly due to regulatory concerns following its classification as a reproductive toxicant 1B in 2010 (31st ATP, 2009/2 DSD; 1st ATP, 790/2009 CLP). The classification mostly affects the consumer use of NMP, but might also have an effect on professional (product) uses and to a lesser extent to industrial uses where the professional and consumer products are made. For example the trade association CEPE has an exclusion list for chemicals to be used in printing inks, indicating that substances classified as category 1A or 1B reproductive toxicants (amongst others) are excluded as raw materials for the manufacture of printing inks and related products supplied to printers. (http://www.cepe.org/EPUB/easnet.dll/ExecReq/Page?eas:template_im=100087&eas:dat_im=050483).

The share accounted for by imports into the EU as pure substance or in a mixture is estimated around 50% of the total tonnage used, accounted for by between 10 and 20 companies. Based on data from questionnaires used for the Annex XV SVHC dossier on NMP, it appears that several hundred tonnes of the imports are in the form of mixtures. Further information regarding the NMP content of imported mixtures was not available from the received information.

Export of NMP was reported to be 1,000 to 2,000 tonnes per annum although it should be noted that this is based on a limited response to the questionnaire and is not considered to represent the EU as a whole. The export of NMP in mixtures is unknown. Since the import of NMP is relatively high, it is expected that export to outside Europe is not high.

The total use of NMP as pure substance or in a mixture is thus estimated to be 36,000–58,000 tonnes (production 20,000-30,000 tonnes, export 1,000–2,000 tonnes, 50% of used NMP imported).

[2] *According to personal communication with industry there are currently two production locations in the EU.*

B.2.2 Uses

This section presents the uses of NMP in industrial and professional settings based on the registration under REACH from the lead registrant. Note that the updated version of the registration dossier and Chemical Safety Report from the lead registrant (November 2012) is used as starting point in this document. However, there might be downstream users of NMP that did not update their dossiers accordingly and still rely on the older version of the Chemical Safety Report (April 2011). The registrations contain separate entries of identified uses for the manufacturing of NMP and its use in various products. The information is supplemented by available information from the Annex XV SVHC dossier, stakeholder consultations and the older version of the Chemical Safety Report. Most uses identified by the Dossier Submitter are covered by the registrations, nevertheless a few uses were found in grey literature, product registries and the older version of the Chemical Safety Report, that were not included in the registration dossier, such as uses in consumer products such as coatings, inks, and cosmetics. It is noted that some uses, parts of the production, and use processes may fall under other legislative frameworks such as the use as medicines (pharmaceuticals) and the use as agrochemicals that may either fall under the Biocides Directive or under the Plant Protection Products Regulation. In case of the agrochemicals, however, exemptions for REACH are only allowed when the substance of interest has been assessed in those frameworks, which is not the case for NMP.

NMP is used as a solvent in various processes in a wide variety of applications. It has a wide range of potential industrial and professional uses and users. In Annex 1 an extensive overview is given on all use processes and the potential uses of NMP. In Annex 1 also pictures are given illustrating the use in some applications. NMP is clearly used in a wide variety of applications. In Annex 2 information from product registers is presented.

The users of NMP have been categorised as given in table B.03 based on the type of sectors, including both the industrial and professional uses within the sectors. A sector is defined as all users that in some way are related to the main activities in that sector. For example, within the sector coaters there are among others formulators of coatings, distributors, coaters in industrial settings, coaters in professional settings and coating related cleaning (technical services and maintenance). Due to the number and diversity of the uses of NMP, a full description of all uses and users would be too elaborative and would lose overview. Therefore, the categorisation is based on major sectors using NMP or specialized sectors using NMP. In the sections below, the NMP using sectors are described with special focus on possible subdivisions within a sector, what specific uses and/or processes are involved, and how the sectors will be considered in the remainder of (part B of) the Background Document. The reader is referred to section F.1.4, Table F.05 – (confidential data), for estimates on the number of workers employed in the specified sectors.

In Annex 1 a translation table is given to be able to compare the categorisation of uses as applied in the registration dossier according the Exposure Scenarios to the categorisation as applied in this Background Document. The uses as described in the Exposure Scenarios may occur in several use categories, as there may be similar processes that are used in several sectors. For example, discharging and charging is a generic use applicable to all sectors or use categories, which in reality may still concern very different ways of transfer. Nevertheless, generic uses have been identified and described separately, noting in what sectors these processes are used. Four key industries, i.e. the non-wire coaters, wire coaters, cleaners and membrane manufacturers, have been selected for a more detailed analysis in the socio-economic assessment of the different risk management options (see chapter F and Appendixes 1 and 2).

Table B.03: *categorisation of users of NMP in this Background Document*

Users of NMP
1. Manufacturers
2. Importers/suppliers
3. Petrochemical industries
4. Formulators
5. Non-wire coaters
6. Wire coaters
7. Cleaners
8. Electronic and semi-conductor industries
9. Battery industries
10. Membrane manufacturers
11. High performance polymer producers
12. Agricultural chemical industry (formulation, synthesis)
13. Pharmaceutical industry
14. Laboratories
15. Functional fluids
16. Construction industry
17. Other (consumer)

Estimates of the use amounts of the major applications of NMP on the EU-27 market are provided in table B.04.

Table B.04*: NMP use amounts per application (based on confidential market analysis from BASF).*

See confidential Annex 3.

Manufacturers

The manufacturers produce NMP in high production volumes at chemical plants. The production of NMP and associated bulk transfers and storage is contained within closed systems. Bulk loading is undertaken outdoors and under containment. Transfer lines are cleared prior to decoupling. The filling of drums or smaller containers is undertaken at dedicated fill points with extract ventilation. Containment or extract ventilation is in place where sampling is undertaken.

The manufacture of NMP is performed in the industrial sector only. Processes involved are the use in closed systems (PROC1-2-3), the transfer of NMP after production (charging and discharging, see below under generic use), sampling and maintenance and cleaning. Registrants do not describe the maintenance and cleaning of systems and equipment related processes. It is considered by the Dossier Submitter that such activities are described by the processes mentioned under 'Cleaners'.

Generic uses that apply to varying sectors

In this section, generic uses are described that apply to multiple sectors.

Charging and discharging

Charging and discharging occurs for all specified use categories and is therefore considered as a generic use, including both industrial and professional workers. In the industrial settings elevated temperatures can be used. It is unclear if professionals are working under elevated temperatures. Registrants describe the charging and discharging of NMP as loading of NMP into marine vessels,

barges, rail cars, road car transport and IBCs (Intermediate Bulk Containers) or repacking NMP in drums or packs. Closed or open transfer lines for bulk transports and dedicated filling point for small transport are used. Small amounts are distributed to laboratories.

It is noted by the Dossier Submitter that the exposure may differ significantly between sectors, where charging and discharging in chemical industries may be at higher scales but with more enclosed processes, while for laboratories the amounts are small, but under more open processes.

Formulators

Formulating of mixtures occurs within several sectors, including industrial and professional uses. For this reason, formulating is described as a generic use.

Formulators use NMP in the preparation of their products, among others coatings, cleaners, polymer membranes, high performance polymer fibres, pharmaceuticals and agrochemicals. Information on formulation of preparations (under REACH referred to as mixtures) was obtained from the registrants, describing mixing in batch or continuous processes and further processing steps such as transfers, storage and packing. The use of the formed formulations is described elsewhere under specific use categories, for example under 'non-wire coaters'.

Formulating occurs in the industrial and professional sector. It involves mainly mixing processes and transfer processes as described by charging and discharging. Such processes might occur in closed systems. In the industrial setting elevated temperatures can be used. It is unclear from the registration dossiers if professionals apply elevated temperatures, as the latest update of the registration dossier (November 2012) no longer includes the application of elevated temperatures by professionals. Further, it is noted that NMP might be used as a sort of intermediate in some formulation processes not ending up in the final product (thus, intermediate not in a sense as described by Art. 3 of REACH). In the remainder of this document the uses described for formulators will cover all formulators. In some parts of the document formulation will be included as part of other use categories like wire coatings (e.g. wire coating formulation and wire coating).

Chemical industry processes

The use of NMP in chemical industry processes encloses the manufacturing of other chemicals where NMP is used somewhere in the process, either as solvent in the synthesis steps or for extraction and thereby differs from formulation processes. This use describes for example the production of bulk and fine chemicals, petrochemicals, pharmaceuticals, and agrochemicals. The chemical industry processing of pharmaceuticals and agrochemicals is mentioned in the respective users' categories, i.e. pharmaceutical industry and agricultural chemical industry. The petrochemical processing is described below in more detail, being a separate industrial sector.

The main sectors of use in relation to this application are in:

- manufacture of bulk, large scale chemicals (including petroleum products) (SU8)
- manufacture of fine chemicals (SU9)

Chemical industry processes are conducted in industrial settings, where mainly closed systems are applied. It is possible that elevated temperatures are used for extraction purposes. In the remainder of part B of the Background Document, the chemical industry processes will relate to all chemical or mixture manufacture.

Polymers

NMP has been widely used in the preparation of various types of polymers: polyurethane (PU), polyaniline (PANI), polyamideimide (PAI), polyimide (PI), polyvinylidene fluoride (PVDF), polysulfone (PFS) and poly ethersulfone (PES), but also in the preparation of poly para-phenyleneterephtalamide (PPTA), polyphenylene sulfide (PPS) and other high performance thermoplastics (HPTP). These polymers are applied in a wide range of applications:

- PU is often used in coatings
- PANI is used for high electrical conductivity thin films to be used in electronics and semiconductor industries
- PAI is used for coatings and wire coatings
- PVDF is used as of high quality coatings, in wire coatings, as binder for cathodes (battery industries), and in the production of membranes
- PI in used for wire coatings, membranes and electronics and semiconductor industries
- PFS and PES are used for membranes

- PPTA is used to produce the para-aramids Twaron and Kevlar that represent the group of high performance polymers
- PPS is used for membranes and high performance thermoplastics

During the stakeholders consultation round the use of NMP in the polymerization of polyphenylene sulfide (PPS), which is used in the automotive industry, has been mentioned. High temperature thermoplastics, among which PAI, PI and PFS, generally show a high level of toughness, stiffness, and a high resistance to solvents and other chemicals. From the stakeholder comments it is not clear if NMP is only used for PPS or also for other high performance thermoplastics (HPTP).
Note that polymers will not be addressed in this document as a separate use category. Instead, the various applications of the different polymers (coatings, wire coatings, electronics and semiconductors, batteries, membranes and high performance polymers) will be treated as use categories in this document. Note that most of the uses of polymers are assumed to be covered with the use categories as defined for this document. However - as polymers are widely used - there might be some uses e.g. as high performance thermoplastics, that are not covered, as no information was available to the Dossier Submitter on these uses. The Dossier Submitter assumes that such a potential use of NMP in polymers is however, sufficiently covered in the document as one of the other uses of polymers could serve as a proxy for such a use.

Importers/Suppliers

The importers and suppliers trade NMP as a pure substance or in products such as in mixtures, in formulations or in articles. The sector may range from large chemical plants to small retailers of products. Importers and suppliers are active in the industrial and professional sector. Processes involved are charging and discharging as described under the generic uses.

As the importers and suppliers use of NMP is limited to charging and discharging, their use of NMP is sufficiently covered by the generic use of 'charging and discharging' and will not be considered separately in the remainder of part B of the Background Document.

Petrochemical industries

NMP is used in the large-scale recovery of hydrocarbons by extractive distillation. Hydrocarbons are highly soluble in NMP and differences in volatility are sometimes considerably increased in the presence of NMP (BASF, 2010). NMP is used by some petroleum refineries (i.e. industrial facilities) as an extraction solvent in the production of lubricant base oils to remove aromatic hydrocarbons (e.g. PAHs) and other polar components. This extraction process generates lubricating oils with lower impact to human health and the environment. This use of NMP is acknowledged in the Integrated Pollution Prevention and Control (IPPC) Reference Document on Best Available Techniques for Mineral Oil and Gas Refineries (February EC, 2003) as Best Available Technology. The environmental benefits include reduction in refinery effluents of more toxic solvents such as phenols and sulphur dioxide and a lower consumption of energy. NMP is recovered and recycled in closed systems. NMP is used particularly because, unlike other commercial solvents and extraction media, its use does not lead to the formation of azeotropes[3] and because NMP has high heat resistance and resistance to chemical insults.

Furthermore, NMP is used in the desulfurization of oil products, the removal of CO2, COS and H2S from gas streams and in butadiene production. Butadiene is usually the first step in the C4 chain (Wiese & Nierlich 2005). White (2007) describes butadiene as a major product of the petrochemical industry. Its largest use is in the production of synthetic rubbers.

Non-wire coaters

NMP is used as a solvent in a wide range of different coating products. NMP is often used in polymer based coatings, such as wire coatings. Polymers such as polyurethanes (PUs), polyamideimides (PIs) and polyvinylidene fluorides (PVDFs) are used as important ingredients in high-quality coatings for metal and other materials (Leading Edge Coating Solutions, 2013). These polymers are used as binder and are often dissolved in NMP as a solvent. Other substances such as

[3] *Which would reduce/remove the potential for distillation of hydrocarbon components.*

silica particles or nanoparticles can be added to the polymer solution to change the characteristics and improve the quality of the coating. NMP is also used in waterborne paints (as a co-solvent/coalescing solvent) as well as in solvent-borne coatings. NMP coatings are reported to be non-corrosive, of high boiling point with excellent solvent power and chemical resistance. The characteristics are favourable for baked coatings that are cured at relatively high temperatures (BASF, 2010). The use in coatings may be under elevated temperatures up to 120 °C. It is unclear if professionals apply elevated temperatures.

The non-wire coaters include sectors that deal with the use of coatings for many purposes. Discrimination is made in the Background Document between non-wire coatings and wire coatings. The reason for this discrimination in the use in coatings (of NMP) is the high quantity of NMP used in the wire coatings sector and the specific characteristics of this sub-use of coatings. The non-wire coaters include many sectors, of which a very large sector is the automotive industry that use NMP in car coatings. Besides that uses in films and medical images and in the textile and leather industry, have been mentioned (personal communication, response to RIVM draft dossier). The latter appears to be replaced already (see part C). Additional information obtained during the public consultation of the restriction dossier (2013/2014) indicated that NMP is used as binder to make food contact materials requiring high temperature and chemical resistance. Details on what type of food contact products is referred to are not given. A separate comment indicated that bakeware is made using NMP in the process to make the coating to metallic substrates.

The processes involved in the use of non-wire coatings are in general open processes involving dipping, rolling, spraying and curing/drying of the coatings. The processes can differ significantly in industrial sectors compared to professional sectors in terms of scale (amount) and technical possibilities of the processes. Processes may be conducted under elevated temperatures.

NMP containing coatings are used in a wide range of different end use sectors, including industrial, professional and possibly also in the consumer sector. Information on the range of different uses of coatings, including non-wire and wire coatings, is included in table B.05. Note that the table includes public (consumer) uses that are outdated as these uses have recently been deleted in the updated version of the registration dossier.

***Table B.05**: Information from consultation (Annex XV SVHC dossier) on uses in coatings (including non-wire and wire coatings).*

Use	Quantity of product (t/a)	Customers
Examples only used industrially		
Production of enameled wire	715-1,305t	100 % industrial
Wire enameling	100-1,500t	100 % industrial
Coalescing solvent in waterborne paints	c. 500t	100 % industrial
Thinner to aid coating spray application	320t	100 % industrial
Specialist coatings	>200t	100 % industrial
Solvent-based high temperature coatings (solvent and water-based and diluent/cleaner)	140-190t	100 % industrial
Solvent for paint resins	100t	100 % industrial
Manufacturing equipment maintenance	8-25t	No data
Co-solvent (at c. 5 %) in screen printing inks and thinner	5t	100 % industrial
Automotive waterborne paint	15t	100 % industrial
Coalescing solvent in automotive paints	1.25t	100 % industrial
Additive for coating esp. technical textiles (solvent for thixotropic agent)	1t	100 % industrial
Component in screen inks	0.8t	100 % industrial
Waterborne paint for steel/automotive components	0.3-0.5t	100 % industrial
Wood impregnation product (co-solvent for fungicide)	0.15t	100 % industrial

Use	Quantity of product (t/a)	Customers
Use in industrial continuous inkjet mixtures (ink)	<1t	100 % industrial
Metal coating for hot environments (prevent corrosion/chemical attack)		100 % industrial
Examples which also include professional use		
Waterborne paints (automotive and other industrial)	100t per year	100 % industrial / professional
Coatings	0.2t	100 % professional
Printing ink (NMP used at ca. 5 % to fuse pigment on PVC film)	0.02-0.2t	100 % professional
Formulation of industrial flooring products	0.001t	100 % professional
Examples which also include public use*		
Waterborne floor finishes	2-4t	95 % professionals, 5 % public
Paint, diluent, remover	2-2.5t	95 % professional, 5 % public
Industrial paints	<2t	95 % professional, 5 % public
Waterborne parquet varnish	1.3t	100 % public
Binder in waterborn PU wood paint	<1t	90 % professional, 10 % public
Binder in waterborn PU top coat	<1t	70 % professional, 30 % public
Epoxy paints	<1t	90 % professional, 10 % public
Universal pigment preparations	<1t	50 % professional, 50 % public
Artists colours (acrylics)	0.7t	100 % professional/amateur artists
Parquet lacquer	0.53t	30 % professional, 70 % public
Sealer wood varnish	0.04t	7 % industrial, rest professional and public
PC9a: paints for metal, concrete, waterborne wall paints, trim paints and translucent wood care paints.	Small amounts	50 % professional painters (trade), 50 % public (retail)
Subtotal (approximate)	**2,220-4,280t**	

** Note that the information on public uses is assumed to be outdated. Consumer uses of NMP in coatings have recently been replaced and thus are expected to decline.*

Wire coaters

Wire coatings can be made from various polymers. The type of polymer used depends on type of application, the thermal resistance and the resistance against solvents required (American Insulated Wire Corp., 2002). NMP is mainly used in the wire coatings made from the most solvent and high temperature resistant polymers: polyamideimides (PAI) and polyimides (PI). According to industry (personal communication, response to RIVM draft dossier, and ref 323 in PC) NMP is especially used in the production of magnetic wire coatings that require a high quality coating. The wire end products are assumed not to contain any remaining NMP. Magnetic wires are used in the manufacturing of e.g. motors, generators and transformers. During public consultation 2013/2014 the total consumption of NMP for the enamelling European market was reported to be in the range of 4000 to 4500 tonnes per year. The information is in line with the information in confidential Table B.04. The demand for high efficiency electrical motors needing PAI coating indicate an

upward trend of PAI, hence an increase of NMP use (not considering any type of restriction). It is however unclear if NMP is used in other types of wire coatings than those needed for high temperature and chemical resistant wire coatings and if so what the market share might be.

The use of wire coatings is described separately from the non-wire coatings, because the sector of wire coaters is very large, being approximately one third of the total tonnage of the use of NMP (see Table B.04). Moreover, the use of wire coaters takes place in the industrial sector only.

Processes involved in wire-coating are similar to the industrial non-wire coatings where open processes are described. Dipping, rolling, pouring of the (heated) enamel containing NMP, which is then allowed to cure, thereby covering the wires. Since it is expected that the industrial use of wire-coatings is more or less similar to the industrial use of non-wire coatings under elevated temperatures, the exposure results for non-wire coatings will be taken forward for the wire-coating sector.

Cleaners

NMP is a powerful solvent and has a high solvating power for plastics, resins, oil and grease. Bader et al (2006) described the use of NMP as a cleaning agent in an adhesive bonding compound and glue production facility. Cleaning of the vessel drums and the stirrers were carried out manually using NMP. Nishimura et al (2009) described a factory, in which NMP was used for cleaning instruments on which liquid resin had been sprayed. The liquid resin used was dissolved in an organic solvent which was composed of more than 90% NMP and less than 10% xylene. According to BASF (2010), NMP is used as an ingredient in paint removers, cleaners and as or in degreasers. It can be used in pure form or in mixtures for removal of oil, carbon deposits and other tarry polymeric residues from metal chambers, pistons and cylinders, as well as for wet cleaning of combustion engines. Industrially, it can be used under elevated temperatures. Since the use of NMP is considered crucial in the manufacturing of electronics, semiconductors, polymers and possibly other products, while basically as cleaner, its role in the manufacturing in the abovementioned products is described as separate use categories. Information on the range of the different uses reported by companies that provided input to this analysis is presented in Table B.06 below (from the Annex XV SVHC dossier).

Xiaofei et al. (2000) describe the cleaning practices in a factory producing lenses and a factory for parts of wire apparatus using NMP. As such, an important sector using NMP as a cleaner is the optical industry. Also in the chemical industries NMP is used as cleaner (part of maintenance). The use of NMP as cleaner in e.g. the electronics and chemical industry is described separately (electronics and semiconductor industries and petrochemical industries). Note that the updated version of the registration dossier provided by the lead registrant does not include any professional use of cleaners. This use described in the table might thus be outdated.

***Table B.06**: Information from consultation on uses in cleaning products (from Annex XV SVHC dossier)*

Use	Quantity of NMP (t/a)	Customers
Cleaning solvent	1t	No data
Mixtures for removal of coatings/paint/graffiti by painters or DIY (including use in aerosol cans)	12t (2009) 0t (2010)	30 % industrial, 70 % DIY*
Paint remover	27.8t	No data
Cleaning of mixing tanks (dissolving residual coating)	30-50t	100 % industrial
Cleaning agents	1-5t	100 % industrial/professional
Subtotal (approximate)	**60-95t**	

** from source unclear whether DIY refers to professional use, consumer use or both.*

Material safety data sheets for the substance indicate use in a range of paint removing products such as:

- Polymer remover containing 30-60 % NMP. This product was primarily used to remove polymer deposits from moulding tools. The company has now replaced NMP in these products due to concerns with the reclassification of the substance.
- Anti-graffiti cleanser containing 5-15 % NMP (mainly professional, this use of NMP is assumed to be phased out in time.
- Stain protecting products containing 1-5 % NMP (used by the general public, this use of NMP is assumed to be phased out in time).
- Graffiti removing towels containing 10-25 % NMP.

Remaining uses of NMP in cleaners are expected to in the industrial sector as the use in the professional sector is no longer included in the updated registration dossier (November 2012). Processes involved are generally open processes where manual applications and high energy processes (including elevated temperatures) might occur similar to the use of non-wire coatings, e.g. brushing, rolling, and spraying.

Electronics and semiconductor industries

Users in the electronics and semiconductor industries of NMP can be separated between two large sectors being the manufacturers of electronic equipment and one of its main sub-branches the conductor and semiconductor industries.

Both sectors use NMP as a carrier solvent and cleaner. The processes involved however differ from the typical use of NMP as cleaner, as the final products manufactured within these sectors require a high level of containment mainly for product quality purposes, i.e. mainly under clean room conditions. Since the use of NMP within this sector is represented best by the use in industrial cleaners, the data for that sector will be used for the electronics sector when it comes to the description of the exposure and will therefore not be dealt with separately in the remainder of part B of this Background Document. In the other sections of the document electronics and semiconductor industries will be treated as a separate use category.

Conductor and semiconductor industries (industrial)

Beaulieu and Schmerber (1991) have described the use of NMP in the microelectronics industry and provide five applications:

- stripping photoresist from wavers (solvent baths), NMP is used for stripping photoresists, mainly positive photoresists and hardly in negative photoresists
- solvent carrier for "die coat" (solvent baths)
- dissolving phenolic residues from "packages"
- pre-softener for ink removal (paint stripper)
- cleaning of mold dies (sprayed onto molds)

More extensive description of the application of NMP in the microelectronics industry can be found in Beaulieu and Schmerber (1991).

A respondent to the questionnaire did not fully agree on the sub-uses defined above and distinguish the following two important processes in which NMP is being used within the European semiconductor industry (personal communication, RIVM questionnaire):

a) wafer cleaning and stripping to remove organic contamination and organic layers and
b) as a solvent in dedicated formulations (i.e. precursor solutions for wafer coatings such as polyimides and anti-reflective coatings). The respondent indicated that polyimides are applied as a protection layer in a wide range of semiconductor products, such as microchips.

According to the Annex XV SVHC dossier, NMP is used as a processing aid in semiconductor manufacture in a closed equipment system because of its effective physical and chemical properties:

- For cleaning (also known as 'stripping') to dedicatedly remove organic contamination and organic layers. NMP is used as a process aid for wafer cleaning. It is important to note that 'cleaning' is very much different from the typical understanding of cleaning in other industrial sectors. Wafer cleaning is done inside enclosed manufacturing equipment which is itself an inside controlled environment known as a clean room.

- As a solvent in dedicated formulations (i.e. precursor solutions for wafer coatings such as polyimides and anti-refection coatings).

The process involves production of semiconductor devices in batch processes in dedicated equipment (litho-track tools) in a photolithography process. The production of semiconductor devices may involve up to 300 manufacturing process steps on as many as 80 different types of equipment. The use of NMP takes place in batch processes with dedicated process equipment tools in a controlled environment, i.e. the clean room. Here, the presence of uncontrolled particles, as well as chemical vapours and gases would constitute an unacceptable risk not only from a safety and health perspective but also from a production viewpoint. Besides, automated chemical delivery systems are installed to create a barrier between workers and the process and protect against chemical and physical hazards in the work environment. Continuous local and equipment exhaust ventilation under alarm are also present.

In semiconductor processes, it is described that about 90-95 % of the solvent used is collected for offsite incineration, <5 % evaporates and <0.5 % is discharged to waste water[4] (ECHA 2010).
The aggregated NMP use for the sector in 2011 was reported but claimed confidential (personal communication, RIVM questionnaire). This high estimation aggregate figure is considered to cover >90% of all European semiconductor uses. NMP is used as a key process aid in the manufacture of semiconductor devices. The Annex XV SVHC dossier provides tonnage levels of NMP usage within the semiconductor industry for some European countries (Table B.07).

***Table B.07**: European semiconductor manufacturing industry usage of NMP as submitted to consultants who drafted the Annex XV SVHC dossier.*

Member State	Uses	Quantity
France	Carrier solvent, cleaner/stripper	< 5 tpa
Italy	Carrier solvent, cleaner/stripper	3 - 5 tpa
Ireland	Carrier solvent, cleaner/stripper	10 - 100 tpa
Netherlands	Carrier solvent, cleaner/stripper	<20 tpa
Germany	Carrier solvent, cleaner/stripper	< 10 - 100 tpa
UK	Carrier solvent, cleaner/stripper	10 – 20 tpa
Austria	Carrier solvent, cleaner/stripper	< 20 tpa

Manufacture of electronic equipment

NMP is used as a solvent for the electronics industry and for producers of printed circuit boards. Mixtures of the substance with common solvents are used for the cleaning and degreasing of single-crystal silicon wafers for integrated circuits (BASF, 2010). NMP is used as a processing aid in pure form or in mixture with other substances (photoresist, BARC and TARC[5]) (ECHA, 2010). A historical use is the use of NMP as a surface cleaner in clean rooms (tabletop and mat cleaner and electrostatic charge neutralizing agent). NMP is reported to be used 100% in industrial applications. Equipment is operated automatically and can be totally or partially enclosed. "Clean room environment" conditions are reported to be applied.

NMP is an important solvent for manufacturing of polyimides that are used in the manufacture of electronic equipment. The main applications for NMP use in electronic equipment manufacture are:

- A photoresist carrier solvent (solvent base for polymer mixtures) used at around 10-100 t/a per location/company.

[4] *This is based on semiconductor exposure scenario Substance C, section 9.1 and contributing scenarios at http://guidance.echa.europa.eu/docs/other_docs/es_project_document_v5.pdf*
[5] *Bottom-side and top-side anti-reflective coatings.*

- A photoresist stripper (cleaning/stripping to remove resist from wafers and photo masks during semiconductor manufacturing) used at around 10-100 t/a per location/company.
- In failure analysis (cleaning/stripping) used at < 5 t/a per location/company.

Battery industries

Information on use of NMP for manufacture of lithium ion batteries was obtained from industry (public consultation Annex SVHC dossier, SVHC-RCOM 10052011) and from the literature. NMP is used both in lithium ion batteries as in other hybrid batteries using nickel, magnesium, or cobalt. In lithium battery production it is applied as a solvent for the binder resins for both the carbon anode and the lithium cobalt oxide cathode, it may be used in gel-polymer lithium ion battery separators/electrolytes, and it may be used in coatings on the outside of the batteries.

In the manufacturing process of the electrode, NMP is used as a solvent for binder resins between a metal foil and an active material for positive/negative electrode agents. From the point of view of proper performance of the electrode, it is essential for a solvent to dissolve PolyVinylidene diFluoride (PVDF) of the binder sufficiently. The solvent with the active material need to be dispersed uniformly on the metal foil with the binder resin. PVDF is often used as a binder to hold the active material particles (e.g. lithium) together and bind them to the cathode. For the anode graphite is mixed with similar binder material. The slurry, made of solvent, binder, active material and additives, needs to disperse the binder uniformly on both sides of the cathode, often made of aluminum foil, and the anode, often made of copper foil. In addition, it is indispensable for the solvent to be vaporized and completely removed from the electrode after coating.
Various electrolites may be used in lithium batteries. One of the electrolytes that may be applied are polymer gel electrolytes, which are produced by casting solutions of PVDF in acetone, MEK, NMP, or THF into an electrolyte solution (Arora & Zhang, 2004; Yang & Hou, 2012; Michot et al 1999). Arora & Zhang (2004) describe that the originally used supported-liquid membranes made from polypropylene, polysulfone, poly(tetrafluoroethylene), or cellulose acetate, which use relative softer solvents will In contrast, Orendorff (2012) indicate that polyethylene and polypropylene are much more common in commercial non-aqueous lithium ion separators than separators in which PVDF is being used. Also for other hybrid batteries using nickel, magnesium, or cobalt NMP is used in the slurry to bind the active material to the electrodes. A description of the developments in the US battery production is provided by Lowe et al (2010).

The production of lithium and other hybrid batteries needs large amounts of NMP. Because of the high price, NMP is recovered from the exhaust gasses after drying the electrodes and is re-used. Several specialized companies are active in this field.

In addition, NMP is used in this industry for cleaning all apparatus before coating (public consultation 2013/2014).

In the remainder of part B of the Background Document, the battery industries will not be dealt with separately but as part of the non-wire coaters categories. When it comes to exposure, the industrial processes described for non-wire coaters is considered to be sufficient for battery production. In other parts of this Background Document the use in battery industries is treated as a separate use category.

Membrane manufactures

NMP is used as a processing aid in the production of polymer based membranes. Various polymers can be used in membrane production such as polysulfone (PFS or PSU), polyethersulfones (PES or PESU), polyimide (PI), polyvinylidene fluoride (PVDF) and polycarbonate as well as polyacrylonitrile (PAN), poly (vinyl alcohol) (PVA), polymethylmethacrylate (PMMA), and ethylene vinyl alcohol (EVAL) (Yang et al 2003, Aroon et al 2010). Aroon et al (2010) indicates that membranes are often produced by phase separation using immersion precipitation in which a solution of a polymer, a solvent, a non-solvent and additives is cast into a film and then converted to a solid state. The polymer solution, with polymer and solvent, is immersed in a non-solvent bath and an exchange between solvent and non-solvent will occur.
The membranes are applied in a variety of (industrial) processes such as gas separation, nanofiltration, ultrafiltration and desalination and as such different types of membranes exist. Membranes produced with NMP are used in a variety of applications, e.g. water filtration, beer/wine

filtration, blood filtration (in medical device sector) and vapour permeation (personal communication, RIVM questionnaire).

During formulation of the membranes exposure to NMP may occur. The production includes a mixing step, where polymerisation of the membrane takes place, washing steps, after which the formed membrane needs to dry. During those steps in the process NMP release to air can occur.

As mentioned in the general process description (formulators), when it comes to the exposure assessment, the production of membranes is covered by formulators. In part B of this document the use of NMP in membrane manufacture will therefore not be dealt with separately. In other parts of this document this use is treated as a separate use category.

High performance polymer producers

NMP is used as a processing aid in the production of poly-aromatic polymers such as (but not exclusively) poly-paraphenylenediamine-terephthalic acid (PPTA, para-aramid). This polymer is subsequently used for the production of high-tensile yarns. PPTA was developed in the 1960's and 70's. Aramids are produced by a reaction between an amine group and a carboxylic acid halide group. In the case of PPTA, p-phenylene diamine (PPD) and terephtaloyl dichloride (TDC or TCl) are used where NMP dissolves the aromatic polymer and CaCl2 occupies the hydrogen bonds of the amide groups (Hearle, 2001). In this particular patented application, NMP is the only known solvent in which the monomers for the polymer can be simultaneously dissolved and polymerized. Up to and including polymerization, this use can be considered as a controlled process, though not fully closed, but after polymerization, the resultant polymer still contains traces of NMP that may evaporate during the production process and may cause worker exposure. The high performance polymer end product is assumed not to contain any remaining NMP. The product is used e.g. in ballistic protection products (personal communication, RIVM questionnaire).

As mentioned in the general process description (formulators), when it comes to the exposure assessment, the production of high performance polymer is covered by formulators. In part B of this document the use of NMP in high performance polymer production will therefore not be dealt with separately. In other parts of this document this use is treated as a separate use category.

Agricultural chemical industries (synthesis and formulation)

NMP is both used in the synthesis of active ingredients and as a co-solvent in the formulation of various agrochemicals (according to information from industry it is used in insecticides, fungicides, herbicides, seed treatment products and bio regulators (BASF, 2010)). In case NMP is used in the synthesis of active ingredients, the use is fully industrial and NMP is assumed not end up in the final product. No further information on this use has been found in the preparation of the Annex XV restriction dossier.

If NMP is used as a co-solvent, NMP will obviously be contained in the final products. The concentration of NMP in herbicides, fungicides and pesticides is < 7%, based on information from OECD SIDS (2007). NMP is used as a co-solvent because of its highly polarity. Data from the Annex XV SVHC dossier show that NMP is still present in European plant protection products and biocides (ECHA 2011, paragraph 2.4.3). NMP has been used as a (co-)solvent for formulation of active ingredients in emusifiable concentrates (ES), microemulsions, liquids for seed treatment (LS) and ultralow volume liquid formulations (UL). Besides the function of solvent for the active ingredients NMP, may have been used in these formulations as an adjuvant enhancing the uptake and downward transport of the active ingredient from apex towards the base of a shoot or a stem (basipetal translocation). Knowles (2005) describes that liquid formulations often contain active ingredients and additives dissolved in organic solvents. Most solvents are being used for emulsifiable concentrates (EC) and ultralow volume liquid (UL) formulations and to a lesser extent in liquid formulations for seed treatments and dispersion concentrates (DC). The advantage of NMP above a number of other solvents is that it is miscible with water.

Up to 2005 NMP was widely used in many formulations, but according to Knowles (2005) it was withdrawn because of toxicological concerns which lead to more stringent US regulation and similar developments within the EU. In general, liquid formulations are thought to decline because the move away from VOC containing products (Knowles, 2005). Products for pesticide formulation containing NMP were available under the tradenames GAF 010, GAF 141, Agsolex 1.

NMP is still permitted in the US as an adjuvant for use in slimicides as a solvent to facilitate spraying (Code of Federal Regulations Title 21 - Food and Drug, (21 CFR 176.3OO(d)), 2012). Slimicides are used in the pulp and paper industry as a biocide to prevent the growth of algae, bacteria and fungi in the cooling and circulating water. Other adjuvants are mentioned in the Code of Federal Regulations. The information on the use of NMP in European biocides is limited. In 2006 Norway notified the application of Rotenone (CAS 83-79-4), a biocide containing up to 10% NMP. Biocides for the water and oilfield and paper industry biocides are being supplied by BASF under the trade-names Myacide and Protectol (BASF, 2000, 2001).

Sectors involved within this category are the manufacturers, formulators and end-users of the agrochemicals. The industrial uses of NMP in the agricultural chemical industry, are covered in the generic use of the chemical industry processes and the formulation processes that have been described earlier (see the generic use section above).

The use of NMP as a co-solvent in agrochemicals is partly professional. These processes are not included in the generic use described before and these processes will therefore be presented separately. The professional processes covered in the companies' registration dossiers include spraying, (trans)-pouring from containers, mixing, equipment clean-downs and disposal.

It is noted that EU Regulation 1107/2009 will ban the use of CMR substances categories 1A and 1B in plant production products, meaning that the use of NMP as a co-solvent will be phased out in time. Personal communication with industry indicates that phase-out will be complete in 2015 (personal communication, RIVM questionnaire). The use of NMP in the synthesis of active ingredients will remain according to industry. More information on the respective legislation for plant protection and biocides is discussed in chapter B.9.1.1 (summary of existing legislation) of this Background Document.

Pharmaceutical industry

NMP is used in the pharmaceutical industry for multiple purposes. It is both used in the production of pharmaceuticals as used in pharmaceutical products.

In the production of pharmaceuticals, NMP is an important solvent used in the extraction, purification, and crystallization of pharmaceuticals (Jouyban et al 2010). BASF (2011a) further reports that it produces high grade NMP (low in free amines) for the solid-phase synthesis of therapeutic peptides to be used in the pharmaceutical industry. An example is provided in Rijkers et al 2005. During the stakeholder consultation (public consultation Annex SVHC dossier, SVHC-RCOM 10052011) it was indicated that NMP may function as a reaction medium in the chemical synthesis of antibiotics for human, animal and agro purposes (e.g. Ertapenem). Note that NMP used during manufacture of pharmaceuticals might not end up in the final product.

Besides the use in the production of pharmaceuticals, NMP is used in pharmaceuticals products for various reasons and in different types of pharmaceuticals. It is being used as a solvent for difficult soluble drugs, but it has also a function as an enhancer for the transdermal delivery of drugs from the aqueous phase. Several studies are available where the effect of NMP as an excipient in pharmaceuticals on the membrane permeability is studied (Lee et al. 2005, Bendels et al 2006). In a review of the pharmaceutical applications of NMP Jouyban et al (2010) indicates that the solubization of drugs by NMP is ambiguous. It may work as a co-solvent, as a complexing agent and as a surfactant. Jouyban et al (2010) mention a number of topical formulations that may contain NMP as a transdermal enhancer. Also the use as a solvent and as extraction medium is reported by industry (Taminco, 2010).

NMP is also used in parenteral formulations for human and veterinary drugs where a standard biodegradable polymer or copolymer is dissolved in a solvent, to be used in a parenteral controlled released delivery systems (Malik et al 2010). Examples of such pharmaceuticals are Eligard using the Atrigel technology and Onyx (Covidien). The solvent used in Atrigel is NMP. A research paper from 2003 mentions "the use of new polymers and solvents to provide additional benefits in long-term drug release and tissue compatibility" as one of the areas for development for Atrigel (Dunn, 2003). The solvents used can be either hydrophobic or hydrophilic. Other information on the use of NMP in pharmaceuticals suggests its use as excipient or inactive ingredient because of its physical properties as polar aprotic solvent.

Sectors included within this category are the manufacturers, formulators and end-users of the pharmaceuticals. The industrial uses of NMP in the pharmaceutical industry, are covered in the generic use of the chemical industry processes and the formulation processes that have been described earlier (see the generic use section above).

Laboratories

The registration dossiers of NMP include the use in laboratories. No specific information has been received from industry on this use. It is anticipated that NMP is used in laboratories during research and development of petrochemicals, pharmaceuticals, all sorts of formulations and functional fluids and as a 'traditional solvent' for laboratories.

Though not covering all laboratory use, it is noted that use in scientific research and development is exempted from restriction according to Article 67(1) of the REACH Regulation (EC, 2006). Only those laboratory processes are involved in this sector, that occur at industrial sites as well as in professional settings.

Functional Fluids

Based on information from the registration dossiers, industrial and professional use of NMP takes place as a functional fluid, for example in cable oils, transfer oils, coolants, insulators, refrigerants, hydraulic fluids in industrial equipment including maintenance and related material transfers. More specifically, functional fluids may comprise hydrolic brake fluids and shock aborbing fluids, which can be used for aircraft control, hydraulically operated die-casting machines, presses and comparable mechanisms. Gartiser & Urich (2002) mention the use of NMP in cooling water systems as an auxiliary additive and estimate the use for industrial cooling systems within Germany to 0.2 tonnes per year. The consumption of NMP was not systematically surveyed. No specific information on this use has been received from industry through consultation and the quantities used in this application are unknown. Processes involved according to the registration dossier are generally open processes as it describes the use of the functional fluid prior to or during maintenance of a closed operating system.

Construction industry

The use of NMP as construction chemical in industrial use is included in the registration dossier, however, what this use actually involves is unclear to date (November 2012). Also personal communication with industry could not clarify this use (personal communication, response to RIVM draft dossier). From literature, the uses of polymer dispersions, powders and solutions are often classified under the construction chemicals. They may be produced on the basis of acrylates, styrene, butadiene and polyurethane and may be applied as filling compounds, roof coatings, sealants and flooring adhesives. Examples are dispersions based on acrylic ester, styrene, butadiene, polyurethane or polycarbonate polyurethane. Many construction products contain mixtures of solvents, such as NMP (HSE, 2003; BASF, 2011b).

The process is industrial, however, whether NMP ends up in the end product resulting in potential exposure of professionals using the construction chemical is not known. Personal communications with industry indicated that NMP is not used in cement, concrete, or asphalt. The registrants described the following processes: roller application or brushing, dipping of articles, production of preparations and articles. Based on the description of the processes involved (in registration dossier) and reports on NMP use in adhesives, binders, and anti-corrosion or waterproofing coatings it seems that NMP may be used as a primer or finish for production of articles.

Other (consumer)

Consumer use of NMP was not mentioned in the updated registration dossier by the lead registrant, nor was the use of NMP advised against. However, consumer use was included in the earlier version of the registration dossier that might still be supported by some of the downstream users of NMP. Notably, one registrant notified the use of NMP in printer ink and toners, available to the general public. Based on public literature and product registers it appears that NMP is used in a number of consumer products such as coatings, cleaners and ink up to a concentration limit of 5%,

although product registers report (illegal) higher concentrations to be present in some of those products (see Annex 2). Whether these consumer uses still exist to date (or whether the cited information on consumer uses is outdated) is uncertain. Anyhow, as indicated in section A.2 the use of NMP by the general public will not be considered in the restriction dossier, because The Netherlands has prepared a harmonised classification and labelling proposal to lower the specific concentration limit of NMP to 0.3% (generic value) submitted on March 1th 2013. If the new specific concentration limit will be adopted in Annex VI of the CLP Regulation, than this will result in a ban on NMP in consumer products as NMP will have no function anymore at concentrations of 0.3%.

B.2.3 Uses advised against by the registrants

According to the lead registrant there are no uses advised against.

B.3 Classification and labelling

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

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, 1-methyl-2-pyrrolidone is listed with index number 606-021-00-7 in Annex VI, part 3 of Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) with the following classification:

***Table B.08**: Classification according to part 3 of Annex VI, Table 3.1 ((list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008*

Index no.	International Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class & Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
606-021-00-7	N-methyl-2-pyrrolidone,1-methyl-2-pyrrolidone	212-828-1	872-50-4	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	H360D*** H319 H335 H315	GHS08 GHS07 Dgr	H360D*** H319 H335 H315		– Repr. 1B H360D: C ≥ 5% STOT SE 3: H335: C ≥ 10%	

*Repr. 1B, H360D*** May damage the unborn child.*
Eye Irrit. 2 H319 Causes serious eye irritation.
Skin Irrit. 2 H315 Causes skin irritation.
STOT Single Exp. 3 H335 May cause respiratory irritation.

***Table B.09**: Classification according to part 3 of Annex VI, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008*

Index no.	International Chemical Identification	EC no.	CAS no.	Classification	Labelling	Concentration Limits	Notes
606-021-00-7	N-methyl-2-pyrrolidone,1-methyl-2-pyrrolidone	212-828-1	872-50-4	– Repr. Cat. 2; R61 Xi, R36/37/38	T R: 61-36/37/38 S: 53-45	– Repr. Cat. 2; R61: C ≥ 5% Xi, R36/37/38: C ≥ 10%	

Repr. Cat. 2; R61 May cause harm to the unborn child.
Xi - R36/37/38 Irritating to eyes, respiratory system and skin

The Netherlands has prepared a harmonised classification and labelling proposal to lower the specific concentration limit for reprotoxicity category 1B of NMP to 0.3% (generic value), submitted on March 1th 2013.

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

All notifiers used the harmonised classification given in section B.3.1, whereas some notifiers have some additional selfclassification.

B.4 Environmental fate properties

Environmental fate properties are considered not relevant for this Background Document.

B.5 Human health hazard assessment

The summarized data for the human health hazard endpoints were adopted from the registration dossiers, CSRs, and/or OECD SIDS. The study reports of the key studies were kindly received from the lead registrant for the endpoints repeated dose toxicity and reproduction and developmental toxicity. Those studies are described in more detail since it was considered that the repeated dose toxicity for the general worker population and the developmental toxicity endpoint (or the endpoints considered in those studies) for pregnant workers are the most critical endpoints. The Dossier Submitter evaluated the studies and adapted when considered necessary the NOAELs and LOAELs for the individual studies. Further, this Background Document is targeted to the use of NMP in industrial settings and by professionals. Therefore, for the relevant toxicity endpoints, the Point of Departure (POD) and DNELs are derived for the dermal and inhalation route as the oral route of exposure is considered to be negligible for workers.

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

Toxicokinetics

The information on the toxicokinetics was obtained from the registration dossier and is summarized below:

- Studies have been carried out in rats using the dermal, inhalation, oral or intravenous routes.
- 1-methyl-2-pyrrolidone (NMP) is well absorbed following inhalation (40%-60%), oral (~100%) and dermal (≤100 % depending on conditions) exposure (Midgley et al., 1992; Ghantous, 1995; Payan et al., 2002; Kennedy and Delorme, 2004). In humans, NMP is rapidly absorbed following exposure by the inhalation, dermal or oral route in human volunteers (Akesson and Paulsson, 1997; Akesson and Jonsson, 1997; Akesson and Jonsson, 2000; Jonsson and Akesson, 2003).
- A distribution study following intravenous administration of radiolabelled NMP in the rat showed distribution to all tissues, with highest levels of radioactivity being observed in the liver, bile and small intestine, kidneys, stomach and testis (Wells and Digenis, 1988). Abstracts of kinetic investigations revealed indications that NMP is able to pass the placenta when pregnant rats were exposed by inhalation or treated orally by gavage. The concentrations found in fetal organs correspond to those of the maternal organs (Sitarek, 2003; Ravn-Jonsen et al., 1992). About 80% of the administered dose is excreted as NMP and NMP metabolites within 24h, mainly via the kidneys. The major metabolite is 5-hydroxy-N-methyl-2- pyrrolidone (5-HNMP). Studies in humans show that NMP is rapidly transformed by hydroxylation to 5-HNMP, which is further oxidized to N-methylsuccinimide (MSI); this intermediate is further hydroxylated to 2-hydroxy-N-methylsuccinimide (2-HMSI). The excreted amounts of metabolites in the urine after inhalation or oral intake represented about 100% and 65% of the administered doses, respectively.

Human volunteer data on toxicokinetics

After oral administration of 100 mg NMP to three healthy male volunteers, 65% of the administered dose was recovered in urine, comprising 2% NMP, 67% 5-HNMP, 0.1% MSI and 31% 2-HMSI (Akesson and Paulsson, 1997). A 6-h topical study in male and female volunteers using a single dose of 300 mg NMP showed peak plasma concentrations of NMP three hours after application. 22–24% of the total dose was recovered in the urine (Akesson and Jonsson, 2000). The pharmacokinetics of NMP was examined in four workers exposed to 0.46–2.84 mg/m^3 for 12 hours per day for a 5 day working week and five volunteers who observed the work processes for a single 8 hour day and were exposed to a mean concentration of 1.15 mg/m^3. NMP levels in plasma and urine were monitored in both workers and volunteers. Metabolic saturation was not predicted at concentrations below approximately 40 mg/m3. Additional information on NMP levels in plasma and urine are available (Xiaofei et al., 2000). Bader and co-workers have confirmed 5-HNMP, 2-HMSI and free NMP (68:31:l at the exposure level of 40 mg/m³ NMP) as the major urinary metabolites following inhalation exposure of 16 male volunteers to concentrations of 10, 40, 80 and 160 mg/m³ NMP (Bader et al., 2007). Half-lives of 3.9, 7.5 and 28 hours for NMP, 5-HNMP and 2-HMSI, respectively, at the exposure level of 40 mg/m³ NMP under resting conditions were reported by these workers (Bader et al., 2008).

To reduce the uncertainty in rat to human extrapolations, Physiology Based PharmacoKinetic (PBPK) models were developed to describe the pharmacokinetics of NMP in both species (Poet et al., 2010). Since in utero exposures are of concern, the models considered major physiological changes occurring in the dam or mother over the course of gestation. The rat PBPK model was used to determine the relationship between NMP concentrations in maternal blood and decrements in fetal/pup body weight. Body weight decrements seen after inhalation exposures occurred at lower NMP blood levels than those observed after oral and dermal exposures. In addition, benchmark dose (BMD) modelling was used to better define a point of departure (POD) for fetal/pup body weight changes by using dose-response information from two key inhalation studies in rats. These PODs and the human PBPK model were then used to estimate human equivalent concentrations (HECs) that could be safely used in the workplace. The geometric mean of the PODs derived from the key studies was estimated to be 350 mg x h/L (expressed in terms of internal dose), a value which corresponds to a HEC of 480 ppm (1979 mg/m^3) (occupational exposure of 8 hours/day for 5 days/week). The BMD human equivalent values that were calculated by means of the rat and human PBPK models based on internal dose (area under the curve for parent NMP) were considerably larger (approximately 4.6 -fold, 105 ppm (rat) as compared to 480 ppm (human)) than would be obtained using rat external concentration as the dose measure.

Conclusions

An evaluation of the toxicokinetic differences between rats and humans to inhalation exposure was made by the Dossier Submitter, based on the toxicokinetic information described above. The Poet et al. study (2010) indicates that at the same external air concentrations, rats will achieve relatively higher internal blood concentrations. The observed differences are however based on an optimized PBPK model. For this reason, the kinetic data for rats and humans were compared to evaluate if the conclusion holds true when experimental data, obtained under similar conditions, support the conclusion made by Poet et al. See for more information Annex 4.

Plasma kinetic data in rats and human volunteers were studied upon inhalation exposure in the range of 1-10 ppm (4.1 to 41 mg/m^3) NMP for 6-8 hours. Albeit none of the data sets available were complete and several shortcomings were noted, the overall picture is quite clear. NMP plasma concentrations in male human volunteers are somewhat lower but in the same order of magnitude compared to those predicted by linear high-to-low exposure extrapolation in male rats. However, the differences are relatively small. Taking into account various uncertainties in the data sets, these differences **cannot** be expressed as a concrete quantitative factor (see Annex 4). Based on the evaluation by the Dossier Submitter, a deviation from the default assessment factor for toxicokinetics (part of the remaining differences factor of 2.5 and for inhalation route of exposure only) is not supported by experimental rat and human data.

Dermal absorption

In the OECD SIDS dossier it is stated that dermal absorption has been extensively studied as it typically poses the greatest potential for human exposure. Studies have been performed in vitro with animal and human excised skin and in vivo in the rat and in human volunteer studies. NMP was applied in aqueous vehicles, organic solutions or neat NMP was applied. Conditions were either under occlusion or not and for duration ranging an hour to 24 hours. The study descriptions on dermal absorption below were taken from OECD SIDS dossier (2007), and from the registration dossier (summary given in Table B.10).

Dermatomed membranes (about 200 - 400 µm thickness) were prepared from human (female, breast skin) and rat (male SD) skin and were mounted in flow-through diffusion cells. Neat NMP or solutions in limonene (65% v/v) or water (35% v/v) were applied using a finite dose volume (6 µl to 0.64 cm² skin) to human and rat skin. Infinite doses (250 ml to 0.64 cm² skin) were applied to human skin only. Immediately following administration, the application site was occluded. NMP is rapidly absorbed through human and rat skin, within 1 h when applied either as neat or diluted in limonene (65%, v/v). Absorption was most pronounced for the 65% (v/v) solution in limonene. The absorption for the 30% (v/v) solution in water was lower than for the neat NMP. Rat skin overestimated human skin permeability for tested NMP preparations. The difference was particularly apparent in the first hour. The absorption profiles for the finite and infinite doses were similar over the first hour but thereafter differed. Investigations on dermatomed rat skin in vitro with application of neat NMP or solutions in limonene (65%) or water (30%) for up to three hours resulted in absorption rates of 3.113 mg/cm²/h, 12.905 mg/cm²/h and 0.906 mg/cm²/h, respectively. After three hours skin penetration amounted to 53%, 98% and 39% for neat NMP, 65% NMP in limonene and 30% NMP in water, respectively (Confidential study report 2002).

After dermal exposure of NMP to rat skin at doses of 0.2, 2 and 20 mg/cm^2 applied to an area of 12 cm^2, there was 50% absorption of the 2 lower doses while 75% of the 20 mg/cm^2 dose was absorbed, suggesting that NMP promotes its own absorption. Maximum blood levels were observed approximately 8 hours after application (Research Triangle Institute, 1991; as cited in OECD SIDS 2007).

The absorption of 14C-radiolabelled NMP in male Sprague-Dawley CD rats was determined following a single topical application of undiluted NMP and also diluted at four concentrations (3, 10, 30 and 65%) in two dose vehicles (water and limonene). For each dose solution, one group of rats was killed at 1, 3, 6 and 24 hours after dosing. A single topical application of 100 % NMP to the clipped area of the male rats resulted in approximately one third of the dose being absorbed and two thirds being evaporated from the dose site. Dilution of NMP with water decreased the absorption of dose with increasing proportions of water in an almost linear relationship. Dilution of NMP with limonene from 65:35 to 10:90 increased the proportion (% of radioactivity) absorbed compared to 100% NMP although the mass (mg) of NMP absorbed did not increase. Under all conditions, very little dose remained at the dose site at 1 hour after dosing, indicating that the equilibrium between absorption and evaporation of dose was rapidly achieved. The proportion of dose that was absorbed was almost entirely eliminated in the urine by 24 hours after dosing (Huntingdon Life Science Ltd Eye, Suffolk, UK (1998).

It was demonstrated that percutaneous absorption rate in rats was proportional to the concentration of NMP applied and was dependent on skin thickness. Maximum absorption fluxes of 9.7 mg/cm^2/h (30 min) and 23.4 mg/cm^2/h (45 min) NMP were determined for 20 µl/cm^2 and 40 µl/cm^2, respectively; absorption decreased when neat NMP was diluted (Payan et al., 2003; as cited in OECD SIDS 2007).

An in vivo dermal absorption study (OECD test guideline 427) with rats (Crl: CD (SD) IGS BR) was performed by a research laboratory in 2003. Animals were exposed for one hour to 0.1 ml neat NMP on 10 cm^2 skin under occlusion, semi-occlusion or without occlusion. A proportion of the dose was removed from the skin by washing the dose site at 1 h post dose. The dose was rapidly absorbed (within 1 hour of dosing) in each treatment group. Highest absorption was observed in the group where there was no occlusion of the dose site and lowest absorption in the group where the dose site was fully occluded. Following dermal application of 14C-NMP at a target dose of 0.1 mL/10 cm^2. the majority (45-77%) of the dose in each dose group was rapidly absorbed within 1 hour of dosing. Highest absorption (57-77%) was observed in the group where there was no occlusion of the dose site and lowest absorption (45-58%) in the group where the dose was fully occluded. The lower absorption seen with occlusion is considered to reflect dilution of the applied

NMP by the transepithelial movement of water that subsequently becomes trapped at the site of occlusion (Confidential study report 2003).

Investigations on dermatomed human skin in vitro with application of neat NMP or solutions in limonene (65%) or water (30%) for up to three hours resulted in absorption rates of 1.650 mg/cm²/h, 6.331 mg/cm²/h and 0.579 mg/cm²/h, respectively. After three hours skin penetration amounted to 37%, 90% and 21% for neat NMP, 65% NMP in limonene and 30% NMP in water, respectively. Examinations of the effect of NMP on skin integrity showed the ability of NMP to enhance its own absorption (Confidential study report 2002).

A comparative skin penetration study with split human skin on different commercial solvents showed a permeation rate of NMP of 17.1 mg/cm²/h, similar to that of DMSO (Ursin et al., 1995; as cited in OECD SIDS 2007).

Another study showed no differences between absorption rates of NMP tested as 3.0% or 0.3% solutions in distilled water and artificial sweat (NMP Producers Group, 2004). Dermatomed human skin membranes were prepared and fitted inside flow through diffusion cells maintained at 32°C. Aliquots of radiolabelled Test Material aqueous solutions (6 in water and 2 in artificial sweat) were dosed to the skin membranes at 250 µl per cell (infinite dose). Receptor fluid (phosphate buffered saline) passed under the membranes was collected at timed intervals up to 24 hours post dosing. The fractions of receptor fluid collected were assayed for total radioactivity by liquid scintillation counting (LSC) to enable the absorption rate of the radiolabelled Test Material to be calculated. A linear correlation was evident between the concentration of NMP in the aqueous dose solutions and the absorption rate at both selected time periods with an R2 of 0.98 (0-3 hours) and an R2 of 0.99 (3-7 hours). There were no significant statistical differences between the absorption rates of NMP from 3.0% and 0.3% NMP solutions in distilled water and artificial sweat (Confidential study report 2004).

A 6-h topical study in male and female volunteers using a single dose of 300 mg NMP showed peak plasma concentrations of NMP three hours after application. 22 – 24% of the total dose was recovered in the urine (Akesson and Jonsson, 2000; as cited in OECD SIDS 2007).

A mean 67.9% absorption of NMP through the skin in 12 human volunteers exposed to 300 mg NMP via a skin patch was observed (Ligocka et al., 2003; as cited in OECD SIDS 2007).

***Table B.10**: Overview of dermal absorption studies*

Species	Type study	Study design	Vehicle	Absorption rate or percentage	Reference
Rat (Sprague-Dawley) and human (Caucasian)	In vitro dermal skin penetration study with human and rat skin (OECD draft Test Guideline 1999, to meet requirements of Directive 91/414/EEC)	Up to 24hrs (percentages presented after 1 and 3 hours)	100%; 30% in water and 65% in limonene	ca. 7/ 37% at 1/ 3 hours; 1.650 mg/cm^2/hr (undiluted NMP; human skin) ca. 23/ 53% at 1/ 3 hours; 3.113 mg/cm^2/hr (undiluted NMP; rat skin) ca. 44/ 90% at 1/ 3 hours; 6.331 mg/cm^2/hr (65% NMP in limonene; human skin) ca. 89/ 98% at 1/ 3 hours; 13.905 mg/cm^2/hr (65% NMP in limonene, rat skin) 0.6/ 21% at 1/3 hours; 0.579 mg/cm^2/hr (30% NMP in water human skin) 0.7 /39% at 1/3 hours; 0.906 mg/cm^2/hr (30% NMP in water, rat skin)	Confidential study report 2002
Rat (strain unknown)	In vivo	0.2, 2, 20 mg/cm^2 applied to 12 cm^2 Unknown duration	Unknown	50% absorption at 0.2 and 2 mg/cm^2. 75% absorption at 20 mg/cm^2	Research Triangle Institute (1991)

Species	Type study	Study design	Vehicle	Absorption rate or percentage	Reference
Rat (Sprague-Dawley)	In vivo EPA OPPTS 870.7600 (Dermal Penetration)	Up to 24 hrs 3, 10, 30, 65% diluted in water and in limonene; 100% neat NMP undiluted	Water and limonene	ca. 32% at 24 h (neat) ca. 15% at 24 h (in aqueous solution) ca. 43% at 24 h (in limonene) No information on influence of concentration.	Huntingdon Life Science Ltd Eye, Suffolk, UK (1998)
Rat (strain unknown)	In vivo	20 and 40 µg/cm^2 Unknown exposure duration	Unknown, absorption decreased when neat NMP was applied	Maximum absorption fluxes of 9.7 mg/cm^2/h (20 µg/cm^2) and 23.4 mg/cm^2/h (40 µg/cm^2)	Payan et al. (2003)
Rat (Crl: CD (SD) IGS BR)	In vivo OECD 427	Exposure regime: 1 hour Doses/conc.: 100 µl /animal over 10cm² skin area Under occlusion, semi-occlusion, type of wrap, or without occlusion	-	ca. 45 - ca. 77% at 1 hour Highest absorption without occlusion	Confidential study report 2003
Human split skin	In vitro	No information	No information	Permeation rate of 17.1 mg/cm^2/h	Ursin et al. (1995)
Human skin	In vitro OECD Draft Guideline 428 for skin absorption	single application, exposure for up to 24 hours	0.1, 0.3, 1.0, 3.0 10.0 and 30% NMP in water and 0.3 and 3.0% in artificial sweat	ca. 80% at 3 - 7 hours No difference between water and artificial sweat as vehicle. No information on influence of concentration on absorption.	Confidential study report 2004
Human skin	Volunteer study	6h topical exposure	Single dose of 300 mg	22-24% recovered in urine	Akesson and Jonsson (2000)
Human skin	Volunteer study, 12 subjects	Skin patch, unknown duration	Single dose of 300 mg	Mean absorption of 67.9%	Ligocka et al. (2003)

Conclusions on dermal absorption

Dermal absorption ranged significantly under various exposure conditions from 7 to 98%, where the highest absorption fraction was found when NMP was applied to the skin with limonene as vehicle. Using human skin the highest absorption fraction observed was 0.8. It appears that NMP can readily permeate the skin, although notably several factors may affect the dermal absorption such as the vehicle (matrix), occlusion, and the duration of contact. Based on the dermal absorption studies, a conservative dermal absorption percentage of 100% will be used throughout the Background Document in case route to route extrapolation is applied to obtain a dermal reference value from an oral reference value. By default, as information was not available to the Dossier Submitter, the oral absorption was set at 100% as well. The use of absorption percentages of 100% for the oral and dermal route is in line with previous conclusions in toxicokinetic studies by Midgley et al., 1992; Ghantous, 1995; Payan et al., 2002; Kennedy and Delorme, 2004.

Oral and inhalation absorption

N-methyl-pyrrolidone (NMP) has been administered in toxicological studies via the dermal, oral and inhalation route. In order to be able to compare the internal doses the absorption must be known for those specific routes. The dermal absorption is discussed above; in this section focus lies on the inhalation route mainly. For the oral route absorption fractions of 0.6 to 1 have been reported (referring to Midgley et al., 1992; Ghantous, 1995; Payan et al., 2002; Kennedy and Delorme, 2004) and thus a absorption fraction of 1 is taken.

The following has been reported for the inhalation route: "N-methyl-pyrrolidone (NMP) is well absorbed following inhalation (40% - 60%) (referring to Midgley et al., 1992; Ghantous, 1995; Payan et al., 2002; Kennedy and Delorme, 2004)" and "The excreted amounts of NMP metabolites in the urine after inhalation or oral intake represented about 100% and 65% of the administered doses, respectively". It is noted that not all these studies even considered inhalation exposures. The study by Ghantous (1995) did consider inhalation exposure.

Table B.10b: *the mean percent recovery of the absorbed dose (Ghantous, 1995)*

Confidential table was deleted.

Based on the results by Ghantous (1995, confidential data not reported) the amounts found in urine + feces + tissues may be considered as the absorption percentage, approximating 100%. Ghantous noted that due to the solvent properties (non-polar and polar) of NMP it would be expected that the substance would cross barriers readily, which was shown for all three routes considered in the study.

A bioavailability of 100% of alveolar ventilation (alveolar ventilation [QPC] is calculated as 2/3 total ventilation) was assumed for inhalation exposures (Poet et al. 2010).

Conclusion on oral and inhalation absorption

The oral absorption was reported to be up to 100% and therefore 100% is taken forward. Considering the findings by Ghantous (1995) and the model assumptions by Poet et al. (2010), the Dossier Submitter concludes that 100% absorption of the inhaled amount would not be a too conservative estimate. For refinement, one could correct for the alveolar ventilation, where Poet assumes that 100% is bioavailable at 67% of the total inhaled volume.

B.5.2 Acute toxicity

Information was obtained from the registration dossiers and OECD SIDS (2007).
1-methyl-2-pyrrolidone has a low acute toxicity by oral, dermal, inhalation, intraperitoneal, and intravenous routes of exposure. Oral LD_{50} values ranged from 3605 to 7725 mg/kg bw in rats and mice (Ansell and Fowler, 1988; BASF, 1963) and dermal LD_{50} values ranged from 5000 to 7000 mg/kg bw in rats (Weisbrod and Seyring, 1980 (not in registration dossier); Weisbrod, 1981 (not in registration dossier); Clark et al., 1984). Reliable inhalation exposure studies were generally conducted with a vapour/aerosol mixture. The 4hr-LC_{50} was >5100 mg/m³ (BASF, 1988a), where 87% was considered respirable. Low toxicity was also observed after intraperitoneal and intravenous injection in rats and mice.

Conclusion

The acute toxicity of NMP is low as was previously concluded in the OECD SIDS (2007).

B.5.3 Irritation

Information was obtained from the registration dossiers and OECD SIDS (2007).
1-methyl-2-pyrrolidone (NMP) is a mild skin and eye irritant in rabbits. In animal studies, exposure to aerosols leads to upper respiratory tract irritation with a NOAEC of 500 mg/m^3 (BASF AG, 1994).

The key skin irritation study in rabbits involving a single application of 0.5 ml NMP under an occlusive dressing has shown a low potential for irritancy. Only slight erythema was observed for the intact and abraded skin. When the examination was repeated 72 h and 7 days after the start of exposure, no effects were observed. (Ansell & Fowler, 1988; Consumer Product Testing Co, 1980; GAF Corp, 1986). A reliable modified Draize test performed in 4 male albino rabbits with a 20 % solution of NMP in isopropyl myristate under occlusive conditions for 24 hours caused only minimal irritation on the day of administration (Sasaki et al., 1999).

New Zealand white rabbits received a single intraocular application of 0.1 ml neat NMP into the conjunctival sac of one eye, the other served as untreated control. Marked conjunctival irritancy including corneal opacity, iritis, and conjunctivitis was observed but effects were reversible (Ansell and Fowler, 1988).

Within a 3 months inhalation toxicity study in male and female Wistar rats to concentrations of 0, 500, 1000 and 3000 mg/m^3 for 6h/day and 5times/week (65 exposures), respiratory tract irritation was observed at ≥1000 mg/m^3. The no observed adverse effect concentration (NOAEC) for local irritation was 500 mg/m^3 (BASF AG, 1994).

Human information

A repeated insult patch test in 50 human subjects, which is only available as a secondary citation, revealed no irritation during 24 hours of exposure (Lee et al., 1987). Skin irritation was reported in several workers after a few days working with NMP using a paper cloth to wipe surplus of NMP from plastic pieces that had been dipped in the solvent (Leira et al., 1992).

Swelling and wrinkling of the skin of their hands without signs of inflammation were observed in 3 employees of a manufacture after exposure of a few minutes for several times during 3 days. These signs were attributed to the hygroscopic effect of NMP on the stratum corneum (Jungbauer et al., 2001).

Acute changes in the pulmonary function and in the nasal volume were not found, nor discomfort or irritating effects after exposure of 6 male volunteers on one single day for 8 hours to concentrations of 0, 10, 25 and 50 mg/m^3 NMP (Akesson and Paulsson, 1997). A human volunteer study on chemosensory effects revealed no indication of respiratory tract irritation (NMP Producers Group, 2005)

In the SCOEL evaluation (SCOEL, 2007) a human volunteer study was described (reported in Bader et al. 2007 and Van Thriel et al. 2007). A comprehensive study in 16 healthy young male volunteers has been undertaken, in order to investigate possible chemosensory effects of NMP under workplace conditions. One subject dropped out of the study at an early stage for reasons unrelated to NMP exposure. Exposure scenarios used in the study were 10 mg/m^3, 40 mg/m^3, 80 mg/m^3 and 25/160 mg/m^3, the latter including peak exposures up to 160 mg/m^3. The 10 mg/m^3 condition was defined as a nonirritating odorous control condition. The subjects were exposed for an 8-hour (typical shift) period. The results showed that NMP could be smelled by the subjects (odor intensity, showing some adaptation over the 8 hour exposure period) and it was reported to be slightly annoying. However other symptomology indicative of an irritant potential, especially trigeminal sensations, were not elicited by NMP. Median intensity ratings of annoyance only reached "moderate" intensities. The odor intensity was rated slightly higher than annoyance, but the ratings exceeded "moderate" only during exposure peaks. The peak concentrations were mirrored by the ratings of odor intensity and annoyance. However, neither nasal flow values (AAR), nor eye blink rates, and breathing rates showed any dose related response, even at the peak exposure of 160 mg/m^3. Behaviorally, none of the neuropsychological tests revealed any NMP-related effect with respect to cognitive abilities of the subjects during the exposures. The authors of the study concluded that NMP can be characterized as an odorous substance without irritant potency even during peak exposures of 160 mg/m^3 (Bader et al., 2007; Van Thriel et al. 2007).

Conclusion

In animals, the substance appears to elicit irritant effects to the skin, eye and respiratory tract. NMP is classified as an irritant for skin, eye and respiratory tract, although the information provided in the registration dossiers would not be sufficient to classify NMP as irritant for skin and eye. Based on the volunteer study a NOEC of 80 mg/m^3 can be derived based on the moderate annoyance observed at the peak exposures to 160 mg/m^3, whereas the volunteers at 80 mg/m^3 for longer periods noted no effects.

B.5.4 Corrosivity

NMP is not corrosive.

B.5.5 Sensitisation

Information was obtained from the registration dossier.
A total of fifteen 24-hour exposures in a repeated insult patch test in human subjects (n = 50) caused minor to moderate transient irritations. No signs of contact sensitisation were observed according to this secondary literature source (Lee et al., 1987a). Negative results were found in two guinea pig studies (Lee et al. 1987a; b), however both studies were not conducted following guidelines. Available data on the analogue N-ethyl-2-pyrrolidone (NEP; CAS 2687-91-4) in the Murine Local Lymph Node Assay (LLNA; OECD 429) showed a statistically relevant increase of ear weight in the top dose (50% in acetone), but without biological relevance. All doses applied showed irritation of the ear skin. NEP does not seem to be a skin sensitizer according to the results from the LLNA.

Conclusion

The data on skin sensitisation with NMP is limited to a secondary source describing a human repeated insult patch test and two guinea pig studies of questionable reliability. The LLNA study with NEP can be considered to be sufficiently reliable. Based on a weight of evidence approach, considering all data, the Dossier Submitter considers that NMP is not a skin sensitizer.

B.5.6 Repeated dosed toxicity

Information was obtained from the registration dossier and OECD SIDS (2007). The study descriptions and NOAELs/LOAELs were adopted in general, unless stated otherwise.

Oral

Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994

Groups of 5 male and 5 female Sprague-Dawley (Crl:CD:BR) rats were exposed to dietary NMP concentrations of 0, 2000, 6000, 18000 or 30000 ppm (0, 149/161, 429/493, 1234/1548, 2019/2269 mg/kg bw/day, males/females) for 28 days. The NOAEL was 6000 ppm for males and 18000 ppm for females (429 and 1548 mg/kg bw/day, respectively), based on reductions in body weight (Table B.11), food consumption (Table B.12) and food efficiency accompanied by changes in clinical chemistry (Table B.14) were observed in males at ≥18000 ppm and in females at 30000 ppm (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994). Slight hematological (slight lymphopenia) and histopathological alterations (hypocellular bone marrow and thymic atrophy) (Tables B.13 and B.15) were judged to be treatment-related but could have been secondary effects due to the impaired nutritional state in young and growing animals.

Table B.11: *Mean body weight gains of male and female rats after exposure to NMP for 28 days, specified per week (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994)*

Mean body weight gains	**PPM/mg/kg Bw/d**				
Males	**0 / 0**	**2000 / 149**	**6000 / 429**	**18000 / 1234**	**30000 / 2019**
Day 0 - 7	76.2	79.2	70.6	35.9 *	15.2 *
Day 7 -14	61.5	52.2	48.3	31.1 *	7.4 *
Day 14 - 21	37.3	46.9	29.7	28.9	15.7 *
Day 21 - 28	44.0	31.4	37.8	35.6	6.7 *
Females	**0 / 0**	**2000 / 161**	**6000 / 493**	**18000 / 1548**	**30000 / 2269**
Day 0 - 7	7.8	18.4	26.9	18.6	-2.3 *
Day 7 -14	24.2	21.4	20.3	14.4	8.4 *
Day 14 - 21	9.0	8.1	11.1	8.0	13.3
Day 21 - 28	16.5	9.5	11.8	13.3	12.9

** p < 0.05, Dunnett's test + ANOVA*

Table B.12: *Mean food consumption of male and female rats after exposure to NMP for 28days, specified per week (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994)*

Mean food consumption	**PPM**				
Males	**0 / 0**	**2000 / 149**	**6000 / 429**	**18000 / 1234**	**30000 / 2019**
Day 0 - 7	27.7	28.8	27.5	20.9 *	17.4 *
Day 7 -14	28.6	28.1	26.8	23.0 *	17.9 *
Day 14 - 21	29.3	30.3	26.4	24.1 *	19.2 *
Day 21 - 28	28.8	29.0	27.2	24.6 *	20.4 *
Females	**0 / 0**	**2000 / 161**	**6000 / 493**	**18000 / 1548**	**30000 / 2269**
Day 0 - 7	9.5	17.4	17.7	17.4	13.3 *
Day 7 -14	20.3	17.9	18.0	18.5	14.6 *
Day 14 - 21	20.6	18.8	21.4	18.5	16.8
Day 21 - 28	20.0	17.5	19.4	18.5	16.8 *

** p < 0.05, Dunnett's test + ANOVA*

Table B.13: *Lymphocytes counts of male and female rats after exposure to NMP for 28 days (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994)*

Lymphocytes count	**PPM**				
Males	**0 / 0**	**2000 / 149**	**6000 / 429**	**18000 / 1234**	**30000 / 2019**
	16328	14401	16015	13397	7591 *
Females	**0 / 0**	**2000 / 161**	**6000 / 493**	**18000 / 1548**	**30000 / 2269**
	14198	9045	9641	10246	6498

** p < 0.05, Dunnett's test + ANOVA*

Table B.14: *Clinical chemistry of male and female rats after exposure to NMP for 28 days (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994)*

Clinical chemistry	**PPM**				
Males	**0 / 0**	**2000 / 149**	**6000 / 429**	**18000 / 1234**	**30000 / 2019**
CHOL (mg / dl)	91	91	87	103	126 *
GLUC (mg / dl)	100	98	97	85 *	79 *
TPROT (g / dl)	7.1	6.1	6.6	6.4	6.1
ALB (g / dl)	4.8	4.5	4.4 *	4.4 *	4.1 *
ALP (u / l)	150	110	132	121	77 *
Females	**0 / 0**	**2000 / 161**	**6000 / 493**	**18000 / 1548**	**30000 / 2269**
CHOL (mg / dl)	102	89	109	127	150 *
GLUC (mg / dl)	97	110	106	100	89
TPROT (g / dl)	7.1	6.7 *	6.9	6.5	6.3
ALB (g / dl)	5.1	4.9	4.9	4.7 *	4.5 *

** p < 0.05, Dunnett's test + ANOVA*

***Table B.15:** Histopathology of male and female rats after exposure to NMP for 28 days (Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994)*

Histopathology	**PPM**				
Males	**0 / 0**	**2000 / 149**	**6000 / 429**	**18000 / 1234**	**30000 / 2019**
Liver hypertrophy	0 / 5	0 / 5	0 / 5	5 / 5	4 / 5
Hypocellular bone marrow	0 / 5	0 / 5	0 / 5	0 / 5	4 / 5
Testes degeneration / atrophy	0 / 5	0 / 5	0 / 5	1 / 5	5 / 5
Thymic atrophy	0 / 5	ND	ND	ND	1 / 5
Females	**0 / 0**	**2000 / 161**	**6000 / 493**	**18000 / 1548**	**30000 / 2269**
Liver hypertrophy	0 / 5	0 / 5	0 / 5	3 / 5	5 / 5
Hypocellular bone marrow	0 / 5	0 / 5	0 / 5	0 / 5	5 / 5
Thymic atrophy	0 / 5	0 / 5	0 / 5	0 / 5	3 / 5

ND = not examined

BASF AG, 1978

Groups of each ten Sprague-Dawley rats per sex received dose level of 0, 258, 516.5, 1033 and 2066 mg/kg bw/day (recalculated from 250, 500, 1000 and 2000 µl/kg bw) by gavage for 28 days. The males showed a dose-dependent retardation of body weight gain from 516.5 mg/kg bw/day onwards. At higher doses effects on immunological cells, kidney weights, and liver weights were observed, without histopathological findings. At the top dose effects on the testes accompanied by testicular lesions, including degeneration of the seminiferous epithelium, were observed. The

NOAEL was 258 mg/kg bw/day (BASF AG, 1978; original study not available to the Dossier Submitter).

Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995

The subchronic toxicity of NMP was investigated in a combined subchronic and neurotoxicity study. Groups of 20 – 26 male and female Sprague-Dawley (Crl:CD:BR) rats received dietary NMP concentrations of 0, 3000, 7500 or 18000 ppm (about. 0, 169/217, 433/565, 1057/1344 mg/kg bw/day, males/females) for 3 months. Ten animals per sex from the control and high dose group were observed for recovery for 1 month after treatment. Decrements in body weight (Table B.16 and B.17), food consumption (Table B.18) and food efficiency were observed at ≥7500 ppm. At 18000 ppm changes in liver and kidney weights were observed without corresponding histopathological findings. In addition, at this level foot splay (not observed after recovery period; Table B.19) and sedative effects (low arousal) were seen in male rats (Table B.20). The NOAEL was 3000 ppm for both sexes (169 mg/kg bw/day in males, 217 mg/kg bw/day in females). A specific target organ for compound-related adverse systemic toxicity was not identified (Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995).

Table B.16: *Mean Body Weight [g] of male and female SD rats receiving dietary NMP for 3 months (Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995)*

Mean body weight (g)	**Dose group (PPM / mg / kg bw / d)**			
Males	**0**	**3000 / 169**	**7500 / 433**	**18000 / 1057**
Day 0	275.0	274.6	273.7	273.6
Day 15	395.0	392.5	382.0	341.2 *
Day 29	467.1	464.1	452.3	400.1 *
Day 57	562.0	553.1	541.2	480.8 *
Day 92	631.9	614.9	608.1	531.2 *
Day 106	652.6	-	-	567.5 *
Day 127	671.1	-	-	618.6
Females	**0**	**3000 / 217**	**7500 / 565**	**18000 / 1344**
Day 0	178.8	179.4	179.2	179.6
Day 15	227.9	224.9	217.2	207.5 *
Day 29	252.4	249.0	239.7	229.3 *
Day 57	284.2	278.2	269.9	256.8 *
Day 92	302.0	295.6	283.3	272.3 *
Day 106	305.6	-	-	304.6
Day 127	323.1	-	-	312.5

** p < 0.05, Dunnett's test + ANOVA*

Table B.17: *Mean Body Weight gain [g] of male and female SD rats receiving dietary NMP for 3 months (Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995)*

Mean body weight gain (g)	**Dose group (PPM / mg / kg bw / d)**			
Males	**0**	**3000 / 169**	**7500 / 433**	**18000 / 1057**
Day 0 - 43	240.4	239.1	217.0 *	166.0 *
Day 43 - 92	116.4	101.2	117.4	91.6 *
Day 92 - 127	28.4	-	-	89.6 *
Females	**0**	**3000 / 217**	**7500 / 565**	**18000 / 1344**
Day 0 - 43	96.7	89.1	77.8 *	65.0 *

Mean body weight gain (g)	Dose group (PPM / mg / kg bw / d)			
Day 43 - 92	26.5	27.1	26.3	27.3
Day 92 - 127	25.6	-	-	35.2

** p < 0.05, Dunnett's test + ANOVA*

Table B.18: *Mean Food Consumption [g] of male and female SD rats receiving dietary NMP for 3 months (Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995)*

Mean food consumption (g)	Dose group (PPM / mg / kg bw / d)			
Males	**0**	**3000 / 169**	**7500 / 433**	**18000 / 1057**
Day 0 - 43	28.9	28.4	27.8	25.2 *
Day 43 - 92	28.4	27.6	27.8	26.0 *
Day 92 - 127	29.4	-	-	31.1
Females	**0**	**3000 / 217**	**7500 / 565**	**18000 / 1344**
Day 0 - 43	20.2	19.4	19.2	18.2 *
Day 43 - 92	19.2	18.6	18.9	17.7 *
Day 92 - 127	21.9	-	-	20.0

** p < 0.05, Dunnett's test + ANOVA*

Table B.19: *Mean Foot Splay [cm] of male and female SD rats receiving dietary NMP for 3 months (Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995)*

Mean foot splay (cm)	Dose group (PPM / mg / kg bw / d)			
Males	**0**	**3000 / 169**	**7500 / 433**	**18000 / 1057**
Week 4	7.9	8.9	9.6 *	9.8 *
Week 8	7.8	9.4	9.7 *	9.8 *
Week 13	7.7	7.4	8.9	9.1
Week 18	6.0	-	-	8.3 *
Females	**0**	**3000 / 217**	**7500 / 565**	**18000 / 1344**
Week 4	7.8	7.3	8.3	8.2
Week 8	7.1	7.3	8.2	8.2
Week 13	8.0	7.2	8.5	8.4
Week 18	7.1	-	-	6.2

** p < 0.05, Bartlett's test, Dunnett's test + ANOVA*

Table B.20: *Functional Observation Battery [number affected/total number] in male SD rats* ***receiving dietary NMP for 3 months*** *(Malley et al., 1999; NMP Producers Group, 1995b; TSCAT, 1995)*

Functional observation battery (number affected / total number)	**Dose group (PPM / mg / kg bw / d), male**			
Low arousal	**0**	**3000 / 169**	**7500 / 433**	**18000 / 1057**
Week 4	1 / 16	1 / 10	2 / 10	5 / 16 *
Week 8	2 / 16	0 / 10	3 / 10	5 / 16
Week 13	4 / 16	3 / 10	3 / 10	9 / 16
Week 18	1 / 10	-	-	2 / 10
Palpebral closure				
Week 4	0 / 16	0 / 10	1 / 10	3 / 16 *
Week 8	2 / 16	0 / 10	2 / 10	2 / 16
Week 13	2 / 16	2 / 10	0 / 10	7 / 16 *
Week 18	1 / 10	-	-	1 / 10

** p < 0.05, Cochran-Armitage trend test for Fisher's Exact test*

NMP Producers Group, 1995b; NMP Producers Group, 1994

Groups of 5 male and 5 female B6C3F1 mice received dietary NMP concentrations of 0, 500, 2500, 7500 or 10000 ppm (about 0, 160, 820, 2500, 3370 mg/kg bw/day) for 28 days. Body weights and food consumption were not affected at any dose (data not shown). A cloudy swelling of the distal portions of the renal tubular epithelia was observed at ≥7500 ppm (males) and 10000 ppm (females) (Table B.21). In females, at 10000 ppm significantly reduced ALP levels were found (Table B.22). One male in the 10000 ppm group died prematurely as a result of renal toxicity. Yellowish discoloration of the urine as indication for systemic availability was observed at ≥2500 ppm. The NOAEL was 2500 ppm based on the kidney effects in males (820 mg/kg bw/day, NMP Producers Group, 1995b; NMP Producers Group, 1994).

Table B.21*: Histopathology of kidneys in exposed B6C3F1 mice to NMP via the diet for 28 days (NMP Producers Group, 1995b; NMP Producers Group, 1994)*

Histopathology	**PPM / mg / kg bw / d**				
Males	**0**	**500 / 160**	**2500 / 820**	**7500 / 2500**	**10000 / 3370**
Kidney Cloudy swelling of epithelia, distal renal tubuli	0 / 5	0 / 5	0 / 5	2 / 5	4 / 5
Females					
Kidney Cloudy swelling of epithelia, distal renal tubuli	0 / 5	0 / 5	0 / 5	0 / 5	3 / 5

Table B.22*: ALP levels in mice exposed to NMP via the diet for 28 days (NMP Producers Group, 1995b; NMP Producers Group, 1994)*

Clinical pathology	**PPM / mg / kg bw / d**				
Males	**0**	**500 / 160**	**2500 / 820**	**7500 / 2500**	**10000 / 3370**
ALP (Mykat / L)	5.18	5.20	4.74	4.49	4.27
Females					
ALP (Mykat / L)	6.96	6.84	5.84	5.76	4.90 **

*** p < 0.01 Kruskall-Wallis + Mann-Whitney U-test*

Malley et al., 1999¸ NMP Producers Group, 1995a

Subsequently, groups of 10 male and 10 female B6C3F1 mice received dietary NMP concentrations of 0, 1000, 2500 or 7500 ppm (about 0, 277, 619, 1931 mg/kg bw/day) for 4 weeks (satellite group) or 3 months (main group). Liver weights were increased in males fed ≥2500 ppm NMP (Table B.24). Centrilobular hypertrophy occurred in the animals of both sexes fed 7500 ppm NMP (Table B.25). The liver was identified as target organ due to weight changes, histopathological findings indicative for an adaptive response to treatment and clinical chemistry showing differences in ALP, triglycerides and cholesterol levels at ≥ 2500 ppm (in satellite group). The NOAEL was determined at 1000 ppm, based on the significantly higher than controls liver weights in males at 2500 ppm observed in the satellite group after 4 weeks exposure. The NOAEL determined by the authors of the study (Malley et al., 1999¸ NMP Producers Group, 1995a) was set at 2500 ppm, which according to the Dossier Submitter is too high even though the liver effects may be of an adaptive nature.

Table B.23: *Clinical chemistry of male and female mice exposed to NMP via the diet (satellite group 4 weeks exposure)(Malley et al., 1999¸ NMP Producers Group, 1995a)*

Clinical chemistry	**PPM / mg / kg bw / d**			
Males	**0**	**1000 / 277**	**2500 / 619**	**7500 / 1931**
ALP (Mykat / L)	6.25	5.67	5.96	4.75 **
CA (mmol / L)	2.69	2.58	2.58	2.53 **
TRIG (mmol / L)	1.14	0.96	0.71 *	0.63 **
CHOL (mmol / L)	2.29	2.40	2.51	2.51
Females				
ALP (Mykat / L)	6.88	6.73	6.05	6.89
CA (mmol / L)	2.60	2.69	2.69	2.59
TRIG (mmol / L)	0.93	1.09	0.89	0.78
CHOL (mmol / L)	2.03	2.34	2.65 **	2.50 **

** p<0.05, ** p <0.01 Kruskall-Wallis + Mann-Whitney U-test*

Table B.24*: liver weights (absolute and relative) of male and female mice exposed to NMP via the diet (main group, 4 weeks exposure) (Malley et al., 1999¸ NMP Producers Group, 1995a)*

Liver and brain weights	**PPM / mg / kg bw / d**			
Males	**0**	**1000 / 277**	**2500 / 619**	**7500 / 1931**
Liver absolute (g)	1,13	1,194	1,299 **	1,34 **
Liver relative (%, related brain weight)	233	242	258 *	274 **
Females				
Liver absolute (g)	1,116	1,162	1,182	1,202
Liver relative (%, related brain weight)	226	225	227	236

** p<0.05, ** p <0.01 Kruskall-Wallis + Mann-Whitney U-test*

***Table B.25**: histopathology of male and female mice liver exposed to NMP via the diet (main group, 4 weeks exposure) (Malley et al., 1999¸ NMP Producers Group, 1995a)*

Histopathology	**PPM / mg / kg bw / d**			
Males	**0**	**1000 / 277**	**2500 / 619**	**7500 / 1931**
Liver, central hypertrophy	1 /10	0 /5	2 /10	9 /10
Females				
Liver, central hypertrophy	1 /10	0 /5	3 /10	10 /10

Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989

The subchronic toxicity was also investigated in Beagle dogs. Six dogs per sex per group received NMP at dose levels of 0, 25, 79, or 250 mg/kg bw/day in the diet for 90 days. No substance-related or permanent change, which was outside the biological or historical control data range, could be noted in any of the examined parameter at any dose level (Tables B.26 to B.28). Thus, the NOAEL was 250 mg/kg bw/day, the highest dose tested (Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989).

***Table B.26**: Mean body weight, body weight change, and food efficiency observed in Beagle dogs exposed to NMP for 90 days via the diet (Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989)*

Dose mg / kg bw / d	**Mean body weight (kg +/- SD)**	**Body weight change (% of initial +/- SD)**	**Food efficiency (BWG / 100 g food) (g +/- SD)**
Males			
0	10,2 +/- 1,2	12,8 +/- 7,7	4,0 +/- 2,4
25	10,5 +/- 0,9	13,2 +/- 5,8	3,8 +/- 1,7
79	10,1 +/- 0,7	11,0 +/- 11,0	3,2 +/- 3,2
250	9,7 +/- 1,4	6,9 +/- 9,1	1,9 +/- 2,7
Females			
0	8,2 +/- 1,7	10,2 +/- 5,7	3,0 +/- 1,9
25	8,0 +/- 1,4	10,9 +/- 5,6	3,1 +/- 1,6
79	8,0 +/- 1,3	9,5 +/- 5,5	2,6 +/- 1,6
250	7,6 +/- 1,0	3,8 +/- 9,3	0,8 +/- 2,5

***Table B.27**: Clinical chemistry in male Beagle dogs exposed to NMP for 90 days via the diet (Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989)*

Clinical chemistry (week 12)	**mg / kg bw / d, Males**			
Protein (g / dl)	6,1	5,8	5,7 *	5,4 *
Albumin (g / dl)	3,9	3,2	3,5 *	3,5 *
Cholesterol (mg / dl)	160	156	131	112 *

** $p < .005$*

***Table B.28**: Relative organ weights in Beagle dogs exposed to NMP for 90 days via the diet (Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989)*

Relative organ weights	**mg / kg bw / d**			
Males	**0**	**25**	**79**	**250**
Liver (%)	3,37	3,28	3,45	3,44
Kidney (%)	0,59	0,52	0,64	0,58
Heart (%)	0,81	0,77	0,78	0,78
Testes (%)	0,15	0,15	0,15	0,16
Adrenals (%)	0,011	0,011	0,014	0,013
Females				
Liver (%)	3,22	3,38	3,67	3,43
Kidney (%)	0,48	,49	0,48	0,51
Heart (%)	0,77	0,78	0,73	0,84
Testes (%)	0,93	1,40	0,85	0,88
Adrenals (%)	0,013	0,014	0,012	0,016

Inhalation

The dose administration of NMP via inhalation is an important factor in repeated dose toxicity after inhalation. A comprehensive research project was performed, wherein a series of short-term inhalation toxicity studies the effects of the mode of exposure (head-nose versus whole-body), influence of humidity and physicochemical status (vapor, aerosol including number/size of droplets) were investigated. Female Sprague-Dawley or Wistar rats were exposed to 0 or 1000 mg/m^3 for 6 hours daily, 5x/week for 2 or 4 weeks. The head-nose exposure caused independently of aerosol fraction and humidity no effects other than slight nasal irritation and colored urine. Whole-body exposure with coarse droplets and high relative humidity caused massive mortality, apathy, decreased body weight and body weight gain, irritation in the nasal region, and severe effects on organs and tissues, while whole body exposure with fine droplets and low or high relative humidity caused no deaths and less severe effects. The difference is likely caused by dermal and oral exposure to the coarse droplets depositing onto the skin. It is noteworthy that NMP exists in various proportions of vapor and aerosol depending on the concentration, temperature and humidity. The maximum vapor phase at room temperature is 1286 mg/m^3 (315 ppm) in dry air (0% relative humidity), 525 mg/m^3 (128 ppm) at normal animal room humidity (50% relative humidity) and 0 mg/m^3 (0 ppm) in humidity saturated air (100% relative humidity, BASF AG, 1995b; BASF AG, 1995a; BASF AG, 1995c; BASF AG, 1989; BASF AG, 1992). The vapor saturation of NMP under 'normal conditions' is considered to be in the range of 480-640 mg/m^3 (120 - 160 ppm) depending on humidity and temperature.

BASF AG, 1993a

After subacute head-nose exposure of aerolized NMP (10% aqueous solution) to groups of each 5 male and 5 female Wistar rats at concentrations of 0, 10, 30 and 100 mg/m^3 (0, 2.5, 7.5, 25 ppm) for 6 hours daily, 5 times/week for 28 days (20 exposures in total) no treatment-related adverse effects were observed. The animals in the high concentration group showed discolored urine and bedding, which indicates systemic availability. The NOAEC was 100 mg/m^3 (BASF AG, 1993a; original study report not available to the Dossier Submitter).

Lee et al., 1987; Lee, 1977; TSCAT, 1989; TSCAT, 1991b

In another subacute study each 15 male and female CD rats were exposed to NMP concentrations of 0, 100, 500, and 1000 mg/m^3 (0, 25, 125, 250 ppm, mainly aerosol) for 6 hours daily, 5 times/week for 4 weeks (21 exposures in total) using whole body exposure. At the high concentration there was excessive mortality (13/30) and the high exposure was discontinued after 10 days. Despite the high systemic toxicity at 1000 mg/m^3 the leukocyte counts and hematology appeared almost unaffected, except for the increased neutrophils and decreased lymphocytes (Table B.29 and B.30). Signs of lethargy and irregular respiration were observed at all

concentrations. No signs of pathological lesions were observed at these concentrations beside slight testicular atrophy. Lee et al. (1987) did not provide quantitative data on the testicular atrophy. The surviving rats were observed for 14 days. In dead animals severe signs of systemic toxicity were noted including bone marrow hypoplasia and atrophy and/or necrosis of the lymphoid tissue in thymus, spleen and lymph nodes (only graphical representations of the effects provided by the author, no quantitative data). In the surviving animals at the high dose, severe testicular atrophy was noticed in two males after ten exposures and in one male at 14 d post-exposure. The NOAEC for systemic toxicity was 500 mg/m^3 based on amongst others mortality and severe testicular atrophy. In contrast to the conclusions made by the study authors it was not possible to derive a NOAEL for local effect, because of the slight irritative symptoms in form of irregular respiration and lethargy already at 100 mg/m^3. Upon cessation the lethargy and irregular respiration were reversible within 30 to 45 minutes (Lee et al., 1987; Lee, 1977; TSCAT, 1989; TSCAT, 1991b; study was not described in the registration dossier).

***Table B.29**: differential leukocyte counts in CD rats exposed to NMP by inhalation for four weeks and two weeks of recovery (Lee et al., 1987)*

Exposure concentration (mg / L)	**Leukocytes (10^3)**		**Neutrophils (%)**		**Lymphocytes (%)**		**Eosinophils (%)**		**Monocytes (%)**		**Basophils (%)**	
Males	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**
0	12,9	13,9	17	16	76	76	0,8	1,5	6,2	7,5	0	0
0,1	15,2	15,0	22	18	69	77	0,4	0,6	7,2	4,2	0	0,2
0,5	13,2	16,8	24	18	68	77	0,4	1,4	7,2	3,6	0	0
1,0	15,9	15,7	33 *	20	61 *	69	1,0	1,0	5,4	10,2	1,0	0
Females												
0	15,2	12,5	22	15	71	80	1,0	0,8	6,0	4,5	0	0
0,1	15,3	12,7	28	17	63	77	1,4	1,4	6,8	4,6	0	0
0,5	16,1	14,1	19	15	73	78	2,4	2,4	8,0	3,8	0	0
1,0	18,4	12,4	36 *	17	57 *	76	2,0	2,0	6,2	5,5	0	0

** significantly higher than controls p < 0.05*

***Table B.30**: Summary of hematological measurements in CD rats exposed to NMP by inhalation for four weeks and two weeks of recovery (Lee et al., 1987)*

Exposure concentration (mg / l)	**Erythrocytes (10^6 / mm^3)**		**Hemoglobin (g%)**		**Hematocrit (%)**		**MCV (Um^3)**		**MCH (10^{-12} g)**	
Males	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**	**exp**	**rec**
0	7,05	5,99	15,4	15,1	50	48	71	80	22	25
0,1	6,97	5,80	15,5	14,9	50	46	72	80	22	26
0,5	7,24	5,67	15,6	14,4	50	46	70	82	22	26
1,0	6,75	6,87	15,4	15,2	49	50	73	73	23	22
Females										
0	6,70	5,48	14,7	14,3	46	44	69	81	22	26
0,1	6,95	4,87	15,3	13,5	49	44	70	90	22	28
0,5	7,00	5,53	15,2	14,4	48	44	69	80	22	26
1,0	6,57	6,6	14,8	13,9	47	46	73	71	23	22

MCV: mean corpuscular volume.
MCH: mean corpuscular hemoblogin.

BASF AG 1994

Ten Wistar rats per sex and group were head-nose only exposed to 0, 500, 1000 and 3000 mg/m^3 NMP (no vehicle used) (0, 125, 250, 750 ppm) for 6 hours daily, 5 days/week for 3 months. These groups were sacrificed and examined at the end of exposure. A satellite group of 10 rats per sex was exposed to 0 or 3000 mg/m^3 for 3 months followed by a 4-week recovery period. The NMP atmospheres consisted of a large proportion (82–92%) of respirable aerosol particles (MMAD 1.6–3.5 µm). Discoloration of the urine was observed at all concentrations as indication of systemic availability. Nasal irritation as shown by crust formation on nasal edges was observed at ≥1000 mg/m^3 (not shown in results tables). At 1000 mg/m^3, the male rats showed a retardation of the body weight gain (not significantly; Table B.31), while at 3000 mg/m^3 in male rats, body weight/body weight gain was significantly decreased and testicular finding in form of cellular depletion was recorded (Table B.34) . Examination of the satellite group after recovery showed a significant lower body weight gain in males and cellular depletion in the testes (Tables B.31 and B.34). At 3000 mg/m^3 hematological and clinical chemistry parameters were significantly different from controls, see Tables B.32 and B.33. The NOAEC for systemic toxicity and local irritation was determined at 500 mg/m^3 (BASF AG, 1994) It is noted by the Dossier Submitter that the systemic NOAEC of 500 mg/m^3 based on these findings is strict as the body weight gain retardation (at day 33, -4.8%) at 1000 mg/m^3 is not significantly different from controls .

***Table B.31**: Mean body weight [g] of male and female Wistar rats during and after inhalation exposure to NMP for 3 months with a 4 week recovery period (BASF AG 1994)*

Dose group (mg /l)	**Main group**					**Recovery group**						
Males	**-1**	**12**	**33**	**61**	**96**	**-1**	**12**	**33**	**61**	**96**	**110**	**124**
0	272,8	307,2	362,0	404,2	427,8	284,0	319,4	376,5	423,5	467,8	490,8	515,8
0,5	274,3	303,5	354,2	395,2	420,8	-	-	-	-	-	-	-
1,0	274,8	299,6	344,8	387,8	416,7	-	-	-	-	-	-	-
3,0	273,1	289,7	329,4 **	373,4	395,9	278,6	293,1 #	336,6 #	375,9 #	399,8 ##	445,7 #	472,5
Females	**-1**	**12**	**33**	**61**	**96**	**-1**	**12**	**33**	**61**	**96**	**110**	**124**
0	186,8	203,5	225,1	240,2	251,1	185,2	199,8	225,2	241,3	245,8	260,8	276,9
0,5	186,4	204,2	227,6	244,9	58,3	-	-	-	-	-	-	-
1,0	184,9	199,4	222,7	239,4	250,0	-	-	-	-	-	-	-
3,0	189,7	203,2	227,3	244,2	253,8	186,1	197,9	223,2	237,7	246,2	267,8	276,8

*** p < 0.01, Dunnett's test and ANOVA*
#p < 0.05
##p < 0.01 Student's T-test

***Table B.32**: Haematology of male and female Wistar rats during and after inhalation exposure to NMP for 3 months with a 4 week recovery period (BASF AG 1994)*

Dose group (mg / l)	**Endpoint Main Group (day 97)**				**Endpoint Recovery Group (day 97)**				**Eindpoint Recovery Group (day 126)**			
Males	**RBC** (10^{12} /l)	**HGB** (mmol/l)	**HCT** (l /l)	**MCV** (10^{-15}l)	**RBC** (10^{12} /l)	**HGB** (mmol/l)	**HCT** (l /l)	**MCV** (10^{-15}l)	**RBC** (10^{12} /l)	**HGB** (mmol/l)	**HCT** (l /l)	**MCV** (10^{-15}l)
0	7,95	8,82	0,411	51,68	7,75	8,75	0,403	51,91	8,30	9,01	0,433	52,12
0,5	8,40	9,30	0,439	52,22	-	-	-	-	-	-	-	-
1,0	8,12	9,22	0,432	53,17	-	-	-	-	-	-	-	-
3,0	8,02	9,14	0,423	52,65	8,25*	9,43**	0,441**	53,35*	8,47	9,29*	0,451*	53,13

Dose group (mg / l)	Endpoint Main Group (day 97)			Endpoint Recovery Group (day 97)			Eindpoint Recovery Group (day 125)		
Females	**HQT** (s)	**Neutro** (10^9/l)	**Lympho** (10^9/l)	**HQT** (s)	**Neutro** (10^9/l)	**Lympho** (10^9/l)	**HQT** (s)	**Neutro** (10^9/l)	**Lympho** (10^9/l)
0	23,7	0,40	3,27	24,6	0,48	2,82	25,5	0,58	2,77
0,5	23,8	0,38	3,14	-	-	-	-	-	-
1,0	25,3	0,44	2,82	-	-	-	-	-	-
3,0	25,9	1,25	2,42	26,5*	0,95	2,45	24,7	0,53	2,52

** p < 0.05*
*** p < 0.01 Student's T-test*

***Table B.33**: Clinical chemistry of male and female Wistar rats during and after inhalation exposure to NMP for 3 months with a 4 week recovery period (BASF AG 1994)*

Dose group (mg/l)	Endpoint Main Group (day 97)					Endpoint Recovery Group (day 97)					Eindpoint Recovery Group (day 126)				
Male	**ALT** (µkat /l)	**INP** (mmol /l)	**ALB** (g/l)	**TRIG** (mmol /l)	**GLUC** (mmol /l)	**ALT** (µkat /l)	**INP** (mmol /l)	**ALB** (g/l)	**TRIG** (mmol /l)	**GLUC** (mmol /l)	**ALT** (µkat /l)	**INP** (mmol /l)	**ALB** (g/l)	**TRIG** (mmol /l)	**GLUC** (mmol /l)
0	1,19	20,7	31,98	2,09	6,81	1,26	2,20	32,55	2,79	7,08	1,08	2,00	31,74	4,13	7,38
0,5	1,32	2,52	34,42*	2,83	6,50										
1,0	1,21	2,26	33,71	2,64	6,51										
3,0	1,52 *	2,39	34,31*	3,67 **	6,65	1,41	2,63 #	34,85#	3,07	5,96 ##	1,17	2,13	32,62	3,13	7,04

Dose group (mg / l)	Endpoint Main Group (day 97)			Endpoint Recovery Group (day 97)			Eindpoint Recovery Group (day 125)		
Female	**ALT** (µkat/l)	**INP** (mmol/l)	**TRIG** (mmol/l)	**ALT** (µkat/l)	**INP** (mmol/l)	**TRIG** (mmol/l)	**ALT** (µkat/l)	**INP** (mmol/l)	**TRIG** (mmol/l)
0	1,05	1,99	2,18	1,24	1,93	1,94	1,03	1,60	1,81
0,5	1,15	2,02	2,35	-	-	-	-	-	-
1,0	1,05	2,01	2,44	-	-	-	-	-	-
3,0	1,23*	2,21	3,48*	1,31	2,25#	2,17	1,06	1,69	2,07

** p < 0.05, ** p < 0.01, ANOVA plus Dunnett's test*
 # p < 0.05,## p < 0.001, Student's T-test

***Table B.34**: Testes weights [absolute and relative] of male Wistar rats during and after inhalation exposure to NMP for 3 months with a 4 week recovery period (BASF AG 1994)*

Organ, Male	**Dose group (mg / l)**			
Main group	**0**	**0,5**	**1,0**	**3,0**
Testes, absolute (g)	3,546	3,541	3,519	3,003*
Testes, bw relative (%)	0,829	0,863	0,856	0,774
Recovery group	**0**	**0,5**	**1,0**	**3,0**
Testes, absolute (g)	3,626	-	-	3,220
Testes, bw relative (%)	0,710	-	-	0,694

** p < 0.05 Dunnett's test*

Dermal

GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

The subacute dermal toxicity was investigated in male albino rabbits. Groups of two rabbits each received doses of 0, 413, 826, 1653 mg/kg bw/day (cited as 0, 0.4, 0.8, 1.6 ml/kg bw/day) on the intact or abraded skin, applied once a day, 5 days per week, for a total period of 4 weeks. Mild local skin irritation was noted after repeated dosing at 413 mg/kg bw/day and above. Beside the death of one rabbit with abraded skin after one week of treatment out of four in total, which received 1653 mg/kg bw/day, no further sign of systemic toxicity was noted by clinical, hematological and histopathological examinations. The body weights, also unaffected by exposure are given in Table B.35. Thus, the no observed adverse effect level (NOAEL) for systemic toxicity was 826 mg/kg bw/day, while for local irritation no NOAEL could be obtained after repeated application (GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963). The LOAEL for irritation effects was 413 mg/kg bw/day.
The original study report is limited in the description of toxicological parameters (the Dossier Submitter agrees with the reliability score of 2 assigned by OECD), although blood parameters and gross pathology took place. After evaluation of the original study report, it remains unclear whether or not the death of a rabbit in the highest dose group was treatment related. Since it cannot be excluded that the death was treatment related, the Dossier Submitter concluded to adopt the derived NOAEL of 826 mg/kg bw/d.

***Table B.35**: Body weights of male albino rabbits after dermal exposure to NMP for 4 weeks (GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963).*

Confidential table was deleted.

Overall repeated dose studies

An overview of the key studies identified in the sections above is presented in Table B.36 per route of administration, followed by a section on conclusion on repeated dose toxicity. In Table B.37 the PODs for risk assessment are presented for both systemic and local effects.

***Table B.36**: Key studies with repeated administration of NMP (adopted from OECD SIDS 2007*

Species, strain, number, sex/group	Duration, concentration,	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Oral				
Rat, Sprague-Dawley (Crl:CD®BR) 5 m 5 f	4 Weeks, 0, 2000, 6000, 18000, 30000 ppm, diet (about. 0, 149/161, 429/493, 1234/1548, 2019/2269 (m/f) mg/kg bw/day)	- ≥18000 ppm: BW (m)↓, FC (m)↓, discoloration of urine, FE (m)↓, GLUC (m)↓, ALB (m)↓, cellular liver hypertrophy (m+f), testes degeneration/-atrophy 30000 ppm: Lymph (m)↓, CHOL (m+f)↓, TPROT (f)↓, ALB (m+f)↓, ALP (m)↓, thymus atrophy (m+f)	1	Malek et al., 1997¸ E.I. du Pont de Nemours and Company, 1994
Rat, Sprague-Dawley 10 m 10 f	4 Weeks, 0, 258, 516.5, 1033, 2066 mg/kg bw/day gavage, (1x/d, 5 d/wk)	≥516.5 mg/kg bw/day: BW (m)↓, ≥1033 mg/kg bw/day: WBC↓, liver/kidney weight↑ 2066 mg/kg bw/day: mortality (1/19f), clinical sign of intoxication, testes weight↓, testicular lesions	2	BASF AG, 1978

Species, strain, number, sex/group	Duration, concentration,	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Mouse, B6C3F1, 5 m 5 f	4 Weeks, 0, 500, 2500, 7500, 10000 ppm diet (about 0, 160, 820, 2500, 3370 mg/kg bw/day)	- ≥2500 ppm: discoloration of urine ≥7500 ppm: epithelial swelling of distal kidney tubuli 10000 ppm: intercurrent death 1/5 m, alkaline phosphatase↓	1	

Species, strain, number, sex/group	Duration, concentration,	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Rat, Sprague-Dawley (Crl:CD®BR) 20 - 26 m 20 – 26 f	3 months including neurotoxicity, 0, 3000, 7500, 18000 ppm diet (about. 0, 169/217, 433/565, 1057/1344 (m/f) mg/kg bw/day)	- ≥3000 ppm: discoloration of urine ≥ 7500 ppm: BW↓, FC↓, FE↓, foot splay (m)↑ 18000 ppm: liver weights (f)↑, kidney weights (m+f)↑, centrilobular liver cell hypertrophy (f), splenic hemosiderin (m+f↑), low arousal (m)↑, slight palpebral closure (m)↑	1	NMP Producers Group, 1995b; NMP Producers Group, 1994; Malley et al., 1999
Mouse, B6C3F1, 10 m 10 f	4 Weeks + 3 months, 0, 1000, 2500, 7500 ppm, diet (about 0, 229/324, 561/676, 1704/2158 (m/f) mg/kg bw/day)	<u>after 4 weeks:</u> NOAEL: 2500 ppm / 516/676 mg/kg bw/d ≥2500 ppm: discoloration of urine, CHOL (f)↑, TRIG (m)↓ 7500 ppm: ALP (m)↓, Ca (m)↓ <u>after 3 months:</u> NOAEL: 2500 ppm / 516/676 mg/kg bw/d ≥2500 ppm: discoloration of urine, liver weights↑ (m) 7500 ppm: centrilobular liver cell hypertrophy (m+f)	1	Malley et al., 1999¸ NMP Producers Group, 1995a

Species, strain, number, sex/group	Duration, concentration,	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Dog Beagle 6 m 6 f	3 months 0, 25, 79, 250 mg/kg bw/day, diet	NOAEL: 250 mg/kg bw/day No treatment-related effect.	1	Becci et al., 1983¸ TSCAT, 1990a; TSCAT,1989
Inhalation				
Rat Wistar 5 m 5 f	4 weeks 0, 10, 30, 100 mg/m^3 (0, 2.5, 7.5, 25 ppm), 6h/d, 5x/week (20 exposures) (aerolized NMP, head-nose exposure)	NOAEC: 100 mg/m^3 Discoloration of urine and bedding	1	BASF AG, 1993a
Rat CD 15 m 15 f	4 weeks 0, 100, 500, 1000 mg/m^3 (0, 25, 125, 250 ppm), 6h/d, 5x/week (mainly aerosol, whole-body exposure)	NOAEC for systemic toxicity: 500 mg/m^3 1000 mg/m^3: mortality, bone marrow hypoplasia, testicular findings atrophy and/or necrosis of the lymphoid tissue in thymus, spleen and lymph nodes in rats exposed for 10 days ≥100 mg/m^3: lethargy, irregular respiration (reversible 30 – 45 min after exposure)	2	Lee et al., 1987; Lee, 1977; TSCAT, 1989; TSCAT, 1991b
Rat Wistar Main group 10 m 10 f Recovery group (control + high concentration) 10 m 10 f	3 months, 4 weeks recovery 0, 500, 1000, 3000 mg/m^3 (0, 125, 250, 750 ppm) 6h/d, 5x/week (mainly aerosol, head-nose exposure)	NOAEC for systemic toxicity and local irritation: 500 mg/m^3 Main group: 3000 mg/m^3: crust formation on nasal edges, BWC↓(m), RBC+HGB+HCT+MCV↑ (m), NEUTRO↑+LYMPH↓ (f), ALT↑, INP↑, TRIG↑, GLUC↓(m), cellular depletion in testes 1000 mg/m^3: crust formation on nasal edges, BW+BWC↓(m), non-significant -4.8% ≥500 mg/m^3: discoloration of urine 4 week recovery: 3000 mg/m^3: BW+BWC↓(m), HGB+HCT↑(m), cellular depletion in testes	1	BASF AG, 1994
Dermal				
Rabbit 4 m	4 weeks 0, 413, 826, 1653 mg/kg bw/day (cited as 0, 0.4, 0.8, 1.6 ml/kg bw/day) (intact and abraded skin, 1x/day, 5x/week)	NOAEL systemic toxicity: 826 mg/kg bw/day NOAEL local irritation: <413 mg/kg bw/day 1653 mg/kg bw/day: mortality in 1/4 rabbits (abraded skin) ≥413 mg/kg bw/day: mild local skin irritation	2	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963
m: male, f: female, ↑: increased, ↓: reduced, BW: body weight, BWC: body weight change, FC: food consumption, FE: food efficiency, WBC: white blood cell count, RBC: red blood cell count, HGB: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, NEUTRO: polymorphonuclear neutrophils, LYMPH: lymphocytes, ALT: alanine aminotransferase, INP: inorganic phosphate, TRIG: triglycerides, GLUC: glucose, CHOL: cholesterol, ALP: alkaline phosphatase, CA: calcium, TPROT: total protein				

** Reliability is based on the Klimisch code.*

Conclusion

The systemic effects of NMP observed in the oral studies were changes in body weight, liver weight, testicular atrophy, thymic atrophy, swelling of distal kidney tubuli, where the critical effects were generally seen in terms of reduced body weight (gain) and food consumption. In the 90-d oral repeated dose study combined with neurotoxicity in rats a NOAEL of 3000 ppm for both sexes (169/217 mg/kg bw/day, males/females) was found, based on effects on body weight, foot splay in males and reversible neurotoxic effects, which is considered the overall NOAEL for oral repeated dose toxicity. In a similar study in mice, without the neurotoxicity tests, a NOAEL of 2500 ppm was found corresponding to 561/676 mg/kg bw/d (males/females) by the study authors, where it is noted that at the NOAEL level elevated liver weights were found in male mice. The liver weights are considered adverse by the Dossier Submitter, thus the NOAEL is 229 mg/kg bw/d, which is in agreement with the overall NOAEL determined above.

Repeated dermal exposure to rabbits resulted in mortality at high dose levels without other signs of systemic toxicity. The NOAEL is 826 mg/kg bw. For local irritation, the LOAEL is 413 mg/kg bw. It is noted that the study from 1963 has some limitations as to the information provided on the vehicle used, the method of application and the dilutions of the substance. Alternatively, the overall NOAEL from the oral repeated dose toxicity using route-to-route extrapolation could be used to determine the POD for risk assessment. The Dossier Submitter assumed absorption percentages of 100% for the oral and dermal route because NMP is absorbed readily via the oral and dermal route. It is noted that the assumption is conservative as the oral absorption is likely to be higher and faster compared to the dermal absorption. This results in an external dermal NOAEL of 169 mg/kg bw/d, based on an oral rat 90-d study.

The inhalation studies show a consistent NOAEC. It should be noted that the way of exposure and environmental conditions could have a major influence on the toxicity of NMP at high concentrations. The 90-day head-nose aerosol exposure of NMP showed a NOAEC of 500 mg/m^3 for local respiratory tract irritation. At higher concentrations systemic effects including testicular atrophy and local respiratory tract irritation occurred in the 90-d study. The 90-d study was preferred to derive the POD over the 28-d study, where at all concentrations lethargy and irregular respiration was observed. The Dossier Submitter considers these effects as an adaptation to NMP exposure that can be irritating to the respiratory tract. Moreover, very severe effects occurred in the 28-d study at 1000 mg/m^3 due to the expected mixed oral (by grooming), dermal and inhalation exposure to NMP as droplets deposit on the skin, in contrast to the mild effects observed at 1000 mg/m^3 in the 90-d study, which were a decrease in body weight and body weight gain. The overall NOAEC was set at 500 mg/m^3 for both local and systemic effects resulting from inhalation exposure.

***Table B.37**: Point of departures for DNEL derivation for repeated dose toxicity.*

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw /day) or NOAEC ppm (mg/m^3)	Toxicological endpoint	Reference
Systemic				
inhalation	Rat, 3 months	500 mg/m^3	mortality, bone marrow hypoplasia, testicular findings atrophy and/or necrosis of the lymphoid tissue in thymus, spleen and lymph nodes, body weight gain reduction	Lee et al., 1987; Lee, 1977; TSCAT, 1989; TSCAT, 1991b; BASF AG, 1994
dermal	Rabbit, 4 weeks	826 mg/kg bw/d	¼ mortality at top dose	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963
dermal (based on oral study)	Rat, 90-d oral study	169 mg/kg bw/d (based on 100% absorption)	body weight, foot splay in males and reversible neurotoxic effects	NMP Producers Group, 1995b; NMP Producers Group, 1994; Malley et al., 1999

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw /day) or NOAEC ppm (mg/m^3)	Toxicological endpoint	Reference
Local				
inhalation	Rat, 3 months	500 mg/m^3	local irritation	BASF AG, 1994
dermal	Rabbit, 4 weeks	413 mg/kg bw/day (LOAEL)	Skin irritation observed at all dose levels	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

B.5.7 Mutagenicity

NMP is not mutagenic in any of the in vitro or in vivo mutagenicity tests (OECD SIDS, 2007).

B.5.8 Carcinogenicity

Information was obtained from the registration dossiers and OECD SIDS (2007), describing the same studies.

Oral

Malley et al., 2001; NMP Producers Group, 1997

NMP was examined for its chronic toxicity and carcinogenic potential in groups of each 62 male and 62 female Sprague-Dawley Crl:CD (SD)BR rats at dietary concentrations of 0, 1600, 5000 or 15000 ppm (about 66/88, 207/283, 678/939 mg/kg bw/day, males/females) for two years. The survival of the female animals was not affected. The survival of the males in the high dose group was lower due an increase in severe chronic-progressive nephropathy as a typical finding in aging male rats. There was a reduction in body weights and retarded body weight gain with a corresponding reduction in food consumption and efficiency at 15000 ppm (Table B.38). The incidence of benign or malignant tumors was not increased among male or female rats, indicating no oncogenic potential up to a dietary concentration of 15000 ppm in male and female rats (approximately: 678/939 mg/kg bw/day in males/females). Only the high dose males revealed treatment-related macroscopic findings consisting of an increased incidence of large kidneys, kidneys diagnosed with chronic nephropathy, fluid in the pleural cavity and small testes (data not shown). There was an increased incidence in splenic hemosiderin as an indication of a higher turn-over of red blood cells at 15000 ppm. In high and mid dose groups discoloration of urine as indication of systemic availability of the test substance occurred. The NOAEL was 5000 ppm, corresponding to approximately 207/283 mg/kg bw/day in males/females (Malley et al., 2001; NMP Producers Group, 1997).

***Table B.38**: Body weight data, food consumption/efficiency in rats exposed to NMP via the diet for 2 years (Malley et al., 2001; NMP Producers Group, 1997).*

Dose level	**PPM / mg / kg bw / d**			
Male	**0 / 0**	**1600 / 66**	**5000 / 207**	**15000 / 678**
Body weight (g) at day 729	629	678	687	518*
Body weight gain (g) days 0 – 729	448	428	437	269*
Food consumption (g /day) at day 729	26,1	26,7	25,9	24,6
Food efficiency (g food / bw gain / d) days 0 - 729	0,023	0,022	0,023	0,015

Dose level	PPM / mg / kg bw / d			
Female	**0 / 0**	**1600 / 88**	**5000 / 283**	**15000 / 939**
Body weight (g) at day 729	504	500	461	326*
Body weight gain (g) days 0 – 729	335	329	386	153*
Food consumption (g /day) at day 729	21,8	22,4	21,6	20,5
Food efficiency (g food / bw gain / d) days 0 - 729	0,021	0,021	0,018	0,010

** p < 0.05 ANOVA and Dunnett*

Malley et al., 2001; NMP Producers Group, 1999a

The oncogenic potential of NMP in the mouse was investigated in groups of each 50 male and 50 female B6C3F1 receiving dietary concentrations of 0, 600, 1200 and 7200 ppm (about 89/115, 173/221, 1089/1399 mg/kg bw/day, males/females) in an 18-month study. There was no effect on survival in male or female mice. NMP caused substance-related effects at 1,200 and 7,200 ppm. Target organ was the liver with respect to increased metabolic activity. Increased liver weights, an increase in the incidence of foci of cellular alteration in the liver and of liver adenoma were noted at 7200 ppm in both sexes. Among the 7200 ppm males, the incidence of liver carcinomas was also increased, while the incidence in females was within the historical control range. Increased liver weights were also observed among the 1200 ppm group males and 3/50 of these animals showed a centrilobular liver cell hypertrophy. Furthermore, discoloration of urine was observed at 7,200 and 1,200 ppm as a sign of systemic availability of the test substance. The NOAEL was 600 ppm (89 mg/kg bw/day) in males and 1200 ppm (221 mg/kg bw/day) in females (Malley et al., 2001; NMP Producers Group, 1999a;).
The raw data was not presented by the Dossier Submitter, because it was considered that the effects observed are not relevant for humans. The liver tumors in mice and underlying liver effects may be directly related to the observed increase in the cellular proliferation rate, which could likely be due to the observed enzyme induction and weak peroxisome proliferation observed in the B6C3F1 mice, which are known to be extremely sensitive to both non-genotoxic and genotoxic effects. The peroxisome proliferation pathway related effects observed in this specific strain of mice are not considered a relevant effect for humans.

Inhalation

Lee et al., 1987; TSCAT, 1990b; WHO: Information Bulletin, 1986; Kennedy, 2008

In a 2-year inhalation study, CD rats (120 per sex per dose level) were exposed (whole body) to NMP vapor concentrations of 0, 10 and 100 ppm (0.04 and 0.4 mg/l) for 6 h/day, 5 days/week. Ten rats per sex were subjected to hematology and blood and urine chemistry analysis after 1, 3, 6, 12, and 18 months of exposure. Ten rats per sex were sacrificed after 3, 12, and 18 months. There was no treatment-related effect on survival. Animals that died within the first 18 months suffered from chronic progressive nephropathy. Beside an increased incidence in animals with wet and/or stained perineal fur as an indication of systemic NMP availability, no specific signs of intoxication were observed clinically. Body weight of males exposed to the high concentration was significantly reduced by about 6 %. Hematology, clinical chemistry, urinalysis as well as gross pathology and histopathology revealed no substance-related findings. Especially, there was no increased incidence in treatment-related benign or malignant tumors in male or female rats at any concentration (for result see Table B.39). Thus, NMP was not oncogenic at the investigated inhalative concentrations of 0.04 or 0.4 mg/l (10, 100 ppm). The NOAEC was 0.04 mg/l (10 ppm) in males due to body weight gain reductions (about 6%) at the high concentration of 0.4 mg/l (100 ppm) in males (Lee et al., 1987; TSCAT, 1990b; WHO: Information Bulletin, 1986; Kennedy, 2008).

***Table B.39**: Incidence of main pathological lesions in rats exposed to NMP by inhalation for two years (Lee et al., 1987)*

		Male		Female	
	Dose level (mg / l)	**0**	**0,4**	**0**	**0,4**
Tissue / lesions	**No. rats / group**	**84**	**85**	**84**	**84**
Kidneys	**No. of tissues examined microscopally**	**82**	**85**	**83**	**82**
	Chronic progressive nephropathy	65	70	22	13
	Glomerulosclerosis	54	62	21	9
	Proteinaceaous casts, renal tubules	68	73	36	35
	Peritubular fibrosis / regeneration, renal tubules	70	74	29	29
	Interstitial inflammation	65	70	24	17
	Inflammation / epithelial hyperplasia, pelvis	5	3	5	10
	Cysts, cortical	17	24	4	5
	Mineralization, corticomedullary junction	0	0	29	17
	Pigmentation, renal tubules	12	12	17	14
	Adenocarcinom, renal tubules	1	0	0	1
	Mesenchymal tumor	2	0	0	0
Bone marrow		**82**	**85**	**83**	**82**
	Hypoplasia, hemopoietic cells	5	10	12	2
	Hyperplasia, erythroid cells	9	5	4	1
Lymph nodes		**80**	**82**	**81**	**79**
	Hemosiderin pigment deposition, thoracic	18	12	24	21
	Hemosiderin pigment deposition, mesenteric	13	17	26	23
	Hemosiderin pigment deposition, mandibular	2	2	1	4
	Hyperplaisa / lympade nitis, mandibular	0	2	2	0
Spleen		**80**	**85**	**83**	**82**
	Hemosiderin pigment deposition	47	56	68	69
	Athrophy	4	6	6	7
	Hyperplasia, lymphoid	4	18	31	20
	Extramedullary hemopoietic foci	40	15	46	44
Lung		**82**	**85**	**83**	**82**
	Bronchopneumonia	1	0	1	0
	Alveolitis, acute, focal	2	10	13	12
	Aggregates, alveolar macrophages	25	17	19	16
	Alveolar cell hyperplasia / aggregate d macrophages	0	4	4	9
	Perivascular cuffing, lymphoid cells	32	30	25	21
	Hyperplasia, peribronchial lymphoid tissue	0	4	2	1
	Adenomatosis, focal	0	0	2	1
	Microgranuloma, focal	1	0	2	0
	Fibrosis, focal, pleura	0	0	8	10

Conclusion

The conclusion on the carcinogenicity potential of NMP as stated in OECD SIDS (2007) and registration dossier is given below. The Dossier Submitter supports the conclusion on carcinogenicity.
NMP was studied for its carcinogenicity potential in an inhalation study, in two oral studies and in one mechanistic study. NMP was not found to be carcinogenic, although the results in the feeding study in B6C3F1 mice showed liver adenomas and carcinomas at the top dose of 7200 ppm in the liver. This specific strain of mice is very sensitive for induction of non-genotoxic liver tumours and these are normally not considered relevant for humans (NMP producers group, 1999a). Since NMP is not mutagenic and the rat carcinogenicity studies showed no carcinogenic response, NMP is not considered to be carcinogenic.

The rat carcinogenicity studies can be used as POD for chronic systemic effects. The studies describe systemic effects in the rat that are also observed in the repeated dose studies. No dermal carcinogenicity study was available, but the oral rat carcinogenicity study could be used as POD after route-to-route extrapolation. The Dossier Submitter assumed absorption percentages of 100% for the oral and dermal route because NMP is absorbed readily via the oral and dermal route. It is noted that the assumption is conservative as the oral absorption is likely to be higher and faster compared to the dermal absorption. The mouse study was not taken forward since the observed effects were not considered to be relevant for humans.

***Table B.40**: Point of departures for DNEL derivation for systemic chronic toxicity*

POD for DNEL derivation (endpoint)	Species and study design	NOAEL (mg/kg bw /day) or NOAEC ppm (mg/m^3)	Toxicological endpoint	Reference
Systemic				
inhalation	Rat carcinogenicity study	40 mg/m3	body weight gain reduction in males	Lee et al., 1987; TSCAT, 1990b; WHO: Information Bulletin, 1986; Kennedy, 2008
dermal (based on oral study)	Rat carcinogenicity study, oral study	207 mg/kg bw/d	chronic nephropathy, fluid in pleural cavity, small testes. Splenic hemosiderin increase	Malley et al., 2001; NMP Producers Group, 1997

B.5.9 Toxicity for reproduction

The information on toxicity for reproduction was gathered from the registration dossier, the OECD SIDS and the study reports that were made available to the Dossier Submitter. Study descriptions and NOAELs/LOAELs were taken from the OECD SIDS dossier, unless stated otherwise.

Fertility

Oral

Exxon Biomedical Sciences, 1991; TSCAT, 1991a

In a two-generation reproduction toxicity study, NMP was administered orally by diet to groups of 30 Sprague-Dawley (Crl:CD®BR) rats per sex. In contrast to the assessment of the authors (Exxon Biomedical Sciences, 1991; TSCAT, 1991a), the U.S. EPA concluded that the reductions in male fertility and female fecundity indices observed at the low and intermediate dose levels (50 and 160 mg/kg bw/day) were biologically (although not statistically) significant, and that a NOAEL was not achieved. Study authors, in contrast, noted that decreased pup survival and decreased reproduction and fertility (F1 parental generation only) were observed together with parental toxicity at the highest dose level (500 mg/kg bw/day). Moreover, the authors of the study noted

that the effects on fertility/reproduction parameters in form of reduced indices observed at the lower doses can be considered to be spurious findings and not treatment-related since all parameters were in the range of the historical control data. However, for clarification this study was independently repeated at 2 different facilities using Sprague-Dawley (Huntingdon) or Wistar (BASF) rats (see below). The study by Exxon Biomedical sciences was not included in the registration dossier and was not available to the Dossier Submitter. The study summary was copied from the OECD SIDS dossier)

NMP producers group, 1999b

In a two-generation reproduction toxicity study (NMP producers group, 1999b), groups of 25 Wistar rats per sex were given 1-methyl-2-pyrrolidone (NMP) via the diet at initial dose levels of 0, 50, 160 or 500 mg/kg bw/day over a 10-week premating period and throughout the mating, gestation, lactation and a rest period between pregnancies. The concentrations in the diet were adjusted regularly in respect to the actual body weight gain. Due to severe pup mortality in the first litter (F1a), the highest dose level was reduced to 350 mg/kg bw/day for the further course of the study. This pup mortality was observed within postnatal day 1-4 and was most likely due to prenatal developmental toxicity. Maternal toxicity (decreased body weight and food consumption) was observed mainly during the lactation period and appeared to be secondary to the high pup mortality. Each generation gave birth to two litters. The parental animals for the second generation were selected from pups of the second litter (F1b). NMP had no adverse effects on reproductive performance or fertility of the F0 or F1 parental animals of all substance-treated groups. All F0 parental rats proved to be fertile after both mating intervals (F1a and F1b). The fertility index of male and female F1 parental animals was decreased for F2a offspring (100, 96, 96 and 88% for 0, 50, 160 and 350 mg/kg bw/day respectively), but was 100% for all dose groups for the F2b litter. When assessed together, fertility was proven for all F1 parental females and thus not affected by NMP. There were signs of systemic toxicity in each of the high dose groups at 500 mg/kg bw/day and also after reduction to 350 mg/kg bw/day. The observed effects in fetuses are provided in Table B.41. Parental toxicity consisted of reduced body weight gain and food intake as well as kidney findings in form of impaired kidney weight and histopathological findings (data not shown). Developmental toxicity was demonstrated by increased pup mortality and reduced body weight gain, including corresponding effects in the investigated organs, in pups treated at 500/350 mg/kg bw/day. Thus, the NOAEL for reproductive performance/fertility was 350 mg/kg bw/day. The NOAEL for parental systemic and developmental toxicity was 160 mg/kg bw/day.

***Table B.41**: Summary of observed effects in foetuses of Wistar rats dosed NMP by oral gavage in a 2-generation study (NMP producers group, 1999b)*

Confidential table was deleted.

NMP producers group, 1999c

In a second two-generation reproduction toxicity study (NMP producers group, 1999c), groups of 30 Sprague-Dawley rats per sex were given NMP via the diet at initial dose levels of 0, 50, 160 or 500 mg/kg bw/day over a 10 -week premating period and throughout the mating, gestation, lactation and a rest period between pregnancies. The concentrations in the diet were adjusted regularly in respect to the actual body weight gain. Due to severe pup mortality in the first litter (F1a), the highest dose level was reduced to 350 mg/kg bw/day for the further course of the study. This pup mortality was observed lactation day 0 through 4 and was most likely due to prenatal developmental toxicity. Maternal toxicity (decreased body weight and food consumption) was observed mainly during the lactation period and appeared to be secondary to the high pup mortality. Each generation gave birth to two litters. The parental animals for the second generation were selected from pups of the second litter (F1b). NMP had no adverse effects on reproductive performance or fertility of the F0 or F1 parental animals of all substance-treated groups. All F0 and F1 parental rats proved to be fertile after both mating intervals (F0 parents: F1a and F1b; F1 parents: F2a and F2b) as demonstrated by the clinical and histopathological examinations. There were no signs of systemic toxicity noted after high dose level reduction to 350 mg/kg bw/day. The F1a pups exposed to 500 mg/kg bw/day had a decrease in mean litter size, pup survival and pup body weights during lactation. After reduction of the high dose level, a decrease in the number of pups surviving lactation and a decrease in pup body weights was observed in F2b pups. The observed effects in fetuses are provided in Table B.42. At necropsy, paternal animals revealed

significant organ weight changes, however, they were considered not treatment-related due to the absence of changes in the other sex and the absence of corresponding histopathological findings (data not shown). Thus, the NOAEL for reproductive performance/fertility and parental systemic toxicity was 350 mg/kg bw/day. The NOAEL for developmental toxicity was 160 mg/kg bw/day.

***Table B.42**: Summary of observed effects in foetuses of SD rats dosed NMP by oral gavage in a 2-generation study (NMP producers group, 1999c)*

Confidential table was deleted.

Sitarek and Stetkiewicz (2008)

Sitarek and Stetkiewicz (2008; study description based on OECD SIDS and registration dossier; original study report not available to the Dossier Submitter) assessed the reproductive toxicity and gonadotoxicity of NMP. Male rats were exposed to NMP via oral gavage in doses of 0, 100, 300 and 1000 mg/kg bw/day for 5 days/week during a total period of 10 weeks before mating and 1 week during mating. Body weight and food and water intake of male rats were studied during exposure. After the 10-week premating exposure period, the exposed males were mated with un-exposed females during one week. After the mating period, the male animals were autopsied and were studied for toxic effects. Analysis included body weight, organ weight, macrospcopic evaluation of organs, and histopathological analysis of testis and epididymis. Evaluation of the pregnant females included behaviour, body weight gain and daily food and water intake. Furthermore, assessment of early postnatal development of the offspring was done until the end of the lactation period (28 days). NMP at a dose of 1000 mg/kg bw/day was found to produce reduced male fertility and extensive damage to seminiferous epithelium in the seminal tubules of the testis. NMP at doses of 100 mg/kg bw/day did not influence the viability or the development of their offspring. Exposure of the males to 300 mg/kg bw/day was found to induce a reduction in postnatal survival until day 4. In the group of the 1000 mg/kg bw/day exposed males, only 2 out of 44 females delivered, and the total number of pups was 6. The NOAEL for fertility effects was determined at 300 mg/kg bw/d, whereas the NOAEL for developmental effects was determined at 100 mg/kg bw/d based on lower (magnitude unknown) viability of the pups.

Inhalation

Solomon et al., 1995

In a two-generation reproduction study in rats 10 males and 20 females per dose level were exposed whole body to 0, 41, 206, or 478 mg/m^3 of NMP vapour (relative humidity 40–60%) for 6 h/day, 7 days/week, for a minimum of 14 weeks (Solomon et al., 1995). Additionally, two satellite groups were tested at 478 mg/m^3 where either only the male or females were exposed. There was no exposure after weaning of the F1 generation and the F2 was generated by mating with additional control animals of the opposite sex. Animals were mated after a 12 week exposure period and both parents and offspring were examined for adverse effects on reproduction and reproductive organs. No effects on reproductive ability or reproductive organs were recorded (Table B.44) nor on developmental toxic parameters (Table B.45), although the number of resorptions seem to be higher than in controls at 478 mg/m^3. However, reduced body weight gain was evident in the F1 offspring whose parents had been exposed to 478 mg/m^3, and also appeared at birth where it persisted till 21 days after birth (Table B.43). This effect was not observed in the satellite group where only the males were exposed (Table B.43). Body weights were also reduced in F1 offspring whose parents had been exposed to exposed to 41 mg/m^3, however not at 206 mg/m^3 and thus not showing a clear dose response. P0 dams showed reduced sensitivity to noise as determined in the premating period. There were no other effects observed in the dams. However, the studied parameters were limited to maternal body weight without information on body weight gain and food consumption. The NOAEC for both developmental and maternal toxicity was reported as 206 mg/m^3 (Solomon et al., 1995). However, as the only observed effect was a reduced sensitivity to sound determined in parental rats before mating, this is also considered a parental systemic effect with a NOAEC of 206 mg/m^3. The study was given a Klimisch score of 2, because of the limited number of animals per group and study protocol different from the current guidelines. Nevertheless, the Dossier Submitter considers the study to be of sufficient quality to take forward in risk assessment. Despite the noted lack of a clear dose response in body weight reduction in F1 offspring and only slight increase in resorptions at 478 mg/m^3 the Dossier Submitter adopts the NOAEC of 206 mg/m^3 determined by the authors.

***Table B.43**: Natural delivery and litter data of the Po and F1 generations after inhalation exposure to NMP (Solomon et al. 1995)*

	Dose (mg / m³)					
	0	**41**	**206**	**478**	**478 (only females exposed)**	**478 (only males exposed)**
PO generation						
Natural delivery and litter data						
Male mating index (%)	27/30 (90)	8/10 (80)	9/10 (90)	18/20 (90)	10/10 (100)	9/10 (90)
Male fertility index (%)	27/27 (100)	8/8 (100)	8/9 (88,9)	17/18 (94,4)	10/10 (100)	8/9 (88,9)
Female mating index (%)	56/58 (96,6)	18/20 (90)	18/19 (94,7)	40/40 (100)	20/20 (100)	20/20 (100)
Female fertility index (%)	53/56 (94,6)	16/18 (88,9)	15/18 (83,3)	37/40 (92,5)	15/20 (75)	17/20 (85)
Gestation index (%)	53/53 (100)	16/16 (100)	15/15 (100)	37/37 (100)	15/15 (100)	17/17 (100)
Mean gestation length N	34	14	14	19	13	15
X (days)	22,6	22,5	22,6	22,7	22,7	22,6
SE	0,08	0,14	0,14	0,11	0,13	0,12
Mean number of offspring/litter						
- Born	13,7	14,0	13,7	14,2	13,9	14,7
- Born alive	13,5	13,9	13,5	14,1	13,9	14,6
- Day 4 PP preculling	13,4	13,9	13,3	13,9	13,6	14,3
- Day 4 PP postculling	8,0	7,9	7,9	8,0	8,0	7,9
- Day 14 PP	8,0	7,9	7,9	8,0	8,0	7,9
- Day 21 PP	8,0	7,8	7,9	8,0	8,0	7,9
Viability index (%)	99,3	100,0	98,6	98,3	98,0	97,7
Lactation index (%)	100,0	98,4	99,0	100,0	100,0	100,0
Sex ratio (% males)	0,53	0,46*	0,43	0,46	0,48	0,50
Offspring weight/litter (g)						
- Day 1 PP	7,5	7,0*	7,1	6,7*	7,1	7,3
- Day 4 PP preculling	10,8	10,0*	10,3	9,6*	10,1	10,5
- Day 4 PP postculling	10,7	9,9*	10,2	9,6*	9,9*	10,6
- Day 14 PP	30,8	27,8*	29,5	28,7*	28,6*	32,0
- Day 21 PP	49,1	45,6*	47,4	46,9*	47,2	51,6*
F1 generation						
Male mating index (%)	20/20 (100)	15/16 (93.8)	15/15 (100)	22/22 (100)		
Male fertility index (%)	18/20 (90)	14/15 (93,3)	14/15 (93,3)	19/22 (86,4)		
Female mating index (%)	19/20 (95)	15/16 (93,8)	15/15 (100)	22/22 (100)		
Female fertility index (%)	18/19 (94,7)	14/15 (93,3)	14/15 (93,3)	19/22 (86,4)		

	Dose (mg / m³)					
	0	**41**	**206**	**478**	**478 (only females exposed)**	**478 (only males exposed)**
Gestation index (%)	17/18 (94,4)	14/14 (100)	14/14 (100)	19/19 (100)		
Data from exposed females mated to unexposed males						
Mean number of offspring/litter						
- Born	14,7	16,1	15,7	13,9		
- Born alive	14,7	15,9	15,7	13,8		
- Day 2 PP	14,6	15,9	15,6	13,8		
Offspring weight/litter (g)						
- Day 1 PP	6,7	6,5	6,7	6,9		
- Day 2 PP	7,5	7,3	7,5	7,7		
Mean number of offspring/litter						
- Born	13,2	13,6	14,0	13,7		
- Born alive	13,2	13,5	14,0	13,6		
- Day 2 PP	13,2	13,3	14,0	13,6		
Offspring weight/litter (g)						
- Day 1 PP	6,4	6,3	6,4	6,5		
- Day 2 PP	7,3	7,2	7,2	7,3		

** significantly different from control, p ≤ 0.05*

***Table B.44**: Testes and ovarian weights of the P0 and F1 generations after inhalation exposure to NMP (Solomon et al. 1995).*

Concentration (mg / m³)	**N**	**Final body weight (g)**	**Testes weight (g)**	**Relative testes weight**
Mean testes weight				
PO generation				
0	20	529 (10,5)	3,47 (0,76)	0,66 (0,016)
41	5	547 (9,8)	3,56 (0,251)	0,65 (0,041)
206	5	559 (25,4)	3,65 (0,113)	0,66 (0,018)
478	15	530 (6,7)	3,60 (0,074)	0,68 (0,017)
F1 generation				
0	20	439 (11,4)	3,36 (0,094)	0,77 (0,013)
41	16	448 (5,8)	3,62 (0,139)	0,81 (0,030)
206	15	457 (11,4)	3,35 (0,082)	0,74 (0,019)
478	22	449 (7,8)	3,42 (0,049)	0,77 (0,015)
Mean ovarian weight				
PO generation				
0	56	369,8 (3,41)	142 (4,08)	38 (1,06)
41	16	361,8 (4,77)	131 (6,98)	36 (1,79)
206	15	360,9 (7,15)	133 (7,15)	37 (1,79)
478*	36	369,4 (4,16)	136 (6,08)	37 (1,71)

Concentration (mg / m^3)	N	Final body weight (g)	Testes weight (g)	Relative testes weight
F1 generation				
0	17	315,8 (4,65)	189 (6,39)	60 (2,57)
41	14	320,5 (7,40)	218 (9,79)	69 (2,75)
206	14	330,2 (8,81)	210 (8,58)	64 (2,25)
478*	19	318,9 (6,27)	198 (6,55)	62 (2,33)

** Original reference states a different concentration of 130 ppm (533 mg/m^3) which is not in line with the publication and is therefore considered an error made by the authors of the paper according to the Dossier Submitter.*

***Table B.45**: Developmental toxicity parameters, including reproduction data, fetal malformations and fetal variations after inhalation exposure to NMP (Solomon et al. 1995).*

Developmental phase	Indicator	0	478 mg/m^3
Summary of reproduction data			
Females pregnant/mated	N	14/14	13/15
Females died	N	0	0
Females with all dead/resorbed	N	0	0
Viable litters	N	14	13
Corpora lutea	Mean	17,3 (0,52)	16,8 (0,35)
Implantations	Mean	15,5 (0,86)	15,8 (0,85)
Dead foetuses	N	0	0
Resorptions	Mean	0,9 (0,21)	1,6 (0,47)
Early	Mean	0,9 (0,21)	1,6 (0,47)
Late	Mean	0,0	0,0
Live foetuses	Mean	14,6 (0,89)	14,2 (0,79)
Males	Mean	8,0 (0,54)	6,5 (0,73)
Females	Mean	6,6 (0,46)	7,7 (0,63)
Fetal body weight	Mean	3,62 (0,07)	3,37 (0,15)
Fetal malformations			
External malformations			
Fetuses/litters examined		205/14	185/13
Micrognathia		1/1	
Visceral malformations			
Fetuses/litters examined		110/14	97/13
Heart/greater vessels		1/1	
Kidney papilla-none			1/1
Aglossia		1/1	
Third ventricle-distended			2/1
Skeletal malformations			
Fetuses/litters examined		205/14	185/13
Clavical-misshapen		1/1	
Pelvis-misshapen		1/1	
Scapula-misshapen		1/1	

Developmental phase	Indicator	0	478 mg/m^3
Sternebra		1/1	
Fused		1/1	
Hemi		1/1	
Vertebra fused		1/1	
Total fetal malformations		2/2	1/1
Affected fetuses/litter		1,0 (0,67)	0,5 (0,51)
Summary of reproduction data			
Developmental phase: fetal variations			
External variations			
Fetuses/litter examined		205/14	185/13
Visceral variations			
Fetuses/litter examined		110/14	97/13
Innominate artery-none		1/1	
Pulmonary arteries-common trunk		4/3	3/3
Renal pelvis-large		2/2	
Reduced		3/2	1/1
Skeletal variations			
Fetuses/litter examined		205/14	185/13
Rib thoracic-rudimentary		12/8	14/6
Cervical-rudimentary			2/2
Vertebra-bipartite centrum		1/1	1/1
Centrum partially ossified		3/2	2/2
Unossified			2/1
Pelvic partially ossified		3/3	9/3
Skull partially ossified		16/7	31/11
Sternebra-partially ossified		27/7	38/8
Unossified		2/1	½
Total fetal variations		65/14	82/13
Affected fetuses/litter		33,5 (5,82)	42,9 (5,70)

Overall studies on toxicity for reproduction - fertility

An overview of the key studies for reproduction toxicity is presented in Table B.46, followed by a conclusion on reproduction toxicity specifically on mulit-generation toxicity studies and the fertility endpoint. In the next section prenatal developmental toxicity studies are described.

***Table B.46**: Key studies on toxicity for reproduction.*

Species, Strain, number, sex/group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Oral				
Rat, Wistar, 25 m 25f	2-generation-study 0, 50, 160, 500/350 mg/kg bw/day, diet	NOAEL reproductive performance/fertility: 350 mg/kg bw/day NOAEL systemic and developmental toxicity: 160 mg/kg bw/day **Effects at 500/350 mg/kg bw/day:** F0: m: kidney weights↑, dilation of kidney tubuli f: BW/BWC + FC↓ (gestation+lactation F1a, gestation F1b), F1a: live born pups↓, mortality until day 21p.p.↑, BWC↓ F1b after reduction to 350 mg/kg bw/day: mortality until day 21p.p.↑, BWC↓ 350 mg/kg bw/day: F1: m: kidney weights↑, dilation of kidney tubuli f: BWC↓ (prior mating +gestation F2a), kidney weights↑, calcification of renal papilla F2a: mortality up to day 4 p.p.↑, BWC↓ F2b: mortality up to day 21 p.p.↑, BWC↓	1	NMP Producers Group, 1999b
Rat, Sprague-Dawley (Crl:CD®BR) 30 m 30 f	2-generation-study 0, 50, 160, 500/350 mg/kg bw/day, diet	NOAEL reproductive performance/fertility and systemic toxicity: 350 mg/kg bw/day NOAEL developmental toxicity: 160 mg/kg bw/day **Effects at 500/350 mg/kg bw/day:** F0: w: BW/BWC + FC↓ (gestation+lactation F1a), F1a: litter size↓ live born pups↓, mortality until day 21p.p.↑, BWC↓ F1b after reduction to 350 mg/kg bw/day: no findings 350 mg/kg bw/day: F1: m+f: no findings F2a: initial BWC↓ F2b: mortality until day 21 p.p.↑, BWC↓	1	NMP Producers group, 1999c

Species, Strain, number, sex/group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability	Reference
Rat, Sprague-Dawley (Crl:CD®BR) 30 m 30 f	2-generation study 0, 50, 160, 500 mg/kg-bw/day	**<u>Effects at 500 mg/kg-bw/day</u>** F0 (parents): Reduced body weight gain (females) (statistically significant) F1b (both sexes): BW and feed consumption ↓ (statistically significant) F1b (males): Male fertility indices for both litters ↓ (statistically significant); small testes but no microscopic changes F1b (females): Female fertility indices for both litters↓ (statistically significant) fecundity indices for both litters ↓ (statistically significant) ; number of females with pigmented macrophages in uterus wall ↓; numbers and sizes of ovarian corpora lutea ↓ All litters: Survival indices and growth rate ↓ **Effects at other dose levels:** Non-significant decreases in fertility and reproduction **Two contrasting conclusions:** (1) Study authors: NOAEL was 160 mg/kg-bw/day (parents/offspring) because fertility/ reproduction parameters that were reduced at lower doses were in the range of the historical control data, the lower-dose effects are not treatment-related. (2) U.S. EPA: NOAEL could not be determined because reduced male fertility and female fecundity at 50 and 160 mg/kg bw/day were biologically significant.	2	Exxon Biomedical Sciences, 1991; TSCAT, 1991a
rat (outbred Imp:WIST) male/female	Reproductive toxicity and gonadotoxic potential study, non-guideline study. 0, 100, 300, 1000 mg/kg (actual ingested (gavage)) Exposure: males 10 weeks plus 1 week during mating females and offspring were not exposed (5 days/week	NOAEL reproductive performance/fertility: 300 mg/kg bw/d LOAEL: 1000 mg/kg bw/d : male infertility and extensive damage to the seminiferous epithelium in the seminal tubules of the testis	2	Sitarek and Stetkiewicz, 2008
Inhalation				
Rat, Wistar, 10 m 20f	2-generation-study 0, 41, 206, 478 mg/m^3 (0, 10, 50, 116 ppm, whole body exposure)	NOAEC reproductive performance/fertility 478 mg/m^3 NOAEC maternal systemic and developmental toxicity: 206 mg/m^3 478 mg/m^3: F0: response to sound↓ (m/f) F1 pups: BW↓	2	E.I. du Pont de Nemours and Company, 1990; Solomon et al., 1995
m: male, f: female, ↑: increased, ↓: reduced, BW: body weight, BWC: body weight change/gain, FC: food consumption				

Conclusion based on multi-generation toxicity studies

The following information is taken into account for the hazard / risk assessment: Two oral reproduction toxicity studies in line with the requirements of OECD 416 were performed in Sprague Dawley and Wistar rats using dietary dose levels of 0, 50 160 and 500/350 mg/kg bw/day. In both studies, the high dose level was reduced to 350 mg/kg bw/day due to severe pup mortality in the first litter. Both rat strains were very similar with respect to the observed findings. All F0 and F1 parental rats proved to be fertile at least after one of the two mating intervals. The NOAEL for reproductive performance/fertility was 350 mg/kg bw/day in both strains. The NOAEL for developmental toxicity in both oral studies was 160 mg/kg bw/day. The NOAEL for maternal toxicity was 160 mg/kg bw/day in the NMP producers group, 1999c for the oral route. The study by Exxon Biomedical sciences (1991), that according to the US EPA resulted in a LOAEL of 50 mg/kg bw/day was not used as POD for risk assessment as two more recent studies by the NMP producers group (1999b; c) provided additional evidence that the results found in the Exxon biomedical sciences (1991) study were not treatment related.

The inhalation route was tested by Solomon et al. (1995) in a two generation study where a NOAEC for reproduction toxicity was 478 mg/m^3 (the top dose) and the NOAEC for maternal systemic and developmental toxicity was observed to be 206 mg/m^3.

Prenatal developmental toxicity

Oral

Saillenfait et al., 2001; Saillenfait et al., 2002

Pregnant Sprague-Dawley rats were treated with aqueous NMP solutions of 0, 125, 250, 500 or 750 mg/kg bw/day during gestational days 6 through 20 by gavage. Significant decrements in maternal body weight gain and food consumption between treatment days 6 – 21 were observed at doses ≥ 500 mg/kg bw/day. The maternal body weight gain was reduced by 9% at 250 mg/kg bw/day, a reduction comparable to the statistically significant reduction in fetal body weight observed at the same dose. In addition, the net weight change in dams was reduced by 11%, 26% and 26% at 250, 500 and 750 mg/kg bw/day, respectively. Post implantation losses and the number of resorptions were increased at 500 mg/kg bw/day, showing a steep dose-response relationship. The rate of fetal malformations was increased at ≥500 mg/kg bw/day. The principal types of malformations consisted of external (anasarca, anal atresia), soft tissue (persistent truncus arteriosus) and skeletal findings (fusion or absence of cervical arches were most prominent). Further findings of developmental toxicity were reduced fetal weights at ≥250 mg/kg bw/day, delayed ossification of skull bones and sternebrae and an increase in skeletal variations at ≥500 mg/kg bw/day. There was also a very low proportion of live fetuses and an increase in the rate of soft tissue variations at 750 mg/kg bw/day. The results are summarized in Tables B.47 and B.48. The NOAEL for maternal toxicity and developmental toxicity is 125 mg/kg bw/day considering biologically relevant impairments in maternal and fetal body weight. The NOAEL for malformations was 250 mg/kg bw/day (Saillenfait et al., 2001; Saillenfait et al., 2002). The Dossier Submitter agrees with the derived NOAELs for maternal and developmental toxicity, however notes that the maternal and developmental effects in the 250 mg/kg bw/d dose group are marginal although in case of the fetal body weight reduction statistically significant.

***Table B.47**: Gestational parameters from pregnant Sprague-Dawley rats given NMP by gavage on GD 6-20 (Saillenfait et al., 2001; 2002)*

	Dose (mg/kg bw/day)				
	0	**125**	**250**	**500**	**750**
All litters[A]	21	22	24	25	25
No. of corpora lutea per dam	14.6 ± 2.4 [B]	14.6 ± 1.6	14.3 ± 1.9	14.5 ± 1.7	14.8 ± 1.7
Mean no. of implantation sites per litter	13.3 ± 3.2	13.6 ± 3.0	13.3 ± 3.2	14.0 ± 2.0	13.8 ± 3.0
Mean % post-implantation loss per litter [C]	4.1 ± 6.1	9.3 ± 21.3	4.5 ± 6.6	10.6 ± 10.5 *	94.2 ± 11.2**

	Dose (mg/kg bw/day)				
	0	**125**	**250**	**500**	**750**
Mean %dead foetuses per litter	0.0 ± 0.0	0.4 ± 1.6	0.0 ± 0.0	1.2 ± 3.4	3.2 ± 7.1
Mean % resorption sites per litter	4.1 ± 6.1	8.9 ± 21.2	4.5 ± 6.6	9.4 ± 8.9 *	91.0 ± 16.0**
Live litters[D]	21	21	24	25	8
Mean no. of live foetuses per litter	12.7 ± 3.1	13.1 ± 2.6	12.7 ± 3.0	12.4 ± 2.1	2.4 ± 2.3 **
Mean % male foetuses per litter	44.2 ± 17.5	46.1 ± 11.9	53.6 ± 14.7*	50.4 ± 17.5	91.7 ± 17.8 **
Foetal body weight (g)					
- All foetuses	5.73 ± 0.5	5.59 ± 0.22	5.18 ± 0.35**	4.02 ± 0.21**	3.01 ± 0.39 **
- Male foetuses	5.79 ± 0.42	5.74 ± 0.25	5.32 ± 0.45**	4.18 ± 0.22**	3.03 ± 0.40
- Female foetuses	5.62 ± 0.50	5.47 ± 0.20	5.02 ± 0.29**	3.88 ± 0.28**	3.09 ± 0.47 **

*, ** *Significant differences from the vehicle control P< 0.05 and P< 0.01, respectively*
[A] *Includes all animals pregnant at euthanization.*
[B] *Values are expressed as means±SD.*
[C] *Resorptions plus dead foetuses.*
[D] *Includes all animals with live foetuses at euthanization.*

***Table B.48**: Incidences of malformations and variations in foetuses of Sprague-Dawley rats given NMP by gavage on GD 6-20 (Saillenfait et al., 2001; 2002)*

	Dose (mg/kg bw/day)				
	0	**125**	**250**	**500**	**750**
Total no. of fetuses (litters) examined [A]:					
External	267 (21	276 (21)	304 (24)	311 (25)	19 (8)
Visceral	134 (21)	138 (21)	152 (24)	156 (25)	10 (6)
Skeletal	133 (20)	138 (21)	152 (24)	155 (25)	9 (5)
A. Fœtal malformations:					
External malformations [B]:					
Anasarca	0	0	0	6 (5)	1 (1)
Proboscis	0	0	0	0	1 (1)
Cleft palate	0	0	0	0	1 (1)
Anal atresia and tail, absent or vestigial	0	0	1 (1)	7 (5)	0
Omphalocele	0	1 (1)	0	0	0
No. (%) of foetuses with external malformations	0	1 (0.4)	1 (0.3)	11 (3.5)**	3 (15.8)**
No. (%) of litters with external malformations	0	1 (4.8)	1 (4.8)	9 (36.0)**	3 (37.5)*
Mean % of foetuses with external malformations per litter (mean ± SD)	0	0.4 ± 1.7 [C]	0.3 ± 1.7	3.3 ± 5.0	20.8 ± 36.5
Visceral malformations:					
Anophthalmia	1 (1)	0	0	0	0
Cardiovascular malformations [between square brackets: as % of total no. of fetuses with visceral malformations]	0 [0%]	0 [0%]	0 [0%]	10# (9) [6.4%]	6 # (4) [60%]
Dextrocardia	0	0	0	1 (1)	0
Truncus arteriosus, persistent [between square brackets: as % of total no. of fetuses with visceral malformations]	0 [0%]	0 [0%]	0 [0%]	5 (4) [3.2%]	2 (2) [20%]
Aorta, transposed	0	0	0	2 (2)	2 (2)

	Dose (mg/kg bw/day)				
	0	**125**	**250**	**500**	**750**
Aorta, overriding and/or enlarged and pulmonary artery, narrow	0	0	0	3 (3)	1 (1)
Interventicular septum defect, solitary	0	0	0	1 (1)	1 (1)
No. (%) of foetuses with visceral malformations	1 (0.7)	0	0	10 (6.4)*	6 (60.0)**
No. (%) of litters with visceral malformations	1 (4.8)	0	0	9 (36.0)*	4 (66.7)**
Mean % of foetuses with visceral malformations per litter (mean ± SD)	0.6 ± 2.7	0	0	6.1 ± 8.7	66.7 ± 51.6#
Skeletal malformations:					
Facial bones, abnormal	0	0	0	0	1 (1)
Atlas and exoccipital, fused	0	0	0	1 (1)	2 (2)
Atlas, axis and/or cervical archs, fused	0	0	0	7 (5)	3 (2)
Cervical archs, absent [D]	0	0	0	2 (2)	1 (1)
Thoracic archs, fused	0	0	0	0	2 (2)
Thoracic centra second and/or fourth absent	0	0	0	2 (2)	0
Vertebrae, thoracic, lumbar, and/or sacral, absent	0	0	0	2 (2)	0
Sacral archs, fused	0	0	0	0	1 (1)
Ribs, absent	0	0	0	1 (1)	0
Ribs, fused	0	0	0	0	2 (2)
Cleft sternum	0	0	0	0	2 (2)
No. (%) foetuses with skeletal malformations	0	0	0	14 (9.0)**	5 (55.6)**
No. (%) litters with skeletal malformations	0	0	0	12 (48.0)**	3 (60.0)**
Mean % foetuses with skeletal malformations per litter (mean ± SD)	0	0	0	9.6 ± 11.7##	46.7 ± 44.7#
No. (%) foetuses with any malformations	1 (0.4)	1 (0.4)	1 (0.33)	30 (9.6)**	11 (57.9)**
No. (%) litters with any malformations	1 (4.8)	1 (4.8)	1 (4.2)	18 (72.0)**	6 (75.0)**
Mean % foetuses with any malformations per litter (mean ± SD)	0.3 ± 1.4	0.4 ± 1.7	0.3 ± 1.7	9.6 ± 8.3##	58.3 ± 43.6##
B. Foetal variations:					
External variations [B]					
Nostril, misshapen	0	0	0	1 (1)	0
Club foot	0	1 (1)	1 (1)	1 (1)	0
No. (%) of foetuses with external variations	0	1 (0.4)	1 (0.3)	2 (0.6)	0
No. (%) of litters with external variations	0	1 (4.8)	1 (4.2)	2 (8.0)	0
Mean % of foetuses with external variations per litter	0	0.3 ± 1.4 [C]	0.3 ± 1.3	0.5 ± 1.9	0
Visceral variations					
Palate rugae, misshapen in the center of palate	0	0	0	1 (1)	0
Uterine horn, small and oviduct, misshapen	0	0	1 (1)	0	0
Ovaries, displaced	0	0	0	1 (1)	0
Testis, displaced	0	0	0	1 (1)	0
Kidney, small	0	0	0	0	1 (1)
Dilated renal pelvis	0	0	0	2 (2)	0
Distended ureter	4 (4)	0	1 (1)	1 (1)	2 (1)
No. (%) of foetuses with visceral variations	4 (3.0)	0	2 (1.3)	5 (3.2)	3 (30.0)**
No. (%) of litters with visceral variations	4 (19.0)	0	2 (8.3)	5 (20.0)	2 (33.3)
Mean % of foetuses with visceral variations per litter	2.7 ± 5.8	0	1.3 ± 4.4	3.3 ± 7.0	16.7 ± 27.9
Skeletal variations					
Skull, incomplete ossifications [D]:					
frontals and parietal	1 (1)	0	0	55## (17)	8## (5)

	Dose (mg/kg bw/day)				
	0	**125**	**250**	**500**	**750**
Supraoccipital	1 (1)	0	0	13 (6)	8## (5)
Interparietal	1 (1)	0	0	0	0
Hyoid, absent	1 (1)	0	0	0	0
Sternebrae:					
first and second, fused	0	0	1 (1)	1 (1)	0
incomplete ossification or absent, no. 5 and/or 6	0	1 (1)	7 (7)	43## (21)	6## (5)
incomplete ossification or absent, other than no. 5 and/or 6	0	0	0	6 (5)	3 (3)
Ribs:					
cervical, rudimentary	2 (2)	1 (1)	6 (6)	19 (10	1 (1)
14th, supernumerary	18 (8)	26 (13)	29 (13)	38 (18)	6 (3)
13th, short (uni or bilateral)	2 (1)	0	0	0	0
Thoracic vertebral centra:					
first absent	0	0	0	2 (2)	2 (2)
incomplete ossification (one or two)	13 (8)	7 (4)	3 (3)	15 (11)	5# (4)
No. (%) of foetuses with skeletal variations	33 (24.8)	33 (23.9)	41 (27.0)	115 (74.2)**	9 (100.0)**
No. (%) of litters with skeletal variations	14 (70.0)	15 (71.4)	19 (79.2)	25 (100.0)*	5 (100.0)
Mean (%) of foetuses with skeletal variations per litter	24.7 ± 20.3	22.6 ± 22.1	26.2 ± 25.8	74.2 ± 24.9##	100.0 ± 0.0##

[A] Only live foetuses were examined
[B] The incidence of individual malformation or defect is presented as number of foetuses (number of litters). A single foetus may be represented more than once in listing of the individual malformations/variations.
[C] Mean ± SD
[D] Absent = alizarine red S negative
**, ** Significant differences from the vehicle control P< 0.05 and P< 0.01, respectively, Fischer's test*
#, ## Significant differences from the vehicle control P< 0.05 and P< 0.01, respectively, Mann-Whitney test

Exxon Biomedical Sciences, 1992; GAF Corp., 1992; TSCAT 1992a;

In a developmental toxicity study, Crl:CD rats were exposed by oral gavage to 0, 40, 125 and 400 mg/kg bw/day NMP on gestation day 6 through 15. Maternal body weight gain was depressed during treatment at 400 mg/kg at GD 6-9, GD 9-12, GD 6-15 (14, 18, and 53 g, respectively at 0 mg/kg compared to 7, 15, and 42 g, respectively at 400 mg/kg). However, there was no statistical difference in weight gain during the overall gestation period (GD 0-21) and after correction for gravid uterine weight. Furthermore, food consumption was unchanged. At 400 mg/kg, reduced fetal body weight (10-11%, significant, $p \leq 0.01$) was observed. At 125 mg/kg bw/d, reduced fetal body weight (3%, significant, $p \leq 0.05$) in femals was observed compared to controls, however, the female fetal body weight was within the historical control range. There were no statistically significant differences between treated and control for any uterine implantation parameter. Foetal variations and malformations were observed in all groups, including controls, although the types and incidences were similar between treated and control groups. An increased incidence of stunted fetuses was observed at 400 mg/kg bw/d (fetuses: 1/340, 1/393, 2/395, and 12/397; litters: 1/21, 1/25, 2/24, and 6/25; at 0, 40, 125 and 400 mg/kg, respectively). The NOAEL for maternal and developmental toxicity were considered as 125 mg/kg/day. (Exxon Biomedical Sciences, 1992; GAF Corp., 1992; TSCAT 1992a; as cited in OECD SIDS 2007).

IRDC, 1991

Groups of 20 inseminated New Zealand White rabbits were administered dose levels of 0, 55, 175 and 540 mg/kg bw/day aqueous NMP solution on gestation day 6 through 18. Maternal toxicity was present at 175 and 540 mg/kg bw/day, expressed as reduced body weight gain at both doses (marked at 540 mg/kg bw/day), reduced feed consumption at 540 mg/kg bw/day, and one abortion at 540 mg/kg bw/day (Table B.49). At 175 mg/kg bw/day, maternal body weight gain was transiently reduced on gestation days 6-12. Developmental toxicity was observed at 540 mg/kg bw/day in form of increased post-implantation loss, due to increased early and late resorptions,

reduced live litter size, and reduced mean uterine weight. Malformations observed at 540 mg/kg bw/day were related to the cardiovascular system and the skeleton. No embryo-/fetotoxic effects or malformations were noted at lower dose levels. The results of the developmental effects are provided in Tables B.50 and B.51. NOAEL for maternal toxicity was 55 mg/kg bw/day and 175 mg/kg bw/day both for developmental toxicity and for malformations (IRDC, 1991). The Dossier Submitter notes that the NOAEL for maternal toxicity is rather conservative, where the effects at 175 mg/kg bw/d were transient. On the other hand, the effects were observed at higher concentrations and appear to follow a dose response relationship. For this reason the effects seen at 175 mg/kg bw/d were taken into account in setting the NOAEL for maternal toxicity.

Table B.49: *Maternal data (rabbits) given NMP by gavage on GD6-18 (IRDC, 1991)*

Confidential table was deleted.

Table B.50: *Gestational parameters of pregnant rabbits given NMP by gavage on GD 6-18 (IRDC, 1991)*

Confidential table was deleted.

Table B.51: *Incidences of malformations and variations in foetuses of rabbits dosed with NMP by gavage on GD 6-18 (IRDC, 1991)*

Confidential table was deleted.

Sitarek et al., 2012

In this study, female Wistar rats were exposed 5 days/week for about 9 weeks (2 weeks before mating and 1 week of mating, 3 weeks of gestation, and 3 weeks of lactation) to NMP by oral gavage at dose levels of 0, 150, 450 and 1000 mg/kg bw/day. After 2 weeks of exposure, females from each exposure group were mated overnight with unexposed males (2 females to 1 male). On the first postnatal day (PND 1), the live and dead pups were counted, weighted and their gender was determined. On day 4 after birth, the litters were culled to eight animals each and balanced for gender (four females and four males) to the extent possible. From birth (PND 1) to weaning (PND 21), the offspring was assessed for the general appearance, litter weight, mean pup weight, and mortality. Females from group 0, 150, and 450 mg/kg were necropsied after 3 weeks of lactation and from group 1000 mg/kg/day with no delivery—at 25th day post mating. Integral indices of toxicity, including body weight on the day of dissection, hematocrit, macroscopic and microscopic evalulation of the internal organs, absolute and relative weight of the internal organ were determined.

Some maternal toxic effects (significance $P<0.05$)were observed such as reduced body weight during gestation in all exposure groups, reduced food and water consumption during the first week of mating (water only) and on days 0, 13 (food only) and 20 of gestation in the 1000 mg/kg bw/day exposed animals. A reduced number of live pups was observed in the high dose group. Fertility index (percent of pregnant females in mating females group) was reduced in the 450 and 1000 mg/kg bw/d groups. Further, the percentage of pups that survived was significantly reduced in the 150 and 450 mg/kg bw/d groups. In the 1000 mg/kg bw/d group, of the 22 inseminated females, 15 were pregnant and eight pups were delivered by only 7 pregnant females (with three live-born and five stillborn). All pups died within 4 days after birth, which prevented further observation of the offspring of the 1000 mg/kg bw/d exposure group. Early resorptions were found in the other eight inseminated females after necropsy at day 25 after insemination, indicating a substantial intrauterine mortality. Further, microscopically endometritis and foci of resorption were noted in uterus in these 8 females, and in four of these females the number of corpora lutea in the ovaries was reduced when compared to controls. Reduced bodyweight was observed in offspring at day 4 (150 and 450 mg/kg bw/day exposure groups), 7, 14, 21 (all 450 mg/kg bw/d exposure group). Based on the effects observed in the dams and offspring in all exposure groups no NOAEL could be established. The LOAEL was set at 150 mg/kgbw/d for maternal and developmental toxic effects.

Inhalation

Saillenfait et al., 2001¸ Saillenfait et al., 2003

Sprague-Dawley rats were exposed to NMP concentrations of 0, 124, 247, 494 mg/m^3 (0, 30, 60 or 120 ppm) during gestational days 6 through 20 for 6 hours daily under whole body conditions. 25 – 26 time-mated pregnant rats were investigated in each group. The exposure of 247 and 494 mg/m^3 caused a transient decrease in body weight gain and food consumption. Maternal toxicity was accompanied by reduced fetal body weight at 494 mg/m^3 only. In particular, the incidence and types of malformations were comparable among all groups. The NOAEC for maternal toxicity was 124 mg/m^3 and for developmental toxicity 247 mg/m^3 (Saillenfait et al., 2001¸ Saillenfait et al., 2003). The Dossier Submitter noted that the NOAEC for maternal toxicity is rather conservative. On the other hand, the effects were observed at higher concentrations and appear to follow a dose response relationship (Table B.52). For this reason the effects seen at 247 mg/m^3 (specific during GD 6-13) were taken into account in setting the NOAEC for maternal toxicity.

Table B.52: *Maternal and gestational parameters from rats inhaling NMP on GD 6-20 (from Saillenfait et al. 2003).*

	0 mg/m^3	**124 mg/m^3**	**247 mg/m^3**	**494 mg/m^3**
n	25	25	25	26
# pregnant at euthanization	24	20	20	25
Body weight [a]				
BW (g) day 0	235 ± 18	235 ± 19	243 ± 20	237 ± 24
BW change (g) day 0-6	35 ± 11	33 ± 8	30 ± 9	32 ± 10
BW change (g) day 6-13	31 ± 7	27 ± 9	25 ± 8 *	23 ± 7 **
BW change (g) day 13-21	104 ± 22	95 ± 31	96 ± 32	89 ± 22
BW change (g) day 6-21	134 ± 27	122 ± 36	122 ± 36	112 ± 25
Absolute BW gain (g) [b]	32 ± 9	28 ± 10	26 ± 11	26 ± 10
Food consumption (g/day)				
Day 0-6	22 ± 2	22 ± 2	22 ± 2	22 ± 2
Day 6-13	23 ± 2	22 ± 1	22 ± 2	21 ± 2
Day 13-21	26 ± 2	24 ± 2	25 ± 3	24 ± 2 *
Day 6-21	25 ± 2	23 ± 2	23 ± 2	23 ± 2 *
Body weight fetuses				
Mean # of live fetuses per litter	13.9 ± 3.8	12.6 ± 4.7	14.0 ± 3.4	12.0 ± 4.1
Fetal BW (g) - all fetuses	5.67 ± 0.37	5.62 ± 0.36	5.47 ± 0.25	5.39 ± 0.45 *

BW = body weight
[a] Values are expressed as means ± SD.
[b] Body weight gain during GD 6–21 minus gravid uterine weight.
, Significant differences from the control (air), P<0.05 and P<0.01, respectively.*

BASF AG, 1991; BASF AG, 1993b

Groups of 15 inseminated Himalayan rabbits were exposed to NMP concentrations of 0, 200, 500 and 1000 mg/m^3 (0, 49, 122, 243 ppm, vapor and vapor-aerosol mixture) for 6 hours daily on gestation day 7 through 19. No mortality occurred and no signs of maternal toxicity were noted in the examined parameters (clinical findings, body weight, body weight gain, corrected body weight, gross pathology) at any concentration. However, a range-finding study, which examined a wider range of parameters, showed maternal toxicity at 1000 and 2000 mg/m^3 with increased liver weights and impaired clinical chemistry parameter. This concentration showed also slight fetotoxicity due to an increased incidence of supernumerary 13th ribs as a further indication of non-specific maternal stress and could be evidence that a minimal toxic dose had been achieved (Table B.53). The NOAEC for maternal toxicity and for developmental toxicity was 500 mg/m^3, (BASF AG, 1991; BASF AG, 1993b). The Dossier Submitter noted the following concerning the experimental

setup of the study: The experimental setup showed that rabbits were placed inside wired cages covered with aluminum foil, except for the breathing zone and rear of the cage, to reduce body contamination with NMP. The cage was subsequently placed in an exposure chamber. Although grooming of the whole body would not be likely, dermal exposure cannot be excluded. The study is therefore considered as a whole body exposure study.

Table B.53: *Incidence of accessory 13th rib(s) in rabbit fetuses after inhalation of NMP (from BASF 1993b*

	0 mg/m^3	**200 mg/m^3**	**500 mg/m^3**	**1000 mg/m^3**
Fetuses evaluated	97	85	95	97
Fetal incidence – n	6	5	10	31 **
Fetal incidence – %	6.2	5.9	11	32

** *Significant differences from the control (air), P<0.01.*

Summary of multiple studies on pre- and postnatal development or neurobehavioral teratogenicity

There were several inhalation studies investigating pre- and postnatal development or neurobehavioral teratogenicity but with only one concentration and thus, were not designed to achieve a NOAEC. The applied concentrations were in a range of 116 to 165 ppm (479 – 680 mg/m^3, presumably aiming at vapor concentration near saturation). The fetal/pup body weight was the most sensitive parameter reduced by less than 10%. Occasionally, only a transient delay of physical development, borderline impairment of behavior but no indication of specific neurotoxicity were observed (E.I. du Pont de Nemours and Company, 1990; Fries et al., 1992; Hass, 1990; Hass, 1991; Hass et al., 1995; Hass et al., 1994; Jakobsen and Haas, 1990; Solomon et al., 1995; as cited by OECD SIDS 2007). Additionally, it was shown that no developmental toxic effects or malformations were noted after exposure of pregnant Sprague-Dawley rats with a nominal concentration of 1750 mg/m^3 (analyzed, 800 ppm) either during gestational days 4 – 8 or 11 – 15 (BASF AG, 1976a; BASF AG, 1976b; BASF AG, 1983/1988).

Solomon et al., 1995

As part of a two-generation reproduction study in rats 10 males and 20 females per dose level were exposed whole body from 0 to 478 mg/m^3 of NMP vapour (relative humidity 40–60%) for 6 h/day, 7 days/week, for a minimum of 14 weeks (Solomon et al., 1995). Animals were mated after a 12 week exposure period and fetuses were examined on gestation day 21 for external, visceral and skeletal defects. No effects on the dams were recorded. However, reduced pup weight was evident at 478 mg/m^3. The NOAEC for developmental toxicity based on a decrease in pup weight in the F1 offspring was reported as 206 mg/m^3 (Solomon et al., 1995). The NOAEC for maternal toxicity was reported in the study as 206 mg/m^3 (Solomon et al., 1995). However, as the only observed effect was a reduced sensitivity to sound determined in female rats before mating, this is also considered a systemic effect with a NOAEC of 206 mg/m^3 (see Tables B.43 to B.45).

It is noteworthy to mention that the vapor saturation concentration of NMP under normal conditions is up to 480-640 mg/m^3 (120 - 160 ppm) depending on humidity and temperature (BASF AG, 1995a). Whole body exposure at higher concentrations would result in mixed exposure (oral/dermal/inhalation).

Dermal

FDRL, 1979

Prenatal developmental toxicity of NMP after dermal application of 0, 75, 237 and 750 mg/kg bw/day was investigated in groups of 25 Sprague Dawley rats. The test compound was applied using water as vehicle under open conditions to an area of 25 cm² skin by rubbing in and was rinsed off after duration of eight hours. Exposure was daily from gestation day 6 through day 15. The dams were fitted with collars to prevent ingestion of the test compound. Reduced body weight gain by 28% was noted at the high dose of 750 mg/kg bw/day; food consumption was not measured. NMP caused clear maternal toxicity (marked decrease in body weight gain) at 750 mg/kg bw/day. The dams treated showed topical signs of irritation with a dose-dependent

increased severity as well as colored urine as an indication of systemic availability. Fetotoxic effects consisted of fewer live fetuses, increased resorption rate, reduced fetal weight and indications of retarded skeletal development as well as an increased appearance of skeletal malformations occurred (e.g., fused, surplus or cleft ribs, fusion of skull bones) at the high dose level. Thus, embryo-/fetotoxicity including malformations occurred only at a dose level of marked maternal toxicity (Table B.54). The NOAELs for maternal toxicity and developmental toxicity were 237 mg/kg bw/day (Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b). The study was assigned a reliability score 2, because of the dose administration by rubbing in under open (no occlusion) skin conditions and a limited duration of the study in comparison to the recent guideline studies. However, despite the limitations the study brings forth, the Dossier Submitter considers that the results are sufficiently well reported and can be used.

Table B.54: *Gestational parameters and fetus skeletal findings from rats dermally exposed to NMP during GD 6-15 (from FDRL 1979).*

	0 mg/kg bw/day	**75 mg/kg bw/day**	**237 mg/kg bw/day**	**750 mg/kg bw/day**
No. females	25	25	25	25
No. pregnant females	24	22	23	24
Average No. live fetuses	11.2	11.9	12.0	9.3 *
Average fetal body weight (g)	3.45	3.49	3.54	2.83 *
No. of resorptions	15	6	4	41 *
Skeletal findings fetuses [a] (number of fetuses affected)				
Missing sternebrae	1	0	5	63
Extra ribs	0	0	2	12 *
Incomplete ossification vertebrae	16	18	26	38
Incomplete closure skull	0	0	0	12 *
Fused atlas and exoccipital (skull)	0	0	0	8 *

** Significant differences from the control, P<0.05.*
[a] Only skeletal findings showing a treatment-related effect are presented

BASF AG, 1993c

Himalayan rabbits (15 per group) were exposed to a 40% aqueous solution of NMP under a semi-occlusive dressing for 6 hours daily. Doses of 0, 100, 300 or 1000 mg/kg bw/day were applied from days 7 – 19 of pregnancy. No adverse effects clinically or on food intake or body weight were observed in the dams although yellow urine indicated that absorption had occurred. There was no increase in malformations in the treated animals. A slight increase in a common variation (supernumerary 13th ribs) in this strain of rabbits at the top dose group was observed. The number of variations was slightly increased and considered treatment-related, but except for sacral vertebral arches and talus ossification not considered biologically relevant. The presence of a thirteenth rib was found to be the most critical effect (Table B.55). The NOAELs for maternal toxicity were 1000 mg/kg bw/day, for developmental toxicity 300 mg/kg bw/day (BASF AG, 1993c).

Table B.55: *Increased incidence of skeletal variations and retardations in rabbit fetuses after dermal exposure to NMP (from BASF 1993c) [a].*

	0 mg/kg bw/day	**100 mg/kg bw/day**	**300 mg/kg bw/day**	**1000 mg/kg bw/day**
Fetuses evaluated	97	81	83	117
Accessory 13th rib(s) – n	1	1	5	18 **
Accessory 13th rib(s) – %	1.0	1.2	6.0	15
Sacral vertebral arch(es) incompletely ossified - n	2	1	0	16 **

	0 mg/kg bw/day	100 mg/kg bw/day	300 mg/kg bw/day	1000 mg/kg bw/day
Sacral vertebral arch(es) incompletely ossified - %	2.1	1.2	0.0	14
Talus incompletely ossified - n	4	1	2	11
Talus incompletely ossified - %	4.1	1.2	2.4	9.4

*** Significant differences from the control, P<0.01*
[a] Only skeletal findings showing a treatment-related effect are presented

Overall on developmental toxicity studies

An overview of key studies on developmental toxicity is provided in Table B.56, followed by conclusions on developmental toxicity per route of administration.

***Table B.56**: Key developmental toxicity studies of NMP (adopted from OECD SIDS 2007)*

Species, strain, number/ group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability		Reference
	Oral				
Rat, Sprague-Dawley 25-27 pregnant f per group	GD 6—20 0, 125, 250, 500, 750 mg/kg bw/day (gavage)	NOAEL maternal and developmental toxicity: 125 mg/kg/ bw 750 mg/kg bw/day: Fetuses: mortality↑, soft tissue variations↑ ≥500 mg/kg bw/day: Dams: FC↓, postimplantation loss↑, resorptions↑ Fetuses: malformations ↑ (external, skeletal, soft tissue), skeletal variations↑, delayed ossification of skull and sternebrae ≥250 mg/kg bw/day: Dams: BWC↓, net BWC ↓ Fetuses: BW↓	1		Saillenfait et al., 2001; Saillenfait et al., 2002
Rat, Sprague-Dawley (Crl:CD®BR) 25 pregnant f per group	GD 6—15 0, 40, 125, 400 mg/kg bw/day (gavage)	NOAEL maternal and developmental toxicity: 125 mg/kg bw/day 400 mg/kg/bw: Dams: BW↓ Fetuses: BW↓, stunts↑	1		Exxon Biomedical Sciences, 1992; GAF Corp., 1992; TSCAT 1992a
Rabbit, New Zealand white 20 pregnant f per group	GD 6—18 0, 55, 175, 540 mg/kg bw/day (gavage)	NOAEL maternal toxicity: 55 mg/kg bw/day NOAEL teratogenicity and developmental toxicity: 175 mg/kg bw/day 540 mg/kg bw/day: Dams: BW↓, BWC↓, FC↓, post-implantation loss↑, resorptions↑, litter size↓, uterine weight↓ Fetuses: malformations↑ (skeletal, soft tissue), skeletal variations↑ 175 mg/kg bw/day: Dams: BW↓, BWC ↓	1		IRDC, 1991

Species, strain, number/ group	Study type, concentrations	NOAEC/NOAEL, findings, remarks	Reliability		Reference
Rat, Wistar, 22-28 pregnant f per group	5 d/w , 9 weeks (2 weeks before mating and 1 week of mating, 3 weeks of gestation, and 3 weeks of lactation 0, 150, 450, 1000 mg/kgbw/d (gavage)	NOAEL fertility females: 150 mg/kgbw/d LOAEL maternal toxicity and developmental toxicity: 150 mg/kgbw/d ≥150 mg/kgbw/d: dams BW↓, Fetuses: BW↓, survival↓ ≥450 mg/kgbw/d: fertility index females↓	2		Sitarek et al., 2012
	Inhalation				
Rat, Sprague-Dawley 25-26 pregnant f per group	GD 6 - 20, 0, 124, 247, 494 mg/m^3 (0, 30, 60, 120 ppm), 6 h/day (vapor, whole body exposure)	NOAEC maternal toxicity: 124 mg/m^3 NOAEC developmental toxicity: 247 mg/m^3 247 mg/m^3: Dams: BWC↓ 494 mg/m^3: Dams: FC↓; Fetuses: BW↓	1		Saillenfait et al., 2001¸ Saillenfait et al., 2003
Rabbit Himalayan Main study: 15 pregnant f per group **Range finding:** 5 pregnant f per group	GD 7—19 Main study: 0, 200, 500, 1000 mg/m^m (0, 49, 122, 243 ppm), 6 h/day (vapor or vapor-aerosol, whole body exposure) **Range finding:** 0, 300, 1000, 2000 mg/m^3 (0, 73, 243, 486 ppm), 6 h/day (vapor or vapor-aerosol, whole body exposure)	NOAEC maternal toxicity: 1000 mg/m^3 NOAEC developmental toxicity: 500 mg/m^3 ≥1000 mg/m^3: Dams (range-finding): liver weight↑, clotting time↑, γ-GT↑, protein↓, albumin↓, globulin↓ 1000 mg/m^3 (main study): Fetuses: skeletal variation (supernumerary 13th ribs)↑ sacral vertebral arches and talus ossification	1		BASF AG, 1991c; BASF AG, 1993b
Rat, Wistar, 10 m 20f	Developmental study within a 2-generation-study 0, 41, 206, 478 mg/m^3 (0, 10, 50, 116 ppm, whole body exposure)	NOAEC developmental toxicity: 206 mg/m^3 478 mg/m^3: F0: response to sound↓ (m/f) F1 fetuses/pups: BW↓	2		E.I. du Pont de Nemours and Company, 1990; Solomon et al., 1995
	Dermal				
Rat, Sprague-Dawley (Crl:CD®BR) 25 pregnant f per group	GD 6—15 0, 75, 237, 750 mg/kg bw/day 8h/day, 1x/day (dermal, open)	NOAEL maternal, developmental toxicity: 237 mg/kg bw/day 750 mg/kg bw/day: Dams: BWG↓, resorption↑ Fetuses: live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	2		Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b
Rabbit Himalayan 15 pregnant f per group	GD 7—19 0, 100, 300, 1000 mg/kg bw/day 6h/day, 1x/day (dermal, semi-occlusive)	NOAEL maternal toxicity: 1000 mg/kg bw/day NOAEL developmental toxicity: 300 mg/kg bw/day 1000 mg/kg bw/day: Fetuses: skeletal variation (supernumerary 13th ribs)↑	1		BASF AG, 1993c
	GD: gestation day, f: female, ↑: increased, ↓: reduced, BW: body weight, BWC: body weight change(gain), FC: food consumption, p.c.: post coitum				

Human data

In a case report (Solomon et al. 1996) a report of a human case of intrauterine growth retardation followed by fetal demise at 31 weeks was described. The female worker was at about 16 weeks of gestation when there was a spill of NMP at work, which the patient cleaned up. She noted that the

latex gloves she was wearing dissolved in the solvent and there was extensive direct skin contact to her hands and into a break in the skin. She felt ill with malaise, headache, nausea, and vomiting over the next 4 days. Although her obstetrician asked for a transfer to an alternative job, she still worked with NMP for 2 weeks. She had daily exposures to an average of 42 hours each week until the 20th week of gestation. Follow-up ultrasound examination 1 month later, showed early intrauterine growth retardation (IUGR). Gestational age determined by biparietal diameter was nearly 25 weeks, whereas humerus and femur length measurements, as well as abdominal circumference, corresponded with a 21-week of gestational age. A follow-up ultrasound 3 weeks later confirmed the presence of IUGR. During this time, maternal weight gain was appropriate for gestational age, and could not be the cause of poor fetal growth. On physical examination 2 weeks later, no fetal activity was detected. The patient was hospitalized for prostaglandin induction, and delivered a stillborn fetus (31th week of gestation). Autopsy revealed a 430 grams male fetus, which appeared clinically to be at 29 weeks gestation. There were no identifiable abnormalities of the organs. Placenta was small for gestational age. It was concluded that the dose of NMP was not known, however there is good reason to believe it was significant and may have produced mild maternal toxicity. On the basis of the evidence from the animal literature, NMP should be considered fetotoxic in humans. In light of the increasingly prevalent use (1996) in industry and potential for widespread consumer exposure, epidemiology studies of the fetotoxicity of NMP are warranted.

Conclusion developmental toxicity

The developmental toxicity of NMP was investigated in 7 studies of which three by the oral route, and two by the dermal and inhalation route.

In one case report, it was reported that a pregnant woman suffered from stillbirth at 31 weeks after she was (dermally) exposed at work to a spill of NMP at about 16 weeks of gestation. The human case description supports the effects observed in the animal studies but cannot be used for risk assessment.

The oral exposure studies in the rat (same strain) showed similar results with an NOAEL for maternal toxicity and developmental toxicity of 125 mg/kg bw/d. Remarkably, the NOAEL in the rabbit study for maternal toxicity was lower, i.e. 55 mg/kg bw/day, where the NOAEL for teratogenicity and developmental toxicity was higher, i.e. 175 mg/kg bw/day. For the oral route it was decided to use the NOAEL from the rat study for maternal and developmental effects of 125 mg/kg bw/day since the rat NOAEL lies between the rabbit NOAEL and rabbit LOAEL of 55 and 175 mg/kg bw/day, respectively, and the observed effects were of a similar nature.

For the dermal route the study results from FDRL (1979) were considered as starting point for the DNEL derivation, i.e. the NOAEL for maternal and developmental effects of 237 mg/kg bw/day being the lowest dermal NOAEL. Although in the OECD SIDS dossier a reliability score of 2 was assigned, the Dossier Submitter found the original study report by FDRL (1979) of sufficient quality to use the results from this study. Regarding maternal effects, the NOAEL from the rat study was chosen over the NOAEL from the rabbit study, because the effects in the rat were more severe at the LOAEL of 750 mg/kg bw/d compared to the effects observed in the rabbit at 1000 mg/kg bw/d, indicating that for the dermal route the rat is more sensitive to NMP exposure. With regard to developmental effects, the developmental toxicity study with rabbits provides a NOAEL of 300 mg/kg bw/d which is in the same range as the NOAEL of 237 mg/kg bw/d in the rat.

Two developmental inhalation studies were performed, one with rats and one with rabbits. In addition, one 2-generation study included a cohort for developmental toxicity. As POD for developmental effects, the NOAEC of 206 mg/m^3 was chosen. The NOAEC of 206 mg/m^3 was derived from the 2-generation study, which included a developmental study, by Solomon et al. (1995). The NOAEC is based on a decrease in fetal and pup weight in the F1 offspring. As POD for maternal toxicity, the NOAEC of 206 mg/m^3 was taken from the same study (Solomon et al. 1995). The NOAEC of 124 mg/m^3 that was derived from the Saillenfait rat studies (2001/2003), is based on a transient reduced body weight gain at 247 mg/m^3 in the Saillenfait study, which is considered as a marginal, but still adverse effect, by the Dossier Submitter. However, taking into consideration that the NOAEC of 206 mg/m^3 lies between the NOAEC and LOAEC and the marginal effect observed at the LOAEC of the Saillenfait study, the Dossier Submitter considers the NOAEC of 206 mg/m^3 a justifiable overall POD.

With respect to the inhalation route of exposure in the developmental toxicity studies, the relatively low saturated vapour pressure and the way NMP was administered (nose-only vs. whole body), was not expected to have had an influence of the NOAECs from those studies. Effects were already seen in two rat studies at levels below the saturated vapour concentration. Possible confounding effects from co-exposure by the oral or dermal route were therefore not expected in the whole body studies used in the developmental toxicity studies.
The reduced sound response in the Solomon study was not taken into account for maternal and systemic toxicity as no such effects were observed in a 90-day inhalation study with much higher exposure levels and no neurologic effects were observed in an oral 90-day combined neurotoxicity and toxicity study. Maternal effects were regarded as specific effects on dams and not as systemic effects because the reduced body weight gain in the developmental inhalation study (Saillenfait, 2001 and 2003) and Solomon study were not observed at this dose level in the repeated dose inhalation study (BASF, 1994).

Overall on toxicity to reproduction – fertility and developmental toxic effects

Three multi-generation studies and 7 prenatal developmental studies were available as key studies for assessment of reproduction toxicity. Since no effects were observed on fertility, no POD was determined for this endpoint.

***Table B.57**: Point of departures for developmental toxicity*

POD for DNEL derivation (endpoint)	Species and duration	NOAEL mg/kg bw / NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Maternal toxicity				
inhalation	Rat, GD 6-20	206 mg/m³	Dams body weight gain decreased (observed in Saillenfait 2001/2003 study)	Solomon et al. 1995 ; Saillenfait 2001/2003 (overall NOAEL)
dermal	Rat, GD 6—15	237 mg/kg bw/day	Reduced body weight gain	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b
Prenatal developmental toxicity				
inhalation	Rat, 2-generation	206 mg/m³	Reduced fetal and pup body weights	Solomon et al. 1995
inhalation	Rat, GD 6-20	247 mg/m³	Reduced fetal body weight	Saillenfait et al., 2001¸ Saillenfait et al., 2003
dermal	Rat, GD 6—15	237 mg/kg bw/day	live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b

B 5.10 Other effects/information

SCOEL recommendation

Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL 2007):
"*Taking into consideration the potential of N-methyl-pyrrolidone (NMP) to produce respiratory irritation and chemosensory effects, both in humans and animals, and systemic toxicity, in particular reproductive toxicity in studies in experimental animals, a health-based OEL (8 -hour TWA) of 10 ppm (40 mg/m³) is recommended. A Short-term exposure limit (STEL) (15 min) of 20 ppm (80 mg/m³) is proposed, in order to limit peaks of exposure which could result in irritation. This recommendation is supported by the results of inhalation studies in animals. While the human*

volunteer study of Bader et al. (Bader et al., 2007) could support an OEL of 20 ppm (80 mg/m³), given the absence of effects other than odour detection and slight perception of annoyance following exposure to up to 160 mg/m³ NMP in this study, the lower value of 10 ppm (40 mg/m³) is recommended in order to provide an adequate margin of safety for possible reproductive effects in exposed workers. In relation to the reproductive toxicity seen in studies with NMP in rats, rabbits and mice, changes seen at exposure levels of 250 - 500 mg/m³ by the inhalation route were minor (decreased pup weight and pup weight gain in the presence of maternal toxicity). NOAECs are in the range 206 - 500 mg /m³. Application of an Uncertainty Factor (UF) of 5 to the lowest figure in this range provides an OEL of 40 mg/m³. NMP is well-absorbed through the skin, both in humans and in animal studies and some systemic toxicity (including developmental toxicity) is seen following dermal uptake. A "skin" notation is therefore considered necessary. Due to the significant dermal uptake of NMP, biological monitoring is also recommended. 5 -HNMP and 2 -HMSI, two key metabolites of NMP, are appropriate biological indicators of exposure, and monitoring of either of these metabolites can be undertaken. The optimum sampling time for 5-HNMP is the first 2-4 h post-exposure, while in the case of the longer half-life metabolite 2-HMSI a urine collection 16 h post-exposure (i.e. on the morning after an 8 h work-shift) is advised. Both parameters should be corrected for urinary creatinine to compensate for diuretic variations. The delayed peak maximum of 16-24 h post-exposure and the long biological half-life makes urinary HMSI especially suitable for the surveillance of accumulative effects during a work week (Bader et al., 2007). However either parameter may be chosen, depending on the available analytical methodology and the conditions pertaining in the particular workplace. For the longer half-life metabolite 2 -HMSI, an 8 -h TWA of 10 ppm (40 mg/m³) corresponds to a biological value of approximately 16 mg/g creatinine, 16 h post exposure for a work scenario without workload and approximately 22 mg/g creatinine for a work scenario with moderate workload (75 Watt). A Biological Limit Value (BLV) of 20 mg/g creatinine is recommended for 2-HMSI, measured on the morning after an 8 h work-shift. This value is intermediate between the work scenario without workload and the work scenario with moderate workload, as assessed by Bader and co-workers and is likely to be representative of a typical work scenario involving some physical activity. For 5-HNMP, an 8-h TWA of 10 ppm (40 mg/m³) corresponds to a biological value of approximately 60 mg/g creatinine, 2-4 h post exposure for a work scenario without workload and approximately 75 mg/g creatinine for a work scenario with moderate workload (75 Watt). A BLV of 70 mg/g creatinine is recommended for 5-HNMP, measured 2-4 hours after the end of exposure. This value is intermediate between the work scenario without workload and the work scenario with moderate workload, as assessed by Bader and Co-workers, and is likely to be representative of a typical work scenario involving some physical activity. At the levels recommended, no measurement difficulties are foreseen, either with the measurement of NMP in air or 5-HNMP or 2-HMSI in urine".*

* The SCOEL 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 total body burden will be established on a case-by-case basis but may in general be of the order of 10% or more of the uptake from respiratory exposure at the 8 hour TWA. It should be noted that a skin notation relates specifically to dermal absorption of the material (whether as solid, liquid or gas), i.e. it is determined by the toxicokinetic properties of the material in relation to the level at which the OEL is established. It does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation, criteria for which are described in Annex VI of Directive 67/548/EEC. According to worker legislation (see section B.9.1.1), employees are obliged to reduce the dermal exposure as much as possible for substances given a skin notation.

The IOEL of the SCOEL obligates member states to establish national exposure limits. When Member States establish a national exposure limit value, they must take into account the IOEL, national legislation and practice. The levels of the national exposure limits may differ due to divergence in assessment methods and differing assessments on (expert judgment of) the actual risks of the chemicals. For example, where the IOEL is health based, member states can also take into account issues around technical and economic feasibility. There is no special argumentation required when a Member State uses a higher exposure limit than the IOEL recommended by SCOEL but there is the obligation for the Member State to inform the Commission and other Member States thereof in order for the Commission to be able to undertake the appropriate action. In Europe, the following national OELs are used: 5 ppm (20 mg/m^3) in Denmark and Norway; 10 ppm (40 mg/m^3) in Finland, Belgium, Ireland and The Netherlands; 20 ppm (80 mg/m^3) in Germany, Austria and Switzerland; 25 ppm (100 mg/m^3) in the United Kingdom and Spain; and 50 ppm (200 mg/m^3) in Sweden. It is noted however that not all OEL values in EU countries could be retrieved and the OELs of Sweden (currently under review) and the United Kingdom were set before the indicative OEL was published by the SCOEL.

The Scientific Committee on Consumer Safety (SCCS, 2011, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_050.pdf) evaluated the use of NMP in cosmetics. The SCCS concluded: "*Based on a worst case assessment with a maximum use concentration of 5% NMP in cosmetic products and a dermal absorption of 100%, the Margin of Safety is considered to be too low. There is an absence of specific information on the actual possible maximum concentrations of NMP present in cosmetic products and specific measurement of dermal absorption of it through skin at relevant concentrations. With the information available at the time of assessment, the SCCS is of the opinion that the presence of NMP with a maximum use concentration of 5% in cosmetic products is not safe for the consumer. A re-evaluation may be possible should relevant data that addresses the above be provided*."

Analytical methods available to determine the concentration of NMP in air

The SCOEL document mentions analytical techniques to measure NMP in air. "The NMP-containing extract can be analysed by gas chromatography (GC), using flame ionisation (FID) or nitrogen-phophorus detection (NPD), with a detection limit corresponding to 0.1 mg/m^3 NMP in air using FID detection and 0.01 mg/m^3 using NPD (as cited in SCOEL 2007: Blome and Hennig, 1984; Andersson and Andersson, 1991; Åkesson and Paulsson, 1997). Alternatively, airborne NMP can be analysed on a continuous basis by photoacoustic IR spectrometry (INNOVA, 1412 Photo Acoustic Field Gas-Monitor) (as cited in SCOEL 2007: Bader et al, 2007)" . There is however no mentioning of a single recommended method for an analytical technique in the SCOEL document.

Additionally: In monitoring studies performed by industries, different methods have been used. In one monitoring study reference is made to the National Institute for Occupational Safety and Health (USA) drawn measurement regulation 1302 "N-methyl-2-pyrrolidone". Other studies describe a TRGS402 standard (German standards) to take samples. With respect to means of analyses, FID detection, FT-IR spectroscopy, and GC techniques were mentioned. According to the Dossier Submitter, there is no preferred method to determine the level of NMP in air (confidential monitoring reports obtained from registrants and downstream users).

Analytical methods available to determine the concentration of NMP in substance / product samples

Several analytical methods for detection of NMP are reported in the literature. Methods have been developed for solid samples (non-biological, such as medical devices, and biological, e.g. meat tissues), liquid samples (organic or aqueous solutions/extracts, as well as biological fluids such as blood, urine, and biofilms), and also for air monitoring. They take into account analysis of both complex matrices (e.g. environmental or biological samples) and pure substance.

Detection/Quantification limits reported are generally at levels of ppm (parts-per-million) and below, which is far below the concentration limit for the classification of NMP in mixtures (0.3%).

Some standard methods for NMP exist, for instance the method 1302 of NIOSH for determination in workplace air. An ISO/DIS method for the determination of NMP in leather is under development.

Determination of NMP in mixtures consists typically of a sample preparation step followed by separation and analysis by a suitable detector. Depending on the type of sample, preparation may include extraction with organic solvents (potentially followed by clean-up steps), headspace analysis, air pumping through sorbents, or may be skipped completely (direct injection to chromatographers). Analytical equipment usually employed for detection and quantification include gas and liquid chromatography coupled with various detectors, e.g. GC-NPD, GC-FID, GC-MS, LC-UV, and LC-MS/MS.

B 5.11 Derivation of DNEL(s)/DMEL(s)

In the derivation of DNELs account has been taken for two worker populations, i.e. workers (general) and the pregnant worker, because of the developmental effects that were observed in the developmental toxicity and 2-generation studies. Further, 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.

Based on the volunteer study by inhalation, repeated dose studies and reproduction toxicity studies PODs were determined for local and systemic effects (see tables B.58 and B.59). Since it is unknown whether the developmental effects are caused by a single exposure in a critical window of effect or that repeated doses are required for the effect (build-up of a critical dose) it is assumed that acute exposure is sufficient to cause the developmental effect. Because the dose regime in developmental toxicity studies cover the main part of gestation, meaning a daily exposure, no corrections or additional uncertainty factors are needed in risk assessment, as described below under subsection 'study duration corrections'.

It appeared from the comparison of the repeated dose studies and developmental toxicity studies that in pregnant rats the critical effects (particularly the reduced body weight gain) occurred at approximately two-fold lower dose levels (all routes), than in non-pregnant females or males in the repeated dose studies. The likely explanation for this phenomenon according to the Dossier Submitter is that the reduced body weight gain in dams is a secondary effect to a developmental toxic effect and not a primary effect on the dams itself. Otherwise one would expect that the same effects would occur at the same dose levels in non-pregnant animals. For this reason, and the decision to derive DNELs for workers and pregnant-worker separately, the maternal systemic toxic effects were not used to derive DNELs for the general worker.

Table B.58: *Summary table for PODs for repeated dose effects*

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw /day) or NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Systemic				
inhalation	Rat, 3 months	500 mg/m3	mortality, bone marrow hypoplasia, testicular findings atrophy and/or necrosis of the lymphoid tissue in thymus, spleen and lymph nodes, body weight gain reduction	Lee et al., 1987; Lee, 1977; TSCAT, 1989; TSCAT, 1991b; BASF AG, 1994
inhalation	Rat carcinogenicity study	40 mg/m3	body weight gain reduction in males	Lee et al., 1987; TSCAT, 1990b; WHO: Information Bulletin, 1986; Kennedy, 2008
dermal	Rabbit, 4 weeks	826 mg/kg bw/d	¼ mortality at top dose	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963
dermal (based on oral study)	Rat, 90-d oral study	169 mg/kg bw/d (based on 100% absorption)	body weight, foot splay in males and reversible neurotoxic effects	NMP Producers Group, 1995b; NMP Producers Group, 1994; Malley et al., 1999
dermal (based on oral study)	Rat carcinogenicity study, oral study	207 mg/kg bw/d	chronic nephropathy, fluid in pleural cavity, small testes. Splenic hemosiderin increase	Malley et al., 2001; NMP Producers Group, 1997
Local				
inhalation	Rat, 3 months	500 mg/m3	local irritation	BASF AG, 1994
dermal	Rabbit, 4 weeks	<413 mg/kg bw/day (LOAEL)	Skin irritation observed at all dose levels	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

Table B.59: *Summary table for PODs for maternal systemic and prenatal developmental toxicity effects*

POD for DNEL derivation (endpoint)	Species and duration	NOAEL mg/kg bw / NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Maternal toxicity				
inhalation	Rat, GD 6-20	206 mg/m³	Dams body weight gain decreased (observed in Saillenfait 2001/2003 study)	Solomon et al. 1995 ; Saillenfait 2001/2003 (overall NOAEL)
dermal	Rat, GD 6—15	237 mg/kg bw/day	Reduced body weight gain	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b
Prenatal developmental toxicity				
inhalation	Rat, 2-generation	206 mg/m³	Reduced fetal and pup body weights	Solomon et al. 1995
inhalation	Rat, GD 6-20	247 mg/m³	Reduced fetal body weight	Saillenfait et al., 2001¸ Saillenfait et al., 2003
dermal	Rat, GD 6—15	237 mg/kg bw/day	live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b

The derivation of the DNELs was performed according to ECHA guidance on the characterisation of the dose-response for human health described in chapter R8 (ECHA, 2012a). The ECHA guidance describes the use of certain exposure condition corrections to take into account differences in exposure durations and absorption factors and the use of assessment factors to extrapolate from animals to humans.

Interspecies differences:

- Allometric scaling: the default factor for allometric scaling from rat to human is a factor 4. From rabbit to human this factor is set at 2.4. Note that in case of inhalation exposure, no allometric scaling factor needs to be applied.
- Remaining differences: this covers any remaining differences between animal and humans on the level of toxicodynamics and –kinetics. By default this factor is set at 2.5 for systemic effects and at 1 for local effects. The Dossier Submitter considered that substance specific information on NMP toxicokinetics, which is a small part of the remaining differences factor, was insufficient to deviate from the default factor of 2.5 for the remaining differences. Toxicological information obtained in different species, i.e. rat, mouse, rabbit and dog seem to indicate that interspecies differences are small, but do not include non-human primate or human data on systemic effects and therefore provide insufficient justification to reduce the factor for toxicodynamic differences between animals and humans. For this reason, the default factor of 2.5 was taken forward in the derivation of the DNELs for systemic effects.

Intraspecies differences:
By default the assessment factor is set at 5 for workers (in comparison with 10 for the general population), because this subpopulation does not include the very young, the very old and the ill. However, developmental effects concern effects upon the fetus. The default factor of 5 for workers, normally used to cover the variability amongst the worker population, does not include the unborn child. Therefore, the default factor for the general population, which includes the unborn child, is taken forward for (prenatal) developmental effects. To summarize, a factor of 5 is taken for (maternal) systemic effects and a factor of 10 is taken for (prenatal) developmental effects, to cover for intraspecies differences. Note that the fact that rat foetuses are exposed during prenatal developmental toxicity studies, does not influence the intraspecies assessment factor as this factor takes account of the intraspecies variability in the human population.

Dose descriptor modification:
The inhalation exposure in experimental studies differs from the human exposure situation. The ECHA guidance describes a correction for the number of hours exposure per day (dependent on study design and work shifts of the worker) and the volume air inhaled by rats and humans during 8 hours (working day). The available data regarding dermal absorption do not provide enough information to conclude on a need for correction regarding differences in absorption between animals and human or for matrix effects.

Study duration corrections:
These might be needed to extrapolate from a sub-chronic to chronic duration. By default a factor 2 is taken. For subacute (28-d study) to chronic a factor of 6 is taken. A factor of 1 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 5d/w 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. 7/5 x 15/21 = 1). Please note that a correction factor of 7/5 is needed for the developmental toxicity study included in the Solomon study since the exposure was during the entire gestation period.

Dose-response assessment factor:
In case the POD is a LOAEL, an additional assessment factor is needed. There is no default value set, since this factor depends on the type of studies, effects observed (severity), and the steepness of the dose-response.

In the registration dossiers the indicative OEL derived by the SCOEL was used as the inhalation DNEL, which is in accordance with ECHA guidance (chapter R8). ECHA guidance, however, also allows registrants or in this case member state competent authorities (MSCAs) to derive their own inhalation DNEL. The OEL is based on the inhalation studies in animals showing developmental effects and taking into account irritation effects observed in the male volunteer studies by Bader et al. (2006; see SCOEL report (2007) and section B.5.10). An overall uncertainty factor of 5 was

considered appropriate to protect the worker population, since the lowest overall NOAEL was used as point of departure, i.e. 206 mg/m^3 from the Solomon et al. (1995) study, and the derived OEL also should be sufficiently protective for local effects. According to the Dossier Submitter, the indicative OEL is not sufficiently protective for the most 'sensitive group of workers' with respect to NMP exposure, i.e. the pregnant women and the unborn child. There was no clear justification for the overall assessment factor of 5 provided nor was it mentioned which uncertainties are accounted for. In the OEL derivation no correction was made for inhalation volume (6.7/10 m^3; ECHA guidance chapter R8), nor was an uncertainty factor applied for remaining differences between animals and humans regarding prenatal developmental toxic effects. Therefore, the Dossier Submitter derived the inhalation DNEL for the pregnant worker and for the 'general' workers, according to the ECHA guidance on the characterisation of the dose-response for human health described in chapter R8.

DNEL derivation worker

***Table B.60**: DNEL derivation for the inhalation route, worker*

DNEL (endpoint) Inhalation	LOAEC mg/m^3 species)	Type of study	Type of effect at LOAEC	Correction for differences in exposure conditions	Corrected NOAEC mg/m^3	Assessment factors	Resulting DNEL mg/m^3	Reference
systemic	500, rat	Repeated dose study, 3 months	Decrease in body weight and body weight gain in males	6/8 6.7/10	251	1 - (AS) 2.5 – (RD) 5 - (IS) 2 – (ED) Total: 25	10	BASF AG, 1994
systemic	40, rat LOAEC 400	Carcinogenicity study 2-years	Reduced body weight gain	6/8 6.7/10	20.6 206	1 - (AS) 2.5 – (RD) 5 - (IS) Total: 12.5 3 – DR: 37.5	1.7 5.5	Lee et al., 1987, and other
local	80, human	Volunteer study		-	80	5 - (IS) Total: 5	16	Bader et al., 2007; Van Thriel et al. 2007

Key: AS = allometric scaling, RD= remaining differences, DR = dose response, IS = intraspecies factor, ED = exposure duration

A repeated dose study and a carcinogenicity study were considered as POD for inhalation DNEL derivation. The repeated dose study was performed using nose-only exposure, thereby eliminating possible oral and dermal exposure. The results in the 90-d study were supported by the results in the 28-d inhalation study that resulted in the same NOAEC for systemic and local effects. The 2-year carcinogenicity study provided a NOAEC of 40 mg/m^3, where effects were observed at 400 mg/m^3 (reduced body weight gain) which is below the NOAEC from the repeated dose studies. It is noted that the carcinogenicity study was performed using whole body exposure and thus possible mixed exposure effects have occurred. The dose spacing in the carcinogenicity study is considered large and the resulting NOAECs seem to be conservative, especially when considering the NOAECs in the other inhalation studies available. If the LOAEC was taken forward as POD, i.e. 400 mg/m^3, and a factor of 3 for LOAEC to NOAEC was applied an inhalation DNEL of 5.5 mg/m^3 would be obtained, which can be considered supportive for the other repeated dose studies, taking into account the possible mixed exposure dermally and orally. Although the carcinogenicity study provided the lowest POD and consequently results in the lowest DNEL, preference was given to the 90-d repeated dose study, because nose-only exposures were considered in that study and is supported by a 28-d repeated dose study showing similar results.

In conclusion, an inhalation chronic systemic DNEL of 10 mg/m^3 is derived for workers based on reduced body weight (gain) in males at the LOAEC in a 90-day inhalation study.

RAC assessment: A NOAEC at 500 mg/m^3 was determined based on a statistically non-significant decrease in body weight gain of 4.8% in male rats at 1000 mg/m^3 at day 33 in a 90 days study (BASF, AG 1994). Although the decreased body weight gain was only statistically significant on day 33 (-9%) at 3000 mg/m^3, an apparent dose-response for the reduced growth rate was indicated at the time points studied (day 12, 33, 61 and 96). However, there were no signs of effects on the body weight gain of females, which perhaps could be interpreted as an inconsistency. However, also in the 2 year inhalation study (Lee et al, 1987), body weight was affected only in the males (a 6% reduction in body weight gain at 400 mg/m^3). There is no information given on body weight in the reporting of the 28 days inhalation study (Lee et al, 1987), but it is noted that excessive mortality was observed at 1000 mg/m^3. The effect on male body weight gain thus seems consistent and substance-related, although slight. Of these studies, the 90 days study is the most, and perhaps only, reliable study, as it used head-nose exposure, whereas the others used whole-body exposure, thus resulting also in oral exposure via grooming. The suggested NOAEC of 500 mg/m^3 is very conservative, and a more robust, alternative NOAEC from this study would be 1000 mg/m^3, based on the statistically significant 9% decrease in body weight at 3000 mg/m^3. It is noted that when the NOAEC of 500 mg/m^3 is not used a study with inhalation exposure of human volunteers (local irritation at 80 mg/m^3) would give a DNEL lower than the one calculated based on the 'new' NOAEC of 1000 mg/m^3. However, since the pregnant worker DNEL is the overall lowest DNEL and the one used in the RAC risk characterisation, other DNELs were not calculated.

***Table B.61**: DNEL derivation for the dermal route, worker*

DNEL (endpoint) DERMAL	NOAEL mg/kg bw	Type of effect at LOAEL	Type of study	Assessment factors	Resulting DNEL mg/kg bw/day	Reference
systemic	826, rabbit	Mortality	Repeated dose study, 4 weeks	2.4 - (AS) 2.5 – (RD) 5 - (IS) 6 – (ED) Total: 180	4.6	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963
Systemic (based on oral study)	169, rat	body weight, foot splay in males and reversible neurotoxic effects	Repeated dose study, 90-d oral	4 – (AS) 2.5 – (RD) 5 – (IS) 2 – (ED) Total: 100	1.7	NMP Producers Group, 1995b; NMP Producers Group, 1994; Malley et al., 1999
Systemic (based on oral study)	207, rat	chronic nephropathy, fluid in pleural cavity, small testes. Splenic hemosiderin increase	Carcinogenicity study, 2-years	4 – (AS) 2.5 – (RD) 5 – (IS) Total: 50	4.1	Malley et al., 2001; NMP Producers Group, 1997
local	413 (LOAEL) rabbit	Skin irritation	Repeated dose study, 4 weeks	1 - (AS) 2.5 – (RD) 3 – (DR) 5 - (IS) 1 – (ED) Total: 37.5	11	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

Key: AS = allometric scaling, RD= remaining differences, DR = dose response, IS = intraspecies factor, ED = exposure duration

One dermal repeated dose study with rabbits was available and two oral studies were considered for route-to-route extrapolation as POD for the dermal DNEL. The dermal study was given a Klimisch score 2 indicating that the study is considered reliable with restrictions, where mortality was found in the top dose. The study description does not allow drawing a conclusion on whether or not the effect was treatment related. Alternatively the oral repeated dose study and oral carcinogenicity study results may be used to determine the dermal DNEL using route-to-route extrapolations. The route-to-route extrapolation was performed under the assumption that absorption via the oral and dermal route is 100%. The Dossier Submitter acknowledges that both approaches are subject to uncertainty and decided to give preference to the dermal repeated dose study, because the relevant route was considered. The fact that both oral studies lead to DNELs in the same range of the DNEL derived from the dermal study is considered supportive of the decision to take the POD from the dermal study.

In conclusion, a dermal chronic systemic DNEL of 4.6 mg/kg bw/day is derived for workers based on NOAEL of 826 mg/kg bw/d and increased mortality at the LOAEL in a dermal 28-day repeated dose toxicity study.

RAC assessment: Based on the death of one of the four rabbits of the top dose (1653 mg/kg/day), the mid dose of 826 mg/kg/day was chosen as the NOAEL. There were no clinical signs of toxicity in the rabbits, which makes it difficult to know whether the death was substance related or not. Since a treatment relation cannot be excluded, the dossier submitter proposes the top dose as a LOAEL. RAC notes that some skeletal variations were observed at a dermal dose of 1000 mg/kg/day in a rabbit developmental toxicity study, and that NMP is known to be highly absorbed through the skin. There is some uncertainty regarding the cause of the death, as the substance-relationship can be questioned by the lack of other signs of toxicity on the three surviving animals (such as effects on body weight, clinical chemistry, haematology, histopathology or clinical signs). While noting this uncertainty, RAC agrees with a NOAEL of 826 mg/kg/day based on this study. RAC notes that a maternal LOAEL of 750 mg/kg/day was observed in a dermal developmental toxicity study in rats (Becci, 1992), where the maternal body weight gain was reduced by 28% during the gestation period (10 days exposure). The NOAEL was 237 mg/kg/day. The clear effect and clear substance relation make this study an alternative and more robust basis for a worker dermal NOAEL. However, the total data base for NMP indicates clearly lower LOAELs/LOAECs for pregnant than for non-pregnant animals, perhaps indicating that the apparent effect on maternal weight in pregnant dams also could be related to developmental toxicity i.e., reduced fetal weight. The rat developmental study is therefore not used as such for adult non-pregnant animals, but is considered to support the rabbit dermal NOAEL. Thus, RAC supports the (overall) NOAEL of 826 mg/kg/day.

DNEL derivation pregnant worker

***Table B.62**: DNEL derivation pregnant worker – inhalation*

DNEL (endpoint) INHALATION	NOAEC mg/m³ (spec.)	Type of study	Type of effect at LOAEC	Corrected for differences in exposure conditions	Corrected NOAEC mg/m³	Assessment factors	Resulting DNEL mg/m³	Reference
Developmental toxicity	206, rat	2-gen study	Reduced fetal and pup weights	6/8 6.7/10 7/5	146	1 - (AS) 2.5 – (RD) 10 – (IS) Total: 25	5.8	Solomon et al. (1995)
Developmental toxicity	247, rat	Dev tox study, GD 6-20	Reduced fetal body weights	6/8 6.7/10 (7/5 x 15/21)	124	1 - (AS) 2.5 – (RD) 10 - (IS) Total: 25	5.0	Saillenfait et al., 2001, Saillenfait et al., 2003
Maternal toxicity	206, rat	2-gen study	Reduced maternal body weights	6/8 6.7/10 7/5	146	1 - (AS) 2.5 – (RD) 5 - (IS) Total: 12.5	11.7	Solomon et al. (1995)

Key: AS = allometric scaling, RD= remaining differences, DR = dose response, IS = intraspecies factor, ED = exposure duration

To derive an inhalation DNEL for the pregnant worker three PODs were selected. The studies were well performed and are considered to be of equal quality by the Dossier Submitter. For this reason, the Dossier Submitter decided to select the lowest resulting DNEL for further use in risk assessment.
In conclusion, an inhalation developmental toxicity DNEL of 5.0 mg/m^3 is derived for pregnant workers based on reduced fetal body weights at the LOAEC in an inhalation developmental toxicity study. This inhalation DNEL is below the inhalation DNEL for the general worker population.

RAC assessment: A NOAEC of 247 mg/m^3 was set based on a statistically significant 5% decrease of the fetal body weight at the next highest dose (LOAEC 494 mg/m^3). The finding is supported by an apparent dose-response at lower dose levels, but the effects on body weights were very slight. The body weight gain of the dams was also affected, with a 19% decreased weight gain over the whole gestation period at 247 and 494 mg/m^3. The effect on the fetal body weight is rather small, but the treatment relationship is supported by finding decreased pup body weights of similar magnitude at the same exposure level in a rat 2-generation study (Solomon et al 1995). Furthermore, in the 2-generation study the effect on the body weight persisted up until weaning, supporting the adversity of the effect. The relevance of the finding is also supported by the observation that effects on body weight are characteristic of NMP toxicity in rats. It is noted that all developmental toxicity studies with inhalation exposure use whole body exposure, which makes the oral contribution to exposure via grooming somewhat unclear. However, mixed exposure via several routes is mainly a problem when droplets or aerosols are being formed, i.e., at concentrations exceeding the vapour saturation concentration, which for NMP is 480-640 mg/m^3. However, exposure through other routes cannot totally be ruled out at the LOAEC of 494 mg/m^3. Overall, RAC supports the proposed NOAEC of 247 mg/m^3.

***Table B.63**: DNEL derivation pregnant worker – dermal*

DNEL (endpoint) DERMAL	NOAEL mg/kg bw	Type of effect at LOAEL	Type of study	Assessment factors[1]	Resulting DNEL mg/kg w/day	Reference
Developmental toxicity	237, rat	live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	Dev tox study, GD 6-15	4 - (AS) 2.5 – (RD) 10 - (IS) Total: 100	2.4	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b
Maternal toxicity	237, rat	Reduced maternal body weight gain	Dev tox study, GD 6-15	4 - (AS) 2.5 – (RD) 5 - (IS) Total: 50	4.8	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b

Key: AS = allometric scaling, RD= remaining differences, DR = dose response, IS = intraspecies factor, ED = exposure duration

To derive a dermal DNEL for the pregnant worker two PODs were selected. The studies were well performed and are considered to be of equal quality by the Dossier Submitter. For this reason, the Dossier Submitter decided to select the lowest resulting DNEL for further use in risk assessment.
In conclusion, a dermal developmental toxicity DNEL of 2.4 mg/kg bw/day is derived for pregnant workers based on NOAEL of 237 mg/kg bw/d and increased fetal mortality, skeletal malformations and other effects at the LOAEL in a dermal developmental toxicity study. This dermal DNEL is below the dermal DNEL for the general worker population.

RAC assessment: The rat dermal developmental toxicity study showed clear evidence of fetal toxicity and malformations at the top dose (750 mg/kg/day), as exemplified by lower (body weight -18%), fewer pups (litter size -17%) and missing sternebrae (63 fetuses affected vs 1 in controls). Although dams also were clearly affected (body weight gain - 28%), the pup effects seem substance-related and not an indirect consequence of maternal toxicity. Thus, RAC supports the dermal NOAEL of 237 mg/kg/day.

Conclusion

The selected DNELs for the calculation of the RCR are presented in Table B.64

Table B.64 *Selected DNELs for the calculation of RCRs*

	Worker (non-pregnant)	Pregnant worker
Inhalation DNEL in mg/m3	10	5.0
Dermal DNEL in mg/kg bw/day	4.6	2.4

	DNEL based on AF=5	
	Workers	Pregnant workers
Inhalation DNEL (mg/m^3)	20	**10**
Dermal DNEL (mg/kg bw/day)	4.6	**4.8**

Derivation of a biological limit value based on biomonitoring

The SCOEL derived a biological limit value (BLV) based on the work by Bader et al. (2007), where a correlation was found between external exposures to air concentrations of NMP and blood concentrations of NMP metabolites 5-HNMP and 2-HMSI. A similar approach could be taken to derive BLVs for NMP based on the inhalation DNELs that were derived above. However, the Dossier Submitter decided not to propose any BLV, since the uncertainties to derive such BLV for the air concentration range of the proposed DNELs are considered to be too large. Required steps with uncertainty are: extrapolation to an air concentration below the test range in Bader et al. (2007), what cut-off value (in other words, what level of conservatism is desired) to select at what period after a work shift for the two metabolites, appraisal of the relation between dermal exposure and BLV and whether or not this relation is sufficiently covered by the correlation between air concentration and blood levels (in other words, is it certain that the BLV based on inhalation exposure is sufficiently protective for dermal exposure).

B.6 Human health hazard assessment of physico-chemical properties

Considered not to be relevant for this Background Document.

B.7 Environmental hazard assessment

Considered not to be relevant for this Background Document.

B.8 PBT and vPvB assessment

Considered not to be relevant for this Background Document.

B.9 Exposure assessment

B.9.1 General discussion on releases and exposure

The Dossier Submitter evaluated the exposure assessments as presented in the registration dossier, but did not attempt to recalculate the exposure estimations using other tools than applied by the registrants. In order to recalculate the worker exposure a more detailed description of the worker tasks and worker environment is needed. In addition, account has to be taken for the very diverse workplaces that are involved in NMP uses. Because such information is not available to the Dossier Submitter and it is impractical to visit all types of workplaces where NMP is used, the exposure estimates as calculated by the registrants in their CSRs, as presented in the registration dossier are used by the Dossier Submitter. The Dossier Submitter took the exposure estimates from the updated version of the registration dossier from the lead registrant and accompanying CSR (November 2012). However, there might be some downstream users of NMP that did not update their dossiers accordingly and still rely on the older version of the CSR (April 2011). The exposure scenarios from the old version of the CSR have not been included in this Background Document.

The registrants used EasyTRA 3.5 (in compliance with ECETOC® Targeted Risk Assessment version 3 (as of July 2012)) to determine the inhalation and dermal exposure of workers to NMP in various exposure scenarios and associated processes (PROCs). If the registrant of the registration dossier derived RCRs[6] above 1, re-iteration of the (exposure) assessment should be performed with higher tier models, till the situation is assessed to be safe (RCRs <1). In that case, Stoffenmanager for the inhalation exposure, and RISKOFDERM for the dermal exposure, respectively, were used to determine the exposure. Since the exact descriptions of tasks of the workers or of the processes are not available to the Dossier Submitter (PROC descriptions are too general and provide little

[6] *In the registration dossier, an inhalation DNEL of 40 mg/m³ was used.*

detail), the risk assessment is based on the exposure estimates provided by the registrant, including the recommendations of the use of risk management measures (RMMs) (see section B.9.1.2.).

With respect to the level of overestimation by using the exposure estiamtes from the registration dossier, it is difficult to provide an estimate for a general level of overestimation, if there is any. Up to date, to our knowledge, there has not been a systematic review of the ECETOC TRA estimations, let alone with focus on the conservativeness. Basically, the default values for each PROC–substance property combination are based on a set of measurements, already in the predecessor EASE 2.0 tool. The defaults for 8h work shifts are based on the 75th to 90th percentile of the measured range of air concentrations per PROC (provided that the OCs indeed apply and are applied correctly). In other words, for 10 to 25 per cent of the cases higher levels were found. In the REACH guidance it is stated that the ECETOC TRA defaults are based on EASE 2.0 and expert judgment from industry. Further it is stated that already in EASE a correction took place for overestimation of exposure as a result of a monitoring bias for 'malpractices', meaning that the measured data were skewed (REACH guidance chapter R14 Occupational exposure estimation). However, the general opinion of occupational hygienists consulted (personal communication) is that without applying PPEs, the ECETOC TRA will provide an overestimation. By how much, they dare not say.

With respect to the effectiveness of the applied RMMs it may be considered that relatively high effectiveness values have been used by default. It is acknowledged that such levels can be achieved, however, occupational hygiene studies have shown that in practice the effectiveness of a single RMM at the workplace show a wide range. E.g. mobile LEV (one of the five LEV categories in the paper), showed a range of -28% to 88% (Fransman et al. 2008) where the defaults used range from 80-95% dependent on the PROC and IND or PROF use.

However, no validation was performed checking whether the first tier approach always results in a conservative estimate or not. Therefore, a common factor by which the true exposure is overestimated cannot be given. To the opionion of the Dossier Submitter, it cannot be concluded even that the estimates obtained are always overestimating the true exposure, because of the rather arbitrary use of the effectiveness of PPEs in the ECETOC TRA tool.

Next to the exposure estimates copied from the CSR, monitoring data were found in literature, in the OECD SIDS dossier (2007) and confidential monitoring data were obtained from stakeholders. The results of the monitoring studies are presented in subsections of B.9.3 and B.9.4. Please note that most monitoring data are generally not representative for the entire sector for several reasons. For example, exposure situations within a sector may differ significantly between exposure sites, because a slightly different product is made requiring different techniques. The exposure monitoring studies are tailor-made to the location to provide the best estimates of the actual exposure at that location, which is in accordance to the guidelines on workplace measurements such as 'Testing Compliance with Occupational Exposure Limits for Airborne Substances' (http://www.arbeidshygiene.nl/~uploads/text/file/2011-12%20BOHS-NVvA%20Sampling%20Strategy%20Guidance.pdf). For this reason, monitoring data cannot be used directly to determine RCRs for an entire sector. On the other hand, monitoring data do provide insight, to be considered with care, on the actual range of exposure levels in a sector indicating what exposure levels are already achievable. It may give an indication whether or not the modelled exposure assessments using the first tier tool are perhaps too conservative or not. Therefore, in the evaluation of the exposure and RCRs the monitoring data will be taken into account in a qualitative way.

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, 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)[7] and the Directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD)[8] further elaborate and expand the general duties in the Framework Directive. Even if NMP is not a carcinogenic or mutagenic substance, the CMD may be of interest, as in 2013 the European Commission will issue a proposal for an amendment of the Directive, expanding its scope to reprotoxic substances cat 1 and 2. Third, some specific legislation pertaining to young workers and pregnant workers applies. In this section, the implications of these three bodies of legislation for NMP will be considered.

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 (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 5 CAD).

The CAD applies not only to classified substances, but also to *any* chemical agent which, whilst not meeting the criteria for classification as dangerous in accordance with (i) and (ii), may, because of its physicochemical, chemical or toxicological properties and the way it is used or is present in the workplace".

The wordings of the CAD, notably "*in every aspect*" and "*any* chemical", make it abundantly clear that NMP falls 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 NMP.

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,
- 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
- 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 safety data sheet in accordance with the provisions of Directive 67/548/EEC or Directive 88/379/EEC[9])" (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 CAD refers to

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[7] Council Directive 1998/24/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 28-6-2007).

[8] Council Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Pb L158)

[9] Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances, to be repealed in 2015 by the CLP Regulation 1272/2008; Directive 88/379/EEC on the classification, packaging and labelling of dangerous preparations, repealed and replaced by Directive 1999/45/EC, which in turn is to be repealed in 2015 by the CLP Regulation 1272/2008. The OSH Directives are currently subject to revision, in order to align OHS regulations with the CLP Regulation (COM(2013) 102 final)

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 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 Directive on Carcinogens and Mutagens 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 NMP 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:

- 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
- adequate ventilation at the source of the risk
- general ventilation

In the realm of 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 safety data sheets.

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

Skin notation

The SCOEL 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 total body burden will be established on a case-by-case basis but may in general be of the order of 10% or more of the uptake from respiratory exposure at the 8 hour TWA. It should be noted that a skin notation relates specifically to dermal absorption of the material (whether as solid, liquid or gas), i.e. it is determined by the toxicokinetic properties of the material in relation to the level at which the OEL is established. It does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation, criteria for which are described in Annex VI of Directive 67/548/EEC.

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/EC.[10] Alignments with the requirements in Regulation 1272/2008 (CLP) are in preparation. The proposed adaption will not influence the scope of the directive.

Specifically, Annex III of Directive 92/58/EC demands that containers used at work for dangerous substances or preparations defined in Directives 67/548/EEC and 88/379/EEC and containers used for the storage of such dangerous substances or preparations, together with the visible pipes containing or transporting dangerous substances and preparations, be labeled (pictogram or symbol against a colored background) in accordance with those Directives. This legislation already applies to the manufacture and use of NMP, and still a risk is determined for most applications of NMP. To our knowledge, no additional measures within this legislation can be taken to reduce the risks due to the exposure to NMP.

Applicability to NMP

It is clear that all of the aforementioned obligations in the worker protection legislation fully apply to any use of NMP in practice, as can also be deducted from Article 2 of REACH which states that the REACH Regulation applies without prejudice to, a.o., 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 NMP for less hazardous substances should be the first measure to be considered. As long as NMP is not, however, listed in Annex XIV or XVII of REACH, it may be questioned whether the substitution of NMP on the basis of the workers protection Directive is to be considered 'reasonable'. The Chemical Agents Directive does leave latitude for the use of NMP, as long as the employer minimizes the 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 NMP 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 organisational 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 NMP "in so far as is *technically* possible" (art. 4 CMD). In this respect, designation of NMP to Annex XVII might be helpful in clarifying what uses of NMP 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.

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[10] *Directive of 24 June 1992 on the minimum requirements for the provision of safety and/or health signs at work.*
[11] *ECJ, June 14 2007, C-127/05, nr. 58, (Commission vs. United Kingdom).*

Protection of young people at work and pregnant workers

In view of its 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 1994/33/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 1994/33/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 R40 (possible risk of irreversible effects), R 46 (may cause heritable genetic damage), R 60 (may impair fertility), and R61 (may cause harm to the unborn child). Alignment with CLP is in preparation, though this will not affect the scope of this directive.

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 NMP. If, however, exposure to harmful conditions may not be precluded, working with NMP 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 1992/85/EEC.[13] Alignment with CLP is in preparation, though this will not affect the scope of this Directive.

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.[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 to the pregnant workers Directive list various specific risks, a.o. working with substances labeled R40 (possible risk of irreversible effects), R 46 (may cause heritable genetic damage). Substances labeled R 60 (may impair fertility), and R61 (may cause harm to the unborn child) are not listed explicitly in the Annexes, but as these are non-exhaustive, it is clear that reprotoxic substances are also indicated. Moreover, the risk phrases 61 (May cause harm to the unborn child), R63 (Possible risk of harm to the unborn child) en R 64 (May cause harm to breast-fed babies) are mentioned in the guidelines on risk assessment developed by the Commission.

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[12] Council Directive 1994/33/EC of 22 June 1994 (Consolidated version 28-6-2007)

[13] 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 27-6-2007)

[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

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 exposure of workers is avoided. If exposure 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 for the whole of the period necessary to protect her safety or health (art. 5 (2)(3)).

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

Plant Protection Product and Biocidal Product legislation

Agrochemicals as specified in the Annex XV SVHC dossier of NMP include insecticides, fungicides, herbicides and seed treatment products. NMP is used as co-formulant in the formulation of agrochemicals and as solvent in the synthesis of active ingredients. These applications of NMP are examples of pesticide or biocide uses. It can be questioned whether the risks in these applications are to be addressed via REACH or by dedicated Plant Protection Products Regulation (PPPR, 1107/2009/EC) or by the Biocidal Product Directive (BPD, 98/8/EC, soon to be replaced by the Biocidal Products Regulation 528/2012/EC).

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 BPD 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. BPD has no specific requirements for co-formulants except for those co-formulants that are substances of concern (SoC). Substances of concern are defined as '*any substance, other than the active substance, which has an inherent capacity to cause an adverse effect to humans, animals or the environment and is present or is produced in a biocidal product in sufficient concentrations to present risks of such effects*' (Milieu ltd, Environmental law and policy 2012). The discussion on the exact criteria of SoC in BPD is ongoing. When a co-formulant is flagged as SoC, a risk assessment will be obligatory both via BPD as via REACH (duplication).

At this moment both the PPPR and the BPD do not limit the use of NMP and according to the registration dossier NMP is 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 XV SVHC dossier of NMP mentions the use of NMP as penetration enhancer in pharmaceuticals and the use as solvent during preparation of pharmaceuticals. It is assumed that these pharmaceuticals are medicinal products, which can be both human and veterinary. 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 and 2011/82/EC) 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 formulation of pharmaceuticals is included in the registration dossier of NMP 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.

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 (RMMs) by the registrant in the updated registration dossier are good occupational hygiene, the use of closed systems (enclosure) and dedicated systems (PROCs 1-2-3-8a), limit on the exposure durations, limit on the NMP concentration in the process, use of local exhaust ventilation (LEV), and the use of gloves (APF5) or the use of gloves in combination with specific training (APF20).

The effectiveness of the LEV is dependent on the process during which it is applied. Its effectiveness for inhalation exposure reduction is for professional users set at 80%, whereas for industrial workers the effectiveness ranges from 90 to 95% exposure reduction. Such effectiveness levels can only be achieved when the LEV is applied properly.

Gloves have an exposure reduction effectiveness of 80% (APF5) to 95% (APF20).

The effectiveness of limiting the exposure duration, or limit on task duration, and limit on NMP concentration is accounted for by assuming a categorical adjustment and linear adjustment, respectively, on the exposure. For example, a PROC wherein NMP is used at a maximum concentration of 25%, the exposure estimate will be multiplied by factor 0.6.

Next to information from the registration dossier, other operational conditions and RMMs may apply to the uses of NMP, which are not described. Operational conditions as post-cleaning materials with water before contacting the materials, avoid spray processes, avoid heating processes, amongst other may reduce the exposure potential. The use of body suits and respiratory protective equipment (RPE) may also be applied as personal protective equipment if other RMMs are not practical. ECETOC guidance on their Targeted Risk Assessment tool (TR093, TR107, TR114) (ECETOC, 2005; 2009; 2012) and ECHA guidance (ECHA 2012b) (Chapter 13 on risk management measures and operational conditions) provide information on how effective such RMMs can be.

B.9.2 Manufacturing

B.9.2.1 Occupational exposure

Manufacturing describes the process of the manufacturing of NMP itself. The manufacturing of other chemicals, mixtures and formulation steps are described under 'use in industrial chemical processes' or 'formulation of preparations'. Manufacturing of NMP is conducted utilizing closed system processes. The process categories assigned to the manufacture of NMP are PROC1, PROC2 and PROC3, where PROC3 is the most 'open' closed system.
Exposure may arise from sampling, technical maintenance and cleaning of the closed systems, which all describe incidental breaching of the system. Sample analysis of NMP, in contrast to taking samples, is supposed to be covered by the exposure scenario 'use in laboratories' and the 'charging and discharging' should cover the distribution and substance transfer of NMP. In those circumstances (especially at elevated temperatures) LEV and gloves (APF 5, 80%) are the RMMs considered. Maintenance and cleaning of the systems are not covered by other exposure scenarios, where exposures may be relevant. Potential exposures may be possible during maintenance activities. NMP is fully soluble in water, allowing thorough cleaning/preparation of equipment prior to maintenance as NMP is partly removed by water rinsing, thereby minimizing potential exposures. In addition, when the potential for exposure to NMP exists during manufacturing or maintenance tasks, proper chemical-specific personal protective equipment (PPE) is specified according to industries (personal communication).

B.9.2.2 Environmental release

Environmental releases were not considered in the Background Document.

B.9.3 Uses by workers in industrial settings

B.9.3.1. General information

Generic uses

Charging and discharging

The charging and discharging exposure scenario describes the distribution processes of NMP, This includes transfer into marine vessels, barges, rail cars, road car transport and IBCs or repacking NMP in drums or packs. Closed or open transfer lines for bulk transports and dedicated fill point for small transport are used. Small amounts are distributed to laboratories. Transfer may occur at elevated temperatures up to 120°C using dedicated or non-dedicated facilities. The processes described are PROC8a, PROC8b and PROC9. The exposure from transfer using closed systems (PROC1, PROC2, and PROC3) is covered by the exposure scenario 'manufacturing of substance' and 'use in industrial chemical processes'.

RMMs in place are gloves (APF5 80%) for all processes and LEV for PROC8a and PROC9 under elevated temperature conditions.

Formulators

The exposure scenario formulation of preparations is a general scenario for all formulation activities covering formulations of coatings, cleaners, dissolving and processing of polymers and the production of membranes. The formulation may occur under elevated conditions up to 120°C for the processes in closed systems (PROC1, PROC2, and PROC3) and up to 60°C for PROC5 (mixing and blending). PROC14 (producing the end-product) already considers elevated temperatures and does not require adaptation for temperature.

In general, if containment is high than no RMMs are required. However, if exposure is likely gloves (APF5 80%) are worn and LEV should be applied according to the registration dossier.

The formulation of coatings (preparations/mixtures) containing NMP includes a wide range of processes undertaken on a variety of scales. Tasks include liquid transfer operations – to and from bulk storage/IBCs (intermediate bulk containers)/drums/smaller containers, mixing in batch or continuous operations, sampling and analysis, storage and cleaning and maintenance operations. Processes may be performed at temperatures close to ambient or up to 120°C. Information from a small number of companies involved in the formulation of different types of coating products including paints and parquet lacquer indicates that the RMMs outlined in the guidance on safe use are in place. For example, liquids are piped between drums and tanks, and LEV and/or general room ventilation is employed. One company indicated that pumps are used for loading of fluids, dissolvers are used for mixing, LEV and Respiratory Protective Equipment (RPE) are employed and protective clothing is used (information from Annex XV SVHC dossier).

Chemical industry processes

Similar to the manufacturing of NMP, the manufacturing of other substances or chemicals describes closed processing systems, wherein NMP is either used as solvent or process chemical. The processes may be under elevated temperatures up to 180°C, leading to higher potential of exposure compared to processes under room temperature. The manufacture of bulk chemicals, fine chemicals, petrochemicals, agrochemicals, and pharmaceuticals are included in this exposure scenario. The processes described are PROC1, PROC2, and PROC3.

Exposure may arise from sampling, technical maintenance and cleaning of the closed systems, which all describe incidental breaching of the system. Sample collection of NMP is supposed to be covered by the exposure scenario 'use in laboratories' and the 'charging and discharging' should cover the distribution and substance transfer of NMP. In those circumstances (especially at elevated temperatures) LEV and gloves (APF 5, 80%) are the RMMs considered. Maintenance and cleaning of the systems are not covered by other exposure scenarios, where exposures may be relevant. In contrast to the manufacturing of NMP, the possible exposure may consist of a mixture of substances.

Jouyban et al. (2010; as cited in Annex XV SVHC dossier) state that NMP is one of the main pharmaceutical co-solvents and that it is an important solvent used in the extraction, purification and crystallisation of drugs. Manufacturing processes in the pharmaceutical sector are tightly controlled in order to achieve the required level of purity of substances used in drugs. In addition, a high level of containment is generally required as most active substances are highly toxic. Pharmaceuticals produced in bulk may be covered by this exposure scenario, however, it is questionable whether the more specialized drugs can be produced under similar conditions.

Little information is available on petrochemical processing. It is assumed that this use will be confined to large, specialist industrial plants where there is a high level of process containment, because of the large bulk processes that take place in petrochemical processing. For this reason, the Dossier Submitter considered that the potential exposure to NMP in petrochemical processing is sufficiently covered by the exposure scenario related to chemical industry processes.

There is little information of manufacturing of agrochemicals specifically. It is expected that the processes are similar as described in this section above.

Importers/Suppliers

See description under generic use: charging and discharging.

Petrochemical industries

See description under generic use: chemical industry processes.

Non-wire coaters

The industrial application of coatings containing NMP includes a wide range of processes undertaken on a variety of scales. Tasks include liquid transfer operations – to and from bulk storage/IBCs/drums/smaller containers, mixing in batch or continuous operations, preparation for application, application by spraying, brushing, roller, and dipping/immersion, film formation or within a fluidised bed system, sampling and analysis, storage and cleaning and maintenance operations. Processes may be performed at temperatures close to ambient or higher up to 100°C (PROC13). In this exposure scenario only the processes not already covered by 'charging and discharging' or 'formulation of preparations' are considered: PROC7, PROC10 and PROC13.

In the registration dossier it is indicated that LEV and gloves (with training) are applied on the workplace. It is anticipated that LEV would be employed in many workplaces at the locations where coating is undertaken, especially where coatings are sprayed. Good general ventilation (70% reduction in inhalation exposure) is a minimum requirement for the use of coatings containing NMP where operations are performed indoors. Protective clothing, gloves and RPE are employed in some workplaces (Annex XV SVHC dossier). Other RMMs include limits on the NMP content of coatings and on the time spent on specific tasks such as manual application and avoidance of handling of wet pieces.

Wire coaters

See description under non-wire coaters.

Cleaners

NMP is used in industrial tank cleaning, the cleaning of small objects in tanks and the manual cleaning of surfaces. Some industrial cleaning processes are undertaken at elevated temperature up to 140°C (PROC13). Activities arising from the use of cleaning products containing NMP that could give rise to exposure include transfer from storage, pouring/unloading from drums or containers, mixing/diluting prior to use, cleaning activities (spraying, brushing, dipping,) and associated cleaning and maintenance of equipment. Different RMMs are likely to be appropriate for different operations under different circumstances, however for the PROCs considered (PROC7, PROC10 and PROC13) both LEV and gloves (with training; APF20 95%) are taken into account, in addition to time restrictions and lower concentrations.

Where cleaning is undertaken on industrial processes, it is possible to contain fluid transfer operations and cleaning operations such as degreasing operations or to employ extract ventilation to minimise inhalation exposures. In the industrial use of cleaning agents containing NMP, RPE fitted with a type A or better filter should be used for operations such as the filling/preparation of equipment, use of high pressure washers and manual application via trigger sprays, dipping, rolling, brushing etc. where exposure by inhalation is likely. It is noted that RPE was not taken into account in the registration dossier. Gloves should be used to limit dermal contact with NMP. For tasks such as spraying, the use of pressure washers and manual application where extensive exposure to NMP is possible, it is desirable to limit the NMP content of the cleaning agents and the length of time dedicated to these tasks on an individual shift (Annex XV SVHC dossier).

The current extent of compliance with the RMMs stipulated in the registration dossier is unknown. Limited information from the questionnaire survey (used to develop the Annex XV SVHC dossier) suggests good compliance in industrial settings. NMP is stored in dedicated tanks or outdoors and workers wear protective coveralls, safety glasses with side shields, helmet, chemical resistant gloves, safety shoes, and an emergency evacuation mask. Another respondent indicated that when the substance is used in solvent based cleaning products, equipment should be suitable for working in an explosive atmosphere and there is a requirement to provide adequate ventilation by LEV and good general extraction where reasonably practicable. If these are not sufficient to maintain concentrations of particulates and solvent vapour below the OEL, the respondent indicated that suitable respiratory protection must be worn (a mask fitted with a type A Filter).

Electronics and semiconductor industries

The process involves the automated production of semiconductor devices in batch processes in dedicated equipment (litho track tools) that is either totally or partially enclosed. “Clean room environment” conditions are applied.

The following main processes are undertaken:
• loading/unloading of wafers to/from automatic enclosed equipment;
• loading/unloading of wafers into partially enclosed equipment;
• maintenance and cleaning of equipment;
• handling and connection of containers;
• sampling.

There is no contact between the workers and NMP during normal semiconductor processing during this unloading process. A high level of containment and use of ventilation is typical in the semiconductor sector (personal communication, ESIA, RIVM questionnaire). The exposure scenario for use in cleaning agents also covers the use as cleaner in semiconductor manufacturing. According to the semiconductor sector, however, the PROC involved are PROC1, 2, 8b, and 9 describing closed systems and dedicated filling and transfer lines. Under no conditions, aerosols may be formed and therefore PROC7 (industrial spraying) is not considered relevant by the semiconductor industry.

Battery industries

See description under non-wire coaters.

Membrane manufacturers

See description under generic use: formulators.

High performance polymer producers

See description under generic use: formulators.

Agricultural chemical industry (synthesis and formulation)

See descriptions under generic uses: chemical industry processes and formulators.

Pharmaceutical industry

See descriptions under generic uses: chemical industry processes and formulators.

Laboratories

Small quantities of NMP are handled in laboratory settings typically within a fume cupboard, on a bench fitted with local exhaust ventilation or under general ventilation. Typical health and safety measures in place in laboratories include the regular maintenance and testing of ventilation systems, careful pouring, replacement of caps/lids on containers after use and wearing suitable gloves. Under REACH there is a specific process category for laboratory use, i.e. PROC15. Gloves should be used where dermal exposure is possible (e.g. during fluid transfer operations), however no gloves are prescribed in the registration dossier.

Functional Fluids

NMP is used as a functional fluid in cable oils, transfer oils, coolants, insulators, refrigerants, and hydraulic fluids in industrial equipment. Exposure may occur during equipment operation, maintenance and related material transfers. It is not known how widely NMP is used in functional fluids or what RMMs are typically in place. The processes described are PROC17 lubrication at high energy conditions and partly open process and PROC18 greasing at high energy conditions. LEV is employed where NMP is used as a functional liquid in open equipment or under high energy conditions (at elevated temperatures, although no longer stated in the registration dossier). Gloves should be used (APF5 80%). No special precautions are required during the operation of closed equipment containing NMP in functional fluids.

Construction industry

The exposure scenario ‘use in construction chemicals’ describes three industrial processes, i.e. PROC10 roller application and brushing, PROC13 dipping of articles, and PROC14 production of articles amongst other by tableting, pelletisation and by compression. However, the exact uses and the resulting exposures are unclear to date, despite communications with stakeholders (November 2012). Regarding the PROCs a relatively high exposure can be expected because the processes describe open processes and active handlings by the worker. Local exhaust ventilation and gloves (APF5 80%) are therefore indicated as RMMs.

Other (consumer)

Not considered in the Background Document.

B.9.3.2 Exposure estimation

B.9.3.2.1 Workers exposure

The exposure estimates for the industrial uses are given in the table below, together with information on the RMMs applied. The exposures were modelled using EasyTRA. EasyTRA generates the inhalation exposure, dermal exposure, and the combined internal body burden exposure. The internal body burden is determined by converting the inhalation exposure (mg/m^3) to an internal exposure by assuming that a worker inhales 10 m^3 during a work shift of 8h, 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 (chapter R14 Occupational exposure estimation).
Although for some exposure scenarios and PROCs RMMs are considered in the calculations, it remains uncertain whether or not those RMMs are indeed applied in practice. For some industrial uses, monitoring data have been provided which are given in the sections below. For most industrial uses, however, there are no monitoring data available. The industrial uses do show some overlap with processes in closed systems and for example how coatings and cleaners are used. The formulations may differ significantly between cleaners and coatings, however, due to their similar use in certain processes a cross-reference may be made between the two industrial uses. It should be noted that no account has been taken for possible consecutive tasks or processes for a worker when a specific process was 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 specific processes, such correction would be impossible to make.

Manufacturers

No specific information is available on exposures at manufacturing sites of NMP. Below the EasyTRA calculated exposures are given.

Table B.65: *Calculated exposures using EasyTRA copied from the registration dossier for manufacture*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Manufacture	1	No	8	1	No	0.04	0.03	0.04
Manufacture	2	No	8	1	No	4.13	1.37	1.96
Manufacture	3	No	8	1	No	12.39	0.69	2.46

Generic uses

Charging and discharging

No specific information is available on exposures during charging and discharging of NMP. Below the EasyTRA calculated exposures are given.

Table B.66: *Calculated exposures using EasyTRA copied from the registration dossier for charging and discharging*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Charging and discharging, industrial	8a	No	4	1	Apf5 (80%)	17.35	2.74	5.22
Charging and discharging, industrial	8b	No	8	1	Apf5 (80%)	14.46	2.74	4.81
Charging and discharging, industrial	9	No	8	1	Apf5 (80%)	14.46	1.37	3.44
Charging and discharging, industrial (elevated temp)	8a	LEV (95%)	4	1	Apf5 (80%)	3.10	1.65	2.09
Charging and discharging, industrial (elevated temp)	8b	No	1	1	Apf5 (80%)	12.91	0.34	2.19
Charging and discharging, industrial (elevated temp)	9	LEV (90%)	4	1	Apf5 (80%)	12.39	0.82	2.59

Formulators

Below the EasyTRA calculated exposures are given for formulators.

Table B.67: *Calculated exposures using EasyTRA copied from the registration dossier for formulators*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Formulation of preparations	1	No	8	1	No	0.04	0.03	0.04
Formulation of preparations	2	No	8	1	No	4.13	1.37	1.96
Formulation of preparations	3	No	8	1	No	12.39	0.69	2.46
Formulation of preparations (up to 60)	5	No	8	1	Apf5 (80%)	20.65	2.74	5.69

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m³)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Formulation of preparations	14	No	8	1	Apf5 (80%)	14.46	0.69	2.75
Formulation of preparations (elevated temp)	1	No	8	1	No	0.04	0.03	0.04
Formulation of preparations (elevated temp)	2	No	8	1	Apf5 (80%)	20.65	0.27	3.23
Formulation of preparations (elevated temp)	3	LEV (90%)	8	1	No	4.13	0.69	1.28
Formulation of preparations (elevated temp)	5	LEV (90%)	8	1	Apf5 (80%)	20.65	2.74	5.69
Formulation of preparations (elevated temp)	14	LEV (90%)	8	1	Apf5 (80%)	20.65	0.69	3.64

There are limited published data for exposure to NMP during its use in the manufacture of glue and adhesives (Bader et al. 2006). The highest level of exposure was associated with cleaning vessels with a shift mean exposure of 15.5 mg/m^3 (approximately 4 ppm). This task was performed manually in the absence of LEV. Biological monitoring indicated a higher than expected systemic exposure to NMP for this individual worker that was attributed to poor compliance with RMMs intended to limit dermal exposure.
According to a producer of high performance polymers, placement of LEV at processes under elevated temparatures was not possible (see also the section on high performance polymer producers). In that case, higher exposures would be anticipated, however confidential monitoring data do not confirm this. Detailed information on the process condition is missing.

***Table B.68**: Inhalation exposure concentrations associated with manufacture of glue / adhesives*

Workplace	Job description	NMP in air TWA (mg/m³)	NMP in air Peak exposure (mg/m³)
Bottling/shipping	Maintenance, foreman	1.0	-
Bottling/shipping	Maintenance	2.8	-
Bottling/shipping	Bottling/shipping	0.9	-
Bottling/shipping	Maintenance, cleaning	2.3	5.9 (42 min)
Production	Mixing, stirrer cleaning	3.4	-
Production	Mixing, stirrer cleaning	6.6	18.7 (19 min)
Production	Vessel cleaning only	15.5	18.0 (42 min), max 85 (5 min)
Both areas, 4 h	Study examiner	-	-
Both areas, 6 h	Study examiner	-	-
Both areas, 8 h	Study examiner	2.8	-

Source: Bader et al. (2006)

More recent unpublished measurement data provided by respondents to the questionnaire and exposure estimates in the registrations indicate that both dermal and inhalation exposures associated with the formulation of coatings containing NMP would be expected to be in the order of 1-7 ppm (4.1 to 29 mg/m^3) for most tasks, provided that appropriate RMMs are employed, although some tasks are associated with moderate exposures (Annex XV SVHC dossier).

Chemical industry processes

Below the EasyTRA calculated exposures are given for chemical industry processes.

Table B.69: *Calculated exposures using EasyTRA copied from the registration dossier for industrial chemical processes*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Industrial chemical processes	1	No	8	1	No	0.04	0.03	0.04
Industrial chemical processes	2	No	8	1	No	4.13	1.37	1.96
Industrial chemical processes	3	No	8	1	No	12.39	0.69	2.46
Industrial chemical processes (elevated temp)	1	No	8	1	No	0.04	0.03	0.04
Industrial chemical processes (elevated temp)	2	LEV (90%)	8	1	Apf5 (80%)	10.33	0.27	1.75
Industrial chemical processes (elevated temp)	3	LEV (90%)	8	1	No	20.65	0.69	3.64

In three monitoring reports, at different work places, NMP air concentrations were measured to be below the 5 mg/m^3 DNEL level (confidential data). The measurements were taken in the period 2000-2005 and in 2012.

Importers/Suppliers

See description under generic use: charging and discharging.

Petrochemical industries

See description under generic use: chemical industry processes.

Non-wire coaters

Below the EasyTRA calculated exposures are given for coaters.

***Table B.70**: Calculated exposures using Stoffenmanager and RISKOFDERM (PROC7) and EasyTRA (PROC10, PROC13) copied from the registration dossier for industrial coaters.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Coatings industrial	7*	LEV (90%)	4	1	Apf20 (95%)	7.96	3.46	4.60
Coatings industrial	7*	LEV (90%)	4	0,5	Apf20 (95%)	18.70	1.73	4.40
Coatings industrial	10	LEV (90%)	8	1	Apf5 (80%)	4.13	5.49	6.08
Coatings industrial	13	LEV (90%)	8	1	Apf5 (80%)	4.13	2.74	3.33
Coatings industrial	13	LEV (90%)	4	1	Apf5 (80%)	12.40	1.64	3.42

** These calculations were performed using Stoffenmanager and RISKOFDERM. For the first calculation of PROC7 it is assumed that the worker is situated in a cabin, limiting the potential inhalation exposure. For the second calculation of PROC7 a limitation of the weight fraction is considered, however the worker is not present in a cabin. The Dossier Submitter notes that the inhalation exposure estimates for PROC13, copied from the registration dossier, are probably mixed up.*

Limited recent measurement data provided by respondents to the questionnaire suggest that current inhalation exposures are in the range of 1 to 7 ppm (4.1 to 28.9 mg/m^3). Inhalation exposure concentrations predicted in the registrations indicate that exposures associated with high temperature coating processes (>20°C above ambient) are likely to be associated with higher levels of exposure than low temperature processes (Annex XV SVHC dossier).

The National Institute of Occupational Safety and Health (NIOSH) has conducted industrial hygiene monitoring of NMP exposure in the United States. In 1996, industrial hygiene samples (personnel and area) were collected at a facility that used a water-based polyurethane coating that was applied to car/truck rubber seals (Mattorano and Trout, 1996). Results for employees working in spray booths ranged from 0.01-1.27 ppm NMP (0.04-5.2 mg/m^3), and 0.01-0.15 ppm (0.04-0.62 mg/m^3) for employees working in the area outside of the spray booth. Area sample results for NMP ranged from 4.5-25 ppm (18.6 – 103 mg/m^3) inside the spray booths to 0.01-0.2 ppm (0.04-0.08 mg/m^3) in the area outside the spray booths.

Worker exposure was also investigated in a screen printing plant, where NMP was detected in concentrations ranging from 7.1 to 22.2 mg/m³ (Auffarth et al. 1988).

In an automobile plant, where NMP is applied as a solvent for varnishes and paints, NMP exposure was determined by biomonitoring its major metabolites 5-HNMP and 2-HMSI in worker-urine samples (Meier et al. 2013). Sixty spot urine samples, preshift and postshift an 8 hour shift, were taken from 14 workers, from the spraying department. Simultaneously, a questionnaire was set out to obtain information on the volunteers, workplace and working tasks and the protective equipment used during those tasks. Three main tasks were considered, i.e. the wipers and packers of the treated panels, the loaders of the spraying system, and the cleaners of the spraying system. The latter two tasks involve working with NMP where loaders use the varnish containing NMP, whereas the cleaners work with cleaning solutions containing NMP up to 100%. The NMP metabolite concentrations in urine, preshift, were in the same range for all tasks. Postshift, the highest urine levels were found in the samples of the cleaners. The table below was adopted from Meier et al. (2013) showing the measured volume (mg/l) and creatinine-related (mg/g creatinine) concentrations of NMP metabolites, where no discrimination between the tasks were made.

***Table B.71**: Biomonitoring data adopted from Meier et al. (2013) for industrial coaters in the automotive sector.*

		Mean	Median (mg l^{-1})	Range	Mean	Median (mg g^{-1} creatinine)	Range
Controls (n=9)							
Postshift	5-HNMP	0.025	< LOD	< LOD-0,07	0.029	<LOD	< LOD-0.09
	2-HMSI	0.033	< LOD	< LOD-0.12	0.025	<LOD	< LOD-0.06
Exposed (n=14)							
Preshift Day 1	5-HNMP	0.74	0.40	0.11-5.06	0.48	0.34	0.14-2.61
	2-HMSI	0.65	0.50	0.24-2.68	0.50	0.37	0.16-1.38
Postshift Day 1	5-HNMP	1.73	0.91	0.12-13.43	1.42	0.91	0.23-8.31
	2-HMSI	0.70	0.51	0.09-2.87	0.64	0.52	0.24-1.70
Preshift Day 2	5-HNMP	3.06	0.58	0.09-25.88	1.72	0.39	0.15-12.50
	2-HMSI	1.42	0.70	0.07-10.00	0.88	0.49	0.04-4.83

Wire coaters

See non-wire coaters for the exposure calculations using EasyTRA. Exposure measurements were performed while handling coated wire at elevated temperatures, stationary measurements of working area and warehouse (storage) and during cleaning operations with PPE (unknown what type of PPE were worn. The exposure levels, respectively, were <1.3, <0.9, <1.3, and 15.2 mg/m^3. No further details are known as the monitoring report was not available to the Dossier Submitter.

Cleaners

Below the EasyTRA calculated exposures are given for cleaners.

***Table B.72**: Calculated exposures using Stoffenmanager and RISKOFDERM (PROC7) and EasyTRA (PROC10, PROC13) copied from the registration dossier for industrial cleaners*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m³)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Cleaning agents, industrial	7*	LEV (95%)	4	1	Apf20 (95%)	7.96	3.46	4.60
Cleaning agents, industrial	7*	LEV (95%)	4	0,5	Apf20 (95%)	18.70	1.73	4.40
Cleaning agents, industrial	10	LEV (90%)	8	1	Apf5 (80%)	4.13	5.49	6.08
Cleaning agents, industrial	13	LEV (90%)	8	1	Apf5 (80%)	4.13	2.74	3.33

** These calculations were performed using Stoffenmanager and RISKOFDERM. For the first calculation of PROC7 it is assumed that the worker is situated in a cabin, limiting the potential inhalation exposure. For the second calculation of PROC7 a limitation of the weight fraction is considered, however the worker is not present in a cabin.*

Recent, although limited, measurement data provided by respondents to the questionnaire suggest that inhalation exposures for tank cleaning in an industrial environment are in the range from 1 to 3 ppm (4.1 to 12.4 mg/m^3) NMP (Annex XV SVHC dossier).

The Concise International Chemical Assessment Document (CICAD, WHO 2001) contains a limited quantity of occupational exposure data that suggested that the OEL (40 mg/m^3) is likely to be currently met during the use of NMP for paint removal. Personal exposure concentrations of NMP for graffiti removers were reported to be up to 10 mg/m^3 as both short peak exposure and 8-h time-weighted average in studies published in 1993 and 2000. It was stated that workers in the paint stripping industry are exposed to NMP concentrations up to 64 mg/m^3 (8-hour time-weighted average TWA) with 1 hour peak concentrations of up to 280 mg/m^3 based in measurements made in 2000.

More recent occupational exposure data for paint removing, conducted as part of a biomonitoring study (Will et al. 2004) showed exposure concentrations of 0.2 to about 1 ppm (0.82 to 4.1 mg/m^3).

In a cross-sectional observation study in Japan at a factory where NMP is used to clean instruments on which resins were sprayed, NMP concentrations were measured in the breathing zone of 15 workers and 15 referent workers (non-exposed subjects) on five consecutive days. The cleaning liquid contained approximately 90% NMP and less than 10% xylene. None of the NMP-workers wore RPE or protective clothing, but did wear disposable thin gloves made of polyethylene. The maximum NMP concentration measured was 0.8 ppm (3.3 mg/m^3). Over five days the mean NMP air concentration in the breathing zone was 0.159 ppm with a standard deviation of 0.110 (0.66 mg/m^3, SD 0.45 mg/m^3). Dermal exposures were not measured. The breakthrough time of the polyethylene gloves was less than 10 minutes with a permeation rate exceeding 0.1 µl/cm^2/min. Urinary samples were taken as well in the study, showing urinary NMP levels of 0.171 mg/l (0.135 mg/l SD) and urinary NMP-creatinine 0.099 mg/g (0.073 mg/g SD) (Nishimura et al. 2009).

Electronics and semiconductor industries

Electronic equipment manufacture

The electronics industry is highly automated and processes are typically enclosed to prevent product contamination as well as limit operator exposure to a range of hazardous substances.

Limited recent measurement data provided by respondents to the questionnaire indicate that current inhalation exposures range from <0.1 to 3 ppm (12.4 mg/m^3) (Annex XV SVHC dossier).

The CICAD (WHO, 2001) contains a limited quantity of occupational exposure data. Measurements reported in 1991 indicated that workers in the microelectronics fabrication industry are exposed to up to 6 mg/m^3 (personal breathing zones; 8-h TWA). Full-shift NMP air concentrations up to 280 mg/m^3 were reported for fixed point measurements when heated NMP (80°C) was being handled but it is unclear whether these measurements were representative of personal exposure concentrations. Exposure concentrations have fallen substantially in most industries over the last two decades (Creely et al. 2007; as cited in Annex XV SVHC dossier).

In a modelling exercise using ART conducted by industry describing production of modern electronics, a median exposure below the DNEL of 5 mg/m^3 was derived, however the interquartile range exceeded that value (confidential data).

Semiconductor industry

Monitoring studies in the semiconductor industry indicated for the various processes that the air concentrations by personal monitoring are below the DNEL of 5 mg/m^3 (personal communication, RIVM questionnaire).

Table B.73: *Semiconductor Activity Types, Descriptions and Reported Exposure Measurement ranges (personal communication ESIA).*

Confidential table was deleted.

A monitoring study, including biomonitoring, showed maximum air concentrations by stationary sampling below the DNEL of 5 mg/m^3. Measurements were performed in 2012 (confidential data).

Battery industries

In a production facility of lithium ion batteries, air concentrations were measured in 2012. Highest concentrations were found during the coating and drying process exceeding the DNEL of 5 mg/m^3 at least two-fold. Other processes were below the DNEL (confidential data).

Membrane manufacturers

See description under generic use: formulator, where air concentrations up to 20.65 mg/m^3 are calculated.

Two monitoring studies were performed in the membrane production industry in 2005 and 2010. The study in 2005 revealed air concentrations exceeding the DNEL of 5 mg/m^3 by approximately 5-fold, where the highest level was fouund during preparation and initiating of the production process. Measurements were taken by personal sampling and stationary sampling. The second study in 2010, showed concentrations below the DNEL, however it should be noted that the monitoring report was poorly described (confidential data).

High performance polymer producers

See description under generic use: formulator, where air concentrations up to 20.65 mg/m^3 are calculated.

NMP measurements were performed in several production facilities of fibres and high tensile yarns (in 2012). Sampling was performed by personal sampling of operators and analysts. NMP concentrations were below the DNEL of 5 mg/m^3 (confidential data).

Agricultural chemical industry (synthesis and formulation)

See the exposure calculations using EasyTRA for the generic uses: chemical industry processes and formulators.

Pharmaceutical industry

See the exposure calculations using EasyTRA for the generic uses: chemical industry processes and formulators.

Laboratories

No specific information is available on exposures at laboratories using NMP. Below the EasyTRA calculated exposures are given.

***Table B.74**: Calculated exposures using EasyTRA copied from the registration dossier for laboratory use*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Laboratory use	15	LEV (90%)	8	1	No	2.07	0.34	0.64

Functional Fluids

No specific information is available on exposures to NMP resulting from the use of functional fluids. Below the EasyTRA calculated exposures are given.

***Table B.75**: Calculated exposures using EasyTRA copied from the registration dossier for industrial use of functional fluids.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Functional fluids, industrial	17	LEV (90%)	8	1	Apf5 (80%)	8.26	5.49	6.67
Functional fluids, industrial	18	LEV (90%)	8	1	Apf5 (80%)	8.26	2.74	3.92

Construction industry

Below the EasyTRA calculated exposures are given for the construction industry using NMP.

***Table B.76**: Calculated exposures using EasyTRA copied from the registration dossier for industrial use of construction chemicals.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Construction chemicals	10	LEV (90%)	8	1	Apf5 (80%)	4.13	5.49	6.08
Construction chemicals	13	LEV (90%)	8	1	Apf5 (80%)	4.13	2.74	3.33
Construction chemicals	14	No	8	1	Apf5 (80%)	14.46	0.69	2.75

The National Institute of Occupational Safety and Health (NIOSH) has conducted industrial hygiene monitoring of NMP exposure in the United States. Industrial hygiene samples (breathing zone samples) of restoration company personnel were taken during the renovation of a residence. The personnel showed airborne concentrations of NMP of 3-4 ppm (12.4 – 16.5 mg/m^3) for an 8-hour time weighted average (TWA) (Kiefer, 1993). These data reflect a sampling period of 140 to 240 minutes, not an 8-hour period. Area sample results showed airborne concentrations of NMP of 3.6 and 7 ppm (14.8 and 28.9 mg/m^3).

B.9.4 Uses by professional workers

B.9.4.1 General information

Manufacturers

Not applicable.

Generic uses

Charging and discharging

Basically the same conditions of use are applicable to the professional use of charging and discharging of substances and mixtures as for the industrial application, with two major differences, i.e. the use does not describe elevated temperature conditions and professionals will not apply LEV. It remains unclear whether or not professionals will apply elevated temperature conditions as well. An additional difference is that the transfer may be at a smaller scale in terms of quantity.

Formulators

Formulation of preparations by professionals is poorly described. Probably after-market mixing and blending is meant here. Process categories PROC3 and PROC5 are mentioned for professionals. According to the registration dossier, gloves are to be used (APF5 80% reduction effectiveness).

Chemical industry processes

Not applicable.

Importers/Suppliers

See charging and discharging.

Petrochemical industries

Not applicable.

Non-wire coaters

The professional application of coatings containing NMP includes tasks such as liquid transfer operations – to and from IBCs/drums/smaller containers, mixing in containers and preparation prior to application (note that transfer operations are likely at much lower scales than in industrial settings), application by spraying, brushing, roller, dipping/immersion and pouring, sampling and analysis, storage and cleaning and maintenance operations. In the registration dossier only application by roller or brush is considered (PROC13, gloves (APF5 80%)), however, it is likely that coatings will be sprayed by professionals, as well.

Typically the professional use of coatings such as paints will occur at a variety of locations such that total containment and/or dedicated extract ventilation would be extremely difficult to achieve. The quantities of NMP used are likely to be smaller than in many industrial environments. The current deployment of RMMs is unknown but it is anticipated that standards of ventilation are likely to be variable. Similarly compliance with recommended PPE – coveralls, gloves and respirators – is likely to be variable, with potentially low levels of compliance where work is undertaken by individuals or small numbers of workers working in isolation with limited supervision. Ideally coatings should be applied outside or, if applied indoors, a good standard of general ventilation should be used. In the absence of extract ventilation, it would be desirable to use a respirator (Type A filter or better) while working with coatings containing NMP, although this is not mentioned in the registration dossier. Gloves should be used to limit dermal exposure. For tasks such as spraying, dipping, immersion or pouring and hand application of coatings where extensive dermal

and inhalation exposure are possible, it is desirable to limit the NMP content of coatings and the length of time dedicated to these tasks on an individual shift (Annex XV SVHC dossier).

Wire coaters

Not applicable.

Cleaners

This specific use is no longer included in the registration dossier. However, it is expected that paint strippers and graffiti removers may still contain NMP and used by professionals. It is acknowledged that such uses may be phased out. The information below is obtained from the Annex XV SVHC dossier.

NMP is used in a wide range of cleaning products including paint strippers and products developed for removing graffiti, amongst others. NMP is also used in industrial tank cleaning, the cleaning of small objects in tanks and the manual cleaning of surfaces. Some industrial cleaning processes are undertaken at elevated temperature. Activities arising from the use of cleaning products containing NMP that could give rise to exposure include transfer from storage, pouring/unloading from drums or containers, mixing/diluting prior to use, cleaning activities (spraying, brushing, dipping, automated and manual wiping) and associated cleaning and maintenance of equipment. Different RMMs are likely to be appropriate for different operations under different circumstances and there is little information about the current deployment of RMMs.

Where cleaning is undertaken on industrial processes, it is possible to contain fluid transfer operations and cleaning operations such as degreasing operations or to employ extract ventilation to minimise inhalation exposures. Professional cleaning should only be undertaken where there is good ventilation, the filling of equipment should be undertaken outdoors and windows and doors should be opened during the manual cleaning of surfaces. In both the industrial and professional use of cleaning agents containing NMP, RPE fitted with a type A or better filter should be used for operations such as the filling/preparation of equipment, use of high pressure washers and manual application via trigger sprays, dipping, rolling, brushing etc. where exposure by inhalation is likely. Gloves should be used to limit dermal contact with NMP. For tasks such as spraying, the use of pressure washers and manual application where extensive exposure to NMP is possible, it is desirable to limit the NMP content of the cleaning agents and the length of time dedicated to these tasks on an individual shift.

The current extent of compliance with the RMMs stipulated in the registration dossier is unknown. Limited information from the questionnaire survey suggests good compliance in industrial settings. One of the respondents, a provider of services in tank cleaning indicated that NMP is stored in a dedicated tank or IBC outdoors and that workers wear protective coveralls, safety glasses with side shields, helmet, chemical resistant gloves, safety shoes, and an emergency evacuation mask. Another respondent indicated that when the substance is used in solvent based cleaning products, equipment should be suitable for working in an explosive atmosphere and there is a requirement to provide adequate ventilation by LEV and good general extraction where reasonably practicable. If these are not sufficient to maintain concentrations of particulates and solvent vapour below the OEL, the respondents mentioned that suitable respiratory protection must be worn (a mask fitted with a type A Filter).

Electronics and semiconductor industries

Not applicable.

Battery industries

Not applicable.

Membrane manufacturers

Not applicable.

High performance polymer producers

Not applicable.

Agricultural chemical industries (formulation)

NMP is used in agrochemicals applied by manual or machine spraying, smokes and fogging and exposure may occur during fluid transfers/pouring from containers, mixing, equipment clean downs and disposal. The spray process by professionals is described by PROC11. The other processes are covered by other exposure scenarios, such as 'charging and discharging'. It is advised that tasks should be limited to less than 4 hours/shift with the exception of spraying and fogging by machine and storage. A protective coverall with 97 % efficiency and a respirator with at least x10 protection are recommended for spraying and fogging by manual application and spraying and fogging by machine should be done from a vented cab supplied with filtered air under positive pressure. Gloves should be used for all tasks where dermal contact is possible, equipment should be drained prior to cleaning and maintenance and NMP must be stored in a closed containers. However, the registration dossier calculates the exposure without taking into account RMMs, except for a concentration limit of 5%.

Pharmaceutical industries

Not applicable.

Laboratories

Small quantities of NMP are handled in laboratory settings typically within a fume cupboard, on a bench fitted with local exhaust ventilation or under general ventilation. Typical health and safety measures in place in laboratories include the regular maintenance and testing of ventilation systems, careful pouring, replacement of caps/lids on containers after use and wearing suitable gloves. Under REACH there is a specific process category for laboratory use, i.e. PROC15. Gloves should be used where dermal exposure is possible (e.g. during fluid transfer operations), however no gloves are prescribed in the registration dossier. A less effective LEV was assumed for professional workers compared to LEV for industrial workers, 80% effectiveness versus 90%.

Functional Fluids

NMP is used as a functional fluid in cable oils, transfer oils, coolants, insulators, refrigerants, and hydraulic fluids in industrial equipment. Exposure may occur during equipment operation, maintenance and related material transfers. It is not known how widely NMP is used in functional fluids or what RMMs are typically in place. The processes described are PROC17 lubrication at high energy conditions and partly open process and PROC18 greasing at high energy conditions. LEV is employed where NMP is used as a functional liquid in open equipment or under high energy conditions (at elevated temperatures, although no longer stated in the registration dossier). Gloves should be used (APF5 80%). For professionals specifically PROC20 is also considered describing heat and pressure transfer fluids in dispersive, professional use but closed systems, such as motor or engine oils. No special precautions are required during the operation of closed equipment containing NMP in functional fluids. In professional use, concentrations of NMP are generally lower.

Construction industry

This specific use is no longer included in the registration dossier, however, it is expected that for some applications such as roofing and water-proofing will occur with NMP. Industry indicated that based on a consultation with downstream users that NMP as additive in cement, concrete and

asphalt has not been used for a number of years. The information below is derived from the Annex XV SVHC dossier.

NMP is used in surface coatings and binders in road and construction activities including paving, manual mastic and in the application of roofing and water-proofing membranes. Tasks are performed outside and include drum/batch transfers, rolling, brushing, machine application of bitumen cutbacks, machine application by spraying/fogging, dipping, pouring and equipment cleaning. RPE (Type A filter or better) is recommended where transfers are carried out at temperatures ≥20°C above ambient temperatures, rolling, brushing and for machine application by spraying/fogging. Other measures that can reduce exposures include the use of long handled tools, automation of the application of bitumen cutbacks and operator training to stay upwind/keep distance from source. In addition, the time spent on individual tasks such as spraying that may give rise to elevated exposures should be limited. Equipment must be drained prior to cleaning and maintenance and NMP stored in sealed containers. Suitable gloves should be worn where dermal contact is possible (Annex XV SVHC dossier).

B.9.4.2 Exposure estimation

B.9.4.2.1 Professional Workers exposure

The exposure estimates for the professional uses are given in the table below, together with information on the RMMs applied. The registrants provided the calculations and information on the RMMs. The exposures were modelled using EasyTRA. For most professional uses there are no measurement data available. Although for some exposure scenarios and PROCs RMMs are considered in the calculations, it remains uncertain whether or not those RMMs are indeed applied in practice. Furthermore, it should be noted that some professional uses were not calculated in the update registration dossier as they were no longer covered, leaving out elevated temperature conditions and spray conditions for coatings and left out cleaning agents and road and construction use for professional use with NMP.

Generic use

Charging and discharging

No specific information is available on exposures during charging and discharging of NMP. Below the EasyTRA calculated exposures are given.

***Table B.77**: Calculated exposures using EasyTRA copied from the registration dossier for professional charging and discharging.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m³)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Charging and discharging, professional	8a	No	1	1	Apf5 (80%)	14.46	2.74	4.81
Charging and discharging, professional	8b	No	4	1	Apf5 (80%)	17.35	2.74	5.22
Charging and discharging, professional	9	No	4	1	Apf5 (80%)	17.35	1.37	3.85

Formulators

No specific information is available on exposures formulating mixtures using NMP. Below the EasyTRA calculated exposures are given.

***Table B.78**: Calculated exposures using EasyTRA copied from the registration dossier for professional formulators.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Formulation of preparations	3	No	8	1	Apf5 (80%)	12.39	0.14	1.91
Formulation of preparations	5	No	4	1	Apf5 (80%)	17.35	2.74	5.22

Importers/Suppliers

See charging and discharging.

Non-wire coaters

No specific information is available on exposures to NMP during coating. Below the EasyTRA calculated exposures are given.

***Table B.79**: Calculated exposures using EasyTRA copied from the registration dossier for professional coaters.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Coatings professional	13	No	8	0,5	Apf5 (80%)	14.46	1.37	3.44

Cleaners

Limited recent measurement data provided by respondents to the questionnaire suggest that inhalation exposures for tank cleaning in an industrial environment are low.

The CICAD (2001) contains a limited quantity of occupational exposure data that suggested that the OEL(40 mg/m^3) is likely to be currently met during the use of NMP for paint removal. Personal exposure concentrations of NMP for graffiti removers were reported to be up to 10 mg/m^3 as both short peak exposure and 8-h time-weighted average in studies published in 1993 and 2000. It was stated that workers in the paint stripping industry are exposed to NMP concentrations up to 64 mg/m^3 (8-hour time-weighted average TWA) with 1 hour peak concentrations of up to 280 mg/m^3 based in measurements made in 2000. Given a trend of decreasing exposure concentrations in most workplace environments in the last years (Creely et al. 2007; as cited in Annex XV SVHC

dossier) it is expected that exposure to professional cleaners will decrease as well. In the recently update registration dossier (November 2012) the use of NMP in cleaning agents for professional use was not mentioned anymore.

Agricultural chemical industries (formulation)

No specific information is available on exposures to NMP from the use of agrochemicals containing NMP. Below the EasyTRA calculated exposures are given.

***Table B.80**: Calculated exposures using Stoffenmanager and RISKOFDERM copied from the registration dossier for use in agrochemicals*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Agrochemicals, professional	11*	No	8	0,05	No	2.97	2.21	2.63
Agrochemicals, professional	11*	No	8	0,05	No	5.27	5.38	6.13

** Exposures were calculated under the assumption that the worker is inside a cabin, located outside (first PROC11) or inside without the use of a cabin (second PROC11). In both cases it is assumed that the worker is segregated from the source of exposure.*

Laboratories

No specific information is available on exposures at laboratories using NMP. Below the EasyTRA calculated exposures are given.

***Table B.81**: Calculated exposures using EasyTRA copied from the registration dossier for use in laboratories.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m^3)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Laboratory use, professional	15	LEV (80%)	8	1	No	4.13	0.34	0.93

Functional Fluids

No specific information is available on exposures to NMP from the use of functional fluids containing NMP. Below the EasyTRA calculated exposures are given.

***Table B.82**: Calculated exposures using EasyTRA copied from the registration dossier for professional use of functional fluids.*

Name	PROC	Ventilation	Duration (max. hours/day)	Concentration (weight fraction)	Gloves (protection factor)	Exposure estimate long-term inhalative (mg/m³)	Exposure estimate long-term systemic dermal (mg/kg bw/day)	Exposure estimate combined (mg/kg bw/day) (worst case internal body burden)
Functional fluids, professional	17	No	8	0,25	Apf5 (80%)	15.49	1.37	3.58
Functional fluids, professional	17	LEV (80%)	4	0,25	Apf5 (80%)	6.20	1.37	2.26
Functional fluids, professional	18	LEV (80%)	4	0,25	Apf5 (80%)	6.20	0.69	1.57
Functional fluids, professional	20	No	8	1	No	20.65	1.71	4.67

B.9.5 Uses by consumer products

Not covered in this Background Document.

B.10 Risk characterisation

The risk characterisation was performed using the exposure estimates from the registration dossier and the DNELs derived in this document by the Dossier Submitter as shown in the table below. Risk characterisation ratios are presented in the tables below for the industrial and professional uses respectively. The RCRs are given for the individual routes of exposure and the combined exposure. No account was taken for the fact that some processes do not span a full working day.

***Table B.83:** DNELs to be used in the calculation of RCRs*

	Worker (non-pregnant)	Pregnant worker
Inhalation DNEL in mg/m3	10	5.0
Dermal DNEL in mg/kg bw/day	4.6	2.4

In the opinion of RAC, the DNELs calculated for pregnant workers should be used for all workers.

	Workers, including pregnant
Inhalation DNEL in mg/m3	10.0
Dermal DNEL in mg/kg bw/day	4.8

The RCRs derived by the Dossier Submitter are in general higher than 1, even for those processes which are relatively 'closed'. Processes described by PROC1 and PROC2 and laboratory use appear to have the lowest risks, which can be related to high level of containment or small scale use of

NMP. Processes with a lower level of containment, elevated temperatures and open high energy processes seem to show the highest RCRs even though in some cases PPE is taken into account. Remarkably, the RCRs for professional uses are not much higher than for industrial uses. The lack of information on the uses at elevated temperatures and some open processes, such as the use as cleaner by professionals, may explain the relatively low RCRs for professionals in comparison to the RCRs for industrial uses.

RCRs > 1 concludes that the described use presents a risk to the worker, but the derived RCRs should be evaluated carefully for the following reasons:

- In the registration dossier, no RCRs > 1 were found and therefore for some process descriptions there was no need to specify RMMs, because the calculated exposure is already below the DNEL used by the registrant. The risk characterisation ratios in the tables above have been determined by comparing the exposure estimates obtained from registration dossiers and the DNELs derived by the Dossier Submitter. It is therefore anticipated that for some processes the registrant would have described additional RMMs, if applicable in real life, and to take these RMMs into account to obtain exposure estimates below the DNEL.
- Furthermore it should be noted that the exposure estimates are first tier exposure estimates, being somewhat conservative in nature. Where possible, monitoring data were taken into consideration to 'evaluate' or compare with the 'conservativeness' of the EasyTRA exposure estimates. It is assumed that the monitoring data provide a realistic view of the exposure to NMP 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.

The possibilities for each ES-PROC combination to apply (additional) RMMs are different. It is taken into account that for most professional uses some RMMs cannot be applied. **Therefore, a qualitative evaluation of the RCRs per ES is given below, where an indication is given of the risks when performing these tasks, notwithstanding that without any additional information the conclusion remains that in case of RCRs > 1 risk are insufficiently controlled.**

B.10.1 RCRs – industrial uses

In the following sections, the RCR values calculated using DNEL values derived by RAC are presented in text boxes.

Manufacturers

RCRs for PROC2 and PROC3 are slightly higher than 1 for general workers and up to 3 for pregnant workers. However, besides the closed batch system there are no RMMs considered by the registrant, whereas such measures could be easily implemented and in many cases are already in place. Due to the conservativeness of the EasyTRA output, the closed batch systems applied and remaining options for RMMs such as applying LEV and gloves, the manufacturing of NMP is not expected to present a safety concern for workers and pregnant workers.

Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EasyTRA output is indeed a conservative estimate and therefore support the Dossier Submitter's conclusion that risks are expected to be sufficiently controlled.

Table B.84: *Industrial worker-RCR for manufacture.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Manufacture	1	0.00	0.01	0.01
Manufacture	2	0.41	0.30	0.71
Manufacture	3	1.24	0.15	1.39

Table B.85: *Industrial worker-RCR pregnant for manufacture*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Manufacture	1	0.01	0.01	0.02
Manufacture	2	0.83	0.57	1.40
Manufacture	3	2.48	0.29	2.77

Conclusion: Risks sufficiently controlled.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Manufacture	1	0.004	0.006	0.01
Manufacture	2	0.41	0.29	0.70
Manufacture	3	1.24	0.14	1.38

Table : Industrial worker, including pregnant, RCR for manufacture, based on exposure presented in Table B 65

Conclusion: Risks related to exposure are not sufficiently controlled for PROC 3.

Generic Uses

Charging and discharging

General workers are not expected to be at risk when performing charging and discharging tasks in industrial settings when performed under room temperatures. It is noted that processes at undedicated facilities presents a RCR > 1 for inhalation, but it is considered that these risks can be controlled easily by LEV as is done for undedicated facilities at elevated temperatures. At elevated temperatures, there is one process activity (PROC9) for which RMMs are already in place, i.e. limited working hours, LEV and gloves, and where a RCR > 1 is derived. For this particular process risks may not be sufficiently controlled. The same conclusion can be drawn for pregnant workers, where it should be noted that the risks are approximately 2-fold higher, but still may be controlled sufficiently when LEVs are placed.

Table B.86: *Industrial worker-RCR for charging and discharging*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Charging and discharging, industrial	8a	1.74	0.60	2.33
Charging and discharging, industrial	8b	1.45	0.60	2.04
Charging and discharging, industrial	9	1.45	0.30	1.74
Charging and discharging, industrial (elevated temp)	8a	0.31	0.36	0.67
Charging and discharging, industrial (elevated temp)	8b	1.29	0.07	1.36
Charging and discharging, industrial (elevated temp)	9	1.24	0.18	1.42

Table B.87: *Industrial worker-RCR pregnant for charging and discharging*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker

Charging and discharging, industrial	8a	3.47	1.14	4.61
Charging and discharging, industrial	8b	2.89	1.14	4.03
Charging and discharging, industrial	9	2.89	0.57	3.46
Charging and discharging, industrial (elevated temp)	8a	0.62	0.69	1.31
Charging and discharging, industrial (elevated temp)	8b	2.58	0.14	2.72
Charging and discharging, industrial (elevated temp)	9	2.48	0.34	2.82

Conclusion: Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs. Dermal exposure may be sufficiently controlled when appropriate protection is worn in combination with training and/or supervision.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Charging and discharging, industrial	8a	1.74	0.57	2.31
Charging and discharging, industrial	8b	1.45	0.57	2.02
Charging and discharging, industrial	9	1.45	0.29	1.74
Charging and discharging, industrial (elevated temp)	8a	0.31	0.34	0.65
Charging and discharging, industrial (elevated temp)	8b	1.29	0.07	1.36
Charging and discharging, industrial (elevated temp)	9	1.24	0.17	1.41

Table : Industrial worker, including pregnant, RCR for charging and discharging, based on exposure presented in Table B 66

Conclusion: Risks related to exposure are not adequately controlledfor most tasks.

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Formulators

RCRs found for formulations of mixtures range up to 2.66 (RCR combined exposure) for workers and 6.18 (RCR combined exposure) for pregnant workers. These RCRs were found for PROC5 (mixing and blending) at temperatures up to 60°C without LEV and at temperatures up to 125°C with LEV. Risks are mainly driven by inhalation exposure as calculated by EasyTRA. Measurement data concerning the formulation of adhesives and coatings show air concentrations in the same range as the calculated values (see section B.9.3.2.). High concentrations were found when proper placement of LEV was not possible. RCRs > 1 are found when processes occur under elevated temperatures even with RMMs considered.

Table B.88: *Industrial worker-RCR for formulators.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	1	0.00	0.01	0.01
Formulation of preparations	2	0.41	0.30	0.71
Formulation of preparations	3	1.24	0.15	1.39
Formulation of preparations (up to 60)	5	2.07	0.60	2.66
Formulation of preparations	14	1.45	0.15	1.60
Formulation of preparations (elevated temp)	1	0.00	0.01	0.01
Formulation of preparations (elevated	2	2.07	0.06	2.12

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
temp)				
Formulation of preparations (elevated temp)	3	0.41	0.15	0.56
Formulation of preparations (elevated temp)	5	2.07	0.60	2.66
Formulation of preparations (elevated temp)	14	2.07	0.15	2.22

Table B.89: *Industrial worker-RCR pregnant for formulators.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	1	0.01	0.01	0.02
Formulation of preparations	2	0.83	0.57	1.40
Formulation of preparations	3	2.48	0.29	2.77
Formulation of preparations (up to 60)	5	4.13	1.14	5.27
Formulation of preparations	14	2.89	0.29	3.18
Formulation of preparations (elevated temp)	1	0.01	0.01	0.02
Formulation of preparations (elevated temp)	2	4.13	0.11	4.24
Formulation of preparations (elevated temp)	3	0.83	0.29	1.11
Formulation of preparations (elevated temp)	5	4.13	1.14	5.27
Formulation of preparations (elevated temp)	14	4.13	0.29	4.42

Conclusion: Risks of NMP can be controlled at room temperature with proper RMMs in place. At elevated temperatures, the risks from inhalation exposure may not be sufficiently controlled even with RMMs.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	1	0.004	0.006	0.01
Formulation of preparations	2	0.41	0.29	0.70
Formulation of preparations	3	1.24	0.14	1.38
Formulation of preparations (up to 60)	5	2.07	0.57	2.64
Formulation of preparations	14	1.45	0.14	1.59
Formulation of preparations (elevated temp)	1	0.004	0.006	0.01
Formulation of preparations (elevated temp)	2	2.07	0.06	2.13
Formulation of preparations (elevated temp)	3	0.41	0.14	0.55
Formulation of preparations (elevated temp)	5	2.07	0.57	2.64
Formulation of preparations (elevated temp)	14	2.07	0.14	2.21

Table : Industrial worker, including pregnant, RCR for formulators, based on exposure presented in Table B 67

Conclusion: Risks related to exposure are not adequately controlled for most tasks. Risks can be controlled with use in closed systems. At elevated temperatures, the risks from inhalation exposure may not be sufficiently controlled even with use of LEV.

Chemical industry processes

The RCRs for PROC2 and PROC3 are slightly higher than 1 for general workers and up to 3 for pregnant workers. However, besides the closed batch system there are no RMMs considered by the registrant, whereas such measures could be easily implemented and in many cases already in place. Due to the conservativeness of the EasyTRA output, the closed batch systems applied and remaining options for RMMs such as LEV and gloves, the use of NMP in chemical processes **under room temperature** is not expected to present a risk for workers and pregnant workers.

Chemical processes described as PROC3, closed batch systems **under elevated temperatures,** lead to much higher exposures, even taken into account LEV and gloves (80%). For processes **under elevated temperatures,** the use of NMP may not be without risk, leaving little room for reducing the exposure by personal protection as these are already in place. Preferably, a closed system with a higher level of containment should be applied to reduce risks if possible.

Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EasyTRA output is indeed a conservative estimate. However, it is unclear whether conditions under elevated temperatures were considered in the measurements. In one of the reports, it is mentioned that the regeneration of the substance took place at 50°C. The exposure scenario described includes temperatures up to 190°C, which seemingly are not covered by monitoring data. The Dossier Submitter is therefore of the opinion that chemical processes under elevated temperatures may not be without risk.

Table B.90: *Industrial worker-RCR for industrial chemical processes.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Industrial chemical processes	1	0.00	0.01	0.01
Industrial chemical processes	2	0.41	0.30	0.71
Industrial chemical processes	3	1.24	0.15	1.39
Industrial chemical processes (elevated temp)	1	0.00	0.01	0.01
Industrial chemical processes (elevated temp)	2	1.03	0.06	1.09
Industrial chemical processes (elevated temp)	3	2.07	0.15	2.22

Table B.91: *Industrial worker-RCR pregnant for industrial chemical processes.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Industrial chemical processes	1	0.01	0.01	0.02
Industrial chemical processes	2	0.83	0.57	1.40
Industrial chemical processes	3	2.48	0.29	2.77
Industrial chemical processes (elevated temp)	1	0.01	0.01	0.02
Industrial chemical processes (elevated temp)	2	2.07	0.11	2.18
Industrial chemical processes (elevated temp)	3	4.13	0.29	4.42

Conclusion: Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Industrial chemical processes	1	0.004	0.006	0.01
Industrial chemical processes	2	0.41	0.29	0.70
Industrial chemical processes	3	1.24	0.14	1.38

Importers/Suppliers

See generic use:charging and discharging.

Petrochemical industries

See generic use: chemical industry process.

Non-wire coaters

Air concentrations and personal samples taken in coating industry resulted in similar air concentrations as EasyTRA estimates, being slightly higher than the DNEL derived for general workers. For this reason, risks for general workers cannot be excluded (RCRs slightly above 1), although it is unknown what RMMs were in place at the specific facility where measurements were taken. The EasyTRA calculation took into account LEV and gloves leaving little room for additional RMMs. The dermal exposure could be controlled by applying additional measures regarding training and supervision of applying protective wear.
The RCRs for pregnant workers are approximately 2-fold higher indicating that risks may not be sufficiently controlled.

Table B.92: *Industrial worker-RCR for non-wire coaters*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings industrial	7	0.80	0.75	1.55
Coatings industrial	7	1.87	0.38	2.25
Coatings industrial	10	0.41	1.19	1.61
Coatings industrial	13	0.41	0.60	1.01
Coatings industrial	13	1.24	0.36	1.60

Table B.93: *Industrial worker-RCR pregnant for non-wire coaters.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings industrial	7	1.59	1.44	3.03
Coatings industrial	7	3.74	0.72	4.46
Coatings industrial	10	0.83	2.29	3.11
Coatings industrial	13	0.83	1.14	1.97
Coatings industrial	13	2.48	0.68	3.16

Conclusion: Risks for general and pregnant workers may not be sufficiently controlled. As mentioned above, under strict conditions the dermal risks may be sufficiently controlled.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings industrial	7	0.80	0.72	1.52
Coatings industrial	7	1.87	0.36	2.23
Coatings industrial	10	0.41	1.14	1.55
Coatings industrial	13	0.41	0.57	0.98
Coatings industrial	13	1.24	0.34	1.58

Table : Industrial worker, including pregnant, RCR for non-wire coaters, based on exposure presented in Table B 70

Conclusion: Risk related to exposure to NMP is not adequately controlled for most tasks

Wire coaters

See non-wire coaters.

Cleaners

Measurement data of NMP air concentrations and EasyTRA calculations are in the same range, where older measurements showed concentrations above the general worker inhalation DNEL. More recent measurements in Japan, showed lower concentrations up to 6 mg/m^3 exceeding the pregnant worker inhalation DNEL of 5 mg/m^3.

Table B.94: *Industrial worker-RCR for cleaners.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Cleaning agents, industrial	7	0.80	0.75	1.55
Cleaning agents, industrial	7	1.87	0.38	2.25
Cleaning agents, industrial	10	0.41	1.19	1.61
Cleaning agents, industrial	13	0.41	0.60	1.01

Table B.95: *Industrial worker-RCR pregnant for cleaners.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Cleaning agents, industrial	7	1.59	1.44	3.03
Cleaning agents, industrial	7	3.74	0.72	4.46
Cleaning agents, industrial	10	0.83	2.29	3.11
Cleaning agents, industrial	13	0.83	1.14	1.97

Conclusion: Risks for pregnant workers may not be sufficiently controlled. Under strict conditions the dermal risks may be sufficiently controlled, by applying additional measures such as training and supervision of the application of protective wear.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Cleaning agents, industrial	7	0.80	0.72	1.52
Cleaning agents, industrial	7	1.87	0.36	2.23
Cleaning agents, industrial	10	0.41	1.14	1.55
Cleaning agents, industrial	13	0.41	0.57	0.98

Table : Industrial worker, including pregnant, RCR for cleaners, based on exposure presented in Table B 72

Conclusion: Risk related to exposure to NMP is not adequately controlled for most tasks

Electronics and semiconductor industry

See cleaners.
It must be noted that the electronics and semiconductor industries have indicated that the exposure estimates derived for the cleaning industry do not reflect their industry as different operational conditions apply, such as clean room conditions and no spraying processes. The Dossier Submitter obtained a limited number of monitoring data which would result in RCRs < 1 for inhalation exposure, but the data may not be representative for the whole electronics and

semiconductor sector. Under the working conditions described by the semiconductor industry it is perceived that risks may be sufficiently controlled within this sector.

Battery industries

See non-wire coaters.

Membrane manufactures

See generic use: formulators.

High performance polymer producers

See generic use: formulators.

Agricultural chemical industries

See generic uses: chemical industry processes and formulators.

Pharmaceutical industry

See generic uses: chemical industry processes and formulators.

Laboratories

Risks are sufficiently controlled.

Table B.96: *Industrial worker-RCR for laboratories.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use	15	0.21	0.07	0.28

Table B.97: *Industrial worker-RCR pregnant for laboratories*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use	15	0.41	0.14	0.56

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use	15	0.21	0.07	0.28

Table : Industrial worker, including pregnant, RCR for laboratories, based on exposure presented in Table B 74

Conclusion: Risk related to exposure to NMP is adequately controlled.

Functional Fluids

The risks for general workers seem to be sufficiently controlled if one considers that the EasyTRA calculations are conservative. The RCRs for pregnant workers however are approximately 2-fold higher indicating that risks may not be sufficiently controlled even with current RMMs in place.

Table B.98: *Industrial worker-RCR for functional fluids*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, industrial	17	0.83	1.19	2.02
Functional fluids, industrial	18	0.83	0.60	1.42

Table B.99: *Industrial worker-RCR pregnant for functional fluids.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, industrial	17	1.65	2.29	3.94
Functional fluids, industrial	18	1.65	1.14	2.79

Conclusion: Risks for pregnant workers may not be sufficiently controlled. Under strict conditions the dermal risks may be sufficiently controlled, by applying additional measures such as training and supervision of the application of protective wear.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, industrial	17	0.83	1.14	1.97
Functional fluids, industrial	18	0.83	0.57	1.41

Table : Industrial worker, including pregnant, RCR for functional fluids, based on exposure presented in Table B 75

Conclusion: Risk related to exposure to NMP is not adequately controlled.

Construction industry

The risks for general workers seem to be sufficiently controlled if one considers that the EasyTRA calculations are conservative and LEV is also used for PROC14, as is the case for the other processes mentioned. The RCRs for pregnant workers however are approximately 2-fold higher indicating that risks may not be sufficiently controlled even with current RMMs in place.

Table B.100: *Industrial worker-RCR for construction chemicals*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Construction chemicals	10	0.41	1.19	1.61
Construction chemicals	13	0.41	0.60	1.01
Construction chemicals	14	1.45	0.15	1.60

Table B.101: *Industrial worker-RCR pregnant for construction chemicals.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Construction chemicals	10	0.83	2.29	3.11
Construction chemicals	13	0.83	1.14	1.97
Construction chemicals	14	2.89	0.29	3.18

Conclusion: Risks for pregnant workers may not be sufficiently controlled. Under strict conditions the dermal risks may be sufficiently controlled, by applying additional measures such as training and supervision of the application of protective wear.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Construction chemicals	10	0.41	1.14	1.55
Construction chemicals	13	0.41	0.57	0.98
Construction chemicals	14	1.45	0.14	1.59

Table : Industrial worker, including pregnant, RCR for construction chemicals, based on exposure presented in Table B 76

Conclusion: Risk related to exposure to NMP is not adequately controlled for most tasks

Overall conclusion RCRs industrial uses

Industrial uses show relatively high levels of containment and good RMM options. Processes conducted in closed systems generally do not give reason for concern, unless processes are conducted under elevated temperatures. Generally it can be concluded that processes under elevated temperatures give reason for concern. Industrial use that involve more open processes are typically performed using LEV and gloves, which may be sufficient to control the risks for general workers, but in most cases are insufficient to control the risks for pregnant workers. It is considered by the Dossier Submitter that risks resulting from dermal exposure may be controlled if very strict conditions are applied to ensure minimal contact with NMP.

B.10.2 RCRs – professional uses

Generic use

Charging and discharging

The RCRs for general and pregnant workers are > 1 for inhalation and for pregnant worker >1 for the dermal route. Better protection with gloves can be easily achieved by training and therefore risks from dermal exposure are controllable. Controlling the risks from inhalation exposure may be more difficult. It is unknown to the Dossier Submitter if professionals that perform charging and discharging tasks, which is a generic use scenario for several other professional uses, what the real-life options are to apply RMMs such as LEV or even RPE. If such measures are possible, the risks may be sufficiently controlled, but this is not expected to be a good solution for all activities within this use.

Table B.102: *Professional worker-RCR for charging and discharging.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Charging and discharging, professional	8a	1.45	0.60	2.04
Charging and discharging, professional	8b	1.74	0.60	2.33
Charging and discharging, professional	9	1.74	0.30	2.03

Table B.103: *Professional worker-RCR pregnant for charging and discharging.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Charging and discharging, professional	8a	2.89	1,14	4,03

Charging and discharging, professional	8b	3.47	1,14	4,61
Charging and discharging, professional	9	3.47	0,57	4,04

Conclusion: inhalation risks from exposure to NMP may not be sufficiently controlled for both general and pregnant workers.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Charging and discharging, professional	8a	1.45	0.57	2.02
Charging and discharging, professional	8b	1.74	0.57	2.31
Charging and discharging, professional	9	1.74	0.29	2.03

Table : Professional user, including pregnant, RCR for charging and discharging, based on exposure presented in Table B 77

Conclusion: Risk related to exposure to NMP is not adequately controlled for all tasks.

Formulators

RCRs for general and pregnant workers are > 1 for inhalation and for pregnant worker >1 for the dermal route. Better protection with gloves can be easily achieved by training and therefore risks from dermal exposure are controllable. Controlling the risks from inhalation exposure may be more difficult. It is unknown to the Dossier Submitter if professionals that formulate preparations, what the real-life options are to apply RMMs such as LEV or even RPE. If such measures are possible, the risks may be sufficiently controlled, but this is not expected to be a good solution for all activities within this use.

***Table B.104:** Professional worker-RCR for formulators.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	3	1.24	0.03	1.27
Formulation of preparations	5	1.74	0.60	2.33

***Table B.105:** Professional worker-RCR pregnant for formulators.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	3	2.48	0.06	2.54
Formulation of preparations	5	3.47	1.14	4.61

Conclusion: inhalation risks from exposure to NMP may not be sufficiently controlled for both general and pregnant workers.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Formulation of preparations	3	1.24	0.03	1.27
Formulation of preparations	5	1.74	0.57	2.31

Table : Professional user, including pregnant, RCR for formulators, based on exposure presented in Table B 78

Conclusion: Risk related to exposure to NMP is not adequately controlled for all tasks

Importers/Suppliers

See generic use: charging and discharging.

Non-wire coaters

The RCRs for general and pregnant workers are > 1 for inhalation. It is unknown to the Dossier Submitter if professionals use coatings, what the real-life options are to apply RMMs such as LEV or even RPE. If such measures are possible, the risks may be sufficiently controlled, but this is not expected to be a good solution for all activities within this use. For example, house painters will not be able to apply LEV and will generally not use any RPE.

Table B.106: *Professional worker-RCR for non-wire coaters.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings professional	13	1.45	0.30	1.74

Table B.107: *Professional worker-RCR pregnant for non-wire coaters*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings professional	13	2.89	0.57	3.46

Conclusion: inhalation risks from exposure to NMP may not be sufficiently controlled for both general and pregnant workers.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Coatings professional	13	1.45	0.29	1.73

Table : Professional user, including pregnant, RCR for non-wire coaters, based on exposure presented in Table B 79

Conclusion: Risk related to exposure to NMP is not adequately controlled.

Cleaners

No data are available from the registration dossier. Exposure monitoring on the use of cleaners by professionals, i.e. removal of graffiti, showed air concentrations that would exceed the inhalation DNEL and thus it may be concluded that risks are not sufficiently controlled for this specific use. Personal communication with industry revealed that this use is reduced significantly and is no longer supported by the lead registrant.

Agricultural chemical industries (formulation)

The use of agrochemicals resulted in RCRs that range from 0.77 to 3.5 (combined RCRs), where low concentrations of NMP (5%) are taken into account. Professional users of agrochemicals generally have access to PPEs such as gloves and RPE (that also protect the operator against the active ingredient) and moreover mainly work outdoors or in greenhouses. As the exposure calculations using EasyTRA did not take into account any RMMs, while such RMMs are quite common, it is anticipated that risks can be controlled sufficiently if such measures are taken.

Table B.108: *Professional worker-RCR for agrochemicals*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker

Agrochemicals, professional	11	0.30	0.48	0.78
Agrochemicals, professional	11	0.53	1.17	1.70

Table B.109: *Professional worker-RCR pregnant for agrochemicals.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Agrochemicals, professional	11	0.59	0.92	1.51
Agrochemicals, professional	11	1.05	2.24	3.30

Conclusion: risks can be sufficiently controlled if proper RMMs are taken.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Agrochemicals, professional (outdoor)	11	0.30	0.46	0.76
Agrochemicals, professional (indoor)	11	0.53	1.12	1.65

Table : Professional user, including pregnant, RCR for agrochemicals, based on exposure presented in Table B 80

Conclusion: Risk related to exposure to NMP is not adequately controlled where the substance is used indoor.

Laboratories

Conclusion: risks are sufficiently controlled.

Table B.110: *Professional worker-RCR for laboratories.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use, professional	15	0.41	0.07	0.49

Table B.111: *Professional worker-RCR pregnant for laboratories.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use, professional	15	0.83	0.14	0.97

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Laboratory use, professional	15	0.41	0.07	0.48

Table : Professional user, including pregnant, RCR for laboratories, based on exposure presented in Table B 81

Conclusion: Risk related to exposure to NMP is adequately controlled.

Functional Fluids

RCRs for the use of functional fluids are around 1 for pregnant workers, with the exception of PROC20 for which combined RCRs are found of 2.4 and 5.8 for general and pregnant workers, respectively. The other activities resulted in lower RCRs, because of the use of RMMs such as LEV

and gloves. If the use of LEV and gloves is possible for PROC20, then risks would be sufficiently controlled for general workers, whereas for the pregnant workers risks cannot be excluded.

Table B.112: *Professional worker-RCR for functional fluids*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, professional	17	1.55	0.30	1.85
Functional fluids, professional	17	0.62	0.30	0.92
Functional fluids, professional	18	0.62	0.15	0.77
Functional fluids, professional	20	2.07	0.37	2.44

Table B.113: *Professional worker-RCR pregnant for functional fluids.*

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, professional	17	3.1	0.57	3.67
Functional fluids, professional	17	1.24	0.57	1.81
Functional fluids, professional	18	1.24	0.29	1.53
Functional fluids, professional	20	4.13	0.71	4.84

Conclusion: activities that fall under PROC20 will lead to insufficiently controlled risks from inhalation of NMP for all workers if no proper RMMs are considered due to the high energy processes.

Name	PROC	RCR inhalative-worker	RCR dermal-worker	RCR combined-worker
Functional fluids, professional	17	1.55	0.29	1.84
Functional fluids, professional	17	0.62	0.29	0.91
Functional fluids, professional	18	0.62	0.14	0.76
Functional fluids, professional	20	2.07	0.36	2.43

Table : Professional user, including pregnant, RCR for functional fluids, based on exposure presented in Table B 82

Conclusion: Risk related to exposure to NMP is not adequately controlled for most tasks.

Other (consumer)

Not considered in this Background Document.

Overall conclusion RCRs professional uses

Professional uses, surprisingly, did not show much higher RCRs than industrial uses. Notably, the lead registrant no longer considered/supported high exposure and risk uses, such as working with NMP at elevated temperatures, spraying processes and manual applications. Nevertheless, especially for inhalation exposure there may be insufficiently controlled risks for all workers for a number of activities. Dermal exposure does not seem to present risks that cannot be controlled, although in some case through requiring training of the use of protective wear to reach higher protection factors.

B.11 Summary on hazard and risk

The hazard and risk of NMP was assessed using information on the hazard from the registration dossiers and the OECD SIDS dossier on NMP and the exposure information obtained from the registration dossier, literature studies and monitoring data.

NMP is classified as a skin, eye and possible respiratory irritant and is classified reprotoxic category 1B based on developmental toxicity. NMP has been studied extensively in the past decades showing a rather complete dataset of toxicological studies. The focus of the Background Document was on the repeated dose toxicity endpoints and the developmental toxicity endpoint. A number of studies in mice, rats, rabbits and one in dogs were available for evaluation by the Dossier Submitter.

In the repeated dose studies often the reduction in body weight (gain) and generic toxicological effects on liver, kidney and thymus weights and histopathology were the most critical. At higher doses these effects worsened and were accompanied by effects on the testes and spleen. There was no specific target organ identified at low to mid doses. In the prenatal developmental toxicity studies and 2-generation studies effects on maternal body weights and foetus weights were most critical. Notably, the body weight changes of the dams occurred at lower concentrations than observed in general animals. At higher concentrations, clear effects on the foetuses were observed such as variations and malformations, reduced litters, stillborn and resorptions amongst other. Despite effects observed on testes and spermatogenesis (slight effects) no reduction in fertility was observed in any of the reproduction toxicity studies.

Since the population of interest in the risk assessment of NMP are the workers, it was decided by the Dossier Submitter to derive DNELs for workers in general, and the pregnant workers specifically, because of the developmental toxic effects of NMP. The point of departures selected for the pregnant workers are based on prenatal developmental toxicity studies and 2-generation toxicity studies, whereas for the general workers the repeated dose studies and carcinogenicity studies (only repeated dose related effects) were considered. Oral exposure was not considered relevant for the worker population and therefore DNELs were derived for the inhalation and dermal route only.

The PODs ultimately used for DNEL derivation for workers are 500 mg/m^3 (NOAEC; reduced body weight gain in rats) and 826 mg/kg bw/d (NOAEL; ¼ mortality in rabbits) for the inhalation and dermal route, respectively. The PODs ultimately used for DNEL derivation for general workers are 247 mg/m^3 (NOAEC; reduced fetal body weight in rats) and 237 mg/kg bw/d (NOAEL; reduced live foetuses and fetal body weight in rats) for the inhalation and dermal route, respectively. Corrections on the POD for inhalation were required to account for hours exposed per day and per week. Assessment factors were used to derive the DNELs. Assessment factors were applied to account for interspecies differences (allometric scaling and remaining differences), intraspecies differences and the exposure duration, according to ECHA guidance, chapter R8. The intraspecies differences for pregnant workers differed from the worker intraspecies factor of 5 (ECHA guidance, default value). Instead, the default value of 10 was adopted which is used to account for intraspecies differences in the general population, since the critical effects concerned the unborn child, whom are not covered by the worker intraspecies differences factor. Based on the PODs and the AFs, the DNELs derived are 10 mg/m^3 and 4.6 mg/kg bw/d for the inhalation and dermal route, respectively. The DNELs derived for pregnant workers are 5 mg/m^3 and 2.4 mg/kg bw/d for the inhalation and dermal route, respectively (see table B.77 and B.78 for details).

Table B.114: *Overview of the PODs and derived DNELs for the worker population.*

DNEL (endpoint)	NOAEC mg/m³ (spec.)	Type of study	Type of effect at LOAEC	Corrected for differences in exposure conditions	Corrected NOAEC mg/m³	Assessment factors	Resulting DNEL mg/m³	Reference
Inhalation, systemic	500, rat	Repeated dose study, 3 months	Decrease in body weight and body weight gain in males	6/8 6.7/10	251	1 - (AS) 2.5 – (RD) 5 - (IS) 2 – (ED) Total: 25	10	BASF AG, 1994
Dermal, systemic	826, rabbit	Mortality	Repeated dose study, 4 weeks			2.4 - (AS) 2.5 – (RD) 5 - (IS) 6 – (ED) Total: 180	4.6	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

DNEL (endpoint)	NOAEC mg/m³ (spec.)	Type of study	Type of effect at LOAEC	Corrected for differences in exposure conditions	Corrected NOAEC mg/m³	Assessment factors	Resulting DNEL mg/m³	Reference
Inhalation, systemic	1000, rat	Repeated dose study, 3 months	Decrease in body weight and body weight gain in males	6/8 6.7/10	251	1 - (AS) 2.5 – (RD) 5 - (IS) 2 – (ED) Total: 25	20	BASF AG, 1994
Dermal, systemic	826, rabbit	Mortality	Repeated dose study, 4 weeks			2.4 - (AS) 2.5 – (RD) 5 - (IS) 6 – (ED) Total: 180	4.6	GAF Corp., 1986; Industrial Biology Research and Testing Laboratories, 1963

Table: Overview of the PODs and DNELs derived by RAC for the general worker population

Table B.115: *Overview of the PODs and derived DNELs for the pregnant worker population.*

DNEL (endpoint)	NOAEC mg/m³ (spec.)	Type of study	Type of effect at LOAEC	Corrected for differences in exposure conditions	Corrected NOAEC mg/m³	Assessment factors	Resulting DNEL mg/m³	Reference
Inhalation Developmental toxicity	247, rat	Dev tox study, GD 6-20	Reduced fetal body weights	6/8 6.7/10	124	1 - (AS) 2.5 – (RD) 10 - (IS) Total: 25	5.0	Saillenfait et al., 2001, Saillenfait et al., 2003
Dermal Developmental toxicity	237, rat	live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	Dev tox study, GD 6-15	-	-	4 - (AS) 2.5 – (RD) 10 - (IS) Total: 100	2.4	Becci et al., 1982; Becci et al., 1981; FDRL, 1979; TSCAT, 1992b

DNEL (endpoint)	NOAEC mg/m³ (spec.)	Type of study	Type of effect at LOAEC	Corrected for differences in exposure conditions	Corrected NOAEC mg/m³	Assessment factors	Resul-ting DNEL mg/m³	Reference
Inhalation Developmental toxicity	247, rat	Dev tox study, GD 6-20	Reduced fetal body weights	6/8 6.7/10	124	1 - (AS) 2.5 – (RD) 5 - (IS) Total: 12.5	10.0	Saillenfait et al., 2001, Saillenfait et al., 2003
Dermal Developmental toxicity	237, rat	live fetuses↓, BW↓, delayed ossification, skeletal malformation↑	Dev tox study, GD 6-15	-	-	4 - (AS) 2.5 – (RD) 5 - (IS) Total: 50	4.8	Becci e al., 1982 Becci e al., 1981 FDRL, 1979; TSCAT, 1992b

Table: Overview of the PODs and DNELs derived by RAC for the pregnant worker population

The registrant estimated exposure to NMP at the workplace using the EasyTRA tool; the EasyTRA tool is based on the principles of the ECETOC TRA tool. Similarly, it uses the same default values for each PROC to determine the exposure to NMP during that process taking into account any RMMs and OCs assigned to the process. According to the information obtained from the registrant, the most common RRMs applied are LEV, gloves and reduction in exposure time and/or concentrations of NMP used in the process. Detailed information on RMMs typically applied in workplaces where NMP is used is not available to the Dossier Submitter.

The exposure was calculated for the following industrial uses: manufacture, importers and suppliers, chemical industry processes (generic use for synthesis processes), formulators (generic use for production of mixtures and articles), coaters, cleaners, laboratory use, functional fluids, and use in construction industry. Professional uses considered are: importers and suppliers, formulators, coaters, laboratory use, agrochemical use and use in functional fluids. Charging and discharging of NMP is a generic process applied in both industrial and professional settings.

In general, exposures resulting from high energy processes (e.g. under elevated temperatures and processes requiring intensive manual applications) and from open processes are relatively high, despite of RMMs taken into account. In industrial settings, processes can be more enclosed and RMM options are better compared to processes and RMM options available in professional settings. Moreover, most open and high energy processes are not supported anymore by the lead registrant as it was indicated that such uses, e.g. professional cleaning with NMP, will diminish in a few years. Therefore, the exposure levels that were calculated by the registrant did not differ much between the industrial and professional uses.

The exposure levels ranged from 0.04 to 20.65 mg/m^3 for the inhalation exposure for industrial uses. Dermal exposure ranged from 0.03 to 5.49 mg/kg bw/d for industrial uses, where it is noted that RMMs are taken into account. The exposure levels ranged from 2.97 to 20.65 mg/m^3 for the inhalation exposure for professional uses. Dermal exposure ranged from 0.14 to 5.38 mg/kg bw/d for professional uses, where it is noted that RMMs are taken into account.

By combining the derived DNELs with the exposure estimates risk characterisation ratios (RCRs) were obtained. The RCRs were in most cases for workers and pregnant workers >1 indicating that there is a risk. We made a qualitative appraisal of the RCR as for some exposure estimates additional RMMs were possible. In the tables below the highest RCRs found for each user category is presented including our appraisal.

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

Table B.116: *Overview of RCRs for workers in the different uses.*

Use	PROC	RCR inhalative	RCR dermal	RCR combined	Conclusion of risk
RCRs industrial uses					
- Manufacturers	3	1.24	0.15	1.39	Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EasyTRA output is indeed a conservative estimate and therefore support the Dossier Submitter's conclusion that risks are expected to be sufficiently controlled
Generic uses: *charging and discharging* - All use categories as defined in table B.03 with industrial use	8a	1.74	0.60	2.33	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.
Generic uses: *chemical industry processes (elevated temp)* - Petrochemical industries - Agricultural chemical industry (synthesis) - Pharmaceutical industry	3	2.07	0.15	2.22	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.
Generic use: *formulation (up to 60)* - Formulators - Non-wire coaters - Wire coaters - Cleaners - Battery industries - Membrane manufacturers - High performance polymer producers - Agricultural chemical industry (synthesis) - Pharmaceutical industry - Functional fluids - Construction industry	5	2.07	0.60	2.66	Risks of NMP can be controlled at room temperature with proper RMMs in place. At elevated temperatures the risks may not be sufficiently controlled even with RMMs.
Coatings process: - Non-wire coaters - Wire coaters - Battery industries	7	1.87	0.38	2.25	Risks may not be sufficiently controlled
Cleaning process: - Cleaners - Electronics and semiconductor industries	7	1.87	0.38	2.25	Risks may be sufficiently controlled (measurement data and EasyTRA calculation are in the same range)
Laboratory use	15	0.21	0.07	0.28	Risks are sufficiently controlled
Functional fluids	17	0.83	1.19	2.02	Risks are sufficiently controlled (EasyTRA calculations conservative)
Construction chemicals	10	0.41	1.19	1.61	Risks are sufficiently controlled (EasyTRA calculations conservative)

Use	PROC	RCR inhalative	RCR dermal	RCR combined	Conclusion of risk
Professional uses					
Generic uses: *charging and discharging* - All use categories as defined in table B.03 with professional use	8b	1.74	0.60	2.33	Inhalation risks may not be sufficiently controlled
Generic uses: *Formulation* - Formulators - Non-wire coaters - Agricultural chemical industry (formulation) - Functional fluids Construction industry	5	1.74	0.60	2.33	Inhalation risks may not be sufficiently controlled
Coating process: Non-wire coaters	13	1.45	0.30	1.74	Inhalation risks may not be sufficiently controlled
Agricultural chemical industry (formulation)	11	0.53	1.17	1.70	Risks can be sufficiently controlled (if proper RMMs are taken)
Laboratories	15	0.41	0.07	0.49	Risks are sufficiently controlled
Functional fluids	20	2.07	0.37	2.44	Activities that fall under PROC20 will lead to insufficiently controlled risks from inhalation of NMP for all workers if no proper RMMs are considered due to the high energy processes.

Highest RCRs chosen from Table B.47 to B.75 and calculated using a DNEL inhalation of 10 mg/m^3 and a dermal DNEL of 4.6 mg/kg bw/day.

Table B.117: *RCRs for pregnant worker.*

Use	PROC	RCR inhalative	RCR dermal	RCR combined	Conclusion on risk
RCRs industrial uses					
- Manufacturers	3	2.48	0.29	2.77	Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EasyTRA output is indeed a conservative estimate and therefore support the Dossier Submitter's conclusion that risks are expected to be sufficiently controlled
Generic uses: *charging and discharging* - All use categories as defined in table B.03 with industrial use	8a	3.47	1.14	4.61	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.
Generic uses: *chemical industry processes (elevated temp)* - Petrochemical industries - Agricultural chemical industry (synthesis) - Pharmaceutical industry	3	4.13	0.29	4.42	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks may not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.

Use	PROC	RCR inhalative	RCR dermal	RCR combined	Conclusion on risk
Generic use: *formulation (up to 60)* - Formulators - Non-wire coaters - Wire coaters - Cleaners - Battery industries - Membrane manufacturers - High performance polymer producers - Agricultural chemical industry (synthesis) - Pharmaceutical industry - Functional fluids - Construction industry	5	4.13	1.14	5.27	Risks of NMP can be controlled at room temperature with proper RMMs in place. At elevated temperatures the risks may not be sufficiently controlled even with RMMs.
Coatings process: - Non-wire coaters - Wire coaters - Battery industries	7	3.74	0.72	4.46	Risks may not be sufficiently controlled
Cleaning process: - Cleaners - Electronics and semiconductor industries	7	3.74	0.72	4.46	Risks may not be sufficiently controlled
Laboratory use	15	0.41	0.14	0.56	Risks are sufficiently controlled
Functional fluids	17	1.65	2.29	3.94	Risks may not be sufficiently controlled
Construction chemicals	14	2.89	0.29	3.18	Risks may not be sufficiently controlled
Professional uses					
Generic uses: *charging and discharging,* - All use categories as defined in table B.03, with professional use	8b	3.47	1.14	4.61	Inhalation risks may not be sufficiently controlled
Generic uses: *Formulation* - Formulators - Non-wire coaters - Agricultural chemical industry (formulation) - Functional fluids Construction industry	5	3.47	1.14	4.61	Inhalation risks may not be sufficiently controlled
Coating process: Non-wire coaters	13	2.89	0.57	3.46	Inhalation risks may not be sufficiently controlled
Agricultural chemical industry (formulation)	11	1.05	2.24	3.30	Risks can be sufficiently controlled (if proper RMMs are taken)
Laboratories	15	0.83	0.14	0.97	Risks are sufficiently controlled
Functional fluids	20	4.13	0.71	4.84	Risks cannot be excluded

Highest RCRs chosen from Table B.48 to B.76 and calculated using a DNEL inhalation of 5 mg/m^3 and a dermal DNEL of 2.4 mg/kg bw/day.

Use	PROC	RCR inhalative	RCR dermal	RCR combined	Conclusion of risk
RCRs industrial uses					
- Manufacturers	3	1.24	0.14	1.38	Measurement data (see section B.9.3.2.) indicates that the the Dossier Submitter's conclusion that risks may be sufficiently controlled
Generic uses: *charging and discharging*	8a	1.74	0.57	2.31	Risks related to inhalation exposure are not sufficiently controlled
Generic uses: *chemical industry processes (elevated temp)*	3	2.07	0.14	2.21	Risks related to inhalation exposure are not sufficiently controlled
Generic use: *formulation*	5	2.07	0.57	2.64	Risks related to inhalation exposure are not sufficiently controlled
Coatings process:	7	1.87	0.38	2.23	Risks related to inhalation exposure are not sufficiently controlled
Cleaning process:	7	1.87	0.36	2.23	Risks related to inhalation exposure are not sufficiently controlled
Laboratory use	15	0.21	0.07	0.28	Risks are sufficiently controlled
Functional fluids	17	0.83	1.14	1.97	Risks related to dermal exposure are not sufficiently controlled
Construction chemicals	10 14	0.41 1.45	1.14 0.14	1.55 1.59	Risks are not sufficiently controlled
Professional uses					
Generic uses: *charging and discharging*	8b	1.74	0.57	2.31	Risks related to inhalation exposure are not sufficiently controlled
Generic uses: *Formulation*	5	1.74	0.57	2.31	Risks related to inhalation exposure are not sufficiently controlled
Coating process: Non-wire coaters	13	1.45	0.29	1.74	Risks related to inhalation exposure are not sufficiently controlled
Agricultural chemical industry	11	0.53	1.12	1.65	Risks related to dermal exposure are not sufficiently controlled
Laboratories	15	0.41	0.07	0.48	Risks are sufficiently controlled
Functional fluids	20	2.07	0.36	2.43	Risks related to inhalation exposure are not sufficiently controlled

Table: Highest RCRs chosen for exposures presented in section B9 and calculated using RAC – calculated DNELs: for inhalation of 10 mg/m^3 and a dermal of 4.8 mg/kg bw/day.

C. Available information on alternatives

C.1 Identification of potential alternative substances and techniques

As explained in chapter B, NMP is an aprotic and medium polar organic solvent. NMP is completely miscible with water. This combination of properties explains the importance of the use of NMP in several applications. NMP as such is mainly used to enhance a chemical reaction driven by its solvent characteristics as part of the process to make a product. In general, it can be stated that industry supports substitution of NMP by other solvents. So far, however, no comparable chemical reactions could be created for the formulation of some of the existing products with similar characteristics. Next to NMP, many organic solvents are available as potential alternatives but the characteristics of these solvents are not exactly equal to NMP. The availability of technical feasible alternatives will differ per use application.

To get an impression of the available alternatives information was collected from the Chemical Safety Report, the Annex XV SVHC dossier and the responses to that document in the public Member State consultation, communication with ECHA, industries and literature. In the first part of this chapter, the alternatives identified are discussed per use category (see table B.03). The use of the alternatives may not be feasible because of their toxicological characteristics (e.g. classification as a carcinogen) or because of technical or economic considerations. This will be dealt with at the end of section C1.

Generic uses

Polymers

Besides NMP, DMF, DMAC and DMSO are all good solvents for many polymers. Often one of these solvents are used in preparing polymer solutions. Sometimes acetone, MEK or triethylphosphate (TEP) are used. Whether these alternative solvents are suitable in the various applications is discussed in the use specific sections below.

Petrochemical industries

As mentioned in part B.2.2 NMP is used in petrochemical industries in a variation of processes. The availability of alternatives is described below per sub-use in the petrochemical industry.

Extraction of aromatic compounds from lube feed stock after distillation and deasphalting

Solvents are used to remove undesirable aromatics and polar components from the desirable paraffins and naphthenes of a lube feed stock. The feed stocks come either from vacuum distillation or from deasphalting. Formerly dearomization of lube feed stock took place with liquid sulphur dioxide. However, this has largely been replaced by using phenol and furfural. Various extraction solvents have been applied. At present, furfural is most applied (40%), followed by phenol (28%) and NMP (11%) (Hombourger et al 2000).

The Reference Document on Best Available Techniques (BREF) for Mineral Oil and Gas Refineries from 2003 (EC 2003a) contains a number of statements on the use of NMP in the aromatic extraction of oil products. The section on best available technique (BAT) for Base Oil Production recommends using N-methyl pyrrolidone (NMP) as solvent in the aromatic extraction. The BREF further states "In some cases, the switch from furfural to NMP may not be justified environmentally or technically especially when producing lower boiling point base oils (e.g transformer oil distillates). Because a solvent switch typically requires different temperature, pressure and solvent volumes, they are typically very costly. Industry claims that considering the information within this document, both NMP and furfural are equally viable solvent candidates. In Industry's opinion, no clear case has been made in the BREF to arrive at one preference." Further alternative solvents mentioned in the BREF for aromatic extraction are phenol and liquid sulphur dioxide.

Section 4.3.2. of the BREF describes the types of solvent to be used in the aromatic extraction unit. It states that "The selection of the type of solvent used in the aromatic extraction has an impact on the energy consumption of the system and the use of a less toxic solvent (furfural and n-methyl pyrrolidone (NMP) can be used in preference to the more toxic selective solvents as phenol and sulphur dioxide)." However, it should be noted that the remarks on the environmentally preferability of NMP throughout the BREF-document does not take into account the classification of NMP as reprotoxic 1B in 2009. The BREF indicates that major modifications would be required for existing units to change from one solvent to another, as the process conditions are different. Under the heading "economics" in section 4.3.2 of the BREF some basic statements are made on the costs for switching between SO2, phenol, furfural and NMP driven processes (EC, 2003a).

The information above suggests that alternatives of NMP for the extraction of aromatic compounds are technically available. However, changing the process from one solvent to another requires major modifications in the extraction process, which is accompanied by high costs.

Aromatic extraction from the light steam cracking effluents

Various aromatics cannot be seperated from the paraffins and naphthenes present in the light oil distillates by distillation because the boiling temperatures of these aromatics are too close to that of the paraffins and naphthenes. Thus, solvent extraction is the most suited and economically feasible separation technique. Hombourger et al (2000) describe that nowadays more efficient solvents, such as diethylene glycol, tetraethylene glycol, sulfolane, NMP, DMSO and N-formyl morpholine (NFM) are present compared to the previous applied dearomization solvents.

In the industrial production of the aromatics benzene, toluene, and xylene (BTX) various liquid-liquid extraction or extractive distillation processes are used to seperate them from the paraffins and naphthenes present in the C6-C8 chain. Six extraction processes applying different solvents have been described extensively in Hombourger et al (2000): the UDEX process using diethylene glycol (DEG), the Sulfolane process using sulfolane, the Arosolvan process using NMP, the Tetra process using tetra ethylene glycol, the Morphylex process using N-formyl morpholine (NFM) and the DMSO process using DMSO and butane. The processes may apply different antisolvents and may use different process temperatures. For example, the sulfolane process is carried out at 100 °C, the process using NMP at 30-60 °C and the process using DMSO-butane at 35 °C. The sulfolane process is most widely applied. The BREF for the large volume organic chemical industry mentions describes the production of BRX in chapter 8. Various separation techniques are described, such as extractive distillation and liquid-liquid extraction. A process description is provided in Table 8.5 of the BREF (EC, 2003b). The BREF states: "As an indication of the complexity of aromatics processes, there are in excess of 70 process licences and over 20 licensors, each with different feedstocks and process characteristics to suit local conditions."

According to Meinersma & de Haan, (2007) polar solvents such as sulfolane, NMP, N-formyl morpholine (NFM), ethylene glycols (EG) or propylene carbonate (PC) are often used for the separation of aromatic hydrocarbons (benzene, toluene, ethyl benzene and xylenes) from C4 - C10 aliphatic hydrocarbon mixtures. To remove aromatic and sulfur hydrocarbons from middle distillate fractions Hassan et al (2009) carried out experiments with solvent extraction using dimethylsulfoxide (DMSO), furfural, NMP + ethyleneglycol (EG) and dimethylformamide (DMF) + EG. They indicated that often solvents such as DMSO, furfural, NMP and DMF were used for such extractions. Experiments to extract PCBs from mineral oils were carried out by Kastanek et al (2012) using the polar aprotic solvents acrylonitrile, DMSO, DMF, NMP and propylene carbonate in order to compare the extraction efficiencies. Kastanek et al (2012) observed that efficiencies ranged from NMP → DMF → DMSO → PC → AC in a single stage extraction at room temperature. They concluded NMP having the best chance to be used in industry.

To conclude: although alternatives are available, the process using NMP cannot simply be replaced by one of the other processes as it needs other chemicals and other process conditions. It is also clear that changes in the downstream use and market of products affect the whole chain.

Butadiene production

Butadiene can be produced by four different processes, which are described in White (2007) and more extensively in American Chemistry Council (2001). One of these processes uses aqueous NMP as a solvent in extractive distillation (BASF/Lurgi), another uses non-aqueous solvent extraction with dimethylformamide (DMF) (ZEON Corp). According to Weissermel & Arpe (2003) the DMF process is most applied, followed by the one using NMP. The other two processes, using acetylene hydrogenation and acetonitrile extraction are less applied (White, 2007, Weissermel & Arpe 2003).

Wiese & Nierlich (2005) describe that the C4 chain is characterised by a highly coupled production and a limited number of end-products. Besides NMP, other solvents, such as acetonitrile (ACN) and dimethylformamide (DMF) are mentioned by Kim et al (2012) as possible solvents to extract butadiene. The BREF for the large volume organic chemical industry mentions acetone, furfural, acetonitrile (ACN), dimethylacetamide, dimethylformamide, and N-methyl pyrrolidone (NMP) as solvents used for butadiene extraction (EC 2003b).
It can be concluded that alternative processes of butadiene extraction not using NMP are available, however, shifting to an alternative process might give high costs.

Desulfurization of oil products

At present, sulfur is generaly removed from oil products by a reaction in which H_2S reacts with sulfur compounds present in the oil at high temperature and pressure, and by using a catalist (hydrosulfurization). Recently, a number of studies have been published which describe the extractive desulfurization of fuels in producing low sulfur fuel oils. As generally removal efficiencies for sulfur are relatively low, it has been suggested to use oxidative desulfurization in which the sulfur compounds are oxidized to the corresponding sulfones, which can be removed more easily in the subsequent extraction process by polar solvents such as NMP, DMF, DMSO and methanol (MeOH) (oxidative sulfurization) (Sampanthar et al., 2006; Zhang et al., 2009; Liu et al., 2012). In contrast to hydrosulfurization, which is relatively costly, oxidative sulfurization can run at lower production costs (Zhang et al., 2009).
From this it can be concluded that alternative processes of desulfurization not using NMP are available. However, it is not known whether the alternatives can be used within the same process or whether process changes are required to shift to alternative substances.

Removal of CO_2, COS and H_2S from gas streams

The desulfurization of raw synthesis gas for gas fired power plants have been described by Higman (1990). In this desulfurization process, sulfur in the raw gas from the Shell Gasification Process (SGP) is washed with NMP in a H_2S absorber conform the Lurgi's purisol desulfurization process. Higman (1990) indicates that a variety of solvents can be used for the desulphurization of the raw gas. Various solvents such as sulfolane, NFM, NMP, triethylene glycol dimethyl ether and 2-(2-aminoethoxy)ethanol are widely applied to remove acidic compounds, such as CO_2 , COS and H_2S, from high-pressure gas streams (Mundhwa et al 2009, Huntsman, 2009). 2-(2-aminoethoxy)ethanol is also mentioned by Huntsman (2009) as a selective solvent for recovery of aromatics from refinery streams.

To conclude, NMP can be used to remove CO_2, COS and H_2S from gas streams, but other solvents have been mentioned as well. No information was obtained about the most applied solvent or the effectiveness.

Non-wire coaters

As mentioned in B.2.2, NMP is used as a solvent in a variety of coatings. In the 1980's and 1990's NMP was used to produce "environmentally friendly" polyurethane coatings. NMP replaced dichloromethane (DCM) as a solvent at that time. Wenzel (2002) shortly describes the production process of polyurethanes dispersions and indicates that NMP is not needed in the low molecular weight polyurethanes as viscosity is not crucial. For the high molecular weight polyurethanes a solvent is needed to reduce the viscosity during production. After concerns were raised in California and later in Europe, NMP-free polyurethane dispersions were being developed. Bayer (2013) states: "Many polyurethane dispersions contain N-methyl pyrrolidone (NMP), because it is often a required part of the production process, while also facilitating film formation. California Proposition 65 and European legislation require special labeling for products containing NMP. For example in Europe, due to the hazard reclassification of NMP, products containing 5% or more NMP will have to be labeled as being irritant and toxic "T"". Wenzel (2002) and Reisch (2008) describe that Bayer developed a NMP-free polyurethane dispersion where NMP is being replaced by acetone during the production process and where the acetone is being removed before shipping the product to the paint makers. The NMP-free polyurethanes mentioned in the article do not require any solvent besides water or use an alternative solvent such as dipropylene glycol dimethyl ether (Reisch, 2008). However, in 2007 NMP was still was one of the most important ingredients for the production of polyurethane dispersions (Dimmers, 2007). Dimmers (2007) describes the preparation of a number of polyurethane dispersions based on vegetable oil without a solvent added. In the examples by Wenzel (2002) and Dimmers (2007) both process and solvents are changed.

Nowadays, NMP has been replaced in a large number of polyurethane dispersions by other solvents, such as acetone, dipropylene glycol dimethyl ether (DPDME) and N-ethyl pyrrolidone (NEP) (e.g. see Bayer 2013; Reichhold, 2012). In a presentation by Morchem S.A. two out of three PU dispersion based adhesives are NMP free, and eight out of nine PU dispersion based coatings are NMP-free (Diaz, 2010). The adhesives and coatings are applied for a large range of applications, e.g. metal coating and automotive. The development of solvent-free urethane acrylic hybrid polymers for coatings has been further described by Calgoci et al (2005) and that of waterborne polyurethane coatings for wood floors by Gertzmann et al (2007). The American Coatings Association Inc (2010) report the availability of NMP-free polyurethane dispersions and oil-modified polyurethanes, available from various producers such as Morchem, Reichhold and Cook composites and Polymers, which can be formulated for wood, textile, leather, concrete, bitumen and other applications. From the stakeholder consultation it was reflected by representatives of the European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE) that the development of the replacement of NMP-containing waterborne polyurethane binders to NMP-free materials would not lead to total new basecoat developments (personal communication, RIVM draft dossier).

Leading Edge Coating Solutions (2013) offers speciality coatings containing PVDF as a polymer. Their PVDF-256 is usually supplied in ethyl acetate or propyl acetate and n-methyl pyrrolidone (NMP), but can also be supplied in acetone/NMP on request. Leading Edge Coating Solutions (2013) provides a cost comparison of their PVDF-coating with other types of coatings, such as acrylics and polyurethanes, and indicates that "The main difficulty in comparing the cost of competing coatings is the problem of "apples versus oranges."" The PVDF coating is expensive on a liter basis, but thickness of application and durability in years should be taken into account in the cost comparison. This indicates that it will also be difficult when NMP containing products are compared to other products based on different constituents.

For a better understanding of the indispensableness of NMP in all different uses of coatings, more insight on the actual type of polymer used in the specific processes and products seem a necessity. At present, such information is lacking for most sectors and it has not been further specified during the stakeholder consultation. For quite a number of applications, such as the leather coating (see the description below) and other examples provided below, NMP-free alternatives are clearly available and marketed by a wide range of producers.

Coating in the automotive industry

From the automotive industry it is known that NMP is still used in the car coating system. However, replacement of NMP is possible via reformulation of the coatings (personal communication, AMEC Questionaire). Note that this would require adaptation of the full coating system both for the industrial and professional uses. Both use the same coatings. At present, there are already NMP-free products for automotive on the market, for instance by Lord Corporation (Lord Corporation, 2013), Dow (Dow, 2013) and BYK, which provides products with NEP and DMSO as alternative (BYK, 2013).

Coating in textile and leather

One of the past applications of polyurethane/NMP dispersions were in the textile and leather coating. Cory (2002) describes the presence of NMP in upholstery and shoe upper leathers as a result of coating with PU-based formulations. NMP is a residual in PU formulations as it was used as a solvent for the urethane polymerization. Highest concentrations of NMP (up to 3000 mg/kg) were found in automotive leather. Cory (2002) indicates that the listing of NMP in Californian legislation (California Proposition 65) in 2001 would force the leather industry to seek for alternatives and indicate that two US chemical suppliers already claim to possess NMP-free finish formulations. Wenzel (2002) indicated that Bayer had also developed NMP free polyurethane dispersions for leather coating. Recent reports from BASF (2010, 2012) indicate the availability of NMP-/ NEP-free polyurethane dispersions to be used for high performance leather seats. At present, NMP-free products are also available from several other PU producers. Clariant (2011) claimed that it eliminated NMP with a concomitant sustainable VOC reduction. No indication is provided on the alternatives used.
In conclusion, alternatives for NMP in polyurethane dispersions to be used in the textile and leather industry are already available and NMP has probably already been replaced by alternatives in a large number of products.

Coating in films and medical images

Some stakeholders indicated that there were no alternatives for replacement of NMP by other solvents in a number of key applications. They indicated that the replacement as a co-solvent in polyurethane dispersions used for VOC compliant waterborne products is expected to take years and may involve high costs for the coatings suppliers. One specific example concerning the top coating in films and medical images was provided. However, it should be noted that a wide range of images are nowadays stored digitally. Even within the medical world there are developments to store information using picture archiving and communication systems (PACS). To what extent this development has replaced hard copy photography and storage in practice has not been verified.

For some remaining critical applications however, no alternatives have yet been found. A key application is the industrial manufacturing of an imaging film used to obtain a hardcopy of medical images and involves the use of NMP as a solvent for a polymer in the top coating of the film. A few years ago a manufacturer of imaging films started a program to study the replacement of NMP. The substitution program resulted in the replacement of NMP in a number of applications, where NMP was being replaced by NEP. The manufacturer describes a number of technical problems using replacement of NMP by 2-Pyrrolidone, a mixture of propylenecarbonate and ethyleen-glycolmonobutylether (EGMBE), ethers of (di) or (tri) propylene glycol and DMSO. These technical problems comprised condensation problems in the drying zone, coating defects, repellencies, and leveling problems (cloudy pattern) and increased haziness in the dried coating (personal communication, RIVM draft dossier). No further information was obtained on possible alternatives in this specific application.

Coating in foodcontact material/bakeware

Information received in the public consultation 2013/2014 from various actors indicated that NMP is used in the production of coatings used in the production of foodcontact material/bakeware. Although the exact use is not fully clear from the information provided, NMP seems to be used specifically in the production of non stick coatings applied to metallic substrates in domestic bakeware. These coatings are characterized by high temperature and chemical resistance. According to the comments received in the public consultation, search for alternatives has been ongoing for years, but did not yet result in successful substitution of NMP.

Wire coaters

NMP is mainly used in the wire coatings made from the most solvent resistant polymers: polyamideimides (PAI) and polyimides (PI). Polyamideimides were originally developed for electromagnetic wire coatings and this is still the main application. They are more thermal resistant, but are also more expensive than most other polymers (McKeen, 2006). PAI and PI are soluble in dipolar aprotic solvents such as N-methyl pyrrolidone (NMP), dimethyl acetamide (DMAC), dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO). IST (1995) offers their wire enamel with NMP as solvent or as NMP in combination with aromatic hydrocarbons or DMAC. The wire enamels offered today by IST still contains 80-100% NMP (IST, 2013). Murray (2006) mentions NEP as replacement solvent for polyamideimides and the paper of 2008 (Murray, 2008) indicates that there are other possible alternatives on the way that might prove technically feasible, but as of yet are not feasible from a costs perpective or undesired from a toxicological perspective. Murray (2008) continues with: "PAI resins used for electrical insulation are almost exclusively used as NMP containing solutions. Alternate solvents that are cost effective have limited solvency for PAI resins or the reaction cannot be carried out in this media. Many patents have been granted on achieving the high thermal and mechanical properties of PAI resins while using low cost solvents such as cresylic acid. Improvements are still needed in alternate solvent PAI resins to reduce applied costs yet maintain the high electrical, thermal, and mechanical properties."Fujifilm (2013a) sells polyamideimide in NMP, in NMP/xylene, in NEP, in NMP/H2O and in NEP/H2O. Some of the products of Solvay are also soluble in water.

Alternative materials used as wire coating are PVC, polyethylene and materials containing ethylene ethyl acrylate copolymer (EEA) and/or ethylene vinyl acetate copolymer (EVA) (Kaneko & Mori, 2009), but also polyester, polyurethane and epoxy-based enamels can be used (DKB Organics PVT.LTD, 2013). DKB Organics offers also NMP-free modified polyimide wire enamels (DKB Organics PVT.LTD, 2013). Sandvik (2013) offers a range of insulation coatings amongst which polyamideimide, but also polyvinylacetate, polyurethane, fluorinated ethylene propylene and polytetrafluoroethylene. Top coats from polyamide and polyamideimide are also offered (Sandvik, 2013). Murray (2006) describes a new technology of polyamideimide wire enamels and explains

that cost considerations are always critical in the development of coatings for the magnet wire industry. According to Murray (2006) efforts to achieve PAI coatings in alternate solvent systems to NMP will be continued. US Patent 8258403B2 by Hitachi Cable Ltd and Hitachi Magnet Wire Corp as assignees describes an insulation coating for electric wires made from polyimide resin or polyamide imide resin with NMP, DMF, DMAC, sulfolane, anisole, siloxolane, butyl cellosolve acetate and lactone as possible solvents. It is stated that the solvents can be used alone or that two or more solvents may be mixed. Industry noted however, that these materials, EEA and EVA, are thermoplastic materials which do not have the thermal properties as needed for electrical devices. Such high thermal properties can only be achieved by using cured polyamide imide films. Polyester, polyurethane and epoxy-based enamels are used as basecoats, because they do not have the required abrasion resistance. Polyurethanes are solderable wire enamels that means the coating disintegrates at elevated temperatures and they cannot be thermally stable. Epoxy based enamels are used as self bonding, that means meltable materials. Polyvinyl acetates have a temperature index of 130, and are therefore inferior to a polyamide imide. Finally, fluorinated ethylene propylene and polytetrafluoro-ethylene cause major problems when the coated wires were recycled, because they generate hydrofluoric acid. In addition, they are not cost competitive compared to polyamide imides (public consultation 2013/2014).

The solubility of the more thermal and solvent resistant polymers such as PAI, PI and PVDF, make the amount of possible alternatives limited to the ones mentioned above: DMF, DMAC and DMSO for PAI and PI. Solvents for PVDF are dimethyl formamide (DMF), dimethyl acetamide (DMAC), tetramethyl urea, dimethyl sulfoxide (DMSO), triethyl phosphate, N-methyl-2-pyrrolidone (NMP) and acetone. In the stakeholder consultation, it was indicated that wire coating takes place at elevated temperatures, which lead to breakdown of DMSO. This breakdown leads to technical problems within the ovens. Industry indicates that sulphur oxides also lead to problems (Personal communication, RIVM draft dossier).

To conclude, for most wire coatings alternatives for NMP seem to be available. From the literature one could also deduce that for the thermal resistant and high quality magnetic wire coatings (PAI), technically feasible alternatives are available for NMP. Based on the literature, it is not clear if these alternatives are technically and economically feasible in practice if they are applied on a commercial basis. During stakeholder consultation, wire coating industry indicated that no alternative for NMP was available, neither expected in the near future (personal communication, RIVM draft dossier).

Cleaners

Cleaning agents in the industrial setting

As mentioned in part B.2.2, NMP is used as a cleaning agent in various industries. Some of these uses are discussed in the dedicated use categories (e.g. electronics and semiconductor industries). In the early nineties NMP replaced methylene chloride (dichloromethane, DCM) as a cleaning agent (Jackson & Gallagher, 1990, Xiaofei et al. 2000, Anundi et al 2000). Jackson & Gallagher (1990) describe that most of the polyurethane was blown out of the machines for polyurethane processing with nitrogen or air followed by pumping through a solvent such as methylene chloride. The alternatives for methylene chloride should amongst other characteristics, have adequate solvent power, be easy to remove and be safe for man and environment. Six solvents fulfilled the criteria: Du Pont's dibasic esther solvent (DBE), NMP, ethyl 3-ethoxypropionate (EEP), propylene carbonate (PC), tripropylene glycol ethyl ether (TPM) and dimethyl phthalate (DMP). Finally DBE and TPM were tested and showed better results than methylene chloride. For certain polyeruthane adhesives the authors recommended a combination of DBE and NMP. For the optical industry, signals have been received that finding alternatives of NMP in the cleaning process might be problematic. There might be more industrial uses for which no alternatives are readily available, however, no information on alternatives for other industrial uses has been received.

Paint stripping and graffity removal

Paint strippers are applied to remove paint from various substrates. Paint strippers generally contain a variety of chemicals which facilitate removing the paint. In the 1970s benzene was applied in paint strippers, but was later replaced by methylene chloride because of the health risks of benzene. Subsequently, methylene chloride was replaced by NMP in the 1990s for the same reason (see for instance Inman, 1991).

Graigner (1991) distinguishes three types of paint strippers: aqueous strippers, solvent strippers and mixed or semi-aqueous strippers. Organic solvents, e.g. NMP, are an important ingredient of solvent strippers. Besides the primary solvent, the products may contain co-solvents such as alcohols, ketones and/or aromatic solvents plus so-called activators such as ammonia, amines, formic acid and phenol. They may also contain minor amounts of thickeners, corrosion inhibitors, surfactants and evaporation retardants to regulate the evaporation. The performance of the paint stripper depends on the type of paint and the composition of the stripper. This already indicates that finding an alternative is not simply replacing NMP by another solvent.

NMP also serves as a solvent for a range of coating polymers such as acrylates, epoxy resins, polyurethane lacquers, printing dyes and insulator plastics (HSE 1997; Åkesson 2001). US Navy (2003) indicate that NMP-based formulas will effectively strip acrylic latex gloss, epoxy spray paint, polyurethane gloss enamel, high gloss polyurethanes and tallow oil alkyd spray paints. The US Navy (2003) indicated that the one step application and the miscibility with water can be considered as advantages of NMP, whereas the cost is mentioned as disadvantage.

Sullivan (1991) describes the performance of some alternatives for methylene chloride. Besides NMP, a combination of ethylene chloride:toluene:methanol (85:10:5) and acetophenone showed to perform well. Also furfuryl alcohol, gamma-butyrolactone and dibasic esters are mentioned in this article. A report from the EC (EC, 2004) on reducing the risks to human health from paint strippers containing dichloromethane identified di-glycol-ethers, di-basic ester, solvent naphta and n-methyl-pyrrolidone as typically used solvents in DCM free paint strippers.

Hickman (1991) mentions some formulations in which acetophenone and methanol/toluene are important ingredients. More recent publications mention DMSO as alternative for NMP (Gaylord 2011). The California Department of Health Services (2006) indicate that for a number of cases to remove paint or graffity soy-based products or use of mechanical methods such as wheat starch blasting might be possible or to change to solvent-free paint strippers. If that is not possible, they recommend benzyl alcohol as a possible safer alternative.

A product sheet by Llyondell describes that NMP is also used for cleaning sulfur containing polymers, such as polysulfides. Polysulfides are commonly applied in aerospace industry, construction and insulating glass industry. The sheet refers to the use of dimethylacetamide or dimethylformamide as alternative for polysulfide sealant removers, but these substances show higher acute toxicity. The sheet also refers to a number of other solvents among which DMSO, GBL, methylene chloride, DBE and acetone, but these showed to be less effective in removing six sulfur containing sealants. Experiments by US Navy (2003) showed that NMP was not effective on cured epoxy and polysulfide adhesives compared to MEK (Methyl ethyl ketone). Kelly & Considine (2006) studied the performance of different hazardous air pollutant free type of paint strippers for army applications to be applied by immersion process and manual process. Among the possible alternatives were paint strippers containing methylene chloride, NMP, hydrogen peroxide and benzyl alcohol. The benzyl alcohol-formic acidic strippers showed to be the most effective product for removing the different chemical agent resistent coatings against which they were tested. Potential alternatives for paint stripping mentioned by Reisch (2008) were benzyl alcohol and ethyl lactate.

The use of NMP for the removal of graffity has been described in various publications (e.g. Anundi et al 2000, Langworth et al 2001). Anundi et al (2000) provide the content of a number of graffiti solutions used by graffiti removers in Stockholm. Four out of the 20 products contained 10-30% NMP. The NMP-free products contained DEGEE (diethylene glycol monoethyl ether), EGBE (ethylene glycol monobutyl ether) or DPBBE (dipropylene glycol monobutyl ether) or a combination of these substances, but there were also products containing sodium hypochlorite, sodium hydroxide, colza oil ester, or formic acid as main ingredient. All graffiti removal products studied by Crook & Simpson (2007) contained NMP in concentrations between 10 and 80%. A paper from Craver et al (2011) mentions monoethanolamine, potassium hydroxide and EGBE as alternatives, but also indicate that preventing graffiti by superior design and local community support is the most environmentally friendly way of dealing with graffity.
Nowadays there are products on the market containing combinations of benzyl alcohol and 3-butoxypropan-2-ol, and combinations of 3-butoxypropan-2-ol, GBL (butyrolactone) and isopropylamine C10-14 alkyl benzene sulphonate. There are also graffity removers containing dioxolanemehylal and a combination of 2-butoxyethanol A3 and ethanolamine. Benzyl alcohol seems to be the most commonly used ingredient. Information received in the consultation

indicated that the use of NMP in graffiti removers has been phased out by some users (personal communication, AMEC Questionaire).

Via the Member State consultation by ECHA, it was confirmed that NEP is used as a component in stripping agents that these are free of dichloromethane (DCM). Via the Member State consultation, information provided indicated that some installers of foam insulation installations who used NMP and products containing NMP to clean their spraying equipment have reported the use of xylene as an alternative for this application. The Member State consultation also indicated that Sweden already has specific rules in place prohibiting the use of possible alternatives for NMP in paint stripping products like the use of gamma-butyrolactone. Specific information on these alternatives has not been provided by industry and its use is expected to be limited.

To conclude, alternatives appear to be available for paint stripping and graffiti removal applications. The phase out of NMP in these applications is already ongoing.

Electronics and semiconductor industries

Electronic industries

No information has been found on the availablility of alternatives of NMP in the electronics industry. However, some comparison with alternatives in the semiconductor industry might be possible as some of the use characteristics are assumed to be comparable.

Alternatives in semiconductor industry (literature)

As mentioned in part B.2.2, five applications of NMP in the microelectronics semiconductor industry can be distinguished:

- stripping photoresist from wavers (solvent baths)
- solvent carrier for "die coat" (solvent baths)
- dissolving phenolic residues from "packages"
- pre-softener for ink removal (paint stripper)
- cleaning of mold dies (sprayed onto molds)

In this section, only alternatives for the use of NMP in photoresist stripping is described as no information on alternatives in the other sub-uses of NMP could be found.

NMP is mainly used in stripping of positive photoresist and hardly for negative photoresists. The information presented below mainly comes from various sources of literature. Information on alternatives received in the consultation is presented in a separate section below.

NMP is hardly used for negative photoresists, such as SU-8. Solvents used for negative photoresists are methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), cyclopentanone, and propylene glycol monomethyl ether acetate (PGMEA). PGMEA replaced more volatile solvents such as N-butyl acetate (NBA) and ethyl lactate (e.g. Darling 2000). Photoresist stripping is applied at the end of the tone processing after hard baking and etching of the photoresist. The process of photoresist stripping has been described by Lee (1996). Lee (1996) distinguishes three different stripping mechanisms: oxidation, e.g. by the so called dry process with O_2 plasma, dissolution with a solvent stripper and reduction with H_2 plasma. Preferred wet strippers based on dissolution, contain a solvent and an amine. The resist is being removed by the processes of penetration, swelling and dissolution (Lee, 1996; Peters et al., 2003). Strippers may also contain surfactants or corrosion inhibitors such as catechol.

The stripping depends on the composition of the resist and the solvent used in the stripping agent (e.g. Chatzichristidi et al 2002). The solvents should preferably have a high boiling point, should decompose only slowly, should remove the photoresist without leaving much residue and should not attack the other layers. Reinhardt & Reidy (2011) describe that early photoresist resins were composed of vinyl polymers, which were dissolved in methylene chloride, tetrachloroethylene and NMP. Rheinhardt & Reidy (2011) further describe the cleaning process using NMP and the problems that had to be solved. Industry indicated in the consultation that NMP removal and cleaning processes are robust and have a wide process window.

Suhard et al (2012) describe the search for alternative wet solvents that are greener and more cost effective for stripping positive and negative photoresist compared to NMP. They tested NMP, DMSO, benzyl alcohol, an aqueous system with an alkaline and two alkaline containing solvent mixtures. NMP, DMSO and benzyl alcohol as well as the two alkaline containing solvents performed well for

the positive photoresist. The three solvents did not perform well for the negative photoresist, whereas the alkalines did. Besides DMSO, sometimes N, N-dimethylformamide (DMF) is mentioned as solvent for photoresists. Cornell University (2013) describes a process where photoresist is being removed by acetone, or by two commercial strippers containing NMP in combination with other solvents. The latter two were more effective in leaving less residue. Other positive strippers mentioned are acetone, trichloroethylene (TCE), and phenol-based strippers, although some sources indicate that acetone is not very well suited as it evaporates very fast. Other positive photoresist strippers are based on a combination of dimethyl sulfoxide and dipropylene glycol monomethyl ether, a combination of dipropylene glycol monomethyl ether and isopropanolamine, a combination of ethyl lactate, 2-Heptanone and propylene glycol monomethyl ether as main constituents or a combination of gamma butyrolactone and dipropylene glycol methyl ether acetate. Trikiriotis et al (2009) describe the development of inorganic photoresists which are etched with SF6/O2 plasma. Such photoresists do not need organic solvents.

Lee (1996) provides an overview of photoresist stripper patents in which NMP, NMP/sulfolane, DMF/sulfolane, DMSO, DMSO/GBL, NMP/DMF, DMAC, and DMF are mentioned as solvents. Analysis of the compositions of various commercial strippers showed a variety of solvents to be present in positive photoresist strippers, with NMP being most abundant used in concentrations between 35 and 100%. Some strippers contained more than 99% NMP. Other solvents that were used in percentages of more than 50% were propylene glycol (in combination with NMP), sulfolane (in combination with NMP), 2-(2aminoethoxy)ethanol (in combination with NMP), butoxyethanol (ethylene glycol monobutyl ether), dimethyl sulfoxide (DMSO), dipropylene glycol monomethyl ether (DPGME) and N-Methylethanolamine). Of a number of products which did not contain NMP, percentage of the alternative constituents could not be retrieved. These products contained dodecylbenzene sulfonic acid, o-dichlorobenzene, perchlorethylene (PER) and phenol or aromatic hydrocarbon solvent (aromatic naphtha C7 gasoline feedstock), naphthalene, and ethylene glycol phenyl ether as solvents. Sometimes 1,3 Dimethyl-2-Imidazolidinone (DMI) is mentioned. Also Challener (2006) indicated that wet strippers are often comprised of NMP as a solvent and monethanolamine as an amine compound.

Although the survey for this document was not an extensive survey into the details of wafer cleaning and stripping, data from suppliers indicated that besides a vast amount of NMP-based positive photoresist strippers, there are NMP-free products on the market. Fujifilm supplies both NMP-based and DMSO based positive photoresist strippers (Fujifilm, 2013b). The EKC/DuPont EKC800 series contains NMP, but EKC922 is composed out of alkylbenzene sulfonic acid as a surfactant, heavy aromatic solvent naphtha, catechol as a corrosion inhibitor and naphthalene. PRX-127 from Rohn&Haas is based on DMSO and DPGDME, ACT970 from Air Products has N-methylethanolamine as main constituent, whereas 600-019 from Mega electronics consists of butoxyhexanol and monoethanolamine. An information sheet by MicroChemicals (2009) indicate acetone, NMP, DMSO and alkaline solutions, such as 3% KOH or NaOH, and the amine/solvent based AZ100 as possible removers, but indicate that acetone is not very suitable because of the high vapour pressure. Futurrex (2013) provide an aqueous based solvent, an ester based stripper and two DMSO based strippers. An AZ formulation sheet indicates that AZ 5200 series photoresist postbaked below 120 °C can be removed by AZ 1500 thinner, AZ EBR solvent, both composed of propylene glycol monomethyl acetate or 1-Methoxy-2-propanol acetate (PGMEA), or by electronic grade of n-butyl acetate and similar solvents. For photoresists post-baked above 120 °C peroxysulfuric acid (Caro's acid). AZ300T stripper, mainly consisted of propylene glycol and NMP, or oxygen plasma dry stripping are recommended (AZ Electronic Material, 2000).

In conclusion, several methods are technically available to perform stripping of photoresists. In strippers used in wet-stripping of positive photoresist NMP is generally applied in concentrations between 35 and 100%. At present, a limited number of NMP-free alternatives are available. No information was gathered on the technical feasibility and the costs of changing from one application to another. The information received during the stakeholder consultation indicated that there is no simple drop-in alternative for NMP available.

Alternatives in semiconductor industry (personal communication, RIVM draft dossier)

During stakeholder consultation it was stressed that cleaning in the semiconductor industry is very different from what is meant by cleaning in other sectors. Industry did not agree with the sub-uses as presented in the literature section above and provided an alternative description on the use of NMP in the semiconductor industry. According to industry, NMP is essentially used as a processing aid in order to enhance a chemical reaction driven by its solvent characteristics. The features on a semiconductor device are measured in nanometers.

The European Semiconductor Industry Association distinguish two important processes in which NMP is being used within the European semiconductor industry:

a. wafer cleaning and stripping to remove organic contamination and organic layers and
b. as a solvent in dedicated formulations (i.e. precursor solutions for wafer coatings such as polyimides and anti-reflective coatings). ESIA indicated that polyimides are applied as a protection layer in a wide range of semiconductor products.

On wafer cleaning, ESIA indicated that "There has been varying degrees of success in inventing suitable alternative chemistries, however, there is no blanket replacement currently available that delivers the same required performance that NMP based cleaning solutions deliver today." Whereas on the solvent in dedicated formulations it was indicated that "For niche areas that do not require the same performance, NMP-free or NMP-light products have been invented. For the majority of semiconductor uses, NMP-free or NMP-light products, which deliver equal or at least acceptable performance as NMP based solutions, still need to be invented and subsequently qualified."

Based upon the information provided by industry it can be concluded that for both sub-uses of NMP no alternative has been found so far that can fully replace the use of NMP.

Overall conclusion on the availability of alternatives in the semiconductor industry

The information on alternatives presented by industry is not fully in line with the information that has been found on alternatives in literature. At least for the photoresist stripping, the information presented in the section above indicates that alternatives could be available. However, as no information has been found on the other sub-uses of NMP in the semiconductor industries, it is not possible to conclude on the availablibity of alternatives of NMP for the full semiconductor industry. It is also realized that, that if an alternative for photostripping is phased in, the whole stripping process needs to be optimized again.

Battery industries

As described in part B.2.2, NMP may have various applications in lithium batteries production and is also used for other hybrid batteries using nickel, magnesium, or cobalt. Looking at alternatives for NMP in the battery application, Zackrisson (2010) carried out experiments in which water replaced NMP as a solvent for the PVDF binder of the cathode. As water was used, another binder was applied. The experiments showed that technically it is possible to replace NMP by water, although the commercial application still has to be proved. There are already commercial binders based on styrene butadiene rubber for application as a binder in lithium batteries that do not need NMP (Targray, 2013). There are also several other efforts to replace PVDF by water soluble binders to reduce the use of NMP (e.g. Pohjalainen et al 2012). Also in industry there are steps forward to water soluble binder based techniques (Muthu & Battaglini, 2009). To what extent these alternatives are already available on a commercial sclae is not clear from the literature.
To conclude, the development on NMP free lithium ion and other hybrid batteries is ongoing, however, at this moment no alternatives have been proven on a commercial scale. Some supporting confidential information has been provided during the public consultation of the Annex XV restriction dossier (public consultation 2013/2014)

Membrane manufacturers

Aroon et al (2010) provides an introduction in the membrane fabrication as well as an overview of a number of combinations of additives, solvents and polymers used. Generally NMP, DMSO, DMF and DMAC are used in membrane preparation as they have a high boiling point, and are miscible with water. THF may also be applied, but is more volatile. The membranes are applied in a variety of (industrial) processes such as gas separation, nanofiltration, ultrafiltration and desalination and as such different types of membranes exist. The choice of a certain polymer strongly depends on the type of application of the membranes. For certain applications, only PVDF, PSU or PES are possible polymers.
The substitution of NMP as a solvent will depend on the type of polymer used. For the relatively solvent resistant polymers such as PAI, PI and PVDF there are less options than for less solvent resistant polymers such as PANI and PU. From the stakeholder consultation it appeared that some

research has been carried out by a membrane manufacturer to replace NMP, but at present still without suitable results.
In conclusion, literature data suggest that alternatives for NMP are available even for the more solvent resistant polymers, but their technic and economic feasibility on production scale has not yet been shown.

High performance polymer manufacturing

In first instance, a combination of HMPT (hexamethylphosphoramide) and NMP (N-methylpyrrolidon) was being used for the polymerization of difficult soluble polymers like PPTA used in the production of high performance polymers. The combination of HMPT/NMP was replaced by a combination of NMP and $CaCl_2$, because HMPT was expensive and was related to certain insecticides. Later on HMPT proved to be carcinogenic. Now, NMP/$CaCl_2$ is both used by Teijin and by DuPont to produce poly(p-phenylene
terephthalamide) (PPTA) under the tradenames Twaron and Kevlar respectively. Also for the production of other aramids NMP may be used (Denchev & Dencheva, 2012).

To conclude: No alternative solvents have been identified so far for this application. The fact that production using NMP and $CaCl_2$ was once patented and used by various producers, indicate that there is probably not an easy phase-in alternative.

Agricultural chemical industries (synthesis and formulation)

As described in part B.2.2, NMP is used in the agrochemical industry both as a solvent in the synthesis of active ingredients and as a co-solvent in the formulation of agrochemicals. The information on alternatives described here only includes the use of NMP as co-solvent. No information has been found on alternatives for the use in the production of active ingredients and therefore it is not possible to conclude on the availability of alternatives to NMP in this process.

Knowles (2005) mentions propylene glycol ethers, ethylene, propylene, and butylene carbonates, methyl-, ethyl-, butyl- and ethylhexyl lactates and gamma-butyrolactone, and tetrahydrofurfuryl alcohol as possible alternative solvents for NMP. He indicates that alternative polar solvents are being investigated as possible replacements. Solvents containing NMP may still be available for the European market (see for instance Agsolex 1 from Ashland). In US-EPA (2006), the use of DMSO as a solvent in pesticides is mentioned.

For the use in biocides, information provided by the producer indicates that the solubility of the active ingredient can be enhanced by either NMP or DMF (BASF, 2000, 2001).

To conclude, alternatives of the use of NMP as a co-solvent in agrochemical products (formulation) are readily available. Personal communication with industry indicated that industry is at this moment replacing the use of NMP as co-solvent and expects to finalise replacement by 2015 (Personal communication, RIVM draft dossier).

Pharmaceutical industry

As described in part B.2.2, NMP is used for multiple purposes in the pharmaceutical industry. It is both used in the production of pharmaceuticals as in pharmaceutical products.

Pharmaceutical production

At the end of 2012 the American Chemical Society offered a grant for research into greener solvents for pharmaceutical production. Besides NMP, DMF and DMAC are mentioned. NMP, DMF and DMAC are used both for reactants and the final product. Their strong dissolving ability causes organic reactions that can not be achieved by weaker solvents. The proposal states "A significant drawback though is often the large quantity of aqueous extractions needed to remove these polar aprotic solvents from processes. This can result in high process mass intensity and substantial wastewater contamination. However, the main disadvantage is that DMF, NMP and DMAC are known reproductive hazards." The proposal mentions the solvents N-formyl morpholine (CAS # 4394-85-8), propylene carbonate (CAS# 108-32-7), and dimethylisosorbide (CAS# 5306-85-4) as possible alternatives, but invites participants to come up with others. DMSO and acetonitrile are

considered to be out of scope of this proposal, although an argumentation is lacking (American Chemical Society Green Chemistry Institute, 2012). In some instances 1,3 Dimethyl-2-Imidazolidinone (DMI) has been mentioned.

To conclude, the disadvantages of the use of polar solvents such as NMP are recognized, but the research grant mentioned above indicates that at present, there are no drop-in alternatives available.

Use in pharmaceutical products

A research paper from 2003 mentions "the use of new polymers and solvents to provide additional benefits in long-term drug release and tissue compatibility" as one of the areas for development for Atrigel (Dunn, 2003). The solvents used can be either hydrophobic or hydrophilic. Although NMP is often applied, alternative solvents mentioned are polyethylene glycol, tetraglycol, glycol furol and DSMO.

Organic solvents are also used as vehicles for precipitation of liquid embolics, where a polymer is mixed with an organic solvent in order to form a solid cast at a specific site in the body (Dudeck et al 2006). Dudeck et al (2006) carried out experiments with DMSO, dimethyl isosorbide, ethyl lactate, glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether), NMP, and solketal (D,L-,-isopropylidene-glycerol). Dimethyl isosorbide and NMP performed better in terms of side effects than the commonly used DMSO in nonadhesive liquid embolics (Dudeck et al 2006).

Bendels et al (2006) carried out experiments with eight difficult soluble drugs measured under 15 combinations of six different excipients and ionic strength adjusters in order to assess the effect of excipients on the permeability. Quantities of excipient were selected to match the concentrations expected in the gastrointestinal fluid under clinically relevant conditions. Excipients tested were potassiumtaurocholate, 2-hydroxypropyl-b-cyclodextrin, potassium chloride, propylene glycol, 1-methyl-2-pyrrolidone (NMP), and polyethylene glycol 400 (PEG). Jouyban et al (2010) compared the properties of NMP with that of other applicable solvents such as ethanol, dimethylacetamide (DMAC), dimethylsulfoxide (DMSO), glycerol, isopropanol and propylene glycol.

Other co-solvents mentioned either applied oral or intravenous:

- N-methylpyrrolidone (NMP) 10–20% (oral, i.v.)
- dimethyl sulfoxide (DMSO) 10–20% (oral or i.v.)
- N,N-dimethylacetamide (DMA or DMAC) 10–30% (i.v.)
- Ethanol 10% (oral, i.v.)
- propylene glycol (PG) 30–60% (oral, i.v.)
- polyethylene glycol 400 40–100% (oral, i.v.)
- diethylene glycol monoethyl ether 30% (oral)

In 2011 the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2011) published the ICH Tripartite Guideline: Impurities: Guideline for residual solvents. Q3C(R5). The ICH proposed to list NMP as a solvent that should be limited in pharmaceutical products (class 2 solvents) because of its inherent toxicity and provided a permissible daily exposure (PDE) and a concentration limit from a toxicological point of view. Alternatives should preferably be taken from the class 3 solvents (solvents with low toxic potential which should be limited by GMP or other qualitybased requirements) or class 2 solvents with higher PDE or concentration limit. Among the Class 3 substances are also substances mentioned for the replacement of NMP in other applications such as acetone, dimethyl sulfoxide (DMSO), ethyl acetate, and formic acid.

To conclude, for many of the uses of NMP in pharmaceutical products, alternatives seem to be available and are even recommended by the ICH (ICH, 2011). However, from the data gathered no information could be retrieved on the percentage of replacement of NMP by alternatives in practice.

Laboratory

During the stakeholder consultation it was indicated that apart from chemical synthesis main laboratory use is in diagnostics and quality control. No further substantial information on laboratory use was found.

The information considered, described the use of NEP and DMSO as alternative for NMP in laboratories mainly as reagent (NEP) or as intermediate for chemical synthesis (DMSO). The Annex XV SVHC dossier on DMF also reported the use of DMF as laboratory chemical. These uses have, however, not been investigated further and no specific information has been received from industry on this use. Industry indicated that although many solvents are being used for laboratory use they are not simply exchangeable. NMP belongs to the group of aprotic solvents as NEP, DMF, DMAC, DMSO, acetonitrile, and toluene. Among these there are low polar solvents (toluene, dichlormethane), medium polar solvents like NMP, NEP, DMF, DMAC, and high polar solvents (DMSO, Formamide).

To conclude, alternatives to NMP in laboratory use might be available. However, the exchangeability of various solvents will differ per actual laboratory use and there might be uses in practice in which no alternatives for NMP are available.

Functional fluids

NMP is used in functional fluids. As described in section B.2.2, various uses as functional fluids exist (cable oils, transfer oils, coolants, insulators, refrigerants, hydraulic fluids in industrial equipment including maintenance and related material transfers). Glycols are also used in functional fluids as a solvent (Huntsman, 2006). If they are used for the same purposes as NMP is not clear from the description. No specific information on the replacement of NMP in functional fluids by alternatives was obtained.

Gartiser & Urich (2002) mention the use of NMP in cooling water systems as an auxiliary additive and estimate the use for industrial cooling systems within Germany to 0,2 tonnes per year. The consumption of NMP was not systematically surveyed. No alternatives were mentioned in the study.

To conclude, it was not possible to draw a conclusion on the availability of alternatives in functional fluids based on the information gathered. This is partly due to the lack of information on the functionality of NMP in these applications.

Construction chemicals

As described in section B.2.2, the use of NMP in construction chemicals might involve polymer dispersions, powders and solutions. However, description of construction chemicals is poor and little information was obtained from the literature on the application of NMP in construction chemicals, nor was it supplied by the NMP-producers. Theoretically, polyurethane dispersions used in construction chemicals may use dipropylene glycol dimethyl ether or other solvents as replacement for NMP.

To conclude, not much information was obtained on application of NMP in construction chemicals, nor on the availability of alternatives. However, there are signals from industry that MNP is not used anymore in construction chemicals. This suggests that alternatives for this application are readily available.

Overall conclusion

A technical equally good alternative for NMP in the major applications (like wire-coatings and membranes) seems to be lacking. For other applications (like non-wire coatings and cleaners) alternatives are already available. Table C.01 provides an overview of the conclusions for the different uses.

Table C.01: *Overview of the availability of alternatives for different uses.*

Use category	Alternative available	Comment
Petrochemical industries	Possibly	Exchangeability will differ per use, technical and economic feasibility not shown
Non-wire coaters	Yes	Alternatives already available
Wire coaters	Possibly	Technical and economic feasibility not shown
Cleaners	Yes	Alternatives already available
Electronics and semiconductor industries	Possibly	Technical and economic feasibility not shown
Battery industries	No	Development ongoing
Membrane manufacturers	Possibly	Technical and economic feasibility not shown
High performance polymer manufacturing	No	Production already > 30 years through similar patented process
Agricultural chemical industries (synthesis and formulation)	Yes (formulation) Unknown (synthesis)	Replacement already ongoing
Pharmaceutical industry	Likely	Information very limited. Replacement recommended by the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
Laboratory	Possibly	Exchangeability will differ per use
Functional fluids	Unknown	
Construction chemicals	Yes	Based on signals that the use of NMP is stopped in this application

Selection of alternatives

Although the previous text in this chapter already indicated that the availability of alternatives may vary per use category and depends on the type of application (e.g. involving the use of chemical resistant polymers or not), the next part of the chapter will focus on the possible selection of alternatives for NMP with a broad range of applications.

In total about 70 alternative solvents have been identified for the whole spectrum of applications for which NMP is being used (see Annex 5). These alternatives have been mentioned throughout this chapter. Some alternatives may be quite specific for a certain application. Hydrogen peroxide for example, has only been mentioned as an alternative for NMP in paint stripping, perchloroethylene and naphthalene have only been mentioned as a solvent in photoresist strippers and ethanol, glycerol and isopropanol has only been mentioned as solvents in pharmaceuticals. These alternatives will not be discussed further here.

There are about 20 alternative solvents that are used in various applications for which NMP is also used. A fast amount of possible alternatives belong to the polar apriotic solvents: N-ethyl pyrrolidone, dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, acetone, propylene carbonate, gamma butyrolactone, dichloromethane, 1,3 Dimethyl-2-Imidazolidinone, sulfolane and hexamethylphosphoramide. Other solvents, such as dipropylene glycol monoethyl ether, diethylene glycol monoethyl ether (2-(2-Ethoxyethoxy)ethanol), ethylene glycol monobutyl ether, methyl ethyl ketone (butanone), benzyl alcohol, and ethyl lactate have been mentioned for similar purposes, but do not belong to the polar apriotic solvents. From these 20 alternatives specifically the polar apriotic solvents NEP, DMF, DMAC, DMSO, THF and acetone are often mentioned as alternative for NMP, as well as sulfolane, and DMI. From the non apriotic solvents ethyl lactate, methyl ethyl ketone and propylene carbonate are most mentioned.

Selection of alternatives for further consideration

The classification of the selected alternatives according to the ECHA classification inventory is provided in Table C.02. Of most substances a harmonised classification is available, but not for DMSO, DEGBE, DEGEE, GBL, DMI and 2-(2aminoethoxy)ethanol.

Table C.02: *Harmonised classification as retrieved from ECHA C&L Inventory database 23 March 2013 (ECHA, 2013).*

Substance	CAS nr	abbrevation	C&LHarmonised classification Hazard Class and Category Code(s) followed by Hazard Statement Code(s)
N-methyl pyrrolidone	872-50-4	NMP	Skin irritation: 2, H315 Eye irritation: 2, H319 STOT SE: 3, H335 Repro 1B, H360D***
N-ethyl pyrrolidone	2687-91-4	NEP	Repro 1B, H360D***
Dimethyl formamide	68-12-2	DMF	Acute tox: 4*, H312/332 Eye irritation: 2, H319 Repro 1B, H360D***
Dimethyl acetamide	127-19-5	DMAC	Acute tox: 4*, H312/332 Repro 1B, H360D***
Dimethyl sulfoxide	67-68-5	DMSO	
Tetrahydrofuran	109-99-9	THF	Flamable lquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H335
Acetone	67-64-1		Flamable lquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H335
Dipropylene glycol monomethyl ether	34590-94-8	DEGBE	
Diethylene glycol monoethyl ether	111-90-0	DEGEE	
Ethylene glycol monobutyl ether (butoxyethanol)	111-76-2	EGBE	Acute tox: 4*, H302/312/332 Skin irritation: 2, H315 Eye irritation: 2, H319
Methyl ethyl ketone = butanone	78-93-3	MEK	Flammable liquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H336
Propylene carbonate	108-32-7	PC	Eye irritation: 2, H319
Gamma butyrolactone	96-48-0	GBL	
Benzyl alcohol	100-51-6		Acute tox: 4* , H302/332
Methylene chloride = dichloromethane	75-09-2	DCM	Carc.:2 H352
Ethyl lactate	97-64-3	EL	Flammable liquid: 3, H226 Eye damage: 1 H, 318 STOT SE: 3, H335
1,3-dimethyl-2-imidazolidinone	80-73-9	DMI	
Sulfolane (tetramethylene sulfone)	126-33-0		Acute tox: 4* , H302
Hexamethylphosphoramide	680-31-9	HMPA	Carc.: 1B, H350 Mutagene: 1B, H340
2-(2-aminoethoxy)ethanol	929-06-6		

** The classification as obtained under annex VII shall than substitute the minimum classification indicated in this annex if it differs from it*

**** In oreder not to lose information from the harmonised classifications for fertility and developmental effects under directive 67/548/EEC, the classifications have been translated only for those effects classified under that directive*

Further information of the desirability of various solvents is provieded in Kerton et al (2009) and IHC (2011). Kerton et al. (2009) developed three solvent categories, i.e., preferred, usable and undesirable based on hazard profiles as described in table C.02. The preferred solvents are classified as 'green' alternatives for NMP. Kerton et al. (2009) also noted that few solvents are inherently green and most solvents can be handled safely in well designed plants with appropriate risk reduction measures in place (good recovery and recycle facilities).

The European Medicines Agency prepared a guideline for residual solvents in medicines. They distinguish four categories, from solvents that should be avoided (class 1) to solvents with low toxic potential (class 3) and solvents for which no adequate toxicological data were found (class 4). NMP was classified in class 2 (Solvents to be limited). Further information on the alternatives can be found in ICH (2011). The data from Kerton et al (2009) and ICH (2011) are summarized in tables C.03 and C.04.
Schäffner et al 2010 indicate that low toxicities and environmentally friendly properties make organic carbonates acceptable alternatives for standard organic solvents and valuable candidates to substitute polar, aprotic solvents such as NMP and DMF.

Table C.03: *A green chemistry-based solvent selection guide distinguishing three categories being preferred, usable and undesirable (Kerton et al., 2009).*

Category	Substance
Preferred	water, acetone (x), ethanol, 2-propanol, ethyl acetate, isopropyl acetate, methanol, methyl ethyl ketone (x), 1-butanol, t-butanol
Usable	cyclohexane, heptane, toluene, methylcyclohexane, methyl t-butyl ether, isooctane, 2-methyltetrahydrofuran, cyclopentyl methyl ether, xylenes, dimethylsulfoxide (x), acetic acid, ethylene glycol
Undesirable	pentane, hexane(s), di-isopropyl ether, diethyl ether, dichloromethane (x), dichloroethane, chloroform, dimethylformamide (x), n-methylpyrrolidone (x), pyridine, dimethylacetamide (x), acetonitrile, tetrahydrofuran, dioxane, Dimethyl ether, benzene, carbon tetrachloride

x: potential alternative mentioned for this application.

Table C.04. *Classification of residual solvents in pharmaceuticals (ICH, 2011)*

Class 1	Benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane
Class 2	Acetonitrile, Chlorobenzene, Chloroform, Cumene1, Cyclohexane, 1,2-Dichloroethene, Dichloromethane (x), 1,2-Dimethoxyethane, N,N-Dimetylacetamide (x), N,N-Dimethylformamide (x), 1,4-Dioxane, 2-Ethoxyethanol, Ethyleneglycol, Formamide, Hexane, Methanol, 2-Methoxyethanol, Methylbutyl ketone, Methylcyclohexane, N-Methylpyrrolidone (x), Nitromethane, Pyridine, Sulfolane (x), Tetrahydrofuran, Tetralin, Toluene, 1,1,2-Trichloroethene, Xylene*
Class 3	Acetic acid, Acetone (x), Anisole, 1-Butanol, 2-Butanol, Butyl acetate, tert-Butylmethyl ether, Dimethyl sulfoxide (x), Ethanol, Ethyl acetate, Ethyl ether, Ethyl formate, Formic acid, Heptane, Isobutyl acetate, Isopropyl acetate, Methyl acetate, 3-Methyl-1-butanol, Methylethyl ketone (x), Methylisobutyl ketone, 2-Methyl-1-propanol, Pentane, 1-Pentanol, 1-Propanol, 2-Propanol, Propyl acetate
Class 4	1,1-Diethoxypropane, 1,1-Dimethoxymethane, 2,2-Dimethoxypropane, Isooctane, Isopropyl ether, Methylisopropyl ketone, Methyltetrahydrofuran, Petroleum ether, Trichloroacetic acid, Trifluoroacetic acid

Class 1 solvents in pharmaceutical products. (solvents that should be avoided)
Class 2 solvents in pharmaceutical products. (solvents that should be limited)
Class 3 solvents which should be limited by GMP or other quality based requirements. (Solvents with Low Toxic Potential)
Class 4 solvents. Solvents for which no adequate toxicological data was found
x: potential alternative mentioned for this application.

When considering the harmonised classification in Table C.01 and the recommendations in Tables C.02 and C.3, the replacement of NMP by NEP, DMF, DMAC, DCM and HMPA is not recommended as these substances are classified or are in the process of being classified as reprotoxic or carcinogenic. GBL is also not recommended as an alternative. It is closely linked with gamma-hydroxybutyric acid (GHB) from which it can also be synthesised. Although GBL may be strictly regulated nationally, there is no international restriction. During stakeholder consultation it was further mentioned that GBL is in practice never used as a sole solvent, but needs co-solvents like cyclohexanone. In the past NMP replaced dichloromethane, because of its toxicity and hexamethylphosphoramide (HMPA) because of its carcinogenity. These two solvents can not be considered as realistic alternatives for the replacement of NMP. As alternatives for HMPA also DMI and DMSO are mentioned.

Acetone, MEK, ethyl lactate and DMSO have been mentioned by Kerton et al (2009) and ICH (2011) as preferable or usable alternatives or as solvents with low toxicity, respectively. In fact, these substances have already replaced NMP in a number of applications such as PU dispersions and graffity removers. Replacement of NMP by NEP was chosen by some suppliers, but will not be recommended because of its proposed classification. Finally some suppliers of PUDs are replacing NMP with organic solvents like acetone and Methyl ethyl ketone (MEK) which is being removed at the end of the PUD preparation. This results in solvent free PUDs which need alterative coalescing agents during drying. This means, however, that all waterborne products that were just introduced to fulfil the requirements of the VOC directive 2004/42/EC, need to be reformulated with binders which suppliers have not yet developed over the full range and are not yet on the market.

After selection based on toxicity characteristics only DMSO, acetone, MEK, ethyl lactate, DMI and 2-(2aminoethoxy)ethanol were selected as possible alternatives. In practice these solvents are already applied in a number of applications. For DMI and 2-(2aminoethoxy)ethanol no harmonised classification is available and only limited information is avaialable on toxicity. 2-(2aminoethoxy)ethanol is registred in ESIS as an HPV and some data are present in the IUCLID dataset. DMI is registred as LPV, and no dataset is present For 2-(2aminoethoxy)ethanol the AEE Consortium has submitted a document within the US High Production Volume Challenge Programme, in order to identify data gaps in the data set, and recommend additional tests, which may be conducted to characterize sufficiently the Screening Information Data Set (SIDS) data elements (AEE Consortium, 2009). Both substances have not been evaluated further. Of the remaining alternatives, it is supposed that DMSO resembles NMP most as it is also a polar apriotic solvents.

Eventually, DMSO was selected as substance as it is also a polar apriotic solvent, it was mentioned as alternative to NMP for most applications, and has most use and hazard information available to be described in more detail in this chapter. Industry also indicated that DMSO is the main long-term alternative to NMP available on the market. Whilst DMSO certainly is not a drop-in substitute for all applications, it has a broad spectrum of uses in which it could replace NMP, significantly reducing environment and/or health risk (public consultation Annex SVHC dossier). The possibility to use DMSO as an alternative to NMP has also been disputed by various stakeholders during the consultation.

C.2 Assessment of DMSO

For DMSO a SIDS Initial Assessment Profile is available, which has been agreed on at SIAM 26, 16-18 April 2008. Parts of the summary concluions of the SIAR of this profile have been incorporated in the assessment below without further editing (OECD, 2008).

C.2.1 Availability of DMSO

The following text is taken from the summary conclusions of SIAR (OECD, 2008). "The worldwide consumption of DMSO is estimated for the year 2004 between 30,000 tpa and 40,000 tonnes per annum. The production sites are located, one in Europe, one in Japan, one in the United States and several sites (3-4) of smaller size in China. Under REACH DMSO is registered within the volume quantity of 1,000 - 10,000 tonnes per annum. With its high polarity combined with a high electric constant, DMSO is known to be an excellent solvent for polar or polarizable organic compounds, and also many acids, alkalis and mineral salts. DMSO is used industrially, and not exclusively, as a reaction, polymerization, clean-up and pharmaceutical solvents, paint and varnish removers,

analytical reagent, in the manufacture of synthetic fibers, industrial cleaners and pesticides and in the electronic industry" (OECD, 2008). DMSO is also used in a number of photoresist strippers. In specific, the use in coatings (paints, inks, adhesives) and cleaning agents are similar to the use of NMP.

According to the SIDS (2008), 50% of the DMSO applications are in the pharmaceutical and agrochemical industries, 25% in the electronics, 10% in fine chemistry and 15% in other applications. Seen the high volume produced, it can be concluded that there is a good availability of DMSO although this may depend on the amount of DMSO needed for the uses that can be replaced by DMSO.

C.2.2 Human health risks related to DMSO

DMSO has no harmonised classification. There is an extensive physico-chemical, environmental and toxicological database available on DMSO demonstrating that DMSO is of low concern for the environment and the human health. (OECD, 2008). There is no valid carcinogenicity study conducted with DMSO according to OECD 414.

C.2.2.1 Toxicokinetic DMSO

"DMSO is well absorbed after oral exposure. Peak plasma concentration of DMSO was attained at 4 hours after oral dosing in humans and at 0.5 hours in rats. DMSO is widely distributed to all body tissues. Higher concentrations of DMSO were found in the kidney, spleen, lung, heart and testes of rats given an oral dose, while higher levels were noted in the spleen, liver and lungs following a dermal dose. In humans, the plasma DMSO clearance half-life was about 11 to 14 hours, and 20 hours after dermal and oral dosing, respectively. A shorter clearance half-life of 6 hours was observed in rats after both routes of exposure. Metabolism of DMSO takes place primarily in the liver and kidneys. The principal metabolite is dimethyl sulfone (DMSO2). Peak plasma levels of DMSO2 in humans were observed at 72 to 96 hours after dosing, and then declined with a half-life of about 60 to 72 hours. DMSO is excreted unchanged or as the metabolite DMSO2 in the urine. In the human, about 13 and 18% of a dermal dose, and 51% and 10% of an oral dose were accounted for by urinary excretion of DMSO and DMSO2, respectively." (OECD, 2008).

"No data is available on the absorption of DMSO by inhalation exposure. However, its physico-chemical properties (low molecular size, high polarity and water solubility) suggest that DMSO is significantly absorbed by the inhalation route. DMSO appears to be readily absorbed through the skin. An in vitro permeability rate of 176 g/m^2.hour has been reported for human skin. Maximal serum concentration of DMSO occurred at 4 to 8 hours following skin contact in humans, and at 2 hours in rats." (OECD, 2008).

C.2.2.2 Acute toxicity of DMSO

"DMSO is of low acute toxicity. In non-guideline studies, LD50 in rats are generally higher than 20,000 mg/kg bw and 40,000 mg/kg bw by the oral and dermal routes, respectively. In an acute inhalation study performed following the OECD TG 403, the LC50 in rats was higher than 5,000 mg/m3 for a 4-hour exposure." (OECD, 2008).

C.2.2.3 Subchronic toxicity DMSO

See chapter C.2.2.6.

C.2.2.4 Irritation DMSO

"A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days. In humans, repeated application of DMSO solution for up to several months could induce transient erythema, burning, stinging and itching, which returned to normal after discontinuation of treatment. In one study in humans, occlusive exposure to DMSO caused cell death of the outer epidermis, followed by rapid

regeneration.
DMSO is slightly irritating for the eye. In studies performed following the OECD TG 405 or the EEC method B.5, a slight to moderate conjunctival irritation, which cleared in 3 days, was observed in the eyes of rabbits. A repeated instillation (100% DMSO, 3 times/day for 6 months) in the eyes of rabbits induced only a temporary lacrimation but did not show any changes in the iris, cornea, lens, retina, conjunctiva and lids. In humans, the instillation of solutions containing 50 to 100% DMSO has caused transient sensation of burning which was reversible within 24 hours." (OECD, 2008).

C.2.2.5 Sensitisation DMSO

"DMSO is not a skin sensitizer. Sensitization tests performed in guinea pigs and mice following methods comparable to the OECD TG 406 were uniformly negative. A skin sensitization assay performed in humans was also negative." (OECD, 2008)

C.2.2.6 Repeated dose toxicity DMSO

"DMSO is of low toxicity by repeated administration. According to the results of a 13-week inhalation toxicity study compliant with the OECD TG 413, the No Adverse Effects Concentration (NOAEC) for DMSO could be established at ca. 1,000 mg/m3 for respiratory tract irritation and ca. 2,800 mg/m3 (the highest concentration tested) for systemic toxicity. Other non-guideline repeated dose toxicity studies performed by different routes of administration and with several mammalian species have also shown that DMSO produced only slight systemic toxicity. With the exception of a decrease of the body weight gain and some hematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common finding observed in these studies is changes of the refractive power of the lens. These ocular changes were observed following repeated oral application of DMSO at doses of around 3,000 mg/kg bw/d in rats for 18 months and 1,000 mg/kg bw/d in dogs for 2 years. Following repeated dermal application, the same effects were observed at doses of around 1,000 mg/kg bw/d in rabbits for 30 days, in dogs for 118 days and in pigs for 126 days. Similar ocular changes were not observed in monkeys following dermal application at doses of up to 9,000 mg/kg bw/d for 18 months (dose levels that caused marked ocular toxicity in sensitive species). Clinical signs of systemic toxicity and the alterations of the lens were also never observed or reported in clinical and epidemiological studies performed in humans, even after exposure to a high dose level (1,000 mg/kg/d for 3 months) or for a long period of time (up to 19 months). Overall, primates appear to be much less sensitive to DMSO ocular toxicity, and the ocular changes observed in rats, rabbits, dogs or pigs are not considered relevant for human health. Then, it is possible to estimate that the No Observed Adverse Effect Levels (NOAELs) by oral or dermal routes would be close to 1,000 mg/kg bw/d." (OECD, 2008).

C.2.2.7 Mutagenicity DMSO

"In studies performed with methods compliant or comparable to OECD guidelines, no genotoxic activity was observed for DMSO in gene mutation assays in *Salmonella typhimurium*, an in vitro cytogenetics assay in CHO cells and an in vivo micronucleus assay in rats. With few exceptions, a large battery of additional *in vitro* and *in vivo* non-guideline studies confirmed the lack of genotoxic potential." (OECD, 2008).

C.2.2.8 Toxicity to reproduction DMSO

"DMSO is not a reproductive toxicant. In a Reproduction/Developmental Toxicity Screening Test performed following the OECD TG 421, the NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on the progeny was considered to be 1,000 mg/kg/day. In addition, no effect was observed on the estrus cycle, the sperm parameters (count, motility and morphology) and the reproductive organs of male and female rats after a 90-day inhalation exposure to DMSO concentrations up to 2,800 mg/m3. In developmental toxicity studies performed according to the OECD TG 414, oral administration of DMSO to pregnant female rats or rabbits during the period of organogenesis was not teratogenic. The NOAELs for maternal toxicity were 1,000 and 300 mg/kg bw/d in rats and rabbits, respectively, and the NOAELs for embryo/foetotoxicity were 1,000 mg/kg bw/d in both species." (OECD, 2008).

C.2.2.9 hazards from physico-chemical properties of DMSO

Despite the low toxicity of DMSO, its physic-chemical properties may present hazards by themselves or from reactions with other chemicals if these are ill-considered. DMSO is known for its skin penetration enhancement of other substances. When DMSO is used as alternative this property of DMSO should be carefully considered. On the other hand, in medicines this property may be a desired one (public consultation 2013/2014).

Chemical reactions with DMSO and other substances can be of violent nature. This section will not deal with all possible reactions with groups of substances, but rather to describe possible reactions that might occur, in order to provide a more complete overview of DMSO as a possible alternative. Please refer to Bretherick's handbook of reactive chemical hazards, and reference therin related to DMSO (Urben (ed.), 2006). A DMSO manufacturer on the other hand stated that these properties are well-known and can be dealt with appropriately.

DMSO has some explosive potential in contact with specific chemicals (sometimes only at elevated temperatures). Based on this information a substitution of NMP by DMSO should be checked very carefully. Depending on the reactant the following reactions are described:

- strong exothermic decomposition reactions
- danger of explosions
- danger of flammability, respectively development of flammable gases or vapours
- Low heat dissipation due to high boiling point of DMSO

Additionally, the pure substance DMSO has no odour but it decomposes quite easily and due to the incorporated sulphur the decomposition products provide a quite distinct odour. Volatile and non-volatile decomposition products might influence the impurity profile/product quality of the newly synthesised product and might not be acceptable by every customer or downstream user.

C.2.2.10 Conclusion on human health DMSO

DMSO has limited human health toxicity as indicated by the absence of self-classification in the majority of notifications and based on the available summaries. It should be noticed, however, that DMSO acts as a skin penetration enhancer for many substances and the traditional rubber handgloves do not - in general – provide the desired protection. The public information on the REACH registration provides the following DNEL information.

Table C.05: *Longterm DNELs for DMSO based on the REACH registrations*

	systemic effects			**local effects**	
	Dermal	**oral**	**inhalation**	**dermal**	**inhalation**
Worker	200 mg/kg bw/day		484 mg/m3	no information available	265 mg/m3
General population	100 mg/kg bw/day	60 mg/kg bw/day	120 mg/m3	-	47 mg/m3

Compared to NMP, DMSO has no CMR properties and is of lower human health toxicity.

C.2.3 Environment risks related to DMSO

"DMSO is a liquid (density 1.1) with no color but in some cases a light characteristic sulfur odor due to traces of the raw material dimethyl sulfide. DMSO has a melting point of 18.5°C and a boiling point of 189°C (at 1,013 hPa). Its log Kow is of –1.35 (measured). DMSO has a vapor pressure of 0.81 hPa at 25°C and a Henry law's constant of 1.17 105 mol.kg-1.atm-1. DMSO is miscible in all proportion with water and with most of the common organic solvents such as alcohols, esters, ketones, ethers, chlorinated solvents and aromatics. DMSO is stable in water and is not expected to volatilize. DMSO Log Koc is estimated to be equal to 0.64. This value suggests that DMSO is mobile in soil. DMSO is not expected to adsorb to suspended solids, sediments and

soils. In atmosphere, DMSO is not susceptible to direct photolysis by sunlight. Calculations indicate DMSO half-life values, for reaction with OH radicals, from ca 2 to 6 h.

Distribution modeling using Mackay Fugacity model Level III, for equal release in the environment (i.e. 1,000 kg/h), indicates that the main target compartment will be soil (60.4%) and water (39.5%) with the remainder partitioning between air (0.0334%) and sediment (0.0723%). DMSO is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor lower than 4.
One readily biodegradation test performed following the norm AFNOR NF T 90-312 concluded that DMSO is readily biodegradable. Nevertheless, based on literature data and weight-of-evidence approach, better expectation is to consider DMSO as inherently biodegradable. For instance, 500 mg/L DMSO were entirely biodegraded within ca. 37h with aerobic settling sludge obtained from the activated sludge process at an opto-electronic plant, under optimized pH/temperature conditions. In a test report following OECD TG 303A, it has been validated that more than 90% DMSO was biodegraded at a concentration of 65 mg/L after 32 days of exposure.

Acute toxicity studies, carried out for some of them according to guidelines similar to OECD guidelines, reveal 48-hour EC50's ranging from 24,600 to 58,200 mg/L for daphnid (Daphnia magna) and 96-hour LC50's ranging from 32,300 to 43,000 mg/L for fish according to the species considered (eg. Ictalurus punctatus, Lepomis cyanellus). Modeling calculation for algae indicates 96-hour EC50 value of about 400 mg/L. On this basis DMSO can be considered non-toxic for aquatic compartment" (OECD, 2008).

C.2.4 Technical and economic feasibility of DMSO

C.2.4.1 Technical feasibility

DMSO is highly stable at temperatures below 150° C. Above, decomposition takes place, following a time-temperature function that can be accelerated by the addition of acids and be retarded by some bases. The decomposition, catalysed by acids, can even be relevant at lower temperatures. DMSO can react vigorously and even explosively with strong oxidizing agents, such as magnesium perchlorate and perchloric acid. These characteristics may limit application of DMSO (Gaylord Chemical Company, 2003).

Petrochemical industries

DMSO has been mentioned for the extraction of aromatic compounds from both the lube feed stock and from the light steam cracking effluents. For the latter, a process with DMSO and butane has been described for the extraction of aromats from C6-C8 chain (Hombourger et al. 2000). Confidential information provided during public consultation describes another extraction process with DMSO (public consultation, 2013/2014). DMSO has not been mentioned as alternative in the butadiene extraction.

Non-wire coaters

Industry indicated that DMSO can be substituted 1:1 NMP for liquid rheology additives for aqueous coatings, pigment concentrates additives, for solvent-borne and solvent-free systems. Laboratory testing has demonstrated that DMSO can also substitute on a 1:1 scale NMP as a coalescing agent and adhesion promoter in waterborne paints for most automotive and industrial uses. Customer approval is ongoing (public consultation Annex SVHC dossier). However, others indicated that for waterborne polyurethane dispersion paint w/o solvents specifically, the high melting point of DMSO and its chemical reactivity lead to breakdown above 150°C to sulphur oxides used to be the main technical limitations for this application (public consultation Annex SVHC dossier). In practice a number of DMSO containing non-wire coatings are available, noting that DMSO is not the only alternative being used in practice. Information from the public consultation indicated that DMSO was not deemed an appropriate substitution for NMP in the food contact materials for which coatings are used for technical reasons and odour annoyance due to sulphur (public consultation, 2013/2014).

Wire coaters

No information was available on wire coating from public literature. Although Murray (2008) did look for alternatives for polyamideimide, the conclusion was that at present no economically feasible alternative existed and further development was needed. However, DMSO was not considered in the paper as a possible alternative. As polyamideimide and polyimide are used, strong solvents have to be used. Although DMSO can be used for dissolving both polymers, there are no data that show it has already been applied in commercial products. Some industries indicated during the consultation that the degradation of DMSO at higher temperatures limitate its use in wire coating.

Cleaners

From the data gathered, it appears that there are a number of substances already in use to replace NMP. Of these substances, benzyl alcohol is frequently used. DMSO is only applied in a limited amount of products. Confidential information provided during the public consultation of the Annex XV restriction dossier describes some of the uses of DMSO (public consultation, 2013/2014).

Electronics and semiconductor industries and Battery industries

DMSO is used as a solvent in semiconductor industries and as a, solvent for polymeric battery separators in lithium ion batteries. These manufacturing environments are already tightly controlled. Specific information indicated that DMSO is a potential alternative for electronics (RCOM, CEFIC) with some technical limitations due to instability of DMSO. More specific information on the limitations, however, has not been provided.

High purity electronic grade of DMSO is used as a major component in some photoresist stripping formulations, and as an additive in specialized post-etch cleaning agents and edge bead removers. In these it may appear together with NMP or with other constituents. No technical limitations were described. DMSO performance is even similar to NMP (public consultation Annex SVHC dossier).

Membrane manufacturers

The use of DMSO is not found suitable for the production of membranes for drinking water filtering purposes, because of technical reasons. Important in the search to alternatives of NMP is that the viscosity of the alternatives needs to be comparable to that of NMP (personal communication, RIVM draft dossier). Contradicting information was received during the public consultation (public consultation 2013/2014).

High performance polymer producers

The information on the production of high performance polymer products does not indicate if DMSO can be used as an alternative for NMP. Information received during the public consultation stated that DMSO can be used in manufacture of several polymers (public consultation, 2013/2014).

Agricultural chemical industries (synthesis, formulation)

DMSO is one of the solvents mentioned as alternative solvent for NMP. From the data is not clear if DMSO is applied in the whole range of applications. Information provided during public consultation indicated that DMSO is used in the whole range of agricultural applications (public consultation, 2013/2014).

Pharmaceutical industry

NMP is among the substances that the ICH proposed to be limited in pharmaceutical products from a toxicological point of views (class 2 solvents). DMSO was, among others, classified by ICH as a class three substance: solvents with low toxic potential which should be limited by GMP or other

quality based requirements (ICH, 2011). Considering other literature, DMSO is already applied in pharmaceutica, but if this considers the whole range of products is not clear. Information provided during public consultation indicated that DMSO is used in the very wide range of pharmaceutical applications (public consultation, 2013/2014).For many other applications DMSO has been indicated as a potentially reactive chemical and that thermal instability can be induced by a range of chemicals / impurities. Industry claims that many incidents have been reported involving this solvent. From a safety point of view alone alternative solvents should be investigated before choosing DMSO as a reaction solvent (public consultation Annex SVHC dossier).

Laboratories

The information considered described the use of DMSO as alternative for NMP in laboratories as intermediate for chemical synthesis. No information is provided on technical limitations.

Functional fluids

The information on functional fluids is too limited to indicate if DMSO could be used as a feasible alternative for NMP in functional fluids

Construction chemicals

The use of DMSO as construction chemical in industrial use also remains unclear to date. No technical information was reported.

Other uses

For many other applications DMSO has been indicated as a potentially reactive chemical and that thermal instability can be induced by a range of chemicals / impurities. Industry claims that many incidents have been reported involving this solvent. From a safety point of view alone, alternative solvents should be investigated before choosing DMSO as a reaction solvent (International organization European Federation of Pharmaceutical Industries and Associations (RCOM, EFPIA)).

C.2.4.2. Economic feasibility

In general, DMSO is cheaper compared to NMP (personal communication, RIVM draft dossier; see also Appendix B, section 2.2.3). However, the selling price of DMSO is country-specific and industry stated that if DMSO would be technically feasible to replace NMP, it would already have been used. The data provided before in this chapter indicate that DMSO have been applied already in some processes and applications, such as the petrochemical industry, non-wire coatings, within photoresist strippers. Within paint stripping, membrane production and pharmaceuticals it seems to have been applied on a limited scale.

An issue concerning costs is that regulatory implications that may be associated with changing the solvent used in any stage of a commercial manufacturing process that is registered with the appropriate regulatory health authorities may invariably require extensive redevelopment of processes and associated interaction/authorisation from health authorities in order to ensure product quality, efficacy and patient safety.

C.2.5. Conclusion on DMSO

The use of DMSO as alternative for NMP has been described by industry for a limited number of applications. It is believed that due to both economic and toxic considerations industry would have

replaced NMP by DMSO if possible[15]. Regarding the remaining uses of NMP as described in chapter B, it is considered that DMSO is not a technical feasible alternative for all applications at this moment. As indicated earlier in this chapter, other solvents may be more feasible to replace NMP for specific applications. E.g. in paint stripping and graffity removal benzyl alcohol seems to be more favourable, whereas in some non-wire coatings acetone is being used. Both substances have a harmonised classification, but do not exhibit reprotoxic or carcinogenic characteristics.

The possible substitution of NMP by DMSO has been described, because DMSO is not classified as dangerous, contributes to the reduction of environmental and human health risks. For certain applications DMSO can definitely been used as described above. However, for other applications, different solvents have been preferred as possible alternatives, because of the limitations of DMSO. Amongst these, DMSO is, able to dissolve and transport other substances trough gloves and skin and can be considered as a skin penetration enhancer. In addition due to the characteristic that industry claimed that DMSO is under specific conditions (above 150°C) thermal instable, the application remains – so far – limited.

[15] *According to information submitted by DMSO manufacturers in the public consultation, DMSO seems to be a suitable alternative in a number of uses and there is no basis for stating that industry would have replaced NMP by DMSO if possible.*

D. Justification for action on a Community-wide basis

D.1 Considerations related to human health and environmental risks

As described in chapter B, NMP is used in many applications and exposure to NMP can be expected for workers (professional and industrial use). NMP is used in all Member States in a wide variety of applications in high volume. The human health risk is at EU-wide scale.

D.2 Considerations related to internal market

Coatings, paint strippers, industrial and consumers cleaners and other applications of NMP are traded freely and used in all Member States. NMP is both manufactured and imported in the EU. Also the products containing NMP are both manufactured in and imported into the EU.

An EU-wide measure, like a restriction or setting a condition to the manufacture or use, would remove the potentially distorting effect that a national measure may have on the free circulation of goods or the conditions in which NMP containing products are used (including the need for additional risk reduction measures). Acting at EU level would ensure a 'level playing field' for all users, manufacturers and importers of NMP and NMP-containing mixtures.

At this moment various national occupational exposure limits exists (between 20 and 200 mg/m3).

D.3 Other considerations

On the 20th of June 2011, NMP has been included in the REACH Candidate List. Therefore, measures for this substance are already taken on a Community-wide basis. Logically, additional measures should also be taken on a EU-wide basis.

D.4 Summary

The main reason to act on an EU-wide basis is the protection of human health from the adverse effects of NMP. Furthermore, the fact that the goods need to circulate freely within the EU stresses the importance of the EU-wide action. Since NMP is already included in the REACH Candidate List, possible additional measures should also be taken on a EU-wide basis.

E. Justification why the proposed restriction is the most appropriate Community-wide measure

E.1 Identification and description of potential risk management options

E.1.1 Risk to be addressed – the baseline

In chapter B the risk of NMP in the different professional and industrial use applications is given based on the exposure scenarios in the registration dossier and the DNEL derived according to the REACH guidance. By combining the derived DNELs with the exposure estimates risk characterisation ratios (RCRs) were obtained. The RCRs were in most cases for workers and pregnant workers >1. It is therefore concluded that risks are not sufficiently controlled for industrial and professional uses, especially when it concerns processes under elevated temperatures, open processes, and processes that require manual activities.

Business As Usual Scenario (BAU)
Table E.01 gives an estimation of the expected trends in the use of NMP in various use categories over the period of 2011 – 2016. This trend estimation is based upon a confidential market study of a major EU supplier of NMP. However the total use of NMP in this study seems to vary quite much from the general estimations of use within the EU (B.2.1).

Table E.01: *Baseline NMP use amounts per application (based on confidential market analysis BASF).*

See confidential Annex 3.

The rationale behind the trends is further explained by the following considerations:

- A decrease is foreseen in the use of NMP in non-wire coating, industrial and professional cleaners and the formulation of agrochemicals because:
  - Several companies have indicated that they have replaced NMP in recent years, particularly because of the reclassification as a category 1B reproductive toxicant.
  - The professional use of NMP in cleaners is not supported in the updated registration dossier.
  - According to industry, the use of NMP in the formulation of agrochemicals will disappear due to REACH legislation and inclusion on the Candidate List.

- An increase or stabilization is foreseen in the use of NMP in wire-coatings, petrochemical processing, pharmaceuticals, membranes, electronics, agricultural chemical synthesis:
  - According to industry no alternatives of NMP exist for these use categories with the same functionality (e.g. flexibility, mechanical stability, thermal stability when it comes to wire-coatings).

The above described baseline includes the effects of the current EU legislation on NMP (classification and placing on the candidate list). As mentioned earlier, the Netherlands has submitted a reclassification dossier proposing to lower the specific concentration limit from 5 to 0.3% for Reprotoxic Category 1B. This would mainly affect consumer use of NMP; however, it might also have an effect on professional uses, as there will be an increased labelling obligation for NMP containing products and mixtures at concentrations of ≥0.3% (at this moment labelling is only required at concentrations ≥5%). Effects of this increased labelling are expected to be minimal and are mainly expected for non-wire coatings and cleaners (where remaining use is already expected to be minimal).

E.1.2 Options for restrictions

Three different restriction options will be assessed in E.2:

1. Restriction on the manufacture and placing on the market and use of NMP for all applications in concentrations equal to or greater than 0.3% by weight (RMO1. Total ban).
2. Restriction on NMP as substance and in mixtures with a derogation under specific conditions for the use in specific industrial applications (RMO2. Restriction with derogations).
3. Harmonised DNEL and safe use demonstration (RMO3). Within RMO3, two different exposure limits (5 mg/m^3 and 20 mg/m^3) will be discussed. In line with recent RAC conclusions on the DNEL for NMP, the exposure limit of 10 mg/m^3 has been added in this Background Document.

Of course, many other potential restriction options could be described as well. The three restriction options mentioned above cover both the extreme possibility (total ban) and two other –logic- options (restriction with derogations and a restriction on the condition of the manufacture and use). In section E.2 some variations within these options are described as well.

E.1.3. Other Union-wide risk management options than restriction

E.1.3.1. REACH Authorisation

In 2011 NMP is placed on the Candidate list for Authorisation. NMP, however, at this moment it is not prioritized for placement on Annex XIV mainly due to the fact that the Netherlands started the preparation of an Annex XV restriction dossier. Besides the various restriction RMO's, authorisation as separate risk management option (RMO4) will also be described in E2.

E.1.3.2. Adjustment of existing indicative Occupational Exposure Limit

Outside the scope of REACH, it is an option to adjust the EU-wide Occupational Exposure Limit (OEL) to control the risks at the workplace. In 2007, the Scientific Committee on Occupational Exposure Limits (SCOEL) has published an indicative OEL of 40 mg/m^3 (8-hour TWA). As this OEL is not binding. Various national OELs exist between 20 and 200 mg/m^3. In view of the Dossier Submitter, the indicative OEL of 40 mg/m^3 does not provide sufficient protection to the worker population (see chapter B), following the REACH guidance. In principle, one could refer the issue back to SCOEL and ask them to provide a new OEL. However, the SCOEL has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. In the case the SCOEL would change the indicative OEL value to the more protective level as indicated in this Background Document, harmonised implementation of such new indicative OEL by all Member States is still not guaranteed.

The SCOEL also has the possibility to set a binding OEL. For only a few chemical agents (asbestos, benzene, hardwood dust, lead and vinyl chloride monomer) a binding OEL has been established at EU level. For binding OELs, Member States must establish a corresponding national binding OEL value that can be stricter, but cannot exceed the Community limit value. A binding OEL takes account of socio-economic and technical feasibility factors. According to SCOEL a binding OEL will only be set if policy considerations are of major importance. Therefore, the Dossier Submitter considers that setting a binding OEL for NMP via SCOEL is not a realistic option.

E.2. Assessment of risk management options

In this section E.2 only a brief description of the four assessed risk management options is presented. In chapter F (socio-economic analysis), a more elaborated analysis of the RMOs can be found that further underpins the argumentation given in this section. Chapter F is supported by two partly confidential reports given in Appendix A and Appendix B, respectively describing the market analysis and cost analysis for NMP.

E.2.1. Restriction option 1: Total ban

As shown in chapter B, almost all applications result in a risk using the EasyTRA tool. For some applications the risks might be sufficiently controlled in current practice (see tables B.79 and B.80). This proposal to restrict the manufacture and use of NMP in all applications would eliminate all exposure to NMP. The concentration limit of 0.3% by weight is based on the proposal for classification of NMP as currently under discussion[16].

E.2.1.1. Effectiveness

E.2.1.1.1 Risk reduction capacity

RMO1 is expected to result in a complete risk reduction of NMP both for industrial and professional uses. However, this reduction might be partially offset by an increase in risks caused by possible alternatives of NMP. For the (mainly industrial) uses where no alternatives are available, the total ban might result in a shift of NMP-using production facilities to non-European countries (like Asia and US). For these uses a risk reduction within the EU will be achieved. The expected risk reduction is further explained in section F.1.3.

The overall risk reduction of a total ban is considered substantial, as the uses for which risks are potentially offset by the use of hazardous alternatives is assumed to be limited.

E.2.1.1.2. Costs and economic effects

RMO1 is expected to result in compliance costs for the few use categories that are expected to comply with a total ban on NMP by the shift to alternatives. Compliance costs are quantified at >25-50M€. However, the majority of the negative economic effects are expected as wider socio-economic effect as the majority of the (mainly industrial) users of NMP are expected to relocate or terminate in the case of a full ban on NMP. This would result in relocation costs, losses in value added for the European economy and in losses in jobs. Furthermore, indirect supply chain effects can be expected, potentially resulting in more economic losses in Europe. Unfortunately, no quantitative estimate of the losses in value added could be given for this scenario. The potentially lost jobs are quantified at moderate to high, however, this includes only a part of the industries that would potentially relocate or terminate. A full description of the expected costs and wider socio-economic effects of this scenario is given in section F.4.1.

E.2.1.1.3. Proportionality

This RMO is deemed not proportional as the wider socio-economic effects for Europe (losses in value added of the European Economy and potential losses in jobs) are expected to be large and although the expected risk reduction is substantial within Europe, the scenario is expected to cause a shift of health risks to outside Europe that is not supportable according to the Dossier Submitter. Further explanation of the proportionality of this (and the other RMOs) is presented in section F.7.3.

[16] *Based on the information available for NMP showing multiple ED10 levels for developmental effects between 4 and 400 mg/kg bw/day and no modifying factors affecting the preliminary potency, NMP is of medium potency and the current specific concentration limit of 5% for developmental toxicity of 1-methyl-2-pyrrolidone should be reduced to a level of 0.3%.*

E.2.1.2. Practicality

E.2.1.2.1. Implementability and manageability

Technical equally good alternatives for NMP in the major applications (like wire-coatings, high performance polymers and membranes) seems to be lacking (see table C.01). It should be noted that since NMP will not end up in the final product in these applications, industry might relocate and move their facilities outside EU. For these industries this RMO is thus not implementable.

For other applications (like non-wire coatings) a prohibition of the manufacture and use will probably result in a shift to other solvents. For these applications RMO1 seems to be implementable and manageable.

E.2.1.2.2. Enforceability

The compliance of relevant actors can be checked (no specific considerations).

E.2.1.3. Monitorability

There are no specific concerns with regard to the monitorability of a total ban. This can be done through enforcement.

E.2.1.4. Overall assessment of restriction option 1

A complete ban on the manufacture and use of NMP is considered not proportional to the risks as it will result in major wider socio-economic losses and changes to many supply chains in which NMP is used. The demonstrated risks (RCR's up to 5) are in view of the Dossier Submitter not justifying this far-reaching risk management option. Especially as it is foreseen that a shift of risks due to the use of NMP outside of Europe is expected as companies that stop activities in Europe, will potentially relocate outside Europe.

E.2.2. Restriction option 2: Restriction with derogations under specific conditions

In this RMO, for the uses for which alternatives appear to be readily available, the use of NMP is banned. Some specific (only industrial) uses of NMP for which alternatives appear not to be available, are derogated within this RMO, however, the derogation is given at specific conditions. The aim of these conditions is that potential risks caused by NMP are reduced as much as possible, ideally to below the Derived No Effect Level. RMO2 is in essence a combination of a ban (RMO1) for some applications and safe industrial use (RMO3) for others. As discussed in E.2.3, the Dossier Submitter expects that in the situation prescribed by RMO3, most likely industry will shift to alternatives if available. Therefore, the risk reduction capacity and the costs for RMO2 and RMO3 will be similar.

Below, the full description of RMO2 is given. Note that there are different ways of defining this RMO. Therefore, three different potential formulations are given below. Proposal A is the proposal for that is taken further in this document e.g. in the socio-economic analysis in part F.

A. Restriction with derogations

1. Shall not be placed on the market, or used:
    a) as substance
    b) as constituent of substances
    c) or in mixtures, in concentrations equal to or greater than 0,3% by weight.

2. By way of derogation, paragraph 1 shall not apply for industrial use by the actors (including manufacturers and formulators) in the following supply chain:
    a) Petrochemical industries
    b) Wire coatings

c) Electronic and semiconductor industries
d) Battery industries
e) Filtration membranes
f) High performance polymers
g) Agricultural chemicals (for synthesis purposes)
h) Pharmaceuticals

3. For the derogations in paragraph 2 (a) to (h) and without prejudice to other Community legislation on worker protection, NMP shall be used in industrial installation only if the following minimum conditions are met:
    a) The substances or mixtures are used in controlled closed systems (according to the definitions set in REACH guidance document R12: use descriptor system; PROCs 1, 2 and 3) and/or best available techniques to reduce inhalation and dermal exposure;
    b) Actors in the supply chain shall maintain an exposure monitoring program in accordance with the BOHS/NVAA standard[17] or a national equivalent thereof.

It is noted that there is room for interpretation of what in fact are best available techniques (BAT). The Dossier Submitter sees this as a serious drawback specifically of RMO2A.
Below two different possible interpretations of the term BAT is given:

1. The term "best available techniques", could be understood as the BATs that have been defined for various sectors as part of the IPPC Directive (2008/1/EC) (replaced by the Industrial Emissions Directive (IED, 2010/75/EU)) and are documented in the so-called BREFs (Best Available Techniques Reference Documents, http://eippcb.jrc.ec.europa.eu/reference/). BAT in this context refer to techniques aimed at preventing environmental exposure, not worker exposure. For this reason, BATs from IPPC and its successor IED do not suit the purpose on NMP (environment vs worker).
2. Alternatively, the term best available techniques could be interpreted not referring to an existing European legal framework. This is how the Dossier Submitter actually intended the term in RMO2A. The Dossier Submitter has used the term in the trivial meaning of the word, having as example the Dutch safety declarations of intent (Arbocatalogi) where OSH best practices and measures are discribed https://osha.europa.eu/fop/netherlands/en/nl_developments/news_article.2007-10-26.1044240052?set_language=en " that could serve as examples of best available techniques.

B. Restriction with derogations, alternative formulation:
Paragraph 1 and 2 equal to proposal A.
As alternative to proposal A above, paragraph 3 can be formulated as:

3. For the derogations in paragraph 2 (a) to (h) and without prejudice to other Community legislation on worker protection, NMP shall be used in industrial installation only if manufacturers/importers and downstream users of the substance use in the chemical safety report submitted in accordance with Articles 10 and 37 of REACH respectively, a Derived No Effect Level (DNEL) of 5 mg/m^3. Further manufacturers/importers and downstream users of the substance shall identify, recommend or implement, as appropriate, the necessary measures to comply with the obligations.

C. Targeted restriction
As alternative, the restriction can be formulated as followed:

1. Shall not be placed on the market, or used:
    a) as substance
    b) as constituent of substances
    c) or in mixtures, in concentrations equal to or greater than 0,3% by weight.

[17] *Testing Compliance with Occupational Exposure Limits for Airborne Substances. BOHS / NVAA, 2011 http://www.bohs.org/StandardCopyPage.aspx?id=97&terms=testing%20compliance*

for the following applications:

a) Non wire coating
b) Professional cleaning
c) Agrochemical formulation
d) Construction materials

Note that in this proposal C, no conditions are set to the uses that are not included in the restriction. Consequently, risks due to the use of NMP for the mainly industrial uses will remain after implementation of this RMO.

Note that the RMO2A that is taken further in the analysis of this document differs substantially from the RMO2 described in Appendix B prepared by AMEC. RMO2 in Appendix B involves a partial ban for only a very limited number of professional uses (non-wire coatings and cleaners), leaving all other (mainly industrial) uses out of the restriction. Effects of this scenario are thus only expected for a small part of the uses of NMP, where RMO2A (further in this document described as 'RMO2') also affects the industrial uses by the conditions set. Consequently, the cost indication for RMO2 in Appendix B does not represent the costs of RMO2 described in this document.

E.2.2.1. Effectiveness

E.2.2.1.1 Risk reduction capacity

RMO2 is expected to result in substantial risk reduction of NMP. For the uses that are included within the scope of the full ban, risks of NMP are fully reduced. However, there is a potential that hazardous alternatives are used as a replacement of NMP and that the risk reduction achieved in these uses are partly or fully offset due to an increase in risks of alternatives. For the uses of NMP that are derogated under specific conditions, also substantial risk reduction is expected, as the conditions set will result in exposure reduction of NMP for workers. The question that raises here is to what extent exposure is reduced and whether this will result in exposure levels of below the level where the DNEL is set. The conditions taken up in the derogation, obligate the users of NMP to use controlled closed systems and/or to use best available techniques to reduce inhalation and dermal exposure. The RMO thereby gives some freedom in the way exposure reduction is achieved within the own organization. The Dossier Submitter however expects that the conditions are set sufficiently strict to reduce exposure to low levels in the majority of the uses as best practice or closed system conditions are expected generally to result in substantial exposure reduction. However, it can be expected that for some specific uses, exposure levels of over 5 mg/m^3 might remain in this scenario and some risks might thus remain. This could for example be expected in some processes at elevated temperatures and in some processes in the wire-coating industry as these are presumably confronted with relatively high exposure levels. This sector will have to put substantial effort in exposure reduction as a consequence of RMO2, but this will probably not result in exposure levels below 5 mg/m^3. Overall, the risk reduction is assumed to be substantial (comparable to RMO3a), however, some risks might remain in specific uses (lower risk reduction potential than RMO3a). Further explanation of the risk reduction potential is given in section F.1.3).

E.2.2.1.2. Costs and economic effects

The Dossier Submitter expects that the costs and wider socio-economic effects of this RMO are more or less equal to the costs of RMO3a. Industries for which alternatives are readily available will, just as in RMO3a shift to these alternatives at similar costs. Other industries are expected to take exposure reduction measures, just as in RMO3a. However, RMO3a tries to achieve this by mains of an obligatory goal (the exposure limit of 5mg/m$^{3)}$), where RMO2 tries to achieve this by setting process conditions. Consequently, RMO2 gives more guidance in how exposure reduction should be achieved compared to RMO3a (although also RMO2 gives of course some freedom in how exposure reduction is achieved). In that sense, costs might be somewhat higher in RMO2 as sub-optimal exposure reduction measures might need to be implemented. However, the Dossier Submitter expects that the extent to which this will happen to be very limited. On the other hand, RMO2 poses less strict conditions to the final exposure level to be achieved. In that sense, industry might implement less exposure reduction measures in RMO2 compared to RMO3a. Especially the most costly measures might not be implemented in RMO2 that would be implemented in RMO3a. Total costs of RMO2 might therefore be somewhat lower than in RMO3a.

Anyhow, all industries that are derogated under specific conditions in this scenario are expected to be able to comply with the conditions and as such, the main economic effect of this scenario is expected as compliance costs. However, some wider socio-economic effects might occur for some very specific coating and cleaning uses of NMP (medical images, foodcontact material/bakeware and optical industry) for which the availability of alternatives are questionable but a derogation is not included within this scenario. It is however, not known whether this actually is a problem. A full explanation on the expected economic effects of RMO2 is given in section F.4.2.

E.2.2.1.3. Proportionality

As both risk reduction and economic effects are expected to be comparable to RMO3a. And although some minor differences are expected both on the benefit (risk reduction) as on the cost (economic effect) side, between RMO3a and RMO2, these are not expected to substantially change the conclusions on proportionality. Similar to that of RMO3a, this RMO is considered to be proportional. Note that as some wider economic effects might occur for some specific users (e.g. medical images, foodcontact material/bakeware and optical industry), the proportionality to these specific users is questionable. However, as these are assumed to be minor uses, this is deemed not to change the overall conclusion on proportionality of this RMO. Further explanation of the proportionality of this RMO is given in section F.6.3.

E.2.2.2. Practicality

E.2.2.2.1. Implementability and manageability

RMO2 will be implementable and manageable for the applications for which alternatives are readily available as the actors involved will fairly easy shift to the use of alternative solvents. For the uses that are derogated under specific conditions, RMO2 is expected to be implementable and manageable, as for all the uses it is thought to be possible to either minimize exposure by implementing controlled closed systems or by implementing best available techniques. The extent to which further exposure reduction measures need to be implemented depends on the current situation within the industry. There might be some problems in the interpretation of the conditions as these are set at a general level and therefore do not specifically indicate what is required within a specific sector.

E.2.2.2.2. Enforceability

The enforceability for the uses that fall within the full ban part of the restriction is not thought to cause any problems as for these industries it can just be checked whether NMP is actually not used anymore.
Some problems in enforceability might occur for the uses that are included as derogation under specific conditions in this RMO. At first because of the definitions of the use categories that are included in the derogation. For enforcement authorities it may not be fully clear in what use category a specific company falls and therefore whether the use of NMP is restricted or whether a company can still use it under certain conditions. Even more problematic in enforcement might be the interpretation of the conditions under which the derogations are given. The various elements contained in the conditions cause that authorities are able to enforce on these various elements. These have been formulated in general terms for all of the use categories derogated and thereby give room for interpretation of the conditions throughout the various use categories. Industries and authorities might think differently on the actual implications of the conditions for specific companies and also difficulties in equal treatment of industries might occur if interpretation is not done in a uniform way. To what extent such difficulties in interpretation will occur in practice is not known, however, these could be substantial as it appears to be very difficult to define the conditions such that they (1) contain enough strict conditions to eliminate risks; (2) are specific enough for various industries to know what is actually expected from them and (3) are expressed in general terms so that they cover a variety of industrial sectors.
The advantage of this RMO in terms of enforcement over RMO3a, is that there is no need to enforce on exposure scenarios for which a certain level of expertise of the enforcement authority is required. Enforcement of actual exposure reduction measures in that sense might be easier. However, the Dossier Submitter expects the problems around the interpretation of conditions to cause this RMO to be more difficult to enforce than RMO3a.

E.2.2.3. Monitorability

Just as the enforceability, the monitorability of this RMO might be somewhat problematic especially due to the difficulties in interpretation of the conditions under which the derogations are given.

E.2.2.4. Overall assessment of restriction option 2

According to the Dossier Submitter, this RMO2 is considered to be economically and technically feasible as well as proportional in terms of costs versus risk reduction. The obtained risk reduction is expected to be substantial and the compliance costs are likely to be affordable to industry and cost effective in terms of costs made per worker for which risk reduction is achieved. Furthermore, hardly any wider socio-economic effects are expected. However, compared to RMO3a, this RMO is considered less desirable as some risks might still remain. Furthermore, in terms of practicality, the RMO is thought to give some serious problems in enforcement as the interpretation of the conditions under which derogations are given appears to be difficult. This might undermine the implementation of the restriction in practice, potentially resulting in sub-optimal effects of the restriction (e.g., low risk reduction in the sectors for which derogations are given). Because of this, overall the RMO is deemed to be sub-optimal.

E.2.3. Restriction option 3. Harmonised DNEL and safe use demonstration

In this RMO3, risk reduction is proposed via a mandatory harmonised DNEL in combination with protection for dermal exposure. Within RMO3, two limit values (a: 5 mg/m^3 and b: 20 mg/m^3) will be discussed. And as RAC recently concluded on a DNEL vanue of 10 mg/m^3, that limit value has also been added to analysis of this dossier.

NMP may only be used if it can be guaranteed that under normal operating conditions the exposure (as 8-hour TWA) will remain below 5 mg/m^3 (RMO3a). Peak exposures (15 min. STEL) must remain below 10 mg/m^3 and must be compensated by lower exposures during the same day in order to remain below the 8-hour TWA value. To give industry sufficient time to adjust their equipment, the restriction entries into force 60 months after inclusion in Annex XVII. This 60 months period is relatively arbitrarily chosen (see E.2.3.2.1). Furthermore, NMP may only be used if dermal exposure is avoided by taking preventative measures.

Alternatively, RMO3 could be defined as:

1. Manufacturers/importers and downstream users of the substance are obliged to use in the chemical safety report submitted in accordance with Articles 10 and 37 of REACH, respectively, a Derived No Effect Level (DNEL) of 5 mg/m^3;
2. Registrants and downstream users of the substance shall identify, recommend or implement, as appropriate, the necessary measures to comply with the obligations resulting from paragraph 1.

The first formulation of RMO3 will be used in the further analysis of RMO3 in this document.
The intention of this restriction option is that the use of NMP is adequately controlled. NMP is a threshold substance and therefore, if the exposure concentration is below the DNEL there will be no occupational risks. Also, the lack of technical alternatives to NMP or alternatives with comparable hazard characteristics is an important argument to consider this risk management option. Adequate control can for example be obtained by the implementation of exposure reduction measures like improved ventilation or respiratory protective equipment.

E.2.3.1. Effectiveness

E.2.3.1.1 Risk reduction capacity

RMO3 introduces a mandatory limit value both for professional as industrial users of NMP. Two levels of a limit value are evaluated: (a) 5 mg/m^3 at the level of the DNEL (inhalation DNEL pregnant worker population, see table B.78), and (b) 20 mg/m^3, a limit values above the derived DNEL. In case the limit value is set at the level of the DNEL, risks will be fully reduced for all the

industrial uses. In case the limit value is set at the level of 20 mg/m^3, only a limited risk reduction is achieved as the majority of the industries are already in this range of exposure (according to the exposure scenarios provided in the registration dossier).

For the professional uses in coatings and agricultural formulation, a mandatory limit value is expected to result in a shift to substance alternatives regardless of the level of the limit value as shifting to alternatives appears to be cheaper than taking exposure reduction measures. For these uses, RMO3 will result in a full risk reduction of NMP. However, as is explained in RMO 1 and 2, this risk reduction might be partially or fully offset by an increase in risks caused by alternatives of NMP. The overall risk reduction of RMO3a is assumed to be substantial, especially in the industrial uses.

In RMO3b the overall risk reduction will be limited as the limit value is set at a level higher than the DNEL. Depending on the current exposure levels, there will be some exposure reduction in the various industrial uses. The resulting RCRs of this scenario are given in section F.1 (see table F.03 and F.04) and the risk reduction capacity is thus limited for RMO3b.

The limit values are for inhalation and thereby do not cover dermal exposure. The risks potentially caused by dermal exposure are expected to be covered by RMO3 as there is an obligation to avoid dermal exposure by taking preventative measures.

A full description of the expected risk reduction of RMO3a and RMO3b for the various use categories of NMP is given in section F.1.3.3.

E.2.3.1.2. Costs and economic effects

In case of a mandatory limit value of 5 mg/m^3 (RMO 3a), all industrial users of NMP will be capable of meeting the limit. Economic effects of this scenario are mainly expected in terms of compliance costs (and some not further specified administrative costs). Wider socio-economic effects are expected not to occur in this RMO. The quantified compliance costs are expected in the range of >40-50M€ excluding wire coaters. The estimate of total costs including wire coaters might go up to XXXX, however, in case of the 60 months timing, compliance costs are assumed to be reduced substantially and the actual compliance cost estimate is assumed to be closer to the total figure excluding wire coaters than to the figure including wire coaters. Unfortunately, it was not possible to come to a quantitative compliance cost figure for wire coaters in this scenario. A full description of the potential compliance costs and wider socio-economic effects of this scenario is presented in section F.4.3.

All industrial users of NMP are assumed to be able to meet the limit value of 20 mg/m^3. In this RMO3b economic effects are expected in terms of compliance costs (and some not further specified administrative costs). No wider socio-economic effects are expected in this scenario. Total compliance costs are quantified in the range of 0-150M€ (for comparison with RMO3a: excluding wire coaters in the range of 0-30M€). A full description of the potential compliance costs and wider socio-economic effects of this scenario is presented in section F.4.3.

E.2.3.1.3. Proportionality

RMO3a is deemed proportional to all use categories of NMP as compliance costs are considered to be of an acceptable magnitude (compared to total production values and per worker for which risk reduction is potentially achieved), as wider socio-economic effects are avoided and as the risk reduction of this scenario is substantial. Although the RMO is deemed well adapted to the situation of wire coaters, further fine-tuning of the RMO for wire coaters to avoid wider socio-economic effects might be considered if reliable information to support this is received in the public consultation. Further explanation of the proportionality is given in section F.6.3.

RMO3b is also deemed to be proportional, but is not the preferred option from a public health point of view. The risk reduction capacity of this scenario is expected to be very limited as for the majority (or all) of the use categories substantial risks will remain, however the compliance costs are also considered to be minimal. In light of this minimal risk reduction capacity for all use categories, this RMO3b is not desirable according to the Dossier Submitter. Further explanation of the proportionality is given in section F.6.3.

E.2.3.2. Practicality

E.2.3.2.1. Implementability and manageability

No problems are expected for the implementation RMO3b. For RMO3a more effort has to be taken by industry. The timing of the entry into force of the restriction will be an important aspect in the implementability and the manageability. If technical adaptations to the equipment can fit into regular maintenance programs, it would improve the implementability. In the restriction proposal a period of entry into force of 60 months is suggested. This 60 month period is relatively arbitrarily chosen. During the stakeholder consultation, industry was asked to react on the acceptable timing for the different RMOs, but only very few answers were provided (see Table F.07). RMO3a is considered to be implementable and manageable according to the Dossier Submitter as all users of NMP are expected to be capable of implementing the required exposure reduction within the given time.

Safe use in compliance with RMO3 should be guaranteed by the use of preventative measures that are applied in the order of the so-called "hierarchy of control", an established concept referred to in the Chemical Agents Directive (98/24/EC), i.e. enclosure, increased local exhaust ventilation, increased general ventilation and if needed personal protective equipment. A similar hierarchy of risk management measures is mentioned in the REACH guidance on information requirements and chemical safety assessment, chapter R14 (the STOP-principle): substitution, technical measures, organizational measures and/or personal measures.

E.2.3.2.2. Enforceability

Enforcing a restriction where the use with exposure over the DNEL is prohibited, is not straightforward. Actually measuring exposure is for most inspectors not a viable option given the demands for an accurate measurement. The compliance of relevant actors can be checked by evaluating the exposure risk assessment drafted by the actor. For an individual company complying with the general risk management measures from the safety data sheet and attached exposure scenario is not sufficient, and therefore enforcement cannot be solely focused on that. Each professional user has to do a specific risk assessment, comparable to the assessment under the Chemical Agents Directive (98/24/EC) to prove compliance with the restriction. The risk assessment can be based on measurements during representative working conditions or on a quantitative risk assessment model like the tier 1 exposure assessment models under REACH. The inspector checking the restriction therefore has to have knowledge of the use and interpretation of both methods. Inspectors regularly checking the worker legislation are expected to be capable of checking a mandatory DNEL as these are used to enforce (national) occupational exposure levels (OELs). In the Netherlands, the occupational inspectorate is allowed to enforce both worker legislation and REACH. However, the Dossier Submitter is not aware of the situation in other EU member states.

E.2.3.3. Monitorability

There are no specific concerns with regard to the monitorability. This can be done through enforcement.

E.2.3.4. Overall assessment of restriction option 3

RMO3a is deemed to be proportional as compliance costs are of acceptable order of magnitude, wider socio-economic effects are avoided and substantial risk reduction is achieved. Furthermore, no real problems are expected in terms of practicality and monitorability. Note, that there is some uncertainty around the actual consequences of this RMO to the wire coating industry as exposure levels in this sector might still be relatively high and substantial exposure reduction is therefore required. However, with the extended time period for this sector, exposure reduction is expected to be implementable and manageable and compliance costs that are acceptable to the industry.

The main advantage of RMO3 is that the use of NMP can continue and that the added value to the European economy that is obtained with the use of NMP can remain in the absence of risk free

alternatives. In that sense this RMO is deemed to be preferable over RMO1. Compared to RMO2, this RMO3 is deemed to be better enforceable as confusion on definitions and interpretations of conditions are avoided in this scenario. Compared to RMO4, RMO3a is assumed to be equal in terms of risk reduction, however, RMO3a gives more certainty for industry regarding legislative obligations for a long time period (see E.2.4) and costs to industry and administrative burdens both to industry and society are expected to be lower for RMO3a compared to authorisation. Overall, according to the Dossier Submitter, RMO3a is deemed to be the preferred risk management option for NMP.

The modified RMO 3 proposed by RAC

RAC has modified RMO3. According to this modified RMO, the entry in Annex XVII would state that the inhalation and dermal DNELs set by RAC shall be used by existing registrants (requiring updating of their CSRs), by new registrants, and by downstream users in their CSRs.

Advantages

In contrast to the restriction proposed by the dossier submitter and other RMOs proposing use of an inhalation DNEL (RMO2b and RMO3), RAC proposes to also include the dermal DNEL in the restriction wording. It would high-light the need to protect against dermal exposure and the exposure scenarios would then have to suggest concrete and use-specific risk management measures to reduce the dermal exposure (e.g., engineering controls or type and thickness of gloves limiting exposure potential). While the dermal risk management measures recommended may not be different than those used when applying the chemical agents directive (or requiring avoiding dermal exposure), it is an advantage from a risk and enforcement point of view to assess the risk in a quantitative manner and have the dermal risk management measures specified in the exposure scenarios.

Additional advantages are that:

- the use of RAC-developed DNELs in updating of the CSRs will ensure that risk management measures, for inhalation and dermal exposure, defined on the basis of a quantitative assessment, are introduced / recommended for all uses until the RCR is below one,

- this option will not require other enforcement approaches than those currently being in place for enforcing registration requirements related to CSRs and implementation of ESs in different member states, and

that monitorability can be ensured by primarily, verification of the registration dossiers by ECHA, and checking of the Safety Data Sheets by the Member State National Enforcement Authorities.

Disadvantages

A disadvantage is that only for import and manufacture requiring a CSR, i.e. $\geq$10 tonnes/year, and the development of exposure scenarios, effective RMMs would be recommended. However, according to an analysis of information provided in registrations, the volume of substances manufactured or imported between 1 and 10 tonnes constitutes <1% of the total volume of NMP used in the EU. The SDSs issued by those registrants would have to include the DNEL value proposed in the restriction, even though exposure scenarios would not be included. It is expected that the lowest benchmark level is applied, in this case the DNEL. In the worst case - the workplaces where these volumes are handled would still have to apply the provisions of the current national worker protection legislation, including the national OEL.

The information on SEA assessment of this RMO wil be added when the SEAC opinion is finalised.

SEAC considerations on the RMO proposed by RAC

The identified additional cost of the restriction proposed by RAC compared to the baseline is €61.5 M in the wire coating sector and €20-30 M in the non-wire coating sector, while no major costs are expected in other sectors. . Further explanation of the proportionality is given in section F.6.3.

E.2.4 Authorisation as risk management option 4

In this section, the authorisation of NMP will be described as a separate risk management option under REACH. NMP is already included in the Candidate list for Annex XIV, however, due to the Dutch initiative to prepare this restriction proposal, it has so far not been further prioritized.

E.2.4.1. Effectiveness

E.2.4.1.1 Risk reduction capacity

Risk reduction in case of an authorisation is expected to be comparable to RMO3a. Industries might shift to alternatives (mainly for the professional uses), apply for an authorisation or stop production in Europe. In case industries apply for authorisation they are expected to take the adequate control route, as for the majority of the industrial uses adequate control is assumed to be technically and economically feasible. In case authorisation is granted, exposure will be reduced to a value below the DNEL in those industries and no risks will remain. There could be some users that would apply for authorisation based upon the SEA route in case adequate control is – in their view - not possible. In that case industry needs to prove that benefits outweigh costs. If such an application would be authorized, there might be some remaining risk. However, the extent to which industry would use the SEA route is assumed to be very limited and the potential remaining risk would therefore also be minimal. In the authorisation scenario there may also be industries that decide neither to shift to alternatives nor to apply for authorisation. These industries cannot continue production in Europe and might either terminate or relocate to non-European countries. In that situation, risks in Europe will be reduced.

The overall risk reduction of authorisation is assumed to be substantial, further explanation of the risk reduction potential of this RMO is given in section F.1.3.

E.2.4.1.2. Costs and economic effects

Also the costs in case of an authorisation are expected to be comparable to RMO3a because the exposure should be reduced to the same level. Additional administrative costs for industry are expected to request for an authorisation application. Furthermore, there might be some 'intangible costs' to industry because of business risks and reputation losses due to the authorisation. In chapter F estimates of the compliance costs, administrative costs and wider socio-economic effects are explained (section F.4.4). Note that as very little is known on the actual industries responses in case of RMO4, very little could be said about the expected economic effects. Overall, however, total economic effects of authorisation are expected to be larger than those of RMO3a but smaller than RMO1.

E.2.4.1.3. Proportionality

As it is uncertain how industry would respond to authorisation, it is difficult to assess the proportionality of this instrument. The costs (compliance costs and administrative costs) and wider socio-economic effects are expected to be somewhere in between RMO3a and RMO1. Some wider economic effects might occur in case of authorisation (more than in case of RMO3a). The risk reduction potential of authorisation is expected to be substantial and more or less equal to the risk reduction capacity of RMO3a. According to the Dossier Submitter the economic effects of authorisation can be proportionate to the risk reduction, depending on the extent to which wider socio-economic effects will occur. If substantial wider economic effects would occur, the proportionality of this scenario could be questioned. Unfortunately, that could not be indicated based upon the available information, so no clear conclusion on the proportionality of this RMO can be drawn based upon the available information. However, the Dossier Submitter expects the extent to which wider socio-economic effects will occur to be limited and as such the Dossier Submitter considers this RMO to be proportional.

E.2.4.2. Practicality

E.2.4.2.1. Implementability and manageability

The administrative requirements of authorisation and the uncertainties around these, are the main disadvantages of authorisation. Requesting for authorisation is costly and time-consuming, both for industry as for authorities especially given the widespread use of the substance. Besides, it gives large uncertainty to industry regarding the continuation of their business. The practicality of authorisation is therefore considered lower than RMO3a.

E.2.4.2.2. Enforceability

The compliance of relevant actors can be checked. but will be specific for the different sectors as authorisation applications will be tailor-made. This makes the enforceability more difficult. So far inspectorates do not have experiences in enforcing authorisation applications.

E.2.4.3. Monitorability

There are no specific concerns with regard to the monitorability. This can be done through enforcement.

E.2.4.4. Overall assessment of risk management option 4

Both authorisation and restriction could in view of the Dossier Submitter result in the same level of risk reduction. Costs for process adaptation and the risk reduction capacities are expected to be similar. The administrative requirements of authorisation and the uncertainties and intangible costs around these, are the main disadvantages of authorisation. Requesting for authorisation is costly and time-consuming, both for industry as for authorities especially given the widespread use of the substance. Besides, it gives large uncertainty to industry regarding the continuation of their business. In view of the Dossier Submitter, the practicality of authorisation is lower compared to restriction option RMO3a.

E.3 Comparison of the risk management options

Table E.02 provides an overview of the risk management options. In view of the Dossier Submitter, option RMO3a is the optimal risk management option in terms of effectiveness, practicality and monitorability. Alternatively, RMO2 and RMO4 could be an option for risk management, however, RMO2 is seen as less effective and less practical and monitorable. For RMO4 the administrative requirements and the uncertainties around it for industry are the main disadvantages compared to RMO3a. Because of this RMO3a is preferred over both RMO2 and RMO4.

Furthermore, according to the REACH legal text, Annex XVII of REACH shall be amended when there is an unacceptable risk to human health or the environment arising from the manufacture, use or placing on the market of substances, which needs to be addressed on a Community-wide basis (see REACH articles 68 and 69).

Table E.02: *Dossier submitters' comparison of the risk management options*

	RMO1: total ban	**RMO2: restriction with derogations under specific conditions**	**RMO3: harmonised DNEL and safe use demonstration**	**RMO4: authorisation**
Intention (background idea)	NMP is a CMR substance and should be substituted.	Technically equally good alternatives are available for some uses, however, these are lacking in other applications. NMP is a threshold substance and therefore adequate control is possible for uses where alternatives are not available. For these uses conditions to reduce exposure are set in general terms to reduce exposure. The intention of this RMO is comparable to that of RMO3.	Technically equally good alternatives are lacking in most applications. NMP is a threshold substance and therefore adequate control is possible. The restriction defines a certain occupational exposure limit to ensure safe use.	NMP is a CMR substance and should therefore be substituted (ultimately), the adequate control route can be followed.
Main advantage(s)	Potential high risk reduction capacity. Easy to monitor. Applies to all uses and industries.	NMP is banned in the uses where phase-out of NMP is already ongoing (formalization of the current situation) and the use of NMP in uses where alternatives are available can remain within specific conditions to reduce exposure.	NMP use can continue, exposure is strictly controlled, comparable to authorisation but with much more certainty for industry.	NMP use can continue, exposure is strictly controlled. Uses with uncontrolled risks will not be authorised unless there are no alternatives. The authorisation procedure foresees to give industry time to find substitutes.
Main disadvantage(s)	Technically equally good alternatives are lacking in most applications. Since NMP will not end up in the final products, industry can move outside EU. Shift to equally hazardous alternatives in coatings. Lack of targeting.	Potential shift to equally hazardous alternatives in e.g. coatings. Difficulties in defining what uses are actually derogated and what not. Furthermore, it appears to be difficult to adequately define the conditions under which derogations are given. This is likely to result in serious problems e.g. of the enforceability. Some risks might remain for the derogated uses if conditions appear not to be strict enough.	Will all companies take the necessary measures?	Granting the authorisation is temporary, large uncertainty for industry. Will all companies take the necessary measures, especially if application requests are combined for different users.
Definition	Straight forward.	Difficult; what uses to derogate, how to define the conditions under which derogations are given?	Challenge; not much experience with this kind of restrictions.	Unclear, no information on how authorisation may take form. Defining the exact uses in the authorisation request will be very important.

	RMO1: total ban	RMO2: restriction with derogations under specific conditions	RMO3: harmonised DNEL and safe use demonstration	RMO4: authorisation
Alternative formulation of the restriction	-	Alternative way to specify the conditions. Or targeted restriction on the uses for which alternatives are readily available (however, this will result in remaining risks in mainly industrial uses).	Alternative wording	-
Effectiveness				
Risk reduction capacity	In principle all risks from NMP could disappear (industry moves out of EU), however, there might be a shift to alternatives with comparable risks to NMP.	Risk reduction capacity is expected to be comparable to RMO3a, however, some risks might remain if conditions appear not to be strict enough.	RMO3a: In principle all risks from NMP will disappear (if all companies comply). For some applications a shift to hazardous alternatives might take place.	Ultimately all risks from NMP will disappear. If no alternatives exist it may still be used temporarily under adequate control.
			RMO3b: Risks reduction is minimal, because the limit is set above the DNEL. In view of health concerns not desirable.	
Costs and economic effects	High wider socio-economic effects for industry and society.	Costs are expected to be comparable to RMO3a, although costs might be lower or higher. Some wider socio-economic effects might occur for specific use categories.	RMO3a: substantial compliance costs, however wider socio-economic effects are expected to be avoided in this scenario, although a chance for substantial wider socio-economic effects for the wire coating sector remains.	Depends on the authorisation requirements and reaction of industry. Total economic effects are assumed to be in between RMO1 and RMO3a.
			RMO3b: Substantial costs to decrease exposure levels, but most companies indicate that this level will not be very problematic.	
Proportionality	Not proportional.	Proportional	RMO3a: Proportional.	Proportional, however, large uncertainties.
			RMO3b: Proportional.	
Practicality				
Implementability	Not possible for the actors in the major applications to comply within a reasonable period.	Expected to be implementable for majority of the use categories, however, problems might occur for specific uses that are not derogated and for which no alternatives are available and problems might occur due to difficult interpretation of the conditions within which derogations are given.	No huge problems are expected for RMO3b. For RMO3a more effort has to be taken. This is also dependent on the timing of the restriction: if it can fit into regular programs to adjust equipment, this would improve the implementability.	Actors will have large problems to make investments due to the temporary character of the authorisation.

	RMO1: total ban	RMO2: restriction with derogations under specific conditions	RMO3: harmonised DNEL and safe use demonstration	RMO4: authorisation
Enforceability	Compliance of relevant actors can be checked.	Enforcement is considered very problematic e.g. as it might not be clear what uses are included in the ban and which are derogated and as conditions within which derogations are given are difficult to interpret for the various sectors (what is actually required?)	National inspectorates are familiar with enforcing occupational exposure limits. No problems are expected.	Compliance of relevant actors can be checked but very specific for the different sectors. This makes the enforceability more difficult.
Manageability	No specific concerns.	Some problems might occur due to difficulty in interpretations of the conditions for derogation.	No specific concerns.	No specific concerns.
Monitorability				
	No specific concerns, can be done through enforcement.	Some problems might occur due to difficulty in interpretations of the conditions for derogation.	No specific concerns, can be done through enforcement.	No specific concerns, can be done through enforcement.

SEAC's view on the different RMOs

SEAC concludes that the RAC proposal seems to be the most appropriate risk management option. It would ensure a safe use of NMP once safe exposure conditions have been identified and implemented. SEAC notes that the higher DNEL value derived by RAC implies that the restriction is significantly less costly than the proposed restriction. SEAC considers the original RMO3 as proposed by the DS to be the second best RMO, provided that exposure limit is adjusted to be in line with the DNEL value proposed by RAC.

None of the other considered RMOs are considered to be more appropriate due to the following reasons:

RMO1 (Total ban on the manufacturing and use): Lack of feasible alternatives and considering that the risks can be sufficiently controlled by application of the RAC-modified proposal.

RMO2 (Ban with derogations under specific conditions): For proposed banned uses the ban would be more costly than necessary to address the risk adequately. For non-banned uses, either the risk will not be controlled (RMO2c), not workable in practice (RMO2A) or similar to the RAC modified proposal (RMO 2b?) assuming that the same DNELs were applied. The partial ban of NMP is not well defined and no justification for this RMO is presented.

RMO4 (Authorisation): If safe use is demonstrated by the applicants, there would be no differences in the level of residual risk. More costly procedures could be balanced with the aim of REACH to phase out CMR substances. However, if a restriction is considered to have major negative impacts on some part of a sector or use, the authorisation scheme may offer the socio-economic route on a case by case basis to ensure a regulation of use adapted to the possibilities for individual companies.

Establishing a binding OEL under the worker prRotection legislation: Similar to the conclusion between the restrictions proposed by the DS and the RAC-modified proposal: neither the indicative nor the binding OEL seems to offer a more appropriate RMO than the RAC-modified proposal.

E.4 Main assumptions used and decisions made during analysis

See section F.5.1.

E.5 The proposed restriction(s) and summary of the justifications

Proposed restriction by the dossier submitter:

NMP may only be manufactured and used if it can be guaranteed that under normal operating conditions the exposure (as 8-hr TWA) will remain below 5 mg/m^3. Peak exposures (15 min. STEL) must remain below 10 mg/m^3 and must be compensated by lower exposures during the same day in order to remain below the 8-hr TWA value. To give industry sufficient time to adjust their equipment, the restriction enters into force 60 months after inclusion in Annex XVII.

Furthermore, NMP may only be manufactured and used if dermal exposure is avoided with protective clothing and gloves, which comply with the requirements of Council Directive 89/686/ECC or other measures.

The exposure level (both inhalation and dermal) must be guaranteed by the use of preventative measures that are applied in the order of the so-called "hierarchy of control", an established concept referred to in the Chemical Agents Directive (98/24/EC), i.e. substitution, enclosure, increased local exhaust ventilation, increased general ventilation, change in operational conditions and if needed personal protective equipment.

The proposed exposure limits takes into account the use of respiratory and dermal protective equipment, other preventative measures are however preferred (as indicated in the Chemical Agents Directive).

Manufacturers and industrial and professional users of NMP must be able to demonstrate at the request of the local authorities that they comply with the above restrictions. This can be done by maintaining an exposure monitoring program in accordance with the BOHS / NVAA[18] Standard or national equivalent.

Table E.03: *Proposed restriction by the dossier submitter.*

Column 1. **Designation of substance**	***Column 2.*** **Conditions of restriction**
XX. N-methylpyrrolidone (NMP) • EC number: 212-828-1 • CAS number: 872-50-4	Shall not be manufactured and used by professional or industrial worker after [xx.yy.zzzz], unless: • the 8-hour TWA exposure will remain below 5 mg/m^3 and the 15 min peak exposure remains below 10 mg/m^3. and • dermal exposure is avoided by preventive measures.

Taking into account modification of the RMO3 proposed by RAC and comments provided by Forum, the following wording is proposed by RAC and SEAC:

Column 1. **Designation of substance**	***Column 2.*** **Conditions of restriction**
XX. N-methylpyrrolidone (NMP) IUPAC name: 1-methylpyrrolidin-2-one EC number: 212-828-1 CAS number: 872-50-4	• Manufacturers, importers and downstream users of the substance on its own or in mixtures in a concentration equal or greater than 0.3% shall use in their chemical safety assessment and safety data sheets by [xx.yy.zzz] a Derived No Effect Level (DNEL) value for workers inhalation of 10 mg/m^3 and a DNEL for workers dermal exposure of 4.8 mg/kg/day.

Justification that action is required on a Community-wide basis

NMP is widely used all over Europe in many applications, like in petrochemical processing, in wire coating production, in electronics and semi-conductor industry and in membrane production. Exposure can be expected for workers by using this substance in the different professional and industrial settings. It is likely that this occupational exposure results in unacceptable risk, for the general worker population and for pregnant workers specifically. Action on a Community-wide basis is required to prevent unacceptable risks from NMP. Applications of NMP are traded freely and are used in all Member States. Action at EU level would ensure a 'level playing field' for all producers, importers and users of NMP and NMP containing products.

NMP has been included in the REACH Candidate list. Therefore, measures for this substance are already taken on a Community-wide basis. Logically, additional measures should also be taken on a EU-wide basis.

Justification that the proposed restriction is the most appropriate Community-wide measure

NMP is a high production volume substance manufactured over 18,000 tonnes per year in Europe and is used in many different industrial and professional settings. NMP is an aprotic and medium polar organic solvent. NMP is completely miscible with water. This combination of properties explains the importance of the use of NMP. NMP is mainly used to enhance a chemical reaction driven by its solvent characteristics as part of the process to make a product. NMP is classified as toxic for the reproduction (Repr. 1B). As demonstrated in chapter B, risks for workers are identified in almost all applications of NMP. Next to NMP, many organic solvents are available as potential alternatives but the characteristics of these solvents are not exactly equal to those of NMP. The availability of technical feasible alternatives differs per use application.

In view of the Dossier Submitter, banning the manufacture and use of NMP in all or in some specific applications is not the right way forward. It is foreseen that either NMP is replaced by another equally hazardous substance or that industry will cease and/or relocate its activities outside Europe. The demonstrated risks (RCR's up to 5) in our view do not justify a major change to many supply chains. NMP is a so-called threshold substance, which means that – at least in principle – NMP can be used without causing a risk for human health. The aim of this restriction proposal is to adequately control the manufacture and use of NMP.

REACH provides the authorities with two possible instruments to regulate the risks caused by a substance: authorisation and restriction. Both authorisation and restriction could in our view result in the same level of risk reduction. The main disadvantage of the authorisation process is that it is costly and time-consuming both for industry as for authorities. Besides that, it gives large uncertainty to industry regarding the continuation of their business because an authorisation request will only be given for a limited period of time.

Outside the scope of REACH, it is an option to adjust the EU-wide Occupational Exposure Limit (OEL) to control the risks at the workplace. In 2007, the Scientific Committee on Occupational Exposure Limits (SCOEL) has published an indicative OEL of 40 mg/m^3 (8-hour TWA). As this OEL is not binding, there exists various national OELs between 20 and 200 mg/m^3. In view of the Dossier Submitter, the indicative OEL of 40 mg/m^3 does not provide sufficient protection to the worker population (see chapter B), following the REACH guidance. In principle, one could refer the issue back to SCOEL and ask them to provide a new OEL. However, the SCOEL has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. In the case the SCOEL would change the indicative OEL value to the more protective level as indicated in this Background Document, harmonised implementation of such new the indicative OEL by all Member States is still not guaranteed. Finally, the OEL by definition only protects workers from the risks following inhalatory exposure[19], while the restriction proposal also shows risks following dermal exposure, for which additional risks management measures are needed. Risk reduction for NMP cannot be guaranteed via this route.

[19] *For NMP a skin notation is mentioned by SCOEL, see B.5.10*

In view of the Dossier Submitter, a restriction in terms of the a mandatory harmonised DNEL combined with an obligation to wear protective clothing is the most appropriate Community wide measure as such a restriction is effective in reducing all risks of NMP against acceptable costs for industry and society. Besides, such a restriction is foreseen to be practical for all users of NMP.

In conclusion, it is the aim of this restriction to adequately control the manufacture and of NMP by setting a limit of 5 mg/m^3 to the 8-hour TWA exposure and the obligation to wear protective clothing and gloves.

F. Socio-economic assessment of the proposed restriction

This socio-economic analysis (SEA) considers the potential positive and negative impacts of the various in Chapter E defined risk management options. In part F.1 the human health effects are discussed as the potential positive effects of the RMOs. F.3 sets the scene for the description of the socio-economic effects as the potential negative effects of the RMOs that are further worked out in section F.4 on socio-economic impacts. In F.5 the uncertainties of the socio-economic analysis are described followed by a concluding section F.6 where the risk reduction capacity, the economic feasibility and the proportionality of the various RMOs are discussed.

F.1 Human health impacts

Based on the hazard characteristics of NMP and current estimated exposure of uses of NMP, the risk characterisation leads to RCRs > 1 (see section B.10). A reduction in the use (RMO 1 and 2) or exposure (RMO 3) of NMP is assumed to result in a reduction in risks and consequently a reduction in negative health effects in humans.
In this section, human health impacts will be discussed. The potential adverse human health effects of NMP are mainly based on results from animal studies. A qualitative description of these potential effects is given, followed by a description of the impossibilities for quantification of the effects. The effectiveness of the restriction is estimated in terms of the risk reduction capacity of the RMO, by assessing the decrease in risk (in terms of lowered RCRs) because of reduced exposure to NMP. Next to that, the potential increases of risk due to increase of exposure to hazardous alternatives is assessed in a more qualitative way. A rough estimation is given of the size of the worker population exposed to NMP, for which a risk reduction is achieved by the various RMOs in this restriction proposal. The analysis is performed taking Europe as a geographical scale. As such, potential changes in human health effects outside Europe are not accounted for.

F.1.1 Qualitative description of health effects of NMP

F.1.1.1. Developmental effects

As described in part B of this Background Document, the most relevant affected human health endpoint of NMP is the developmental effect. It is concluded from several animal studies performed via different exposure routes (dermal, oral and inhalation) that NMP exposure during gestation causes maternal toxicity and results in lower maternal body weight and reduced food consumption. Fetuses experience effects on their body weights and skeletal variations or malformations. At higher NMP exposure levels, fetal resorptions[20] are increased as well.

Relevancy for humans

As described in one case report (see B 5.9; Solomon et al., 1996), a pregnant woman exposed during her work to a spill of NMP was ill for about 4 days. She returned to work, and could possibly have been exposed to NMP for another few weeks. After 1 month, physical examination showed early Intra Uterine Growth Retardation (IUGR). Two weeks later, no fetal activity was detected, and the patient delivered a stillborn fetus (31 weeks of gestation). Autopsy revealed no identifiable abnormalities to the fetus. Of course, there are more causes of IUGR such as poor maternal weight gain, vascular or renal disease, anemia, hypoxia, smoking, drugs, alcohol, abnormalities of the placenta or cord, or fetal infection. However, this patient lived a healthy life and was not at high

[20] *The disintegration and assimilation of the dead fetus in the uterus at any stage after the completion of organogenesis which, in humans, is after the 9th week of gestation.*

risk for IUGR. In addition, this laboratory worker could have been exposed to other chemicals than only NMP in the laboratory.
This human case study information together with the information from animal studies on toxicokinetics and developmental toxicity, supports the assumption that the developmental endpoint demonstrated in rodents is also relevant for humans. In conclusion, NMP shows developmental effects in animal studies, appears to have a similar metabolism of NMP in rats as in humans and was reported to possibly cause IUGR and fetal death in one human case study.
From this, potential endpoints for further investigation in the human health impact assessment are:

- IUGR
- Stillbirth

F.1.1.2. Systemic health effects after chronic exposure

Chronic NMP exposure could possibly cause negative health effects for all workers (female and male). In repeated-dose animal studies, the adverse systemic effects found were changes in body weight, testicular atrophy, thymic atrophy and swelling of distal kidney tubuli. After inhalation exposure, local respiratory tract irritation has been found as well. The most critical effects in the animal studies in general were reduced body weight, reduced body weight gain (in rats) and reduced food consumption.

Relevancy for humans

When extrapolating the chronic systemic effects of NMP described in animals to humans, it could mean that a person would eat less and loose some body weight, probably combined with some loss in general well-being. The effects of NMP found in organs in animal studies are difficult to extrapolate to human health effects. Whether specific effects to organs will occur in humans is uncertain. Besides, these effects are so-called sub-clinical and no clear disease can be determined from the combination of slightly affected organs (testis, kidneys, thymus).
In an experimental exposure study with human volunteers, using concentrations as high as current European OELs and STELs, NMP caused predominantly odor effects. Analyses showed that during eight investigated exposure scenarios none of the five sensations, i.e. nauseous, prickling, burning, "sneeze", and tickling, were significantly different from the ratings obtained at baseline levels. Acute NMP concentrations up to 160 mg/m^3 do not cause severe sensory irritation (Van Thriel et al., 2007). However, information from a human study with chronic exposure is not available.

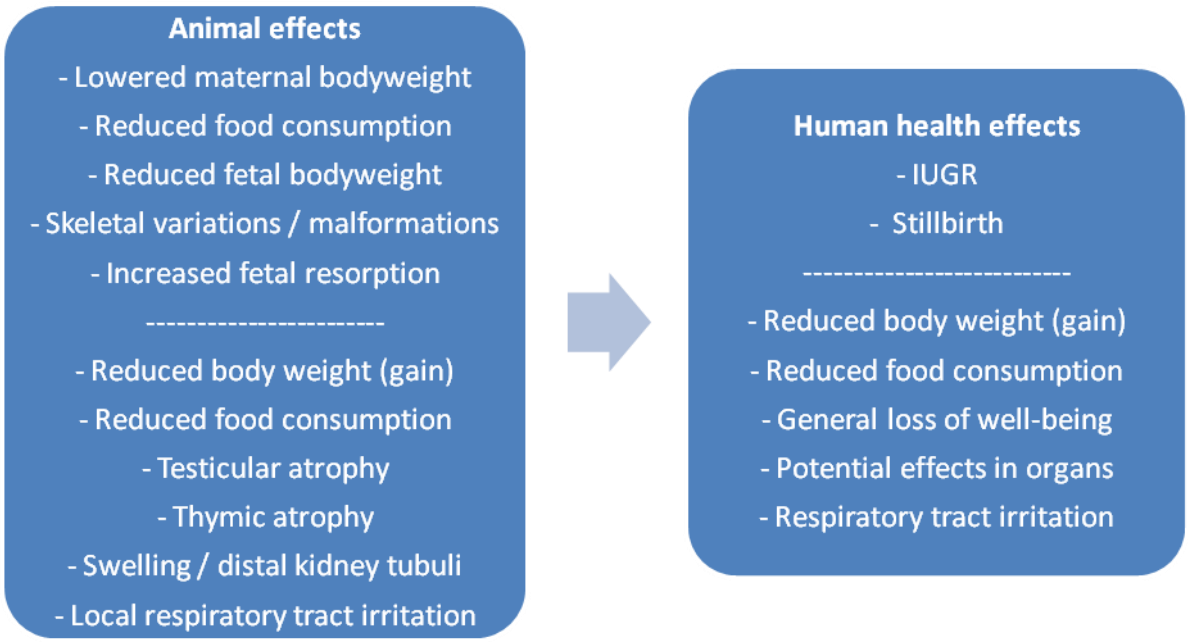
The lack of clear human health effects after acute NMP exposure and absence of chronic exposure information does not mean that humans are not negatively affected by chronic exposure of NMP. The critical effects of reduced body weight (gain) and food consumption could also be noted in humans. The subclinical effects described in the animal studies are adverse and definitely undesirable in humans.
Potential endpoints for further investigation in the health impact assessment are:

- Decrease in body weight
- Decrease in body weight gain[21]
- Decrease in food consumption
- General loss of well-being
- Potential effects on organs
- Respiratory tract irritation

[21] *In animal studies, body weights of rats are monitored. Because rats still gain weight within the study period, body weight gain is also one of the study parameters to which effects can be measured.*

Figure F.01: *Potential effects of NMP in animals and potential effects in humans*

Above the dashed line are the developmental effects, below the dashed line are the general acute and chronic toxic effects.



F.1.2. Possibility of quantification of the health effects of NMP in humans

Text box 1: *Possible methodology for a Health Impact Assessment for chemicals within REACH*

As noted in the RPA report (2011; Part 1) "Assessing the Health and Environmental Impacts in the Context of Socio-economic Analysis Under REACH" prepared for DG Environment, the resultant RCRs are essential for the chemical risk assessment process, while the extent to which they provide information with which to perform a SEA is limited. This is due to the fact that they do not provide information on the severity or extent of effects that might be anticipated to occur in an exposed human population (Chapter 3.6.2 of the RPA report).
The same report mentions that there are different approaches for the quantification of the change in health impacts:

- use of a simple physical indicator of change in risk as a proxy for impact; for example, change in usage, change in exposure levels and/or frequency, change in concentrations of a chemical in consumer products, or changes in emissions in the workplace or to the environment
- full quantification of the change in human health impact that may arise from the risk reduction measures under consideration.

Key elements in health impacts according to RPA report Chapter 6.1.1 are:

a) current levels of exposure to the chemical and the anticipated changes in exposure due to risk management
b) dose-response or other data linking exposure to different health outcomes
c) data on the population exposed both prior to and after regulation
d) based on the above, estimates of the number of cases of a particular disease outcome attributable to exposure to the chemical of concern (or chemicals more generally)
e) data on the economic value of changes in health outcomes.

Key elements a) to c) leading to d) can be quantified by using "health metrics" for which the RPA report (Chapter 6.1.2) provides 4 options (quoted):

1. "dose-response functions: these provide a direct indication of the probability that someone exposed to a substance at a given dose level will contract the health effect of concern. Epidemiological data are frequently inadequate to inform their development and they are not linked to the usually available epidemiological health metrics (odds ratio, relative risk ratio or attributable risk). They can, however, be derived from benchmark dose and margin of safety estimates using models which extrapolate from the underlying animal data;
2. attributable fractions: these provide an indication of the burden of disease within a population. Through the use of relative risk ratios or odds ratios, the impacts of changes in exposure – i.e. from current exposures to no exposure - on the attributable fraction can be calculated, indicating the associated reduction in the disease burden for the associated population;
3. prevalence or incidence: in the absence of a dose-response function or relative risk and odds ratios, statistical data on the prevalence or incidence of a disease within a population can be used to provide a starting point for predicting changes in impacts. However, this requires additional assumptions on how a change in exposure may change prevalence or incidence. For example, by calculating the difference in prevalence or incidence for an exposed and an unexposed population; and
4. the risk characterisation ratio (RCR) together with the margin of safety (MOS): the margin of safety data on its own provides no means of quantifying the change in health impacts that would arise from a regulatory measure; it is only possible to quantify the change in impacts if the MOS data are fed into the various models that are available to allow extrapolation of a dose-response function."

Possible approaches to quantify health effect in humans are elaborated by RPA and summarized in textbox 1. The Dossier Submitter sees in theory two possible routes for quantitative health impact assessment (the points 1 and 3 as mentioned above). In the case of NMP, calculated exposure estimates, taken from the registration dossier(s), are available. For the endpoint of developmental toxicity, the clinical endpoint in the human situation can presumably be a decrease in fetal body

weight and stillbirth. The fact that the clinical endpoint or the related disease in the human situation is not clear provides difficulties for the quantification of human health effects. For NMP the Dossier Submitter sees no possibilities for quantification of the potential effects due to data constraints and high uncertainties. However, we will nevertheless go into the possible routes to explain why we think quantification of health impacts in this case is not possible.

Both methods have been applied in previous restriction dossiers, as described in the textbox below.

Text box 2: *Examples of HIA for chemicals*

Approach A. Using dose-response relationship
(point 1 from the RPA report (2011))
In the restriction dossier on Lead in jewelry, a dose-response relationship established in humans between IQ levels and blood lead levels was used to assess the health impact (point 1). Using dose-response relationships, estimated number of the population exposed and making assumptions to extrapolate from animal studies to the human situation was also described in the report by Schuur et al. (2008). In nine cases involving restriction on chemicals in consumer products it was attempted to stretch the extrapolation, to find out what problems were encountered while going from risk assessment to health impact assessment. Health impact was assessed, however with large ranges surrounding the final numbers, expressed in Disability Adjusted Life Years (DALYs).

Approach B. Starting point is prevalence
(point 2 from the RPA report (2011))
The prevalence of skin allergy caused by Chromium was the starting point for the health impact assessment in the restriction dossier on Chromium VI in leather products (point 3). This approach could be used for the assessment of the health effects due to occupational exposure to chemicals uses

the actual occurrence of a certain disease in the (worker) population as a starting point. From that point on one could try to estimate the contribution of exposure to a specific substance to the occurrence of the disease in the population. This approach was used e.g. by Baars et al. (2005), who performed an exploratory study on the burden of disease due to exposure to chemicals at the workplace. Nine diseases were linked to exposure to a substance, the number of cases per year were determined, and combined with the assumed percentage of the disease due to occupational exposure to the substance. This was extended with another study with reproduction health effects as the endpoint (Dekkers et al., 2006). For this endpoint, experts on reproduction, on occupational exposure and on risk and health impact assessment, were brought together to perform an expert elicitation. With those results, the authors concluded on the impact (expressed in DALY's), but with a lot of discussion and a large uncertainty in the numbers.

Besides the approaches given in Textbox 2, an option to assess in some quantitative way the effectivity of the various RMOs in a restriction dossier on human health risks, is to assess the risk reduction capacity of the RMOs. An assumption can be made on the decrease in exposure caused by the implementation of an RMO. This will lead to a change, a decrease, in the RCRs. This approach (somewhat point 4 from the RPA report) is not a human health impact assessment, but merely a quantification of the effect of an RMO on RCRs. For NMP, it is described in F.1.2.3 as approach C.

F.1.2.1 Calculation based on experimental animal studies: from animal studies to human health impact (approach A)

A health impact assessment can be performed starting with animal study results, extrapolating from an adverse (subclinical) no-effect-level in an animal to an exposure level resulting in a disease in workers. To do this the following steps need to be taken:

1. Determine the relevant health endpoints (adverse sub-clinical and clinical effects) in the target population based on effects observed in animals and (when available) humans
2. Determine the effect level in animals (to be used as point of departure)
3. Translate effect levels in animals to effect levels in humans in order to define the exposure-effect relation in humans

4. Extrapolate the adverse subclinical effect to a clinical effect in humans

This exposure-effect relation could then be used to further quantify potential human health impacts by combining this with the expected decrease in exposure and the size of the population. To be able to make these extrapolations, a number of estimates or assumptions need to be made. The information to base such assumptions on is very limited in the case of NMP. The above mentioned steps cannot be made at a sufficient level of certainty mainly due to the absence of relevant information about health impacts on humans. In the following tables, the different steps are described for developmental effects, and for systemic effects after chronic exposure.

Table F.01: *Theoretical steps for quantification of developmental effects of NMP*

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.1, a qualitative description is given of the possibility to extrapolate effects demonstrated in animals to effects in humans. The one human case study gives an indication of potential effects in humans: IUGR and stillbirth. However, one case study (one person) does not provide enough evidence to draw conclusions on.
2: No effect level to effect level in animal studies	In animals, developmental effects are observed at the LOAEL, being the lowest level where adverse effects were observed, in contrast to the NOAEL where no effects are observed.
3: Effect level in animal to effect level in human	In risk assessment, extrapolation factors are used to calculate from the NOAEL/C in animals to a safe level in human aiming at protecting the human population for any adverse effects. In case of human health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals (e.g. a LOAEL) to those in humans. To be able to do that substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As no human data is available on the exposure-effect relationship of the developmental endpoint and given the large uncertainties in quantitative extrapolation from animal effect levels to human effect levels, this step was considered not possible in case of NMP. An additional point of difficulty is the exposure (duration, timing) during gestation and the extrapolation to pregnancy.
4: Subclinical to clinical effects	Both IUGR and stillbirth are clinical effects, so no further extrapolation required here.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be derived on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (see F.1.4)

Table F.02: *Theoretical steps for quantification of chronic health effects of NMP*

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.2. a qualitative explanation is given of the possibility to extrapolate effects seen in animals to effects in humans. However, as for chronic effects, no human (case) study is available, general adverse effects in animals are one-to-one extrapolated to humans. For the more specific effects in organs, no indications are given of potential effects in humans. The potential human effects indicated are reduced body weight (gain), reduced food consumption, general loss of wellbeing. However, as no human studies are available, not enough evidence is available to draw conclusions on.
2: No effect level to effect level in animal	In the risk assessment part (B), a NOAEL/C was derived for the described adverse health effects demonstrated in the animal studies. From those studies, a LOAEC, the lowest level of exposure in the animal study where adverse effects were demonstrated, can be derived as well. Based on this information it is possible to indicate some kind of exposure-effect relationship in animals.

Extrapolation step	Explanation
3: Effect level in animal to effect level in human	In risk assessment, extrapolation factors are used to calculate from the NOAEL/C in animals to a safe level in humans aiming at protecting the human population for any adverse effects. In case of health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals to those in humans. To be able to do that substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As no human data is available linking exposure levels to effects, this extrapolation is not possible in case of NMP.
4: Subclinical to clinical effects	The observed chronic systemic effects in animal studies after exposure to NMP are not very specific. That makes the step from adverse effects in animals to relevant, actual occurring subclinical or even clinical effects in the human situation rather difficult. The step from the observed subclinical effects to a specific disease in humans is not possible.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be made on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimation available for some use categories (F.1.4)

Conclusion

For developmental effects, the first step of establishing the relevant human health effect or disease could be done, because there is some supporting information from one human case study. The relevant human health effect could be concluded to be lowered fetal growth (IUGR) and stillbirth. However, the quantitative steps to go from the NOAEL in animals to an effect level during pregnancy of a worker cannot be taken without making many too far-stretched assumptions.
Based on available information and accepted risk assessment methodologies, we can determine whether or not subjects are at risk. The expectation is that NMP exposure can cause adverse effects in humans, however currently we are not able to quantify those adverse effects in the population.

F.1.2.2. Calculation based on prevalence and incidence studies on diseases caused by NMP (approach B)

This approach includes the use of prevalence data, the number of people suffering from the disease, as a starting point. After that, assumptions have to be made about the percentage of the total number of people with the disease attributable to exposure to NMP.

Developmental effects

In the case of NMP, the developmental effects in humans can be described as IUGR and stillbirth. For example for stillbirth, or perinatal death, some prevalence numbers are found for the Dutch situation (www.nationaalkompas.nl). Perinatal death is defined as the sum of stillbirth and early-neonatal death. The number is expressed per 1000 live-and stillborn which in the Netherlands is 9.4 based on data from 2008.
To be able to estimate the IUGR or stillbirth caused by NMP, estimates are required on the percentage of total IUGR/stillbirth (in Europe) caused by NMP. With the emphasis on "caused by NMP", as one can easily extrapolate the share of stillborns to the European population as whole, but it is far more difficult to relate this to NMP exposure. On the basis of the available data, it is even impossible to make these estimates. Reason for that is that no data are available on the relation between exposure (dose levels as well as dose timing) in humans and the endpoint stillbirth or IUGR. Another reason is that there are many potential causes of IUGR and stillbirth besides NMP.

Chronic health effects

The systemic health effects found in animal studies after chronic exposure caused by NMP do not clearly relate to actual specific clinical effects in the human population. Therefore, this approach based on actual occurrence in the population is not applicable to further quantify chronic effects caused by NMP. No disease can be singled out to be used as a starting point for such a quantification.

F.1.3. Risk reduction capacity as indication of potential health effects (approach C)

It is possible to use the performed risk assessment (RCR calculations) by assuming an effect of the different RMOs on the exposure levels. Taking the decreases in exposure into account (if possible quantitatively), RCRs for the situation after implementation of the restriction can be calculated. Using this approach, the effectiveness of risk reduction capacity of the RMO on the human health risks, can be assessed in terms of RCRs.

F.1.3.1 RMO1 Total ban

RMO1 is a restriction on the placing on the market and use of NMP for all applications in concentrations equal to or greater than 0.3% by weight. It is assumed that this will result in a total ban, so in no exposure at all. Therefore, all RCRs will decrease to zero.
It can be concluded that in the case of RMO1, there will be no remaining risk after implementation of the restriction caused by NMP. No health effects because of NMP, not for the pregnant worker, nor for other workers will remain.

F.1.3.2 RMO2 Restriction on the use of NMP in coatings

RMO2 is a restriction with derogations for specific industrial uses that is given under certain conditions. For the uses that are included in the restriction, concentrations equal to or greater than 0.3% by weight are not allowed. It is assumed that this will result in a total ban for these users, so in no exposure at all. Therefore, all RCRs will reduce to zero. For the uses that are derogated, the conditions set to the derogation are expected to result in exposure reduction compared to the current situation. Although no specific exposure limit is included in this RMO (as is in RMO3a), the exposure is considered to drop below 5 mg/m^3 for many of the use categories and processes. As such, the risk reduction capacity of this RMO is considered comparable to the risk reduction capacity of RMO3a for many uses of NMP. However, there might remain some processes within specific use categories in which risks might remain. This is for example expected for the wire-coating sector.

F.1.3.3 RMO 3 Harmonised DNEL and safe use demonstration

In the case of a mandatory harmonised DNEL, the exposure to NMP in all working situations needs to be lower than the harmonised DNEL of 5 mg/m^3. The resulting RCRs will then be lower than 1. In the case of this RMO, there will be no remaining risk or health effects of NMP for anyone. This is demonstrated in Table F.03 and F.04.
The Dossier Submitter proposes a mandatory DNEL for inhalation of 5 mg/m^3. Industry mentioned that it would be difficult for some uses to reach an exposure level similar or below this DNEL. To provide some insight in the resulting RCRs in case a higher limit value than the DNEL is proposed, the Tables F.03 and F.04 also include a limit value of 20 mg/m^3.

Note that in this Table only the effect of a harmonised DNEL on the inhalation route is reviewed. The RCRs for the dermal route in the current situation show for some uses a risk by themselves, and contribute to the total RCRs. However, in B.11 it is assumed that when proper RMMs are in place, the risks by dermal route can be sufficiently controlled.

RMO3a (harmonised DNEL of 5 mg/m^3):
When the harmonised DNEL for inhalation of 5 mg/m^3 would be implemented, and under the assumption that exposure levels are met, risks will be sufficiently controlled. For the exposure situation by inhalation, this is shown in Table F.03 (column RMO3, RCR under harmonised DNEL), for the general worker and in Table F.04 for the pregnant worker. For the exposure situation via the dermal route, it can be assumed that the use of proper RMMs (suitable gloves/clothing) will sufficiently control the risks.

RMO3b (exposure limit value of 20 mg/m^3):
Reviewing the results estimated for a limit value of 20 mg/m^3 in Table F.03 and F.04, it is shown that for almost all uses this exposure limit value will be met already in the current exposure situation. Only for pregnant workers, still some uses need to adapt the exposure to meet that limit value.
Again, it is assumed for the exposure situation via the dermal route that proper RMMs (suitable gloves/clothing) will sufficiently control the risks.

Table F.03: *Effectiveness of RMO 3 on the RCRs for general worker*

Current situation: For all uses, the highest RCRs (and corresponding exposure estimates) are chosen from the risk characterisation ratios summarized in Table B.47 to B.75. These RCRs are calculated using a DNEL inhalation of 10 mg/m³ and a dermal DNEL of 4.6 mg/kg bw/day derived for chronic, inhalation, general worker.
RMO3: RCRs are calculated using the DNEL of 10 mg/m³ (for general worker), but assuming exposure estimates that meet the harmonised DNEL of 5 mg/m³ (RMO3a), or exposure estimates that meet a chosen limit value of 20 mg/m³ (RMO3b).
Uses with a conclusion that risk can be sufficiently controlled (current situation) are provided in grey. For dermal RCRs is it assessed that even for uses with RCRs above 1 with proper RMMs risks can be sufficiently controlled.

Current situation							**RMO3**			
			DNEL inhalation for general worker of 10 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR Inha-lative**	**RCR Der-mal**	**RCR Com-bined**	**Conclusion of risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**
RCRs industrial uses							**Only inhalation!**			
Manufacturers	3	12.4	1.24*	0.15	1.39	Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EASY TRA output is indeed a conservative estimate and therefore support the Dossier Submitter's conclusion that risks are expected to be sufficiently controlled	≤5	≤0.5	12.4	1.24
Generic uses: *charging and discharging*All use categories as defined in table B.03 with industrial use	8a	17.4	1.74	0.60	2.33	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks might not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.	≤5	≤0.5	17.4	1.74

Current situation							**RMO3**			
			DNEL inhalation for general worker of 10 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR Inha-lative**	**RCR Der-mal**	**RCR Com-bined**	**Conclusion of risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**
Generic uses: *chemical industry processes (elevated temp)* - Petrochemical industries - Agricultural chemical industry (synthesis) - Pharmaceutical industry	3	20.7	2.07	0.15	2.22	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks might not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.	≤5	≤0.5	≤20	≤2
Generic use: *formulation (up to 60)* - Formulators - Non-wire coaters - Wire coaters - Cleaners - Battery industries - Membrane manufacturers - High performance polymer producers - Agricultural chemical industry (synthesis) - Pharmaceutical industry - Functional fluids - Construction industry	5	20.7	2.07	0.60	2.66	Risks of NMP can be controlled at room temperature with proper RMMs in place. At elevated temperatures the risks might not be sufficiently controlled even with RMMs.	≤5	≤0.5	≤20	≤2

Current situation							**RMO3**			
			DNEL inhalation for general worker of 10 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR Inhalative**	**RCR Dermal**	**RCR Combined**	**Conclusion of risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**
Coatings process: - Non-wire coaters - Wire coaters - Battery industries	7	18.7	1.87	0.38	2.25	Risks might not be sufficiently controlled	≤5	≤0.5	18.7	1.87
Cleaning process: - Cleaners - Electronics and semiconductor industries	7	18.7	1.87*	0.38	2.25	Risks might be sufficiently controlled (measurement data and EASY TRA calculation are in the same range)	≤5	≤0.5	18.7	1.87
Laboratory use	15	2.1	0.21	0.07	0.28	Risks are sufficiently controlled	2.1	0.21	2.1	0.42
Functional fluids	17	8.3	0.83	1.19	2.02	Risks are sufficiently controlled (EASY TRA calculations conservative)	≤5	≤0.5	8.3	0.83
Construction chemicals	10	4.13	0.41	1.19	1.61	Risks are sufficiently controlled (EASY TRA calculations conservative)	4.1	0.41	4.1	0.41
Professional uses										
Generic uses: *charging and discharging* - All use categories as defined in table B.03 with professional use	8b	17.4	1.74	0.60	2.33	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	17.4	1.74

Current situation							**RMO3**			
			DNEL inhalation for general worker of 10 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR Inha-lative**	**RCR Der-mal**	**RCR Com-bined**	**Conclusion of risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 10 mg/m³)**
Generic uses: *Formulation* - Formulators - Non-wire coaters - Agricultural chemical industry (formulation) - Functional fluids - Construction industry	5	17.4	1.74	0.60	2.33	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	17.4	1.74
Coating process: - Non-wire coaters	13	14.5	1.45	0.30	1.74	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	14.5	1.45
Agricultural chemical industry (formulation)	11	5.3	0.53	1.17	1.70	Risks can be sufficiently controlled (if proper RMMs are taken)	≤5	≤0.5	5.3	0.53
Laboratories	15	4.1	0.41	0.07	0.49	Risks are sufficiently controlled	4.1	0.83	4.1	0.41
Functional fluids	20	20.7	2.07	0.37	2.44	Activities that fall under PROC20 will lead to insufficiently controlled risks from inhalation of NMP for all workers if no proper RMMs are considered due to the high energy processes.	≤5	≤0.5	≤20	≤2

RCR above 1, but as described in B.10, assessed that risks can be sufficiently controlled

Table F.04: *Effectiveness of RMO 3 on the RCRs for pregnant worker*

Current situation: For all uses, the highest RCRs (and corresponding exposure estimates) are chosen from the risk characterization ratios summarized in Table B.48 to B.76. These RCRs are calculated using a DNEL inhalation of 5 mg/m³ and a dermal DNEL of 2.4 mg/kg bw/day derived for chronic, inhalation, pregnant worker.
RMO3: RCRs are calculated using the DNEL of 5 mg/m³ (for pregnant worker), and assuming exposure estimates that meet the harmonised DNEL of 5 mg/m³ (RMO3a), or exposure estimates that meet a chosen limit value of 20 mg/m³ (RMO3b).
Uses with a conclusion that risk can be sufficiently controlled (current situation) are provided in grey. For dermal RCRs is it assessed that even for uses with RCRs above 1 with proper RMMs risks can be sufficiently controlled.

Current situation							**RMO3**			
			DNEL inhalation for pregnant worker of 5 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR inha-lative**	**RCR der-mal**	**RCR com-bined**	**Conclusion on risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**
RCRs industrial uses							**Inhalation only!**			
- Manufacturers	3	12.4	2.48*	0.29	2.77	Measurement data of air concentrations of NMP at the production plants where NMP or other chemicals are produced (see section B.9.3.2.) suggest that the EASY TRA output is indeed a conservative estimate and therefore support the Dossier Submitter's conclusion that risks are expected to be sufficiently controlled	≤5	≤1	12.4	2.5
Generic uses: *charging and discharging* - All use categories as defined in table B.03 with industrial use	8a	17.4	3.47	1.14	4.61	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks might not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.	≤5	≤1	17.4	3.5

Current situation							**RMO3**			
			DNEL inhalation for pregnant worker of 5 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR inha-lative**	**RCR der-mal**	**RCR com-bined**	**Conclusion on risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**
Generic uses: *chemical industry processes (elevated temp)* - Petrochemical industries - Agricultural chemical industry (synthesis) - Pharmaceutical industry	3	20.7	4.13	0.29	4.42	Inhalation exposure to NMP may be too high if proper RMMs are not in place. Risks might not be sufficiently controlled when processes take place under elevated temperatures even with RMMs.	≤5	≤1	≤20	≤4
Generic use: *formulation (up to 60)* - Formulators - Non-wire coaters - Wire coaters - Cleaners - Battery industries - Membrane manufacturers - High performance polymer producers - Agricultural chemical industry (synthesis) - Pharmaceutical industry - Functional fluids - Construction industry	5	20.7	4.13	1.14	5.27	Risks of NMP can be controlled at room temperature with proper RMMs in place. At elevated temperatures the risks might not be sufficiently controlled even with RMMs.	≤5	≤1	≤20	≤4

Current situation							**RMO3**			
			DNEL inhalation for pregnant worker of 5 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR inha-lative**	**RCR der-mal**	**RCR com-bined**	**Conclusion on risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**
Coatings process: - Non-wire coaters - Wire coaters - Battery industries	7	18.7	3.74	0.72	4.46	Risks might not be sufficiently controlled	≤5	≤1	18.7	3.7
Cleaning process: - Cleaners - Electronics and semiconductor industries	7	18.7	3.74	0.72	4.46	Risks might not be sufficiently controlled	≤5	≤1	18.7	3.7
- Laboratory use	15	2.1	0.41	0.14	0.56	Risks are sufficiently controlled	2.1	0.41	2.1	0.41
- Functional fluids	17	8.3	1.65	2.29	3.94	Risks might not be sufficiently controlled	≤5	≤1	8.3	1.7
- Construction chemicals	14	14.5	2.89	0.29	3.18	Risks might not be sufficiently controlled	≤5	≤0.5	14.5	2.9
Professional uses										
Generic uses: *charging and discharging,* - All use categories as defined in table B.03, with professional use	8b	17.4	3.47	1.14	4.61	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	17.4	3.5

Current situation							**RMO3**			
			DNEL inhalation for pregnant worker of 5 mg/m³				**RMO3a: Harmonised DNEL of 5 mg/m³**		**RMO3b: limit value of 20 mg/m³**	
Use	**PROC**	**Exposure estimate long-term inhalative (mg/m³) from B.10**	**RCR inha-lative**	**RCR der-mal**	**RCR com-bined**	**Conclusion on risk**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**	**Assumed exposure estimate long-term inhalative (mg/m³)**	**RCR inhalative (calculated with DNEL of 5 mg/m³)**
Generic uses: *Formulation* - Formulators - Non-wire coaters - Agricultural chemical industry (formulation) - Functional fluids - Construction industry	5	17.4	3.47	1.14	4.61	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	17.4	3.5
Coating process: - Non-wire coaters	13	14.5	2.89	0.57	3.46	Inhalation risks might not be sufficiently controlled	≤5	≤0.5	14.5	2.9
- Agricultural chemical industry (formulation)	11	5.3	1.05*	2.24	3.30	Risks can be sufficiently controlled (if proper RMMs are taken)	≤5	≤0.5	5.3	1.1
- Laboratories	15	4.1	0.83	0.14	0.97	Risks are sufficiently controlled	4.1	0.83	4.1	0.83
- Functional fluids	20	20.7	4.13	0.71	4.84	Risks cannot be excluded	≤5	≤0.5	≤20	≤4

F.1.3.4 RMO 4 Authorisation

Depending on the industries response to authorisation, risks on NMP will be reduced e.g. by the shift to alternatives, by exposure reduction (if authorisation is given via the adequate control route) or by the stop of use of NMP in case of relocation or termination. Some risks of NMP might remain in case authorisation would be given via de socio-economic route. However, the extent to which that will occur is expected to be very limited.

Additional health impacts / risks of alternatives

RMO1:

In case of a total ban, in some uses (see Chapter C) NMP would be replaced by alternatives. As some of the known alternatives have hazardous characteristics, there is a possible increase in the risk (not further quantified) due to the shift to these substances.
From the alternatives discussed in Chapter C, possible functional replacements could be DMAC, NEP, DMF, and DMSO. As also mentioned in C.1 (Table C.02) these alternatives also have hazardous properties.

- DMAC is already classified as a reproductive toxicant category Repr. 1B under CLP (Annex VI CLP).
- For NEP, the C&L proposal, a classification similar to NMP (CLP Repr. 1B: CLH report, 2011) will be discussed by the RAC in 2013. At the moment, NEP is already classified as Repro 2.
- DMF is already classified as a reproductive toxicant category Repr. 1B under CLP.

DMAC, NEP and DMP are all three, similar to NMP, reproductive toxicants with DNELs for systemic chronic effects close to the DNEL of NMP[22]. Therefore, all three substances are not considered as suitable alternatives, because human health risks will not decrease.
DMSO has no harmonised classification (see table C.02 in chapter C). The self-classifications under the CLP regulation vary between notifiers. A majority of the notifiers uses no classification. A minority of the notifiers indicate that the substance causes skin irritation (Skin Irrit. 2), causes serious eye irritation (Eye Irrit. 2) and may cause respiratory irritation (STOT SE 3). Some individual notifiers classify the substance as suspected of causing genetic effects (Muta. 2) (1 out of 518 notifiers) or as harmful if inhaled (Acute Tox. 4) (4 out of 518 notifiers). It can be concluded that DMSO would be a safer alternative because it has no CMR related hazardous properties. DNELs (systemic chronic effects) reported for DMSO for inhalation as well as for the dermal route are a factor of 10 higher compared to those for NMP. Without actually performing an exposure and risk assessment, it could be assumed that the human health risks using DMSO as alternative for NMP would be lower. Industry however claims DMSO has explosive properties when used at high temperatures, which might complicate the use of DMSO as alternative in some uses (see for more information part C).
In part C also more specific alternatives are indicated. Some of these have hazardous characteristics comparable to or less severe than NMP (see Table C.02). A shift to these alternatives might result in some risk reduction.

For other uses, a ban might possibly result in relocation of the industrial activities to outside Europe. For these uses risk reduction would then be achieved in Europe, while risks then might increase outside Europe (however, note that impacts outside Europe are outside the scope of this analysis).

To conclude, in the opinion of the Dossier Submitter, NEP, DMF and DMAC are not suitable alternatives for NMP, based on human health hazard characteristics (as these also are reproductive toxicants that have DNELs comparable to NMP). Taking into account the human health hazard

[22] *From the registration dossiers (ECHA website) DNELs are provided for inhalation (worker, chronic) for NMP, DMAC, DMF and NEP respectively of 40, 36, 15 and 50 mg/m³. The DNEL for DMSO is 484 mg/m³.*

properties of DMSO, it could be concluded that DMSO would be a possible alternative for NMP. However, in part C it was concluded that DMSO based on use characteristics is not a suitable alternative for all use categories.

RMO2:

For the uses that are included in the restriction (e.g. non-wire coatings, professional cleaners, agricultural chemical formulation and use in construction industry). The ban is expected to result in the replacement of NMP with alternative substances, e.g. NEP or DMSO. See the explanation on these alternatives above under RMO1 (part 1). For some other uses, that are not derogated (the use in medical images, foodcontact material/bakeware and optical industry), alternatives might not be available and replacement with hazardous alternatives resulting in an increase in risks might thus not occur for these uses.

RMO3:

For some of the professional applications a mandatory DNEL will result in the replacement of NMP with substance alternatives. For the majority of the industrial uses a mandatory DNEL will result in exposure reduction and no use of alternative substances. For some industrial uses this might imply relocation to outside Europe as DNEL cannot be met.

RMO4:

For the uses for which alternatives are readily available (non-wire coatings, professional cleaners, agricultural chemical formulation and use in construction industry) the shift to hazardous alternative might cause an increase in risks of alternatives, as described under RMO1.

Overall

With regard to a risk reduction based on health effects, the potential profit for RMO1 and RMO3b is minimal. In the case of RMO2 and RMO3a, there is a significant effect on the calculated RCRs, which will results in a decrease in expected adverse health effects.

F.1.4. Population potentially at risk

To obtain an impression of the potential scale of the human health risks caused by NMP, the market analysis in Appendix A estimates the number of workers potentially exposed to NMP for 5 selected use categories[23]. For the majority of these uses an 'upper bound' estimate of the worker population is given based upon general EU statistics available for NACE code use categories[24] of which NMP is assumed to be part. For some of the uses a more accurate 'actual' estimate is given scaling up the number of workers at a company's level to a European level. The limited data availability results in substantial uncertainties in the outcome of both methods. For some uses both methods are applied to provide information on the uncertainty surrounding the estimate of the number of people potentially exposed. Table F.05 gives an overview of the available information on the number of EU workers potentially exposed to NMP.

F.1.4.1 Pregnant and potentially pregnant worker

As explained in F.1.2 NMP has a developmental effect on the unborn child and thus the pregnant worker is the target population. It is unknown whether the potential effect is coupled to exposure in a specific period of the pregnancy. However, it is known that potential effects occur due to exposure during the pregnancy period. Based on this information it is assumed that the population at risk regarding developmental effects, consists of pregnant workers *during the full period* of their pregnancy. As explained in part B.9.1.1, Directive 1992/85/EEC is already in place for the protection of pregnant workers to potential risks caused by e.g. reproduction toxic substances like NMP. With this Directive, the employer is to take the necessary measures to ensure that exposure of pregnant workers is avoided. Personal communication with some of the NMP using industries

[23] *Manufacture and distribution, industrial and professional cleaning, industrial and professional non-wire coatings, wire coatings and membranes.*
[24] *See the market analysis in Appendix A section 1.3.4 for further explanation on the NACE code categories used.*

indicated that there are indeed preventive measures in place to protect pregnant workers. In at least one industry, workers are informed about the potential hazardous effects of NMP before they enter the job and workers will temporary be replaced to a NMP free environment during the period of their pregnancy to avoid exposure to NMP (personal communication). Another industry notes that most plants have no female workers working at the jobs where they could potentially be exposed (personal communication).

The potential risk for pregnant workers might however remain, as women might not know that they are pregnant in the early days of their pregnancy, or, as women might not tell their employer before the 10^{th} -week of their pregnancy. Because of this, it could be argued that all female workers during their reproductive period (20-45 years; CBS, 2007) should be included in the population at risk for this endpoint. As is calculated and explained in the text box 3 below, around 57% of the female worker population is at the reproductive age and on a yearly basis 3.5% of the female worker population becomes pregnant. These percentages give an indication of the female population potentially at risk, however, the population actually experiencing developmental effects caused by exposure to NMP will presumably be much lower.

F.1.4.2 All workers

This involves the full worker population as both pregnant and non-pregnant workers might suffer from chronic effects due to exposure to NMP. In 2011 the EU counted a total of 217'000'000 workers (EUROSTAT, 2012) of which only a minor part might come into contact with NMP.

The actual estimates of number of workers potentially exposed to NMP are used further on in the analysis to indicate the number of people for which risk reduction is achieved to get an idea of the scale of the potential risk reduction.. Furthermore, the number of workers potentially exposed is used to give an impression of the number of people that might lose jobs in case industries shut down due to the RMO (see section F.4). This is possible as the actual estimate of the workers potentially exposed rather represents the number of workers that are related to NMP.

Note that the upper bound figures are based on NACE code categories that potentially involve more than NMP related work. The relevance of the NACE code categories is discussed in table 1.6 of Appendix A, market analysis. Because of the high uncertainty, these upper bound figures are not further used in the socio-economic analysis.

Table F.05 below gives an overview of the number of workers that are potentially exposed to NMP per use category. For the further analysis only the actual average estimates will be used, as the upper bound figures and the estimates of the number of female/reproductive and pregnant workers are thought to be very uncertain. Below the risk reduction potential in terms of workers for which risk reduction is achieved is explained per RMO.

In RMO1 full or partial risk reduction is expected in case of shift to alternatives as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional**) and potentially for part of the **membrane manufacturers**. Quantitative estimate is confidential: XXXX. Complete risk reduction of NMP is expected in Europe in case industry terminates (and potentially relocates). This is potentially expected for **manufacturers, importers/suppliers**, petrochemical industries, specialty coating (medical images, foodcontact material/bakeware) , **wire coating industry (coaters and formulators**), optical industry (cleaning), electronics and semiconductor industry, battery industry, (part of the) **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry, laboratories and functional fluid users. Quantitative estimate is confidential: XXXX.

In RMO2 full or partial risk reduction in case of shift to alternatives is expected for the uses for which the use of NMP is fully banned in this RMO and for which alternatives are readily available, as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional**), professional cleaners, agricultural chemical formulation and construction industry. Quantitative estimate is confidential: XXXX.
Complete or partial risk reduction for those users that comply with the conditions of the derogation: **manufacturers, importers/suppliers**, petrochemical industries, **wire coating industries (coaters and formulators**), electronics and semiconductor industry, battery industry, **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical

industry (synthesis) and pharmaceutical industry. Quantitative estimate: XXXX. Complete risk reduction of NMP is expected in Europe in case industry terminates or relocates. This is potentially expected for (**part of) manufacturers, importers/suppliers**, medical images, foodcontact material/bakeware (coatings), **wire coating industry (coaters and formulators**), optical industry (cleaning), functional fluid users and (non-R&D) laboratories. Quantitative estimate: XXXX. However, as some of these actors are likely to comply with the RMO, these users are expected to obtain risk reduction via exposure reduction.

In RMO3a full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional**). Quantitative estimate: XXXX. Complete risk reduction of NMP is expected in Europe in case industry terminates or relocates. This is potentially expected for (**part of) manufacturers, importers/suppliers**, medical images, foodcontact material/bakeware (coatings), **wire coating industry (coaters and formulators**), optical industry (cleaning), battery industries, agricultural chemical synthesis industries, pharmaceutical industry, functional fluid users. Quantitative estimate: XXXX. However, as these actors are likely to comply with the RMO, these users are expected to obtain risk reduction via exposure reduction. Complete risk reduction for those users that comply with the limit value: **manufacturers, importers/suppliers**, petrochemical industries, non-wire coating industry (medical images, foodcontact material/bakeware), **wire coating industries (coaters and formulators**), cleaners (optical industry), electronics and semiconductor industry, battery industry, **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis, formulation), pharmaceutical industry and functional fluid users. Quantitative estimate: XXXX.

In RMO3b full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for: non-wire coaters (**automotive industry, both industrial and professional**). Quantitative estimate is confidential: XXXX. Minor to no risk reduction is expected for the users that adapt to the limit value of 20 mg/m^3 as this value is a factor 4 above the harmonised DNEL. Risks will thus remain for manufacturers, importers/suppliers, petrochemical industry, non-wire coatings (medical images, foodcontact material/bakeware), wire coaters and formulators, cleaners (optical), electronics and semiconductor industry, battery industry, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry and functional fluid users.

In RMO4, full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for: non-wire coaters (**automotive industry, both industrial and professional**). Quantitative estimate: XXXX. Complete risk reduction of NMP is expected in Europe in case industry stops activity (termination or relocation) and in case authorisation is given based upon adequate control. Potentially some remaining risks for companies that receive authorisation based upon the SEA route. As it is not known what will actually occur in practice, no quantitative estimate of workers for which risk reduction is achieved is given. However, this is assumed to be somewhat similar to that of RMO3a.

Text box 3: *EUROSTAT data on the female worker population*

In total, the EU had in 2011 84'300'000 females at the reproductive age (20-44 year). In the same year the EU had a total of 98'700'000 female workers of which 56'000'000 females were at the reproductive age of 20-44 years (57%). In 2011, there were 5'200'000 live births in the EU (Eurostat, 2012). It is assumed that on average a working woman has an equal number of children compared to a non-working EU female citizen every year. From these data it is calculated that reproductive female EU workers gave birth to a total of 3'500'000 children in 2011 ($5.2 * 56.0 / 84.3 * 10^6$). Assuming that every birth involves one pregnant worker for nine months, it is calculated that approximately 3.5% of the total female worker population becomes pregnant in a year (3'500'000 * 100% / 98'700'000). One should recognize that the total number of pregnancies can be higher as miscarriage and stillbirth are not included in these figures. The total number of pregnancies can also be lower as multiple births are not included. The estimate above might thus be an under or over estimation depending on the net effect of the mentioned factors. Besides, one should recognize that this 3.5% is an average, assuming equal distribution of reproductive women over the female work population in various sectors. In practice, it might be the case that specific sectors have a higher/lower share of reproductive female workers.As indicated by some comments in public consultation, these statistical estimates might be an overestimate when it comes to the number of pregnant workers working in sectors where potential for exposure to NMP exists. In the public consultation the regulation in place to prevent exposure of pregnant workers to substances toxic for reproduction was also mentioned. It needs to be considered that the proposed restriction offers protection also during the period before a woman is aware of the pregnancy and measures can be taken to prevent further exposure.

Table F.05: *Overview of the estimates of the number of workers potentially exposed to NMP per use categories*

	Number of workers				**Female workers**		**Reproductive female workers**		**Pregnant workers**	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
NMP suppliers										
NMP manufacturers	n/a	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
NMP importers	n/a	XXXX	XXXX	XXXX	49%	XXXX	57%	XXXX	3.5%	XXXX
Petrochemical industries										
Petrochemical industries	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Cleaning products and non-wire coatings										
Coating formulators	160,000[1, 2]	n/a	n/a	<5,500	30%	<1,650	57%	<950	3.5%	<60
Cleaning formulators	98,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Cleaners and coaters (general)	n/a	n/a	n/a	n/a	9-75%	n/a	57%	n/a	3.5%	n/a
Professional cleaning	3,400,000	n/a	n/a	n/a	9-75%	n/a	57%	n/a	3.5%	n/a
Optical (cleaning)	43,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Medical images, foodcontact material/bakeware	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	3.5%	n/a
Manufacturers of furniture (cleaning)	1,080,000	~0	~0	~0	30%	~0	57%	~0	3.5%	~0
Painting and glazing (cleaning)	662,000	~0	~0	~0	n/a	n/a	57%	n/a	3.5%	n/a
Treatment and coating of metals	260,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
Automotive (coating and cleaning, includes manufacturing of motor vehicles and maintenance and repair)	2,500,000	XXXX	XXXX	XXXX	9-49%	XXXX	57%	XXXX	3.5%	XXXX
Manufacturers other transport equipment	710,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Wire coatings										
Wire coaters	n/a	4,000	4,000	4,000[3]	30%	1,200	57%	700	3.5%	40[6]
Formulators	160,000[2]	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
Electronics and semiconductor industries										
Electronics and semiconductor industries	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Battery industries										
Battery industries	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Membranes										
Membrane manufacturer (water filtration)	n/a	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
Membrane manufacturer (vapour permeation)	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a
High performance polymer producers										
High performance polymer producers	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a
Agricultural chemicals										
Agricultural chemical formulation	n/a	n/a	n/a	n/a	37%	n/a	57%	n/a	n/a	n/a
Agricultural chemical synthesis	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
Pharmaceutical industry										
Pharmaceutical industry	n/a	n/a	n/a	XXXX	n/a	n/a	57%	n/a	n/a	n/a
Other										
Laboratories	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	n/a	n/a
Functional fluids	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	n/a	n/a
Construction chemicals	n/a	n/a	n/a	n/a	9-30%	n/a	57%	n/a	n/a	n/a
Total										
Total of available data	9,000,000	XXXX	XXXX	XXXX		XXXX		XXXX		XXXX

n/a = not available
This table is based on the market analysis table 6.1 presented in Appendix A.
(1)Of this estimate of coating formulators XXXX workers are estimated to work on formulation of automotive coating (actual estimate).
(2)This estimate of coating formulators and wire coating formulators are the same estimate, this is only included once in the total figure.
(3)Industry estimates that the double amount of jobs is lost in case production ceases (XXXX).
(4)Industry estimates that XXXX jobs will be lost in case production ceases (average estimate XXXX jobs).
(5)Confidential information
(6)Information received in the public consultation indicates that the number of female and pregnant wonen working in the wire coating sector at locations where there is some exposure to NMP is much more limited than the figure presented here in the document. The actual figure might even be close to zero according to the branche organisation of wire coaters.

The quantified estimates given in table F.05 do not take into account the baseline (confidential) presented in Annex 3 .

This was not done e.g.
1. as changes in tonnages of NMP used as presented in the baseline figures do not necessarily translate one to one to a change in number of workers potentially exposed;
2. as both the baseline figures on volumes used as the number of worker estimates are very uncertain, combining these figures might only introduce changes in the margins of uncertainty and would not change the overall picture, and
3. as it is unclear from the figures provided by industry that were used as the basis for the estimation of the benefit indicators (risks and number of workers), what year these estimates actually represent and whether these do or do not already include a baseline trend.

However, as it might be more correct to account for the baseline in presenting the benefit estimates, estimates of the number of workers potentially exposed combined with the baseline figures are presented below in table F.05A as a sensitivity analysis to the original worker table F.05. Such a combination is made under the assumption that there is a one to one relation between the tonnage of NMP used and the number of workers exposed. Furthermore, it is assumed that the worker figures presented in table F.05 represent the situation in 2011 and do not yet include any baseline trend. It should be noted that it is uncertain whether there assumptions are correct.

Table F.05A below gives an overview of the number of workers potentially exposed to NMP. The table includes the original estimates from table F.05, presented as 2011 estimates. Besides that a 2016 estimate is included in table F.05A, combining the 2011 figure with the baseline trend presented in Annex 3. Unfortunately, the use categories used in the baseline figures are of a different level of detail than the available figures on the number of workers. It is therefore not always easy to make the comparison as it is for example uncertain whether the general trend figure for cleaning or coating uses does apply to a very specific cleaning or coating use. The dossier submitter here made its own judgment based on the available information. The only use category for which this assumption has a substantial result on the final estimate, is the automotive sector. Based on the information available from the automotive sector (see market and cost analysis in the Appendices to the Background Document) it was decided to deviate from the general baseline trend for cleaning and coating industries (XXXX). As a sensitivity analysis, a worst case estimate was included in table F.05A assuming that the general trend of the coating sector does apply to the automotive sector.

As the baseline trends differ per use category, the effect also differs per use category. The fact that for many of the use categories no quantitative estimate of the number of workers is available makes it difficult to draw clear and straight forward conclusions on the overall effect of the baseline trend to the worker population. This is also shown from the table F.05A below. Reviewing the total upper bound 2011 and 2016 estimates (which was not further used in the document as the figure represents a very worst case estimate that is assumed to differ too much from the actual situation) shows an overall reduction of the total number of workers due to the effects of the baseline trend. However, if the total 2011 and 2016 actual estimates are reviewed, it is shown that the effect of the baseline trend only exists in the margins of uncertainty of the figures. As the total figures are rounded, this effects is not shown in these total figures (the 2016 estimate is a fraction higher compared to the 2011 estimate). The 2016 worst case estimate shows that the information on the baseline trend for the automotive industry is relatively important for the effects on the number of workers. This is logic as this sector has the highest number of workers potentially exposed to NMP from all of the sectors of which quantitative information is available. Unfortunately, it is uncertain what the actual trend is in this sector. However, based on the available information from the sector, the dossier submitter assumes that a trend of around XXXX does better reflect the actual situation than the general baseline estimate for the cleaning or the coating sectors.

From the use categories of which no quantitative estimates of the number of workers potentially exposed to NMP are available and combining the baseline trend data of these use categories to the estimates of the total tonnages of NMP used per use category in 2011, it can be shown that the categories with large declining trends (cleaning and coating sectors), already had a low use of NMP in 2011 (respectively X and X % of the total use, according to the figures from Annex 3) except for the agricultural chemical formulation (XXXX of the total use and an expected reduction of XXXX). For all other use categories for which baseline trend data are available but no quantitative estimates of workers are available (petrochemical industries, electronics industry, part of the

membrane industry and agricultural chemical synthesis) trend of XXXX is expected. These sectors in 2011 represent respectively X, X, part of X and X of the total use of NMP. Again assuming that the estimate of the tonnages of NMP used in a sector are a proxy for the number of workers potentially exposed (note that this is not necessarily the case), the figures presented above suggest that if more quantitative information of workers potentially exposed to NMP would have been available, the baseline trend would likely increase the number of workers potentially exposed.

Overall, reviewing the baseline figures the following can be said on the remaining uses of NMP without implementation of additional measures:

- With certainty remain: petrochemical industry, wire coating industry, electronics and semiconductors, membrane industries, high performance textile producers, agricultural chemical synthesis, pharmaceuticals.
- Expected to remain (some uncertainty): specific coating applications (automotive industry), battery industries.
- Uncertain whether will remain: specific coating applications (medical images, foodcontact material/bakeware), specific cleaning applications (optical cleaning), laboratories, functional fluids.
- Certain that will not remain: general coating and cleaning applications (that do not require the specific aprotic characteristics of NMP), construction industry.

Table F.05A: *Overview of the estimates of the number of workers potentially exposed to NMP per use categories for 2011 and 2016 based upon the information from the baseline trend (confidential) presented in Annex 3*

	Number of workers				**Female workers**		**Reproductive female workers**		**Pregnant workers**	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
NMP suppliers										
NMP manufacturers –*no baseline estimate available*	n/a	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
NMP importers – *no baseline estimate available*	n/a	XXXX	XXXX	XXXX	49%	XXXX	57%	XXXX	3.5%	XXXX
Petrochemical industries										
Petrochemical industries – *2011 estimate*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Petrochemical industries – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Cleaning products and non-wire coatings										
Coating formulators – *2011 estimate*	160,000[1, 2]	n/a	n/a	<5,500	30%	<1,650	57%	<950	3.5%	<60
Coating formulators – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Cleaning formulators – *2011 estimate*	98,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Cleaning formulators – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Cleaners and coaters (general)	n/a	n/a	n/a	n/a	9-75%	n/a	57%	n/a	3.5%	n/a
Professional cleaning – *2011 estimate*	3,400,000	n/a	n/a	n/a	9-75%	n/a	57%	n/a	3.5%	n/a
Professional cleaning - *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
Optical (cleaning) – *2011 estimate*	43,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Optical (cleaning) – *2016 estimate assuming baseline trend of XXXX**	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Medical images, foodcontact material/bakeware – 2011 *estimate*	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	3.5%	n/a
Medical images, foodcontact material/bakeware – 2016 *estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Manufacturers of furniture (cleaning) – *2011 estimate*	1,080,000	~0	~0	~0	30%	~0	57%	~0	3.5%	~0
Manufacturers of furniture (cleaning) – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Painting and glazing (cleaning) – *2011 estimate*	662,000	~0	~0	~0	n/a	n/a	57%	n/a	3.5%	n/a
Painting and glazing (cleaning) – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Treatment and coating of metals – *2011 estimate*	260,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Treatment and coating of metals – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Automotive (coating and cleaning, includes manufacturing of motor vehicles and maintenance and repair) – *2011 estimate*	2,500,000	XXXX	XXXX	XXXX	9-49%	XXXX	57%	XXXX	3.5%	XXXX
Automotive (coating and cleaning, includes manufacturing of motor vehicles and maintenance and repair) – *2016 estimate assuming baseline trend*	2,500,000	XXXX	XXXX	XXXX	9-49%	XXXX	57%	XXXX	3.5%	XXXX

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
*of 0%***										
Automotive (coating and cleaning, includes manufacturing of motor vehicles and maintenance and repair) - *2016 estimate assuming worst case estimate of baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Manufacturers other transport equipment – *2011 estimate*	710,000	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Manufacturers other transport equipment – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Wire coatings										
Wire coaters – *2011 estimate*	n/a	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
Wire coaters – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Formulators – *2011 estimate*	160,000[(2)]	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
Formulator – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Electronics and semiconductor industries										
Electronics and semiconductor industries – *2011 estimate*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a
Electronics and semiconductor industries – *2016 estimate assuming baseline trend of +5%*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Battery industries										
Battery industries – *no baseline information available*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	3.5%	n/a

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
Membranes										
Membrane manufacturer (water filtration) - *2011 estimate*	n/a	XXXX	XXXX	XXXX	30%	XXXX	57%	XXXX	3.5%	XXXX
Membrane manufacturer (water filtration) – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Membrane manufacturer (vapour permeation) – *2011 estimate*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a
Membrane manufacturer (vapour permeation) – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
High performance polymer producers										
High performance polymer producers – *no baseline information available*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a
Agricultural chemicals										
Agricultural chemical formulation – *2011 estimate*	n/a	n/a	n/a	n/a	37%	n/a	57%	n/a	n/a	n/a
Agricultural chemical formulation – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Agricultural chemical synthesis – *2011 estimate*	n/a	n/a	n/a	n/a	30%	n/a	57%	n/a	n/a	n/a
Agricultural chemical synthesis – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Pharmaceutical industry										
Pharmaceutical industry – *2011 estimate*	n/a	XXXX	XXXX	XXXX	n/a	n/a	57%	n/a	n/a	n/a

	Number of workers				Female workers		Reproductive female workers		Pregnant workers	
	Upper bound	**Actual high**	**Actual low**	**Actual average**	**% of total workers**	**Actual average**	**% of female workers**	**Actual average**	**% of female workers**	**Actual average**
Pharmaceutical industry – *2016 estimate assuming baseline trend of XXXX*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Other										
Laboratories – *no baseline information available*	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	n/a	n/a
Functional fluids – *no baseline information available*	n/a	n/a	n/a	n/a	n/a	n/a	57%	n/a	n/a	n/a
Construction chemicals – *no baseline information available*	n/a	n/a	n/a	n/a	9-30%	n/a	57%	n/a	n/a	n/a
Total										
Total of available data – *2011 estimate*	9,000,000	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Total of available data – *2016 estimate assuming baseline trend*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Total of available data – *2016 estimate assuming baseline trend WORST CASE AUTOMOTIVE ESTIMATE*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

n/a = not available
This table is based on the market analysis table 6.1 presented in Appendix A.
(1)Of this estimate of coating formulators XXXX workers are estimated to work on formulation of automotive coating (actual estimate).
(2)This estimate of coating formulators and wire coating formulators are the same estimate, this is only included once in the total figure.
**It can be questioned whether the general baseline trend figure for the cleaning industry (XXXX) applies to the optical industry. No direct signals are available from the sector suggesting an ongoing trend, however, the data available on alternatives (part C) shows that alternatives for this specific application might be problematic. However, as no quantitative worker estimates of this specific use are available, no deviation from the general trend is assumed here.*
***It is questioned whether the general baseline trend figure for the coating (and cleaning) industry (XXXX) applies to the automotive industry. Signals from the sector do not show a substantial decline of the use of NMP, e.g. as costs of switching to alternatives are substantial. For this specific sector it is therefore assumed that the baseline trend for this sector deviates from the general trend for coatings and cleanings and is assumed to be 0%. However, the trend of -20% is included as a worst case estimate.*

F.2 Environmental impacts

As the Background Document is targeted on potential human health effects, potential environmental effects are not considered in this document.

F.3 Setting the scene for socio-economic impacts

The socio-economic impacts of the different RMOs strongly depend on the reactions of the sectors and individual companies concerned: the 'industry response'. Basically, four types of industry response can be distinguished:

- **substitution**: the company switches to alternative substances instead of NMP;
- **exposure reduction**: NMP continues to be used, but measures are taken to reduce employee exposure to the substance;
- **relocation**: the company continues its operations and its use of NMP, but transfers the location of its operations to a country outside the EU where NMP controls are less stringent;
- **termination**: the company discontinues its operations with NMP (which may lead to production increases in competing firms outside the EU).

The types of costs and wider socio-economic effects related to each of these industry responses are discussed in section F.3.1. In the following section (F.4) the results of the market and cost analysis of NMP are presented, explaining the socio-economic impacts of the restriction to various sectors. These socio-economic impacts are described in terms of costs and wider socio-economic effects, (including distributional effects and social effects) of the various RMOs. Further details on the (quantitative estimates of) socio-economic impacts are presented in the market and cost analysis in respectively Appendix A and B. The information on socio-economic impacts presented here, has been provided by industry (personal communication, AMEC consultation) and has been checked with publicly available information whenever possible[25]. Note that the market and cost analysis in the Appendices only presents information for five selected uses of NMP[26]. Besides that, other users[27] have also provided information on the expected socio-economic impacts in a consultation round. These are also included in this section of the document. The industry estimates of these users, however, have not been crosschecked with publicly available data.

Note that uncertainties in the quantitative socio-economic impact estimates[28] are high. All values presented should be seen as indicative values representing the order of magnitude of socio-economic effects rather than actual estimates of effects.

F.3.1 Costs and wider socio-economic impacts

Depending on the expected industry response to the various RMOs, the socio-economic impacts will consist of various elements. An overview of the possible costs and wider socio-economic impacts linked to that, are presented in table F.06 below. For the various RMOs the expected costs and wider socio-economic impacts are explained in section F.4 of this document.

Table F.06: *Overview of the costs and wider socio-economic impacts by type of industry response*

Industry response	Costs	Wider socio-economic impacts
Substitution	• Compliance costs (e.g.: process adaptation costs, additional costs for alternative substances, reformulation costs (R&D)) • Administrative costs	• Possible impact on product quality, process complexity etc. • Employment impact (if the substitute has a higher or lower labor intensity)
Exposure reduction	• Compliance costs (e.g. process	• Change in labor conditions (e.g.

[25] *Quantitatively for the costs to the automotive industry, wire-coaters and membrane manufacturers.*
[26] *Manufacture and distribution, industrial and professional cleaning, industrial and professional non-wire coatings, wire coatings and membranes.*
[27] *Electronic and semiconductor industry, high performance polymer producers and construction chemical industries.*
[28] *Including number of workers potentially exposed, compliance cost estimates, relocation cost estimates and turnover/employment affected.*

Industry response	Costs	Wider socio-economic impacts
	adaptation costs; in some cases also possible premature depreciation of assets / capital destruction) • Administrative costs like costs for additional exposure testing (monitoring program)	need to wear protective clothing)
Relocation	• Relocation costs (e.g. costs for capital investment, potential transportation costs, costs (savings) for (training of) staff) • Possible capital destruction (premature depreciation of assets that cannot be relocated)	• Change in employment (loss of jobs in the EU; increase in jobs elsewhere) • Transfer of value added from EU to other country (with associated shift in e.g. tax flows) • Indirect impact through economic linkages (e.g. supply chain effects)
Termination	• Possible capital destruction (premature depreciation of assets)	• Change in employment (loss of jobs in the EU; increase in jobs elsewhere) • Transfer of value added from EU to other country (with associated shift in e.g. tax flows) • Indirect impact through economic linkages

In case the industry response is 'substitution' or 'exposure reduction', the main costs are those that are made to comply with the legislation, in other words: compliance costs. In addition, there will be administrative costs to authorities due to monitoring and enforcement activities and possibly for the companies themselves (e.g. authorization procedures, measuring and reporting obligations).
If the industry response is 'relocation', then the company will incur costs associated with moving its operations from the EU to a non-EU country. Clearly, this decision will only be taken if these 'relocation costs' are lower than the compliance costs that it would incur if it had decided to stay in the EU. If relocation is a consequence of the restriction[29], these relocation costs should be included in the overall analysis of economic effects regardless of the nationality of the company (European or non-European).The industry response 'termination' implies a cost if the capital stock related to the NMP related process is not yet fully depreciated. Such capital destruction costs (which in some cases may also occur with a 'relocation' and an 'exposure reduction' industry response) can be reduced by phasing in the RMO or by delaying its requirements.

Wider socio-economic effects are likely to be small in the case of the industry responses 'substitution' and 'exposure reduction', since this presumably does not lead to major changes in output or employment. They will be more significant in case of 'relocation' and 'termination'. Employment and value added will shift from the EU to another country, even if they remain within the (multinational) company in case of relocation. This will have indirect impacts in other parts of the supply chain, and it might further result in distributional and social impacts. Note that in case industry decides not to comply with the RMO, industry will *either* stop activities in Europe and relocate outside Europe themselves ('relocation') *or* stop activities completely without replacement ('termination'). In case of relocation it is assumed that no reduction in turnover or value added will occur for the company that relocates[30]. However, potentially wider socio-economic impacts might occur for Europe as the added value of the companies' activities no longer contributes to the EU's GDP.
The reduction in intra-EU economic welfare (GDP), or 'value added foregone' resulting from relocation or termination might in principle be estimated by taking the production value (turnover) of the companies involved and subtracting from this figure the costs of all inputs except capital and labor. Unfortunately, it was not possible to obtain such figures due to lack of data on production costs. Only information on the turnover that is potentially affected is available for some of the use categories. A

[29] *Note that there might be various factors that all together will cause the industry to relocate. It might therefore be somewhat difficult to know what part of relocation costs can actually be attributed to the restriction.*
[30] *Note that relocating industries might face temporal affected turnover, however, these are not included in this analysis.*

'value added foregone' estimate is expected to be substantially lower than the 'affected turnover'[31] presented in this section. The figures on affected turnover presented should therefore not be treated as indicators of economic losses, but rather as illustrations of the size of the sectors involved.[32]

The compliance costs and relocation costs estimates in the following section are expressed in terms of Present Value (PV) for a period of 15 years and are discounted at a level of 4%. The period of 15 years has been chosen, as this is the longest reported time required to adapt to the legislation across industries and RMOs (personal communication, AMEC consultation). Note that one-off costs are not necessarily spread out and discounted over this 15 year period, but might also be spread out over a shorter time period depending on the period indicated by industry. Yearly costs are discounted and added over the 15 year period. The estimates of turnover potentially affected are expressed as yearly figures. As the uncertainties around the presented cost estimates (and the estimates on affected turnover and the number of workers) are high, all estimates presented in this SEA have been rounded.

Note that whether effects will occur as direct compliance costs or as wider socio-economic impacts is based upon industry's assessment of what would happen in case of the various RMOs. This assessment of industries could somehow be checked by comparing various industry responses, the availability of alternatives and current (expected) exposure levels. Nevertheless, these industries responses are uncertain for example as there is some incentive for industry to overestimate effects of the RMO's and translate this into their expected responses to the RMOs. This brings significant uncertainties with them in both the estimate of the costs and the wider socio-economic effects as industries responses in practice might be different from what is stated in this analysis.

F.3.2 Timing of the restriction and the coupled economic and wider socio-economic costs

The timing of the restriction will significantly influence economic effects as industries need time to change their processes to comply with the legislation. The industry responses and the connected estimates of costs and wider socio-economic impacts given by industries are (in most cases) independently given from the starting point of entry into force of the restriction. In other words, industry did not specify the timing of the entry in to force for which the indications of responses and economic impacts were given.
For these industries it is not known what time period is reasonable. Some industries, however, did give indications of reasonable timeframes for entry into force of the various RMOs. The statements on costs and economic impacts of these industries are assumed to count for these given timeframes. Based on the available information, it is not possible to estimate changes in costs and impacts at changing timeframes. One can only assume that the presented figures will increase in case shorter timeframes are proposed and that the presented estimates will decrease in case longer timeframes are proposed. The table F.07 below gives an overview of the estimates on acceptable timing of entry in to force of the RMOs provided by industry. Note that these estimates might be overestimated as there is some incentive for industry to propose long required timeframes.

[31] In Appendix B the term 'lost revenue' is used for the possible reduction in intra-EU production value that can be attributed to the RMO. However, we prefer the term 'affected turnover' so as to avoid confusion, since it is not a cost item comparable to compliance costs.
[32] One should also note that even if estimates of 'value added foregone' would be available, these figures can still not be treated as costs in a social cost-benefit or cost-effectiveness analysis. Whether or not this 'value added foregone' is a cost depends on the question if the production factors (capital and labor) can be productively re-employed or not.

Table F.07: *Overview of acceptable timing for the entry into force of the restriction as indicated by industry, in years*

Users of NMP	**RMO1**	**RMO2**[1)]	**RMO3a** 5 mg/m^3	**RMO3b** 20 mg/m^3
Manufacturers	>10	1-10	1-10, depending on the value of the limit value	
Importers/suppliers	n/a	n/a	n/a	n/a
Petrochemical industries	n/a	n/a	n/a	n/a
Formulators (general)	n/a	n/a	n/a	n/a
Non-wire coaters (car coaters)	n/a	n/a	n/a	n/a
Wire coaters	x / 10-15	x	x	x / 10-15
Wire coaters formulators	5	0	0	0
Cleaners (optical cleaners)	n/a	n/a	n/a	n/a
Electronic and semi-conductor industries	x	n/a	n/a	0
Battery industries	n/a	n/a	5-6[30]	n/a
Membrane manufacturers[2)]	2-5 / x	2 / n/a	2 / n/a	
High performance polymer producers	5 / x	n/a	n/a	n/a
Agricultural chemical industry (formulation, synthesis)	n/a	n/a	n/a	n/a
Pharmaceutical industry	n/a	n/a	n/a	n/a
Laboratories	n/a	n/a	n/a	n/a
Functional fluids	n/a	n/a	n/a	n/a
Construction industry	-	-	-	-

x = Industry expects to cease (as no alternatives are assumed to be available at this moment).
- = Not relevant for industry (as the RMO will not affect the industry or as industry is already phasing out NMP)
n/a= Not available
[1)] The acceptable timing of RMO2 is assumed to be comparable to RMO3a
[2)] Different responses have been received for this use category
[3)] Information received in public consultation indicates that a period of 5-6 years is required for at least 1 company in this sector.

Geographical scale

The analysis of costs and wider socio-economic impacts is (similar to the analysis of human health impacts) performed taking the European Union as geographical boundary. As such, the economic impacts of a restriction are only calculated for the EU industry.

F.4 Socio-economic impacts

Below, the potential costs and wider socio-economic impacts of the various RMOs will be discussed based on the socio-economic impact structure presented in table F.06 of section F.3.

F.4.1 RMO1

Compliance costs

Chapter C on alternatives shows that for most of the non-wire coaters, coating formulators, some membrane manufacturers (depending on the polymer used) and agrochemical formulation, technically feasible alternatives are readily available or are expected to be found within a reasonable timeframe. For these users, the expected industry response is 'substitution', and compliance cost estimates are presented in table F.08 below. The quantified compliance costs are costs calculated for the NMP using

industries. Industries however, might be able to transfer the extra costs to their costumers depending on the price transmission elasticity[33] of the products traded. It is not known to what extent that will occur.

Wire coaters and formulators and high performance polymer manufacturers expect not to be able to cope with a total ban as alternatives for most of these applications are at this moment not available and are not expected to be so in the near future. These industries are expected to cease activities in Europe and will potentially relocate outside Europe ('relocation' or 'termination') and effects are therefore not expected in terms of compliance costs. The responses of the petrochemical industry, optical cleaners, coaters of medical images, foodcontact material/bakeware, electronics and semiconductor industries, battery producers, pharmaceutical industries, agricultural chemical synthesis industries, laboratories and functional fluids to a total ban of NMP are uncertain. For parts of their processes alternatives seem to be available, however, for other processes, finding alternatives might be more problematic. Section G.2 gives an overview of the responses to RMO1 of various industrial sectors according to industry. This indicates that for the majority of the above presented uses, relocation or termination is the expected response[34]. However, as said there is some uncertainty in the estimation of their responses, and as such, compliance costs might occur for these parties in case of a total ban. As manufacturers, suppliers and formulators will lose (parts of) their customers because of this, these actors might stop activities in Europe as well. Responses of these actors will also be 'termination' or 'relocation'. As these users will not comply with RMO1, no compliance costs are calculated for these industries. An overview of all potential compliance costs for RMO1 is presented in table F.08 below.

Table F.08: *Compliance costs to various actors due to RMO1*

NMP producers/users	**RMO1** Total ban 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers and importers/suppliers	-	-	For the uses for which alternatives are available, industry might supply alternatives as these are typically made by the same companies. However, as the applications for which alternatives are available is limited, industry expects to collapse in Europe and thus no compliance costs are expected. Potential wider socioeconomic effects to this sector are discussed in the section below.
Petrochemical industries	n/a	n/a	No compliance costs as industry is expected to shut down activities in Europe. However, as alternatives seem to be available for some applications, some might in fact change operations within Europe on the long term. Potential wider socioeconomic effects to this sector are discussed in the section below.
Non-wire coatings, incl. formulators	Minimal	Minimal	This use represents mainly professional users and industrial and professional formulators of coatings. No quantitative cost estimates are available for these uses. However, for many of the coating users, costs are assumed to be limited as the majority of industries have already shifted to alternatives. Car coaters, film coaters (medical images) and producers of foodcontact material/bakeware are excluded from this category as these are presented as separate users in this table.
Coatings - automotive	20	30	Total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate is provided by industry and has been crosschecked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car

[33] *The price transmission elasticity of product B with respect to product A is the percentage change in the price of product B in response to a 1% price increase of product A.*

[34] *Note that for the petrochemical industry, wire coaters, for some processes in the electronics and semi-conductor industries and for some membranes substance alternatives might be available (see part C), however, the technical and economic feasibility of these alternatives have not been proven. Furthermore, some of the alternatives might have hazardous characteristics comparable to NMP and are therefore not seen as real alternatives.*

NMP producers/users	**RMO1** Total ban 15y PV (€ million)		**Explanation**
	Low	**High**	
			manufacturers and 50% for auto repair shops.
Coatings – medical images, foodcontact material/bakeware	n/a	n/a	It is uncertain how industry will respond to a total ban. However, there are indications (chapter C) that replacement of NMP is problematic in these application. Digital presented medical images might serve as alternatives, however, this has not been further verified. Information received in the public consultation indicated that availability of alternatives to NMP in the production of foodcontact material/bakeware is problematic. Potential wider socioeconomic effects to this sector are discussed in the section below.
Wire coating formulators	-	-	Cost estimates are available for the reformulation of wire-coating formulators. However, it is uncertain whether reformulation will be successful and as the wire coaters are assumed to shut down, the formulators are assumed to follow. As such the available costs for reformulation have not been included here. Instead the socio-economic effects for this industry sector are explained in the section on wider socio-economic effects below.
Wire coaters	-	-	As no alternatives seem to be available for this applications, wire coaters are expected not to be able to comply with a total ban. No compliance costs are expected for this sector. Wider socioeconomic effects to this sector are discussed in the section below.
Cleaners – optical	n/a	n/a	It is uncertain how industry using NMP in cleaning activities will respond to a total ban and what costs are expected. For some of the industrial cleaning uses alternatives might be available, however, there are indications that replacement of NMP is problematic for example for optical cleaners (personal communication, AMEC questionnaire). Potential wider socioeconomic effects to this sector are discussed in the section below.
Electronics and semiconductor industries	n/a	n/a	Industries expect to cease production in case of a total ban. However, part of the industry might shift to alternatives as these seem to be available for some of the uses. It is therefore not clear whether compliance costs are to be expected for this use category or whether all effects are in terms of wider socio-economic effects (described in the next section).
Battery industry	n/a	n/a	It is uncertain how industry will respond and what the compliance costs will be for this sector. However, as alternatives are not available, the battery industry might not to be able to survive in Europe, as has been confirmed in the public consultation by various industry actors. This could imply that no compliance costs can be expected for this sector, instead, wider socio-economic effects might occur (described in the next section).
Membrane manufacturers	5	20	This industry estimate is based on redesign of the production process using alternatives in cases possible. Estimates include 70-80% labour costs and 20-30% capital investment (personal communication, AMEC questionnaire). One-off costs are spread out and discounted over a period of 5 year, as industry indicated that as required adaptation time. No cross-check of the industry estimate was possible. There are potential competition effects as non-EU producers are still able to use NMP. The figure represents costs for one membrane manufacturer. There might be more manufacturers in Europe that decide to shift to alternatives, however, depending on the polymer used in the membranes, finding alternative solvents might be more difficult. Some actors are therefore expected to stop activities within Europe, resulting in wider socio-economic effects. In the public consultation information has been received indicating that no alternative to NMP is currently available for a specific application. A total ban would likely result in a stop in business in Europe for that application.

NMP producers/users	**RMO1** Total ban 15y PV (€ million)		**Explanation**
	Low	**High**	
High performance polymer	-	-	As no alternatives seem to be available for this application, industry is expected not to be able to comply with a full ban on NMP, instead, wider socio-economic effects are expected (described in the next section).
Agricultural chemical formulation	0	0	Industry is phasing out NMP at this moment in agricultural chemical formulations and is expected to be free of NMP by 2015 (personal communication, RIVM questionnaire). The potential costs made by industry to shift to alternatives are therefore not connected to the restriction.
Agricultural chemical synthesis	n/a	n/a	It is uncertain how industry will respond and what the compliance costs will be for this sector as it is unclear whether alternatives are available for this application. Potential wider socioeconomic effects to this sector are discussed in the section below.
Pharmaceutical industry	n/a	n/a	It is uncertain how industry will respond and what the compliance costs will be for this sector. Alternatives are likely to be available, however, it is not known whether that is the case for all pharmaceutical applications and it is not known what costs would be connected to a potential shift to alternatives. Potential wider socioeconomic effects to this sector are discussed in the section below.
Laboratories	n/a	n/a	It is uncertain how industry will respond and what the compliance costs will be for this sector. Potential wider socioeconomic effects to this sector are discussed in the section below.
Functional fluids	n/a	n/a	It is uncertain how industry will respond and what the compliance costs will be for this sector. Potential wider socioeconomic effects to this sector are discussed in the section below.
Construction industry	0	0	Industry is assumed to already have shifted to alternatives so no compliance costs are expected for this sector.
Total	>25	>50	As for many users no cost estimate is available, this total figure is expected to give a minimal estimate of the compliance costs in case of RMO1. Note however, that the available costs estimates might be overestimates. Because of this the underestimation of the total figure might be partly offset.

- *n/a not available*
'-' *not relevant*

Administrative costs

Besides compliance costs to industry/society there will be administrative costs both to industry as to authorities due to:

- Administrative actions of industries
- The process of dossier development, review by ECHA's RAC and SEAC
- Enforcement and monitoring activities

No quantitative estimates of these administrative costs could be made.

Costs of relocation and premature depreciation

There has been one industry providing a quantitative estimate for potential relocation costs of around XXXX. The given costs estimate could not be crosschecked with publicly available data and is therefore given at a high level of uncertainty. Besides, it is not known whether this one industry relocation cost figure is representative for other NMP using industries. It is therefore not possible to scale up the relocation cost figure of this one company to a total relocation costs figure. It is therefore not known what total relocation costs can be expected in case of RMO1.

Wider socio-economic effects

As mentioned in the section on compliance costs above, the majority of users of NMP might cease activities in Europe in case of a complete ban on NMP, although there appears to be quite some uncertainty around these industry responses. The shut-down of factories in Europe will result in losses in jobs and losses in added value of the industries in Europe. This loss can be substantial depending on the industry affected.

The market gap resulting from the shutdown of European industries will presumably be taken over by other companies. The loss in economic activity and jobs of one company will thus potentially be offset by an increase in economic activity and jobs of another company. In this way the effect could be described as a spatial reallocation of economic activity. As the companies that take over activities will very likely do that outside Europe (as NMP can still be used there), this reallocation effect might have net socio-economic consequences for Europe. Unfortunately, due to data constraints, no quantitative estimate of the losses in added value could be made. Instead, estimates of the turnover of companies potentially affected are given in table F.14. Besides, estimates of potential losses in jobs are given for some of the use categories. As explained earlier in section F.3, note that the estimates of the turnover affected presented in table F.14 below are not a good indicator for these real wider socio-economic losses, as turnover does not represent the real added value of the industry. It however, give an illustration of the size of the sector involved.

Some industries indicated that they would possibly relocate activities to outside Europe in case of a total ban. This response is likely especially for the big multinational companies. Activities in that case, are restarted by the same company elsewhere outside Europe. In case a relocation, there will be distributional effects for Europe in terms of losses in added value and jobs comparable to the case of a complete shutdown (termination). Net economic effects for a company itself however, will be in terms of relocation costs and not in terms of turnover affected as this is expected to be offset by the increase in turnover of the new production facility. Note that there might nevertheless be a temporary turnover effect for the multinational company. Which percentage of the companies that shut down activities in Europe will actually relocate is not known.

Above, mainly the potential direct effects to industries of the RMO are described. Effects however, are not necessarily limited to the industrial actors using NMP, but might be passed on through the supply chain, both upstream and downstream resulting in indirect effects. For example, shut down of the wire-coating industry will not only affect wire coaters themselves, but also the formulators of wire coatings and potentially the industries using high quality coated magnetic wires (e.g. manufacturers of motors, generators, transformers). These might be faced with an increase in transport costs and a potential loss in product quality (as products from outside Europe are of lower quality according to the sector – despite the fact that these non-EU products are produced using NMP). Besides, it might become less attractive for magnetic wire using industries to settle in Europe (personal communication, AMEC questionnaire). A membrane manufacturer also suggests a potential reduction in quality of imported products compared to European products that will not anymore be produced. According to the industry representatives, this might be problematic for some very specific users of the end products (personal communication, RIVM consultation). For car coatings, no significant supply chain or competition effects are expected, as the supply chain is expected to be able to absorb the cost increase. The cost incurred in reformulation would not significantly affect the overall price of vehicles and on the EU market and the restriction will affect all formulators equally. Potential indirect effects have not been further quantified in the analysis.

Tables F.09 below give an overview of the turnovers and jobs potentially affected in case of a full ban on NMP.

Table F.09: *Potential turnover affected and jobs lost of various actors due to RMO1*

NMP producers/users	**Turnover affected RMO1** (€ million pa)		**Jobs lost RMO1** (number of workers)	**Explanation**
	Low	**High**	**Average**	
Manufacturers	10	60	XXXX	Potentially affected turnover from NMP sales. In case industry cease activities in Europe, it is estimated that this would result in a loss of jobs in Europe.
Importers/suppliers	10	60	XXXX	Potentially affected turnover from NMP sales. In case importers/suppliers cease activities in Europe, it is estimated that this would result in a loss of jobs in Europe.
Petrochemical industries	n/a	n/a	n/a	Turnover and jobs in the petrochemical industry that can be connected to the use of NMP are not known.
Coaters – medical images, foodcontact material/bakeware	n/a XXXX	n/a XXXX	n/a XXXX	Turnover and jobs in coating industry for medical images that can be connected to the use of NMP are not known. As indicated in the public consultation (2013/2014), wider socio-economic effects might occur for producers of foodcontact material/bakeware. One actor indicates that the EU market for these bakeware products exceeds 60 million € pa and that 1000 EU jobs are related to this industry. These figures are included here, however, note that these figures have not been checked and are thus somewhat uncertain.
Wire coating formulators	50	150	XXXX	This figure represents industries' estimate of the turnover potentially affected in case of the shutdown of the industry. Both low and high estimates have been crosschecked with publicly available information on revenues and are in a comparable range. Also an estimate of the number of jobs that are connected to the formulation of wire coatings using NMP is available. It is assumed that the number of jobs potentially lost is equal to the number of workers connected to NMP in the sector.
Wire coaters	2000	3000	8000	This figure represents industries' estimate of the turnover potentially affected due to shut down of the sector. The scale of the estimate is in the range of publicly available sales data. Also an estimate of the number of jobs that are connected to the production of wire coatings using NMP is available. It is assumed that the number of jobs potentially lost is equal to the number of workers connected to NMP in the sector. Information received in the public consultation suggests that wider socio-ecoomic effects will be much higher as also actors down the supply chain will be seriously affected and might stop activities in Europe (e.g. motor manufacturers, manufacturers of generators, transformers, relays, automobile industry). No quantitative estimates of such potential down stream effects are available.
Cleaners - optical	n/a	n/a	n/a	Turnover and jobs in the optical industry that can be connected to the use of NMP are not known.
Electronic and semi-conductor industries	n/a	n/a	n/a	Turnover and jobs in the electronic and semiconductor industries that can be connected to the use of NMP are not known.

NMP producers/users	**Turnover affected RMO1** (€ million pa)		**Jobs lost RMO1** (number of workers)	**Explanation**
	Low	**High**	**Average**	
Battery industry	n/a	n/a	n/a	Turnover and jobs in the battery industries that can be connected to the use of NMP are not known, although signs have been received in the public consultation that these effects will occur for some of the actors in this sector. One actor indicated in the public consultation that besides effects to the sector itself, also supply chain effects might occur, causing additional turnover effects and losses in jobs to down stream users of batteries (e.g. automotive industry).
Membrane manufacturers	n/a	n/a	XXXX	Turnover in the membrane manufacturing that can be connected to the use of NMP is not known. However, an estimate of the jobs potentially lost in case of a restriction on NMP in the membrane industry is available.
High performance polymer producers	n/a	n/a	n/a	Turnover and jobs in the high performance polymer production that can be connected to the use of NMP are not known.
Agricultural chemical industry (synthesis)	n/a	n/a	n/a	Turnover and jobs in the agricultural chemical synthesis industries that can be connected to the use of NMP are not known.
Pharmaceutical industry	n/a	n/a	n/a	Turnover and jobs in the pharmaceutical industries that can be connected to the use of NMP are not known.
Laboratories	n/a	n/a	n/a	Turnover and jobs in laboratories that can be connected to the use of NMP are not known.
Functional fluids	n/a	n/a	n/a	Turnover and jobs due to the use of NMP containing functional fluids are not known.
Total	>2,000	>3,500	XXXX	As not all industries are included in the estimate, the total turnover and job figures should be seen as minimum estimates. On the other hand, however, the estimates are provided by industry and might be overestimated.

- *Non-wire coaters and formulators, cleaners and formulators, agricultural chemical industry (formulation) and construction industry are not presented in this figure as these are expected to comply with the full ban.*
- *n/a not available*

Overview of the total socio-economic effects of RMO1

As explained in section F.3, the total socio-economic effects are built up out of various elements. In case of RMO1, the total socio-economic effects might consist of compliance costs, administrative costs, relocation costs, potential capital destruction, potential losses in added value due to loss in economic activity, losses in jobs and potential product quality losses. What effects will actually occur depends largely on the industries response to RMO1, which is e.g. determined by the availability of technically and economically feasible alternatives.

Unfortunately, there is substantial uncertainty in the industries responses to RMO1, resulting in uncertainties around the type of socio-economic effects that can be expected and in the total socio-economic effects expected. Reviewing table F.08 together with the information on quantities of NMP used in various use categories (confidential table X03.1), shows that for about 25%[35] of the NMP used, it is known at a reasonable certainty that industry will comply with the total ban and shift to

[35] ***Cleaners, non-wire coaters, half of the membrane manufacturers, agricultural chemical formulation*** *and construction industry (for the latter not quantitative estimate available):* XXXX.

alternatives. For these users compliance costs are estimated. For about 30%[36] of the current quantity of NMP used, it is known at a reasonable certainty that industry will relocate or terminate in case of a total ban resulting in lost value added and losses in jobs. For the other 45%[37] of the NMP use, it is uncertain how industry will respond, however, it is likely that these users of NMP will relocate or terminate as alternatives for these applications seem not to be available. Note that for some of the use categories quantities of NMP used are not known, consequently, these uses have not been included in the above percentages.

Based on the information presented in the section above, it is likely that non-wire coaters including car coaters, some membrane manufacturers, agricultural chemical formulation industry and construction industry are able to comply with a total ban by shifting to alternatives. **The overall quantified compliance costs for these sectors are estimated in the range of >25-50 million € over 15 years**. Note that the cost figures presented are industries' own estimation of the compliance costs that could only partly be checked. Actual costs might be lower in the case that industry would have strategically overestimated the compliance costs. Potentially, some of the use categories for which responses to a total ban are uncertain (the 45%), might in practice of a total ban decide to shift to alternatives. In such a case, the total estimate of compliance costs might be under estimated. However, the extent to which this might happen is assumed to be limited as for most of the applications no alternatives are available.

Besides compliance costs, other costs (relocation and premature depreciation) and socio-economic effects are expected in case of a total ban. **In fact, the majority of the socio-economic effects are expected to be in this category as the majority of the users is expected not to be able to comply with a total ban and might consequently shift their production to outside the EU or go out of business (relocation or termination).** Based upon the information presented above, it is assumed that at least the manufacturers/suppliers, wire coaters and wire coating formulators and the high performance polymer manufacturers will cease activities in Europe. Furthermore, petrochemical industries, some specific coating and cleaning users (optical industry, medical images, foodcontact material/bakeware), electronics and semi-conductor industries, battery industries, some membrane manufacturers, agricultural chemical syntheses industries, pharmaceutical industries, laboratories and users of functional fluids might cease activities in Europe. This would result in losses in added value in Europe including the loss of jobs. Unfortunately, no quantitative estimate of the loss in added value due to the shift in economic activities is available for these uses. What is available is an estimate of the turnover potentially affected and the potentially lost jobs in Europe for some of the users. Lost jobs are estimated in the order of XXXX[38]. However, note that this only includes some of the users of NMP that would potentially shut down (manufacturers, importers/suppliers, wire coating industry (coaters and formulators), part of the membrane manufacturers: with this approximately 40% of the current total NMP use that is potentially lost is quantified versus 75% of the total NMP uses that would potentially shut down). The actual number of jobs lost could thus potentially be larger as for almost half of the use categories that potentially would shut down, no quantitative estimate of jobs is available. Furthermore, note that this only includes jobs lost due to direct effects, because of supply chain effects the actual losses in jobs could be larger. On the other hand, the estimate is based upon industries estimate of the number of jobs potentially lost, that could be overestimated. Also and as stated previously, some of the users of NMP that indicated to relocate or terminate in case of a full ban, might in fact decide to substitute. In that case, the total number of jobs lost might be lower than estimated.

The socio-economic effects might furthermore involve administrative costs, relocation costs, potential capital destruction and potential product quality losses. However, due to the lack of information, these could not be further specified for this RMO.

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[36] ***Wire coaters*** *and high performance polymer manufacturers (for the latter not quantitative estimate available):* XXXX.

[37] ***Petrochemical industries, electronics and semiconductor industries****, battery industry,* ***half of the membrane manufacturers, agricultural chemical synthesis, pharmaceutical industries,*** *laboratories and functional fluids (for batteries, laboratories and functional fluids no quantitative estimate available):* XXXX.

[38] *Estimate of the potential losses in jobs for* ***manufacturers, importers/suppliers, coaters for foodcontact material/bakeware, wire coating industry (coaters and formulators****), half of the* ***membrane manufacturers****:* XXXX ***workers.***

F.4.2 RMO2

This RMO presents a restriction with derogations under specific conditions. As this RMO has only be designed late in the process of developing this document, this RMO was not included in the industry consultation on costs performed by AMEC (see Appendix B). The RMO2 presented in Appendix B differs substantially from RMO2 included in this Background Document and the cost estimates given in Appendix B for RMO2 could therefore not be used in this document. The Dossier Submitter expects that the costs and wider socio-economic effects of RMO2 of this document are more or less equal to the costs and wider socio-economic effects of RMO3a. However, at some points the economic effects might be different from RMO3a. The expected costs and wider socio-economic effects per use category of NMP are discussed in the sections below. Note that the costs and wider socio-economic effects of the uses derogated under specific conditions still relate to the limit value of 5 mg/m^3 as originally proposed by the Dossier Submitter. The costs related to the DNEL value of 10 mg/m^3 as proposed by RAC are added to the section on RMO3 and slightly differ for some of the use sectors presented here.

Compliance costs

As said, the economic effects of this RMO2 are expected to be comparable to RMO3a as the expected industry responses are comparable. The main economic effects of this scenario are expected as compliance costs. Industries for which alternatives are readily available will, just as in RMO3a shift to these alternatives at similar compliance costs as these are not allowed to continue the use of NMP in RMO2. All industries that are derogated under specific conditions in this scenario are expected to be able to comply with the required conditions. These users are expected to take exposure reduction measures, just as in RMO3a, resulting in comparable compliance costs. However, this RMO2 gives some more guidance in how exposure reduction should be achieved compared to RMO3a, giving less freedom to industry in what measures to take to reduce exposure. In that sense, compliance costs might be somewhat higher as sub-optimal exposure reduction measures might be implemented. However, the Dossier Submitter expects the extent to which this will happen to be very limited. On the other hand, RMO2 poses less strict conditions to the final exposure level to be achieved. In that sense, industry might implement less exposure reduction measures in RMO2 compared to RMO3a. Especially the most costly measures might not be implemented in RMO2 that would be implemented in RMO3a. Total costs of RMO2 might therefore be somewhat lower than in RMO3a. There are some specific use categories for which the availability of alternatives are uncertain and for which no derogation is included in RMO2. For these uses wider socio-economic effects might occur and are explained in the section on wider socio-economic effects below. Note that for these users, the economic effects of RMO2 might differ from RMO3a.

Table F.10 below gives an overview of the compliance costs of RMO2. The quantitative estimates come directly from RMO3a, the explanation given in the table reflects on the representativeness of the cost figure of RMO3a for this scenario.

Table F.10: *Compliance costs to various actors due to RMO2*

NMP producers/users	**RMO2 – ban with derogations** 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers	Minimal	Minimal	Manufacturers can continue the production of NMP for the derogated uses. The manufacturers however, need to comply with the conditions set to the derogations. However, as the exposure levels in this use are already very low and manufacturers are already expected to work in controlled closed systems, the compliance costs are just as in RMO3a expected to be minimal.
Importers/suppliers	n/a	n/a	Importers and suppliers can continue the import/supply of NMP to the derogated uses in this scenario. The importers/suppliers however, do have to meet the conditions set to the derogations. Just as in RMO3a the compliance costs for industrial users are expected to be minimal, compliance costs for the professional uses are not known.

NMP producers/users	**RMO2 – ban with derogations** 15y PV (€ million)		**Explanation**
	Low	**High**	
Petrochemical industries	0	Minimal	This use is exempted from the full ban and can therefore meet the RMO by complying with the conditions set. The petrochemical industry is expected to already broadly comply with the conditions, and compliance costs are therefore expected to be minimal.
Non-wire coatings and coating formulators	Minimal	Minimal	This category represents industrial and professional users and formulators of coatings. These users are not allowed to use NMP anymore and are expected to shift to alternatives of NMP. No quantitative cost estimates are available for these uses. However, for many of the coating users costs are assumed to be limited as the majority of the industries have already shifted to alternatives. Car coaters, coatings in medical images, foodcontact material/bakeware and wire coaters are excluded from this category as these are presented as separate users in this table.
Coatings - automotive	20	30	This sector is not allowed to use NMP anymore in case of RMO2 and is expected to shift to alternatives. Total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate comes from industry and has been cross-checked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car manufacturers and 50% for auto repair shops.
Coatings – medical images, foodcontact material/bakeware	n/a	n/a	As this involves a use as non-wire coating, NMP is not allowed to be used in medical images. However, as there are some signals that substance alternatives for this use are not readily available. On the other hand, medical images might already be largely replaced by digital images. It is thus not known how these users will respond and whether compliance costs or wider socio-economic effects will occur. Information received in the public consultation indicated that availability of alternatives to NMP in the production of foodcontact material/bakeware might be problematic.
Wire coaters and formulators	XXXX	XXXX	Wire coaters and formulators are exempted in this RMO under specific conditions. It is expected that especially wire coaters will need to put substantial efforts in further exposure reduction to comply with the conditions. Current exposure in this sector might be relatively high (~80 mg/m^3), systems are at the moment not controlled closed systems and best available techniques to reduce exposure are assumed not to be current practice within the sector. In this scenario, wire coaters might go for implementation of best available techniques or for implementation of controlled closed systems. Some confidential information on this aspect is received during public consultation.
Cleaners – optical	n/a	n/a	This use is not allowed to use NMP anymore in case of RMO2. Signals have been received from industry (personal communication, AMEC questionnaire) that alternatives might not be readily available for this specific cleaning use. The optical industry thus might get problems in complying with this RMO potentially resulting in wider socio-economic effects. Whether these would actually occur is uncertain as it is not known how crucial NMP is to this sector. Potential compliance costs to these users are not known. For other industries that use NMP for cleaning and that are not presented as separate use categories in this table it is assumed that alternatives are readily available. For these users compliance costs are assumed to be limited as many users have already shifted to alternatives.
Electronic and semi-conductor industries	0	Minimal	Electronics and semiconductor industries are exempted in this RMO under specific conditions. This industry is working at highly automated processes working in clean rooms. As such, current exposure levels are already very low (see section B.9.3.2.1) and industry is expected to broadly already meet the conditions set. Compliance costs to this sector are thus expected to be minimal.

NMP producers/users	**RMO2 – ban with derogations** 15y PV (€ million)		**Explanation**
	Low	**High**	
Battery industries	n/a	n/a	Battery industries are exempted in this RMO under specific conditions. Some further exposure reduction to comply with the conditions, might be required, however, the extent to which this is required is assumed to be limited. Information received in the public consultation suggests that at least some action is required for specific steps in the production process of industries in this section. This suggests that there might be at least some costs for actors in this sector. However, another actor in the public consultation provided exposure estimates that are currently already below 5 mg/m^3, suggesting that processes are already well controlled and no additional costs would occur for this sector. The overall compliance costs for this sector are not known.
Membrane manufacturers	20	20	Membrane manufacturers are exempted in this RMO under specific conditions. Further exposure reduction to comply with the conditions is expected to be required. The extent to which this would happen is assumed to be comparable to RMO3a. One membrane manufacturer states to be able to further reduce exposure (personal communication, RIVM questionnaire). It is assumed that this statement is representative for the full membrane sector. A quantitative estimate of compliance costs is provided by the industry. The estimate includes costs for additional exposure reduction measures and for extra exposure measurements. One-off costs are spread out over 2 years as industry states to take two years to adopt the system. The cost estimate has been scaled up to the full NMP using membrane sector in Europe assuming that 50% of the companies require to take additional measures for exposure reduction. The cost estimate has been cross-checked with publicly available data. This estimate based on publicly available information is significantly lower than the figure provided by industry (order of magnitude 0.5-2 million €). However, as the uncertainties around the cross-check are too high to conclude upon the validity of the here presented figure, the figure has not been included in the cost estimate presented here.
High performance polymer producers	n/a	n/a	High performance polymer producers are exempted in this RMO under specific conditions. Industry is expected to take further emission reduction measures to comply with the conditions for derogation, comparable to those in RMO3a. No quantitative estimate of compliance costs are available, however, industry says costs are acceptable (personal communication, AMEC questionnaire).
Agricultural chemical industry (formulation, synthesis)	minimal	minimal	The use of NMP in agricultural chemical formulation is not allowed anymore under RMO2. However, as industry is already phasing out this use shifting to alternatives regardless of a restriction, no additional compliance costs are expected for these users. Agricultural chemical synthesis is exempted in this RMO under specific conditions. Further exposure reduction might be required to comply with the conditions, however, as the processes used in agricultural chemical synthesis are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.
Pharmaceutical industry	minimal	minimal	The pharmaceutical industry is exempted in this RMO under specific conditions. Further exposure reduction comparable to RMO3a is expected to be required to comply with the conditions for derogation, especially in processes at elevated temperatures. As the processes used in the pharmaceutical industry are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.

NMP producers/users	**RMO2 – ban with derogations** 15y PV (€ million)		**Explanation**
	Low	**High**	
Laboratories	n/a	n/a	The use of NMP in laboratories is not allowed anymore after implementation of RMO2. However, to the extent to which laboratories are working on scientific research and development, the use is exempted from the restriction according to REACH article 67.1. There might however be some laboratory uses that do not fall within the category of R&D, that therefore need to shift to alternatives. Alternatives will be available for some of these laboratory uses, but might not be for some others. No estimate is available of potential compliance costs to these users.
Functional fluids	n/a	n/a	The use of NMP in functional fluids will be banned after implementation of RMO2. As it is not known whether alternatives are available for this use, shifting to alternatives might not be possible. Economic effects might thus either be expected as compliance costs or as wider socio-economic effects. A quantitative estimate of potential compliance costs is not available.
Construction industry	0	0	NMP cannot be used anymore in construction industry after implementation of RMO2. As the use within this industry is already thought to be phased out (personal communication AMEC consultation). No compliance costs are expected in this scenario.
Total including wire coating industry	XXXX	XXXX	As for some users no cost estimate is available, this total figure is expected to give a minimum estimate of the compliance costs in case of RMO2. Note however, that the costs estimates that are available might be overestimates. Because of that, the underestimation of the total figure might be fully or partly offset. Note that there is substantial uncertainty around the cost estimates in this RMO as there are quite some uncertainties around the actual implications of the conditions within which the derogations are given for various sectors.
Total excluding wire coating industry	>40	>50	

- *n/a not available*

Administrative costs

The conditions within which derogations are given ask explicitly for a monitoring program. The scenario requires that employers demonstrate that adequate protection of the workers has been achieved by providing evidence that the exposure is controlled beyond 5 mg/m^3 (in case of RMO3A). This can be demonstrated by means of modeling or measurements. This is the same level of evidence as is currently required by Council Directive 98/24/EC, the only difference being the exact limit that needs to be respected (indicative OEL vs mandatory DNEL). The REACH restriction will thus not require another way of measurements than that worker protection people in general already do. The REACH restriction, will however, if adopted, lead to a lowering of the limit that needs to be respected in the workplace. The lowering of the limit may affect the administrative costs in two ways:

1. it may increase the need for measurements in workplaces and;
2. it may lead to situations where more RMMs are required

Note that point 1. is treated in this document as administrative costs, where 2. is treated as compliance costs. Whether this will be the case depends on the real level of exposure. When real levels are above 1/10 of the limit value, companies are prompted to do more measurements and, if the real exposure is found to be higher than the work place limit, they are obliged to implement additional RMMs. Hence, it's not the REACH approach as such that makes the difference but the mere fact that a lower workplace exposure limit is set by this REACH restriction compared to the current one. In that way, it might have an effect on administrative costs for industry. No additional administrative costs are expected for authorities.

Unfortunately, no quantitative estimate of the potential administrative costs is available. However, if these additional administrative costs would occur in this scenario, they are assumed to be only a fraction of the compliance costs estimated above.

Costs of relocation and premature depreciation

Costs of relocation and premature depreciation may occur in some industries such as manufacturers, medical images, foodcontact material/bakeware, wire coating industries, optical industries, functional fluid users and laboratories. It remains highly uncertain if the RMO2 in practice could mean that despite the derogation the derogated industries will relocate. Therefore, no quantitative estimate of the potential costs is available.

Wider socio-economic effects

Just as is expected in RMO3a, the main economic effects of RMO2 are expected in terms of compliance costs. However, for some very specific uses of NMP that are not included in the list of derogations, and for which the availability of alternatives is uncertain, wider economic effects potentially occur. For these use categories, the effects of RMO2 potentially differ from the effects in RMO3a. Furthermore, there is a chance for wider economic effects to the wire coating industry in case the sector is not capable of meeting the conditions set at acceptable costs and a chance that manufacturers, importers/suppliers lose parts of their NMP markets.

Table F.11: *Potential turnover affected and jobs lost of various actors due to RMO2*

NMP producers/users	**Turnover affected RMO2** (€ million pa)		**Lost jobs RMO2** (number of workers)	**Explanation**
	Low	**High**		
Manufacturers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales as part of the industry is expected to shift to alternatives. However, this loss is expected to be minimal especially as manufacturers are typically also producing alternatives of NMP. Sales might reduce significantly (roughly one third) in case the wire coaters terminate, however, that is considered unlikely. NMP manufacturers might consider relocation of production. That could result in further added value losses for the European chemical industry and potential loss in jobs. The quantitative estimate given is based upon a 30% reduction in the sector, however, it is unlikely that this would actually occur in case of RMO2.
Importers/suppliers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales as part of the industry is expected to shift to alternatives. However, this loss is expected to be minimal especially as importers are typically also supplying alternatives of NMP. Sales might reduce significantly (roughly one third) in case the wire coaters terminate, however, that is considered unlikely. That could result in further added value losses for the European chemical industry and potential loss in jobs. The quantitative estimate given is based upon a 30% reduction in the sector, however, it is unlikely that this would actually occur in case of RMO2.
Coatings – medical images, foodcontact material/bakeware	n/a XXXX	n/a XXXX	n/a XXXX	As said, due to a potential absence in alternatives for this use, there are potential economic losses and losses in jobs for this use due to RMO2. It is however, very uncertain whether these wider socio-economic effects will actually occur e.g. as digital images could potentially be an alternative. As indicated in the public consultation 2013/204, wider socio-economic effects might occur for producers of foodcaontact material/bakeware. One actor indicates that the EU market for these bakeware products exceeds 60 million € pa and that 1000 EU jobs are related to this industry. These figures are included here, however, note that these figures have not been checked and are thus somewhat uncertain.

NMP producers/users	**Turnover affected RMO2** (€ million pa)		**Lost jobs RMO2** (number of workers)	**Explanation**
	Low	**High**		
Wire coating formulators	50	150	XXXX	As is explained in the section on wire coaters below, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, the wire coating formulators are expected to follow. The quantitative figure presents the turnover of formulators that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, potential losses in jobs are estimated. Whether these wider socio-economic effects will actually occur is not known.
Wire coaters	2000	3000	8000	As is explained in the section on wire coaters in section F.4.3, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, added value is lost. The quantitative figure presents the turnover of wire coaters that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, losses in jobs might occur and are estimated. Whether these wider socio-economic effects will actually occur is not known. Information received in the public consultation 2013/2014 suggests that wider socio-ecoomic effects in case the wire coating sector stops activity in Europe, will be much higher as also actors down the supply chain will be seriously affected and might stop activities in Europe as well (motor manufacturers, manufacturers of generators, transformers, relays, automotive industry). No quantitative estimates of such potential down stream effects are available.
Cleaners - optical	n/a	n/a	n/a	As said, due to a potential absence in alternatives for this use, there are potential economic losses and losses in jobs for this use due to RMO2. It is however, uncertain whether these wider socio-economic effects will actually occur for this sector e.g. as it is not known how crucial NMP is to the optical industry and whether it is not known whether alternatives are really lacking. No quantitative estimate of potential wider socio-economic effects is available.
Functional fluids	n/a	n/a	n/a	As said, due to a potential absence in alternatives for this use, there are potential economic losses and losses in jobs for this use due to RMO2. It is uncertain whether these wider socio-economic effects will actually occur for this use. No quantitative estimate of potential wider socio-economic effects is available.
Laboratories	n/a	n/a	n/a	The potential absence of alternatives of NMP for (non-R&D) laboratory applications might hamper laboratories in Europe resulting in wider socio-economic effects. No estimate is available of potential wider socio-economic effects to these users.
Total	2,100	3,200	XXXX	As not all industries are included in the estimates, the total turnover and job figures could be seen as minimum estimates. However, as it is uncertain whether turnovers are actually affected and jobs are actually lost, it is not known whether these wider socio-economic effects actually occur. In that sense, total estimates might very well be over estimates.

Petrochemical industries, non-wire coaters and formulators, cleaners (general) and formulators, electronics and semiconductor industries, battery industries, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (formulation) and pharmaceutical industries and construction industries are not included in this table as these users are all assumed to comply with a limit value of 5 mg/m^3.

n/a not available.

Overview total socio-economic effects RMO2

In the section above socio-economic impacts of RMO2 have been discussed in terms of compliance costs, other costs, turnover potentially affected and potential losses of jobs. The economic effects of this RMO2 are assumed to be to a large extent comparable to RMO3a. The main socio-economic effects are expected in terms of compliance costs.
The overall quantified compliance costs of RMO2 are in the range of XXXX including the high estimate compliance costs for the wire coating industry and >40-50 million € over 15 years excluding the wire coating industry. Whether the high compliance costs to wire coaters that are included in the estimate above will actually occur in practice is uncertain and depends on the interpretation of the conditions set to the wire coaters. It is reasonable to assume that wire coating machines will not be replaced fully after implementation of the RMO but that wire coaters challenge the interpretation of the conditions and argue to comply with taking additional exposure reduction measures to the older machines. Total quantified compliance costs would in that case be somewhere between the two figures including and excluding wire coaters (see for the full description on potential compliance costs for wire coaters in section F.4.3 below). The total costs are assumed to be an underestimate as for some of the users no quantitative estimate of compliance costs is available. The costs estimates that are available come from industry and have been crosschecked with publicly available data partly. These costs estimates might be somewhat overestimated as there is an incentive for industry to overestimate costs. The underestimation of the total cost figure may be partly or fully offset by the overestimation of the individual cost figures. Note that there is substantial uncertainty around the cost estimates in this RMO as there are quite some uncertainties around the actual implications of the conditions within which the derogations are given for various sectors. The quantitative costs estimate should be seen as indicative for the order of magnitude rather than as an actual figure.

In addition to the compliance costs, some other costs (relocation and/or premature depreciation) and wider socio-economic effects might occur to some specific use categories**, e.g. medical images, foodcontact material/bakeware, wire coating industries, optical industries, functional fluid users and laboratories. Wider socio-economic effects could occur e.g. in terms of lost added value, lost jobs and hampered economic development. Whether such effects will occur in practice is uncertain and will largely depend on the availability of alternatives and the actual interpretation of the conditions set for derogated uses. Note that these wider economic effects of this RMO2 might differ somewhat from the potential wider socio-economic effects of RMO3a.**

F.4.3. RMO3

Industry responses to RMO3 depend on the actual value at which the limit value is set. For this socio-economic analysis two different values are included:

a) RMO3a: Exposure limit value (at the level of the harmonised DNEL) of 5 mg/m^3
b) RMO3b: Exposure limit value of 20 mg/m^3

These limit values were chosen based on the DNEL value calculated by the Dossier Submitter for NMP (see section B.5.11) and the industry's responses to various limit values and connected socio-economic effects received in industries' consultation.
In line with RACs conclusions on the DNEL, an additional limit value of 10 mg/m^3 has been added to the analysis as an adjustment to RMO3a, as the expected socio-economic effects of limit values of 5 and 10 mg/m^3 are largely similar (see cost analysis in Appendix B and industry responses presented in table G.01 in part G). This RMO is indicated as RMO3aa.

Compliance costs

The compliance costs in case of mandatory limit values of 5 mg/m^3, 10 mg/m^3 and 20 mg/m^3 are presented respectively in the tables F.12, F.12A and F.13 below. They are mainly related to the expected dominant industry response: exposure reduction. These compliance costs are at first costs to the NMP using industries, although costs might be passed on to customers and society, depending on the price transmission elasticity of the products traded. It is not known to what extent that will occur.

Table F.12: *Compliance costs to various actors due to RMO3a*

NMP producers/users	**RMO3a – Limit value** 5 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers	Minimal	Minimal	Manufacturers are at this moment already at exposure levels close to 5 mg/m^3 (see section B.9.3.2.1). Additional exposure reduction measures are expected to be required e.g. for maintenance processes and processes under elevated temperatures. However, this is assumed to be possible at minimal costs.
Importers/suppliers	n/a	n/a	It is not known whether importers are able to meet this limit value and what the compliance costs will be for importers and suppliers. Reviewing the exposure scenarios provided by the lead registrant (see section B.9.3.2.1 and B.9.4.2.1) current exposure levels can go up to 20 mg/m^3.The Dossier Submitter assumes that importers and suppliers will be capable of further reducing exposure, e.g. by using dedicated facilities or closed systems, at least for the industrial processes. For industrial users costs might be comparable to for example manufacturers and are estimated to be minimal. However, for professional users emission reduction might require more effort, leading to potential significant compliance costs. These compliance costs however, could not be quantified.
Petrochemical industries	0	Minimal	As petrochemical industries are predominantly working with closed systems, exposure levels are expected to be very low already for the majority of the processes (see B.9.3.2.1). Some additional action might be required to reduce exposure especially in applications at elevated temperatures, however compliance costs to realize this are assumed to be minimal.
Non-wire coatings and coating formulators	Minimal	Minimal	This category represents industrial and professional users and formulators of coatings. No quantitative cost estimates are available for these uses. However, for many of the coating users costs are assumed to be limited as the majority of the industries have already shifted to alternatives. Car coaters, coatings in medical images, foodcontact material/bakeware and wire coaters are excluded from this category as these are presented as separate users in this table.
Coatings - automotive	20	30	As costs to reduce exposure are assumed to be higher than costs for reformulation (see appendix B section 5.3.4), total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate comes from industry and has been cross-checked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car manufacturers and 50% for auto repair shops.
Coatings – medical images, foodcontact material/bakeware	n/a	n/a	It is uncertain how industry will respond to a mandatory limit value and what the compliance costs will be for these users. Reviewing the exposure scenarios provided by the lead registrant (see B.9.3.2.1 and B.9.4.2.1) shows that coaters are currently at exposure levels of up to 20 mg/m^3. However, according to the Dossier Submitter it is uncertain whether the exposure scenarios on coatings provided by the lead registrant sufficiently cover the use of NMP in medical images and foodcontact materials/bakeware. As such, current exposure levels are uncertain, as is the capability to further reduce exposure in this use. The Dossier Submitter assumes that it is possible by means of personal protective equipment (as a last measure) to reduce exposure to below the DNEL, however, potentially at substantial compliance costs. Information received in the public consultation 2013/2014 indicated that additional costs might be made by industry producing foodcontact material/bakeware if exposure limits are to be reduced (millions of Euros), however, this cost estimate has not been further specicied and it is unclear for what exposure level the cost estimate was given.

NMP producers/users	**RMO3a – Limit value** 5 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
Wire coaters and formulators	<480	>480	Wire coaters say not to be able to reduce exposure levels to below the DNEL. However, estimates of potential compliance costs are provided by industry. As this sector is an important user of NMP in terms of quantities and expected growth, and the estimation of compliance costs for this sector is somewhat complicated, compliance costs for this sector are discussed in a separate section below.
Cleaners – optical	n/a	n/a	It is uncertain whether the optical industry is capable of reducing exposure to this limit value. There are signals from industry (personal communication, AMEC questionnaire) that alternatives might not be readily available and that exposure reduction to below 10 mg/m^3 might be problematic. The Dossier Submitter, however, assumes that it is however possible by means of personal protective equipment (as a last measure) to reduce exposure to below the DNEL. This could, potentially occur at substantial compliance costs for these specific uses. It is uncertain whether costs are feasible to the sector and thus whether the industry will decide to comply with the exposure limit value. For other industries that use NMP for cleaning and that are not presented as a separate use categories in this table it is assumed that alternatives are readily available. For these users compliance costs are assumed to be limited as many users have already shifted to alternatives.
Electronic and semi-conductor industries	0	Minimal	This industry is working at highly automated processes working in clean rooms. As such, current exposure levels are already in the range of the DNEL (see section B.9.3.2.1). Industry is thus expected to be capable of meeting this limit value at minimal costs.
Battery industries	n/a	n/a	According to section B.9.3.2.1, exposure currently is around 10 mg/m^3. Information received in the public consultation 2013/2014 shows that current exposure levels might be somewhat higher (up to 20 mg/m^3). One industry actor from this sector indicated that investment costs in this scenario will be substantial and besides that also increased running costs (e.g. for extra energy use) could be expected. Costs in the range of million € are suggested in the public consultation for this single company that responded. The costs might even be higher if a new building is required. The company indicates that these costs are disproportional, however, no further underpinning is given to support this statement. Another actor from the battery sector that responded in the public consultation showed exposure data that currently is already below 5 mg/m^3, thereby suggesting that the current situation already complies with the proposed DNEL of RMO3a. For this actor no additional costs might occur in case of RMO3a. The received signals thus vary throughout the actors that replied in the public consultation and its is therefor not possible to conclude upon the expected compliance costs of RMO3a for the battery sector.
Membrane manufacturers	20	20	One membrane manufacturer states to be able to further reduce exposure (personal communication, AMEC questionnaire). It is assumed that this statement is representative for the full membrane sector. A quantitative estimate of compliance costs is provided by the industry. The estimate includes costs for additional exposure reduction measures and for extra exposure measurements. One-off costs are spread out over 2 years as industry states to take two years to adapt the system. The cost estimate has been scaled up to the full NMP using membrane sector in Europe assuming that 50% of the companies requires to take additional measures for exposure reduction. The cost estimate has been cross-checked with publicly available data. This estimate based on publicly available information is significantly lower than the figure provided by industry (order of magnitude 0.5-2 million €). However, as the uncertainties around the cross-check are too high to conclude upon the validity of the here presented figure, the

NMP producers/users	**RMO3a – Limit value** 5 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
			figure has not been included in the cost estimate presented here. Additional information received in the public consultation 2013/2014 that a limit value of 10 mg/m^3 is fully acceptable, indicating limited costs to achieve this for this actor. No specific statement is made on the acceptability of a 5 mg/m^3 limit is presented. However, some (not further explained) confidential cost figures are presented for this specific actor. As it is not very clear what these figures actually represent, these have not been included here.
High performance polymer producers	n/a	n/a	Industry is said to be capable of meeting this limit value at acceptable costs for further exposure reduction (personal communication, AMEC questionnaire). What acceptable costs are is not known.
Agricultural chemical industry (formulation, synthesis)	minimal	minimal	As NMP is already phased out in agricultural chemical *formulation*, there are no compliance costs expected for these users. It is not known whether exposure reduction to below the DNEL is possible for agricultural chemical *synthesis* and what compliance costs would be connected to that. According to the registration dossier (see section B.9.3.2.1) current exposure levels are limited for most of the processes, but go up to 20 mg/m^3 and thus further exposure reduction would be required, especially in processes at elevated temperatures. As the processes used in agricultural chemical synthesis are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.
Pharmaceutical industry	minimal	minimal	It is uncertain how pharmaceutical industry would respond to a mandatory limit value and what the compliance costs will be for these users. According to the registration dossier (see section B.9.3.2.1) current exposure levels are limited for most of the processes, but go up to 20 mg/m^3 and thus further exposure reduction would be required, especially in processes at elevated temperatures. As the processes used in the pharmaceutical industry are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.
Laboratories	0	0	As no risks are calculated for laboratory uses in the exposure scenarios provided by the lead registrants (see B.9.3.2.1 and B.9.4.2.1), it is assumed that laboratories already comply with the DNEL. As such, no compliance costs are expected for these users.
Functional fluids	n/a	n/a	It is uncertain how functional fluids users would respond to a mandatory limit value and what the compliance costs will be for these users. Reviewing the exposure estimates presented in B.9.3.2.1 and B.9.4.2.1 shows that current exposure is at levels up to 20 mg/m^3. Further reduction of this exposure is assumed to be possible via exposure reduction measures, potentially at substantial costs.
Construction industry	0	0	According to an industry representative, NMP is already phased out in construction industry (personal communication, AMEC consultation). This is assumed to be the case for the full construction industry sector and therefore no further costs are expected due to a mandatory limit value.
Total including wire coating industry	>40	>530	As for some users no cost estimate is available, this total figure is expected to give a minimum estimate of the compliance costs in case of RMO3a. Note however, that the costs estimates that are available might be overestimates. Because of that, the underestimation of the total figure might be fully or partly offset. Especially the cost figure for wire coaters is assumed to be overestimated.
Total excluding wire coating industry	>40	>50	

- *n/a not available*

Table F.12A: *Compliance costs to various actors due to RMO3aa*

NMP producers/users	**RMO3aa – Limit value** 10 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers	0	0	Manufacturers are at this moment already at exposure levels close to 5 mg/m^3 (see section B.9.3.2.1). No additional exposure reduction is therefore required.
Importers/suppliers	n/a	n/a	It is not known whether importers are able to meet this limit value and what the compliance costs will be for importers and suppliers. Reviewing the exposure scenarios provided by the lead registrant (see section B.9.3.2.1 and B.9.4.2.1) current exposure levels can go up to 20 mg/m^3.The Dossier Submitter assumes that importers and suppliers will be capable of further reducing exposure, e.g. by using dedicated facilities or closed systems, at least for the industrial. For industrial users costs might be comparable to for example manufacturers and are estimated zero. However, for professional users emission reduction might require more effort, however costs to these actors are assumed to be minimal.
Petrochemical industries	0	0	As petrochemical industries are predominantly working with closed systems, exposure levels are expected to be very low already for the majority of the processes (see B.9.3.2.1). No further exposure reduction is assumed to be required for these actors.
Non-wire coatings and coating formulators	Minimal	Minimal	This category represents industrial and professional users and formulators of coatings. No quantitative cost estimates are available for these uses. However, for many of the coating users costs are assumed to be limited as the majority of the industries have already shifted to alternatives. Car coaters, coatings in medical images, foodcontact material/bakeware coaters and wire coaters are excluded from this category as these are presented as separate users in this table.
Coatings - automotive	20	30	As costs to reduce exposure are assumed to be higher than costs for reformulation (see appendix B section 5.3.4), total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate comes from industry and has been cross-checked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car manufacturers and 50% for auto repair shops.
Coatings – medical images, foodcontact material/bakeware	n/a	n/a	It is uncertain how industry will respond to a mandatory limit value and what the compliance costs will be for these users. Reviewing the exposure scenarios provided by the lead registrant (see B.9.3.2.1 and B.9.4.2.1) shows that coaters are currently at exposure levels of up to 20 mg/m^3. However, according to the Dossier Submitter it is uncertain whether the exposure scenarios on coatings provided by the lead registrant sufficiently cover the use of NMP in medical images and food contact material/bakeware. As such, current exposure levels are uncertain, as is the capability to further reduce exposure in this use. The Dossier Submitter assumes that it is possible by means of personal protective equipment (as a last measure) to reduce exposure to below the 10 mg/m^3, however, potentially at substantial compliance costs. Information received in the public consultation 2013/2014 indicated that additional costs might be made by industry producing foodcontact material/bakeware if exposure limits are to be reduced (millions of Euros), however, this cost estimate has not been further specified and it is unclear for what exposure level the cost estimate was given. SEAC observed, that according to the commenting party current yearly solvent monitoring program of operators, personal airborne concentrations are between 1 and 6 mg/m3 average 3mg/m^3 in

NMP producers/users	**RMO3aa – Limit value** 10 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
			standard processing conditions and airborne concentrations of between 12 and 20 mg/m^3 at cleandown periods.
Wire coaters and formulators	61.5	61.5	Wire coaters say not to be able to reduce exposure levels to below the 10 mg/m^3. However, estimates of potential compliance costs are provided by industry. As this sector is an important user of NMP in terms of quantities and expected growth, and the estimation of compliance costs for this sector is somewhat complicated, compliance costs for this sector are discussed in a separate section below.
Cleaners – optical	n/a	n/a	It is uncertain whether the optical industry is capable of reducing exposure to this limit value. There are signals from industry (personal communication, AMEC questionnaire) that alternatives might not be readily available and that exposure reduction to below 10 mg/m^3 might be problematic. The Dossier Submitter, assumes that it is possible by means of personal protective equipment (as a last measure) to reduce (or remain) exposure to below the 10 mg/m^3. This would probably be possible at minimal costs. However, it is uncertain whether costs are feasible to the sector and thus whether the industry will decide to comply with the exposure limit value. For other industries that use NMP for cleaning and that are not presented as a separate use categories in this table it is assumed that alternatives are readily available. For these users compliance costs are assumed to be limited as many users have already shifted to alternatives.
Electronic and semi-conductor industries	0	Minimal	This industry is working at highly automated processes working in clean rooms. As such, current exposure levels are already in the range of the 5 mg/m^3 (see section B.9.3.2.1). Industry is thus expected to be capable of meeting the 10 mg/m^3 limit value at minimal or no costs.
Battery industries	n/a	n/a	According to section B.9.3.2.1, exposure currently is already around 10 mg/m^3. Information received in the public consultation 2013/2014 shows that current exposure levels might be somewhat higher (up to 20 mg/m^3). One industry actor from this sector indicated that investment costs in this scenario will be substantial and besides that also increased running costs (e.g. for extra energy use) could be expected to achieve limit values of around 5 mg/m^3. Costs in the range of million € are suggested in the public consultation for this single company that responded. The costs might even be higher if a new building is required. The company indicates that these costs are disproportional, however, no further underpinning is given to support this statement. Whether such costs are also expected to meet limit values of around 10 mg/m^3 is not known. Another actor from the battery sector that responded in the public consultation 2013/2014 showed exposure data that currently is already below 5 mg/m^3, thereby suggesting that the current situation already complies with the 10 mg/m^3. For this actor no additional costs might occur. The received signals thus vary throughout the actors that replied in the public consultation and its is therefor not possible to conclude upon the expected compliance costs of RMO3aa for the battery sector. However, the Dossier Submitter assumes that compliance costs to this sector are minimal.
Membrane manufacturers	Minimal	Minimal	One membrane manufacturer states to be able to further reduce exposure (personal communication, AMEC questionnaire). It is assumed that this statement is representative for the full membrane sector. A quantitative estimate of compliance costs is provided by the industry. The estimate includes costs for additional exposure reduction measures and for extra exposure measurements. One-off

NMP producers/users	**RMO3aa – Limit value** 10 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
			costs are spread out over 2 years as industry states to take two years to adapt the system. The cost estimate has been scaled up to the full NMP using membrane sector in Europe assuming that 50% of the companies requires to take additional measures for exposure reduction. The cost estimate has been cross-checked with publicly available data. This estimate based on publicly available information is significantly lower than the figure provided by industry (order of magnitude 0.5-2 million €). However, as the uncertainties around the cross-check are too high to conclude upon the validity of the here presented figure, the figure has not been included in the cost estimate presented here. Additional information received in the public consultation 2013/2014 indicated that a limit value of 10 mg/m^3 is fully acceptable, indicating limited costs to achieve this for this actor.
High performance polymer producers	n/a	n/a	Industry is said to be capable of meeting the limit value of 5 and 10 mg/m^3 at acceptable costs for further exposure reduction (personal communication, AMEC questionnaire). What acceptable costs are is not known, however, these are assumed to be minimal.
Agricultural chemical industry (formulation, synthesis)	Minimal	Minimal	As NMP is already phased out in agricultural chemical *formulation*, there are no compliance costs expected for these users. It is not known whether exposure reduction to below the 10 mg/m^3 is possible for agricultural chemical *synthesis* and what compliance costs would be connected to that. According to the registration dossier (see section B.9.3.2.1) current exposure levels are limited for most of the processes, but go up to 20 mg/m^3 and thus further exposure reduction would be required, especially in processes at elevated temperatures. As the processes used in agricultural chemical synthesis are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.
Pharmaceutical industry	minimal	Minimal	It is uncertain how pharmaceutical industry would respond to a mandatory limit value and what the compliance costs will be for these users. According to the registration dossier (see section B.9.3.2.1) current exposure levels are limited for most of the processes, but go up to 20 mg/m^3 and thus further exposure reduction would be required, especially in processes at elevated temperatures. As the processes used in the pharmaceutical industry are typically closed systems that are largely automated and controlled (comparable to the petrochemical industry), further exposure reduction is assumed to be possible, presumably at minimal costs.
Laboratories	0	0	As no risks are calculated for laboratory uses in the exposure scenarios provided by the lead registrants (see B.9.3.2.1 and B.9.4.2.1), it is assumed that laboratories already are at limit values of around 5 mg/m^3. As such, no compliance costs are expected for these users.
Functional fluids	n/a	n/a	It is uncertain how functional fluids users would respond to a mandatory limit value and what the compliance costs will be for these users. Reviewing the exposure estimates presented in B.9.3.2.1 and B.9.4.2.1 shows that current exposure is at levels up to 20 mg/m^3. Further reduction of this exposure is assumed to be possible via exposure reduction measures, potentially at substantial costs.
Construction industry	0	0	According to an industry representative, NMP is already phased out in construction industry (personal communication, AMEC consultation). This is assumed to be the case for the full construction industry sector and therefore no further costs are expected due to a mandatory limit value.

NMP producers/users	**RMO3aa – Limit value** 10 mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
Total including wire coating industry	>80	>90	As for some users no cost estimate is available, this total figure is expected to give a minimum estimate of the compliance costs in case of RMO3a. Note however, that the costs estimates that are available might be overestimates. Because of that, the underestimation of the total figure might be fully or partly offset. Especially the cost figure for wire coaters is assumed to be overestimated.
Total excluding wire coating industry	>20	>50	

- *n/a not available*

Table F.13: *Compliance costs to various actors due to RMO3b*

NMP producers/users	**RMO3b – Limit value** 20mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers	0	0	Manufacturers are already at lower exposure levels so no compliance costs are expected here.
Importers/suppliers	0	Minimal	According to the exposure scenarios for importers and suppliers (see B.9.3.2.1 and B.9.4.2.1), exposure levels are already below 20 mg/m^3, so additional costs for these users to comply with this limit value are assumed to be minimal.
Petrochemical industries	0	Minimal	According to the registration dossier, exposure levels are below or around the 20 mg/m^3 at this moment. Some compliance costs might occur for some very specific processes, however, these are expected to be minimal.
Non-wire coatings and coating formulators	0	Minimal	This category represents industrial and professional users and formulators of coatings. Coaters in the automotive sector and wire-coaters are excluded from this category as these are presented as separate users in this table. No quantitative cost estimates are available for these uses. However, for many of the coating users costs are assumed to be limited as the majority of the industries have already shifted to alternatives and where NMP is still used, exposure is already below the level of 20 mg/m^3 (see B.9.3.2.1 and B.9.4.2.1).
Coaters - automotive	Minimal	30	As costs to reduce exposure are assumed to be higher than costs for reformulation, total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate comes from industry and has been crosschecked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car manufacturers and 50% for auto repair shops. Note, however, that the assumption that industry will reformulate might not be correct as according to the registration dossier, exposure is already in the range of the 20 mg/m^3 (see B.9.3.2.1 and B.9.4.2.1). If industrial and professional users would decide to comply with the restriction by reducing exposure, costs might be minimal.
Coatings – medical images, foodcontact material/bakeware	0	Minimal	It is uncertain how industry will respond to a mandatory limit value and what the compliance costs will be for these users. However, according to the registration dossier, exposure levels are already in the range of the limit value (see B.9.3.2.1 and B.9.4.2.1) so compliance costs are assumed to be minimal. It should however be said that it is uncertain whether this use is adequately represented

NMP producers/users	**RMO3b – Limit value** 20mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
			in the exposure scenarios on coatings provided by the lead registrant. As such these is some uncertainty around the current exposure level and the potential compliance costs. Information received in the public consultation 2013/2014 indicated that additional costs might be made by industry producing foodcontact material/bakeware if exposure limits are to be reduced (millions of Euros), however, this cost estimate has not been further specicied and it is unclear for what exposure level the cost estimate was given. The Dossier Submitter assumes it to be unlikely that such additional costs will occur at the limit value of 20 mg/m^3.
Wire coaters and formulators	0-70	120	Wire coaters say to have serious problems in reducing exposure to below 20 mg/m^3. However, estimates of potential compliance costs are provided by industry. As this sector is an important user of NMP in terms of quantities and expected growth, and the estimation of compliance costs for this sector is somewhat complicated, compliance costs for this sector are discussed in a separate section below.
Cleaners – optical	0	Minimal	The majority of the cleaning uses phased out the use of NMP already, so no compliance costs are expected to occur for these users. There might be some niche uses - like the optical industry - where NMP is still used as a cleaner. These, mainly industrial uses are assumed to have limited exposure levels around or below the limit value of 20 mg/m^3, so only minimal costs are expected here. It should however be said that it is uncertain whether this use is adequately represented in the exposure scenarios on cleaning provided by the lead registrant. As such these is some uncertainty around the current exposure level and the potential compliance costs. However, there are signals that exposure reduction below 10 mg/m^3 might be problematic (personal communication, AMEC consultation). Reduction to levels of 20 mg/m^3 is assumed to be possible.
Electronic and semi-conductor industries	0	0	According to the registration dossier (see B.9.3.2.1), exposure of NMP in this industry is already below 20 mg/m^3 so compliance costs are assumed to be around zero.
Battery industries	0	Minimal	According to the registration dossier (see B.9.3.2.1), exposure of NMP in this industry is already below 20 mg/m^3 so compliance costs are assumed to be around zero. Information received in the public consultation 2013/2014 suggests that current exposure is indeed below 20 mg/m^3, however, nevertheless some costs are indicated by the actor for this scenario, propbably to manage emissions at non-regualr activities. These costs are indicated to be acceptable to the actor. Another actor from the battery sector indicated that current exposure levels are already below 5 mg/m^3, and in that case no additional costs would occur at least for this actor. Based on this information it is difficult to draw overall conclusions for the battery sector, but it seems reasonable to assume that if there are costs to the sector, these costs would be minimal.
Membrane manufacturers	0	Minimal	According to the registration dossier (see B.9.3.2.1, exposure of NMP in this industry is at this moment around 20 mg/m^3. There might be some compliance costs for this sector, however, these are assumed to be minimal. According to an industry actor reducing up to 10 mg/m^3 would imply minimal changes (personal communication, AMEC questionnaire), this implies that 20 mg/m^3 can be obtained without further investments. Information received in the public consultation 2013/2014 indicates that current exposure levels are already below 20 mg/m^3 and thus no additional costs are expected for these actors.
High performance polymer producers	0	Minimal	According to the registration dossier (see B.9.3.2.1), exposure of NMP in this industry is at this moment around 20 mg/m^3. There might be some compliance costs for this sector, however, these

NMP producers/users	**RMO3b – Limit value** 20mg/m^3 15y PV (€ million)		**Explanation**
	Low	**High**	
			are assumed to be minimal. According to an industry actor exposure levels of 10 mg/m^3 would be fully acceptable (personal communication, AMEC questionnaire). This implies that limits of 20 mg/m^3 can be obtained without further investments.
Agricultural chemical industry (formulation, synthesis)	0	Minimal	As NMP is already phased out in agricultural chemical *formulation*, there are no compliance costs expected for these users, For agricultural chemical synthesis exposure is assumed to be currently around 20 mg/m^3 (see B.9.3.2.1). Potentially some compliance costs for exposure reduction in the agricultural chemical synthesis might occur. However, these costs are assumed to be minimal.
Pharmaceutical industry	0	Minimal	According to the registration dossier, exposure of NMP in this industry is at this moment around 20 mg/m^3 (see B.9.3.2.1). There might be some compliance costs for this sector, however, these are assumed to be minimal.
Laboratories	0	0	As no risks are calculated for laboratory uses in the exposure scenarios provided by the lead registrants (see B.9.3.2.1 and B.9.4.2.1), it is assumed that laboratories already comply with the DNEL. As such, no compliance costs are expected for these users.
Functional fluids	0	Minimal	According to the registration dossier, exposure of NMP in this industry is already around 20 mg/m^3 (see B.9.3.2.1 and B.9.4.2.1) so compliance costs are assumed to be minimal.
Construction industry	0	0	According to an industry representative, NMP is already phased out in construction industry (personal communication, AMEC consultation). This is assumed to be the case for the full construction industry sector and therefore no further costs are expected due to a mandatory limit value.
Total	**0-70**	**150**	The costs estimates might be somewhat overestimated as there is some incentive for industry to overestimate costs.

Administrative costs

No estimate of potential administrative costs to industries and authorities coupled to this RMO is available. Administrative costs for e.g. to prove (industries) or check (authorities) compliance to the restriction might be substantial. However, the Dossier Submitter assumes that these costs will be minimal compared to the compliance costs to industry presented above.

Costs of relocation and premature depreciation

Costs of relocation and premature depreciation may occur in some industries such as wire coating industries (formulators), battery industries, agricultural chemical industries and pharmaceutical industries. It remains highly uncertain if the RMO3 in practice could mean that these industries will relocate as the compliance costs are considered bearable within the five year period. No quantitative estimate of the potential costs is available.

Wider socio-economic impacts

As the majority of the sectors seems to be capable of reducing exposure levels to 5, 10 and 20 mg/m^3, the wider socio-economic impacts in terms of losses in value added and losses in jobs seem to be limited in case of RMO3 a, aa and b. Also indirect supply chain effects are assumed to be limited in case of RMO3 a, aa and b. However, the extent to which wider socio-economic impacts occur in case of a mandatory limit value depends on the actual value at which the limit value is set. Especially at the lower limit value, there is uncertainty for some of the use categories whether they have the capability to reduce exposure to the required levels. The users for which some uncertainty exists on the capability to reach the limit value, are discussed in further detail in the tables below. Unfortunately,

due to data constraints, no quantitative estimate of the losses in added value could be made. Instead, estimates of the turnover of companies potentially affected are given in the tables. Besides, estimates of potential losses in jobs are given for some of the use categories. As explained earlier in section F.3, note that the estimates of the turnover affected presented in the table below are not a good indicator for these real wider socio-economic losses, as turnover does not represent the real added value of the industry.

Table F.14: *Potential turnover affected and jobs lost of various actors due to RMO3a*

NMP producers/ users	**Turnover affected RMO3a– DNEL** (€ million pa)		**Lost jobs RMO3a – DNEL** (number of workers)	**Explanation**
	Low	**High**		
Manufacturers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales. Sales might reduce significantly (roughly one third) in case the wire coaters terminate. NMP manufacturers might consider relocation of production. That could result in further added value losses for the European chemical industry and potential loss in jobs .
Importers/ suppliers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales. Sales might reduce significantly (roughly one third) in case the wire coaters terminate. This could potentially result in loss in jobs .
Coatings – medical images, foodcontact material/ bakeware	n/a XXXX	/a XXXX	n/a XXXX	It is uncertain how industry will respond to a mandatory limit value. Reviewing the exposure scenarios provided by the lead registrant (see B.9.3.2.1 and B.9.4.2.1) shows that coaters are currently at exposure levels of up to 20 mg/m^3. The Dossier Submitter assumes that it is possible also for this coating application to reduce exposure to the level of the DNEL, potentially at substantial costs. However, in case such costs are not bearable to the industry, industry might shut down, resulting in losses in value added and losses in jobs. No quantitative estimate of losses or turnover potentially affected is available for this sector. Information received in the public consultation 2013/2014 indicated that potentially wider socio-economic effects might occur to industry producing foodcontact material/bakeware if exposure limits are to be reduced (millions of Euros), however, it has not been further specicied for what exposure levels this would be likely. And it is thus very uncertain whether these effects would occur in this scenario. One actor indicates that the EU market for these bakeware products exceeds 60 million € pa and that 1000 EU jobs are related to this industry. These figures are included here, however, note that these figures have not been checked and are thus somewhat uncertain.
Wire coating formulators	50	150	XXXX	As is explained in the section on wire coaters below, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, the wire coating formulators are expected to follow. The quantitative figure presents the turnover of formulators that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, potential losses in jobs are estimated. Note that extended timing of the restriction for wire coaters, might avoid this industry to relocate or terminate and would in that case prevent this wider socio-economic effects to occur.
Wire coaters	2000	3000	8000	As is explained in the section on wire coaters below, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, added value is lost. The quantitative figure presents the turnover

NMP producers/ users	**Turnover affected RMO3a– DNEL** (€ million pa)		**Lost jobs RMO3a – DNEL** (number of workers)	**Explanation**
	Low	**High**		
				of wire coaters that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, losses in jobs might occur and are estimated. Note that extended timing of the restriction for this sector, might avoid this industry to terminate and would in that case prevent these wider socio-economic effects to occur. Information received in the public consultation 2013/2014 suggests that wider socio-ecoomic effects in case the wire coating sector stops activity in Europe, will be much higher as also actors down the supply chain will be seriously affected and might stop activities in Europe as well (motor manufacturers, manufacturers of generators, transformers, relays, automotive industry). No quantitative estimates of such potential down stream effects are available.
Cleaners - optical	n/a	n/a	n/a	It is uncertain how optical cleaners will respond to a mandatory limit value at the level of the DNEL. Adequate control is assumed to be possible, however, if costs to achieve this are not bearable to industry might terminate resulting in losses in value added and potential losses in jobs. Such potential losses could not be quantified for this sector neither are figures on turnover available.
Battery industries	n/a	n/a	n/a	According to section B.9.3.2.1, exposure currently is around 10 mg/m^3. As indicated by an industry actor in the public consultation 2013/2014, current exposure levels might be higher than indicated in section B and with that costs for exposure reduction might be higher than initially expected. Costs to reduce emissions to the level of 5 mg/m^3 are according to one industrial actor that replied to the public consultation disproportional. This might be an indication that the actor will go out of business in Europe under this scenario, potentially resulting in losses in added value and losses in jobs in Europe. However, as no further underpinning is given for the statement of disproportionality, it is not possible to draw clear cut conclusions here. Another actor from the battery sector that responded in the public consultation showed exposure data that currently is already below 5 mg/m^3, thereby suggesting that the current situation already complies with the proposed DNEL of RMO3a. The received signals thus vary throughout the actors that replied in the public consultation and its is thus not known how the battery sector would reply to this RMO3a overall. If (part of) the battery industry would, however, shut down in Europe wider socio-economic effects (losses in turnover and losses in jobs) might be larger than only the battery sector due to supply chain effects (e.g. for the automotive industry) as indicated by one actor in the public conslutation.
Agricultural chemical industry (synthesis)	n/a	n/a	n/a	It is not known whether exposure reduction to below the DNEL is possible for agricultural chemical *synthesis*. According to the registration dossier (see section B.9.3.2.1) current exposure levels go up to 20 mg/m^3 and thus further exposure reduction would be required. As these include all industrial processes that presumably are largely automated and controlled, further exposure reduction is assumed to be possible, presumably at minimal costs. If costs to achieve this are not bearable to industry (which is deemed very unlikely), industry might terminate or relocate resulting in losses in value added and losses in jobs for Europe. However, this is very unlikely for this sector as NMP is presumably not of major importance for this sector.

NMP producers/ users	**Turnover affected RMO3a– DNEL** (€ million pa)		**Lost jobs RMO3a – DNEL** (number of workers)	**Explanation**
	Low	**High**		
Pharmaceutical industry	n/a	n/a	n/a	It is uncertain how pharmaceutical industry would respond to a mandatory limit value and what the compliance costs will be for these users. According to the registration dossier (see section B.9.3.2.1) current exposure levels go up to 20 mg/m^3 and thus further exposure reduction would be required. As these likely include all industrial processes that presumably are largely automated and controlled, further exposure reduction is assumed to be possible, presumably at minimal costs. If costs to achieve this are not bearable to industry (which is deemed very unlikely), industry might terminate or relocate resulting in losses in value added and losses in jobs for Europe. However, this is very unlikely for this sector as NMP is presumably not of major importance for this sector.
Functional fluids	n/a	n/a	n/a	It is uncertain how functional fluids users would respond to a mandatory limit value. Reviewing the exposure estimates presented in B.9.3.2.1 and B.9.4.2.1 shows that current exposure is at levels up to 20 mg/m^3. Further reduction of this exposure is assumed to be possible via exposure reduction measures, potentially at substantial costs. However, if costs to achieve this are not bearable to industry, industry might terminate resulting in losses in value added and losses in jobs for Europe. Such potential losses could not be quantified for this sector.
Total	2,100	3,200	XXXX	As not all industries are included in the estimates, the total turnover and job figures could be seen as minimum estimates. However, as it is uncertain whether turnovers are actually affected and jobs are actually lost, it is not known whether these wider socio-economic effects actually occur. In that sense, total estimates might very well be over estimates.

Petrochemical industries, non-wire coaters and formulators, cleaners (general) and formulators, electronics and semiconductor industries, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (formulation) and laboratories and construction industries are not included in this table as these users are all assumed to comply with a limit value of 5 mg/m^3.
n/a not available.

Table F.14A: *Potential turnover affected and jobs lost of various actors due to RMO3aa*

NMP producers/ users	**Turnover affected RMO3aa – 10 mg/m³** (€ million pa)		**Lost jobs RMO3aa – 10 mg/m³** (number of workers)	**Explanation**
	Low	**High**		
Manufacturers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales, however, this effect is assumed to be minimal. Sales might reduce significantly (roughly one third) in case the wire coaters terminate. NMP manufacturers might consider relocation of production in that case. That could result in further added value losses for the European chemical industry and potential loss in jobs.
Importers/ suppliers	3	15	XXXX	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales, this effect however, is assumed to be minimal. Sales might reduce significantly (roughly one third) in case the wire coaters terminate. This could potentially result in loss in jobs .
Coatings – medical images, foodcontact material/ bakeware	n/a XXXX	n/a XXXX	n/a XXXX	It is uncertain how industry will respond to a mandatory limit value. Reviewing the exposure scenarios provided by the lead registrant (see B.9.3.2.1 and B.9.4.2.1) shows that coaters are currently at exposure levels of up to 20 mg/m³. The Dossier Submitter assumes that it is possible also for this coating application to reduce exposure to the level of 10 mg/m³, potentially at substantial costs. However, in case such costs are not bearable to the industry, industry might shut down, resulting in losses in value added and losses in jobs. No quantitative estimate of losses or turnover potentially affected is available for this sector. Information received in the public consultation indicated that potentially wider socio-economic effects might occur to industry producing foodcontact material/bakeware if exposure limits are to be reduced (millions of Euros), however, it has not been further specicied for what exposure levels this would be likely. And it is thus very uncertain whether these effects would occur in this scenario. One actor indicates that the EU market for these bakeware products exceeds 60 million € pa and that 1000 EU jobs are related to this industry. These figures are included here, however, note that these figures have not been checked and are thus somewhat uncertain.
Wire coating formulators	50	150	XXXX	As is explained in the section on wire coaters below, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, the wire coating formulators are expected to follow. The quantitative figure presents the turnover of formulators that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, potential losses in jobs are estimated. Note that extended timing of the restriction for wire coaters, might avoid this industry to relocate or terminate and would in that case prevent this wider socio-economic effects to occur.
Wire coaters	2000	3000	8000	As is explained in the section on wire coaters below, the sector might either terminate or comply and achieve exposure reduction. In case wire coaters terminate, added value is lost. The quantitative figure presents the turnover of wire coaters that is potentially affected as estimated by industry. The estimate has been crosschecked with publicly available information and is in a comparable range. Besides, losses in jobs might occur and are estimated. Note that extended timing of the restriction for this sector, might avoid this industry to terminate and would in that case

NMP producers/ users	**Turnover affected RMO3aa – 10 mg/m^3** (€ million pa)		**Lost jobs RMO3aa – 10 mg/m^3** (number of workers)	**Explanation**
	Low	**High**		
				prevent these wider socio-economic effects to occur. Information received in the public consultation suggests that wider socio-ecoomic effects in case the wire coating sector stops activity in Europe, will be much higher as also actors down the supply chain will be seriously affected and might stop activities in Europe as well (motor manufacturers, manufacturers of generators, transformers, relays, automotive industry). No quantitative estimates of such potential down stream effects are available.
Cleaners - optical	n/a	n/a	n/a	It is uncertain how optical cleaners will respond to a mandatory limit value at the level of 10 mg/m^3. Adequate control is assumed to be possible, however, if costs to achieve this are not bearable to industry might terminate resulting in losses in value added and potential losses in jobs. Such potential losses could not be quantified for this sector neither are figures on turnover available.
Battery industries	n/a	n/a	n/a	According to section B.9.3.2.1, exposure currently is around 10 mg/m^3. As indicated by an industry actor in the public consultation, current exposure levels might be higher than indicated in section B and with that costs for exposure reduction might be higher than initially expected. Costs to reduce emissions to the level of 5 mg/m^3 are according to one industrial actor that replied to the public consultation disproportional. Whether this is also the case for exposure limites of around 10 mg/m^3 is not known. Another actor from the battery sector that responded in the public consultation showed exposure data that currently is already below 5 mg/m^3, thereby suggesting that the current situation already complies with the limit of 10 mg/m^3. The received signals thus vary throughout the actors that replied in the public consultation and its is thus not known how the battery sector would reply to this RMO3aa overall. If (part of) the battery industry would, however, shut down in Europe wider socio-economic effects (losses in turnover and losses in jobs) might be larger than only the battery sector due to supply chain effects (e.g. for the automotive industry) as indicated by one actor in the public conslutation. The Dossier Submitter assumes it not very likely that such wider socio-economic effects will occur for this sector in case of this limit value of 10 mg/m^3.
Agricultural chemical industry (synthesis)	n/a	n/a	n/a	It is not known whether exposure reduction to below the 10 mg/m^3 is possible for agricultural chemical *synthesis*. According to the registration dossier (see section B.9.3.2.1) current exposure levels go up to 20 mg/m^3 and thus further exposure reduction would be required. As these include all industrial processes that presumably are largely automated and controlled, further exposure reduction is assumed to be possible, presumably at minimal costs. If costs to achieve this are not bearable to industry (which is deemed very unlikely), industry might terminate or relocate resulting in losses in value added and losses in jobs for Europe. However, this is very unlikely for this sector as NMP is presumably not of major importance for this sector.
Pharmaceutical industry	n/a	n/a	n/a	It is uncertain how pharmaceutical industry would respond to a mandatory limit value and what the compliance costs will be for these users. According to the registration dossier (see section B.9.3.2.1) current exposure levels go up to 20 mg/m^3 and thus further exposure reduction would be required. As these likely include all industrial processes that presumably are largely automated and controlled, further exposure reduction is assumed to be possible, presumably

NMP producers/ users	**Turnover affected RMO3aa – 10 mg/m³** (€ million pa)		**Lost jobs RMO3aa – 10 mg/m³** (number of workers)	**Explanation**
	Low	**High**		
				at minimal costs. If costs to achieve this are not bearable to industry (which is deemed very unlikely), industry might terminate or relocate resulting in losses in value added and losses in jobs for Europe. However, this is very unlikely for this sector as NMP is presumably not of major importance for this sector.
Functional fluids	n/a	n/a	n/a	It is uncertain how functional fluids users would respond to a mandatory limit value. Reviewing the exposure estimates presented in B.9.3.2.1 and B.9.4.2.1 shows that current exposure is at levels up to 20 mg/m³. Further reduction of this exposure is assumed to be possible via exposure reduction measures, potentially at substantial costs. However, if costs to achieve this are not bearable to industry, industry might terminate resulting in losses in value added and losses in jobs for Europe. Such potential losses could not be quantified for this sector.
Total	2,100	3,200	XXXX	As not all industries are included in the estimates, the total turnover and job figures could be seen as minimum estimates. However, as it is uncertain whether turnovers are actually affected and jobs are actually lost, it is not known whether these wider socio-economic effects actually occur. In that sense, total estimates might very well be over estimates.

Petrochemical industries, non-wire coaters and formulators, cleaners (general) and formulators, electronics and semiconductor industries, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (formulation) and laboratories and construction industries are not included in this table as these users are all assumed to comply with a limit value of 10 mg/m³.
n/a not available.

Table F.15: *Potential turnover affected and jobs lost of various actors due to RMO3b*

NMP producers/ users	**Turnover affected RMO3b – 20mg/m³** (€ million pa)		**Lost jobs RMO3b – 20mg/m³** (number of workers)	**Explanation**
	Low	**High**		
Manufacturers	0	1	0	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales (mainly to the automotive industry). However, as NMP manufacturers typically produce the alternative substances used by the automotive industry, this turnover of NMP will very likely be replaced by turnover of alternatives. No added value or job losses are expected here.
Importers/ suppliers	0	1	0	Estimate represents the turnover that could potentially be affected due to reduction in NMP sales (mainly to the automotive industry). However, as NMP importers typically also supply the alternative substances used by the automotive industry, this turnover of NMP will very likely be replaced by turnover of alternatives. No added value or job losses are expected here.
Wire coaters and formulators	0	3150	XXXX	As is explained in the section on wire coaters below, the sector might comply and achieve exposure reduction. There is a small chance that wire coaters will still terminate at a mandatory limit value of 20 mg/m³. In that case the turnover potentially affected and the lost jobs are

NMP producers/ users	Turnover affected RMO3b – 20mg/m³ (€ million pa)		Lost jobs RMO3b – 20mg/m³ (number of workers)	Explanation
	Low	High		
				comparable to RMO3a.
Total	0	3150	XXXX	The actual total estimates are assumed to be limited both in terms of turnover affected as in terms of lost jobs as the wire coating sector is assumed to be capable of meeting this limit value.

Petrochemical industries, non-wire coaters and formulators, cleaners (general) and formulators, electronics and semiconductor industries, battery industries, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis and formulation), pharmaceutical industry, laboratories, functional fluids and construction industries are not included in this table as these users are all assumed to comply with a limit value of 20 mg/m³.
n/a not available.

Compliance costs, other costs and wider socio-economic effects to wire coaters

SEAC observation

In the public consultation the European Winding Wire Group (EWWG) has submitted information on the proposed restriction indicating severe economic impacts as indicated above. On request from SEAC EWWG has further considered the impacts should RMO3aa be implemented as considered.

EWWG estimates that in RMO 3aa about 50% of existing 4,000 wire coating lines already comply with the limit of 10 mg/m³ (although there might be problems for non-continuous operations taking place up to 10 times per year for the invidual worker), implying that 2,000 lines would have to be renewed.

Within the next 6 years, which is the expected period before the restriction is implemented, imply phasing-out of non-compliant wire coating lines, further 800 lines would be replaced due to normal business cycle. Hence, 1,200 lines would have to be replaced before the normal business cycle replacement.

EWWG considers 50% of these lines to be horizontal lines, where replacement is expected to cost €150,000 € per line, and 50% to be vertical lines where replacement is expected to cost €250,000 per line[39]. In addition, EWWG estimates installation costs to be 30,000 € per line. In 2014 prices the average replacement cost per line would then be €230,000.

A restriction would therefore mean advanced investment of total €276 M. As derived in table 15a opportunity cost[40] of the advanced costs would be €61,5M in total for the first 30 years which is the expected lifetime of wire coating lines.

However, investment in new production lines is considered to imply other co-benefits of buying new machines in terms of more efficient production that would off-set the costs further (capacity, running costs, etc.). As there is no information on comparative efficiency of the new production lines, it is not possible to quantify the off-set.

[39] Price information from EWWG of comment 23 July 2014. In their first comment (Ref. 303) EWWG uses an average price of €120,000.
[40] Opportunity cost is the cost associated with opportunities that are foregone by not putting the companies resources to their highest value of use. This can be a benefit, profit of value of something that must be given up to achieve something else. As every resource can be put to alternative uses every action or decision has an associated opportunity cost. An example for a company's opportunity cost of capital is if an investment in a project would not have been done the company could have earned a return by investing in something else. The correct value would then be the return that the firm could earn on a "similar" investment.

Table 15a

Remaining lifetime of wire coating lines where advanced replacements is envisaged, years	Part of investment	Projection factor	Interest m€	Opportunity costs total, m€
1	30.67	1.04	1.2	1.2
2	30.67	1.08	2.5	3.7
3	30.67	1.12	3.8	7.6
4	30.67	1.17	5.2	12.8
5	30.67	1.22	6.6	19.4
6	30.67	1.27	8.1	27.5
7	30.67	1.32	9.7	37.2
8	30.67	1.37	11.3	48.5
9	30.67	1.42	13.0	61.5

If after 30 years, advanced reinvestment a second time should be taken into account the opportunity cost would increase by €19M ($61.5/(1.04^{30}$ =19). However this (as well as the similar costs of €10.5M after 60 years) has not been taken into account due to uncertainty of industry after so many years.

For non-continuous operations, such as factory closures and starts, heavy maintenances, long maintances, EWWG considers that it is not always possible to comply with the RAC proposal.

Therefore, EWWG proposes that it is accepted that individual workers 10 times per year may be exposed to inhalation levels above the 10 mg/m^3 for a maximum of 8 hours. However, the industry did not provide SEAC any indication what the possible exposure levels for non-continuous operations might be. They did also not consider other methods of exposure reduction, for example job rotation / shortening of exposure duration. As the industry did not specify what would be an exposure in these exempted episodes of exposure, it is not possible to assess the proposal.

According to information submitted by EWWG in the consultation on the draft opinion the total yearly production value (PV) of the wire coating sector is estimated to be €3 billion, of which €2.4 billion is directly linked to the cost of copper, which is said to be transferred directly to customers. Assuming a constant production value, the total discounted production value of following 15 years (half of expected lifetime of wire coating lines) would be €33 billion and the discounted PV not counting copper would be €6.7 billion.

The ratio between the opportunity costs (without taking co-benefits into consideration) and the discounted PV15 years is 0.2% and 0.9% respectively.

In evaluating this ratio it should be taken into consideration that the opportunity costs are attributable to the wire coating lines established before 2000 that represent about 1/3 of the total number. SEAC has no information on how much these old lines contribute to in terms of the production value, but for these lines the opportunity cost/production value ratio will be higher than the calculated 0.2% and 0.9%.

According to EWWG the sector is a low profit industry, making it difficult for individual companies to bear high costs.

This was the reason for the DS to propose a relatively long period of entry into force of 60 months after the inclusion into Annex XVII. The length of the proposed period is not supported by specific information presented in the dossier. In the public consultation on the submitted Annex XV report, the wire coating sector has stated that a period of 60 months is not sufficient and EWWG has proposed a prolonged derogation period for this sector (15 years). In the consultation of the draft opinion, EWWG has indicated again that a longer transition period is essential.

SEAC has estimated the opportunity cost for the advanced investments in case extension of the deadline for implementation of risk reduction measures should be considered.

Table 15b: Opportunity costs per year

Year where lines have to comply	2020	2021	2022	2023	2024	2025	2026	2026	2027
Opportunity Costs[1], million €	61.5	48.5	37.5	27.5	19.4	12.8	7.6	3.7	1.2

Due to the uncertainty with regard to the economic feasibility it is not possible for SEAC to conclude on whether the costs are bearable or not for the whole wire coating industry and in particular for the individual companies of concern. SEAC therefore considers that for this use it might be justified to extend the deadline for implemention of required risk reduction measures (see Table 15b above)

In the consultation on costs that AMEC performed, some specific data was retrieved on the compliance costs for wire coaters to achieve various limit values. These estimates are confidential.

Figure F.02: *Compliance costs for wire coaters at various limit values – confidential figure*

[confidential information in text has also been deleted]

Information received in the public consultation indicates that in many European wire couting companies a substantial part of the machinery is 20 years or older. Furthermore, there are conflicting signals from industry about current exposure levels. According to the registration dossier of the lead registrant, current exposure in the wire coating sector is comparable to these of general industrial coaters, and is already below 20 mg/m^3. The very limited exposure data that is available from wire coating processes show very low exposure levels of which three are below 5 mg/m^3 and one is at 15.2 mg/m^3. Note that information received from the EWWG in the public consultation indicates total costs for the wire coaters of 480 million €, which is well in the range of the above estimate for RMO3a. Note furthermore, that this estimate does not account for the statement from industry that it is not possible to achieve exposure levels of below 5 mg/m^3 for some specific processes. Whether that actually is the case, is not known by the Dossier Submitter. It however, seems reasonable to assume that further exposure reduction to below the DNEL using personal protection equipment would be possible for all processes as a last exposure reduction measure. If this would only be required for some very specific processes, it might also be practically feasible to achieve this. Another substantial factor of uncertainty can be found within the timeframe in which the RMO needs to be implemented.

It could anyhow be the case that the compliance costs for wire coaters are not bearable to industry and that industry would terminate in case of a mandatory limit value. Obviously, this is more likely to occur at a limit value of 5 mg/m^3 than of 20 mg/m^3. The compliance costs in case of RMO3a could be very substantial for the companies that need to replace the older machinery. Industry states to currently work at very small margins and might therefore not be capable of dealing with further increase in costs. We are talking about 10-20 SMEs companies that typically have 100s of large (10-15 meters long) enameling machines in place. According to industry, the enameling machines have long life times (see section 3.6.3 of the market analysis in Appendix A). Information received in the public consultation indicates a typical lifetime of the wire coating machinery of 20-30 years, this appears to be longer than what had been previously assumed before the public consultation. Premature depreciation would besides the high replacement costs result in capital destruction. The compliance costs as estimated for RMO3a are assumed not to be economically feasible to industry. However, as the correctness of the quantitative estimate is questioned, the economic feasibility of

RMO3a to the wire coating industry can also be questioned and no hard conclusion could be drawn on this issue. The key to reduction of compliance costs for the wire coating sector can be found in an extended timing of the restriction so that the replacement of machinery can be more in line with natural replacement times. The indication received in the public consultation that typical life time of the wire coating machinery is 20-30 years, might ask for an extended timing of the measure for this specific sector. In accordance with the logic taken in the original dossier, it is assumed that the current stock of machinery within Europe is already half its lifetime. The based upon that assumption, Dossier Submitter suggests that with an extended implementation period of 10-15 years for the wire coating sector, the replacement of older machinery for the wire coating industry will be more in line with the natural replacement times compared to the industry estimate of compliance costs given in this section. The costs should therefore be seen as belonging to the normal investment cycle (business investments that are required anyhow, regardless of the restriction). The majority of the costs indicated by industry should in that case not be seen as compliance costs but as regular investments. An implementation time of 10-15 years in that sense should be sufficient to replace the majority of the machine stock within its natural replacement time. However, it is not known what fraction of the costs should be treated as regular investments and what as compliance costs. It is therefore not possible to estimate compliance costs to wire coaters of this scenario. However, it could be assumed that the majority of the costs are regular investments and only a minor fraction of the costs represents compliance costs in case of the extended timing. According to a comment received in the public consultation, at limit values of 5-10 mg/m^3 and an implementation period of 5 years, 1/5th or 15-25% of the estimated compliance costs would be regular investments, the rest being compliance costs. The reasoning behind this is that lifetime of the machinery is 5 times longer than the implementation period. Following this logic, compliance costs to the wire coating sector would significantly be reduced at longer implementation periods of 10-15 years. The argumentation on timing given above of course involves major uncertainties and the underpinning of the extended timing is still very narrow. However, based upon the information that is available at the moment, this is the best estimate that can be made by the Dossier Submitter.

Note that this proposed change in timing for the wire coating sector compared to the original dossier, has not been changed consistently troughout the Background Document.

Overview total socio-economic effects RMO3 a and b

In the section above socio-economic impacts of RMO3 a, aa and b have been discussed in terms of compliance costs, turnover potentially affected and potential losses of jobs. As the majority of (or all) industries are expected to be capable of meeting the limit values of respectively 5, 10 or 20 mg/m^3 the majority of the socio-economic effects are expected in terms of compliance costs.

The overall quantified compliance costs for a mandatory DNEL of 5 mg/m^3 are in the range of XXXX including the wire coating industry and >40-50 million € over 15 years excluding the wire coating industry. These total costs are assumed to be an underestimate as for some of the users no quantitative estimate of compliance costs is available. The costs estimates that are available come from industry and some have been crosschecked with publicly available data. These costs estimates might be somewhat overestimated as there is some incentive for industry to overestimate costs. Furthermore, the total cost estimate might be overestimated, as it does not account for the implementation period of the restriction of 5 years. The underestimation of the total cost figure may therefore be partly or fully offset by the overestimation of the individual cost figures. This is assumed to be especially the case for the total cost estimate including wire coaters. The quantitative costs estimate should be seen as indicative for the order of magnitude rather than as an actual figure.

For some of the use categories it is certain that limit values can be met, for others it is not certain but likely. In terms of quantities of NMP used: under RMO3a for about 50%[41] of the NMP used, it is not fully certain whether the limit value of 5 mg/m^3 is technically and economically feasible. Note however, that for some of the uses for which it is uncertain whether compliance costs can be met (medical images, foodcontact material/bakeware, optical industries, battery industries and functional fluids) no information on the quantities of NMP used are available. As a consequence these uses are not included in the 50% estimate and the actual percentage might thus be somewhat higher. Of this ~50% estimate, especially for the wire coating sector it is questionable whether such high costs will actually occur and whether compliance costs are technically and economically feasible for the industry

[41] *Estimate consists of wire coating industries, agricultural chemical synthesis and pharmaceutical industries: XXXX*

sector. For these users potentially wider socio-economic effects might occur. However, the Dossier Submitter assumes that compliance costs for wire coaters (and other industries) at an implementation time of 5 years (as proposed) are lower than what is estimated by industry as part of the costs can be considered as regular investment costs rather than compliance costs. The compliance costs to wire coaters could therefore be bearable. This would lead to compliance costs of RMO3a that are lower than the figures presented above including wire coaters (XXXX), however the figures excluding compliance costs for wire coaters presented (>40-50 million € over 15 years) are assumed to be too low as some compliance costs for wire coaters could still be expected. However, no quantitative estimate of compliance costs to wire coaters for this scenario could be given based upon the available information. **The Dossier Submitter however, assumes that other costs (relocation, premature depreciation) and wider socio-economic effects to the wire coating sector are avoided in case of a timing of 5 years and that no wider socio-economic effects will occur as a result of this RMO3a (and b)**. It should however be realized that this is a rather delicate issue, as, if the wire coating industry is to terminate in case of a mandatory limit value of 5 mg/m^3, wider socio-economic impacts might be substantial. Especially as effects are expected to be passed on through the supply chain potentially affecting a large number of magnetic wire users and the quality of wire coating products might be affected.

When it comes to RMO3b, all industries are thought to be able to reach this limit at acceptable costs, only for wire-coaters there are still some questions posed by industry.

Compliance costs of the added RMO3aa are calculated to be approximately €80- 90 million. Similar uncertainties and considerations as presented in the conclusive section for RMO3a apply to the RMO3aa scenario.

F.4.4. RMO4: Authorisation

Compliance costs and administrative costs

As explained in part G, industries responses in case of an authorisation are uncertain and compliance costs of an authorisation are therefore difficult to estimate. The uncertainties around responses are high as the responses of individual actors for example depend on how other actors in the supply chain of NMP respond and are influenced by the actual timing of the review period (which is not known at the moment of application). However, in general one could state that the majority of the industrial users for which no alternatives are available at reasonable costs, are likely to follow the adequate control route and – if granted – costs might be in line with the costs of RMO3a (assuming a similar DNEL value). However, the costs to industry in case of an authorisation can be divided in different categories and costs for exposure reduction might not be the only costs made. There will for example also be direct costs in terms of e.g. the application fee and for hiring consultancies to prepare an application. These costs are unique for the authorisation process (and will as such not occur in case of a restriction). Besides, there might be 'intangible' costs to industry e.g. due to business risks and reputation losses that could occur in case of authorisation. The fact that industry is not familiar with the authorisation yet, makes that uncertainties for industry surrounding the authorisation process are substantial (whether to expect approval of an authorisation? What review period to expect? Etc.). Due to these types of costs and uncertainties, industries might decide not to apply for authorisation (but rather stop activities: terminate or relocate), whereas in case of RMO3a they would try to comply with the DNEL. Whether such a difference between RMO3a and RMO4 would occur in practice is not known.

From industry consultation, some information was received on industries responses and potential compliance costs. The majority of the industries assume that total economic effects to industry (including compliance costs, administrative costs, costs of relocation and premature depreciaton, and wider socio-economic effects) in case of an authorisation lay in between the costs of a total ban (RMO1) and a mandatory DNEL (RMO3a).
Compliance costs will only occur in case industry decides to apply for authorisation. Table F.12 below gives an overview of the compliance costs in case of an authorisation. The total costs are expected in the range of XXXX million € over 15 years. However, note that this is assumed to be an underestimate, as for many of the users of NMP no quantitative estimate of compliance costs is available. Note that this underestimate maybe net out with an overestimation of the available cost

estimates provided by industry. As the cost estimates are given at substantial uncertainty, these should be seen as indicative ranges rather than actual estimates.

Note that RAC concluded on a DNEL of 10 mg/m^3 instead of the originally proposed DNEL of 5 mg/m^3 of the Dossier Submitter. The limit value that needs to be achieved by industry to achieve adequal control thus changed and the required effort from industry to comply with this RMO might be more limited than what is indicated below. Total economic effects to industry (including compliance costs, administrative costs, costs of relocation and premature depreciaton, and wider socio-economic effects) in case of an authorisation will probably lay in between the costs of a total ban (RMO1) and a limit value of 10 mg/m^3 (RMO3aa presented in the previous section).

Table F.16: *Compliance costs to various actors due to RMO4, Authorisation*

NMP producers/ users	**RMO4 Authorisation** 15y PV (€ million)		**Explanation**
	Low	**High**	
Manufacturers	XXXX	XXXX	Estimates from one of the three EU manufacturers are available but confidential. These costs have been scaled up to all EU manufacturers This cost estimate has not been crosschecked and the quantitative estimate should be seen as very uncertain. Industry might also decide to relocate instead of applying for authorisation.
Importers/ suppliers	n/a	n/a	One importer expects to apply for authorisation and therefore some compliance costs can be expected. However, it is not known what these costs are and what percentage of the use of NMP would remain in case of an authorisation.
Petrochemical industries	n/a	n/a	It is uncertain what would happen in case of an authorisation and therefore also uncertain whether there will be compliance costs for the petrochemical industry.
Non-wire coaters and coating formulators	Minimal	Minimal	This use represents mainly professional coaters and industrial coating formulators. Wire coaters, car coaters and film coaters are excluded from this category as these are presented as separate users in this table. For the coating industry, the effect of an authorisation is assumed to be similar to the situation of a total ban (RMO1) as alternatives are readily available and shifting to alternatives is assumed to be cheaper than applying for authorisation. No quantitative cost estimates are available for these uses. However, for many of the coating users, costs are assumed to be limited as the majority of industries have already shifted to alternatives.
Coaters - automotive	20	30	As alternatives are readily available, total costs to EU automotive industry are estimated for reformulation of the car coating system. One-off costs are spread out over 2 years as industry states to take two years to reformulate the system. This cost estimate comes from industry and has been cross-checked with general information on reformulation costs. The crosscheck is roughly in line with the figures presented here, assuming that a total of 100 reformulations are required. It is assumed that 50% of costs would be for car manufacturers and 50% for auto repair shops.
Coaters– medical images, foodcontact material/ bakeware	n/a	n/a	It is uncertain how industry will respond to an authorisation, however, there are indications (part C) that replacement of NMP is problematic. So industry would potentially apply for authorisation following the adequate control route, resulting in compliance costs.
Wire coaters and wire coating formulators	-	-	According to industry, the uncertainties around authorisation are too high to continue production in case of an authorisation. Industry is expected to rather shut down activities in Europe than apply for authorisation. SEAC notes that according to EWWG the import of coated wires is less than 0.5 % of the EU market. Furthermore, SEAC considers the uncertainty related to authorization to be a communication issue and a question when setting the length of the review period. Some formulators mention confidential information on possibilities for reformulation. For this sector potentially wider socio-economic effects

NMP producers/ users	**RMO4 Authorisation** 15y PV (€ million)		**Explanation**
	Low	**High**	
			would occur (see section below). Information received in the public consultation 2013/2014 suggests that wider socio-ecoomic effects in case the wire coating sector stops activity in Europe, will be much higher as also actors down the supply chain will be seriously affected and might stop activities in Europe as well (motor manufacturers, manufacturers of generators, transformers, relays, automotive industry). No quantitative estimates of such potential down stream effects are available.
Cleaners – e.g. optical	n/a	n/a	It is uncertain how the cleaning industry will respond to an authorisation. For many cleaning uses alternatives are assumed to be available, and users have already replaced NMP. For the optical industry signals have been received from industry (personal communication, AMEC questionnaire) that replacement of NMP is problematic, so the optical industry might apply for authorisation using the adequate control route. The compliance costs for this sector are not known.
Electronic and semi-conductor industries	n/a	n/a	In is uncertain how industry would respond to authorisation. Potential costs of applying for authorisation following the adequate control route for this industrial sector.
Battery industries	n/a	n/a	In is uncertain how industry would respond to authorisation. Potential costs of applying for authorisation following the adequate control route for this industrial sector.
Membrane manufacturers	n/a	n/a	Signals from industries how to respond in case of authorisation are not uniform. One actor expects to apply, another expects to relocate (personal communication, AMEC questionnaire). Potentially there will be some compliance costs for this sector, however, no quantitative estimate of these costs is available.
High performance polymer producers	-	-	Industry does not expect to survive in Europe on the long term in case of authorisation. According to industry, the uncertainties around authorisation are too extensive to justify further investments. Furthermore, alternatives are not available at this moment, but even if they would be found in the future, costs of rebuilding the facility to shift to a potential alternative are expected to be very high (~200-300 million€) such that relocation would be the preferred option also in that situation (personal communication, AMEC questionnaire). As such, no compliance costs are expected for this sector. Wider socio-economic effects might occur to this sector. An alternative scenario would be that the industry would apply for an authorisation following the adequate control route resulting in compliance costs (unknown). However, such a scenario is not supported by (part of the) industry.
Agricultural chemical industry (formulation, synthesis)	n/a	n/a	In formulation of agrochemicals the use of NMP is already phased out, so no effect of authorisation is expected for this use. It is uncertain how the agrochemical synthesis would respond to authorisation. Potentially actors would apply for authorisation following the adequate control route resulting in compliance costs. What these compliance costs are, is not known.
Pharmaceutical industry	0.1	0.4	Information has been received from the pharmaceutical industry regarding compliance costs for authorisation of DMAC (EU Pharmaceutical Industry's Chemical Legislative Working Group, no date). Assuming that compliance costs for the authorisation of DMAC is comparable to that of NMP, the costs given for DMAC have been scaled (based on quantities DMAC/NMP used within the pharmaceutical industry). The cost estimate consists of costs for R&D for alternate process, validation of manufacturing process, regulatory requirements (fee and development of dossier), quality assurance and

NMP producers/ users	**RMO4 Authorisation** 15y PV (€ million)		**Explanation**
	Low	**High**	
			potential additional development. The costs presented are all assumed to be one-off costs that are made in one year[42]. Note that the pharmaceutical industry for DMAC mentions that due to the costs and uncertainties of authorisation, industry might rather relocate production outside Europe than applying for authorisation. As quantities of NMP used in the pharmaceutical industry are substantially lower than DMAC, this is considered less likely to happen in case of authorisation of NMP. The wider socio-economic effects in case of authorisation of NMP are therefore assumed to be limited.
Laboratories	n/a	n/a	It is uncertain how laboratories would respond to authorisation. Potentially (non-R&D) actors would apply for authorisation resulting in compliance costs.
Functional fluids	n/a	n/a	It is uncertain how users of functional fluids would respond to authorisation. Potentially actors would apply for authorisation resulting in compliance costs.
Construction industry	0	0	NMP seems not to be used anymore in the construction industry, so no (compliance) costs are expected for this sector.
Total	XXXX	XXXX	As for many users no cost estimate is available, this total figure is expected to give a minimum estimate of the compliance costs in case of RMO4. Note however, that the available costs estimates might be overestimates. Because of that, the underestimation of the total figure might be partly offset.

n/a not available

Costs of relocation and premature depreciation

Some industries indicate that they would potentially relocate in case of an authorisation. The users that potentially relocate activities to outside Europe are manufacturers, petrochemical industry, specialty coaters (films/medical images), foodcontact material/bakeware or cleaners (optical industry), electronics and semi-conductor industries, battery industries, membrane manufacturers, high performance polymer producers, agricultural chemical industry (synthesis), pharmaceutical industry, laboratories and users of functional fluids. No quantitative estimate of potential relocation and premature depreciation costs are available, however, the number of users that potentially would relocate indicate that relocation costs might be substantial in this scenario.

Wider socio-economic effects

In case industry decides not to go for authorisation nor shift to alternatives, wider socio-economic effects might be either in terms of losses in jobs and/or value added lost. Potential losses in jobs and turnover potentially affected (as an estimate of the value added lost is not available) in case of authorisation are described in the sections below.

Turnover potentially affected

When industry terminates or reduces production (manufacturers, suppliers) in case of an authorisation, turnover of industries are potentially affected, potentially resulting in losses in added value for the European economy. Losses in added value might occur for the same list of industries given under relocation costs depending on their actual response to an authorisation. No quantitative estimate of the potential losses in value added or turnover potentially affected is available for the majority of the uses. Only for high performance polymer production a quantitative estimate has been provided by industry (order or magnitude of XXXX, personal communication, AMEC questionnaire). As mentioned earlier, the order of magnitude of turnover potentially affected in case of an authorisation

[42] *Note that periods of <12-36 months are mentioned for the various cost elements, however, for the sake of simplicity, all costs assumed to be made in the first year and are consequently not been discounted.*

can be expected in between the turnover potentially affected in case of RMO 1 and RMO3a. Note that turnover potentially affected is not the same as added value lost, as turnover includes production costs that need to be subtracted from the turnover estimate.

Potential lost jobs

As the uncertainties around how industries will respond in case of an authorisation are large (apply for authorisation or relocate/terminate) it was not possible to provide a reliable estimate of the potential jobs lost. However, it can be concluded that the extent to which this is expected to happen will be between the estimate of RMO1 and RMO3a.

Overview of the total socio-economic effects of RMO4

As said, the total socio-economic effects of RMO4 depend on the industry response to authorisation. As there is little information available on the expected industry responses, it is not possible to give an estimate of the total socio-economic effects of this RMO. However, what is known is that the total socio-economic effect is expected to lie in between the effects of RMO1 and RMO3a**.**

F.5 Uncertainties in the socio-economic analysis

The socio-economic analysis (as presented in the preceding sections of part F) of this dossier is surrounded by various uncertainties. Uncertainties exist for example in the assumptions made in the analysis and the input data used in the analysis. Uncertainties occur due to the lack of data, errors in models, choices and assumptions made, ignorance and variability. To get a feeling of the reliability of the end results, the various assumptions and decisions made during the analysis and an overview of the uncertainties within the various parameters used in the analysis are discussed in the sections below.

F.5.1 Main assumptions used and decisions made during the analysis

Various assumptions have been made in the preparation of the socio-economic analysis of this document. As the assumptions and choices made have an effect on the results of the analysis, it is important to be well aware of these assumptions and choices. Below an overview and explanation is given of the major choices and assumptions made in the analysis:

- Baseline: the baseline presented in part E of the document (that is further explained in 1.2.3 and 1.2.4 of the market analysis in Appendix A) is based upon information provided by major suppliers of NMP on the current market trends. The presented trends have been further verified by signals from various actors in the supply chain of NMP via a consultation round (personal communication, AMEC questionnaire). However, as no extensive market analysis could be performed for this document, the presented trends incorporate significant uncertainties especially when looking into the medium to long term future. The socio-economic analysis started from the current situation and did not explicitly take into account the trends presented in the baseline. This approach was taken because the available data on costs did not allow to account for the trends accurately, as it is not clear what the starting point is of the data provided by industry (current situation or baseline including trends). Furthermore, the available data on trends is confidential, meaning that large parts of the SEA would turn confidential if these would have been included in the analysis. Only for those uses where it was clearly indicated by industry that the uses have been phased out already or will be phased out in the near future, these trends have been incorporated in the SEA. Potential effects of the indicated trends in the baseline both on the benefit as on the cost estimate is discussed in the qualitative uncertainty analysis in the section below.
  Note that the potential effects of the current reclassification proposal of NMP - that has been prepared by the Netherlands simultaneously with this restriction proposal - have not been incorporated in the baseline. This is acceptable as the consequences of this reclassification proposal are expected for consumer uses of NMP that are not included in the scope of this restriction proposal. There, however, might be some effects for professionals in case the labeling requirement for professionals becomes stricter due to the reclassification (labeling obligation might shift from >5% NMP to >0.3% NMP). This could reveal if there are still some professional uses left below 5% NMP where we are currently not aware of as these are not

labeled at this moment. In that way, the potential effects for professional cleaners (both in terms of costs and health benefits) might be larger than described in the SEA.

- RMOs: three different restriction RMOs have been defined in this document for comparison. Besides the three restriction scenarios, also the authorisation route is included in the assessment as an alternative RMO, as this is seen as a possible route for risk reduction. The RMOs take different approaches in addressing the risks and differ e.g. when it comes to the scope or approach of the restriction. The RMOs do not deviate in the timing of the restriction, as with the available data it is not possible to accurately estimate the effects of changes in timing on e.g. the economic effects of the RMOs. However, as timing might be an important parameter to come to a balance of positive and negative effects of a restriction, potential effects of the timing of the restriction are discussed in section F.3 when it comes to costs of the RMOs. The proposed timing of the restriction of 60 months is assumed to be sufficiently long to reduce compliance costs to acceptable levels e.g. for the wire coating sector. The effects of timing of the restriction have not been reviewed in terms of human health effects as no quantitative analysis of health effects has been performed. From a human health risk reduction potential, it would be best to start the RMO as soon as possible, as risk reduction capacity is then the largest. However, it might be that industry chooses for a hazardous alternative or for shutting down activities in Europe in case not enough time is given to shift to a safer alternative. In that sense a longer time period might be more appropriate in terms of risk reduction achieved or expected wider socio-economic effects.
- Geographical scale: as explained earlier, the SEA has been performed taking the European Union as geographical boundary. As such, the economic impacts of a restriction are only calculated for the EU industry. This is acceptable as the majority of the NMP using industry outside the EU is expected not to experience changes due to the restriction as for most uses NMP is not found in the final products. Note that there are some uses for which NMP containing products or pure NMP are currently imported from outside Europe (e.g. coatings). The potential economic costs to these actors have not been included in the analysis. Note that there might also be some (positive) economic effects (and potential human health risk increases) to industries outside Europe in case production activities are relocated or taken over by non-European industries as a consequence of the shutdown of activities in Europe. These potential costs and benefits are not accounted for in this analysis, although these are mentioned at some points if the Dossier Submitter assumed it to be relevant.
- The market and cost analysis in the Appendices A and B prepared by AMEC serve as the basis for the socio-economic analysis. In the market and cost analysis, a selection was made of 4 use categories of NMP (cleaning, non-wire coating, wire coating and membranes) plus the manufacturing and supply of NMP for which a detailed analysis was prepared, as it was not possible to study all use categories in detail with available resources. The use categories were selected to capture a representative sample of the actual existing use categories. However, the remaining use categories vary too much to be able to conclude on the consequences of the RMOs for all use categories based upon what is seen in the selected use categories. Making a selection as such incorporates major uncertainties in the analysis as part of the market of NMP remains unknown and the potential socio-economic effects to these industry sections is very uncertain. In part F attention is given to all use categories, to be very clear on what information is available and what information is missing. The uncertainties incorporated due to the selection of use categories will be further discussed in section F.5.2 below. A full justification of this selection is given in section 1.3 of the market analysis. Furthermore, note that the RMO2 described in Appendix B differs substantially from the RMO2 defined in this document. RMO2 in Appendix B involves a partial ban for only a very limited number of professional uses (non-wire coatings and cleaners), leaving all other (mainly industrial) uses out of the restriction, where RMO2 in the document represents a ban with derogations under specific (exposure reducing) conditions. Consequently, the cost indication for RMO2 in Appendix B does not represent the costs of RMO2 described in this document. It is assumed that the costs and wider economic effects of the RMO2 of this document are more in line with the costs and wider economic effects of RMO3a. This assumption was taken as the intention and the expected consequences of the two RMOs are assumed to be comparable. As this assumption might not be fully correct, this assumption is further discussed in the section on uncertainties below.
- Economic impacts: the figures on compliance costs (and relocation costs) are presented as 15 year Present Value. The period of 15 year was chosen as this is the longest adaptation time across industries and RMOs claimed by industry. Note that this does not mean that all one-off costs are spread out over this 15 year period. One-off costs have been distributed equally over the years industry indicated to take making these costs. This time period varies per use category and RMO between 1 and 15 years. Annual costs have been added up over a period of

15 years. Both one-off costs as annual costs have been discounted at a level of 4%. The turnovers potentially affected are expressed as yearly figures and do not give an indication of cost to industry or society as the turnover figures include non-factor production costs[43] that need to be subtracted from the turnover figures to obtain an indication of the added value of an industry. The turnover figures are however presented to give an idea of the size of the sector/industry that might potentially be affected. The same counts for the estimate of the number of workers that potentially lose jobs.

- Human health impact assessment: as described in section F.1, no quantitative human health impact assessment has been prepared for this document. The choice not to do this was made as the available data was found insufficient to quantify the potential effects. The main reason was that no quantitative relationship could be derived between human health effects and exposure. Quantitative impacts would be so uncertain that the numbers would not have an actual meaning. Instead of going for quantitative impacts, an (extensive) qualitative description was given next to some alternative quantitative proxies of the potential health effects (risk reduction potential, population of workers for which the risk is reduced) to provide insight in the magnitude of the potential effects.

F.5.2 Overview of the uncertainties

The table below gives an overview of the main parameters of the SEA and the uncertainties surrounded with these parameters. This overview was prepared for scrutiny of the SEA and to be able to validate the conclusions based upon this analysis.

Table F.17: *Overview of the main parameters and potential uncertainties in the SEA*

Elements of the SEA	Explanation of potential uncertainties
Baseline trend	For some of the uses of NMP there are indications of a growing or a declining market. Economic effects: In the quantitative estimations of (wider) economic effects it is not clear for all use categories and RMOs whether the trends are incorporated in the cost figures provided by industries. For the majority of the figures it is assumed that the effects of trends are not incorporated and the figures might thus be over- or underestimated. For the automotive industry costs might be overestimated as there is a downward trend for non-wire coatings. However, the trend is defined for the non-wire coating category as a whole and it is not known whether it applies to the automotive sector specifically. From personal communication with the coating industry (RIVM questionnaire) it seems that the strong decrease in NMP use does not occur in the automotive industry (however, industry did mention that compliance costs presented might be overestimated). For the wire coating industry a growing trend is estimated by NMP suppliers. However, this trend is contradicted by some of the wire coaters. They state that the use of NMP in wire coatings is stable (personal communication, RIVM draft dossier). The economic effects for this sector thus seem not to be overestimated. For the membrane manufacturers the economic effects might be under estimated as there is an increase in the use of NMP for this application. The overall use of NMP seems to be growing and the economic effects for manufacturers and suppliers might thus be under estimated. (Note that the global share of Europe in NMP production decreased significantly (see section B.2.1), however, this does not necessarily mean that the total amount used or produced in the EU did reduce as well). Overall, the effects will be in the order of magnitude of XXXX of the current estimate and this will thus not substantially change the general picture of the analysis. For the qualitatively described economic effects, trend figures have been incorporated in the analysis. Benefits: For the benefit part the effect of the trends are expected to be minimal as human health effects have not been quantified. The analysis of risk reduction will not change because of these trends. Only the figures on number of workers potentially exposed could change for some of the use categories. These effects are comparable to what is described in red for the costs and will be in the range of XXXX.

[43] *Non-factor costs are all production costs except those that represent rewards for the production factors labour (wages) and capital (profits). Non-factor costs include, for instance, the cost of raw materials and other inputs purchased by the producer.*

Elements of the SEA	Explanation of potential uncertainties
Selection of use categories	As mentioned earlier, market and cost figures have only been collected for a limited number of use categories. Because of this, part of the picture of the economic effects and wider economic effects is missing or only partly given based on personal communication with industry. Because of this, most of the total quantitative estimates of compliance costs, relocation costs, turnover potentially affected and jobs potentially lost/workers for whom exposure reduction might be achieved are underestimated. Note that part of this underestimation might be offset by an overestimation of the available quantitative estimates (e.g. on costs).
Availability of alternatives	Part C presents an extensive overview to the potential substance (and technical) alternatives of NMP in the various applications. This review largely depends on information found in literature or internet. Sometimes it is however difficult (or impossible) to judge whether alternatives are technically and economically feasible for very specific use applications. Especially in cases where signals from literature differ from the signals received from industry, it was not possible for the Dossier Submitter to take a strong position on the actual availability of alternatives. When reviewing RMO2 and RMO3, exposure reduction measures can be seen as alternatives. A brief evaluation of the potential exposure reduction of various potential measures and costs for exposure reduction is given in section B.10.1. , B.10.2 and in sections F.4.2, F.4.3 and F.6.2. However, there remains quite some uncertainty both when it comes to the technical feasibility as the economic feasibility of exposure reduction of RMO2 and 3 for the various uses of NMP e.g. as current situations in sectors are not known in detail, as information on costs and financial situations of sectors is limited etc. The analysis should be interpreted in light of these uncertainties and should be seen as the Dossier Submitter's best attempt to evaluate the technical and economically feasibility of these (sometimes undefined) measures based upon the limited available information. The availability of alternatives influences the industry responses to the various RMOs. The uncertainties around the actual availability of alternatives thus also incorporate uncertainties in the industries responses to the various RMOs that are discussed below.
Industries responses to the RMOs	Whether there will be economic costs or wider socio-economic effects, depends on industries responses to the various RMOs. Information on how industry will respond to the different RMOs has been provided by various industry actors in a consultation round (AMEC questionnaire). These industry estimates have been evaluated by AMEC and the Dossier Submitter e.g. by comparing responses of the different industries, comparing responses with the information on the availability of alternatives and current exposure levels. Nevertheless, it is difficult to get an objective picture on actual responses upfront and there is a chance that responses as they are included in this analysis are not in line with what will occur in practice in case the RMO is implemented. It could thus be that in this SEA compliance costs are estimated as industry is expected to adapt to a certain scenario, however, that in practice industry will relocate or terminate resulting in wider socio-economic effects that have not been indicated in the SEA (or vice versa). The effect of such errors in the estimates of industries responses might be substantial. Furthermore, and as stated earlier, RMO2 as presented in this document has not been reviewed in the cost analysis presented in Appendix B as RMO2 was changed substantially after the market and cost analysis were finalized. It was assumed in this document that industries responses to the 'new' RMO2 are comparable to RMO3a. However, this assumption might not hold completely as RMO2 might be less strict in terms of risk reduction compared to RMO3a and might for example be stricter when it comes to administrative requirements. Where possible/appropriate, this is explained qualitatively in the text e.g. on economic effects, however, it has not been reflected upon in the quantitative estimates of the economic effects. The quantitative estimates of e.g. compliance costs of RMO2 might thus be somewhat over estimated.
Risk reduction	An RCR contains of an exposure estimate and a DNEL. The uncertainties of a DNEL are contained in the methodology (use of assessment factors). The exposure component in the RCRs contains uncertainties. The exposure estimates used are obtained from the registration dossier. The lead registrant has provided exposure estimates for all uses, including the downstream ones, which need to result in an RCR below 1 taking into account the DNEL derived by the lead registrant. It is possible that those estimates obtained using an exposure tool are higher than the actual exposure values, as illustrated by the available measurements for manufacturers. It is difficult to assess if factors used like use duration or LEV, are stretched to a maximum level (resulting in a RCR<1, while the actual situation is differently. On the other hand, the effectiveness of RMMs might be interpreted with a higher level than they have in the real workplace situation, resulting in underestimates. Furthermore, exposure scenarios for downstream uses might be interpreted differently, as for example shown for the wire coaters. Assumptions on the effectiveness of the different RMOs are made, these seem to be logic.

Elements of the SEA	Explanation of potential uncertainties
Worker estimates	The market analysis presented in the confidential Appendix A provides various estimates of the number of workers potentially exposed to NMP. The upper bound figures are based upon Eurostat data for NACE code use categories that might involve NMP. These figures are not very NMP specific and are therefore not further used in the SEA. The actual estimates provided have been derived in two different ways: 1. The estimate is based upon industry specific data that has been scaled up to the full use sector using assumptions on the size of the sector; 2. The estimate is based upon Eurostat data that has been combined with industry specific data to come to an actual estimate. Although the assumptions used to derive the actual estimate have some basis in available market data, the actual estimates given are still very uncertain. The actual worker figures have been further specified in reproductive female workers and pregnant workers using general EU statistics. There are substantial uncertainties to these figures as they are non-NMP specific and there might be several factors due to which the situation for NMP could differ from general EU statistics (for example effects of the existing pregnant worker legislation). The estimates of reproductive and pregnant workers only serve as an illustration of the potential order of magnitude of the workers that face developmental effects. Information received in the public consultation also suggests that the indication of the number of female and pregnant workers included in this document is an over estimate, and might in practice be close to zero at least for the wire coating sector. Nevertheless, implementing the DNEL values proposed by RAC may provide additional protection in relation to other health risks identified in section B, such as reduced body weight (gain), reduced food consumption, general loss of wellbeing, effects on organs, eye, skin, respiratory irritation for all workers. The actual estimate figures of all workers are used to estimate the number of workers for whom risk reduction is achieved. Note however, that the figures estimate the workers *potentially* exposed and as there is not much information available on the number of workers actually working with NMP, the estimate rather represents the number of workers that are *related* to NMP. As this might also include people that will in practice not come into contact with NMP, some of the figures presented might be overestimates. As such, however, the figures could also be used to estimate potential losses in jobs if industries terminate or relocate due to a restriction. It should be noted that this assumption is not necessarily correct as the number of people losing jobs could be higher (in case the full industry ceases) or lower (in case workers are replaced to other parts of the business that do survive). For two industries, personal communication (AMEC questionnaire) with industry provided an additional estimate of the potential lost jobs in case production is ceased. All worker estimates should be seen as indicative rather than absolute numbers. Note that the total figures given, are assumed to present an under estimate as for many of the use categories no quantitative estimate of the number of workers is available.
Compliance cost estimate	The compliance costs estimates were provided by various industry actors. The underpinning of the estimates provided by industry is very limited and that makes it difficult to judge whether the figures presented are appropriate or reasonable. Industries estimates have been crosschecked with publicly available data whenever possible. The data availability for cross checks, however, is very limited and the cross checks were performed based on very general data on costs for exposure reduction measures and reformulation costs. To apply these general data to the specific NMP using industries, assumptions were made e.g. on the type and quantity of exposure reduction measures and the amount and complexity of reformulations required. As information to base such assumptions upon is very limited, wide ranges have been taken to see in what range the estimates provided by industry were found and to evaluate whether these ranges are found reasonable. The cross check in that sense serves more as a tool to get some idea whether the industry estimates are in a reasonable range rather than coming up with an alternative estimate. For some compliance cost estimates it was not possible to perform a crosscheck as not enough information is available to do so. The compliance cost figures are thus surrounded with substantial uncertainties and should be seen as indicative ranges rather than actual numbers. To give an example of the uncertainties surrounded with the cost estimates given, it is good to mention that substantial costs have been estimated by the wire coating industry to adapt to limit values in the range of about 20-40 mg/m^3, whereas the exposure scenarios presented in the updated version of the registration dossier provided by the lead registrant present values for the wire coating industry that are already below 20 mg/m^3 in the current situation. Here the information provided by the lead registrant is not in line with the information on costs coming from downstream users in the consultation round and it is unclear whether costs have been overestimated or exposure levels have been underestimated. Compliance costs are expressed as 15 year Present Value discounted at 4%. One-off costs are spread out equally over the adaptation time indicated by industry (varying between actors and RMOs between 1 and 15 year). The effects of the chosen discount rate and the distribution of costs over the years are minimal compared to the uncertainties surrounding the cost figures themselves and therefore no quantitative sensitivity analysis was performed

Elements of the SEA	Explanation of potential uncertainties
	on these assumptions. Note that as for many use categories no quantitative compliance cost estimate is available, the total compliance cost figures are an under estimate of the actual total compliance costs.
Relocation costs estimate	Data on relocation costs were only provided by one industrial actor for one RMO (confidential data). This estimate could not be cross checked and the given estimate should be seen as highly uncertain. The estimate should thus rather be seen as an indicative value on the potential magnitude of these costs rather than as an actual estimate. There might be more industries that in case of an RMO decide to relocate and the figures given might thus be under estimates of the actual relocation costs.
Turnover potentially affected	Estimates on the turnovers potentially affected have been provided by various industries for those RMOs where industries indicate to relocate or terminate. For some industries the turnovers potentially affected are estimated based upon publicly available data on current turnovers. When public data on turnover is available besides the industry estimate, the figures have been compared to see whether these are in the same range. As turnovers potentially affected could not be given for all of the industry sectors that potentially terminate, the total figures of the turnovers potentially affected presented should be seen as under estimates. The aim of presenting the turnover potentially affected is to get an idea of the size of the industry sectors that will potentially relocate or terminate and thereby getting an idea of the potential magnitude of the wider socio-economic effects. However, as mentioned earlier, note that the turnover potentially affected does not represent the potential losses in added value for Europe in case industries terminate or relocate. To obtain an estimate of such added values lost, data on production costs of the inputs used to obtain the turnover (non-factor costs) need to be subtracted from the turnover figures. Unfortunately, it was not possible to come to an estimate of added values potentially lost due to the lack of data on production costs. Note that the estimates whether industry would relocate/terminate or adapt to the legislation are provided by industry as well and in the actual situation of an RMO industry might in fact try to comply with the legislation in case of a restriction contradicting with the termination/relocation indicated here (resulting in compliance costs instead of wider socio-economic effects, see point earlier made).
Total production value	For some of the use categories information on the total production value was provided in the market analysis in Appendix A as an indication of the importance of the sectors to the European economy. Upper bound figures are given for some of the use categories based upon Eurostat data for NACE code use categories that might involve NMP. These figures are not very NMP specific and are not further used in the SEA. Actual estimates are also provided using NMP specific data. These actual estimates are sometimes based upon the total production value from Eurostat and sometimes on actual sales/turnover figures. Total production value provided by Eurostat is defined as: '*Production value measures the amount actually produced by the unit, based on sales, including changes in stocks and the resale of goods and services. The production value is defined as turnover, plus or minus the changes in stocks of finished products, work in progress and goods and services purchased for resale, minus the purchases of goods and services for resale, plus capitalized production, plus other operating income (excluding subsidies). Income and expenditure classified as financial or extra-ordinary in company accounts is excluded from production value*'. As such, the total production values can be interpreted as an estimate of the revenues of the sector. These figures on the total production value are used to get an idea of industries ability to meet compliance costs (see section F.6.2 below). It is recognized, that expressing the compliance costs as a percentage of the turnover does not necessarily indicate industries ability to cope with compliance costs. However, if compliance costs are only <1% of the turnover (total production value) and on average the sector is well paying with a return of at least a few percentages on its turnover, it can be assumed that there is a reasonable level of economic feasibility for the industry. As the assumptions taken in this analysis might not hold for all use categories of NMP, the conclusions on the economic feasibility based upon the total production value are not clear cut and involve uncertainties.
Cost effectiveness estimates	The cost effectiveness figures presented in F.6.3 (below) are based upon the average of the low and high compliance cost estimates and the average actual estimate of the number of workers for which risk reduction is achieved. As both the estimates of compliance costs as the estimates of the number of workers for which risk reduction is achieved are highly uncertain, also these cost effectiveness figures are given at substantial level of uncertainty. Because of this and due to the fact that figures are only available for a very limited number of use categories and no benchmark for costs per worker is available, it is not possible to draw clear cut conclusions on proportionality based upon the presented figures. Furthermore

Elements of the SEA	Explanation of potential uncertainties
	it should be noted that potential increased risks of alternatives are not included in the estimate and the cost effectiveness figures for some of the uses (e.g. automotive industries) might be overestimated.
Proportionality assessment	All costs and benefits of the various RMOs are presented in table F.25. As no quantitative benefit estimate is available and the information presented on socio-economic costs are highly uncertain, it is difficult to present an accurate comparison of costs and benefits and come to clear cut conclusions on the proportionality. The proportionality analysis presented in this document thus per definition involves some subjective interpretation of the available data on economic effects and benefits. The proportionality assessment has been performed by comparing compliance costs and wider socio-economic effects to the expected risk reduction. This analysis has been further supported by estimates of the cost effectiveness of the RMOs for specific sectors whenever available. If information on cost-effectiveness is lacking, the RMO is likely to be proportional as long as no wider economic effects are expected and expected risk reduction is substantial. In case wider economic effects are expected to be substantial, the proportionality of a measure can be questioned. According to the Dossier Submitter, this is seen as the best way of approaching the proportionality with the data that was available.

F.6 Summary of the socio-economic impacts

F.6.1 Reduction in health effects

A restriction on NMP will result in a reduction in systemic health risks in all workers. Besides, there will be reduction in risks for developmental effects in pregnant workers in those cases where early pregnancy is not known and/or mentioned to the employer. As explained in sections F.1, no quantitative description of the reduced human health impacts due to the various RMOs is given. Instead, the expected health gains are expressed in terms of risk reduction capacity explaining the effect of the various RMOs in terms of RCR reduction due to the decrease in exposure. For alternatives, a qualitative evaluation of a potential increase in risks (and potential health effects) due to the use of substance alternatives is performed by reviewing the hazard characteristics of alternatives. Furthermore, a quantitative estimate of the population potentially working with NMP that might experience health gains due to the various restriction options, is provided.

RMO1 is expected to result in a complete risk reduction of NMP both for industrial and professional uses. However, this reduction might be partially offset by an increase in risks caused by possible alternatives of NMP. For the (mainly industrial) uses where no alternatives are available, the total ban might result in a shift of NMP-using production facilities to non-European countries (like Asia and US). For these uses a risk reduction within the EU will be achieved (which will presumably be offset by an increase in risks outside Europe). The overall risk reduction of a total ban within Europe is considered substantial, as the uses for which risks are potentially offset by the use of hazardous alternatives is assumed to be limited.

RMO2 is expected to result in substantial risk reduction of NMP. For the uses that are included within the scope of the full ban, risks of NMP are fully reduced. However, there is a potential that hazardous alternatives are used as a replacement of NMP and that the risk reductions achieved in these uses are partly or fully offset due to an increase in risks of alternatives. For the uses of NMP that are derogated under specific conditions, also substantial risk reduction is expected, as the conditions set will result in exposure reduction of NMP for workers. The question that raises here is to what extent exposure is reduced and whether this will result in exposure levels of below the level where the DNEL is set. The Dossier Submitter expects that the conditions are set sufficiently strict to reduce exposure to low levels in the majority of the uses as best practice or closed system conditions are expected generally to result in substantial exposure reduction. However, it can be expected that for some specific uses, exposure levels of over 5 mg/m^3 might remain in this scenario and some risks might thus remain. This could for example be expected in some processes in the wire-coating industry as these are presumably confronted with relatively high exposure levels. This sector will have to put substantial effort in exposure reduction as a consequence of RMO2, but this will probably not result in exposure levels below 5 mg/m^3. Overall, the risk reduction is assumed to be substantial (comparable to RMO3a), however, some risks might remain in specific uses (lower risk reduction potential than RMO3a).

RMO3 introduces a mandatory limit value both for professional as industrial users of NMP. For the sake of this socio-economic analysis two levels of a limit value are evaluated: RMO3a: 5 mg/m^3 at the level of the DNEL, and RMO3b: a limit value just above the derived DNEL, i.e. 20 mg/m^3. In case the limit value is set at the level of the DNEL, risks will be fully reduced for the industrial uses. In case the limit value is set at the level of 20 mg/m^3, only a very limited risk reduction is achieved as the majority of industries are already in this range of exposure (according to the exposure scenarios given in the registration dossier).
For the professional uses in coatings, a mandatory limit value is expected to result in a shift to substance alternatives regardless of the level of the limit value as shifting to alternatives appears to be cheaper than taking exposure reduction measures. For these uses RMO3 will result in a full risk reduction of NMP. But, as is explained in RMO1 and RMO2, this risk reduction might be partially or fully outbalanced by an increase in risks caused by alternatives of NMP. The overall risk reduction of this scenario is assumed to be significant, especially in the industrial uses.
In RMO3b the risk reduction for industrial users will be limited as the limit value is set at a level higher than the DNEL. Depending on the current exposure levels, there will be some exposure reduction in the various industrial uses. However, this exposure reduction is minimal and could be theoretical rather than an actual reduction. The resulting RCRs of this option are given in section F.1 (see tables F.03 and F.04) and risks in case of a limit value of 20 mg/m^3 will thus remain. A limit value of 20 mg/m^3 might even result in a risk increase for these uses where exposures are already below the 20 mg/m^3. However, that is a rather theoretical possibility that might not occur in practice.
The limit values are for inhalation and thereby do not cover dermal exposure. The risks potentially caused by dermal exposure are expected to be covered by RMO3 as an obligation to wear protection clothing and gloves is included in the restriction.

Risk reduction in case of RMO4, authorisation, is expected to be comparable to RMO3a. Industries might either shift to alternatives (mainly for the professional uses) or apply for an authorisation. In case industries apply for authorisation they are expected to take the adequate control route, as for the majority of the industrial uses adequate control is assumed to be possible. In case authorisation is granted, exposure will be reduced to a value below the DNEL in those industries and no risks will remain. There could be some users that would apply for authorisation based upon the SEA route in case adequate control is not possible. In that case industry needs to prove that benefits outweigh costs. If such an application would be authorized, there might be some remaining risk. However, the extent to which industry would use the SEA route is assumed to be very limited and the potential remaining risk would therefore also be minimal. In the authorisation scenario there might also be industries that decide neither to shift to alternatives nor to apply for authorisation. These industries cannot continue production in Europe and might either cease activities completely or relocate to non-European countries. In that situation, risks in Europe will be reduced (which will presumably be offset by an increase in risks outside Europe).

To conclude, RMO3a and authorisation have the largest potential risk reduction capacity in Europe. However, when a worldwide perspective is taken, RMO3a has the largest risk reduction capacity.

F.6.2 Technical and economic feasibility

Definitions

To review the acceptability of alternatives, an assessment of the technical and economic feasibility of alternatives is required. Technical feasibility considers the availability and effectiveness of substitutes of NMP. This has been discussed in part C. Note that part C mainly discusses alternatives in terms of substance alternatives and technical process alternatives and concludes that for many of the industrial uses of NMP alternatives are not readily available. For RMO3 of this restriction proposal, one could define alternatives differently as the possible process adaptations taken to reduce exposure levels to below the mandatory limit value. It should be recognized that it is in practice difficult to review the technical feasibility of alternatives (both in terms of substance alternatives as in terms of exposure reduction). Good understanding of the technical process of various industry sectors would be required, which appears to be difficult for an 'outsider'. Anyhow, in this Dossier an attempt has been made to evaluate the technical feasibility of alternatives for the various uses of NMP.

Coming to economic feasibility, unfortunately there is no clear definition available from the REACH legal text. The ECHA guidance on socio-economic analysis of restrictions states that 'economic feasibility is normally defined as a situation where the economic benefits exceed the economic costs'

(ECHA, 2008). This definition is rather vague[44] and closely relates to the definition of the proportionality of the restriction (discussed in the section below). However, there is a difference between economic feasibility and proportionality as the first takes the perspective of the industrial actors, whereas proportionality is reviewed from the perspective of society as a whole. In this way, economic feasibility has something to do with *the capacity of industry to deal with the costs connected to various RMOs*. The question that can be asked to check whether costs are economically feasible is whether industry will survive in case compliance costs need to be made. As such, the economic feasibility of alternatives will be reviewed in this Dossier. If an industry is not able to cope with the additional costs caused by a RMO, its likely response will be relocation or termination of its activities and thus according to our definition, this would not be economically feasible. Economic feasibility can therefore also be expressed in terms of 'expected industry response': if the expected response is 'substitution' or 'exposure reduction', compliance costs are apparently not prohibitive and the RMO can be considered economically feasible. Furthermore, signals from actual replacements of NMP by alternatives (or actual achievement of low exposure levels) give support that alternatives are in fact both technically and economically feasible and can be used as proxies for the technically and economically feasibility of the scenario for a certain use category.
Note that this interpretation of economic feasibility depends largely on the signals received from industry whether they expect to be able to deal with a specific RMO. The Dossier Submitter tried to evaluate the signals received from industry, however, the available data to do this was often limited. The conclusions on economic feasibility presented below are therefore surrounded by uncertainties.

Technical and economic feasibility of substance alternatives

When it comes to substance alternatives, DMSO is the only alternative resulting from the analysis in part C with a lower hazard profile than NMP. Prices of DMSO are presented in section 2.2.3 of the cost analysis in Appendix B and are on average at 1.3€/kg compared to 2.5€/kg for NMP. Prices of DMSO thus appear to be significantly lower than NMP, however, as no information is available on the replacement ratio of DMSO versus NMP in the various uses, it is not possible to conclude upon a change in costs in case DMSO is used as an alternative. Furthermore, it is not known whether process changes would be required and whether the quality of the end product would be affected. Due to these uncertainties it is not possible to conclude upon the economic feasibility of DMSO as alternative to NMP in general terms.

From an human health hazard perspective NEP is not seen as an alternative of NMP, however, from a practical (or technically feasibility) perspective, NEP might serve as an alternative and there are signals (personal communication, AMEC questionnaire) that NEP has already replaced NMP in various uses. It might thus be the case that in practice a restriction would cause a shift from NMP to NEP, especially in the professional uses. Unfortunately, not enough data was found on prices of NEP to get an accurate picture of the price of this substance. An average price of 2.2€/kg is given in the cost analysis in Appendix B, however, this average is not deemed reliable as the range in cost data on NEP is too high (0.75-3.75 €/kg). Note that also for NEP, no data is available on the replacement ratio. However, as NEP is similar to NMP, the assumption that the replacement ratio is 1:1 seems reasonable. For the same reason it is assumed that no substantial process changes are required to NMP with NEP, neither would the quality of products be substantially affected (presuming that NEP is a technically feasible alternative). Replacement with NEP might increase costs, however, due to uncertainties it is not possible to conclude upon the economic feasibility of NEP as alternative to NMP in general.

Also DMAC is from a human health hazard perspective not an alternative that might be used as an alternative in practice. The cost analysis in Appendix B gives an average figure of 1.2€/kg. However, also for this substance no information on e.g. the replacement ratio and potential required process changes is available for the various uses, so no general conclusion on the economic feasibility of the DMAC could be given.

For some of the use categories of NMP (non-wire coatings, professional cleaners, agricultural chemical formulation and construction industry), alternatives are said to be readily available (personal communication, AMEC questionnaire). In these uses NMP seems to be already largely replaced by substance alternatives. And although it is often not known specifically with what substances NMP has

[44] *The previous restriction dossiers (on lead and its compunds in jewellery, on DMFu, on mercury in measuring devices and on phenylmercury compounds) do not provide an unambiguous definition or approach of economic feasibility either.*

been replaced, the fact that the majority of these users did already shift to alternatives indicate that technical and economically feasible alternatives are available.

For all the other use categories the availability of technically and economic feasible alternatives is questionable (for some more than for others).

Technical and economic feasibility of exposure reduction

As explained above, exposure reduction can be seen as the 'alternative' of both RMO2 and RMO3. The technically and economically feasibility of these exposure reduction measures has not be reviewed per use category in part C, the potential for exposure reduction per use category has been elaborated upon in part B.9.1.2. Below the technical and economic feasibility of exposure reduction is further discussed.

Inhalation exposure

NMP is a solvent with a relatively high boiling point and low vapour pressure. It can be calculated that under normal atmospheric conditions and room temperature (0% humidity), the saturated air concentration will be around 1300 mg/m^3 (at 50% humidity the saturated air concentration is around 480-640 mg/m^3 according to BASF inhalation studies (BASF AG, 1995b; BASF AG, 1995a; BASF AG, 1995c; BASF AG, 1989; BASF AG, 1992). In practice, however, for many activities described in the industrial sectors closed systems and dedicated systems (PROCs 1-2-3-8a)are already in use, the NMP concentration in the mixture may be limited, or work shifts are limited in duration. The actual exposure levels are therefore already much lower than the above calculated theoretical level according to the calculated exposure levels using EasyTRA by the registrant. To better understand the technical feasibility of exposure reduction measures, below an overview is given of the exposure reduction efficiencies of various possible measures, besides the possibility of the more costly option of upgrading systems.

The effectiveness of different types of ventilation according to the ECETOC guidance (technical report 107, 109 and 114) are:

- General ventilation: 30% reduction
- Enhanced general ventilation: 70% reduction
- Local exhaust ventilation (LEV): 75-95% reduction

The air concentrations will be further lowered if NMP is used in a mixture (ECETOC):

- Concentration NMP >25%: no reduction
- Concentration NMP 5-25%: 40% reduction
- Concentration NMP 1-5%: 80% reduction
- Concentration NMP <1%: 90% reduction

The effectiveness of personal respiratory protective equipment is by default set at 90% or 95%.

Dermal exposure

The effectiveness of gloves according to ECETOC are:

- Any glove / gauntlet without permeation data and without training: 0% reduction.
- Gloves with permeation data indicating that the material of construction offers good protection for the substance: 80% reduction.
- Chemically resistant gloves (as above) with basic employee training: 90% reduction.
- Chemically resistant gloves in combination with specific activity training: 95% reduction (industrial users only).

In view of the Dossier Submitter, dermal exposure can be controlled using appropriate protective clothing and gloves in all industrial and professional applications.

Technical feasibility of exposure reduction in RMO2

In RMO2 a list of specific use categories (manufacturers, importers and suppliers, petrochemical industries, wire coating industries, electronics and semiconductor industries, battery industries, membrane manufacturers, high performance polymer manufacturing, agricultural chemical industries for synthesis purposes and pharmaceutical industries) are derogated from the restriction under specific conditions. The conditions define the process circumstances within which NMP can still be used. The conditions can be summarized as controlled closed conditions (PROC 1, 2, and 3) and/or the use of BAT for exposure reduction.

The under RMO2 mentioned derogated industries typically have highly developed technical systems. Some industrial sectors already use solely closed systems according to REACH guidance R.12 PROC 1,2, and 3, and other sectors may already work with BAT as they produce very specific products requiring high quality standards. However, the Dossier Submitter does not have information on the BAT per each sector and whether or not at present the industrial sectors already work with BAT. The lack of information leads to speculation on the effectiveness of RMO2 on risk reduction for the derogated industries under the specified conditions as it is not known what actual measures will need to be taken to comply with the conditions. Furthermore the conditions are not clear cut and might be open for multiple interpretation.

The Dossier Submitter notes that the petrochemical industries, agricultural and pharmaceutical industries, where NMP is used for synthesis only, will not be affected by RMO2, since all processes involved are considered to be either PROC1, 2, or 3 according to the registration dossier. Nevertheless it should be noted that exposure calculations for PROC3 under elevated temperatures including LEV (90%) show air concentrations of approximately 20 mg/m3, indicating that there still may be a risk as was previously concluded in section B.10.1.

The other industrial sectors may be faced with substantial costs as they would have to develop or shift to new technical systems to at least a closed system (PROC3) for all activities or apply systems regarded as BAT in their facilities. As mentioned above, knowledge on this point is lacking and thus it is unclear if adaptations to systems are needed. In any case, if the processes remain as they are, risks may not be sufficiently controlled as indicated in section B.10.1. If not, it may be assumed that exposure is reduced further, but to what level remains unknown. The Dossier Submitter assumes that for the majority of the industrial sectors exposure reduction will be comparable to that of RMO3a. However, note that this assumption might thus not be correct for all of the sectors. Moreover, such reductions may not be achieved by applying PPEs as this is not considered a BAT.

Technical feasibility of exposure reduction RMO3a

RMO3a proposes a mandatory exposure limit of 5 mg/m^3 in the breathing zone of the worker. In this scenario, almost all users that decide to continue the use of NMP need to further reduce exposure levels.

The Dossier Submitter is of the opinion that all industries have sufficient means to reduce the exposure to a level below the derived DNEL of 5 mg/m^3. The Dossier Submitter acknowledges that some of the reduction measures may come with substantial costs to industry; moreover such reductions may require the development of a new technical system with a higher level of containment for some specific processes.

In case of the manufacturing, importing and supplying, petrochemical, agricultural and pharmaceutical industries, the highest exposures are expected from processes that occur under elevated temperatures in close batch systems. Note that NMP is used only in synthesis processes here, and not in formulation of preparations (mixtures). The highest calculated exposure level by the registrant using EasyTRA, including LEV with 90% effectiveness resulted in approximately 20 mg/m^3. Discharging and charging, though not specifically related to industrial chemical processes, provided similar estimates, however exposure durations maximally four hours per day. Theoretically, the exposure levels can be reduced further (taking occupational hygiene strategies into account) by upgrading the technical system ensuring a higher level of containment (e.g. from PROC3 to PROC2 would reduce exposure by 2-fold at elevated temperature) or by applying LEV with higher effectiveness (from 90% to 95% effectiveness, 2-fold reduction). Ultimately, PPE can be applied as well, where RPE could further reduce the personal exposure (95% effectiveness). Preferably, technical adaptations of the processes should be performed, however if not feasible, the DNEL level of 5 mg/m^3 can be reached by applying RMM such as an upgraded LEV, use of RPE, or limiting the durations of shifts even further. Most monitoring studies seem to support this view, see section B.9.

Industries that formulate preparations (mixtures), such as the wire coaters, electronics and semiconductor industries, membrane and high performance polymer manufacturers, and also the functional fluids sector, have more open or high energy processes that drive the exposure. For this reason, these industries may have to invest more in exposure reducing measures as there may be a higher need for adapting the technical systems to reduce exposure. Possibilities of proper placement of LEVs are less and wearing PPE such as RPE may not be a desirable measure as exposures are generally continuous rather than intermittent, which is more likely the case for PROC1 to PROC3. Theoretically, applying LEV with higher effectiveness (from 90% to 95% effectiveness, 2-fold

reduction), RPE (95% exposure reduction) should already reduce the exposure to a breathing zone level of 5 mg/m^3, however it is uncertain whether such measures are effective enough in practice. The Dossier Submitter believes that it will be in good practice situations.

Laboratorial use of NMP will be unaffected by RMO3 as it is considered that risks are sufficiently controlled.

Economic feasibility of exposure reduction measures

Appendix B, section 2.3.2 gives an overview of costs for various risk management measures. However, these are indicative costs that are not industry specific and might thus not reflect actual costs of risk management for NMP using industries. As such, these indicative costs could not be used to define costs for exposure reduction for the various sectors and evaluate the economic feasibility to various sectors. As such, industries own estimations of costs have been used in the cost analysis e.g. of RMO3a, and based on these cost estimates and an evaluation of the industry responses, the economic feasibility of various RMOs to various sectors will be discussed below.

Overview of the economic feasibility of various RMOs and use categories of NMP

Section F.4 extensively discusses the expected costs and wider socio-economic effects in case of various RMOs for various use categories of NMP. These are summarized here to come to conclusions on the economic feasibility of alternatives to the various users. A quantitative assessment of the economic feasibility is presented in table F.18 below.

Table F.18: *Qualitative review of the economic feasibility of the various RMOs for various use categories of NMP*

Risk management option	Assessment of economic feasibility
RMO 1	In case of a total ban only the industries for which alternatives are readily available or expected to be available in the near future (non-wire coatings, professional cleaners, some membrane manufacturers, agricultural chemical formulation industry and construction industry) are expected to continue their activities in Europe. For these sectors signals have been received that majority of the users have already replaced NMP. For these sectors, this RMO therefore would meet the 'feasibility' criterion. All other mainly industrial users (petrochemical industries, wire coating industries, medical images, foodcontact material/bakeware, optical cleaners, electronics and semi-conductor industries, battery industries, some membrane manufacturers, high performance polymer producers, agricultural chemical synthesis, pharmaceuticals, laboratories (R&D exempted) and functional fluids) will potentially terminate or relocate; for them, the feasibility criterion would potentially not be met. Wider socio-economic effects to these users are assumed to be substantial.
RMO 2	The effects of RMO2 are assumed to be more or less equal to that of RMO3a and so is the economic feasibility for the majority of the use categories. For the majority of the uses that are not allowed to use NMP after implementation of the RMO (non-wire coaters, professional cleaners, agricultural chemical formulation and construction industry), alternatives are readily available and industry seems not to have problems in shifting to these alternatives as this is already an ongoing process. However, there are some specific uses that are not derogated in this RMO for which there are signals that no alternatives are readily available (medical images, foodcontact material/bakeware, optical industry, functional fluids and laboratories (non-R&D). These users might terminate or relocate in case of RMO2, however, it is not known whether that would actually happen in practice. It is therefore questionable whether this RMO is economically feasible for these users. The uses that are exempted under specific conditions in RMO2 are assumed to be able to meet these conditions. Only for the wire coating sector there are some questions whether the costs to comply with the conditions are bearable to the sector. However, as both the interpretation of the conditions for this sector (what do wire coaters actually have to do to comply) and the costs for various potential measures (see confidential section on wire coaters in F.4.3) are very uncertain, it is not possible to draw clear cut conclusions on the economic feasibility of RMO2 for this sector. Potentially wider socio-economic effects to this sector might occur.
RMO3a	In case of a mandatory DNEL of 5 mg/m^3 all industrial users of NMP will be capable of

Risk management option	Assessment of economic feasibility
(5 mg/m^3)	meeting the DNEL (technically feasible), however, potentially at substantial compliance costs. According to the sector itself, wire coaters would face serious problems to meet this DNEL value as complying with this DNEL would imply the full replacement of the wire coaters current machinery which would require high investment costs. According to industry, such costs would result in the termination of the wire coating industry in Europe (with consequently potentially large supply chain effects). However, as explained in the confidential part on wire coaters in section F4.3,, there are quite some uncertainties on the actual current situation in the wire coating sector in Europe (what exposure levels are currently achieved, what is the state of the art technology in the sector, what is the timing for which compliance costs are calculated, etc.). The Dossier Submitter received conflicting information e.g. on the current exposure level within the sector in Europe and was not able to check the correctness of the presented figures on compliance costs. The Dossier Submitter assumes that costs might very well be much lower in practice, especially as the proposed implementation time of RMO3a is substantial (5 years, see section F.4.3 for further explanation). Based upon the available information it was therefore not possible to draw conclusions on the economic feasibility of RMO3a for the wire coating industry. The Dossier Submitter assumes that compliance costs can be economically feasible to industry. Regarding the other use categories, exposure reduction to below 5 mg/m^3 is assumed to be bearable to industry and thus economically feasible. However, these is some uncertainty around the economic feasibility of RMO3a for medical images, foodcontact material/bakeware, optical cleaners and functional fluids as very limited information on their expected responses is available. For these users it is thus not possible to come to conclusions about economic feasibility. However, it is thought that the absence of data should not be a reason for excluding uses from the restriction as that would give the wrong incentive to industry. As such, the measures for these uses are assumed to be economically feasible until the opposite is proven.
RMO3b (20 mg/m^3)	All industrial users of NMP are assumed to be able to meet this exposure limit value and for the majority of the uses this is expected to be possible at no or minimal costs as this exposure level is already widely achieved throughout various sectors. Only for the wire coaters there are some signals that limit values of 20 mg/m^3 might be problematic. However, real problems seem to occur below 20 mg/m^3 and because of that compliance costs to this sector are assumed to be acceptable. The economic feasibility criterion is therefore met for all of the use categories. No or only very limited wider socio-economic effects are expected in this scenario.
RMO 4 Authorisation	There is less information available on industry responses and costs in case of authorisation and therefore it is also difficult to assess whether industry will apply for authorisation or whether there will be wider socio-economic effects in this scenario. As such it is difficult to conclude upon the economic feasibility of this RMO for the various sectors. Many of the industrial users will presumably be able to demonstrate safe use and in that sense responses and compliance costs might be comparable to RMO3a. However, the uncertainties and timeframe coupled to authorisation also represents a 'cost' to industry. The risk of not receiving an authorisation or the risk of not receiving second term authorisation might prevent industry from further investing in a facility and thus prevent them of applying for authorisation. Industry in that case might terminate or relocate. Authorisation might thus not be economically feasible for some users of NMP and will be for some others . The extent to which this scenario is economically feasible to industry is assumed to be somewhere between the situation of RMO3a and RMO1.

Table F.19 below gives an overview of the economic feasibility of the various RMO discussed in this Background Document.

Table F.19: *Comparison of the economic feasibility of the various RMOs*

RMO	RMO1	RMO2	RMO3a	RMO3b	RMO4
Economically feasible?	Not economically feasible to majority of the sectors using NMP	Economically feasible to majority of the sectors using NMP, although, some sectors for which the economic feasibility is	Economically feasible to all sectors using NMP, although, some questions on economic feasibility for the wire coating sector	Economically feasible to all sectors using NMP	Difficult to draw conclusions on economic feasibility based upon the limited data available. Assumed to be

		questioned			in between RMO1 and RMO3a

Compliance costs as percentage of the total production value

To further underpin the conclusions on economically feasibility made in the qualitative discussion above, and get an idea of industries actual ability to meet the compliance costs, the compliance costs could be expressed as a percentage of the profit of the various sectors. However, unfortunately not enough data is available to come to such profit estimates for the sectors working with NMP. What is available is an estimate of the total production value of various sectors. The total production value is a proxy for the turnover of a specific sector[45]. It is recognized, that expressing the compliance costs as a percentage of the turnover does not necessarily indicate industries ability to cope with compliance costs. However, if compliance costs are only <1% of the turnover (total production value) and on average the sector is well paying with a return of at least a few percentages on its turnover, it can be assumed that there is a reasonable level of economic feasibility for the industry. The table below expresses the average compliance costs per year[46] as a percentage of the yearly total production value. As actual production values are only available for manufacturers, importers, non-wire coating formulators, automotive industry (industrial) and wire coaters and formulators, the percentage could only be calculated for these use categories.

The total production values of various industries are given in Appendix A prepared by AMEC. The upper bound total production values are presented in table 6.1 of the market analysis and come from Eurostat. The representativeness of these upper bound figures for the NMP value chain can be questioned (see table 1.6 of the market analysis). AMEC therefore also provided actual estimates of the total production value using NMP specific industry data. These actual estimates are sometimes based upon the total production value from Eurostat and sometimes on actual sales/turnover figures. Only these actual estimates have been used to compare with compliance costs.

[45] *Total production value provided by Eurostat is defined as: 'Production value measures the amount actually produced by the unit, based on sales, including changes in stocks and the resale of goods and services. The production value is defined as turnover, plus or minus the changes in stocks of finished products, work in progress and goods and services purchased for resale, minus the purchases of goods and services for resale, plus capitalized production, plus other operating income (excluding subsidies). Income and expenditure classified as financial or extra-ordinary in company accounts is excluded from production value'.*

[46] *The average of the low and high estimate of 15 year PV are divided by 15 to come to an 'annual' figure. Note that this is not the same as annual costs as investments are depreciated over a longer time period (up to 15 year).*

Table F.20: *Compliance costs as percentage of the total production value*

		RMO1		RMO2		RMO3a		RMO3b	
Use categories	**ATPV**	**CC**	**% CC of ATPV**	**CC**	**% CC of ATPV**	**CC**	**% CC of ATPV**	**CC**	**% CC of ATPV**
Manufacturer	36	-	**-**	Minimal	**Minimal**	Minimal	**Minimal**	0	**0%**
Importer	36	-	**-**	n/a	**n/a**	n/a	**n/a**	n/a	**n/a**
Formulators (non-wire coating)	<1,200	Minimal	**Minimal**	Minimal	**Minimal**	Minimal	**Minimal**	Minimal	**Minimal**
Automotive industrial + formulators	2,065	1	**0.04%**	1	**0.04%**	1	**0.04%**	1	**0.04%**
Wire coaters and formulators	3,095	-	**-**	XXXX	**XXXX**	XXXX	**XXXX**	6	**0.2%**

ATPV = Actual Total Production Value (in million € per year)
CC = Compliance Costs (average of low and high estimate in million € per year = PV over 15 year/15)
- = no compliance costs
n/a = not available

Table F.20 shows that for the manufacturers, formulators and the automotive industry, the compliance costs are only a minor fraction of the total production value. Even for the wire coating industry in RMO2 and RMO3a, the compliance costs are only slightly over 1%[47]. This estimate of the wire coaters should be reviewed in light of the uncertainties around the actual situation of the wire coating industry that has been discussed in section F.4.3. The actual compliance costs are assumed to be lower than what is presented by industry, e.g. as industry will have substantial time to implement the RMOs. However, on the other hand, the sector is said to work at small margins and the assumptions taken on the total production value used in this analysis, might not be valid for this sector. Therefore, it is according to the Dossier Submitter not possible to draw clear cut conclusions on the economic feasibility of compliance costs for the wire coating sector based on these quantitative estimates. RMO3b is seen as economically feasible for wire coaters as compliance costs are only a small percentage of the total production value.

F.6.3 Proportionality

Similar to the 'feasibility' criterion, the concept of 'proportionality' within the context of REACH does not have a clear-cut and generally accepted definition. Basically, one might say that a RMO is proportional if social benefits outweigh social costs, i.e. the proportion between these parameters is higher than 1. In practice, however, a substantial part of the information needed to calculate both social costs and social benefits is usually lacking, unreliable, or only known with a wide margin of uncertainty. An analysis of proportionality will therefore in most cases necessarily consist of a discussion in which a mixture of quantitative and qualitative data is presented, leading to conclusions that are supported by the available evidence but unavoidably also depend on a number of assumptions and some subjective assessments. A cost effectiveness analysis can be used as tool for the proportionality assessment in case costs and benefits cannot be fully quantified.

To support the proportionality analysis, cost effectiveness figures are presented for some of the use categories for which enough data is available. The cost effectiveness figures express compliance costs per worker for which risk reduction is potentially reduced. With the help of a benchmark, these figures are used to conclude upon the proportionality of the RMOs. However, as data availability is limited, the cost effectiveness approach could only be used for some specific use categories and RMOs. Overall, to review the proportionality of the restriction in this section, the benefits in terms of the reduced human health effects (or risks) are compared to the costs and wider socio-economic effects for industry. As

[47] *In case the high compliance cost estimate is used a percentage of XXXX of the total production value is calculated.*

there is no quantitative estimate of the health effects, the weighing of costs and benefits is not clear cut and gives room for subjective interpretation. This is also the case as both the benefits and the estimates of costs and wider socio-economic effects and cost effectiveness figures are surrounded by substantial uncertainties, as is described in section F.5. The analysis below should be interpreted taking into account these uncertainties.

Cost effectiveness

In the absence of a fully quantified cost benefit analysis, a cost effectiveness analysis can help in evaluating the proportionality of the restriction proposal. This approach has been used earlier e.g. in the underpinning of the restriction on mercury in measuring devices. In that dossier, compliance costs were expressed per kg of mercury not placed on the market due to the restriction. The amount of mercury not placed on the market served as a proxy for reduced human health and environmental effects by assuming that all mercury placed on the market will eventually enter the environment.
To get an impression of the cost effectiveness of the various risk management measures to the various user categories, the compliance costs are expressed per worker for which risks are potentially reduced. The number of workers for which exposure is potentially reduced, is taken as a proxy for reduced human health effects in this cost effectiveness analysis. This is a new approach of reviewing the cost effectiveness that has not been seen in earlier restriction proposals. For this Background Document the number of workers is seen as a better proxy of reduced human health effects than the amount of NMP used as RMO2, RMO3 and RMO4 might result in exposure reduction and presumably not (or only limited) in a reduced use of NMP. One should realize that the number of people for which risk reduction is achieved, is not a perfect proxy for reduced health impacts as it does not account for exposure levels and coupled human health effects.

Both the compliance costs as the number of workers for which exposure reduction is achieved, are given at substantial uncertainty and not available for all of the use categories. For compliance costs, the average of the low and the high 15 year PV estimates presented in tables F.8– F.11 in section F.4 divided by 15 to come to 'annualized' estimates are used. For the number of worker estimates, the average actual estimates of table F.5 are used. Only those use categories for which estimates of both compliance costs as worker figures are available, are included in this analysis. Table F.24 below gives an overview of the cost effectiveness of the various RMOs for the different use categories. Note that, as the worker estimates provided in table F.5 are confidential, also the cost effectiveness figures are confidential.

The use categories with low costs per worker are more cost effective than the use categories with high costs per worker. The cost effectiveness figures range between minimal costs per worker to XXXX per worker. Unfortunately, no benchmark was found to compare the cost effectiveness figures with. In the absence of a well-founded benchmark, the benchmark is here set to 20,000-40,000 € per worker[48], comparable to the average yearly wage of workers within Europe[49]. Note that this is a rather arbitrary benchmark. When annualized compliance costs are substantially lower than the benchmark, the measure is seen as cost effective. As soon as the compliance costs represent a substantial part of the value of the benchmark, the cost effectiveness (and therefore also the proportionality) of the measure for that sector can be questioned. The lower cost effectiveness figures indicated as "minimal costs" (manufacturers, suppliers and membrane manufacturers) or XXXX (automotive industry) per worker are seen as indicators that the proportionality criterion is met, as this is only a very small fraction of the wage costs paid for a worker and industry indicated not to have much problems in taking these investments to further protect workers. However, note that potential increased risks for workers due to the potential use of hazardous alternatives are not included in this analysis. This might cause the actual cost effectiveness figures to increase as the number of workers for which risk reduction is achieved might in practice be limited (this is e.g. relevant for the automotive industry and

[48] *According to EUROSTAT (2013), the median gross annual earnings of fulltime employees in countries of the European Union in 2006 varied between below 10,000 € per year to a bit less than 50,000 € per year.*

[49] *The argumentation here is that if risks to workers are reduced, it is prevented that the worker becomes disabled. In practice of course it is not known whether and what percentage of workers will actually become disabled due to the exposure of NMP. In that way, the benchmark might be too high. On the other hand, the wage benchmark does not include a factor for the suffering/pain in case of illness or disability and in that sense the benchmark might also be too low.*

some membrane manufacturers that might shift to substance alternatives in specific scenarios). Somewhat higher cost effectiveness figures in the range of XXXX per worker are obtained for membrane manufacturers and wire coaters in specific scenarios. These amounts are still seen as an acceptable fraction of the wage paid for these workers. For the higher estimates of XXXX per worker the proportionality of the measure might become questionable, although one could still argue that these costs can be proportionate to the risk reduction. However, the uncertainties around the compliance costs for these sectors (manufacturers in RMO4 and wire coaters in RMO3a) are too high and the benchmark not reliable enough to draw clear cut conclusions based upon the quantitative cost effectiveness data.

Unfortunately, cost effectiveness figures are only available for a very limited number of use categories and the uncertainties around both the compliance costs figures as the workers figures are large. The figures and conclusions based upon the figures should be interpreted in light of these uncertainties.

Comparing costs, wider socio-economic effects and benefits

To come to an overall conclusion on the proportionality of the various RMOs to various use categories of NMP, costs, wider socio-economic effects and benefits are compared. Table F.25 below gives an overview of these costs and benefits per risk management option. Costs and wider socio-economic effects are expressed in terms of potential compliance costs, relocation costs, turnover affected and in lost jobs; benefits are expressed in terms of qualitatively described health benefits, risk reduction potential and in potential worker populations for which risk reduction is achieved.

RMO1

From table F.25, it can be seen that the compliance costs of this scenario are limited (quantified at >25-50M€ over 15 years). Although various sectors that would potentially make compliance costs are not included in the quantitative cost estimate, the chance that these sectors will actually be faced with compliance costs is deemed not very likely as alternatives of NMP seem not to be readily available for these uses. As such, the majority of the industries are expected not to be able to comply with this RMO and the majority of the economic effects are expected in terms of wider socio-economic effects. The relocation costs, turnover potentially affected (>2,000-3,500 M€ yearly turnover) and lost jobs (XXXX) are potentially large in this scenario.
Reviewing table F.25 shows that the risk reduction capacity of this scenario is substantial for all use categories. Also the potential number of workers for whom risk reduction is achieved is thought to be substantial (XXXX due to the shift to alternatives and XXXX due to industries relocation or termination). Note that for the use categories where alternatives are available, risk reduction due to NMP could be partially of fully offset due the potential use of hazardous alternatives. Furthermore, one should realize that risk reduction is mainly obtained due to the termination or relocation of NMP using industries in Europe. In case of relocation a risk increase outside Europe might result (of course combined with economic benefits outside Europe). Table F.21 below gives the main argumentation on the proportionality of RMO1 for various use categories of NMP.

Table F.21: *Main argumentation on the proportionality of RMO1 for various use categories of NMP*

Use category	Proportionality analysis
Manufacturer, importer/supplier, petrochemical industries, non-wire coating formulators, medical images, foodcontact material/bakeware, wire coaters (incl. formulators), optical cleaners, electronics and semiconductor industries, battery industries, part of the membrane manufacturers, high performance polymer producers, agricultural chemical synthesis, pharmaceutical industries, laboratories, functional fluids	Although there are some uncertainties around the industry responses, the Dossier Submitter expect these users to terminate or relocate in case of a full ban on NMP as alternatives for the majority of these users seem not to be available. Negative effects are expected to be substantial in terms of wider socioeconomic effects (lost value added and losses in jobs). Significant risk reduction is assumed to be achieved as NMP will not be used anymore. However, according to the Dossier Submitter, the substantial wider economic losses cannot be justified against the potential risk reduction. Not in the last place, because this scenario is thought to result in a shift of risks problems from Europe to other non-European countries. As such, this RMO is considered not proportional for this group of users.
Non-wire coatings, cleaners, part of the membrane manufacturers, agricultural chemical formulation ,	These users are all expected to comply with a total ban on NMP as alternatives of NMP are readily available and already in use by the majority of the actors. Compliance costs are expected to be limited and

Use category	Proportionality analysis
construction industries	are deemed to be proportional compared to the number of workers for which risk reduction is obtained. Although the benefits might be fully or partially offset by the use of hazardous alternatives, the measure is deemed proportional for these users.

To conclude, overall this RMO is deemed not proportional by the Dossier Submitter as the wider socio-economic effects for Europe are expected to be large and although risk reduction for Europe is substantial, the scenario is expected to cause a shift of health risks to outside Europe which is not supportable.

RMO2

The proportionality analysis of RMO2 is assumed to be comparable to RMO3a as the majority of the costs and benefits of both scenarios are expected to be comparable. However, some differences might occur for some specific use categories. From table F.25, it can be seen that the compliance costs of this scenario can potentially be substantial, especially for some use categories. The quantified compliance costs are in the range of >40-50M€ over 15 year excluding wire coaters. Compliance costs of wire coaters can be substantial, having the capacity to increase total compliance costs up to XXXX over 15 year. However, these costs are assumed to be overestimated e.g. as all costs for new machinery are accounted for as compliance costs while part of the costs would likely be regular business investments in case of an implementation timing of 5 years (as proposed). Compliance costs to wire coaters might also be lower if conditions are met implementing additional exposure reduction measures to older machines instead of shifting to new machinery. Actual compliance costs might in fact be in between the estimate including and excluding wire coaters. Wider socio-economic effects are expected to be limited in this scenario. However, some wider socio-economic effects might occur for these use categories for which no derogation is included in the RMO, but for which the availability of alternatives is uncertain. This is the case for medical images, foodcontact material/bakeware, optical industry, functional fluids and (non-R&D) laboratories. Furthermore, there is a small chance that wider socio-economic effects occur for the wire coating sector in case these are unable to meet the conditions set to the derogation.

Table F.22: *Main argumentation on the proportionality of RMO2 for various use categories of NMP*

Use category	Proportionality analysis
Manufacturer, importer/supplier, petrochemical industries, non-wire coating formulators, electronics and semiconductor industries, battery industries, membrane manufacturers, high performance polymer producers, agricultural chemical synthesis, pharmaceutical industries	Although there are uncertainties around the industry responses, the Dossier Submitter expect these users are able to reduce exposure taking measures to comply with the conditions set to the derogation for these users. For the majority of the users this will imply only minimal costs, for some users the compliance costs might be somewhat larger (however, note that for the latter category also the reduced risks are expected to be larger). The risk reduction capacity of this scenario is thought to be substantial, although some risks might still remain in case the conditions appear not to be strict enough. As such potential reproductive and chronic effects to workers are expected to be reduced. The expected compliance costs are deemed proportional to the risk reduction for these use categories. The cost effectiveness figures available for this scenario show costs per worker that are deemed acceptable in light of the risk reduction and the sectors for which no cost effectiveness figures are available are expected to fall within a similar range of costs per worker.
Medical images, foodcontact material/bakeware, optical industry, laboratories and functional fluids	These users are included within the full ban of RMO2. However, the availability of alternatives to these uses is uncertain. Potentially wider socio-economic effects might occur to these users. If these wider socio-economic effect actually occur, the proportionality to these users can be questioned according to the Dossier Submitter, even if the risk reduction potential is substantial. However, uncertainties on what would actually happen to these sectors are large and as such it is not possible to draw clear conclusions on the proportionality for these users.
Wire coaters and formulators	Due to uncertainties in the interpretation of the conditions set to this sector it is not known what measures will actually be taken by the sector. However, as explained in

Use category	Proportionality analysis
	section F.3.2 and F.4.3, compliance costs representing full shift to new machinery are assumed to be an overestimate of the compliance costs of this scenario. Compliance costs to wire coaters might be lower as part of the costs for new machinery that are now accounted for as compliance costs could in fact be regular business investments in case of an implementation timing of 5 years and as the conditions could potentially be met by implementing additional exposure reduction measures to older machines instead of shifting to new machinery. The Dossier Submitter anyhow expects that wire coaters are able to comply with the conditions (although there is some uncertainty here). Risk reduction of this sector is expected to be substantial as substantial exposure reduction measures are expected to be taken to comply with the conditions. However, some risks might still remain for the workers in this sector. The cost effectiveness figures for this use categories are expected to reduce towards levels that are deemed proportional, although no firm conclusion could be drawn for this sector. The Dossier Submitter however, expects compliance costs to be proportional to the risk reduction and assumes that wider socio-economic effects to this sector are avoided. It should anyhow be stated that the situation for wire coaters is a rather delicate and a chance of termination of this sector might still exist in this scenario. As wider socio-economic effects are expected to be large if the sector terminates (e.g. due to potential supply chain effects), this should be avoided according to the Dossier Submitter. If reliable additional information on this sector is received in the public consultation, the conclusions to this sector might be reconsidered.
Non-wire coatings, cleaners, agricultural chemical formulation, construction industries	These users are all expected to comply with the RMO by shifting to alternatives. Compliance costs are expected to be limited and are deemed to be proportional compared to the number of workers for which risk reduction is obtained. Although the benefits might be fully or partially offset by the use of hazardous alternatives, the measure is deemed proportional for these users.

To conclude, overall this RMO is deemed proportional as compliance costs are deemed to be of an acceptable magnitude (compared to total production values and per worker for which risk reduction is achieved), as wider socio-economic effects are to a large extent avoided and as the risk reduction of this scenario is substantial. The Dossier Submitter notes that with respect to the risk reduction potential, RMO3a is preferred over RMO2. Although the RMO2 is deemed well adapted to the situation of wire coaters, further fine-tuning of the RMO for wire coaters to avoid wider socio-economic effects might be considered if reliable information to support this is received in the public consultation, the same counts for medical images, foodcontact material/bakeware, optical industry, functional fluids and (non-R&D) laboratories.

RMO3a

From table F.20, it can be seen that the compliance costs of this scenario can potentially be substantial, especially for some use categories. The quantified compliance costs are in the range of >40-50M€ over 15 year excluding wire coaters. Compliance costs of wire coaters can be substantial, having the capacity to increase total compliance costs up to XXXX over 15 year. However, these costs are assumed to be overestimated e.g. as all costs for new machinery are accounted for as compliance costs while part of the costs would likely be regular business investments in case of an implementation timing of 5 years (as proposed, see further explanation in F.4.3). Actual compliance costs might in fact be in between the estimate including and excluding wire coaters. Wider socio-economic effects are expected to be avoided in this scenario.

Table F.23: *Main argumentation on the proportionality of RMO3a for various use categories of NMP*

Use category	Proportionality analysis
Manufacturer, importer/supplier, petrochemical industries, non-wire coating formulators, medical images, foodcontact material/bakeware, wire coater formulators, optical cleaners, electronics and semiconductor industries, battery industries, membrane manufacturers, high performance polymer producers, agricultural chemical synthesis, pharmaceutical industries, laboratories, functional fluids	Although there are some uncertainties around the industry responses, the Dossier Submitter expect these users are able to reduce exposure to the level of the DNEL. For the majority of the users this will imply only minimal costs, for some users the compliance costs might be somewhat larger (however, note that for the latter category also the reduced risks are expected to be larger). The risk reduction capacity of this scenario is thought to be substantial, as exposure will be reduced to below the Derived No Effect Level and as such no risks will remain for all use categories. As such potential reproductive and chronic effects to workers are expected to be avoided. The expected compliance costs are deemed proportional to the risk reduction for these use categories. The cost effectiveness figures available for this scenario show costs per worker that are deemed acceptable in light of the risk reduction and the sectors for which no cost effectiveness figures are available are expected to fall within a similar range of costs per worker.
Wire coaters	As explained in section F.4.3, actual compliance costs to wire coaters are uncertain. The estimate presented by the industry is assumed to be overestimated and the actual compliance costs in case of an implementation time of 5 years are assumed to be lower. Unfortunately, no quantitative estimate could be made. However, as major part of the costs now presented as compliance costs by the sector would in fact be regular business investments, the actual compliance costs are assumed to be reduced to acceptable levels. The Dossier Submitter therefore expects that the RMO is economically feasible to the wire coating industry and wider socio-economic effects are assumed to be avoided. The not further specified compliance costs are assumed to be proportional to the risk reduction as this is assumed to be substantial and as no wider socio-economic effects are expected. It should anyhow be stated that the situation for wire coaters is a rather delicate and a chance of termination of this sector might still exist in this scenario. As wider socio-economic effects are expected to be large if the sector terminates (e.g. due to potential supply chain effects), this should be avoided according to the Dossier Submitter. If reliable additional information on this sector is received in the public consultation, the conclusions to this sector might be reconsidered.
Non-wire coatings, cleaners, agricultural chemical formulation , construction industries	These users are all expected to comply with the RMO by shifting to alternatives. Compliance costs are expected to be limited and are deemed to be proportional compared to the number of workers for which risk reduction is obtained. Although the benefits might be fully or partially offset by the use of hazardous alternatives, the measure is deemed proportional for these users.

To conclude, this RMO is deemed proportional to all use categories of NMP as compliance costs are deemed to be of an acceptable magnitude (compared to total production values and per worker for which risk reduction is achieved), as wider socio-economic effects are avoided and as the risk reduction of this scenario is substantial. Although the RMO is deemed well adapted to the situation of wire coaters, further fine-tuning of the RMO for wire coaters to avoid wider socio-economic effects might be considered if reliable information to support this is received in the public consultation.

RMO3b

From table F.25, it can be seen that for most user categories the compliance costs of this scenario are expected to be minimal. Total compliance costs are quantified at 0-150M€. The only substantial costs included in this figure are presented for the wire coating industry, however, as explained in F.4.3 (section on compliance costs and wider socio-economic effects to wire coaters), the correctness of this compliance cost estimate is questioned and could very well be lower. Wider socio-economic effects are not expected in this scenario.

The risk reduction capacity of this scenario is deemed to be very limited as for the majority (or all) of the use categories substantial risks will remain. In light of the minimal risk reduction capacity for all use categories, the potential compliance costs or wider socio-economic effects are not justified according to the Dossier Submitter, even though the costs are expected to be minimal.

To conclude, this RMO is deemed to be proportional in a sense that both benefits and costs of the RMO are relatively low, however from a health concern point of view this RMO3b is definitely not the preferred option.

RMO4, authorisation

As it is uncertain how industry would respond to authorisation, it is difficult to assess the proportionality of this instrument. However, as is explained in table F.25 the costs (compliance costs and administrative costs) and wider socio-economic effects are expected to be somewhere in between RMO3a and RMO1. Compliance costs and administrative costs of this RMO are assumed to be somewhat higher than RMO3a as next to costs for exposure reduction (to prove adequate control) industry will face costs to apply for authorisation and will face business risks due to the uncertainty of the authorisation. These additional costs are assumed to be more extensive than administrative costs to authorities – not quantified - in case of a restriction. These higher costs might cause industry to shut down in case of an authorisation (where in case of RMO3a industry would comply to the DNEL). As such wider economic effects of authorisation might be more substantial than those in RMO3a, however, not as extensive as in case of RMO1. As explained in table F.25 the risk reduction potential of authorisation is assumed to be substantial and more or less equal to the risk reduction capacity of RMO3a. According to the Dossier Submitter the costs of authorisation can be proportionate to the risk reduction, depending on the extent to which wider socio-economic effects will occur. Unfortunately, that could not be indicated based upon the available information, so no clear conclusion on the proportionality of this RMO can be drawn based upon the available information.

Table F.24: *Estimation of the cost effectiveness of various RMOs for various use categories expressed as yearly compliance costs (€) per worker for which risk reduction of NMP is achieved, confidential*

Confidential table was deleted

Table F.25: *Overview potential costs, wider socio-economic effects and benefits (compliance cost and relocation cost estimates as expressed as 15 year Present Value expressed in million €, turnover potentially affected is expressed as a annual figure €)*

	Costs and wider socio-economic effects	**Benefits/risk reduction**
	Overview of the potential compliance costs, relocation costs, turnover affected and loss of jobs	**Qualitative description of health gains and reduced number of workers at risk**
RMO1	• Compliance costs potentially occur for petrochemical industries, non-wire coaters (**automotive** and medical images, foodcontact material/bakeware), cleaners, electronics and semiconductor industries, battery industry, (part of the) **membrane manufacturers**, agricultural chemical synthesis, pharmaceutical industry, laboratories, functional fluids users. Quantitative estimate: **>25-50M€**. • Relocation costs potentially occur for manufacturers, petrochemical industries, specialty coating (film/medical images, foodcontact material/bakeware), optical industry (cleaning), electronics and semiconductor industry, battery industry, (part of the) **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry, laboratories and functional fluid users. Quantitative estimate is confidential: XXXX • Affected turnover potentially occurs for **manufacturers, importers/suppliers**, petrochemical industries, specialty coating (medical images, foodcontact material/bakeware), **wire coating industry (coaters and formulators)**, optical industry (cleaning), electronics and semiconductor industry, battery industry, (part of the) membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry, laboratories and functional fluid users. Quantitative estimate of the annual turnover involved: **>2,000-3,500M€** • Losses of jobs potentially occur for the same use categories as of which the turnover is potentially affected. **manufacturers, importers/suppliers, foodcontact material/bakeware producers, wire coating industry (coaters and formulators) and membrane manufacturers** are included in the quantitative estimate . Quantitative estimate is confidential: XXXX *Note that some of the use categories are listed for potential compliance costs, relocation costs and turnover affected. In practice, only one or two of the effects will occur depending on the industry response.*	• Reduction of systemic health risks for all workers and of developmental risks in pregnant workers will be achieved. • Full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional)** and potentially for part of the **membrane manufacturers.** Quantitative estimate is confidential: XXXX • Complete risk reduction of NMP is expected in Europe in case industry terminates (and potentially relocates). This is potentially expected for **manufacturers, importers/suppliers**, petrochemical industries, specialty coating (medical images, foodcontact material/bakeware) , **wire coating industry (coaters and formulators**), optical industry (cleaning), electronics and semiconductor industry, battery industry, (part of the) **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry, laboratories and functional fluid users. Quantitative estimate is confidential: XXXX

	Costs and wider socio-economic effects	**Benefits/risk reduction**
	Overview of the potential compliance costs, relocation costs, turnover affected and loss of jobs	**Qualitative description of health gains and reduced number of workers at risk**
RMO2	• Compliance costs potentially occur for **manufacturers**, importers/suppliers, **petrochemical industries**, **non-wire coating industry** (**automotive**, medical images, foodcontact material/bakeware), **wire coaters and formulators**, cleaners (optical industry), **electronics and semiconductor industry**, battery industry, **membrane manufacturers**, high performance polymer manufacturers, **agricultural chemical industry (synthesis, formulation)**, **pharmaceutical industry,** laboratories and functional fluid users. Quantitative estimate including wire coaters is confidential XXXX**.** Quantitative estimate excluding wire coaters: >**40-50M€**. Note that the compliance cost figure stated here for wire coaters is expected to be an overestimate of the actual compliance costs (see section F.4.2 and F.4.3 for further explanation). Actual total compliance costs might be in between the two estimates. • Relocation costs might potentially occur for the same use categories as the potential affected turnover below. No quantitative estimate is available. • Affected turnover potentially occurs for **(part of) manufacturers, importers/suppliers**, medical images (coating), **foodcontact material/bakeware producers, wire coating industry (coaters and formulators)**, optical industry (cleaning), functional fluid users and laboratories (non-R&D). Quantitative estimate of the annual turnover involved: **2,100-3,200M€**. Note that wire coaters are expected to comply with the RMO as it is expected to be possible to meet the conditions set for derogation at acceptable costs. For these users no actual turnover is expected to be affected. Only for medical images, foodcontact material/bakeware, optical industry, functional fluid users and (non-R&D) laboratories, turnover might be affected. • Losses of jobs potentially occur for the same use categories as for which the turnover is potentially affected. **30% of the manufacturers and importers/suppliers, foodcontact material/bakeware producers,** and **wire coating industry (coaters and formulators)** are included in the confidential quantitative estimate: XXXX	• Reduction of systemic health risks for all workers and of developmental risks in pregnant workers will be achieved. • Full or partial risk reduction in case of shift to alternatives is expected for the uses for which the use of NMP is fully banned in this RMO and for which alternatives are readily available, as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional),** professional cleaners, agricultural chemical formulation and construction industry. Quantitative estimate: XXXX • Complete risk reduction of NMP is expected in Europe in case industry terminates or relocates. This is potentially expected for **(part of) manufacturers, importers/suppliers**, medical images, foodcontact material/bakeware (coatings), **wire coating industry (coaters and formulators)**, optical industry (cleaning), functional fluid users and laboratories. Quantitative estimate: XXXX. • Complete or partial risk reduction for those users that comply with the conditions of the derogation**: manufacturers, importers/suppliers**, petrochemical industries, **wire coating industries (coaters and formulators**), electronics and semiconductor industry, battery industry, **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis) and pharmaceutical industry. Quantitative estimate: XXXX
RMO3a	• Compliance costs potentially occur for **manufacturers**, importers/suppliers, **petrochemical industries**, **non-wire coating industry** (**automotive**, medical images, foodcontact material/bakeware), **wire coaters and formulators**, cleaners (optical industry), **electronics and semiconductor industry**, battery industry, **membrane manufacturers**, high performance polymer manufacturers, **agricultural chemical industry (synthesis, formulation)**, **pharmaceutical industry** and functional fluid users. Quantitative estimate including wire coaters is confidential XXXX. Quantitative estimate excluding wire coaters: 40-50M€. Note that the compliance cost figure stated here for wire coaters is deemed not feasible and the implementation time for this use category is therefore increased to 15 years. This is expected to reduce compliance costs to acceptable levels. Actual total compliance costs might thus be in between the two estimates. • Relocation costs might potentially occur for the same use categories as the potential affected turnover e below. No quantitative estimate is available. • Affected turnover potentially occurs for **(part of) manufacturers,**	• Reduction of systemic health risks for all workers and of developmental risks in pregnant workers will be achieved. • Full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for non-wire coaters (**automotive industry, both industrial and professional).** Quantitative estimate: XXXX • Complete risk reduction of NMP is expected in Europe in case industry terminates or relocates. This is potentially expected for **(part of) manufacturers, importers/suppliers**, medical images, foodcontact material/bakeware (coatings), **wire coating industry (coaters and formulators)**, optical industry (cleaning), battery industries, agricultural chemical synthesis industries, pharmaceutical industry, functional fluid users. Quantitative estimate: XXXX.

	Costs and wider socio-economic effects	**Benefits/risk reduction**
	Overview of the potential compliance costs, relocation costs, turnover affected and loss of jobs	**Qualitative description of health gains and reduced number of workers at risk**
	importers/suppliers, medical images (coating), **foodcontact material/bakeware producers, wire coating industry (coaters and formulators)**, optical industry (cleaning), battery industries, agricultural chemical synthesis industries, pharmaceutical industry, functional fluid users. Quantitative estimate of the annual turnover involved: **2,100-3,200M€**. Note that wire coaters are expected to comply with the RMO at the proposed extended time frame, also for the other users presented here it is deemed unlikely that the turnover will be actually affected. The affected turnover might very well be zero. • Losses of jobs potentially occur for the same use categories as for which the turnover is potentially affected. **30% of the manufacturers and importers/suppliers, foodcontact material/bakeware producers** and **wire coating industry (coaters and formulators)** are included in the confidential quantitative estimate: **11,000 jobs**. As all users of NMP might very well be able to comply with this RMO, the actual number of jobs lost might also be zero.	• Complete risk reduction for those users that comply with the limit value**: manufacturers, importers/suppliers**, petrochemical industries, non-wire coating industry (medical images, foodcontact material/bakeware), **wire coating industries (coaters and formulators**), cleaners (optical industry), electronics and semiconductor industry, battery industry, **membrane manufacturers**, high performance polymer manufacturers, agricultural chemical industry (synthesis, formulation), pharmaceutical industry and functional fluid users. Quantitative estimate: (200+110+4000+2000+1500) **>8000 workers**
RMO3b	• Compliance costs potentially occur for **importers/suppliers**, **petrochemical industries**, **non-wire coating industry** (**automotive, medical images, foodcontact material/bakeware), wire coating industry (coaters and formulators), cleaners (optical industry), membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis, formulation), pharmaceutical industry and functional fluid users**. Quantitative estimate: **0-150M€** • Relocation costs might potentially occur for the same use categories as the potential losses in revenue below, however these are expected to be very limited. No quantitative estimate is available. • Affected turnover potentially occurs for **(part of) manufacturers, importers/suppliers** as the use of NMP might reduce due to a shift to alternative by professional uses. However as alternatives might be supplied by the same users, actual losses are expected to be limited. Potentially there will also be some turnover affected for the wire coating industry they are not able to adapt to the limit value, however this effect is deemed unlikely. Quantitative estimate of the turnover involved: **0-3150M€** • Losses in jobs are not expected, potentially some in the **wire coating industry** depending on their capability to adapt. Quantitative estimate is confidential: XXXX	• Reduction of systemic health risks for all workers and of developmental risks in pregnant workers will be achieved. • Full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for: non-wire coaters (**automotive industry, both industrial and professional).** Quantitative estimate is confidential: XXXX • Minor to no risk reduction is expected for the users that adapt to the limit value of 20 mg/m^3 as this value is a factor 4 above the harmonised DNEL. Risks will thus remain for manufacturers, importers/suppliers, petrochemical industry, non-wire coatings (medical images, foodcontact material/bakeware), wire coaters and formulators, cleaners (optical), electronics and semiconductor industry, battery industry, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis), pharmaceutical industry and functional fluid users.

	Costs and wider socio-economic effects	**Benefits/risk reduction**
	Overview of the potential compliance costs, relocation costs, turnover affected and loss of jobs	**Qualitative description of health gains and reduced number of workers at risk**
RMO4	• Compliance costs are expected to be in line with RMO3a. Compliance costs potentially occur for **manufacturers**, importers/suppliers, petrochemical industries, non-wire coating industry (**automotive**, medical images, foodcontact material/bakeware), wire coaters and formulators, cleaners (optical industry), electronics and semiconductor industry, battery industry, membrane manufacturers, high performance polymer manufacturers, agricultural chemical industry (synthesis, formulation), pharmaceutical industry, laboratories and functional fluid users. Quantitative estimate: XXXX • Relocation costs, losses in added value and losses in jobs might occur for these uses that decide not to apply for authorisation and that are unable to shift to alternatives. It is not known for how many users this will be the case, however, the quantity is assumed to be in between RMO1 and RMO3a.	• Reduction will be achieved of systemic health risks for all workers and of developmental risks in pregnant workers. • Full or partial risk reduction in case of shift to alternatives is expected as reduction of risks of NMP might be undone by a risk increase of the alternatives of NMP. This is expected for: non-wire coaters (**automotive industry, both industrial and professional).** Quantitative estimate: XXXX • Complete risk reduction of NMP is expected in Europe in case industry stops activity (termination or relocation). • Complete risk reduction for those users that receive authorisation based on the adequate control. Potentially some remaining risks for companies that receive authorisation based upon the SEA route.

The use categories presented in bold are included in the quantitative estimate.
The losses in jobs and the reduced workers at risk estimates are calculated based upon the actual average estimate of workers potentially exposed to NMP presented in table F.05. Note that as for many industrial sectors no estimates on the number of workers are available, the estimates given here are expected to be underestimates of the actual number of workers.

G. Stakeholder consultation

G.1. General

Since a lot of information is available on NMP, it was decided not to carry out an extensive general stakeholder consultation.

An Annex XV SVHC dossier was prepared by ECHA in February 2011. During the public consultation of the proposal to include NMP in the Candidate list, several stakeholders submitted further information in relation to the use of NMP including possible alternatives. Also the REACH registration dossier, the USEPA risk assessment and the OECD SIDS document were used as important information sources.

All registrants of NMP were informed at 7 September 2012 on the intention from the Netherlands to submit an Annex XV restriction by April 2013. The registrants were asked to be involved in the preparation of the dossier. Further, direct contact was made with the lead registrant and several downstream users for the main applications (plastic and membrane production, coating and cleaning industries).

RIVM questionnaire: A questionnaire was sent out on 5 October 2012 to the identified industry representatives; see Annex 6 for the list questions. Several meetings with industry were organised to further discuss important aspects considering the manufacture, use, hazard, exposure, risk and alternatives for NMP (Enschede 12 October 2012 , Bilthoven, 15 November 2012 and Ludwigshafen, 22 November 2012). Also many phone calls and mail contacts were made.

AMEC questionnaire: In commission of the Dutch authorities, the consultant AMEC gathered additional information regarding the market and cost analysis. In the confidential Appendix A and the confidential Appendix B the report of AMEC is given. AMEC contacted several stakeholders with specific questions regarding the possible economic impacts of restricting the use of NMP. This questionnaire is listed in Annex 7. Again the reaction on these questionnaire were followed up by phone calls and emails.

RIVM draft dossier: On 4 February 2013, a draft version of the Annex XV restriction dossier has been sent to industry stakeholders and to the European Trade Union Institute. The comments and suggestions received have been taken into account finalising the restriction dossier.

Information obtained via the several stakeholder consultation activities is presented throughout this dossier by mentioning "personal communication", followed by the company name (in the confidential version only) and the consultation round (RIVM questionnaire, AMEC questionnaire or RIVM draft dossier).

An overview of companies and organisations responded to the questionnaires or draft version of the dossier is given below:

- Abbvie
- Agfa – Gevaert
- AISE – International Association for soaps, detergent and maintance products
- AkzoNobel
- IVA insulations
- BASF
- CEPE
- Deutsche Bauchemie
- Dow
- DuPont
- Elantas
- ESIA – European Semiconductor Industry Association
- ETUI – European Trade Union Institute
- EWWG – Europacable Winding Wire Group
- FIRA – Furniture Industry Research Association
- ISP Ashland
- London Underground

- LyondellBasell
- Merck
- NVZ – Nederlandse Vereniging van Zeepfabrikanten
- NXP Semiconductors
- Parker Hannifin Manufacturing Netherlands
- PPG Packaging
- SH - elektrodraht
- Teijin Aramid
- X-Flow

G.2. Industry response to different risk management options

G.2.1 Industries response to RMO 1. Total ban

The section below presents on overview of industries likely responses to RMO1. The information is based upon consultation of the industry together with information on the availability of alternatives (part C) and expected possibilities for further exposure reductions by the implementation of RMMs. The responses to industry also depend on the date of entry into force of the restriction as this might give industries time to adapt to the measure. More information on industries responses can be found in the Cost Analysis chapter 3 in Appendix B.

How the different NMP producing/using industries are expected to respond to a total ban depends on the availability of technical and economically feasible alternatives.

Manufacturers and importers/suppliers are expected to stop the production and import of NMP in Europe. Manufacturers might shift to the production of alternatives (e.g. NEP) or relocate the production facility to outside Europe. Importers might also start the import of substance alternatives of NMP.

Petrochemical industries are expected to be affected by a total ban as alternatives seem not to be readily available. However, the actual response is not known and will depend on the process where NMP is used.

As many *non-wire coaters and cleaners* already stopped the use of NMP, a total ban will not affect non-wire coaters and cleaners. However, there might be some uses where NMP is still used. These are expected to shift to substance alternatives as these are readily available on the market and the phase-out of NMP in these uses is already ongoing.

For the car industrial and professional users and formulators, replacement of NMP coatings is possible, however, requires the reformulation of the total coating system.

For some of the more specific industrial coating and cleaning processes (e.g. in medical images, foodcontact material/bakeware and the optical industry) the availability of alternatives is uncertain and there are signals that a total ban of NMP might be problematic for them (personal communication). A number of these specific industrial are therefore treated as separate use categories.

Wire coaters have indicated to stop activities in Europe as no alternatives are said to be available for high quality magnet wire coatings. However, from literature it seems that alternatives might be available. Other industries outside Europe will likely take over activities. In addition, there is a potential effect on the European downstream users of NMP based wires expressed by industry. Although downstream users might buy magnetic wires from outside Europe as NMP is not contained in the final product.

Electronic and semi-conductor industry and battery industries expect to lose production in Europe in case of a total ban. However, a part of the industry might shift to NEP or DMAC as these are alternatives found for (some of) these applications.

Membrane manufacturers will - depending on the type of membranes produced - stop production in Europe and relocate industry to outside Europe or change process using alternatives like DMAC, DMF or NMAC.

High performance polymer producers expect to run out of business as alternatives are not available and relocating facilities to outside Europe is too expensive according to the industry.

Agricultural chemical formulation is not expected to be affected by the ban depending on the date of entry into force as industry is already phasing out NMP as co-solvent and expects to be free of NMP by 2015. However, NMP is also used in the *synthesis* of active substances. What the effect on this use will be is not known.

Pharmaceutical industry uses NMP for multiple purposes. Although various alternatives are mentioned in part C it is uncertain how the industry will respond to a total ban.

For *laboraties* and users of *functional fluids* it is not known how they will respond to a total ban on NMP.

Construction industry is not expected to be affected by the ban as the use of NMP as construction chemical is assumed already to be replaced by alternatives.

G.2.2 Industries response to RMO 2. Targeted restriction

In case of a partial ban for professional industry mainly non-wire coaters, agricultural chemical formulation, laboratories and functional fluid users are affected. Effects to these industries are comparable to the effects described under RMO1. As most of the professional users already phased out NMP, RMO2 will presumably have no effect for the majority of the professionals. The few professionals that are still left using NMP are likely to shift to substance alternatives already available on the market. The most substantial effect is expected to be the automotive industry, as both industry and professional auto repair shops use the same coatings, there is a need to fully reformulate the car coating system. Besides that NMP manufacturers / suppliers can expect a slight decrease in production / import. More information on industries responses can be found in the Cost Analysis chapter 4 in Appenix B.

G.2.3 Industries response to RMO 3. Harmonised DNEL and safe use demonstration

The section below presents on overview of industries likely responses to RMO3. The information is based upon consultation of the industry together with information on the availability of alternatives (part C), information on current exposure levels and expected possibilities for further exposure reductions by the implementation of RMMs. However, as the information on technically feasible alternatives and possibilities for further exposure reduction is rather limited, it was difficult to check industries estimate. Besides, contact persons where often unsure about the actual exposure concentrations. This gives substantial uncertainty to the presented responses to the various proposed exposure limit values. The responses to industry also depend on the date of entry into force of the restriction as this might give industries time to adapt to the measure. More information on industries responses can be found in the Cost Analysis chapter 5 in Appendix B.

Industry response in this scenario depends on the actual level of the exposure limit. The DNELs derived in this Background Document are set at 5-10 mg/m^3 for inhalation and 2.4-4.6 mg/kg for dermal for respectively pregnant and all workers. However, to prepare to the potential change of the DNEL industry responses to a wider range of exposure limits is investigated here.

Manufacturers at this moment already achieve levels of 10 mg/m^3 (8-hr TWA) and are capable of reducing exposure levels to 5 mg/m^3 at their own plant. At all exposure limit values a decrease in sale is expected as some downstream users of NMP will not all be able to comply.

Importers/suppliers could not tell what exposure levels are achievable to them. However, as manufacturing, import might decrease at exposure limit values that are lower than the current OEL due to lower NMP sales.

Petrochemical industries are expected to be able to meet exposure limit values down to 5 mg/m^3 as these are expected to be highly automated processes. No information on this has been received from industry.

General non-wire coaters and cleaners (formulators) that still use NMP, are expected to shift to non-NMP alternatives regardless of the level of the limit value as alternatives are readily available and are expected to be cheaper than taking emission reduction measures. The automotive industry might however try to adapt to the limit value as reformulation required for these industrial and professional users are expected to be extensive. Industry itself was unsure what limit values are achievable. In the industrial setting values of 5 mg/m^3 are assumed to be achievable, however, for professionals values down to 10 mg/m^3 might only be achievable at high costs, 20 mg/m^3 might be more realistic. Comparing potential costs for reformulation to costs of additional RMMs shows that reformulation is likely to be cheaper and therefore might be the preferred option for the automotive industry.

For the optical industry there are indications from an NMP manufacturer that complying with any of the proposed exposure limit values (1-20 mg/m^3) might be problematic. For the use of medical images, foodcontact material/bakeware it is not known how users will respons to mandartory limit value.

Wire coater formulators expect to be able it adapt to exposure limit values of around 10 and 5 mg/m^3. For the *wire coaters* at this moment levels at around 80 mg/m^3 are achieved, however, further reduction is expected to be problematic especially for cleaning and filling activities in the process. Starting at values of 40 mg/m^3 a competitive disadvantage is expected by industry. Limit values of 20 mg/m^3 can be achieved by introducing further emission reduction measures at high costs that might not be economically feasible. Further reduction to <10 mg/m^3 will cause closure of wire coaters and indirectly also wire coating formulators according to industry. Note that these signals received from industry in the consultation round, do not match with the current exposure levels stated in the registration dossier.

Electronic and semi-conductor industries and battery industries are expected to be capable of achieving exposure limit values down to 5 mg/m^3 as processes are performed in highly controlled and automated conditions.

Membrane manufacturers are assumed to be able to reduce exposure by implementing further RMMs. A level of 10 mg/m^3 is expected to be achievable at minimal investment. Levels of 5 mg/m^3 are likely to be achievable at higher investments.

High performance polymer producers will be able to achieve limit values of 5-10 mg/m^3 by implementing additional RMMs.

Agrigulture chemical formulation is expected not to be affect by a mandatory limit value as industry is already phasing out the use of NMP. For *agricultural chemical synthesis,* no information was received on how industry will react to a mandatory limit value.

For the *farmaceutical industry*, no information was received on how industry will react to a mandatory limit value.

For *laboraties* and users of *functional fluids* it is not known how they will respond to a mandatory limit value for NMP.

Construction industry is not expected to be affected by the mandatory limit value as the use of NMP as construction chemical is assumed already to be replaced by alternatives. In case there would be any use left, a mandatory limit value would be equal to a ban (resulting in a shift to alternatives) as reduction in exposure is assumed not to be possible.

Table G.01: *Industries responses to the various exposure limit values based on cost analysis by AMEC, Appendix B.*

NMP producers/users	**Ability to meet the limit value and industry response**			
	1 mg/m³	**5 mg/m³**	**10 mg/m³**	**>20 mg/m³**
Manufacturers	No, relocate	Yes	Yes	Yes
Importers/suppliers	?	?	?	?
Petrochemical industries	Yes	Yes	Yes	Yes
Non-wire coaters and cleaners (formulators)	Expected to shift to alternatives			
Car coaters	No, reformulate	Probably not, reformulate	Maybe, but reformulate	Yes, but reformulate
Optical cleaners	Probably not, potentially closing of industry			
Wire coaters (formulators)	No, close of industry	No, close of industry	No, close of industry	Yes
Electronic, semi-conductor and battery industries	No, close of industry	Yes	Yes	Yes
Membrane manufacturers	No, relocate	Yes	Yes	Yes
High performance polymer producers	Yes at high costs	Yes	Yes	Yes
Agricultural chemical formulation	Expected to shift to alternatives already in 2015 (no effect of restriction)			
Agricultural chemical synthesis	Yes	Yes	Yes	Yes
Pharmaceutical industry	Uncertain	Uncertain	Uncertain	Uncertain
Laboratories	Uncertain	Uncertain	Uncertain	Yes
Functional fluids	Uncertain	Uncertain	Uncertain	Yes
Construction industry	Already shifted to alternatives			

G.2.4 Industries response to RMO4. Authorisation

The section below presents on overview of industries likely responses to RMO4 based on personal communication with various industry actors.

Manufacturers and importers/suppliers response will depend on responses of other industry. Some manufacturers/suppliers express that they will probably apply for authorisation. They might stop production/supply and will consider relocation to outside Europe on the long term.

Non-wire coaters might reformulate and shift to alternatives as these are readily available for many of the applications.

It is uncertain how the *wire coating industry* would respond to authorisation. One industrial actor expresses that authorisation would be problematic for the sector.

Cleaners are expected to shift to alternatives whenever available. However, there might be some special cleaning uses where alternatives are not available. It is uncertain how these users would respond.

It is uncertain how e*lectronics and semiconductor industries* would respond to authorisation. Some might apply, however, industry also indicated that the cost of the authorisation process would put the European industry at risk.

One *Membrane manufacturer* producing membranes indicate that they would relocate the facility to China in case of an authorisation. Another manufacturer expressed that he would apply for authorisation.

Construction industries are expected not to respond as this industry already stopped the use of NMP.

For the *petrochemical industry, battery industries, high performance polymer producers, agricultural chemical industry, pharmaceutical industry, laboratories, users of functional fluids* no information is available on industries responses to authorisation.

G.3. Public consultation on the Annex XV restriction report (18 September 2013 – 18 March 2014)

After submission of the Annex XV restriction report, ECHA organised a six-month public consultation on the restriction report from 18 September 2013 to 18 March 2014. During the consultation, 57 comments were received from stakeholders, representing industry, trade and NGOs as well as individuals and Member State Competent Authorities (MSCAs). The comments received, as well as the responses from the dossier submitter (the Netherlands) and from the (co-) rapporteurs of RAC and SEAC are made available on the ECHA website:

http://www.echa.europa.eu/web/guest/previous-consultations-on-restriction-proposals

G.4. Public consultation on the SEAC draft opinion (16 September – 14 November 2014)

After the agreement on the SEAC draft opinion in September 2014, ECHA organised a public consultation on the SEAC draft opinion. During the 60-day consultation period, 14 comments were received from stakeholders, representing mainly industry, but also some MSCAs. Based on the discussion at SEAC-25 in November 2014, SEAC made some adjustments to the justification of its opinion, including a suggestion to extend implementation time for the wire coating sector.

The comments received, as well as the responses from the SEAC (co-)rapporteurs are available on the ECHA website:

http://www.echa.europa.eu/web/guest/previous-consultations-on-restriction-proposals

References

References chapter B

Akesson B and Paulsson K (1997). Experimental exposure of male volunteers to N-methyl-2-pyrrolidone (NMP): acute effects and pharmacokinetics of NMP in plasma and urine. Occup. Environ. Med. 54, 236-240.

Akesson B and Jonsson BAG (1997). Major metabolic pathway for N-methyl-2-pyrrolidone in humans. Drug. Metab. Disp. 25, 267—269.

Akesson B and Jonsson B (2000). Biological monitoring of N-methyl-2-pyrrolidone using 5-hydroxy-N-methyl-2-pyrrolidone in plasma and urine as biomarker. Scand. J. Work. Environ. Health 26, 213-218.

American Insulated Wire Corp. (2002). A Guide to Wire and Cable Construction. Pawtucket, Rhode Island, USA. Download 10022013:
http://www.siongboon.com/projects/2007-12-22_cable_wiring/A%20Guide%20to%20Wire%20and%20Cable%20Construction.pdf

Ansell JM and Fowler JA (1988). The acute oral toxicity and primary ocular and dermal irritation of selected N-alkyl-2-pyrrolidones, Fd. Chem. Toxic. 26, 475-479.

Aroon MA, Ismail AF, Montazer-Rahmati MM, Matsuuraa T (2010). Morphology and permeation properties of polysulfone membranes for gas separation: Effects of non-solvent additives and co-solvent. Sep. Pur. Technol. 72: 194–202

Arora P, Zhang ZJ (2004). Battery Separators. Chem. Rev. 104, 4419-4462.

Auffarth J, Hohmann R, and Tischer M (1988). Stoffbelastungen in Siebdruckereien. GA53. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Wirtschaftsverlag NW, Bremerhaven, Germany.

Bader M, Rosenberger W, Rebe T, Keener SA, Brock TH, Hemmerling HJ, Wrbitzky R (2006). Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility. Int Arch Occup Environ Health 79: 357–364

Bader M. Wrbitzky R.; Blaszkewicz M.; van Thriel C (2007). Human experimental exposure study on the uptake and urinary elimination of N-methyl 2-pyrrolidone (NMP) during simulated workplace conditions. Arch Toxicol (2007) 81:335-346. Testing laboratory: Institute for Occupational Physiology at the University of Dortmund, Dortmund, Germany.

Bader M, Wrbitzky R; Blaszkewicz M; Schäper M; van Thriel C; (2008) Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch Toxicol (2008), 82:13 -20.

BASF AG (1963). Department of Toxicology, unpublished data, (XIII/27), 11 Apr 1963.

BASF AG (1976a). Department of Toxicology, unpublished data, (XXV/436), 10 Sept 1976

BASF AG (1976b). Department of Toxicology, unpublished data, (XXV/436), 16 Sept 1976.

BASF AG (1978). Department Toxicology, unpublished study, (XXV/436), 22 May 1978.

BASF AG (1983/1988). Department of Toxicology, unpublished data, (XXV/436), 23 Aug 1983 and Suppl. 1, 27 May 1988.

BASF AG (1988a). Department of Toxicology, unpublished results, project No. 13I0548/877054, 10 Feb 1988.

BASF AG (1989). Department of Toxicology, unpublished results, project No. 36I0794/87088, 03 Jan 1989.

BASF AG (1991). Department of Toxicology, unpublished results, project No. 21R0544/90049, 20 Aug 1991.

BASF AG (1992). Department of Toxicology, unpublished results, project No. 36I0794/87088, 21 Apr 1992.

BASF AG (1993a). Department of Toxicology, unpublished results, project No. 40I0544/90067, 26 Oct 1993.

BASF AG (1993b). Department of Toxicology, unpublished results, project No. 41RO544/90100, 09 Jul 1993.

BASF AG (1993c). Department of Toxicology, unpublished results, project No. 44RO544/90078, 07 Jul 1993.

BASF AG (1994). Department of Toxicology, unpublished results, project No. 50I0544/90061, 04 Jan 1994.

BASF AG (1995a). Department of Toxicology, unpublished results, N-Methylpyrrolidone: Synopsis of project Nos. 36I0587/89023, /89042, /89044, /89045, /89054, /89069, /89070, and supplement report (Techn. Part), 19 May 1995.

BASF AG (1995b). Department of Toxicology, unpublished results, project No. 36I05876/89023, 19 May 1995.

BASF AG (1995c). Department of Toxicology, unpublished results, project No. 36I0587/89045, 19 May 1995.

BASF (2000). Paper industry biocides. Ludwigshafen , Germany, BASF Aktiengesellschaft Specialty Chemicals. Download 04032013:
http://www2.basf.us/biocides/pdfs/PIB_Brochure.pdf

BASF (2001). Water and oilfield biocides. Ludwigshafen , Germany, BASF Aktiengesellschaft Specialty Chemicals. Download 04032013:
http://www2.basf.us/biocides/pdfs/WOB_Brochure.pdf

BASF (2011a). BASF News Release september 2011. BASF showcases expertise at CPhI worldwide in Frankfurt. Download 05042013:
http://basf.com/group/corporate/en/function/conversions:/publish/content/news-and-media-relations/news-releases/downloads/2011/P446-CPhI-e.pdf

BASF (2011b). Product Overview Additives and Dispersions for the Construction Chemicals Industry. Download 07032013: http://www.basf.com/group/corporate/en/literature-document:/Brand+Melcret-Brochure--Product+Overview+Additives+and+Dispersions+for+the+Construction+Chemicals+Industry-English.pdf

Beaulieu HJ and Schmerber KR (1991). N-pyrol (NMP) use in the microelectronics industry. Appl. Occup. Environ. Hyg. 6, 874-880.

Becci PJ, Gephart LA, Koschier FJ, and Johnson WD (1983). Subchronic feeding study in Beagle dogs of N-Methylpyrrolidone. J. Appl. Toxicol. 3, 83-86.

Becci PJ, Knickerbocker MJ, Parent RA, and Burnette LW (1981). Teratogenic evaluation of N-methylpyrrolidone in Sprague-Dawley rats. Toxicologist 1, 29-30 (abstract).

Becci PJ, Knickerbocker MJ, Reagan EL, Parent RA, and Burnette LW (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats. Fundam. Appl. Toxicol. 2, 73-76.

Bendels S, Tsinman, O, Wagner B, Lipp D, Parrilla I, Kansy M, Avdeef A. (2006). PAMPA -Excipient Classification Gradient Map. Pharmaceutical Res. 23: 2525-2535.

Clark B, Furlong JW, Ladner A, Slovak AJM (1984) Dermal toxicity of dimethyl acetylene dicarboxylate, N-methyl pyrrolidone, triethylene glycol dimethyl ether, dioxane and tetralin in the rat, Int. Res. Comm. System Med. Sci. 12, 296-297.

Consumer Product Testing Co. (1980). Primary dermal irritation study (FIFRA) in albino rabbits. ISP inventory No. 1961-010-01.

Danish product register (2012). Data obtained during public consultation.

Dunn, R (2003). Application of the ATRIGEL® Implant Drug Delivery Technology for Patient-Friendly, Cost-Effective Product Development. Drug Development & Delivery 3(6) September 2003, Posted On: 3/28/2008. Download 06022013: http://www.drugdeliverytech.com/ME2/dirmod.asp?sid=&nm=&type=Publishing&mod=Publications%3A%3AArticle&mid=8F3A7027421841978F18BE895F87F791&tier=4&id=FA7F2855909844BE9E4F02C0D1C870F8

E.I. du Pont de Nemours and Company (1990). Medical Research Project 3872-001/HLR 294-90, unpublished data, 05 Oct 1990.

E.I. du Pont de Nemours and Company (1994). Medical Research Project 9736-001/HLR 92-94, unpublished data, 13 May 1994 (sponsored by NMP Producers Group, USA).

EC (2003). Reference Document on Best Available Techniques (BREF) for Mineral Oil and Gas Refineries. Download 27022013: http://eippcb.jrc.es/reference/

EC, 2006. REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006,

ECETOC (2005) Technical report 93. Targeted Risk Assessment.

ECETOC (2009). Technical report 107. Addendum to ECETOC Targeted Risk Assessment Technical Report No. 93

ECETOC (2012). Technical report 114. ECETOC TRA version 3: Background and Rationale for the Improvements.

ECHA, 2012a. Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. ECHA-2010-G-19-EN

ECHA, 2012b. Guidance on information requirements and chemical safety assessment. Chapter R.13: Risk management measures and operational conditions

ECHA 2011, Annex XV SVHC dossier. Proposal for identification of a substance as a CATEGORY 1A OR 1B CMR, PBT, vPvB or a substance of a EQUIVALENT LEVEL OF CONCERN.

ECHA (2010): Exposure Scenarios for the Semiconductor Industry Examples. http://guidance.echa.europa.eu/docs/other_docs/es_project_document_v5.pdf.

Edwards RD, Jurvelin J, Saarela K, and Jantunen M (2001). VOC concentrations measured in personal samples and residential indoor, outdoor and workplace microenvironments in EXPOLIS-Helsinki, Finland, Atmospheric Environment 35, 4531-4543.

EFSA 2009. Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. The EFSA Journal (2009) 1150, 1-72

Exxon Biomedical Sciences (1992). Project No. 136534, 05 Jun 1992 (sponsored by GAF Corp., Wayne, USA). See also GAF Corp. 1992.

Exxon Biomedical Sciences (1991). Project No. 236535, 26 Nov 1991 (sponsored by GAF Corp., Wayne, USA)

Finnish product register (2012). Data obtained during public consultation.

Food and Drug Research Laboratories (FDRL, 1979). Lab. No. 6161, unpublished report, 18 Oct 1979 (submitted to GAF Corp., Wayne, NJ, USA).

Fransman W, Schinkel J, Meijster T, Van Hemmen J, Tielemans E, Goede H. (2008) Development and evaluation of an exposure control efficacy library (ECEL). Ann Occup Hyg. 2008 Oct;52(7):567-75. doi: 10.1093/annhyg/men054. Epub 2008 Aug 14. Review.

Fries AS, Haas U, Jacobsen BM, Jelnes JE, Lund SP, and Simonsen L (1992). N-methylpyrrolidone effekter pa fosterudrikling, centralnervesystem, testikler og saed hos rotter [Toxic effects of N-methylpyrrolidone on fetal development, the central nervous system, testes and semen in rats]. Arbejdmiljofondet, Copenhagen (English summary).

GAF Corp. (1992). Developmental Toxicity study in rats with N-Methylpyrrolidone. Project No.: 136534, unpublished data, Exxon Biomedical Sciences, East Millestone, NJ, USA.

GAF Corp. (1986). M-Pyrol. Summary of Toxicity Information, Jul 1986.

Gartiser S, Urich E (2002). Environmentally compatible cooling water treatment chemicals. Berlin, German Federal Environmental Agency, UmweltBundesAmt.

Ghantous, 1995 NMP Producers group (1995c). Oral, dermal and inhalation pharmacokinetics and disposition of [2-14C] NMP in the rat. Report No. 630-95, Ghantous HN, November 17, 1995, Haskell Laboratory for Toxicology and Industrial Medicine, USA, unpublished report.

Hass U (1990). Prenatal toxicity of N-methylpyrrolidone in rats: postnatal study. Teratology 42(2), abstract P37, 31A-32A.

Hass U (1991). Relationship between reduced body weight and delayed development in a behavioral teratology study. Teratology 43, abstract NTS 54, 500.

Hass U, Jakobsen BM, Lund SP (1995). Developmental toxicity of inhaled N-methylpyrrolidone in the rat. Pharmacol. Toxicol. 76, 406-409.

Hass U, Lund SP, and Elsner J (1994). Effects of prenatal exposure to N-methylpyrrolidone on postnatal development and behavior in rats. Neurotoxicol. Teratol. 16, 241-249.

Hearle JWS, (2001). High-performance fibres. Cambridge, England, Woodhead Publishing Ltd.

HSE (2003). HSE information sheet. Solvent. Construction Information Sheet No 27 (revision 2). Download 17042013: http://www.hse.gov.uk/pubns/cis27.pdf

Huntingdon Life Sciences (HLS) Ltd. (1998). [14C]-N-methylpyrrolidone: topical application: dermal absorption study in the rat. Report 982974.

Industrial Biology Research and Testing Laboratories (1963). Twenty day subacute dermal toxicity study in rabbits with GAF - Methyl-Pyrrolidone. ISP inventory No. 1963-001-01.

International Research and Development Corp. (IRDC, 1991). No. 637-002, 17 Dec 1991 (sponsored by Atrix Lab. Inc. and GAF Chemicals Corp.).

Jakobsen BM and Hass U (1990). Prenatal developmental toxicity of N-methylpyrrolidone inhalation in rats: a teratogenicity study. Teratology 42(2), abstract F6, 18A-19A.

Jonsson BAG, and Akesson B (2001). N-Methylsuccinimide in plasma and urine as biomarker of exposure to N-methyl-2-pyrrolidone. Int. Arch. Occup. Environ. Health 74, 289-294.

Jonsson BAG and Akesson B (2003). Human experimental exposure to N-methyl-2-pyrrolidone (NMP): toxicokinetics of NMP, 5-hydroxy-N-methyl-2-pyrrolidone, N-methylsuccinimide and 2-

hydroxy-N-methylsucciniimde (2-HMSI), and biological monitoring using 2-HMSI as a biomarker. Int. Arch. Occup. Environ. Health 76, 267-274.

Jouyban A, Fakhree MAA, Shayanfar A (2010). Review of Pharmaceutical Applications of N-Methyl-2-Pyrrolidone. J. Pharm. Pharmaceut. Sci. 13(4): 524 - 535.

Jungbauer FHW, Coenraads PJ, and Kardaun SH (2001). Toxic hygroscopic contact reaction to N-methyl-2-pyrrolidone. Contact Dermatitis 45, 303-304.

Kennedy GL and Delorme MP (2004). Letter from DuPont Haskell Laboratory to the NMP Producers Group, 14 April 2004.

Kennedy GL (2008) Tumor Incidences from the 2 year inhalation carcinogenicity study of Lee et al. 1987, DuPont, personal communication, March 2008

Kiefer M (1993). NIOSH HHE Report No. HETA-93-0844-2411, Rosebud Company, Atlanta, Georgia, USA.

Knowles A (2005). Chemical and Engineering News. Agrow Reports DS243. T&F Informa UK Ltd. Code of Federal Regulations Title 21 - Food and Drugs, . (21 CFR 176.3OO(d)), 2012).

Leading Edge Coating Solutions (2013). LECS brand coatings. Download 31012013: http://ledgecs.com/lecs-brand-coatings. Gahanna, OH, USA.

Lee KP, Chromey NC, Culick R, Barnes JR, and Schneider AP (1987). Toxicity of N-methyl-2-pyrrolodone (NMP): Teratogenic, subchronic, and two-year inhalation studies. Fundam. Appl. Toxicol. 9, 222-235.

Lee KP (1977). Pathology Report, 14 Jan. 1977. In: TSCAT, OTS0534849, 02 Dec 1991.

Lee PJ, Langer R, Shastri VP (2005). Role of n-methyl pyrrolidone in the enhancement of aqueous phase transdermal transport. J. Pharm. Sci. 94(4):912-917.

Leira HL, Tiltnes A, Svenden K, and Vetlesen L (1992). Irritant cutaneous reactions to N-methyl-2-pyrrolidone (NMP). Contact Dermatitis 27, 148-150.

Lowe M, Tokuoka S, Trigg T, Gereffi G (2010). Lithium-ion Batteries for Electric Vehicles: The US Value Chain. Durham, NC, USA, Center on Globalization, Governance & Competitiveness Duke University

Malek DE, Malley LA, Slone TW, Elliott GS, Kennedy GL, Mellert W, Deckardt K, Gembardt C, Hildebrand B, Murphy SR, Bower DB, and Wright GA (1997). Repeated dose toxicity study (28 Tags) in rats and mice with N-Methylpyrrolidone (NMP). Drug Chem. Toxicol. 20, 63-77.

Malik K, Singh I, Nagpal M, Arora S (2010) Atrigel : A potential parenteral controlled drug delivery system. Der Pharmacia Sinica 1 (1): 74-81. Download 06022013: http://pelagiaresearchlibrary.com/der-pharmacia-sinica/vol1-iss1/DPS-2010-1-1-74-81.pdf

Malley LA, Kennedy GL, Elliott GS, Slone TW, Mellert W, Deckardt K, Kuttler K, Hildebrand B, Banton MI, Parod RJ, and Griffiths JC (2001). Chronic toxicity and oncogenicity of N-Methylpyrrolidone in rats and mice by dietary administration. Drug Chemical. Toxicol. 24, 315-338.

Mattorano D and Trout D (1996). NIOSH HHE report No. 96-0266-2702. Cooper Engineered Products, Bowling Green, Ohio, USA.

Meier S, Schindler BK, Koslitz S, Koch HM, Weiss T, Käfferlein HU, Brüning T. (2013). Biomonitoring of Exposure to N-Methyl-2-Pyrrolidone in Workers of the Automobile Industry. Ann Occup Hyg. 2013 Jan 20. [Epub ahead of print]

Michot T, Nishimoto A, Watanabe M (1999). Electrochemical properties of polymer gel electrolytes based on poly(vinylidene fluoride) copolymer and homopolymer. Electrochim. Acta 45: 1347–1360.

Midgley I, Hood AJ, Chasseaud LF, Brindley CJ, Baughman S, and Allen G (1992). Percutaneous Absorption of co-administered N-methyl-2-[14C]pyrrolidinone and 2-[14C]pyrrolidinone in the rat. Fd. Chem. Toxic. 30, 57-64.

Milieu ltd. Environmental Law and policy (2012). Technical assistance related to the scope of REACH and other relevant EU legislation to assess overlaps. Prepared by Milieu Ltd for DG Environment of the European Commission under Service Contract 070307/2009/550863/SER/D3.

National Institutes of Health (2004). Household Products Database (last updated 12 May 2004), available at http://householdproducts.nlm.nih.gov/.

Nishimura S, Yasui H, Miyauchi H, Kikuchi Y, Kondo N, Takebayashi T, Tanaka S, Mikoshiba Y, Omae K, Nomiyama T (2009). A Cross-sectional Observation of Effect of Exposure to N-Methyl-2-Pyrrolidone (NMP) on Workers' Health. Industrial Health 47: 355–362

NMP Producers Group (1994). Repeated dose toxicity study with N-Methylpyrrolidone in B6C3F1 mice - Administration in the diet for 4 weeks (range-finding study). Department of Toxicology of BASF AG, Ludwigshafen, Germany, Project No. 40C0225/93030, unpublished report.

NMP Producers Group (1995a). N-Methylpyrrolidone - Subchronic oral toxicity study in B6C3F1 mice - Administration in the diet for 3 months. Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen, Germany, Project No. 60C0225/93053, unpublished report.

NMP Producers Group (1995b). Subchronic oral toxicity: 90-Tag feeding and neurotoxicity study in rats with N-Methylpyrrolidone (NMP). E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, USA, project No.: 9737-001, unpublished report.

NMP Producers Group (1997). Oncogenicity study with N-Methylpyrrolidone (NMP) - Two-year feeding study in Sprague-Dawley rats. E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, USA, project No.: 9738-001, unpublished report.

NMP Producers Group (1999a). N-Methylpyrrolidone: Carcinogenicity study in B6C3F1 mice - Administration in the diet for 18 months. Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen, Germany, Project No. 76C0225/93065, unpublished report.

NMP Producers Group (1999b). N-Methylpyrrolidone (NMP): Two generation reproduction toxicity study in Wistar rats - Administration in the diet. Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen, Germany, Project No. 70R0056/97008, unpublished report.

NMP Producers group (1999c). Two-generation reproduction toxicity study with N-Methylpyrrolidone (NMP) in Sprague-Dawley rats - Administration in the diet. Huntingdon Life Science, East Millestone, NJ, USA, project No.: 97-4106, unpublished report.

NMP Producers Group (2005). Human volunteer study on chemosensory effects and evaluation of a threshold limit value in biological material of N-methyl-2-pyrrolidone (NMP) after inhalational and dermal exposure - Chemosensory effects. Institute for Occupational Physiology at the University of Dortmund (IfADo), Germany, unpublished report, draft 12 Sep 2005.

OECD SIDS (2007) SIDS Initial Assessment Report on 1-methyl-2-pyrrolidone.

Orendorff CJ (2012). The role of separators in lithium-ion cell safety. The electrochemical society Interface summer 2012 61-65. Download 11022013:
http://www.electrochem.org/dl/interface/sum/sum12/sum12_p061_065.pdf

Payan JP, Beydon D, Fabry JP, Boudry I, Cossec B, and Ferrari E (2002). Toxicokinetics and metabolism of N-[14C]methyl-2-pyrrolidone in male Sprague-Dawley rats: a saturable NMP elimination process. Drug Metab. Disp. 30, 1418-1424.

Poet TS, Kirman CR, Bader M, van Thriel C, Gargas ML, and Hinderliter PM (2010). Quantitative risk analysis for N-methyl-pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. Toxicol. Sci. 113: 468 -482.

Ravn-Jonsen A, Edelfors S, Hass U, and Lund SP (1992). The kinetic of N-methyl-2-Pyrrolidone in pregnant rats and their fetuses compared with non-pregnant rats. Tox. Lett., Suppl. P5/P8, 136.

Rijkers DTS, Kruijtzer JAW, Killian JA, Liskamp RMJ (2005). A convenient solid phase synthesis of S-palmitoyl transmembrane peptides. Tetrahedron Letters 46: 3341–3345.

Saillenfait AM, Gallissot F, Langonné I, and Sabate JP (2002). Developmental toxicity of N-Methyl-2-Pyrrolidone administered orally to rats. Fd. Chem. Toxicol. 40, 1705-1712.

Saillenfait AM, Gallissot F, Langonne I, Sabate JP, Morel G (2001). Developmental toxicity of N-Methyl-2-Pyrrolidone administered by gavage or inhalation to rats. Poster abstract, 29th Conference of the European Teratology Society, 2-5 Sep 2001, Balatonfüred, Hungary.

Saillenfait AM, Gallissot F, and Morel G (2003). Developmental toxicity of N-Methyl-2-Pyrrolidone in rats following inhalation exposure. Fd. Chem. Toxicol. 41, 583-588.
Sasaki H, Kojima M, Nakamura J, and Shibasaki J (1990). Acute toxicity and skin irritation of pyrrolidone derivates as transdermal penetration enhancer. Chem. Pharm. Bull. 38, 2308-2310.

SCOEL (2007). Recommendation from the Scientific Committee on Occupational Exposure Limits for n-methyl-2-pyrrolidone. SCOEL/SUM/119 August 2007.

Sitarek K (2003). Excretion and maternal-fetal distribution of N-Methyl-2-Pyrrolidone in rats. Reproductive Toxicology 17, 475-508 (abstract).

Sitarek K & Stetkiewicz J (2008). Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats. International Journal of Occupational Medicine and Environmental Health 21: 73-80.

Sitarek K., Stetkiewicz J., Wasowicz W., 2012. Evaluation of Reproductive Disorders in Female Rats Exposed to N-Methyl-2-Pyrrolidone. Birth Defects Res (Part B) 95:195-201, 2012.

Solomon HM, Burgess BA, Kennedy Jr. GL, and Staples RE (1995). 1-Methyl-2-pyrrolidone (NMP): reproductive and developmental toxicity study by inhalation in the rat. Drug Chem. Toxicol. 18, 271-293.

Solomon GM, Morse EP, Garbo MJ, Milton DK (1996). Stillbirth after occupational exposure to N-methyl-2-pyrrolidone. A case report and review of the literature. JOEM, 38:7.

Swedish Product Register (2003). Data base information.

Swiss Product Register (2005). Data base information, April 2005.

TSCAT (1989). OTS0528118, Doc I.D. 40-89107058, 07 Jul 1989 (US EPA).

TSCAT (1990a). OTS0528073, Doc I.D. 40-90107092, 05 Jan 1990 (GAF Corp.).

TSCAT (1990b). OTS0530507, Doc I.D. 40-90107123, 18 Sep 1990 (E.I. Dupont du Nemours).

TSCAT (1991a). OTS0532510, Doc I.D. 40-91107125, 11 Sep 1991 (GAF Corp.) (150).

TSCAT (1991b). OTS0534849, Doc I.D. 88-920000398, 02 Dec 1991 (E.I. Dupont de Nemours & Co.). See also Lee, 1977.

TSCAT (1992a). OTS0539109, Doc I.D. 88-920001848, 17 Apr 1992 (ISP, Wayne, USA).

TSCAT (1992b). OTS0555033, Doc I.D. 88-920008215, 31 Aug 1992 (E.I. Dupont de Nemours & Co.) [FDRL Teratology studies No. 6210 6161].

TSCAT (1995). OTS0558844, Doc I.D. 44620, 22 Nov 1995 (NMP Producers Group) [DuPont HLR 81-95].

Van Thriel C, Blaszkewicz M, Schäper M, Juran SA, Kleinbeck S, Kiesswetter E, Wrbitzky R, Stache J, Golka K, Bader M. (2007). Chemosensory effects during acute exposure to N-methyl-2-pyrrolidone (NMP). Toxicol Lett. 2007 Dec 10;175(1-3):44-56. Epub 2007 Sep 29.

Weisbrod D and Seyring B (1980). Vergleichende Untersuchungen zur akuten Warmblüter- sowie zur Fischtoxizität der technischen Lösungsmittel N-Methyl-pyrrolidin-2-on und N-Methyl-E-caprolactam. In: RK Mueller (1980). Toxikologische und analytische Probleme bei Lösungsmittelexpositionen. Forschungsteilprojekt Akute Intoxikationen, Abteilung für Toxikologische Chemie des Instituts für Gerichtliche Medizin der Karl-Marx-Universität Leipzig (Bereich Medizin), 55-59.

Weisbrod D (1981). Tagungsbericht. Akad. Landwirtsch.-Wiss. DDR 187, 211-217.

Wells DA, and Digenis GA (1988). Disposition and metabolism of double-labeled [3H and 14C] N-Methyl-2-Pyrrolidone in the rat. Drug Metabol. Dispos. 16, 243-249.

White WC (2007). Butadiene production process overview. Chem Biol Interact. 166(1-3):10-14.

WHO (1986). Information Bulletin 12, IARC/Lyon, Jun 1986.

WHO (2001). Concise International Chemical Assessment Document (CICAD) 35, N-Methyl-2-2Pyrrolidone, Geneva, Switzerland.

Wiese KD, Nierlich F (2005). Upgrading of C4 streams: Present and future trends. Erdöl, Erdgas, Kohle 121 (3) : 16-21.

Will W, Leuppert G, and Rossbacher R (2004). Poster: Dermal and Inhalative Uptake of N-Methyl-2-pyrrolidone (NMP) during Paint Stripping of Furniture. 6th International Symposium on Biological Monitoring in Occupational and Environmental Health, Heidelberg, Germany.

Xiaofei E, Wada Y, Nozaki JI, Miyauchi H, Tanaka S, Seki Y, and Koizumi A (2000). A linear pharmacokinetic model predicts usefulness of N-methyl2-2pyrrolidone (NMP) in plasma or urine as a biomarker for biological monitoring for NMP exposure. J. Occup. Health 42, 321-327.

Yang MC Liu TY (2003). The permeation performance of polyacrylonitrile/polyvinylidine fluoride blend membranes. J. Membr. Sci. 226 (2003) 119–130

Yang M, Hou J (2012). Membranes in Lithium Ion Batteries. Membranes 2: 367-383.

Links:

BASF 2010: N-Methylpyrrolidone (NMP), BASF website www2.basf.us/diols/bcdiolsnmp.html, accessed 3 November 2010. In preparation of Annex XV SVHC report on NMP.

CEPE: http://www.cepe.org/EPUB/easnet.dll/ExecReq/Page?eas:template_im=100087&eas:dat_im=050483; date of access August 8 2012

ECHA public registration: http://echa.europa.eu/web/guest/ information-on-chemicals/registered-substances; date of access August 8 2012

SCCS: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_050.pdf

Taminco (2010): Functional chemicals – NMP, Taminco website, accessed 4 November 2010 (http://www.taminco.com/products/products/nmp.html?product_id=14).

SER on OELs: http://www.ser.nl/nl/grenswaarden/n%20methyl%202%20pyrrolidon%20damp.aspx (accessed April 17, 2013)

References chapter C

Petrochemical industry

EC (2003a). Reference Document on Best Available Techniques (BREF) for Mineral Oil and Gas Refineries. Download 27022013: http://eippcb.jrc.es/reference/

EC (2003b). Reference Document on Best Available Techniques in the Large Volume Organic Chemical Industry. Download 27022013: http://eippcb.jrc.es/reference/

Hassan SI, Sif El-Din OI, Sahar Tawfik M (2009). Solvent Refining of Straight Run Diesel Fuel by Various Solvents Phase Equilibrium. J. Appl. Sci. Res. 5(5): 515-521.

Higman C, Grünfelder G (1990). Clean Power Generation From Heavy Residues. The LURGI SGP-IGCC Concept. Presented at the Conference "Power Generation and the Environment", Institution of Mechanical Engineers, London, November 1990. Download 31012013: http://www.higman.de/gasification/papers/imeche.pdf

Hombourger T, Gouzien L, Mikitenko P, Bonfils P (2000). Solvent extraction in the oil industry. In: Wauquier JP (2000). Petroleum Refining Volume 2: Separation Processes, Chapter 7, p. 359-456 Edions Technip, Paris.

Huntsman, 2009. Technical Bulletin. Amine applications and properties data. Download 22032013. http://www.huntsman.com/portal/page/portal/performance_products/Media%20Library/a_MC348531CFA3EA9A2E040EBCD2B6B7B06/Products_MC348531D0B9FA9A2E040EBCD2B6B7B06/Amines_MC348531D0BECA9A2E040EBCD2B6B7B06/files/amine_applications_and_properties_data_2009.pdf

Liu D, Gui J, Park YK, Yang S, Gao Y, Peng X, Sun Z. (2012). Deep removal of sulfur from real diesel by catalytic oxidation with halogen-free ionic liquid. Korean J. Chem. Eng., 29(1), 49-53.

Meinersma GW, De Haan AB (2007). Conceptual Process Design for Aromatic/Aliphatic Separation with Ionic Liquids. Conceptual Process Design for Aromatic/Aliphatic Separation with Ionic Liquids Proceedings of European Congress of Chemical Engineering (ECCE-6), Copenhagen, 16-20 September 2007.

Mundhwa M, Elmahmudi S, Maham Y, Henni A (2009). Molar Heat Capacity of Aqueous Sulfolane, 4-Formylmorpholine, 1-Methyl-2-pyrrolidinone, and Triethylene Glycol Dimethyl Ether Solutions from (303.15 to 353.15) K. J. Chem. Eng. Data 54 (10): 2895–2901.

Kastanek P, Kastanek F, Maleterova Y, Solcova O, Sobek J, Hajek M. (2012). Extraction of polychlorinated biphenyls from oils using polar aprotic solvents. 3rd International Conference on Industrial and hazardous waste management, Crete, 2012. download 22032013: http://www.srcosmos.gr/srcosmos/showpub.aspx?aa=16634

Sampanthar JT, Xiao H, Dou J, Nah TY, Rong X, Kwan WP (2006). A novel oxidative desulfurization process to remove refractory sulfur compounds from diesel fuel. Appl. Catalysis B: Environmental 63: 85–93.

Weissermel K, Arpe JA (2003). Industrial Organic Chemistry. Weinheim, Wiley-VCH Verlag GmbH & Co. 4rd edition

White WC (2007). Butadiene production process overview. Chem Biol Interact. 166(1-3):10-14.

Wiese KD, Nierlich F (2005). Upgrading of C4 streams: Present and future trends. Erdöl, Erdgas, Kohle 121 (3) : 16-21.

Zhang G, Yu F, Wang R. (2009). Research advances in oxidative desulfurization technologies for the production of low sulfur fuel oils. Petroleum & Coal 51(3): 196-207.

Polymers

Wenzel W (2003). Polymer binders manufacturing processes and properties with particular consideration of NMP problems. JALCA 98 (11): 431 - 434.

Membranes

Aroon MA, Ismail AF, Montazer-Rahmati MM, Matsuuraa T (2010). Morphology and permeation properties of polysulfone membranes for gas separation: Effects of non-solvent additives and co-solvent. Sep. Pur. Technol. 72: 194–202

Non wire coaters

BASF (2010). BASF in Greater China Report 2010. Shanghai, China, BASF (China) Co. Ltd. Download 09012013: http://www.basf.com/group/corporate/en_GB/function/conversions:/publish/content/about-basf/facts-reports/reports/2010/BASF_Report_Greater_China_en_2010.pdf

BASF (2012). Product Information. All China Leather Exhibition 2012: BASF showcases innovative and high performance solutions. Singapore, BASF South East Asia Pte. Ltd. Download 09012013: http://www.performancechemicals.basf.com/ev/internet/leather/en_GB/news/events/leather_exhibition_2012

Bayer (2013). NMP-free polyurethane dispersions. Download 07032013: http://www.bayercoatings.de/BMS/DB-RSC/BMS_RSC_CAS.nsf/id/COEN_7YKHHN_PUR_Dispersions_-_NMP-free

Calgoci EC, Hegedus CR, Walker FH, Tempel DJ, Pepe FR, Yoxheimer KA, Boyce AS (2005). Solvent-free urethane-acrylic hybrid polymers for coatings. JCT CoatingsTech 2 (13): 28-36.

Clariant (2011). Green Technologies for the Leather Production. Presentation 45th Leather Research Industry Get Together (LERIG), 29 January 2011. Download 05022013: http://www.clri.org/LERIG2011/GreenMark/clariant.pdf

Cory NJ (2002). An update on environmental constraints. JALCA 97 (12): 496-505.

Diaz M (2010). New NMP free polyurethane dispersion (PUDs) grades. Coatings, Adhesives & Printing Inks. Presentation American Coatings SHOW – Charlotte 2010. Download 04032013: http://www.american-coatings-show.com/Filestore.aspx/MorchemNMPfreePUDs-ACS.pdf?fair=acs&type=file&key=43ca9198-4239-4a21-9631-a4465e5b8a36&language=en&filegroup=&filetype=file&indexfile=true

Dimmers M (2007). Sustaining resources. Polymers Paint Colour Journal 197(4515): 22-24.

Gertzmann R, Irle C, Schmitt P (2007). Waterborne Polyurethane Coatings for Wood Floors – The Next Generation. Pittsburg PA, USA, Bayer MaterialScience, LLC, White Papers. Download 31012013: http://www.thomasnet.com/white-papers/abstract/100692/waterborne-polyurethane-coatings-for-wood-floors-the-next-generation.html#null

Reichhold (2012). UROTUF®. Water-borne Urethanes. Download 01032013: http://www.adamrichardrottinghaus.com/downloads/WEB-Urotuf-Brochure.pdf

Reisch (2008). Solvent users look to replace NMP. Chemical and Engineering News 86(29): 32
The American Coatings Association Inc (2010). Americans Coatings show 2010. ACS 2010 Outlook. Exhibitors emphasize innovation. Download 15032013: http://www.coatingstech-digital.com/coatingstech/201004#pg27

Wenzel W (2002). NMP-free polyurethane products for the leather industry: a new challenge for finishing. Leather International. Download 25022013: http://www.leathermag.com/features/featurenmp-free-polyurethane-products-for-the-leather-industry-a-new-challenge-for-finishing

Leading Edge Coating Solutions (2013). LECS brand coatings. Download 31012013: http://ledgecs.com/lecs-brand-coatings. Gahanna, OH, USA.

Wire coaters

McKeen LW (2007). Fluorinated Coatings and Finishes Handbook: The Definitive User's Guide and Databook. PDL Handbook Series. Norwich, NY, USA, William Andrew Publishing.

IST (1995). Technical Bulletin #ML-1-95 - #ML-4-95. Parlin, New Jersey, USA, Industrial Summit Technology. Download 31012013: http://www.istusa.com/pdf/Pyre-ML-Technical-Bulletin.pdf

IST (2013). Pyre-ML, Polymide Resin. Download 31012013: http://www.istusa.com/pyre-ml/#specifications

Fujifilm (2013a). Polyamide-Imide Polymers (PAI). Download 31012013:
http://www.fujifilmusa.com/products/specialty_chemicals/polyamide-imide-polymers/index.html

Kaneko N, Mori J (2009). Separation of Wire Coating Materials for Recycling. Proceedings of the 58th International Wire & Cable Symposium/IICIT. Charlotte, NC, USA November 8 to 11, 2009. Download 31012013:
http://iwcs.omnibooksonline.com/data/papers/2009/P_11.pdf

Sandvik (2013). Wire insulating coatings. Download 31012013 :
http://www.smt.sandvik.com/en/products/wire/insulation-and-coating/insulation-coatings/
DKB organics PVT Ltd (2013). Range of wire enamels. Indore, India, DKB Organics Pvt. Ltd. Download 31012013:
http://www.dkborganics.com/images/fina_dkb.pdf

Murray TJ (2006). New Technology of Polyamideimide Wire Enamels. Download 31012013:
http://www.elantas.com/fileadmin/ELANTAS/downloads/tongling/innovation/technical-papers/New_Technology_of_Polyamideimide_Wire_Enamels_seminar2006.pdf

Murray TJ (2008). Poly(amide-imides): Wire Enamels with Excellent Thermal and Chemical Properties. Macromol. Mater. Eng. 2008, 293, 350–360

Cleaners

Xiaofei E, Wada Y, Nozaki JI, Miyauchi H, Tanaka S, Seki Y, and Koizumi A (2000). A linear pharmacokinetic model predicts usefulness of N-methyl2-2pyrrolidone (NMP) in plasma or urine as a biomarker for biological monitoring for NMP exposure. J. Occup. Health 42, 321-327.

Jackson HL, Gallagher RJ Jr (1990). DBE purges polyurethane equipment without methylene chloride
risks. Elastomerics 122(10): 56-60.

Inman TB (1991). Current Practices and Processes for Paint Stripping in Professional Furniture Refinishing. . In: Reducing Risk in Paint Stripping Proceedings of an International Conference February 12-13, 1991 Washington, D.C. . page 155-158. Washington D.C., USA, US-EPA

Graigner JF (1991). An Overview of Paint Stripping Practices in the Metalforming Industries. In: Reducing Risk in Paint Stripping Proceedings of an International Conference February 12-13, 1991 Washington, D.C. . page 32-38. Washington D.C., USA, US-EPA

HSE (Health and Safety Executive) (1997) N-Methyl-2-pyrrolidone. Risk assessment document. EH72/10, ISBN 0717615286, HSE Books, Sudbury, UK.

Åkesson 2001). N-Methyl-2-pyrrolidone. Concise international chemical assessment document 35, International Programme on Chemical Safety, World Health Organization, Geneva, http://www.inchem.org/documents/cicads/cicads/cicad35.htm

US Navy (2003). N-methyl pyrrolidone based cleaners and strippers. Download 04012013:
http://www.p2sustainabilitylibrary.mil/P2_Opportunity_Handbook/5_10.html

Sullivan CJ (1991). NMP Formulations for Stripping In the OEM market sector. In: Reducing Risk in Paint Stripping Proceedings of an International Conference February 12-13, 1991 Washington, D.C. . page 39-42. Washington D.C., USA, US-EPA

EC (2004). Effectiveness of vapour retardants in reducing risks to human health from paint strippers containing dichloromethane. Brussels, European Commision, Expert Team for Vapour Retarding Additives.

Hickman JC (1991). Comparative Performance of Substitute Paint Stripper Formulations. In: Reducing Risk in Paint Stripping Proceedings of an International Conference February 12-13, 1991 Washington, D.C. . page 163-172. Washington D.C., USA, US-EPA

Gaylord (2011). DMSO in Paint Stripping products A safe alternative to NMP. Gaylord Chemical Company LLC. Download 31012013:

http://www.gaylordchemical.com/uploads/images/pdfs/DMSO-in-Paintstripping-applications.pdf

California Department of Health Services (2006). N-Methylpyrrolidone (NMP). Richmond, CA, USA, California Department of Health Services, Occupational Health Branch. Download 09022013: http://www.cdph.ca.gov/programs/hesis/Documents/nmp.pdf

Kelly J, Considine T (2006). Performance Evaluation of Hap-Free Paint Strippers vs. Methylene-Chloride-Based Strippers for Removing Army Chemical Agent Resistant Coatings (CARC). Aberdeen Proving Ground, MD, USA, U.S. Army Research Laboratory, report ARL-TR-3823.

Anundi H, Langworth S, Johanson G, Lind M L, Akesson B, Friis L, Itkes N, Söderman E, Jonsson BAG, Edling C (2000). Air and biological monitoring of solvent exposure during graffiti removal. Int. Arch. Occup. Environ. Health 73, 561-569.

Langworth S, Anundi H, Friis L, Johanson G, Lind ML, Söderman E, Akesson BA (2001). Acute health effects common during graffiti removal. Int Arch Occup Environ Health. 74(3):213-8.

Reisch M (2008). Solvent users look to replace NMP. Chemical and Engineering News 86 (29): 32

Crook V, Simpson A (2007). Protective glove selection for workers using NMP containing products - Graffiti removal. Harpur Hill, Buxton, UK, Health and Safety Laboratory. HSL report HSL/2007/41.

Craver VA, Kohm S, Singer R (2011). Environmental Implications of Graffiti Removal Techniques. Transportation Research Board 90th Annual Meeting, January 23-27 2011, Washington D.C. Download 010222013: http://amonline.trb.org/12jnj2/1

Semiconductor industry

Darling RB (2000). EE-527: MicroFabrication. Negative Photoresists. Presentation. Washington D.C., USA, Department of Electrical Engineering, University of Washington. Download 11022013: http://www.ee.washington.edu/research/microtech/cam/PROCESSES/PDF%20FILES/Photolithography.pdf

Lee WM (1996). A proven sub-micron photoresist stripper solution for post metal and via hole processes. Hayward CA, USA, EKC Technology Inc. Download 21032013: http://www.slideshare.net/waimunlee/hydroxylamine-cleaning-chemistries

Peters D, Molnar L, Rovito R (2003). Development of fluoride-containing solvent-based strippers. FUTURE FAB International Issue 14 - Wafer processing. Download 13022013: http://www.future-fab.com/documents.asp?grID=214&d_ID=1667

Chatzichristidi M, Raptisa I, Diakoumakosa CD, Glezos N, Argitis P, Sanopoulou M (2002). Strippable aqueous base developable negative photoresist for high aspect ratio micromachining. Microelectronic Engineering 61–62: 729–735.

Rheinhardt A, Reidy RF (eds.) (2011). Handbook for Cleaning for Semiconductor Manufacturing: Fundamentals and Applications. Salem MS, USA, Scrivener Publishing LLC.

Suhard S, Claes M, Civale Y, Nolmans P, Tezcan DS, Travaly Y, (2012). ESH friendly solvent for stripping positive and negative photoresists in 3D-wafer level packaging and 3D-stacked IC applications. Diffusion and Defect Data Part B: Solid State Phenomena 187: 223-226.

Cornell University (2013). Photolithography Resist Processes and Capabilities. Download 11022013: http://www.cnf.cornell.edu/cnf_process_photo_resists.html

Trikiriotis M Bae WJ, Schwartz E, Krysak M, Ober CK, Giannelis EP, Lafferty N, Xie P, Smith B Zimmerman PA (2009). Inorganic photoresists based on hafnium oxide. Presentation 6th International Symposium on Immersion Lithography Extensions 22-23 October 2009. Download 11022013: http://www.sematech.org/meetings/archives/litho/8715/pres/O-APM-03_Trickeriotis_Cornell.pdf

Fujifilm (2013b). Fujifilm Photoresist strippers. Download 07042013: http://www.fujifilmusa.com/products/semiconductor_materials/photoresist-ancillaries/photoresist-strippers/index.html#overview

Challener C (2006). Photoresists: shaping the future of electronics technology. JCT Coatings Tech. 3(4): 54-59.

Futurrex (2013). Futurrex, Inc. Photoresist removers. Download 21032013. http://futurrex.com/en/products/resist-removers.html

MicroChemicals (2009). Photoresist Removal. Revised: 2009-12-15. Download 21032013: http://www.microchemicals.eu/technical_information/photoresist_removal.pdf

Batteries

Muthu J, Battaglini J (2009). Advancements in water-based Processing for large format lithium ion cells. Download 12022013: http://www.internationalbattery.com/pdf/InternationalBattery_ManufacturingWhitePaper.pdf

Pohjalainen E, Räsänen S, Jokinen M, Yliniemi K, Worsley DA, Kuusivaara J, Juurikivi J, Ekqvist R, Kallio T, Karppinen M (2012). Water soluble binder for fabrication of Li4Ti5O12 electrodes. J. Power Sources, 226: 134–139.

(Targray, 2013). Lithium-ion Battery Binders. Download 05042013: http://www.targray.com/li-ion-battery/anode-materials/binders.php

Yang M, Hou J (2012). Membranes in Lithium Ion Batteries. Membranes 2: 367-383.

Zackrisson M, Avellán L, Orlenius J (2010). Life cycle assessment of lithium-ion batteries for plug-in hybrid electric vehicles - Critical issues. J Cleaner Production 18: 1519-1529.

Agrochemicals

Knowles A (2005). Chemical and Engineering News. Agrow Reports DS243. T&F Informa UK Ltd. Code of Federal Regulations Title 21 - Food and Drugs, . (21 CFR 176.3OO(d)), 2012).

BASF (2000). Paper industry biocides. Ludwigshafen , Germany, BASF Aktiengesellschaft Specialty Chemicals. Download 04032013: http://www2.basf.us/biocides/pdfs/PIB_Brochure.pdf

BASF (2001). Water and oilfield biocides. Ludwigshafen , Germany, BASF Aktiengesellschaft Specialty Chemicals. Download 04032013: http://www2.basf.us/biocides/pdfs/WOB_Brochure.pdf

Pharmaceuticals

Bendels S, Tsinman, O, Wagner B, Lipp D, Parrilla I, Kansy M, Avdeef A. (2006). PAMPA -Excipient Classification Gradient Map. Pharmaceutical Res. 23: 2525-2535.

Dudeck O, Jordan O, Hoffmann KT, Okuducu AF, Tesmer K, Kreuzer-Nagy T, Rüfenacht DA, Doelker E, Felix R (2006). Organic Solvents as Vehicles for Precipitating Liquid Embolics: A Comparative Angiotoxicity Study with Superselective Injections of Swine Rete Mirabile. AJNR Am J Neuroradiol 27:1900–1906.

Dunn, R (2003). Application of the ATRIGEL® Implant Drug Delivery Technology for Patient-Friendly, Cost-Effective Product Development. Drug Development & Delivery 3(6) September 2003, Posted On: 3/28/2008. Download 06022013: http://www.drugdeliverytech.com/ME2/dirmod.asp?sid=&nm=&type=Publishing&mod=Publications%3A%3AArticle&mid=8F3A7027421841978F18BE895F87F791&tier=4&id=FA7F2855909844BE9E4F02C0D1C870F8

ICH (2011). ICH Harmonised tripartite guideline. Impurities: Guideline for residual solvents. Q3C(R5). International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Download 30012013: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R5_Step4.pdf

Jouyban A, Fakhree MAA, Shayanfar A (2010). Review of Pharmaceutical Applications of N-Methyl-2-Pyrrolidone. J. Pharm. Pharmaceut. Sci. 13(4): 524 - 535.

American Chemical Society Green Chemistry Institute (2012). 2013 ACS GCI Pharmaceutical Roundtable Research Grant for Greener Solvent Research. Download 04012013: http://portal.acs.org/preview/fileFetch/C/CNBP_031107/pdf/CNBP_031107.pdf

Laboratory

No references were found.

Functional fluids

Gartiser S, Urich E (2002). Environmentally compatible cooling water treatment chemicals. Berlin, German Federal Environmental Agency, Umwelt BundesAmt.

Huntsman (2006). Ethylene Glycol - Diethylene Glycol - Triethylene Glycol. Download 24032013: http://www.huntsman.com/portal/page/portal/performance_products/Media%20Library/a_MC348531CFA3EA9A2E040EBCD2B6B7B06/Products_MC348531D0B9FA9A2E040EBCD2B6B7B06/Glycols_MC348531D11A3A9A2E040EBCD2B6B7B06/files/eg_deg_teg_brochure_full.pdf

Construction Fluids

No references were found.

General

AEE Consortium, 2009. U.S. High production volume (HPV) challenge program. Sponsored substance 2-(2-aminoethoxy)ethanol. CAS number 929-06-6. Download 24032013: http://www.epa.gov/hpv/pubs/summaries/ethanol2-2amino/c16831tp.pdf
ECHA (2013). ECHA C&L Inventory database. Download 23032013: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

Gaylord Chemical Company (2003). Technical bulletin reaction solvent. Dimethyl sufoxide (DMSO). Download 11042013: http://chemistry-chemists.com/N3_2011/U/DMSO-technical_bulletin.pdf

Kerton FM, Clark JH, Kraus GA (2009). Alternative Solvents for Green Chemistry. RSC Green Chemistry Series. ISBN 10 085404163X ISBN 13 9780854041633 .

Schäffner B, Schäffner F, Verevkin, SP, Börner A (2010). Organic carbonates as solvents in synthesis and catalysis. Chem. Reviews 110 (8): 4554-4581

OECD (2008). Summary Conclusions of the SIAR on Dimethyl sulfoxide (DMSO). SIAM 26, 16-18 April 2008. Paris, OECD. Download 24032013: http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)4/part6&doclanguage=en

US-EPA (2006b). Decision document US-EPA. Inert reassessments: One exemption from the requirement of a tolerance for dimethyl sulfoxide (CAS Reg. No. 67-68-5). Download 11042013: http://www.epa.gov/opprd001/inerts/dimethyl.pdf

Lord Corporation (2013). New Aqueous, NMP Free Coating Designed by LORD Corporation. Download 29012013: http://www.lord.com/emea/news-center/new-aqueous-nmp-free-coating-designed-by-lord-corporation

BYK (2013). Additives for Coil coatings: top coats. Download 07032013: http://www.byk.com/en/additives/applications/adhesives-sealants/solvent-borne,-solvent-free.php

Dow (2013). PRIMAL™ Binder U-91. Download 27022013: http://www.dow.com/products/product-line/primal-for-leather/#/products/product/primal-binder-u-91/?&_suid=136609660928701121278779807 9937

AZ Electronic Material (2000). AZ 5200 Information sheet. Download 21032013:

http://cleanroom.ien.gatech.edu/media/resources/processing/AZ5200.pdf

Denchev Z, Dencheva N (2012).Manufacturing and Properties of Aramid Reinforced Composites. In: Bhattacharya D, Fakirov S (eds.).Synthetic Polymer-Polymer Composites, Chapter 8. Munich, Germany, Hanser Publishers.

Urben (Ed.) 2006. Bretherick's Handbook of Reactive Chemical Hazards. ISBN 9780123725639.

References chapter E

Arbocatalogi (Dutch safety declarations of intent), https://osha.europa.eu/fop/netherlands/en/nl_developments/news_article.2007-10-26.1044240052?set_language=en. Checked on 06 January 2014.

BREFs (Best Available Techniques Reference Documents, http://eippcb.jrc.ec.europa.eu/reference/. Checked on 06 January 2014.

IPPC Directive (2008/1/EC) replaced by the Industrial Emissions Directive IED (2010/75/EU)

References chapter F

Baars AJ, Pelgrom SMGJ, Hoeymans FHGM, van Raaij MTM (2005). Gezondheidseffecten en ziektelast door blootstelling aan stoffen op de werkplek – een verkennend onderzoek. RIVM rapport 320100001/2005

Dekkers S, van Benthem J, Piersma AH, Eysink PED, Baars AJ (2008). Ziektelast van effecten op de voortplanting ten gevolge van blootstelling aan stoffen op de werkplek. Best professional judgement. RIVM Rapport 320017001/2008 (in Dutch).

Nationaal Kompas (2013). http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/aandoeningen-perinataal/vroeggeboorten/omvang/. Checked on 01 February 2013.

Schuur AG, Preller L, ter Burg W, Kramers PGN, Kroese ED, van Engelen JGM, Bausch-Goldbohm RA, van Kranen HJ, van Raaij MTM (2008). Health impact assessment of policy measures for chemicals in non-food consumer products. RIVM Report 320015001/2008
TNO rapport V7740

van Thriel C, Blaszkewicz M, Schäper M, Juran SA, Kleinbeck S, Kiesswetter E, Wrbitzky R, Stache J, Golka K, Bader M (2007). Chemosensory effects during acute exposure to N-methyl-2-pyrrolidone (NMP). Toxicology Letters 175, 44–56

ECHA, 2008. Guidance Socio-Economic Analysis – Restrictions. Guidance for the implementation of REACH, May 2008.

Eurostat, 2012. Statistics on employment and demographics have been collected from Eurostat. http://appsso.eurostat.ec.europa.eu, Checked on 15 January 2013.

EUROSTAT, 2013. : "File:Median gross annual earnings of full-time employees, 2006 (1) (EUR).png" - Statistics Explained (2013/7/5)
http://epp.eurostat.ec.europa.eu/statistics_explained/index.php?title=File:Median_gross_annual_earnings_of_full-time_employees,_2006_(1)_(EUR).png&filetimestamp=20121001124304

EU Pharmaceutical Industry's Chemical Legislative Working Group, no date. Request for exemtion from REACH Authorisation (Annex XIV) for pharmaceutical uses of N,N-Dimethylacetamine (DMAC) CAS 127-19-5 as a solvent in the production of Medicinal Products

Annex 1. Uses of NMP

NMP is used in various processes in a wide variety of applications. It thereby has a wide range of potential industrial, professional and consumer users. The table below gives an overview of the use processes and the potential users of NMP. The table starts from the exposure scenarios provided by the lead registrant (Chemical Safety Report 2012-11-14) and downstream users (Chemical Safety Report 2011-04-01) describing the 'use processes' (column 1). From there it gives further explanation of the actual uses included in the various exposure scenarios, giving examples where possible (column 2). In the last column (3) the various users per use process are indicated. The wide use of NMP makes it impossible to cover all the specific uses in one table, however, this table tries to cover and explain the main uses of NMP.

Table X01.1: *Uses and users of NMP*

Exposure scenario and use process	Explanation and example of the use	Users
MANUFACTURE		
Manufacturing (ES1)	• Production of NMP	Manufacturers of NMP (1)
GENERIC USE *(industrial)*		
Chemical processes (ES2)	• Synthesis of bulk and fine chemicals (1,4) • Extraction of petrochemicals (1), large scale recovery of hydrocarbons by extractive distillation (3), lube oil processing (2), natural gas and synthetic gas purification (2) • Synthesis and extraction of pharmaceuticals (1) • Synthesis of active ingredients of agrochemicals (1) *This process includes use at elevated temperatures up to 180°C (1)*	• Petrochemical industry • Pharmaceutical industry • Agrochemical industry
Charging and discharging substances and mixtures (ES3)	• Distribution of NMP (1) • (Re)filling (1) *This process includes use at elevated temperature up to 120°C, with exception of PROC 8a (1)*	General sub-use that applies to all industrial uses Importers and suppliers
Formulation of preparations (ES5)	• Formulation of coatings (1) • Formulation of cleaners (1) • Formulation of agrochemicals (co-solvent) (1) • Formulation of pharmaceuticals (1) • Membrane production (1) (including drinking water and waste water filters, beer/wine filters, filters for ultrafiltration/ e.g. dialysis) • High performance polymer production *This process includes formulation at elevated temperatures up to 120°C for PROC 1-3 and up to 60°C for PROC 5 (1)*	General sub-use for formulation in industrial settings for various industrial users: • Non-wire coating formulators • Wire coating formulators • Cleaner products producers • Membrane manufacturers • High performance polymer producers • Agrochemical formulators • Pharmaceutical formulators
INDUSTRIAL USE		
Coatings (ES10)	NMP is used as solvent in wide variation of non-wire coatings and in wire coatings. <u>Non-wire coatings</u> NMP is used both in solvent and water-based coatings and it is used both 'directly' as solvent in coatings as 'indirectly' as solvent in binders that are used typically in water-based coatings (according to one paint industry representative).	Non-wire coaters e.g.: • Automotive/metal (3,4) • Plastics • Textiles • Foundry • Printing • Wall/concrete (3) • Wood (3)

Exposure scenario and use process	Explanation and example of the use	Users
	The NMP containing coatings are used as base coat, intermediate layer or topcoat and attribute for heat and flame protection, special effect lacquers, insulation, clear coat and transparent lacquer. NMP containing coating is used in different type of coatings processes: coil-coating, baking paint, powder coating, radiation curing and dip paint. Examples of coating types that are indicated as uses of NMP: • Paints, inks, adhesives (1) • Solvent-based high temperature coatings (4) • High temperatures coatings up to 100°C (1,2) • Water-based paints (4) • Binders for paints, typically used in water-based polyurethane dispersions (PUD) • Coating for hot environments (metal, prevent corrosion/chemical attack) (4) • Paint resins (4) • Polymer coatings (e.g. Teflon) (1) • Epoxy paints • Pigment preparations • Thinner to aid coating spray application(4) Examples of applications of coatings that are indicated as NMP uses: • Coalescing solvent in waterborne paints in automotive/metal/steel industries (4) • Coating solvents for the synthetic resins and reaction solvents for engineering plastics (solvent for synthetic resin, polyimide resin) (4) • Additive for coating especially technical textiles (solvent for thixotropic agent) (4) • Inject inks (3), component in screen printing inks (3,4) and thinner (co-solvent at c. 5%) (4), use in industrial continuous inkjet mixtures (ink) (4) • Concrete/wall coatings (3) • Wood coatings and care products, e.g. parquet lacquers (3), industrial flooring products (4) • Non-stick bakeware/coockware (3) • Urathene dispersions (2) • Specialist coatings (4) • Polymer coating in production of batteries (1) <u>Wire coatings</u> • Production of wire coatings/wire enameling (polyimide resin, PU, silicon, other resins) (1) • Typically polyamideimide (PAI) coatings.	Wire coaters
Cleaning agents (ES12)	NMP is used in various types of cleaning processes and products as e.g.: • Cleaners at elevated temperatures up to 140°C (1) • General cleaners (1,3), cleaner solvent (4) • Degreaser (3) • Cleaning and de-fluxing (1) Examples of cleaning products: • Paint removers (2,3,4) • Graffiti removers (2) • Mixtures for removal of coatings/paint/graffiti by painters or DIY (including use in aerosol cans) (4) • Floor strippers(2) • Solvent for plastics, resins, oil and grease (3) Examples of cleaning processes: • Injection head cleaning (2) • Industrial degreasing (2) • Wet cleaning of combustion engines (3) • Cast-molding equipment cleaning (2) • Cleaning of mixing tanks (dissolving residual coating) (4)	General sub-use of cleaning in a variation of industries, e.g.: • Petrochemical industry • Electronics and semi-conductor industry (1) • Optical industry (1) • Wire and non-wire coating formulators • Furniture manufacturer • Automotive industry • Maritime industry • Aeronautic industry • Optical industry

Exposure scenario and use process	Explanation and example of the use	Users
	• Removal of oil, carbon deposits and other tarry polymeric residues from metal chambers, pistons and cylinders (3), • Cleaning in electronic and optical equipment manufacture (1)	
Laboratory (ES7)	• Use in laboratory (1)	General sub-use for various NMP using industries and potentially for lab activities in non-NMP using industries
Functional fluids (ES13)	This process includes the use of NMP in e.g.: • Cable oils (1,3) • Transfer oils (1,3) • Hydraulic fluids in industrial equipment including maintenance and related transfers (1,3) • Coolants (1,3) • Insulators (1,3) • Refrigerants (1,3)	General sub-use as functional fluids for not further specified industries (2)
Construction chemicals (ES9)	• It is unclear what this use actually involves. • Articles In this process NMP is used e.g. as: • Solvent (carrier/photoresist) (2,3,4) • Cleaner/stripper (photoresist) (2,4) • Adhesive/binder (1) • Failure analysis (cleaning/stripping) (4) • De-fluxing (2) • Waterproofing (1 – old CSR) Edge bead remover (2)	Construction industry Article production (undefined)
GENERIC USE (*professional)*		
Charging and discharging substances and mixtures (ES4)	• Refilling (1) *No elevated temperatures* #(1)	General sub-use applicable to practically all professional uses • Importers/suppliers (1)
Formulation of preparations (ES6)	• Formulation of coatings (1) • Formulation of cleaners (1) • Formulation of agrochemicals (1)	General sub-use for formulation in professional settings • Professional coaters • Professional cleaners • Agricultural chemical formulation
PROFESSIONAL		
Coatings (ES11)	NMP is used both in solvent and water-based coatings and it is used both 'directly' as solvent in coatings as 'indirectly' as solvent in binders that are used typically in water-based coatings (according to one paint industry representative). The NMP containing coatings are used as base coat, intermediate layer or topcoat and attribute for heat and flame protection, special effect lacquers, insulation, clear coat and transparent lacquer. NMP containing coating is used in different type of coatings processes: coil-coating, baking paint, powder coating, radiation curing and dip paint. Examples of coating types that are indicated as uses of NMP: • Paints, inks, adhesives (1,4) • Waterborne paints (3) • Binders for paints, typically used in water-based polyurethane dispersions (PUD) (according to one paint industry representative) • High/elevated temperature coating (1,2) • Urathene dispersions (2) • Styrene latexes (2)	NMP is potentially used in a wide range of non-wire coatings and thereby has a wide range of potential professional users e.g.: • Automotive/metal (3,4) • Plastics • Leather • Textiles • Foundry • Printing • Wall/concrete (3) • Construction • Wood (3) • Artist colours • MVR

Exposure scenario and use process	Explanation and example of the use	Users
	• Acrylic latexes (2) • Epoxy paints (4) • Universal pigment preparations (4) Examples of applications of coatings that are indicated as NMP uses: • Concrete coatings (3) • Waterborne wall paints (4) • Wood coatings and care products, e.g. parquet lacquers (3,4), waterborne parquet varnish (4), waterborne floor finishes (4), sealer wood varnish (4) • Binder in waterborne PU wood paint/topcoats (4) • Trim paints and translucent woodcare paints (4) • Paints/coatings for metal (3,4) • Automotive paints (3), waterborne paints (automotive) (4) • Printing ink (NMP used at concentrations of 5 % to fuse pigment on PVC film) (4) • Screen printing inks (3) • Inject inks (industrial&general public) (3) • Decorative and protective waterborne paints (3) • Artists colours (3) • Artists colours (acrylics) (4)	
Cleaning agent No longer supported by lead registrant, not explicitly advised against.	NMP is used in cleaning processes and products as e.g.: • Cleaner(1, 3), cleaning solvent(4) • Degreaser(3) • Solvent for plastics, resins, oil and grease(3) Examples of cleaning products: • Paint removers (2,3,4) • Graffiti removers (2) • Mixtures for removal of coatings/paint/graffiti by painters or DIY (including use in aerosol cans) (4) • Floor strippers (2) Examples of cleaning processes: • Injection head cleaning (2) • Wet cleaning of combustion engines (3) • Cleaning of mixing tanks (dissolving residual coating) (4) • Removal of oil, carbon deposits and other tarry polymeric residues from metal chambers, pistons and cylinders (3)	General exposure scenario for cleaning processes in a variation of professional uses, e.g.: • Paint/graffiti • Mixing tank • Injection head/printing • Shoe producers • …
Agrochemicals (0, ES15)	NMP is used as co-formulant ((co)solvent) in herbicide, pesticide and fungicide formulations (2). This includes: • Formulation of insecticides, fungicides, herbicides, seed treatment products and bio-regulators (4) • Not further defined uses in agriculture.	Users of agricultural chemical formulations
Laboratory (ES8)	• Use in laboratory (1)	General sub-use for not-further defined laboratories
Functional fluids (0, ES14)	This process includes the use of NMP in e.g.: • Cable oils (1,3) • Transfer oils (1,3) • Hydraulic fluids in industrial equipment including maintanance and related transfers (1,3) • Coolants (1,3) • Insulators (1,3) • Refrigerants (1,3)	General sub-use as functional fluids for not further specified professional users (2)
Road and construction applications No longer supported by lead registrant, not explicitly advised	• Use of surface coatings and binders in road and construction activities (1) • Including paving, manual mastic (high grade construction adhesive/binder (in e.g. asphalt, joint-sealers, and other), roofing and waterproofing membranes(1)	Road and construction workers

Exposure scenario and use process	Explanation and example of the use	Users
against		
CONSUMER USE		
Coatings No longer supported by lead registrant	• Printing ink (1, but not by lead registrant) • Printing ink in toners (1) • Ink in pen (1) • Inject inks (2) • Use in not further specified coatings/paints	Consumers
Cleaners No longer supported by lead registrant	• Paint remover (3)/cleaner • Graffiti remover	Consumers
Cosmetics No longer supported by lead registrant	• Production of cosmetics (5)	Consumers

(1) Registration dossiers
(2) From OECD table
(3) From function description Annex XV
(4) From application/use description Annex XV
(5) SCOEL report on NMP (2007)

Wire coating

Figure X01.1: *Two pictures of enameling machines in a wire coating factory.*

Every machine has 1 or 2 lines containing, first a drawing unit for the copper wire, then the application system of liquid enamel deposited on the copper wire and calibrated by dies, than a curing oven with the catalyst, the cooling unit, all of these repeated many times to get the right coating, then the spooler. Typically, such a spool contains 400kg of cured enamelled wire, which means 500 km and 8 hours enamelling.

Semi-conductor industries

Figure X01.2: *Two pictures from the wafer cleaning process in the semi-conductor industries.*

NMP for semiconductor use in wafer cleaning and as a solvent process is performed inside a closed manufacturing equipment system which is itself inside a controlled environment known as a 'clean room'. There is no contact between the workers and NMP during the normal semiconductor manufacturing processing and during this loading/unloading process of the wafers in batch.

Annex 2. Information from product registers.

Product registers in the US and Europe indicated that NMP has been used and perhaps still is used in several consumer products. Currently, the use of NMP in consumer products is allowed up to a concentration limit of 5% (since 2010). According to industry at this concentration NMP is applied in for example coatings and sealants. In the OECD SIDS dossier on NMP the following uses are mentioned, where it should be noted that the concentration limit of 5% was not set for NMP at the time the registers were viewed:
"*Sources such as the National Environmental Trust indicate that products purchased by consumers, which may contain NMP, include household cleaning agents, adhesives and sealants, and coated fabrics (National Environmental Trust, 2004). The U.S. National Institutes of Health Household Products Database indicates that NMP is found in auto fuel system cleaners (30 – 40 % NMP), various paint removers (40 – 70 % NMP), various floor cleaners (10 % NMP), and herbicides, fungicides, and pesticides (< 7 % NMP) (National Institutes of Health, 2004).*
The Swedish Products Register of 2003 quantifies the total number of registered NMP-containing products on the Swedish market with 471, resulting in a total volume of 1,264 tons NMP per year. The total number of consumer products is given with 73, containing the following concentrations (weight percentage) of NMP: 0 – 2 % (29 products), 2 – 20 % (32), 20 – 80 % (11) and 80 – 100 % (1). The total number and corresponding production quantity of products containing 0 – 2 %, 2 – 20 %, 20 – 80 % and 80 – 100 % NMP is reported to be 128 (21 tons/year), 250 (403 tons/year), 62 (260 tons/year) and 31 (580 tons/year), respectively (Swedish Products Register, 2003).
The Danish Product Register of 2004 includes 809 products with a total quantity of 609 tons NMP per year. The total number of products containing NMP concentrations of 0-2%, 2-20%, 20-50% and 50-100% are 401, 270, 74 and 64 respectively. NMP is used in a variety of materials including adhesives, cleaning agents, coloring agents, construction materials, agricultural chemicals and solvents (Danish Product Register, 2004).
The Swiss Product Register from April 2005 states a total number of 2432 registered NMP-containing products on the Swiss market: 2018 products for industrial and 414 products for consumer use. The number of products containing NMP concentrations of 0.1, 1, 10, 50 and 100 % are given with 278, 417, 907, 286 and 130 for industrial use and with 34, 108, 209, 56 and 7 for consumer use, respectively. Products containing the highest NMP concentrations of up to 100 % are reported for cleaning agents, hardeners, paints, dyes, lacquers, sealing masses, photographic chemicals, fungicides, products for galvanization and solvents. Most of the NMP-containing products are used for paints, dyes, lacquers (39 %), followed by cleaning agents (14 %), glues, surfacers, cements, sealing masses (11 %), auxiliary material (11 %) and solvents, degreasers, diluters, (paint) strippers (9 %) (Swiss Product Register, 2005)." (OECD SIDS, 2007).

A more recent consultation on uses of NMP in Europe the following information was obtained, note that the information is not exclusive for consumer use.

***Table X02.1**: Information from the Swedish product registry.*

	Number of consumer products	**Quantity tonnes**	**Concentration range (%)**
Paints and varnished	71	13.4	0.06 – 13
Paint removers	14	4.5	13 – 68
Cleaners	7	6.8	0.9 – 15
Polishes	4	0.2	0.06 – 2
Others	9	0.1	0.2 - 5

The use is steadily and rapidly decreasing, in 2004 the annual turn-over in all products was 1300 tonnes and in 2010 it had decreased to 420 tonnes.

The Finnish product registry from 2011 states the following:
"there are at least 29 products on the market containing NMP which are made available to the general public. This group includes, e.g., cleaning agents (graffiti removing agents, oven & grill cleaners, paint strippers) and lacquers. There might be many more products available for consumers; notifying whether or not the product is made available to the general public is voluntary."

***Table X02.2**: Information from the Finnish product registry.*

Use category (UC62)	Tonnage (2011)	Typical concentration	Nr of products
Adhesives, binding agents	1.76	1-10 %	11
Cleaning/washing agents	5.81	5-40 %	40
Colouring agents	0.026	1-7 %	5
Electroplating agents	confidential	confidential	<4
Laboratory chemicals	confidential	confidential	<4
Lubricants and additives	-	-	6
Pesticides, agricultural	0	1-15 %	5
Non-agricultural pesticides and preservatives	confidential	confidential	<4
Pharmaceuticals	confidential	confidential	<4
Photo chemicals	0.004	-	8
Process regulators	0.0055	-	4
Reprographic agents	confidential	confidential	<4
Solvents	93.1	-	14
Welding and soldering agents	confidential	confidential	<4
Others	151.3	-	14
Paints, lacquers and varnishes	3.94	1-10 %	27
Surface treatment	confidential	confidential	<4
all current products	272.9		147

Key to interpretation of the table: no information or lots of variation, 0 < 0.00005 < 4: 1, 2 or 3 products on the market (at least one however).

In Cyprus, NMP is found to be used by some pharmaceutical companies mostly as a laboratory agent for the analysis of an analytical test on an ingredient or an excipient. The substance is also used as a constituent by coating industry for the production of paint removers and other coatings. The approximate annual import for 2010 was about 900 Kg.

According to the Irish CA: Based on information from a dedicated project targeting domestic foam insulation, installation contractors, we have learned that some installers are using NMP to clean their spraying equipment, in open, heated baths. NMP is present as a solvent in approximately 50 authorised veterinary medicinal products including pour-ons (at concentrations up to 35 %v/v), solutions for injection (at concentrations up to 98%v/v), spot on solutions (at concentrations up to 50 %v/v), solutions for fish treatment (at concentrations up to 65 %v/v) and sheep dips (at concentrations up to 20%v/v/). NMP is solvent used either in synthesis of active substances or as an excipient in medicinal products.
Synthesis: the extraction, purification, and crystallization of active substances as a class 2 solvent.
Excipient: mostly as a solubilising agent in controlled-released delivery systems, but this use is outside the scope of the guidelines for controlling human medicinal production in Ireland. There is one human medicinal product authorised in Ireland containing NMP – Eligard powder and solvent for solution for injection.

NMP is used as a solvent and a surfactant in cosmetic products. The final concentration of NMP in cosmetic products is not known. An SCCS opinion was published in 2011 (http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_050.pdf)

concerning NMP and its classification as a reproductive toxin Cat 1B at 5%. The opinion concludes that based on a worst case assessment with a maximum use concentration of 5% NMP in cosmetic products and a dermal absorption of 100%, the Margin of Safety is considered to be too low. The SCCS concludes that at a maximum concentration of 5% in cosmetic products, NMP is not safe for the consumer.

Annex 3. Confidential information

Annex 4. Inhalation KINETICS of NMP in RAT versus MAN

Next tier assessment of interspecies differences in inhalation kinetics of rat versus man.

Summary

Plasma kinetic data in rats and human volunteers were studied upon inhalation exposure in the range of 1-10 ppm NMP for 6-8 hours. Albeit none of the data sets available were complete and several shortcomings were noted, the overall picture is quite clear. NMP plasma concentrations in male human volunteers are somewhat lower but in the same order of magnitude compared to those predicted by linear high-to-low exposure extrapolation in male rats. However, the differences are relatively small. Taking into account various uncertainties in the data sets, these differences **cannot** be expressed as a concrete quantitative factor.

Introduction

As critical effect for the derivation of a DNEL for workers upon exposure via inhalation, the effects in a rat developmental inhalation study are used (POD = Point of Departure).
This effect is considered to be due to NMP itself and not a metabolite (REACH Restriction Report - December 2012 and various other sources: e.g. Poet, 2010; SCOEL/SUM/119, August 2007). There is some indication that humans have a more favourable toxicokinetic profile than rats, with respect to inhalation exposure to NMP. This was described in the NMP Chemical Safety Report (CSR) of 2012-11-13 as well as in Poet, 2010 and SCOEL, 2007). It was regarded important to scrutinize the available data in this respect to find out the following: Is there sufficient reasoning to use an additional assessment factor (in this case <1 as humans are hypothesised to be have more favourable toxicokinetics than rats) for interspecies differences in toxicokinetics on top of the usual assessment factors as listed in Tables R. 8-4 and R.8-6 in the REACH Guidance (Chapter R.8: Characterisation of dose [concentration]-response for human health - Version 2.1, November 2012).

For this assessment of possible interspecies differences in kinetics, a relevant **POD** was chosen as assessment of possible kinetic differences is most relevant at exposure levels taken forward to risk characterisation. This is an inhalation NOAEL 206 mg/m^3 or about **50 ppm** based on effects in the rat, i.e. 5% reduction in pup body weight (Solomon, 1995). This POD was converted to a preliminary DNEL by using the relevant AF's (total AF of 25 and 50 for non-pregnant and pregnant workers. This resulted in preliminary DNELs in the order of magnitude of 4-8 mg/m^3. Therefore, the exposure level range of 1-10 ppm NMP exposure levels were chosen as most relevant range for assessment of interspecies differences in inhalation kinetics.

The central questions that prompted the current assessment are: Do the available data provide indications that humans on average are in favour to inhaled NMP from a toxicokinetic perspective than rat at relevant inhalation exposure to NMP? In other words, do humans exhibit lower plasma concentrations than rats upon inhalation exposure in the range of 1-10 ppm? And if so, can and should that difference be expressed in a concrete quantitative factor below 1 (man versus rat)?

Sources and methods

About 30 references containing kinetic information that were listed in the CSR were screened on title, for about 20 of them, abstracts were obtained. From this list, about 15 full papers or study reports were obtained and used as basis for the current assessment of interspecies differences between rat and man in the relevant exposure concentration range of 1-10 ppm.

At the end of this Annex, a list of papers can be found that were used in the indicated order of importance. High priority was given to full papers containing experimentally determined blood levels of the parent chemical NMP in rats and human volunteers exposed to airborne NMP at the most relevant external (airborne) concentrations, being the range of 1-10 ppm (4-40 mg/m3).

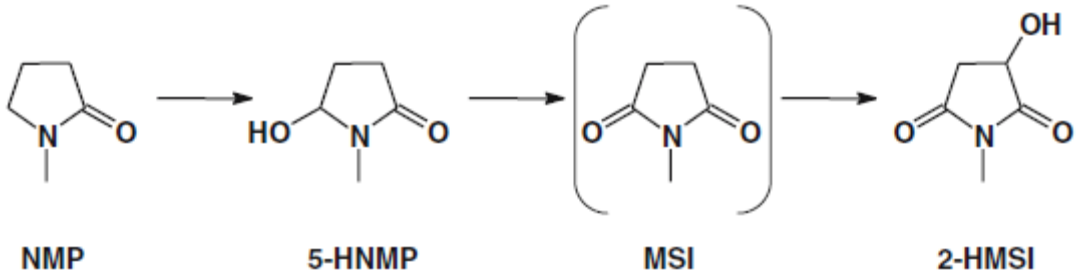
For some human volunteer data found in figures in some papers (plasma time-course data), the original source information was not found in the open literature. In these cases, the plasma time-course measurements as published in a graph, were scanned and digitized using the DigitizeIt 1.5.7 software.

In various papers, plasma levels of NMP are expressed as ppm. For easy conversion to mg/l plasma, it was assumed that the density of plasma is 1 (1 kg/l) where actual the density of plasma is approximately 1.025 kg/l.

Results

From these papers (and other documents summarised in the CSR) it was concluded that NMP is absorbed relatively easy upon inhalation as well as dermal exposure and subsequently metabolised according the following scheme in rats and humans:

Figure X04.1: *Metabolisation of NMP in rats and humans.*



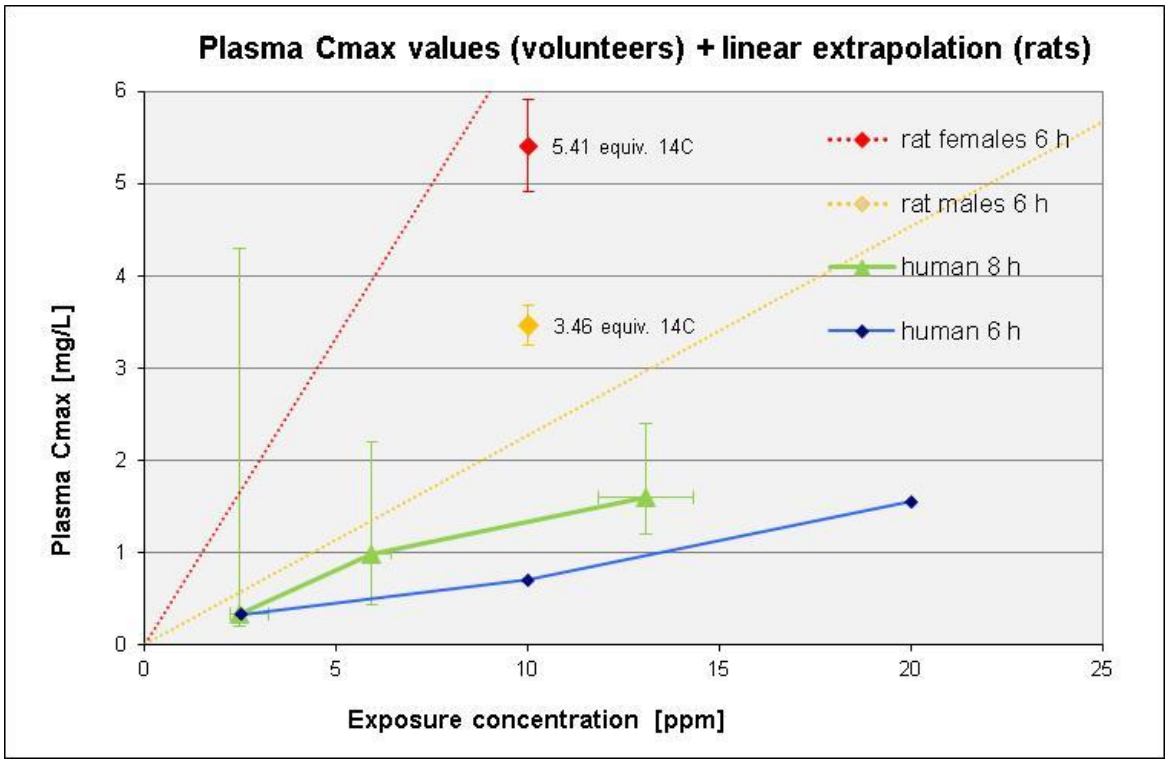
NMP as well as its metabolites 5-HNMP and 2-HMSI are readily excreted in urine. Quite some papers discussed the usefulness of these metabolites in urine for biomonitoring purposes due to the linear correlation between inhaled NMP concentrations, NMP concentrations in blood plasma and NMP, 5-HNMP and 2-HMSI concentrations in urine.

In Figure X04.1, a compilation of the most relevant measured NMP plasma levels from rat and humans can be seen. From rat, one study was available (Ghantous, 1995), for humans two studies (Akesson and Paulsson, 1997; Poet, 2010). Note the differences in exposure duration 6 h rats, and 6 h (Poet , 2010) and 8 h (Akesson and Paulsson, 1997) in male volunteers. All data presented are mean values for n=4 (rats per sex) and n=8 (humans). There was quite some variation between the individual rats and male volunteers. Standard deviations as presented in the original reports can be found in the Appendices at the end of this Annex.

Note also the difference in studied exposure concentration for which NMP measurements in plasma were available. From the rat study, plasma levels of chemical NMP in the 10 ppm exposure groups were below the limit of quantification. Only ^{14}C-equivalent concentrations were available. For straight comparison, only the rat plasma levels of the 100 ppm exposed groups were included in the figure and linear extrapolation to 0 ppm + 0 mg/l plasma was performed.

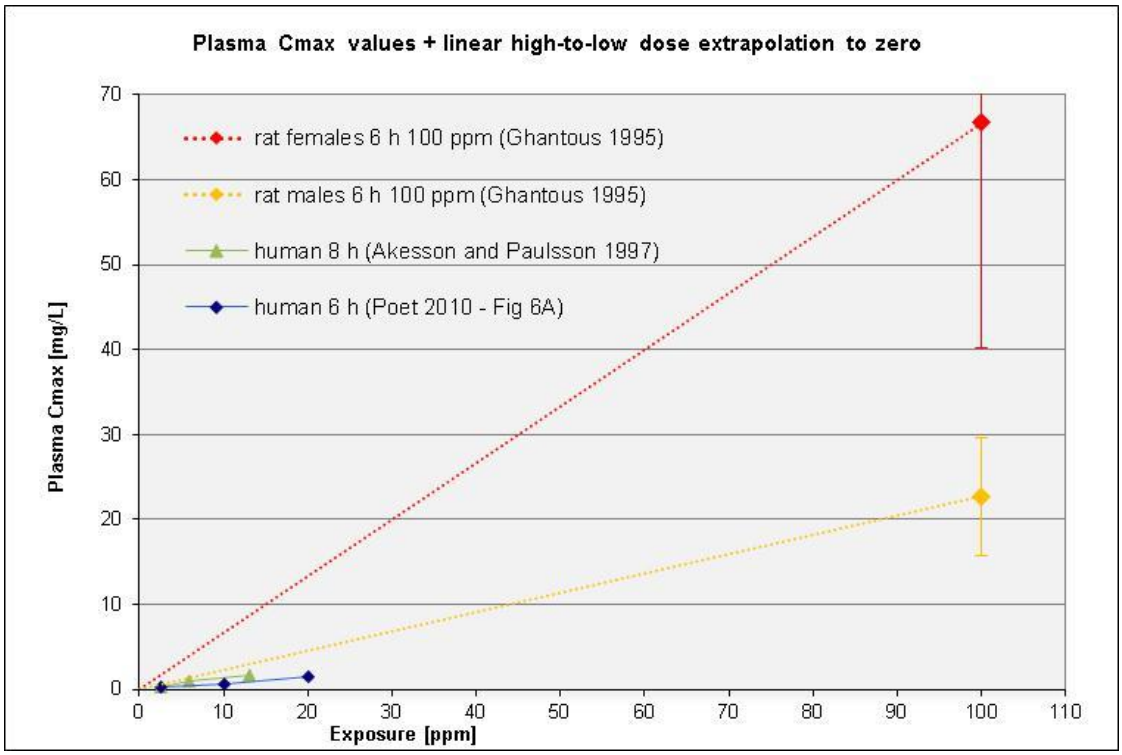
In Figure X04.2, the high exposure C_{max} values in rats can be seen. The red and yellow dotted lines in Figure X04.2 and the figure X04.3 are the same high-to-low dose extrapolation lines down to zero.

Figure X04.2: *Plasma C_{max} values upon airborne exposure in rats and human volunteers.*



C_{max} values were mostly found around the end of the exposure window. Mean C_{max} values are presented. Green triangles are from Akesson and Paulsson 1997 (n=6, 8 h). Blue diamonds from Poet 2010 (n=8, 6 hours; no ranges or standard deviation found). Male volunteers (Akesson and Paulsson 1997) exhibit quite large interindividual differences (albeit the values at the various exposure levels represent the same six men). Mean levels are presented, lower and upper plasma level indicated by error bars. The extremely high upper level measured at 2.5 ppm is probably an outlier (see discussion). The rat values (5.41 and 3.46 ^{14}C-equivalents for females and males, respectively) represent total radiolabel (NMP + metabolites). At 10 ppm, NMP plasma levels were below the limit of detection. See also discussion for further information. For rats, a linear extrapolation to zero is shown starting at the plasma NMP values measured for males and females at 100 ppm (22.7 and 66.7 mg/l, respectively). Red and orange lines represent linear extrapolation down to zero from 100 ppm measurements in female and male rats, respectively.

Figure X04.3 *– Plasma C_{max} values upon airborne exposure in rats and human volunteers (large version).*



Includes measured plasma NMP levels in female + male rats at 100 ppm including their SD (quite large for females). Plasma C_{max} values upon airborne exposure in rats and human volunteers. Same data as in Figure A3.1 with x-axis and y-axis expanded in order to show rat C_{max} values measured at 100 ppm.

Human plasma concentrations are a little lower at shorter exposure duration (6 h versus 8 h). More important for the purpose of this assessment, human plasma concentrations remain below the high-to-low exposure level extrapolated male and female rat plasma concentrations. It is noted that plasma NMP levels as well as the AUCs were higher in females compared to males at 100 ppm (66.7 versus 22.7, i.e. 3-fold). This was also the case for ^{14}C-NMP-equivalents (Table X04.1) although the difference was much smaller (82.5 versus 72.2 mg/l plasma). This indicates lower metabolic clearance in female compared to male rats.

Another important note is the difference in exposure scenario. Rats were exposed nose-only whereas male volunteers where exposed via airborne levels. The latter may cause dermal exposure as well, meaning that the internal plasma levels reflect cumulative exposure (via inhalation and via skin).

Table X04.1: *Ghantous, 1995. Rat inhalation study. Plasma kinetics.*

	T_{max} [h]	C_{max} [mg/l]	±	$t_{1/2}$ [h]	AUC [mg*h/l]	±
Females						
10 ppm ^{14}C	6.5	5.4	0.5	3.4	42.5	4.7
100 ppm ^{14}C	6.5	82.5	12.1	3.0	696.6	33.8
100 ppm	7.0	66.7	53.0	1.6	383.3	257.5
Female/Male RATIO						
10 ppm ra	1.08	1.54		1.62	1.65	
100 ppm ra	1.04	1.14		1.50	1.30	
100 ppm	2.00	2.94		1.07	3.30	
Males						
10 ppm ^{14}C	6.0	3.5	0.2	2.1	25.8	2.1
100 ppm ^{14}C	6.3	72.2	12.2	2.0	534.4	93.0
100 ppm	3.5	22.7	13.9	1.5	116.1	66.2

Italic data are ^{14}C-equivalents or half-lives of total radiolabel.

Another important observation was the apparent large interindividual variation in NMP plasma levels in human volunteers in the Akesson and Paulsson (1997) study as shown in Figure X04.2. In this figure also the rat female and male ^{14}C-equivalence plasma levels of ^{14}C-NMP were indicated for reasons of comparison.

Occupational exposure levels

In a number of references that were used to set up biomonitoring instruments, occupational airborne concentrations were presented. In general, the time-weighted average (TWA) exposure levels do not exceed 1.1 ppm (4.52 mg/m3). The papers that were considered in more or less detail can be found in reference list.

Discussion

When assessing interspecies differences in the TK of NMP, variations in exposure scenario's should be taken into account. Differences found may be dependent on the exposure scenario's.

Interspecies difference in the 1-10 ppm exposure range

The data strongly indicate that human males do not show higher plasma levels upon similar exposure levels and durations. Taking all available data that were obtained under experimental conditions (rats and human volunteers), human plasma NMP levels seem to remain below the rat plasma NMP levels in the 1-10 ppm exposure range. Nevertheless, there are some caveats that are discussed below.

Nose-only (rat) versus ambient air (human: dermal + inhalation)

In the most relevant rat study, rats were exposed via nose-only exposure, meaning that dermal absorption is probably negligible. In all human volunteer studies, exposure was via ambient air, meaning, a significant part of the systemic exposure and plasma levels could be due to dermal exposure. This is substantiated by the study finding of Bader et al (2008) that showed that absorption via the skin may exceed to approximately half of the total systemic dose. For the scope of this assessment, this phenomenon does not influence the general observation that at relevant exposure concentrations and taking variations in exposure time into account, human plasma levels remain below rat plasma levels. If rats would have been exposed 'whole body', their plasma levels would probably be even higher, leaving human plasma levels even more below the rat plasma levels.

Exposure duration

In Figure A3.1 it can be seen that upon 8 h exposure, mean human plasma levels are a little higher than at 6 h exposure. But even the 8 h exposure mean maximum plasma levels remain below the extrapolated mean maximum plasma levels in rat, for male as well as female rats.

Sex differences

In the rat study, males and females were studied. Variation between animals seems to be larger for the female animals. So the individual rat data were examined in the study report of Ghantous (1995). This reveals that the exact values presented in the report (preciseness) of the mean NMP plasma levels and their standard deviation is questionable. Some missing values as well as outliers seem to have influence the means and standard deviation to a large extent.
Nevertheless, taking these uncertainties into consideration, it is seems obvious that some sex-differences exist with respect to clearance. Female rats seem to have lower capacity for metabolic clearance.

Interindividual differences

For rats (Ghantous, 1995), quite some variations were observed. Especially the female plasma NMP levels presented with large variation (66.7 ± 53.0 mg/l). In-depth review of the individual animal data revealed that this is very probably due to one outlier. It is therefore unlikely that this is due to real interindividual differences. It seems more likely that this is due to experimental errors. Probably, the average C_{max} presented for plasma NMP in females is erroneously high due to one extreme outlier value. When looking at Fig. 1, it seems that at 10 ppm, the level of total radiolabel (^{14}C-equiv) is lower than the (extrapolated) level of NMP itself. This is impossible and thereby another reason why the 100 NMP average plasma levels in females probably should have been lower, bringing the red extrapolation line below the measured data point of total plasma radiolabel for female rat at 10 ppm of 5.4 equiv.

Regarding human male volunteer data, especially the paper of Akesson and Paulsson contains quite a large variation but only for one exposure concentration. For the lowest exposure concentration (2.5 ppm), a very large upper value was published. This is quite strange as the distance between the mean levels presented in the paper and the upper values was much smaller for the medium and high exposure (6.25 and 12.5 ppm). This concerns the same six volunteers that were exposed on different days to the four concentrations (including zero exposure; not indicated in the figure). So there could be some erroneous data especially with respect to the upper levels published.

Combined interspecies and sex differences

In the current assessment, for rats, male and female kinetic data are available. However, for humans, only male data were available. It remains uncertain as to whether the apparent sex differences in rat are real or caused by measurement errors. Especially the female plasma levels exhibit some rather extreme outliers (Ghantous 1995).

Possible influence of induction of metabolic clearance enzymes

All kinetic data available were obtained upon single exposure. It remains unclear as to whether repeated exposure (being the relevant exposure scenario for the developmental effects) would cause increased (enzyme induction) or decreased (enzyme inhibition) metabolic clearance. This uncertainty cannot be accounted for by an uncertainty factor and remains a qualitative uncertainty. The same pertains to possible interspecies differences in possible induction or inhibition processes.

Consideration of target tissue (foetuses) using PBK modelling approach

Preferably, risk characterisation is performed using actual expected human target tissue exposures and measured or simulated experimental animal target tissue exposures. In 2010, Poet et al developed a physiologically-bases kinetic (PBK) model to extrapolate findings from animal toxicity studies to humans. They used the rat PBK model to determine the relationship between NMP concentrations in maternal blood and decrements in foetal/pup body weights following exposures to NMP vapour. The area-under-the-curve (AUC) in maternal blood at the POD was used as basis to back-extrapolate (reverse dosimetry) the same AUC in human blood to human equivalent external exposure concentrations (HEEECs) using a human PBK model. These HEEECs could be used to calculate risk characterisation ratio's (RCRs) for the various human exposure scenarios. A preliminary assessment revealed that the Poet (2010) modelling approach contained limitations. They preclude its utility for quantitative rat to human extrapolation. An in-depth assessment of this

approach would include at least model implementation and assessment of the model parameters, in particular with respect to the assumptions used regarding scaling of metabolism parameters and sensitivity analyses. This is beyond the scope of the current assessment.

Tissue dose versus plasma levels

Preferably, interspecies comparisons are performed based on target tissue dose level. However, the information available was insufficient in this respect. Also, a clear Mode of Action with substantial support for a particular target tissue should be available, which was not the case either.

General

Finally, it is important to realise that the quality of the database used for this assessment is in general rather limited. Only the Ghantous study (1995) was performed under GLP. All other data on rats and humans were from public literature. Also, it is important to realise the various caveats and uncertainties discussed above.

Although important to be mentioned, in-depth discussion of the possible relevance of the above mentioned uncertainties was regarded as beyond the scope of this assessment. Some of the uncertainties could be reduced by incorporating physiologically-based kinetic (PBK) modelling in a further in-depth assessment. This could enable a more integrated assessment of NMP kinetics by combining various sources of data, that is to say on exposures via different routes (i.v., oral, dermal), in different species (rat, humans), at different exposure times and sampled in different matrices (blood, tissues, urine, microsomes). An in-depth assessment would have to start with actual implementation of the PBK model published (Poet, 2010) and challenging various parameter values, assessment of the validity of the parameterisation, and sensitivity analysis.

Conclusion

The data available that could be assessed show that on average, humans do not show higher plasma NMP levels upon inhalation exposure in the 1-10 ppm ambient air range. However, the information does not justify the conclusion that on average, humans have significantly more favourable toxicokinetics than rats. Nor is the information sufficient to express in a concrete quantitative factor.

References

	Year	Paper	Spec.	How	Route	Conc [ppm]	Duration [h]	What	Analyte	Remarks
1	1997	**Akesson** B and **Paulsson** K **(1997).** Experimental exposure of male volunteers to N-methyl-2-pyrrolidone (NMP): acute effects and pharmacokinetics of NMP in plasma and urine. Occup. Environ. Med. 54, 236-240.	Human	Volunteer	Dermal + Inhalation	2.5 + 6 + 13	8	plasma conc + half lives	NMP	present
1	2000	**Anundi** H, Langworth S, Johanson G, Lind M L, Akesson B, Friis L, Itkes N, Söderman E, Jonsson BAG, and Edling C **(2000).** Air and biological monitoring of solvent exposure during graffiti removal. Int. Arch. Occup. Environ. Health 73, 561-569.	Human	Worker	Dermal + Inhalation	1.01 ± 0.89	8	air + plasma + urine	NMP + 5-HNMP + 2-HMSI	present
1	1995	**Ghantous** HN, **(1995).** Oral, dermal and inhalation pharmacokinetics and disposition of [2-14C] NMP in the rat. Report No. 630-95, November 17, 1995, Haskell Laboratory for Toxicology and Industrial Medicine, unpublished report.	Rat	**NOSE ONLY !!**	I.v. + Oral + Dermal + Inhalation	10 + 100	6	plasma conc	NMP	present
1	2010	**Poet** TS, Kirman CR, Bader M, van Thriel C, Gargas ML, and Hinderliter PM **(2010).** Quantitative risk analysis for N-methyl-pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. Toxicol. Sci. 113: 468 -482.	Human Rat	PBK	Dermal + Inhalation	2.5 + 10 + 20	6	plasma conc	NMP	present
1	2000	**Xiaofei** E, Wada Y, Nozaki JI, Miyauchi H, Tanaka S, Seki Y, and Koizumi A **(2000).** A linear pharmacokinetic model predicts usefulness of N-methyl2-2pyrrolidone (NMP) in plasma or urine as a biomarker for biological monitoring for NMP exposure. J. Occup. Health 42, 321-327.	Human	Volunteer + Worker	Dermal + Inhalation	0.24-0.38 + 0.09-0.69	8+12	plasma conc + urine	NMP	present

	Year	Paper	Spec.	How	Route	Conc [ppm]	Duration [h]	What	Analyte	Remarks
2	2000	**Akesson** B and **Jonsson** B **(2000).** Biological monitoring of N-methyl-2-pyrrolidone using 5-hydroxy-N-methyl-2-pyrrolidone in plasma and urine as biomarker. Scand. J. Work. Environ. Health 26, 213-218.	Human	Volunteer	Dermal + Inhalation			plasma conc	5-HNMP	present
2	2008	**Bader** M; Wrbitzky R; Blaszkewicz M; Schäper M; van Thriel C; **(2008)** Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch Toxicol (2008), 82:13 -20.	Human	Volunteer + Worker	Dermal + Inhalation			air + urine	NMP + 5-HNMP + 2-HMSI	present
2	2007	**Bader** M; Wrbitzky R; Blaszkewicz M; van Thriel C. **(2007).** Human experimental exposure study on the uptake and urinary elimination of N-methyl 2-pyrrolidone (NMP) during simulated workplace conditions. Arch Toxicol (2007) 81:335-346.	Human	Volunteer	Dermal + Inhalation			air + urine	NMP + 5-HNMP + 2-HMSI	present
2	2001	**Jonsson** BAG and **Akesson** B **(2001).** N-Methylsuccinimide in plasma and urine as biomarker of exposure to N-methyl-2-pyrrolidone. Int. Arch. Occup. Environ. Health 74, 289-294.	Human	Volunteer	Dermal + Inhalation			air + plasma + urine	MSI	present
2	2003	**Jonsson** BAG and **Akesson** B **(2003).** Human experimental exposure to N-methyl-2 -pyrrolidone (NMP): toxicokinetics of NMP, 5 -hydroxy-N-methyl-2 -pyrrolidone, N-methylsuccinimide and 2 -hydroxy-N-methylsuccinimide (2 -HMSI), and biological monitoring using 2 -HMSI as a biomarker. Int. Arch. Occup. Environ. Health 76, 267 -274.	Human	Volunteer	Dermal + Inhalation			air + plasma + urine	2-HMSI	present
3	2006	**Bader (2006)** Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility. Int Arch Occup Environ Health (2006) 79: 357–364	Human	Worker	Dermal + Inhalation			air + urine	NMP + 5-HNMP + 2-HMSI	present

	Year	Paper	Spec.	How	Route	Conc [ppm]	Duration [h]	What	Analyte	Remarks
4	1997	**Akesson** B and **Jonsson** B **(1997).** Major metabolic pathway for N-methyl-2-pyrrolidone in humans. Drug. Metab. Disp. 25, 267—269.	Human	Volunteer	Oral			urine half lifes	Pathway	present
4	2002	**Akrill** P, Cocker J, and Dixon S **(2002).** Dermal exposure to aqueous solutions of N-methyl pyrrolidone. Toxicol. Letters 134, 265-269.	Human	Worker	Dermal			urine		abstract
4	2003	**Ligocka** D, Lison D, and Haufroid V **(2003).** Contribution of CYP2E1 to N-methyl-2-pyrrolidone metabolism. Archives of Toxicology 77, 261-266.	Human Rat	Exp	Dermal + Microsomes			urine	5-HNMP	present
4	2002	**Payan** JP, Beydon D, Fabry JP, Boudry I, Cossec B, and Ferrari E **(2002).** Toxicokinetics and metabolism of N-[14C]methyl-2-pyrrolidone in male Sprague-Dawley rats: a saturable NMP elimination process. Drug Metab. Disp. 30, 1418-1424.	Rat	Exp	Dermal			blood + urine		present
4	2003	**Sitarek** K **(2003).** Excretion and maternal-fetal distribution of N-Methyl-2-Pyrrolidone in rats. Reproductive Toxicology 17, 475-508 (abstract).	Rat	Exp	Oral - Dams and pups			distribution + excretion		abstract present
4	2006	**Sitarek** K **(2006).** Tissue distribution and excretion of N-methyl-2-pyrrolidone in male and female rats. International Journal of Occupational Medicine and Environmental Health 19: 142-148.	Rat	Exp	Oral - Male + female			distribution + excretion		abstract
4	1988	**Wells** DA, and Digenis GA **(1988).** Disposition and metabolism of double-labeled [3H and 14C] N-Methyl-2-Pyrrolidone in the rat. Drug Metabol. Dispos. 16, 243-249.	Rat	Exp	Intraven.			plasma	Radiolabels	present
5	2003	Bader M, Rosenberger W, Rebe T, and Wrbitzky R (2003). V40: Feldstudie zur äußeren and inneren Belastung mit N-Methyl-2-pyrrolidon bei der Anwendung von Harzlösern zur Kessel- and Werkreinigung. Arbeitsmed. Sozialmed. Umweltmed.	Human							Less relevant. German.

	Year	Paper	Spec.	How	Route	Conc [ppm]	Duration [h]	What	Analyte	Remarks
		38, 135. Supporting study.								
5	2005	Carnerup A, Saillenfait AM, and Joensson BOG (2005). Concentrations of N-methyl-2 - pyrrolidone (NMP) and its metabolites in plasma and urine following oral administration to rats. Food Chemical Toxicology 43, 1411 - 1447.	Rat							Not relevant
5	2003	Health and Safety Laboratory (2003). Workplace respiratory, dermal and systemic exposure to N-methyl pyrrolidone in the UK. Report Number: HSL/ECO/2003/04, Sheffiled, UK	Human							Not relevant, research on gloves
5	2004	Kennedy GL and Delorme MP (2004). Letter from DuPont Haskell Laboratory to the NMP Producers Group, 14 April 2004.	NR							Not relevant = letter
5	1992	Midgley I, Hood AJ, Chasseaud LF, Brindley CJ, Baughman S, and Allen G (1992). Percutaneous Absorption of co-administered N-methyl-2-[14C]pyrrolidinone and 2-[14C]pyrrolidinone in the rat. Fd. Chem. Toxic. 30, 57-64.	Rat		Dermal					Not relevant
5	2003	Penney MS (2003). Physiologically-based pharmacokinetic modeling of the skin absorption of N-Methyl-Pyrrolidone in vivo. Toxicology, 192, 79-80.			Dermal					Not relevant
5	1992	Ravn-Jonsen A, Edelfors S, Hass U, and Lund SP (1992). The kinetic of N-methyl-2-Pyrrolidone in pregnant rats and their fetuses compared with non-pregnant rats. Tox. Lett., Suppl. P5/P8, 136.	Rat	Pregnant	Femal pregnant Fetus					Abstract
5	2005	Rawson BV, Cocker J, Evans PG, Wheeler JP, and Akrill PM (2005). Internal contamination of gloves: Routes and consequences. Annals Occupational Hygiene Advance Access, 17 May 2005, 1-7.	Human		dermal					Not relevant

	Year	Paper	Spec.	How	Route	Conc [ppm]	Duration [h]	What	Analyte	Remarks
5	1991	Research Triangle Institute (1991). Absorption, distribution, metabolism and elimination of N-Methyl-2-Pyrrolidone (NMP) in rats after oral and dermal administration. Project RTI/3662/00-13P,11 Jul 1991, unpublished report.	Rat		Oral Dermal					Not relevant
5	1988	Wells DA, Thomas HF, and Digenis GA (1988). Mutagenicity and cytotoxicty of N-methyl-2-pyrrolidone and 4-(methylamino) butanoic acid in the Salmonella/microsome assay. J. Appl. Toxicol. 8, 135-139.	vitro							Not relevant. No TK.
5	2004	Will W, Leuppert G, and Rossbacher R (2004). Poster: Dermal and Inhalative Uptake of N-Methyl-2-pyrrolidone (NMP) during Paint Stripping of Furniture. 6thInternational Symposium on Biological Monitoring in Occupational and Environmental Health, Heidelberg, Germany.	Human	Work						Poster, not relevant
5	2003	Wrbitzky R and Bader M (2003). Summarized report on current NMP biomonitoring activities. Department of Occupational Medicine, Hannover, Germany.	Human	Work	Monitoring report					Not relevant

Annex 5. Overview alternatives to NMP.

substance	CAS.nr.		Generic uses: Polymer production	Petrochemical industries	Non wire coaters	Wire coaters	Cleaners	Electronic industries	Semiconductor industries	Battery industries	Battery industries	Membrane manufacturers	High performance polymer manufacturing	Agricultural chemical industries	Pharmaceutical industry	Laboratory	Functional fluids	Construction chemicals
N-ethyl pyrrolidone	2687-91-4	NEP	x		x		x									x	x	
Dimethyl formamide	68-12-2	DMF	x	x		x	x		x			x		x	x	x		
Dimethyl acetamide	127-19-5	DMAC	x			x	x					x		x	x	x		
Dimethyl sulfoxide	67-68-5	DMSO	x	x	x	x	x		x			x		x	x	x		
Tetrahydrofurane	109-99-9	THF									x	x						
Tetramethyl urea	632-22-4	TMU				x												
Acetone	67-64-1		x		x	x	x		x		x							
Methanol	67-56-1	MeOH		x														
Ethanol	64-17-5														x			
Acetylene	74-86-2			x														
Acetonitrile	75-05-8			x												x		
Acrylonitrile	107-13-1			x														
N-formyl morpholine	4394-85-8			x											x			
Formamide	75-12-7															x		
Triethyl phosphate = phosphoric acid triethyl ester	78-40-0	TEP	x			x												
Glycols																	x	
Dipropylene glycol monobutyl ether	29911-28-2	DEGBE					x											
Dipropylene glycol monomethyl ether	34590-94-8	DPGME			x				x									
Diethylene glycol monoethyl ether	111-90-0	DEGEE					x								x			
Tripropylene glycol ethyl ether	25498-49-1	TPM					x											
Trimethyl glycol dimethyl ether (triglyme)	112-49-2	TEGDME		x														
Di-glycol ethers							x											
Ethylene glycol	107-21-1			x														
Diethylene glycol	111-46-6			x														
Polyethylene glycol	25322-68-3	PEG													x			
Tetraglycol = tetraethylene glycol dimethyl ether (31692-85-0)	143-24-8														x			
Glycol furol = tetrahydrolfurfuryl alcohol polyethylene glycol ether	31692-85-0														x			
Furfuryl alcohol = 2-furylmethanol	98-00-0						x											
Furfural	98-01-1																	
Tetrahydrofurfuryl alcohol	97-99-4													x				
Propylene glycol	57-55-6								x						x			
Propylene glycol ethers (o.a. 20324-33-8)														x				

substance	CAS.nr.		Generic uses: Polymer production	Petrochemical industries	Non wire coaters	Wire coaters	Cleaners	Electronic industries	Semiconductor industries	Battery industries	Battery industries	Membrane manufacturers	High performance polymer manufacturing	Agricultural chemical industries	Pharmaceutical industry	Laboratory	Functional fluids	Construction chemicals
Ethylene glycol monobutyl ether (butoxyethanol)	111-76-2	EGBE					x		x									
Dipropylene glycol methyl ether acetate	88917-22-0	DPMA							x									
Propylene glycol monomethyl acetate (2-methoxy-1-methylethyl acetate)	108-65-6	PMA							x									
Propylene glycol monomethyl ether	107-98-2	PGME							x									
Tetraethylene glycol	112-60-7	Tetra EG		x														
Ethylene glycol phenyl ether	122-99-6								x									
Dipropylene glycol dimethyl ether	111109-77-4				x													x
Methyl ethyl ketone = butanone	78-93-3	MEK	x				x				x							
2-Heptanone (butyl acetone) (amyl methyl ketone)	110-43-0								x									
Organic carbonates														x				
Propylene carbonate	108-32-7	PC		x			x								x			
Dibasic esther		DBE					x											
Ethyl 3-ethoxypropionate	763-69-9	EEP					x											
Dimethyl phthalate	84-66-2	DMP					x											
Sodium hypochlorite	7681-52-9						x											
Sodium hydroxide	1310-73-2						x		x									
Potassium hydroxide	1310-58-3						x		x									
Colza oil esther							x											
Formic acid	64-18-6						x											
Monoethanolamine	141-43-5	MEA					x		x									
Isopropanolamine	78-96-6						x		x									
N-methylethanolamine	109-83-1								x									
Combinations of several substances							x											
Gamma butyrolactone	96-48-0	GBL					x		x					x				
Acetophenone	98-86-2						x											
Methanol/toluene/ethylene chloride							x											
Toluene	108-88-3															x		
Benzyl alcohol	100-51-6						x		x									
Dimethyl sorbide	5306-85-4													x				
Peroxysulfuric acid	7722-86-3								x									
Benzyl alcohol/formic acid							x											
Methylene chloride = dichloromethane	75-09-2	DCM			x		x									x		
Trichloroethylene = 1,1,1-trichloroethane	71-55-6	TCE							x									
Hydrogen peroxide	7722-84-1						x											
Ethyl acetate	141-78-6				x													

substance	CAS.nr.		Generic uses: Polymer production	Petrochemical industries	Non wire coaters	Wire coaters	Cleaners	Electronic industries	Semiconductor industries	Battery industries	Battery industries	Membrane manufacturers	High performance polymer manufacturing	Agricultural chemical industries	Pharmaceutical industry	Laboratory	Functional fluids	Construction chemicals
Propyl acetate	109-60-4				x													
n-butyl acetate	123-86-4								x									
Ethyl lactate	97-64-3	EA					x		x						x			
Methyl-, ethyl-, butyl- and ethylhexyl lactates														x				
Solvent naphta (various CAS-nrs, e.g. 64742-94-5)							x											
Alkaline containing solvents									x									
Phenol	108-95-2								x									
Xylene = methylbenzene (various CAS-nrs)	1330-20-7				x		x		x									
1,3-Dimethyl-2-imidazolidinone	80-73-9	DMI							x						x			
D,L-isopropylidene-glycerol	100-79-8														x			
Ethanol	64-17-5														x			
Glycerol	56-81-5														x			
Isopropanol	67-63-0	IPA													x			
Sulfolane (tetramethylene sulfone)	126-33-0			x		x			x									
o-dichlorobenzene	95-50-1								x									
Perchlorethylene	127-18-4	PER							x									
Aromatic hydrocarbon solvent (aromatic naphtha C7 gasoline feedstock)	64741-68-0								x									
Naphthalene	91-20-3								x									
Hexamethylphosphoramide	680-31-9	HMPA											x			x		
2-(2-aminoethoxy)ethanol (diethylene glycolamine)	929-06-6			x					x									
Additional remarks**				**1**	**3, 4**	**5**	**6**			**7**	**8**	2			**9**			

*** Additional remarks:*
1) Alternative processes available
2) Application strongly depend on the type of polymer used
3) NMP only needed in high-molecular weight PU dispersions
4) NMP-free product available (from BASF, Bayer, Clariant and others)
5) Application strongly depend on type of wire and thus polymer applied
6) DBE and NMP showed better results than the others
7) Development to water based binders, not yet on industrial scale
8) PVDF based electrolytes
9) ICH proposed to limit use of NMP as a solvent in pharmaceutical products

Annex 6. Questionnaire industry NMP by RIVM.

05-10-2012
<note: tables are deleted>

General

1. We base our dossier e.g. on the registration dossiers, the CSR and on the Annex XV dossier (and comments) of NMP. Do you foresee changes or updates in this information that are important for us to consider?

Uses

2. In the available documents on NMP different uses are defined. For our restriction proposal, we propose a categorisation of main-uses and sub-uses of NMP (see table 1). With this, we do not intend to cover all uses in detail, but we hope to cover all major use categories. Could you please check our proposal in terms of correctness and completeness? Are there key (sub-)uses that are not in our proposal or are there key (sub-)uses that you think will require special attention for specific reasons?

3. Are the estimated quantities of NMP used in various use categories correct? (see Table 2, Table 2.a., Table 2.b.). Can you (roughly) specify the average % of use by industrial, professional and consumer uses per use category (table 2)? Could you indicate the use quantities for the following uses: functional fluids, road and construction applications, conductor and semi-conductor industries, production of polymers and batteries, cosmetics and consumer coating printing inks?

4. According to SCOEL, NMP is also used in the formulation of cosmetics. Is this use still relevant?

5. Is NMP used as intermediate during formulation processes, if yes, during what specific formulations?

6. Are there consumer uses/products that contain NMP in concentrations < 5%w/w?

7. This table does not include the amount of NMP in imported mixtures and articles. Can you provide estimations on the import quantities of NMP in mixtures and articles?

8. What is the concentration of NMP used in the different main uses?
   So far we only found the following information of paint removing products:
   - Polymer remover containing 30-60 % NMP. This product was primarily used to remove polymer deposits from moulding tools. The company has now replaced NMP in these products due to concerns with the reclassification of the substance.
   - Anti-graffiti cleaner containing 5-15 % NMP.
   - Stain protecting products containing 1-5 % NMP (used by the general public). Again, this product has been reformulated to remove NMP due to labelling concerns.
   - Graffiti removing towels containing 10-25 % NMP.

9. What is the minimal concentration of NMP required in the different (main) uses for the substance to be effective?

Marked trends

The Annex XV SVHC dossier on NMP mentions different trends:
- Downward trend in coatings
- Downward trend in cleaning agents
- Upward trend in electronic equipment manufacturing (due to the use in PV cells)
- Stabilizing trend in petrochemical processing industry
- Unknown trend in agrochemicals, pharmaceuticals and functional fluids

- Unknown trend in laboratory, road and construction applications, conductor and semiconductorindustries, production of polymers and batteries, cosmetics
- Unknown trends in manufacturing, import, distribution, formulation/(re)packing

Questions on trends:

10. Can you provide us with quantitative information that backs-up the stated trends (e.g. historic data / expert estimates of quantities and concentrations of NMP used)? What trend lines would you forecast for the coming decades (2010, 2015, 2020, 2030)? What are the main reasons for the trends?

11. Besides the trend information specified per use, can you give information on trends specified to consumer, professional and industrial uses?

12. What would be the effect of reclassification (CLH) of NMP on the consumer use of NMP? (Aim of the reclassification is to lower the concentration limit from 5% to 0.3%)

Toxicology/DNEL

13. A number of toxicological studies that are included in the SCOEL report (2007) are not included in the IUCLID dossier and CSR.
    - The Solomon et al. 1995 study, describing a two-generation inhalation study was not taken up in the dossier. Can the registrant provide the raw data from this study as it may be relevant for deriving an inhalation DNEL?

14. Why was the OEL used for RCR calculations for the general public?
15. Why was the acute/short-term dermal DNEL (worker and general public) not based on the developmental toxicity endpoint?

Exposures

16. Does the exposure assessment for the formulation and packing of substances and mixtures processes cover the manufacturing of coatings, cleaners, agrochemicals, cosmetics, pharmaceuticals, electronic equipment, (semi-) conductors and batteries, functional fluids, petrochemicals and road and construction application products?

17. Does the exposure assessment of the use of cleaners (at elevated temperatures) cover the use of NMP in the production of electronic equipment, (semi-) conductors and petrochemicals?

18. Is NMP still present in the final product in case of electronic equipment, (semi-) conductors, cosmetics, pharmaceuticals and petrochemicals?

19. It is noted that the exposure assessment sometimes takes into account the RMMs between brackets, even though the registrant states that they are good advice only and go beyond REACH CSA. However, if such RMMs are not taken into account RCRs > 1 will be obtained. See for example ES11a, PROC5 or ES5a, PROC13. Is it correct to base the exposure calculations taking into account these RMMs?

20. The registrant states that "natural ventilation" or a "good standard of ventilation" leads to a 70% reduction, which is acceptable when the emission source is in a far-field location. However, such reduction cannot be applied in a PROC10 situation, where the emission source can be expected to be in close range. In such cases, it is considered that dilution by natural ventilation is insufficient. Can you clarify for the other PROCs that the exposed worker is outside the near-field exposure area?

21. Technical maintenance and cleaning is covered by PROC8a (in general) and by PROC10 (for laboratory use), why were these specific PROCs selected?

22. How is the exposure assessed for cleaning staff?

23. Cleaning equipment is mentioned for professional use of coatings, but it is unclear by which PROC this exposure is covered. Can you clarify?

24. The exposure assessment for ink and toners (only by one registrant) is based on ECETOC TRA. ECETOC TRA does not contain default values for ink and toners. Can the registrant provide the input parameters for the exposure assessment?

25. Is the use of gloves while applying finger paint a realistic RMM in practice?

26. Some uses / processes as defined in the CSR seem to be very similar (e.g. use in laboratories), however, the exposure estimates differ. Can you define the exposure scenarios in more detail so that the scenarios are better understood and differences between scenarios are explained?

27. Can workers in the practice of their work be exposed to NMP in range of different processes? What would be a realistic worst case scenario? This is especially relevant in case where use duration limitations are mentioned in the process desciptions. The total work duration should amount up to 8 hrs.

28. Do you have specific monitoring programs to monitor the emission/exposure of NMP to the work floor/workers? If yes, can you give an impression of such a monitoring program?

29. In literature, a number of monitoring studies have been published, showing exposures higher than the OEL (e.g. Bader et al. 2007; Beaulieu and Schmerber, 1991 and Akesson and Jonsson, 2000). Are those exposure measurements still representative?

Alternatives

We distinct between substance alternatives and technical alternatives (process changes) to reduce the exposure of NMP.

30. As market trends of NMP in general are said to decrease, one can assume that a number of industries might already shift to the use of alternatives. Is this the case, and if so, what alternatives are already used and for what applications /uses?

Substance alternatives

31. We produced a cross-table (Table 3) of the (main and sub) uses of NMP and the various substance alternatives that we found so far, to see what alternatives are available for what uses:
    - Is the table correct when it comes to the technical feasibility of alternatives to the specific uses?
    - Do you know other substance alternatives that are not yet indicated in the table (especially for the uses for which no alternatives are indicated at this moment)?
    - What would you see as reasonable 'key' alternatives for the different uses?
    - Do you have additional information on the substance alternatives in terms of e.g.: replacement ratio, potential change in functionality, availability to industry/industrial sectors, required changes in production process?
    - Are there (sub-)uses for which you know that no substance alternatives are available at this moment?
    - Are there R&D activities on the development of alternatives for NMP within your (or other) company(s)? For what application of NMP?

Technical alternatives

32. For what processes would it be possible/reasonable to reduce exposure compared to the current situation by applying technical measures (per sub-use and industrial, professional and consumer uses)?

33. What technical measures are these and in which processes/uses can these be applied? Would there be a 'key' technical alternative that is applicable to a variation of different processes?

34. Do you have additional information on technical alternatives in terms of e.g.: effectivity in emission reduction, potential change in functionality, availability to industry/industrial sectors?

35. For what processes no further emission reduction can be expected by applying technical measures?

36. Can reduction in NMP concentration in an NMP containing product be a possible 'alternative' to reduce the emission/exposure of NMP? For what uses of NMP can this be the case?

37. Are there R&D activities within your company on the development of process improvement reducing (worker) exposure?

Time period of adaptations

38. Can you specify the time period required by industry/industrial sectors to shift to the technical or substance alternative? Please specify per main technical / substance alternative and per industrial sector.

39. Can you give a clarification of the stated time period in terms of:
    - Required R&D activities for product / process adaptations.
    - Stock-renewal time for NMP products (product expiration date).
    - Other.

Costs

Costs related to NMP

40. What is the (average) price of NMP? Are there significant fluctuations over time?

41. Can you give an (average) estimation of the cost structure of different industries producing and using NMP? What percentage of the costs goes to NMP, labour, etc?

42. What is the market value of NMP industries in Europe? What is on average the turnover coming from NMP production in Europe? What is the average turnover of NMP using industries?

43. What are the costs of monitoring per unit of output?

Costs related to substances alternatives

44. What would be your estimate of the (additional) costs of substances alternative compared to NMP? Indicate a range and/or specify per (main) use and (main) alternative.

45. Would shifting to a substance alternative require product or process adaptation:
    - Would this require additional costs for process investment (i.e. capital expenditure)? Would there be loss in value of existing capital?
    - Would this require additional operating costs (i.e. maintenance, labour, monitoring, compliance, others)?
    - Would this require additional testing of the product and/or process? What are the expected additional costs for testing?
    - Would shifting to the alternative substance imply additional costs to industry in terms of lost product functionality (reduced product quality)?

46. What would be the expected price effect (in percentage of current price) of the increases in costs to the different (consumer, professional and industrial) users of NMP? Would this be a temporal or a structural increase?

Costs related to technical alternatives

47. What would be your estimate of the additional costs (capital expenditures, operation, investment, testing, monitoring, others) of the different possible process adaptations? Indicate a range and/or specify per use and process alternative.

48. Would shifting to the technical alternative imply additional costs to industry in terms of lost product functionality (reduced product quality)?

General cost aspects

49. Do you expect additional administrative costs to industry due to a (targeted) restriction on NMP?

50. Would changes up in the NMP supply chain caused by a (targeted) restriction, have effects to downstream users (other than potential increase in price)?

Annex 7. Questionnaire NMP industry by AMEC

02-01-20

NMP Restriction Dossier Questions

Part 1 - Market Analysis

NMP Uses

1.1 For companies: how much NMP (or NMP-containing products) does your company use or supply? For industry associations: much NMP (or NMP-containing products) do your members use or supply (total and/or average)?

[Answer]

1.2 For what purposes do you/your members use or supply NMP or NMP-containing products? Please specify quantities and concentrations if known.

[Possible uses: Cleaning / coating / functional fluid / other. Please specify all that apply.] Details

1.3 Do you believe these answers are representative of the industry as a whole?

[Answer]

Costs / Sales

2.1 What proportion of your costs or sales does NMP (or NMP-containing products) account for?

[Answer]

2.2 Are these fixed or variable costs?

[Answer]

Competition

3.1 Where is your competition based? (EU or extra-EU?)

[Answer]

3.2 Would a restriction of NMP at EU level put you at a competitive disadvantage relative to your non-EU competitors?

[Answer]

Part 2 - Cost Analysis

The risk management options (RMOs) under consideration only cover industrial and professional uses of NMP, and not consumer uses. They are:

- RMO 1: Total ban (concentration limit of 0.1%) for all uses
- RMO 2: Partial ban (concentration limit of 0.1%), covering professional uses only
- RMO 3: Harmonised DNEL and safe use demonstration:
  - Harmonised DNEL, which is still under development within the RIVM, but with provisional figures as follows:
    - NMP may only be used if it can be guaranteed that under normal operating conditions the exposure (8-hr TWA) will remain below 5 mg/m3 (provisional figure).
    - Peak exposures (15 min. STEL) must remain below 10 mg/m3 (provisional figure) and must be compensated by lower exposures during the same day in order to remain below the 8-hr TWA value.
  - Preventative measures to keep exposures below DNEL:
    - Preventative measures are applied in the order of the so-called "hierarchy of control", an established concept referred to in the Chemical Agents Directive (Directive 98/24/EC), i.e. enclosure, increased local exhaust ventilation, increased general ventilation.
    - Personal protective equipment is allowed in exceptional situations, such as repairs or accidents, but not as a routine measure for normal operations.
  - Exposure monitoring program, annual measurements report:
    - Industrial and professional users of NMP must be able to demonstrate at the request of the local authorities that they comply with the above restrictions.
    - This can be done by maintaining an exposure monitoring program in accordance with the BOHS / NVAA Standard or national equivalent.
    - The monitoring program must include at least once yearly a comprehensive exposure measurement report covering all employees (or a representative sample thereof) with exposure and/or all activities leading to exposure to NMP.

Defining the RMOS

4.1 The RMOs defined above are still under development by RIVM. Do you have any comments or suggestions on them?

[Comments / suggestions]

RMO 1: Total ban (concentration limit of 0.1%) for all uses

5.1 What would your organisation's likely response be?

[Possible answers: no change / chemical alternative / technical alternative / industry relocation / other] Details:

5.2 What would the main costs be?

	Total cost (€)	**% of total costs of the firm**
Capital costs:		
Operational costs:		
Administrative costs:		
Other:		

5.3 Would there be any significant product quality impacts? Might these then lead to other (e.g. safety, security) impacts?

[Especially relevant if there are safety implications or if reduced product quality leads to greater / more frequent product use] Details:

5.4 Would there be any significant supply chain impacts?

Upstream costs / impacts: Downstream costs / impacts:

5.5 How much time would your organisation require to adapt to this RMO?

[Possible answers: 1, 3, 5 years] Details:

RMO 2: Partial ban (concentration limit of 0.1%), covering professional uses only

6.1 What would your organisation's likely response be?

[Possible answers: no change / chemical alternative / technical alternative / industry relocation / other] Details:

6.2 What would the main costs be?

	Total cost (€)	**% of total costs of the firm**
Capital costs:		
Operational costs:		
Administrative costs:		
Other:		

6.3 Would there be any significant product quality impacts? Might these then lead to other (e.g. safety, security) impacts?

[Especially relevant if there are safety implications or if reduced product quality leads to greater / more frequent product use] Details:

6.4 Would there be any significant supply chain impacts?

Upstream costs / impacts: Downstream costs / impacts:

6.5 How much time would your organisation require to adapt to this RMO?

[Possible answers: 1, 3, 5 years] Details:

RMO 3: Harmonised DNEL and safe use demonstration

The proposed mandatory DNEL for this RMO remains under development by RIVM, so the values provided above should be viewed as provisional and indicative only. RIVM are currently actively considering a value of 5 mg/m3 (8-hr TWA), compared to SCOEL value of 40 mg/m3. However, other possible values include 1 mg/m3 and 10 mg/m3. While the eventual proposed DNEL is being developed, we are very interested in finding out whether there is a particular value below which your expected costs would increase exponentially and/or your likely response would change.

7.1 Is there a particular DNEL value below which your expected costs would increase exponentially and/or your likely response would change? Please specify.

[Answer: yes/no + details] Details:

7.2 - What would your organisation's likely response be at the possible DNEL values?

[Possible answers: no change / chemical alternative / technical alternative / industry relocation / other. You may also consider alternative working practices and/or equipment, e.g. increased ventilation, greater worker rotation] 1 mg/m3: 5 mg/m3: 10 mg/m3:

7.3 What would the main costs be?

	Total cost (€)	**% of total costs of the firm**
Capital costs:		
Operational costs:		
Administrative costs:		
Other:		

7.4 Would there be any significant product quality impacts? Might these then lead to other (e.g. safety, security) impacts?

[Especially relevant if there are safety implications or if reduced product quality leads to greater / more frequent product use] Details:

7.5 Would there be any significant supply chain impacts?

Upstream costs / impacts: Downstream costs / impacts:

7.6 How much time would your organisation require to adapt to this RMO?

[Possible answers: 1, 3, 5 years] Details:

RMO 4: Alternative to restriction: Authorisation

Authorisation is, by definition, not proposed as a possible restriction in the dossier. However, we recognise that it is a real possibility if the restriction proposal is not accepted. As such, we are interested in gathering information on the possible impacts this might have, to be discussed under the uncertainty analysis.

8.1 What would your organisation's likely response be?

[Possible answers: no change / chemical alternative / technical alternative / industry relocation / other] Details:

8.2 What would the main costs be?

	Total cost (€)	**% of total costs of the firm**
Capital costs:		
Operational costs:		
Administrative costs:		
Other:		

8.3 Would there be any significant product quality impacts? Might these then lead to other (e.g. safety, security) impacts?

[Especially relevant if there are safety implications or if reduced product quality leads to greater / more frequent product use] Details:

8.4 Would there be any significant supply chain impacts?

Upstream costs / impacts: Downstream costs / impacts:

8.5 How much time would your organisation require to adapt to this RMO?

[Possible answers: 1, 3, 5 years] Details:

Ranking RMOs

9.1 Please rank the proposed RMOs, with 1 = best and 4 = worst.

	RMO 1	**RMO 2**	**RMO 3**	**Authorisation**
Description	**Total ban**	**Restriction on the professional use**	**Harmonised DNEL and safe use demonstration**	**Authorisation**
Risk reduction capacity				
Overall cost				
Proportionality				
Economic feasibility				
Technical feasibility				
Practicality (implementability, enforceability, manageability)				
Monitorability				
Regulatory consistency				
Regulatory effectiveness (effort government needed)				

Reclassification

Reclassification is being considered in a parallel process to this restriction one. It is therefore not considered as a potential RMO in this dossier. However, potential reclassification may affect the answers given above, which is worth considering.

10.1 Would reclassification of NMP so that its labelling requirements in consumer products applied from a concentration of 0.3% (instead of the current 5%) alter any of the likely responses, costs, rankings or other impacts described above?

[Answer]