ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

SUBSTANCE NAME: DIMETHYLFORMAMIDE (DMF)

IUPAC NAME: N, N-DIMETHYLFORMAMIDE

EC NUMBER: 200-679-5

CAS NUMBER: 68-12-2

CONTACT DETAILS OF THE DOSSIER SUBMITTER:

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PROPOSAL FOR A RESTRICTION

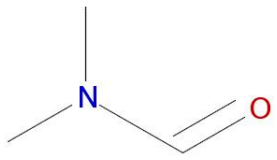
Summary

Identity of the substance

The substance N,N-dimethylformamide is a mono constituent substance (organic origin) having the identifiers as listed in Table 1.

Table 1 - Substance identity

EC number:	200-679-5
EC name:	N,N-dimethylformamide
CAS number:	68-12-2
CAS name:	Formamide, N,N-dimethyl-
IUPAC name:	N,N-dimethylformamide
Index number:	616-001-00-X
Molecular formula:	C_3H_7NO



Scope and condition of restriction

The restriction dossier shall apply to N,N-dimethylformamide whatever its purity. Throughout the proposal the public name Dimethylformamide or its abbreviation DMF is used.

DMF may only be manufactured and used if it can be assured that under normal operating conditions the exposure will remain below the determined harmonised worker DNEL for long-term inhalation exposure of 3.2 mg/m^3. Additionally, DMF 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 determined long-term

DNEL for dermal exposure (worker) of 0.79 mg/kg bw/day has to be met also. Both DNELs have been derived according to the relevant ECHA REACH Guidance (please refer to Annex B: Information on hazard, emission/exposure and risk).

The exposure levels (inhalation and dermal) must be ensured by the use of preventative and protective measures (e.g. elimination, substitution, enclosure, increased local exhaust ventilation and general ventilation, change in operational conditions, administration, behaviour and if needed personal protective equipment) that are applied according to the "hierarchy of control" principle, which is an established concept referred to in the Chemical Agents Directive (Directive 98/24/EC). It should be used at all times when implementing controls to eliminate the hazard or reduce the risk of a hazard. This is done by giving preference to the use of the "engineering controls". These types of strategies should be used, where possible, because they are less subject to human failure and because they are less disruptive and uncomfortable for people working in the area. Back-up controls (such as PPE and administrative controls) should only be used as a last resort or as a support to other control measures.

Manufacturers, formulators, industrial users and professional users of DMF must be able to demonstrate at the request of enforcement authorities that they comply with the above restrictions. This can be done by maintaining an adequate exposure monitoring program.

Referring to the proposed restriction (see Table 2), a transitional period of two years is recommended.

Proposed restriction

Table 2 - Proposed Restriction

Column 1: Designation of Substance	Column 2: Conditions of Restriction
XX. N,N-dimethylformamide EC No.: 200-679-5 CAS No.: 68-12-2	• 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.zzzz] a worker based harmonised Derived No Effect Level (DNEL) value for long-term inhalation exposure of 3.2 mg/m^3 and a worker based harmonised DNEL for long-term DNEL dermal exposure of 0.79 mg/kg bw/day.

The proposed restriction aims to restrict the uses of the substance on its own or in mixtures in a concentration equal or greater than 0.3%.

The substance is used in the laboratory chemicals and has an industrial use resulting in manufacture of another substance (use of intermediates). This substance is also used in the following areas: scientific research and development and for the manufacture of chemicals, machinery and vehicles.

Summary of the justification for the restriction

- Identified hazard and risk

Most of the information was obtained from the registration dossier (Taminco, 2014) and OECD SIDS (2004).

DMF is classified as toxic for reproduction 1B, acute tox. 4 (inhalation and dermal route) and as eye irritant 2.

In various repeated dose toxicity studies in rats and mice with chronic and subchronic exposure by inhalation, the predominant target organ was the liver (NOAEC as point of departure for chronic inhalation DNEL - rat and mouse - 25 ppm corresponding to 80 mg/m³).

There are no dermal repeated dose toxicity studies available for DMF. Alternatively the oral repeated dose studies (sub-acute and sub-chronic) may be used to determine the dermal DNEL using route-to-route extrapolations. Preference is given to the 28-d study because dosing by gavage is a more precise treatment method as well as the narrower dose spacing provides a more precise NOAEL (238 Mg/kg bw/ day for reduced body weights and food consumption, hepatic and kidney damage rapresented by chages in clinical chemistry (increased total bilirubin and GPT, AP, urea and creatinine).

Reproductive toxicity, i.e. reduced fertility and fecundity, was observed in the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses ≥ 4000 ppm (appr. 820 mg/kg bw/day). The maximal tolerated dose (MTD) for generalized toxicity was 1000 ppm (appr. 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both off-spring generations at ≥ 4000 ppm. Reduced F2 pup weight was observed at ≥ 1000 ppm (NOAEL F0, F1 fertility: 1000 ppm; NOAEL, F1 developmental toxicity 1000 ppm; LOAEL, F2 developmental toxicity: 1000 ppm).

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral or dermal administration) and in mice (oral administration). In rats embryo-/foetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo- /foetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF. (Rabbit: NOAEC (inhalation) maternal toxicity and teratogenicity as well as embryo-/foetotoxicity 50 ppm; NOAEL (oral, gavage) maternal toxicity and embryo-/foetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo- /foetotoxicity 200 mg/kg bw/day).

The DNEL proposed for the inhalation route is based on NOAELs resulting from repeated dose toxicity studies (that are in the same order of magnitude of the reproductive/developmental studies).

The exposure assessment for DMF at the workplace was performed by using a TIER 1 (exposure modelling) and a TIER 2 (measured data) approach with a respective risk characterisation. For the TIER 1 approach, the software tool CHESAR v2.2/v2.3 (2013) was used which implements ECETOC TRA v3.1 (2004, 2012) for exposure modelling referring to Human Health. The exposure was calculated for all identified uses as described in section B.2 of the Annex B: Information on hazard, exposure-emission and risk and in Annex A: Manufacture and uses. Due to the fact that relevant measured data from several different industrial sites was available, a TIER 2 assessment was additionally elaborated. By means of the detailed and complex approach for this risk assessment, exposure estimations and risk characterisations take the current state of the art into account. All exposure calculations for Human Health are based on recent information on detailed process conditions provided by the relevant Downstream Users. According to the obtained information, the most common RMMs applied are LEV, gloves, respirators and reduction in exposure time and/or concentrations of DMF used in the process.

In general, exposures resulting from processes under elevated temperatures, processes requiring intensive manual applications and open processes are relatively high which, however, can be addressed by the applied RMMs and OCs. In general, the estimated exposure

levels ranged from 0.021 to 4.568 mg/m³ for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranged from 0.002 to 7.072 mg/kg bw/day (systemic, long-term). It should be emphasised that for both exposure routes, strict RMMs as implemented by the industry were already taken into consideration. In many cases, exposures without any RMMs would be higher at least by an order of magnitude.

The highest exposure levels were estimated for specific applications involving as mentioned above elevated temperatures, intensive manual applications and open processes. These tasks bear a potential risk towards Human Health. Inhalation exposure was estimated up to 4.568 mg/m³ (systemic, long-term) while dermal exposure was estimated to amount up to 7.072 mg/kg bw/day (systemic, long-term) for these processes.

By combining the derived DNELs with the exposure estimates, risk characterisation ratios (RCRs) were obtained. Many RCRs were above the trigger value of 1.0. A potential unacceptable risk for workers was, therefore, identified for the industrial uses for the production of fine chemicals, pharmaceuticals, polymers as well as textiles, leather and fur. Applications described by PROC 10 and PROC 19 were found to bear a certain risk for human health. Moreover, combined exposure that may arise from different exposures to the same substance across different tasks or activities has been additionally assessed for DMF. A safety concern for workers was revealed as well.

Justification that action is required on a Union-wide basis

The main reason for acting on a Community-wide basis is the protection of human health from the adverse effects of DMF due to its reprotoxic (Category 1B) properties. Based on information from the registration dossier and this restriction dossier, there is strong evidence that DMF is potentially used in all EU Member States and that in some industrial settings occupational exposure results in unacceptable risk. Action on a Community-wide basis is required to prevent unacceptable risks from DMF.

According to the EU's Treaty, free movement of goods needs to be guaranteed in order not to distort the internal market. Therefore, acting on a Community-wide basis ensures equal treatment of both - EU producers and importers. Furthermore, it gives a clear signal to non-Community suppliers and provides a "level playing field" by preventing competition distortion and allows equal protection of human health across the EU.

Effectiveness

Due to the fact that there are no alternatives available that can replace DMF for all its uses, the proposed restriction is considered to be the most appropriate measure from a risk reduction capacity perspective, as it is clearly targeted to the identified risks. In summary, this option provides more legal certainty and is expected to result in a complete risk reduction of DMF.

Practicality (implementability, enforceability and manageability)

According to the received information from industry representatives, the industrial gases industry would face no difficulty under the proposed restriction because the current exposure levels are well below the proposed DNELs. The proposed restriction is however not implementable for the man-made fiber industry and the textile coating industry. Both industries currently operate under the occupational exposure limit (IOEL) of 15 mg/m³. The proposed restriction would require a reduction from 15 mg/m³ to 3.2 mg/m³, which would not be economically feasible for both industries. In order to meet more severe DNEL values, exponentially increasing investments and costs would be needed. Both industries face fierce international competition and would not be able to pass on the increased costs on customers.

The restriction proposed is deemed to be enforceable.

Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement. Further, monitoring of exposure levels is already carried out under worker protection legislation and hence, it should be no problem to adopt similar activities.

Report

1. The problem identified

1.1. Hazard, Exposure / emission and risk

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

Dimethylformamide is listed by Index number 616-001-00-X of Regulation (EC) No 1272/2008 in Annex VI, Part 3, as follows:

Table 3 - Harmonised Classification of DMF according to Annex VI of Regulation (EC) No 1272/2008 (CLP)

Index No	International Chemical Identification	EC No	CAS No	Classification		Labeling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
616-001-00-X	N,N-dimethyl formamide; dimethyl formamide	200-679-5	68-12-2	Repr. 1B Acute Tox. 4 Acute Tox. 4 Eye Irrit. 2	H360D** H332 H312 H319	GSH08 GSH07 Dgr	H360D** H332 H312 H319			

(*) For certain hazard classes, including acute toxicity and STOT repeated exposure, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification.

Repr. 1B, H360D**	May damage the unborn child.
Acute Tox. 4, H332	Harmful if inhaled.
Acute Tox. 4, H312	Harmful in contact with skin.
Eye Irrit. 2, H319	Causes serious eye irritation.

Table 4 - Self classification in addition notified among the aggregated self classification in the C&L inventory

Hazard Class and Category Code(s)	Hazard Statement Code(s)

Flam. Liq. 3	H226
STOT RE 2	H373
Acute Tox. 3	H331
Acute Tox. 4	H302
Repr. 1A	H360
STOT SE 1	H370
STOT RE 1	H372
Eye Dam. 1	H318
Muta. 2	H341

Most of the notifiers used the harmonised classification given in Table 3. Some notifiers submitted slightly different self classifications given in Table 4.

1.1.2 Hazard assessment

The summarized data for the human health hazard endpoints were adopted from the registration dossier, CSR and/or OECD SIDS (2004). Additionally, some recent literature data were used as well. 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. The data on toxicokinetics, dermal absorption and human case studies were extracted from the articles publicly available. Repeated dose toxicity studies, inhalation and dermal routes are described in more detail following because they are the hazard end-points relevant for the purpose of the risk assessment. This Annex XV restriction dossier is targeted to the use of DMF in industrial settings and by professionals. Therefore the starting points and then DNELs are derived for the dermal and inhalation routes as the oral route of exposure is considered to be negligible for workers.

The N(L)OAEC selected for risk assessment for inhalation route is based on the Malley et al. (1994) repeated dose toxicity study. In chronic inhalation studies Crl: CD BR rats were exposed over a period of 2 years and Crl: CD-1 (ICR) BR mice were exposed for 18 months at concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m³) 5 d/w and 6 h/d. In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity (serum sorbitol dehydrogenase), increased liver weights and some histopathological findings in the liver. There was no compound related increase of tumors. Similar findings were observed in mice. At 400 ppm liver weights were increased in both sexes and at 100 ppm in the males. At all concentrations tested minimal to mild hepatocellular hypertrophy was observed (incidence being dose-related). Individual hepatocellular necrosis together with some other histopathological findings (minimal to moderate kupffer cell hyperplasia with pigment accumulation of lipofuscin and hemosiderin) were seen in all groups (also control, incidence being greater in DMF-treated animals). A NOEC was not achieved in mice due to morphological changes seen in the liver at all three test concentrations; nevertheless they expected the NOEC to be close to 25 ppm due to the minimal changes observed at this concentration. These minimal changes included a slightly (for the males significantly) increased incidence of hepatocellular hypertrophy, dose-related and statistically significantly increased incidence of hepatic single cell necrosis in both sexes, and dose-related (for the males significantly) increased incidences of hepatic kupffer cell hyperplasia and pigment accumulation. For rats, the NOEC is 25 ppm (80 mg/m³) based on the body weight

changes, clinical chemistry changes and hepatotoxic effects observed at 100 and 400 ppm. LOAEC was 100 ppm (300 mg/m³).

The NOAEL selected for risk assessment for dermal route (based on oral study) is based on the BASF, 1977 repeated dose toxicity study, as no reliable repeated dose dermal toxicity studies are available, dermal DNELs have been derived using oral-to-dermal route-to-route extrapolation. The worst case assumption of 100% dermal absorption is implemented in the route-to-route extrapolation, based on the results of available studies evaluating dermal absorption of DMF in liquid and/or vapour form in humans which show that DMF can be readily absorbed via the skin (Mráz and Nohová, 1992; Nomiyama et al., 2001; Chang et al., 2004 - please refer to toxicokinetic section).

In a 28-day study, Sprague–Dawley rats received 250, 500, 1000 and 2000 µL N,N-dimethylformamide/kg bw (about 238, 475, 950 and 1900 mg/kg bw/day) by gavage on 5 days/week. In the highest dose group all animals died, mostly at the beginning of the study. At 1000 µL/kg bw/day all animals were affected by reduced food consumption and reduced body weight, males already at the beginning, females at the end of the study. Hepatic injury was characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Relative liver weights were increased in both sexes. Histological examination revealed an acute to subacute hemorrhagic liver dystrophy with necrosis in both sexes in the two high dose groups. Disturbances in kidney function were characterized by elevated urea (females) and creatinine values, the latter one in both sexes. Relative kidney weights were increased in the males. At 250 and 500 µL/kg bw/day reduced food consumption in the males and at 500 µL/kg bw/day reduced body weight was observed in the males. For the observation of increased relative liver weights in both sexes and of increased relative kidney weights in the males no histopathological correlate was found. NOAEL of 238 mg/kg bw/day and LOAEL of 475 mg/kg bw/day were established. In Table 5 the studies considered for repeated dose effects.

Table 5 - Summary table for points of departures for repeated dose effects

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
Inhalation	Rat, 2 years	NOAEC: 25 ppm (80 mg/m³)	Decreased body weights, clinical chemistry changes, and liver injury.	Malley et al., 1994
Inhalation	Mouse, 18 months	LOAEC: 25 ppm (80 mg/m³)	Hepatocellular hypertrophy (males), hepatic cell necrosis and increased incidence of hepatic Kupffer cell hyperplasia and pigment accumulation (both sexes)	Malley et al., 1994
Inhalation	Rat, 13-week	NOAEC: 200 ppm (NTP study report) 100 ppm (SIDS report)	Concentration-dependent depression in body weight occurred in rats exposed at 400 (6–11%) and 800 ppm (20–22%).Microscopic liver injury	NTP, 1992; Lynch et al., 2003
Inhalation	Mouse, 13-week	NOAEC: 50 ppm (female) (NTP report) NOAEC: 400 ppm (SIDS report)	Increased liver weight, hepatocellular hypertrophy	NTP, 1992; Lynch et al., 2003

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
Dermal (based on oral study)	Rat, 28-days	NOAEL: 238 mg/kg bw	Reduced body weights and food consumption, clinical chemistry changes, liver injury	BASF, 1977
Dermal (based on oral study)	Rat, 13 weeks	NOAEL: 12 mg/kgbw/day (about 200 ppm in feed)	Increased liver weights	TSCATS: OTS 0520880, 1960; TSCATS: OTS 0571664, 1960; TSCATS: OTS 0572893, 1960

* effects observed at dose levels higher than indicated at NOAEL

Derivation of DNEL(s)

The DNELs (Derived No Effect Level) derivation is limited to inhalation and dermal route of exposure as it is expected that oral exposure is not relevant for workers if normal hygienic measures are in place.

Although DMF represents an acute hazard by dermal and inhalation routes (the substance is classified for these endpoints), acute systemic DNELs have not been derived because they can be covered by the long-term systemic DNELs which are more protective. Since exposure to DMF did not result in irritation symptoms of respiratory tract of treated animals in the repeated dose inhalation studies and in occupationally exposed workers, no specific DNEL for local effects could be derived. Intermittent and irregular respiration observed in treated animals during the acute inhalation study may indicate irritating (local) effects to respiratory tract, but this effect occurred merely at the same level of systemic toxicity. Therefore, no local DNEL for acute inhalation exposure has to be derived.

Similarly, DMF is not irritating to skin in humans and therefore no DNEL for local effects in case of long-term dermal exposure has been derived. The respective systemic DNELs will sufficiently cover local effects.

Since absorption of DMF through the skin is significant and equal to oral absorption (please refer to Annex B: Information on hazard, emission/exposure and risk, toxicokinetic section), route-to-route extrapolation is considered to be appropriate to derive dermal long-term DNELs based on oral studies.

In Table 6 the point of departures for the derivation of DNELs are reported.

Table 6 - Point of departures for DNELs derivation for repeated dose toxicity

Starting point for DNEL derivation (systemic)	Species and duration	NOAEL (mg/kg bw) or NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Inhalation	Rats, 2-years	25 ppm (80 mg/m³)	Decreased body weights, clinical chemistry changes, liver injury	Malley et al., 1994
Dermal (based on oral study)	Rats, 28-days	238 mg/kg bw	Reduced body weights and food consumption, clinical chemistry changes, liver injury	BASF, 1977

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

Dose descriptors modification

The ECHA Guidance describes a correction of the dose descriptor (i.e. NOAEL, LOAEL) into correct point of departure for the following situations:

Bioavailability (absorption):

Absorption of DMF into the body is significant and, therefore, set to 100 % as a worst case for all exposure routes if no route-to-route extrapolation is intended. Absorption is assumed to be the same for experimental animals and humans for all exposure routes. Thus, no adjustments of points of departure regarding absorption rates in animals and humans per exposure routes were performed.

Route-to-route extrapolation:

As no reliable repeated dose dermal toxicity studies are available, dermal DNELs have been derived using oral-to-dermal route-to-route extrapolation. The worst case assumption of 100% dermal absorption is implemented in the route-to-route extrapolation, based on the results of available studies evaluating dermal absorption of DMF in liquid and/or vapour form in humans which show that DMF can be readily absorbed via the skin (Mráz and Nohová, 1992; Nomiyama et al., 2001; Chang et al., 2004 -please refer to toxicokinetic section in the Annex B: Information on hazard, emission/exposure and risk).

Exposure conditions:

The inhalation exposure in experimental studies differs from the human exposure situation. ECHA REACH Guidance describes a correction for the number of hours exposed per day (depending on study design and work shifts of the worker). Normally, daily 6-hour exposure duration is applied in animals' studies, while 8-hour exposure for workers (working shift) is

considered resulting in a factor of 6/8. The dose descriptors were corrected as described in Appendix R.8-2 of the above mentioned guidance document.

Respiratory volumes:

ECHA REACH Guidance also describes the volume air inhaled by rats and humans during 8 hours (working day). A factor of 6.7/10 for differences in the respiratory volumes by light work (10 m^3) and no activity (6.7 m^3) in workers was applied in case inhalation studies were used.

Interspecies differences:

•Allometric scaling (**AS**): the default factor for allometric scaling from rat to human amounts to 4. From rabbit to human this factor is set to 2.4 and from mouse to human a factor of 7 is applied. It should be additionally noted that in case of inhalation exposure, no allometric scaling factor needs to be applied (ECHA REACH Guidance R.8).

•Remaining differences (**RD**): this covers any remaining interspecies differences between animals and humans referring to toxicodynamics and –kinetics. By default this factor is set to 2.5 for systemic effects.

Toxicological information obtained from different species, i.e. rat, mouse and rabbit, seems to indicate that interspecies differences are small. There are also various human data available for the critical health effects: hepatotoxicity and alcohol intolerance (see Annex B: Information on hazard, emission/exposure and risk). The data, however, are partially of poor quality due to certain deficiencies such as unknown health status of investigated human population and confounding factors, i.e. cigarette smoke, drinking habits, simultaneous exposure to other chemicals, etc. The data set provides insufficient justification to reduce the factor for toxicodynamic differences between animals and humans. Moreover, a quantitative difference between the metabolic pathway of DMF to AMCC, which is the reactive metabolite probably responsible for hepatotoxic potential, was observed in humans and rodents (please refer to toxicokinetic section in Annex B: Information on hazard, emission/exposure and risk). A relatively higher proportion of AMCC was determined in humans compared to animals. Mainly for this reason, the default factor of 2.5 was applied for the derivation of DNELs for systemic effects, despite there is no obvious hint that this metabolic difference is of significant toxicological relevance.

Intraspecies differences (**ID**):

By default the assessment factor for intraspecies differences is set to 5 for workers (in comparison with 10 for the general population), because this subpopulation does not include more sensitive subpopulations such as young, old and/or sick people. Developmental effects also concern effects on the fetus which may not be fully addressed in the default factor of 5 for workers. However, with reference to RAC opinion ECHA/RAC/RES-O-0000005316-76-01/F on NMP, there is no specific guidance concerning pregnant workers. It is noted that an interpretation of the guidance document would lead to using an assessment factor of 5 also for pregnant workers. DNELs and RCRs for developmental effects based only on assessment factor of 5 for workers will therefore be presented. To sum it up, a factor of 5 is taken for (maternal) systemic effects and for (prenatal) developmental effects. It should be noted that the fact of rat foetuses being 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.

Study duration corrections:

These corrections might be needed to extrapolate from a sub-chronic to chronic study duration. By default a factor of 2 is taken. For sub-acute (28-d study) to chronic exposure a factor of 6 is applied. A factor of 1 may be considered if it concerns local effects which are not driven by duration. In case the point of departure is derived from a prenatal developmental toxicity study, correction is made neither for exposure duration nor for the dose description

concerning daily exposure. A correction is not required from a daily exposure of rats (7d/w) to a 5d/w exposure of workers due to the limited exposure during GD period (generally 15 days during a gestation period of 21 days in the rat). This (potential) correction would approximate to a correction factor of 1 (i.e. 5/7 x 21/15 = 1).

Dose-response assessment factor:

The points of departure used in the DNEL derivation, are all based on NOAELs. There were usually three doses used with a spacing range of 2-4 fold and a clear dose-response was observed. Therefore, no additional assessment factor is needed.

Derivation of DNELs

DNELs were derived for workers only (no distinction between pregnant and no pregnant workers), therefore for inhalation and dermal exposure, the only relevant routes of exposure for workers.

All the relevant studies (reported in Table 7), have been taken into account in consideration of the potential effects of the substance for the inhalation route.

Table 7 - DNELs derivation for the inhalation route

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
25 ppm (ca.80 mg/m³), rat	Combined repeated dose and carcinogenicity study, 2 years	Body weights lower than controls, clinical chemistry changes, and liver injury	6/8 6.7/10	40.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.2	Malley et al., 1994
25 ppm (ca.80 mg/m³), mouse	Combined repeated dose and carcinogenicity study, 18 months	Hepatic injury	6/8 6.7/10	40.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.2	Malley et al., 1994
200 ppm, rat ca. 610 mg/m³ (NTP, 1992; Lynch et al., 2003) 100 ppm Ca. 300 mg/m³	Repeated dose study, 13 week	Microscopic liver injury	6/8 6.7/10	306.5 150.8	1 (AS) 2.5 (RD) 5 (IS) 2 (ED)	12.3 6.0	NTP, 1992; Lynch et al., 2003

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
(SIDS report)							
50 ppm, mouse (female) ca 150 mg/m³	Repeated dose study, 13 week	Increased liver weight, hepatocellular hypertrophy	6/8 6.7/10	75.4	1 (AS) 2.5 (RD) 5 (IS) 2 (ED)	3.0	NTP, 1992; Lynch et al., 2003
1000 ppm in drinking water (219 mg/kg bw), mouse OK	Continuous breeding study up to F2 generation	Craniofacial and sternebral malformations	1/0.38 6.7/10	386.1	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	30.9	Fail et al., 1998
Foetotoxicity:30 ppm (90 mg/m³); teratogenicity: 300 ppm (910 mg/m³), rat	Dev. Tox. study, GD 6-15	Reduced body weight, high incidence of fetuses with ossification variation at 300 ppm (LOAEC)	6/8 6.7/10	45.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.6	TSCATS: OTS 0516779, 1978
50 ppm (150 mg/m³), rabbit OK	Dev.tox. study, post inseminat ion days: 7-19	Reduced fetal body weights, increased incidence of variations including teratogenicity	6/8 6.7/10	75.4	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.0	BASF, 1989b; Hellwig et al., 1991
1000 ppm in drinking water (219 mg/kg bw), mouse ok	Continuous breeding study up to F2 generation	Reduced body weight in females, reduced fertility and fecundity, reduced number of litters and	1/0.38 6.7/10	386.1	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	30.9	Fail et al., 1998

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
		litter size, effects on prostate weight and epididymal spermatozoa concentration					
30 ppm (90 mg/m³), rat OK	Dev. Tox. study, GD 6-15	No effect; reduced body weight (6-15 GD) at 300 ppm (LOAEC)	6/8 6.7/10	45.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.6	TSCATS: OTS 0516779, 1978
50 ppm (150 mg/m³), rabbit Ok	Dev.tox. study, post inseminat ion days: 7-19	No effect	6/8 6.7/10	75.4	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.0	BASF, 1989b; Hellwig et al., 1991
150 ppm (450 mg/m³), rabbit OK		Retardation of body weight gain. No clinical symptoms	6/8 6.7/10	226	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	18.0	

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

The dose descriptors from a combined repeated dose and carcinogenicity study (Malley et al., 1994) and a sub-chronic study for both rats and mice (NTP, 1992; Lynch et al., 2003) were considered as points of departure for inhalation DNEL derivation (highlighted point of departure in Table). The results of the rat chronic study of Malley et al. (1994) were supported by the results of the 13-w inhalation study (NTP, 1992; Lynch et al., 2003). The same toxicity effects were observed: reduced body weight and liver injury. The NOAEC for other systemic effects were, however, different: 80 mg/m³ in the combined 2-year study vs. 610 mg/m³ in the 13-w study in rats and 80 mg/m³ vs 150 mg/m³ in female mice (no NOAEC could be identified for male mice). The LOAEC of 300 mg/m³ for rats from the combined study is below the NOAEC of 610 mg/m³ in the 13-w study, whereby SIDS report states to use the NOAEC of 300 mg/m³ in place of 610 mg/m³ based on the findings observed in the liver function assays (i.e. increased serum cholesterol). Since exposure conditions (6h/d, 5d/w, vapour) were the same in both studies, such differences could be due to different species (Crl:CD BR rats vs. Fischer 344 rats and Crl:CD-1 (ICR)BR mice vs. B6C3F1 mice) and the exposure duration (3 months vs. 2 years in rats and 18 months in mouse). Additionally, the dose spacing in the combined study was twice as large as in the 13-w study, therewith the resulting NOAEC in the combined study (the lowest dose tested) appears to be sufficiently conservative

(25 ppm vs. 50 ppm, the lowest dose in the 13-w study). It should be noted that a clear NOAEC for mice was not attained in both studies due to the morphological changes observed at all exposure levels but were minimal at 25 ppm in the 2-year mice study. Therefore, preference should be given to rat studies. A slight difference in the NOEC between rat and mice is covered by the remaining differences factor which is exactly the purpose of this factor. Comparing the DNELs from the points of departures of both studies for rats, they are all in the same order of magnitude, but the lowest DNEL of 3.2 mg/m³ will be taken forward for workers.

In conclusion, an inhalation chronic systemic DNEL of 3.2 mg/m³ is derived for workers based on the decreased body weights, clinical chemistry changes, and liver injury at the NOAEC in the 2-year study in rats (Malley et al., 1994). The long-term inhalation DNEL covers also short-term exposures.

There are no dermal repeated dose toxicity studies available for DMF. Alternatively the oral repeated dose studies (sub-acute and sub-chronic) may be used to determine the dermal DNEL using route-to-route extrapolations. The route-to-route extrapolation was performed assuming 100 % absorption via the oral and also 100 % absorption via dermal route. Although both studies are old (not conducted in accordance with GLP standards and an OECD guideline), they are well documented and provide sufficient results to establish a NOAEL. The difference is that DMF was administered by gavage in the 28-d study while animals received the test substance via food in the 13-w study. The NOAEL of 60 mg/kg bw from the 13-w study is close to NOEL because no effects were observed at this dose level. The only finding was increase in relative liver weights without any histopathological correlate (TSCATS: OTS 0571664, 1960). The dose spacing of this study is not optimal as the LOAEL is 300 mg/kg. The effects observed at NOAEL in the newer 28-d study also included increased liver weights, but reduced body weights and increased kidney weights were additionally determined. The derived DNELs are in the same order of magnitude showing that the study results support each other. Preference is given to the 28-d study because dosing by gavage is a more precise treatment method as well as the narrower dose spacing provides a more precise NOAEL (spacing 28 day by a factor of 2 instead of 5 as in the 90 day study).

In conclusion, a dermal chronic systemic DNEL of 0.79 mg/kg bw/day is derived based on NOAEL of 238 mg/kg bw/d and reduced body weight, clinical chemistry changes, liver injury at the LOAEL in a dermal 28-day repeated dose toxicity study (BASF, 1977). The long-term dermal DNEL covers also short-term exposures.

All the relevant studies (reported in Table 8), have been taken into account in consideration of the potential effects of the substance for the dermal route.

Table 8 - DNEL derivation for the dermal route

NOAEL mg/kg bw (species)	DNEL (endpoint) dermal	Type of study	Type of effect at LOAEC	Assessment factors	Resulting DNEL (mg/kg bw)	Reference
238	Dermal (based on oral study)	Rat, 28-days (gavage)	Reduced body weights and food consumption, hepatic and kidney damage rapresented by chages in clinical chemistry (increased total bilirubin and GPT, AP, urea and creatinine),	4 (AS) 2.5 (RD) 5 (IS) 6 (ED)	0,79	BASF, 1977
60	Dermal (based on oral study)	Rat, 13-week (feeding study)	Increased liver weights, liver injury (observed at the highest dose level of 300 mg/kg bw)	4 (AS) 2.5 (RD) 5 (IS) 2 (ED)	0.6	TSCATS: OTS 0520880; TSCATS: OTS 0571664; TSCATS: OTS 0572893, 1960
200, rabbit	Developmental toxicity (dermal route- semi occlusive)	Dev.tox. study, Post insemination 6-18	Several malformations	2.4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.7	BASF (1984); Hellwig et al., 1991
94, rat	Developmental toxicity (dermal route, open application)	Dev.tox. study, GD 6-10 and 13-15	Several malformations	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	1.9	BASF (1976); Hellwig et al., 1991
500, rat	Developmental toxicity (dermal route)	One-gen. study (exposure duration: 164 days)	Reduced pup survival, skeletal malformations at the higher dose levels	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	10	TSCATS: OTS 0518158, 1973
200, rabbit	Maternal toxicity (dermal route; semi occlusive)	Dev.tox. study, Post insemination 6-18	Lower body weigth and non significant postimpatation loss	2.4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.7	BASF (1984); Hellwig et al., 1991

NOAEL mg/kg bw (species)	DNEL (endpoint) dermal	Type of study	Type of effect at LOAEC	Assessment factors	Resulting DNEL (mg/kg bw)	Reference
LOEC/ NOEC 94, rat	Maternal toxicity (dermal route, open application)	Dev.tox. study, GD 6-10 and 13-15	Lower placental weights	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	1.9	BASF (1976); Hellwig et al., 1991
500, rat	Maternal toxicity (dermal route)	One-gen. study (exposure duration: 164 days)	No effect. Reduced body weights (both sexes) at the higher dose levels	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	10	TSCATS: OTS 0518158, 1973

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

Conclusion

The selected DNELs (hilighted in Table 7 and in Table 8) for the calculation of the RCR are presented in Table 9. One important major result is that the pregnant worker including the unborn child and the non-pregnant worker are equally sensitive to the toxicological properties of DMF other than reprotoxic properties (see Annex – Information on hazard, emission/exposure and risk). For the calculation of the RCR the lowest value is always chosen.

Table 9 - Selected DNELs for the calculation of RCRs

	Workers
Long-term Inhalation DNEL (mg/m³)	3.2
Long-term dermal DNEL (mg/kg bw/day)	0.79

Environmental fate properties are considered not relevant for this restriction dossier.

1.1.3 Exposure Assessment

Manufacturing

The manufacturing scenario describes the process of the manufacturing of DMF itself and its distribution processes (charging/discharging). DMF is produced either via catalysed reaction of dimethylamine and carbon monoxide in methanol or via the reaction of methyl formate with dimethylamine. It may also be prepared on a laboratory scale by reacting dimethylamine with formic acid.

Within the EU, DMF is manufactured within high integrity contained systems where little potential for exposure exists (PROC 1), according to ECHA (see Tables A1, A3, A4 and A5) in section B.2 Manufacture and uses of the Annex A: Manufatcure and uses for an exhaustive list of PROC). Occasional controlled exposure is only expected during sampling (PROC 2) for quality analysis purposes (PROC 15) and during un-coupling and coupling activities related to transferring operations (PROC 8b). Exposure may also arise from incidental breaching of the system for technical maintenance and/or cleaning of the closed system. Charging/discharging is undertaken outdoors under containment (semi-closed process). This includes transfer into

barges, rail cars, road car transport and IBCs as well as repacking of DMF in drums or packs. In case of increased process temperatures relevant to sampling or critical un-coupling/coupling activities, respiratory protection equipment is additionally used to ensure adequate control of exposure.

The exposure estimation using CHESAR v2.3 for manufacture is given in the Table B91 - Manufacture of substance - calculated exposures using CHESAR v2.3 and the measured data in Table B9 - Manufacture of substance – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Formulation of substance

The formulation scenario describes all formulation activities involved in the production of fine chemicals, pharmaceuticals, polymers, textiles and other products. Formulation of the substance takes mainly place in closed systems (PROC 1, PROC 2 and PROC 3) or semi-closed systems (PROC 4). In case of open processes for mixing and blending in batch processes (PROC 5), respiratory protection equipment is used to guarantee operational safety. General transfer processes from/to vessels/large containers at dedicated (PROC 8b) and non-dedicated (PROC 8a) facilities including un-coupling and coupling activities take place indoors with local exhaust ventilation. LEV also applies for drum and small package filling including weighing (PROC 9). For processes at increased temperatures (up to 90 °C), respiratory protection equipment is mandatory. This also accounts for laboratory activities (PROC 15) involving application temperatures of ≤60 °C.

The exposure estimation using CHESAR v2.3 for formulation of substance is given in the Table B93 - Formulation of substance - calculated exposures using CHESAR v2.3 and the measured data in Table B94. Formulation of substance – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the production of fine chemicals

This Exposure Scenario refers to the DMF usage for the production of fine chemicals which describes the synthesis of chemicals such as Active Pharmaceutical Ingredients (API) and crop protection ingredients. In general, a wide range of processes has been indicated by Downstream Users. Manufacture of fine chemicals is mostly carried out in batch processes with synthesis being followed by separation and purification steps. This is undertaken in closed (PROC 1, PROC 2 and PROC 3) as well as semi-closed (PROC 4) and open systems (PROC 5) at temperatures up to 170 °C. In case of open processes which could result in significant exposure, extract ventilation and respiratory protection equipment are indicated as compulsive Risk Management Measurements. Batch processes might be carried out under pressure, under vacuum or at elevated temperatures. Bulk liquids are mainly transferred (PROC 8a, PROC 8b and PROC 9) directly to above – or below ground bulk storage tanks. In general, these liquids are piped into the plant and exposure is mainly expected during un-coupling and coupling activities. Process operations typically involve a batch reactor into which different raw materials are discharged by a carrier solvent (i.e. DMF). Spent solvents are usually collected and recovered on-site. For particular fine chemical preparations, additional processes involving tableting, compression, extrusion and pelletisation (PROC 14) might take place. Furthermore, manual activities involving hand contact (PROC 19, not further specified) have been indicated bearing significant dermal exposure. Nevertheless, resulting exposure for the production of fine chemicals is predominately related to volatiles so that respiratory protective device is compulsory for many processes at high process temperatures and/or low level of containment. During product synthesis, sampling and analytical verification (PROC 15) of the fine chemicals and the solvent itself is expected at different production steps.

The exposure estimation using CHESAR v2.3 for the industrial use for the production of fine chemicals is given in the Table B95. Industrial use for the production of fine chemicals - calculated exposures using CHESAR v2.3 and the measured data in Table B96. Industrial use

for the production of fine chemicals – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the production of pharmaceuticals

Within the pharmaceutical industry and in-vitro diagnostic (IVD) medical devices industry, DMF and similar solvents are used in Lab R&D and in the supply chain of Active Pharmaceutical Ingredients (APIs) and IVD Medical Devices. DMF is mainly used as solvent in syntheses and for crystallizing. Frequently, polar aprotic solvents are important for both solubilization of reactants and required product.

The application of solvents mainly occurs in closed processes (PROC 1, PROC 2 and PROC 3) – partly at elevated process temperatures up to 120 °C. Infrequently, DMF is used in semi-closed processes (PROC 4) including charging, sampling or discharge of material. Mixing and blending operations can also take place in open processes (PROC 5) at increased process temperatures which provide the opportunity for significant exposure. For semi-closed and open processes (indoor use), occupational health and safety is guaranteed by mechanical extract ventilation and/or respiratory protection. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated (PROC 8a) facilities take place indoors with extract ventilation and respiratory protection. This also applies for drum and small package filling including weighing (PROC 9). For the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b), mechanical extract ventilation (i.e. LEV) is often applied, especially at high solvent concentrations up to 100 %. Exhaust ventilation also needs to be implemented for quality control of finished products and R&D activities (PROC 15). Furthermore, manual activities involving hand contact (PROC 19, not further specified) have been indicated bearing significant dermal exposure.

The exposure estimation using CHESAR v2.3 for industrial use for the production of pharmaceuticals is given in the Table B 97 - Industrial use for the production of pharmaceuticals - calculated exposures using CHESAR v2.3 and the measured data in Table B 98 - Industrial use for the production of pharmaceuticals – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the production of polymers

Solvents are used in many different processes within the polymer manufacturing industry (i.e. for dry and wet spinning techniques). The application of solvents occurs in closed processes (PROC 1, PROC 2 and PROC 3) and also in semi-closed processes (PROC 4) including charging, sampling or discharge of material at different process temperatures (up to 140 °C). To ensure occupational safety, semi-closed processes are associated at least with exhaust ventilation (for indoor use) and/or with respiratory protection (for outdoor use). Applied RMMs and OCs mainly depend on process temperature, concentration of substance and place of use.

Rarely, mixing and blending operations take place in open processes (PROC 5) which provides the opportunity for significant contact. Here, occupational health and safety is guaranteed by application of respiratory protection equipment. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated facilities (PROC 8a) including un-coupling/coupling activities take place indoors with extract ventilation and respiratory protection. This also applies for the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b) and for drum and small package filling including weighing (PROC 9). Quality control of finished products and R&D activities (PROC 15) are undertaken under strict RMMs as well involving extract ventilation and respiratory protection. Processes which involve significant dermal contact (PROC 10 – Roller application or brushing) have also been indicated by Downstream Users. Despite strict PPEs such as gloves with specific activity training (APF 20) applied for this application, dermal exposure has been estimated to be relatively high.

The exposure estimation using CHESAR v2.3 for industrial use for the production of polymers

is given in the table Table B99 - Industrial use for the production of polymers - calculated exposures using CHESAR v2.3 and the measured data in Table B100 - Industrial use for the production of polymers – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the production of textiles, leather and fur

DMF is widely used as solvent in the production of polyurethane coated textiles such as artificial leather, rain and protection wear, footwear, medical mattress covers and surgical incise films. In general, hide and skin storage and beamhouse operations are followed by tanyard operations, post-tanning operations and finishing operations. These operations mainly take place in closed processes (PROC 1, PROC 2 and PROC 3) at elevated process temperatures up to 100 °C. Semi-closed (PROC 4) and/or open processes (PROC 5) at ambient temperatures (≤ 40 °C) are performed under strict RMMs (exhaust ventilation, respiratory protection). These RMMs also apply for general transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at dedicated (PROC 8b) facilities and for drum and small package filling including weighing (PROC 9). Some companies have additionally indicated that roller and dipping applications (PROC 10, PROC 13) at elevated temperatures (up to 200 °C) are performed under strict conditions for the manufacture of textiles, leather and fur. This comprises local exhaust ventilation and respiratory protection. Quality control (PROC 15) applying exhaust ventilation is undertaken as well.

The exposure estimation using CHESAR v2.3 for production of textiles, leather and fur is given in the Table B101 - Industrial use for the production of textiles, leather and fur - calculated exposures using CHESAR v2.3 and the measured data in Table B102 - Industrial use for the production of textiles, leather and fur – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the manufacture of non-metallic mineral products

This Exposure Scenario describes the usage of DMF for the manufacture of non-metallic products. One specific application is the usage for coating processes. Storage and formulation of DMF is only performed in closed systems (PROC 1, PROC 2 and PROC 3) where only slight opportunity for contact occurs (e.g. through sampling). Process temperatures are increased up to 45 °C. In this case, industrial spraying (PROC 7) is performed as automated and closed process at elevated process temperatures (up to 250 °C) under strict operational conditions (i.e. operators control room is enclosed and separated from this process).

The exposure estimation using CHESAR v2.3 for manufacture of non-metallic mineral products is given in the Table B103 - Industrial use for the manufacture of non-metallic mineral products - calculated exposures using CHESAR v2.3 and the measured data in Table B104 - Industrial use for the manufacture of non-metallic mineral products - measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use for the manufacture of perfumes / fragrances

This Exposure Scenario refers to the production of perfumes/fragrances. Relevant operations are only carried out in closed batch processes (PROC 3) with synthesis at temperatures up to 50 °C being followed by separation and purification steps. Respiratory protection need to be worn. Transfer processes of substances or preparations (sampling, loading, filling, dumping, etc.) are merely performed from/to vessels/large containers at dedicated facilities (PROC 8b). Respiratory protection is applied as well. Described transfer processes also include uncoupling/coupling activities.

The exposure estimation using CHESAR v2.3 for Industrial use for the manufacture of perfumes/fragrances is given in the Table B105 - Industrial use for the manufacture of perfumes/fragrances - calculated exposures using CHESAR v2. is enclosed in Annex B: Information on hazard, emission/exposure and risk.

Industrial use in the petrochemical industry

DMF is used as an extraction agent in petrochemical industry. The actual processes are closed and controlled (PROC 1 and PROC 2) at ambient process temperatures up to 40 °C. Unloading tanks takes either place in closed systems (PROC 2, outdoor) or semi closed-closed processes (PROC 8b, indoor) at ambient process temperatures (≤ 40 °C). For the latter one, respiratory protection is applied. The substance is internally recycled several times in a continuous process at temperatures up to 160 °C (PROC 1). Sampling of the products is either performed at elevated temperatures up to 100 °C (outdoor) or at slightly elevated temperatures up to 45 °C (indoor). Enhanced general ventilation for indoor operations is only applied for sampling at elevated temperatures.

The exposure estimation using CHESAR v2.3 for Industrial use in the petrochemical industry is given in the Table B106 - Industrial use in the petrochemical industry - calculated exposures using CHESAR v2.3 and the measured data in Table B107 - Industrial use in the petrochemical industry – measured data both enclosed in Annex B: Information on hazard, emission/exposure and risk.

Professional use as laboratory agent

The substance DMF is exclusively used in industrial settings, except for the use as laboratory chemical (which is the only use registered for professional workers). Strict occupational controls and chemical hygiene procedures are applied, since the handling of hazardous chemicals is day-to-day routine for this profession.

Handling of the substance can be described by intensive laboratory activities (PROC 15) at small scale laboratories. General transfer processes (charging/discharging) incl. weighing are undertaken from/to vessels/large containers at non-dedicated facilities (PROC 8a). Local exhaust ventilation is applied for all laboratory activities. Respiratory protection for charging and discharging may be applied if no additional RMM such as a fume extraction hood has been come into effect.

The exposure estimation using CHESAR v2.3 for the laboratory agent is given in the Table B108 - Professional use as laboratory agent - calculated exposures using CHESAR v2.3 is enclosed in Annex B: Information on hazard, emission/exposure and risk.

Combined human exposure assessment

DMF is only used by industrial or professional workers and does not end up in articles. Conclusively, only occupational exposure towards DMF is to be expected. Secondary exposure via the environment can be excluded as well since the substance is readily biodegradable and no potential for bioaccumulation exists.

However, a worker can perform different tasks during an 8 h working day. Thus, accumulated or combined human exposure within one identified use needs to be assessed. For such an assessment, a complete working day (8 h) under realistic worst case conditions should be considered.

Since specific information about combined exposure is lacking, accumulated exposures from explanatory exposure scenarios is calculated.

- The scenario “Industrial use for the production of fine chemicals” serves as a first basis and combined exposure for outdoor applications is assumed for the manufacturing step (contributing scenario 4) and a charging/discharging task (contributing scenario 12). Although only a 5 h working day is covered by these tasks, high exposures are associated for both processes. Thus, the combination of these tasks is considered as suitable.

- As a second approach, combined exposures are assessed for the scenario “Industrial use for the production of textiles, leather and fur” covering a full working day of 8

hours. Combined exposure for indoor applications has been calculated based on charging and discharging (contributing scenario 7) and manufacture (contributing scenario 8).

The exposure estimation using CHESAR v2.3 Combined human exposure is given in the Table B109 Combined exposure based on the exposure scenario "Industrial use for the production of fine chemicals" and the measured data in Table B110 - Combined exposure based on the exposure scenario "Industrial use for the production of textiles, leather and fur both enclosed in Annex B: Information on hazard, emission/exposure and risk.

For all the uses described above no exposure to consumers is given and indirect exposure of humans via the environment was not considered in the restriction dossier.

1.1.4 Risk Characterisation

The risk characterisation was performed using the exposure estimates by CHESAR v2.3 and the DNELs both derived as described in the section above. Risk characterisation ratios are presented in the tables below for each industrial and professional use as laboratory agent, respectively. The RCRs are given for the individual routes of exposure and the combined (total) exposure. Combined or so called accumulated exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for two exposure scenarios as well.

RCRs derived are often higher than 1, even for those processes with a high containment. Processes described by PROC 1 have the lowest risks, which can be related to high level of containment. Processes with a lower level of containment, elevated temperatures and open high energy processes seem to show much higher RCRs although in some cases PPEs and strict OCs are taken into account. RCRs > 1 indicate that the described use may present a risk to the worker.

There is a variety of possibilities for each ES-PROC combination to apply (additional) RMMs. It is well accepted that for many applications some RMMs cannot be applied. In case of very specific information available referring to RMMs already implemented, manual refinements of the exposure estimations were performed. In any case, a qualitative evaluation of the RCRs per ES is given in the tables below. Possible (unaccepted) risks are indicated and discussed.

Manufacturing

RCRs for outdoor applications (PROC 2 and PROC 8b) are higher than 1. For PROC 2, only the combined RCR is slightly above 1 which is mainly based on inhalation exposure. The ECETOC modelling approach as implemented in CHESAR v2.3 also indicates PROC 8b to bear a certain risk for industrial workers. For both processes, additional RMMs such as local extraction systems for outdoor applications (not implemented in ECETOC TRA v2.3) or respiratory protection were not applied by the Dossier Submitter. The general inhalation exposure reduction by outdoor applications is assumed to be only 30 % by the modelling tool. Due to the conservativeness of CHESAR v2.3 output, the (semi-)closed systems applied and remaining options for the RMMs such as outlined above, the manufacturing of DMF is not expected to bear a safety concern for workers.

Measurement data of air concentrations of DMF at the production plant suggest as well that the CHESAR v2.3 output is indeed conservative.

Calculated RCR values using CHESAR v2.3 for Manufacture of substance is given in the Table B111 - Manufacture of substance - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Risks sufficiently controlled if specific RMMs and/or OCs are applied.

Formulation of substance

Combined RCRs for PROC 2 and PROC 8a are slightly higher than 1. Nevertheless, it is considered that these risks can be controlled easily by applying LEV or a respiratory protection. A decrease of the exposure/task duration would have a similar impact. Even open processes at elevated temperatures such as PROC 5 have been assessed to bear an acceptable risk with RCRs <1. Due to the conservativeness of CHESAR v2.3 output and remaining options for the RMMs such as outlined above, formulation of DMF is not expected to bear a safety concern for workers.

Measurement data of air concentrations of DMF for the formulation stage suggest that risks are sufficiently controlled.

Calculated RCR values using CHESAR v2.3 for formulation of substance is given in the Table B112 - Formulation of substance - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Risks sufficiently controlled if specific RMMs and/or OCs are applied.

Industrial use for the production of fine chemicals

RCRs for indoor (PROC 2) and outdoor (PROC 2, PROC 8b) applications are slightly higher than 1 for the combined exposure route. In case of PROC 2 this is driven by inhalation exposure while dermal exposure is more critical for PROC 8b. Nevertheless, it is considered that these risks can be controlled easily by applying LEV (indoor applications) or a respiratory protection (outdoor application). Combined RCRs would decrease to < 1. A reduction of the exposure/task duration would have a similar impact – at least for PROC 2.

The RCR for PROC 19 is well above the trigger value of 1 (combined RCR = 9.5) which is mainly based on high dermal exposure. This result has been obtained although application of strict RMMs (gloves with the highest protection factor; APF = 20) took already place in the model calculation. Therefore, risks might not be sufficiently controlled for the dermal exposure route.

Measurement data of air concentrations of DMF for the industrial use suggest that risks associated with inhalation exposure are sufficiently controlled.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of fine chemicals is given in the Table B113 - Industrial use for the production of fine chemicals - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. Dermal exposure is expected not to be sufficiently controlled in case of specific applications such as hand-mixing with intimate contact. A certain risk for industrial worker is therefore identified.

Combined exposure

RCRs for inhalative and the combined exposure route as calculated for an industrial worker performing two different tasks at the same day (here: PROC 2 and PROC 8b) are higher than the trigger value of 1. Although it is believed that inhalation exposure can be further decreased by changing OCs (e.g. decrease of process duration for transfer activity), dermal exposure remains high leading to an overall combined RCR of > 1. Strict PPEs such as gloves with a high protection level (APF 20) have already been implemented in the calculations. Thus, the industrial use for the production of fine chemicals may bear a safety concern for workers.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of fine chemicals combined is given in the Table B114 - Industrial use for the production of fine chemicals - calculated RCR values based on combined exposure using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. Dermal exposure has been evaluated as more critical since additional RMMs and/or OCs cannot be applied to further decrease the dermal RCR. This leads to RCRs above 1 in terms of combined exposure. Therefore, risks associated with performing PROC 2 and PROC 8b may not sufficiently controlled.

Industrial use for the production of pharmaceuticals

The RCRs for PROC 2, PROC 8a and PROC 8b are slightly above 1. For these processes, the combined exposure route has been identified as critical. Additional RMMs such as LEV for PROC 2, respiratory protection for PROC 8b or further decrease of the process duration were not applied by the Dossier Submitter. Conclusively, it is assumed that the risks associated with these charging and discharging activities can be sufficiently controlled.

The RCR for PROC 19 is well above the trigger value of 1 (combined RCR = 9) which is mainly based on high dermal exposure. This result has been obtained although application of strict RMMs (gloves with the highest protection factor; APF = 20) took already place in the model calculation. Therefore, risks may not be sufficiently controlled for the dermal exposure route.

Measurement data of air concentrations of DMF for the industrial use do not lead to clear conclusions if inhalation exposure is sufficiently controlled or not. Some data points have been indicated to be below the iOEL value of 15 mg/m³. This cannot be compared to the derived DNEL values.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of pharmaceuticals is given in the Table B115 - Industrial use for of pharmaceuticals - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. Dermal exposure is expected not to be sufficiently controlled in case of specific applications such as hand-mixing with intimate contact. A certain risk for industrial worker is therefore identified. A similar conclusion has been drawn referring to the industrial use for the production of fine chemicals.

Industrial use for the production of polymers

RCR values above 1 have only been identified for PROC 10. The combined RCR is close to 2.5. Strict RMMs for both inhalation and dermal exposure such as LEV, respiratory protection and gloves were already taken into consideration for exposure modelling. Decreasing the exposure duration may lead to decreased exposure values and RCRs < 1. However, since PROC 10 is part of the production process, decreasing the process duration to a certain extend does not seem to be applicable here. Thus, the industrial use of DMF for the production of polymers may bear a safety concern for workers.

Measurement data of air concentrations of DMF for the industrial use indicates that inhalation exposure is sufficiently controlled. Nevertheless, data for critical processes such as PROC 10 is not available. Therefore, measured data cannot completely overrule the exposure calculations performed by CHESAR v2.3.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of polymers is given in the Table B116 - Industrial use for of polymers - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. This also applies for dermal exposure. However, processes performed at elevated temperatures with no containment and high associated exposure (i.e. PROC 10) bear a potential risk for industrial workers. Inhalation as well as dermal exposure may not sufficiently controlled for those applications.

Industrial use for the production of textiles, leather and fur

RCR values above 1 were identified for two activities described by PROC 10 and PROC 13. PROC 10 indicates a certain risk for dermal and combined exposure while PROC 13 bears a risk in terms of combined exposure. Strict RMMs such as LEV, respiratory protection and gloves are already implemented in the calculations. Modifications of the OCs such as the process duration do not seem to be applicable here. Both processes are part of the manufacturing process and exposure duration reduction to a certain extent does not seem to be applicable. Conclusively, risks cannot be guaranteed to be sufficiently controlled.

Measurement data of air concentrations of DMF for the industrial use indicates that inhalation exposure is sufficiently controlled for PROC 1 and PROC 8b under specific RMMs and OCs. Nevertheless, data for critical activities such as PROC 10 and PROC 13 is not available. Therefore, measured data cannot completely overrule the exposure calculations performed by CHESAR v2.3.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of textiles, leather and fur is given in the Table B117 - Industrial use for the production of textiles, leather and fur - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. This also applies for dermal exposure. However, processes performed at elevated temperatures with no containment and high associated exposure (i.e. PROC 10, PROC 13) bear a potential risk. Combined exposure is not sufficiently controlled for those applications, respectively.

Combined exposure

RCRs for combined exposure as calculated for an industrial worker performing two different tasks at the same day are higher than 1 for both exposure routes. Although it is believed that inhalation exposure can be slightly decreased by stricter OCs (e.g. decrease of process duration for transfer activity), dermal exposure remains high leading to RCRs of > 1. Strict PPEs such as gloves with a high protection level (APF 20) have already been implemented in the calculations. Risks may not be sufficiently controlled.

Calculated RCR values using CHESAR v2.3 for Industrial use for the production of textiles, leather and fur combined is given in the Table B118 - Industrial use for the production of textiles, leather and fur - calculated RCR values based on combined exposure using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Inhalation exposure to DMF may not be sufficiently controlled although proper RMMs and OCs are already in place. Dermal exposure has been evaluated as even more critical under the assessed conditions. RCRs for all exposure routes remain above 1 even if strict RMMs and OCs are applied. Therefore, risks associated with this combined exposure (PROC 9 and PROC 10) may not be sufficiently controlled.

Industrial use for the manufacture of non-metallic mineral products

RCRs above 1 have not been identified for this industrial use. All combined RCRs are even below 0.1 showing that no risks are indicated. Critical processes such as PROC 7 (industrial spraying) may be associated with a certain risk. However, an automated process is described in this case for which worker exposure can be practically excluded (worker separated from

the workplace). Conclusively, the industrial use for the manufacture of non-metallic mineral products is not expected to bear a safety concern for workers.

Measured data as shown in confirms these conclusions. In any case, air concentrations of DMF are well below the derived inhalation DNEL.

Calculated RCR values using CHESAR v2.3 for Industrial use for the manufacture of non-metallic mineral products is given in the Table B119 - Industrial use for the manufacture of non-metallic mineral products - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Risks sufficiently controlled if specific RMMs and/or OCs are applied.

Industrial use for the manufacture of perfumes / fragrances

The combined RCR for PROC 8b has been calculated to be slightly above 1. Although strict RMMs such as gloves with high protection level and respiratory protection are already implemented in the calculations, further RMMs such as LEV could be applied for the transfer process. A decrease of the process duration would influence both dermal and inhalation exposure. Both refinements would lead to a combined RCR below 1. The industrial use for the manufacture of perfumes / fragrances is therefore not expected to bear a safety concern for workers.

Calculated RCR values using CHESAR v2.3 for Industrial use for the manufacture of perfumes / fragrances is given in the Table B120 - Industrial use for the manufacture of perfumes / fragrances - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Risks sufficiently controlled if specific RMMs and/or OCs are applied.

Industrial use in the petrochemical industry

RCRs above 1 are only identified for PROC 9 which is mainly based on inhalation exposure. Strict RMMs decreasing inhalation exposure such as LEV and respiratory protection have not been implemented in the exposure modelling. Consequently, inhalation exposure can be easily decreased by a certain extent. Risks associated with the industrial use in the petrochemical industry are expected to be acceptable.

The conclusions by the Dossier Submitter are also confirmed by measured data as contained in Table B. Referring to this table, only one exposure value of 4.75 mg/m³ is above the inhalation (long-term) DNEL. However, this value represents a peak exposure and cannot be compared with the 8-h TWA as displayed by the long-term DNEL.

Calculated RCR values using CHESAR v2.3 for Industrial use for the petrochemical industry is given in the Table B121 - Industrial use for the petrochemical industry - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

Conclusion: Risks sufficiently controlled if specific RMMs and/or OCs are applied.

Professional use as laboratory agent

RCRs above 1 are identified for the transfer process in terms of dermal and combined exposure. The dermal RCR is, however, only slightly above 1. Furthermore, the effectiveness of gloves (i.e. 90%) for professional workers assumed by the modelling tool is considered to be quite conservative. Especially laboratory staff is supervised and familiar with handling hazardous substances. Conclusively, the dermal protection factor is believed to be much higher in this case which is not sufficiently addressed within the modelling tool. Due to the

conservativeness of CHESAR v2.3 output, the professional use of DMF as laboratory agent is not expected to bear a safety concern for workers.

Calculated RCR values using CHESAR v2.3 for Industrial use as laboratory agent is given in the Table B 122 Industrial use as laboratory agent - calculated RCR values using CHESAR v2.3 and enclosed in Annex B: Information on hazard, emission/exposure and risk.

1.2. Justification for an EU wide restriction measure

DMF is a high production volume substance which has been registered with a total tonnage band of 10.000 - 100.000 t/a and the substance is used in many industrial settings. It has also a registered use as intermediate. Part of the tonnage is produced in the EU; part of it is imported from non-Community manufacturers. No direct export from the EU has been reported in the registration dossiers. The outcome of the analysis on exposure of workers clearly shows, that for a few specific areas of use, risks on a Community-wide level are present which need to be controlled and eliminated.

REACH provides two possible instruments to authorities to regulate risks caused by a substance: Restriction and Authorisation. Accordingly, in the present document the restriction and authorisation routes have been assessed with respect to their effectiveness in reducing the risk, their proportionality to the risk, their practicality and their monitorability. The restriction and authorisation options differ from each other with regard to their scope and have been described in detail in section 2.2 of this report and were evaluated for their socio-economic impact in Annex E: Impact Assessment.

DMF is an aprotic and medium polar organic solvent with limited technical feasible alternatives and for the fast majority of applications, adequate substitutes are lacking. Hence, the Dossier Submitter considers that banning of the manufacturing and uses of DMF, which is the ultimate consequence of an authorisation process, is not an appropriate risk management option. It is expected that the substance becomes substituted by another equally hazardous substance or that industry is forced to cease and/or relocate its activities outside Europe.

Furthermore, it needs to be considered that DMF is a threshold substance, which means that the toxicological endpoint will have a theoretically identifiable dose threshold and thus a potentially 'safe' level of exposure (ECHA, 2012). Consequently, DMF can be used without causing a risk for human health as long as the threshold is undercut through adequate control of exposure. Due to the identified costs and severe socio-economic impact, the lack of feasible alternatives for most of the uses and considering that the risks can be adequately controlled by the proposed restriction, authorisation is not proportional for DMF.

Additionally, the authorisation procedure is more costly for both – for applicants and for authorities. If save use is demonstrated, there would be no difference in residual risk, compliance costs or monitoring of implementation, whether the restriction or authorisation route is used. In case the socio-economic route within the authorisation procedure is applied, the risk would not be reduced to the same extent of the proposed restriction.

Restricting the use of DMF with mandatory occupational exposure limit (OEL) to control the risk at the workplace was considered. However, feedback on the RMOA from Member States and the Commission demonstrates that REACH Annex XVII is not considered being the appropriate regulation for the setting of workplace exposure limits. For this purpose, there is already specific legislation in place, which should be applied (Directive 98/24/EC). An OEL-based restriction could furthermore generate enforceability difficulties and a possible interaction between REACH enforcement authorities and authorities competent for the control of occupational safety. Furthermore, the use of an existing indicative OEL (IOEL) value for conducting a quantitative risk assessment was also considered. As for an OEL also for the derivation of an IOEL there is no legally binding or compelling reason to use the threshold derivation methods as set by the respective REACH guidance. The IOEL for DMF is above the long-term inhalation DNEL for workers derived in accordance with the REACH methodology. Moreover, the OEL and the IOEL, by definition, only protect 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. Hence, in view of the Dossier Submitter, a restriction based on mandatory harmonised long-term inhalation and long-term dermal DNELs combined with an obligation to use respective personal protection equipment and operational conditions is considered to be the most appropriate Community wide measure as such a restriction is effective in reducing all risks of DMF with acceptable costs for industry and society.

Considering the aforementioned and the outcome of the Socio-Economic Analysis Annex E: Impact Assessment, a restriction based on two harmonised worker DNELs (inhalation + dermal) is for the Dossier Submitter (DS) the most appropriate Community-wide measure. Such a restriction would ensure the safe use of DMF by respecting the proportionality principle and ensuring a high level of practicality and monitorability. Moreover, this measure would follow the specified route for managing substances under REACH through a Chemical Safety Assessment by applying Derived No Effect Levels (DNELs).

1.3 Baseline

The objective is to prevent or to adequately control exposure of DMF to workers in order to prevent ill health. Worker exposure information in the Restriction Dossier (see Annex B: Information on hazard, emisson/exposure and risk section B.9 and B.10) indicate clear evidence that risks are arising from identified uses relevant for different sector groups. Thus, risks need to be sufficiently controlled.

Therefore, the Restriction Proposal is targeted to the critical uses of DMF in industrial settings. The primary routes of industrial exposure to DMF are skin contact and inhalation. No specific risks have been identified concerning consumer uses or the environment compartment.

The main use of DMF (ca. 80%) is as a solvent in chemical synthesis of pharmaceuticals, agrochemicals and fine chemicals, and in addition, used in electronic industry and as a solvent in the synthesis of artificial fibers or artificial leather. The pharmaceutical industry also uses DMF to sterilise powders and ampules and in various quality control applications. The 20% remaining applications are assumed to be used as intermediate, as laboratory chemical, as cleaning solvent and in formulations.

The substance is potentially used in all Member States while the use is expected to be higher in some Southern EU countries. The Chemical Safety Assessment of the Lead Registrant of DMF identified for some processes occupational exposure which might lead to risks towards human health. ECHA's Draft Recommendation Document (2012) identifies use of DMF in mixtures such as sealants, strippers, paints, coatings, mastics or glue as source for potential significant exposure of workers, especially professionals, within the EU.

Not all of these uses were identified in the registrants' CSR. Therefore, it could be considered that DMF is not used in mixtures such as strippers and mastics anymore. The exposure assessment presented for industrial and professional uses covers the remaining uses as well as additional uses which were not mentioned in ECHA's Draft Recommendation Document (2012). DMF in mixtures such as glues, sealants, coatings and paints are used for the production of textiles, leather and fur. DMF containing coatings are additionally used for the manufacture of non-metallic mineral products. Paints and polymeric coatings may be also used for the production of polymers.

Consequently, there is clear evidence that human health risks are potentially arising from some industrial processes at EU-wide scale.

Hazard

The information is adopted from the registration dossier, OECD SIDS report (2004) on DMF and literature studies.

N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD50 rat (oral) 3040 mg/kg bw, LC50 rat (inhalative, 4 h) > 5900 mg/m³, LD50 rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (90 day feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m³), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m³); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m³ and 1210 mg/m³ , respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m³).

DMF does not induce chromosome aberrations or gene mutations in various test systems in vivo and in vitro . In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m³) by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral- or dermal administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m³); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

DMF was studied for its carcinogenicity potential in three inhalation studies, which provides contraversial results for this endpoint. No increased incidence of hepatic tumors occurred in the 2-year inhalation study in rats and mice, while during another 2 year-inhalation study to DMF vapour increased incidences of benign and malignant neoplasms in two rodent species, hepatocellular adenomas and carcinomas in F344 rats and hepatocellular adenomas and carcinomas and hepatoblastomas in BDF1 mice were observed. A critical evaluation of the manuscripts revealed that technical aspects of two carcinogenicity studies substantially deviated from the OECD 451 guideline. The doses selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. In addition, the selected animal species (F344 rats) were more sensitive to DMF

and therefore may have contributed to increased tumor incidence observed. In humans, case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

Regarding ADME parameters, DMF is absorbed via all exposure routes in animals and in humans. In humans, after high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flashing and palpitations) were seen. With respect to the metabolism of DMF the following conclusion can be drawn: N-hydroxymethyl-N- methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono- N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming Smethylcarbamoylglutathione. The GSH and its sequel adducts (S-methyl-carbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl- N-acetyl-cysteine) seem to be responsible for developmental toxic effects. At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance.

Risk

Regarding REACH requirements, the substance DMF was registered in 2010. The Identified Uses mentioned in the registration dossier at that time were updated in February 2014. As a consequence, the whole risk assessment was sufficiently revised in the CSR. This comprised the inclusion of exposure scenarios, additional exposure calculations for specific applications and a separate TIER 2 assessment which is based on measured data.

Tiered approach for risk assessment

The following approach was applied for the restriction dossier.

In order to achieve an adequate refinement of the risk assessment - in terms of a tiered approach - all identified Downstream Users of the Lead Registrant were requested to provide specific information regarding their use patterns of the substance. For this purpose, two consecutive questionnaires were provided to the Downstream Users. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. Due to this detailed and complex approach, exposure estimations and risk characterisations take the current state of the art into account.

The Dossier Submitter analysed the questionnaires with a high level of detail and extracted relevant information according to the respective industry sectors (SUs) as indicated in the questionnaires. Therefore, current exposure and risk information for each industry sector was gained which could be used for refinements of the risk assessment initially performed by the lead registrant in the REACH standard registration. Furthermore, the amount of DMF used by the different industry sectors could be roughly estimated. Since not all Downstream Users provided actual numbers of the amount of DMF used, the tonnage information as given in Table A2 provides only the minimum tonnages of DMF used by industry.

The exposure towards DMF at the workplace was assessed in a first step by a TIER 1 (exposure modelling) approach. For this approach, the software tool CHESAR v2.2/v2.3 was used which implements ECETOC TRA v3.0 for exposure modelling referring to Human Health. Due to the fact that relevant measured data from several different industrial sites was available, a TIER 2 assessment was additionally elaborated.

Cleaning and maintenance were not identified as tasks resulting in high levels of exposure. However, the resulting exposure was not systematically considered in all identified uses.

Therefore – exposure assessment via modelling for cleaning / maintenance is presented as a separate section, which is applicable to all industrial uses presented.

Results of risk assessment

According to the risk assessment as shown in section B.9 and B.10 of the Annex B: Information on hazard, emission/exposure and risk, exposures resulting from processes under elevated temperatures as well as processes requiring intensive manual applications and open processes are relatively high. Risks associated with those activities, however, can only be partly addressed by the applied RMMs and OCs. Conclusively, risks may not be sufficiently controlled for some applications.

In general, the estimated exposure levels ranged from 0.021 to 4.568 mg/m³ for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranged from 0.002 to 7.072 mg/kg bw/day (systemic, long-term). It should be emphasised that for both exposure routes, strict RMMs as implemented by the industry were already taken into consideration. In many cases, exposures without any RMMs would be higher at least by an order of magnitude.

By combining the derived DNELs with the exposure estimates, risk characterisation ratios (RCRs) were obtained. Many RCRs were above the trigger value of 1.0. A potential unacceptable risk for workers was, therefore, identified for the industrial uses for the production of fine chemicals, pharmaceuticals, polymers as well as textiles, leather and fur. Applications described by PROC 10, PROC 13 and PROC 19 were found to bear a certain risk for human health. Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been additionally assessed for DMF. A safety concern for workers was revealed as well.

The TIER 2 Assessment based on measured data showed that inhalation exposure is generally below the inhalation DNEL of 3.2 mg/m³. However, some data points have been indicated to be below the iOEL value of 15 mg/m³. This could not be compared to the derived DNEL value for inhalation exposure.

Furthermore, measured data for open high energy processes including manual handling as declared above to bear a certain risk is not available. Results of the TIER 2 Assessment, can thus not overrule the conclusions of unacceptable risks referring to specific tasks/processes.

Overall, it is therefore concluded that risks are not sufficiently controlled for certain applications which are performed in a variety of industry sectors (Table 10). It was also shown in the exposure modelling approach that applied (strict) RMMs and/or OCs for these applications cannot decrease exposures to an adequate (acceptable) level. The table below summarises all tasks which bear a potential safety concern for workers.

Table 10 - Overview of application which have been assessed to bear an unacceptable risk

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Industrial use for the production of fine chemicals	PROC 19; (indoor, process temp. ≤ 40 °C)	0.571	**8.951**	**9.522**	Dermal exposure to DMF is well above the derived dermal DNEL. Even with proper RMMs, exposure cannot be decreased to an acceptable level. Risks may not be sufficiently controlled.
	Combined exposure: PROC 2 and PROC 8b as described in section B.9.4*	**1.066**	**0.92**	**1.986**	Inhalation exposure may be decreased by adaption of the process duration for transfer processes. Nevertheless, the combined RCR would still remain above 1, even with strict RMMs/OCs. Risks may not be sufficiently controlled.
Industrial use for the production of pharmaceuticals	PROC 19; (indoor, process temp. ≤ 40 °C)	0.057	**8.951**	**9.008**	Dermal exposure to DMF is well above the derived dermal DNEL. Even with proper RMMs, exposure cannot be decreased to an acceptable level. Risks may not be sufficiently controlled.
Industrial use for the production of polymers	PROC 10; (indoor, process temp. ≤ 130 °C)	**1.428**	**1.042**	**2.469**	Inhalation as well as dermal exposure is above the derived reference values. Even with strict RMMs, RCRs above 1 for all exposure routes were calculated. Risks may not be sufficiently controlled.

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Industrial use for the production of textiles, leather and fur	PROC 10 (indoor, process temp. ≤ 200 °C)	0.999	1.042	2.041	Dermal exposure is above the derived reference value. Only with strict OCs, inhalation exposure could be decreased to a safe level slightly above the inhalation DNEL. However, even with these OCs and in combination with RMMs, RCRs for dermal and combined exposure routes remain above 1. Risks may not be sufficiently controlled.
	PROC 13 (indoor, process temp. ≤ 200 °C)	0.999	0.521	1.52	Only with strict OCs and RMMs, inhalation exposure could be decreased to a safe level slightly below the inhalation DNEL. However, even with these strict measures, the RCR for combined exposure routes remains above 1. Risks may not be sufficiently controlled.
	Combined exposure: PROC 9 and PROC 10 as described in section B.9.7*	1.285	1.303	2.588	Both inhalation and dermal exposure is above the respective DNELs. Inhalation exposure may be decreased by adaption of the process duration for transfer processes. Nevertheless, the dermal as well as the combined RCR would still remain above 1, even with strict RMMs/OCs. Risks may not be sufficiently controlled.

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Others	Combined exposure	n.a	n.a.	n.a.	Combined exposures that may arise from different tasks or activities for identified uses other than described above bear a potential health concern as well. Since no information on combined exposures has been made available, unacceptable risks may be relevant. Risks may not be sufficiently controlled.

*Please refer to Annex: Information on hazard, exposure/emission and risk

2. Impact Assessment

2.1 Introduction

In most cases where a concern related to a substance has been identified, there will be several options for addressing this concern. All of the different legislative measures that may be potentially applicable have different strengths and weaknesses which will vary depending on the case. Due to the fact that DMF is already included in the Candidate List and subject to strict Classification & Labelling requirements (CHL), beside Authorisation only the following risk management options (RMOs) have been considered:

RMO 1 – Complete restriction

The first RMO is the total ban for placing on the market and use of DMF for all applications in the EEA.

RMO 2 – Proposed restriction

This option is a combination of the following measures:

a. Harmonisation of national OELs (currently there exist various national OELs between 15 and 30 mg/m^3) with REACH compliant DNELs, which means in practice: DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure will remain below 3.2 mg/m^3. According to Article 2(4) of REACH, employers and manufacturers must be compliant with both chemical and occupational legislations.

b. Dermal exposure is avoided by preventative measures to comply with the harmonised DNEL for dermal exposure of 0.79 mg/kg bw/day.

RMO 3 – Authorisation

Under REACH, another mechanism for limiting the use of harmful substances is Authorisation (Title VII). Authorisation is applicable to DMF as it has been identified as Substances of Very High Concern (SVHC) according to REACH Article 57(c), was placed on the Candidate list for Authorisation in 2012 and was included in the 5th Reccomendation for the inclusion in the Annex XIV in 2014. Hence, the third RMO is the authorisation procedure for DMF in the EEA.

European Commission grants authorisations if it is shown that the risk linked to use of the substance is sufficiently managed.

Other Union-wide risk management options than restriction or authorization

Other non-REACH RMOs were not found completely suitable and efficient, because the existing non-REACH legal requirements did so far not provide adequate control for all risks to be addressed (please see also section: *Discussion of the existing DMF IOEL (2009/161/EC) and comparison with the DNEL derivation* in Annex B: Information on hazard, exposure-emission and risk).

2.2 Risk management options

2.2.1 RMO 1 – COMPLETE RESTRICTION

Economic impact

According to the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in the Annex E: Impact assessment):

1. industrial gas industry: The application of RMO 1 to the industrial gases sector would lead to a social loss of 200 to > 300 M€;

2. fiber industry: RMO 1 would likely have very severe impacts on the sector, as they would lead to a complete termination of manufacturing of man-made fibers in the EEA. Stated in numbers, this RMO would represent at least 501 to 610 M€ in identified monetary impacts. In the worst case, these impacts would represent 703 to 811 M€;

3. coating textile industry/ PU Coatings and Membranes Sector: A complete restriction of DMF would represent at least 365 – 505 M€ in identified monetary impacts. In the worst case, these impacts would represent 593 – 690 M€;

4. pharmaceuticals sector: This sector provided limited information regarding potential effects of analysed RMOs. Nevertheless, it shows that a complete restriction would likely force the responding companies to move manufacturing and laboratory operations using DMF to non-EU countries and/or outsource these activities to companies outside the EU, particularly in India and China; Therefore, the wider socio-economic effects to these users are assumed to be substantial.

5. other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. Overall, it only can be concluded that a complete restriction would lead to business termination in different sectors in the EEA and relocation to non-EU. As above, the wider socio-economic effects to these users are assumed to be substantial.

Human health and environmental impact

RMO1 is total ban for placing on the market and use of DMF for all applications. Such total ban will eliminate any industrial/professional exposure towards DMF at all. Therefore, the respective RCRs will decrease to zero (RCR = 0). It can be concluded that in case of RMO1, there will be no remaining risk for industrial/professional worker caused by DMF after implementation of the total ban. No health effects because of DMF will remain for workers.

It is important to consider that RMO 1 and RMO 2 have a substally same human health impact as, applying the proposed DNEL, the risk will be anyway under control. The methodology

applied for the health impact assessment is reported below for the RMO 2 and in more detail in Annex E.

Other impacts, praticability and monitorability.

Regarding to praticability, it is very difficult to substitute DMF and alternatives or techniques for the uses are currently not known, as many other available aprotic solvents have the same intrinsic properties with regards to reproductive toxicity as DMF (e.g. DMAC and NMP). Due to the absence of suitable alternatives, implementability is clearly lacking and as long as a suitable (less harmful) alternative is not available, the total ban of DMF as aprotic solvent used by different industry sectors could not result in a benefit for human health. Regarding monitorability, there are no specific concerns as this can be done through enforcement.

RMO 1 would not be manageable for all sectors that currently use DMF because they should terminate their business.

Regarding enforceability, there are no specific concerns.

Proportionality

Risk reduction for industrial uses within the EU can be ensured (respective RCRs will decrease to zero) with this option, but the risks will only be shifted outside EU and revert somewhat due to import of articles containing DMF from non-EU countries. This option is considered not to be proportional (further explanation of the proportionality can be found in the Annex E: Impact assessment), as the same health effects can be obtained with a partial restriction with a lesser economic impact/.

Overall assessment of RMO 1

The risk reduction capacity of this RMO is limited: although reduction of risk for industrial uses within the EU can be ensured, the problem will only be shifted outside EU, where it cannot be addressed with this option.

Regarding enforceability and monitorability there are no substantial differences to the other RMOs, but the practicability of this option is lower, as implementability is clearly lacking due to the absence of suitable alternatives.

2.2.2 RMO 2 - Proposed Restiction

Economic impact

Based on the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in the Annex E: Impact assessment):

1. industrial gas industry: No significant impacts are to be expected, as European producers are currently using DMF under conditions that meet the standards corresponding to this RMO;

2. fiber industry: Estimated impacts would be 501 to 610 M€in the best case and 703 to 811 M€ in the worst case;

3. coating textile industry/ PU Coatings and Membranes Sector: Estimated impacts would be 365 to 505 M€ in the best case and 593 - 690 M€ in the worst case;

4. pharmaceuticals sector: This sector provided no information regarding potential effects of analysed RMO 2; Since this sector is able to implement the proposed risk reduction measures, it is assumed that the sectoral costs to comply with the proposed restriction

are moderate as no other information has been made available to the Dossier submitter.

5. other industries: Other sectors provided no information regarding potential effects of analysed RMO. In conclusion, the economic impacts assessment assumes that, for those sectros where cost information has not been made available, costs are moderate, and therefore the cost information available from the three sectors gives a reasonable picture of the costs to be used in the proportionality comparison.

Human health and environmental impact

Based on the hazard characteristics of DMF and the estimated exposures, the risk characterisation leads to RCRs > 1 for some applications (see Annex B: Information on hazard, emission/exposure and risk B.9 and B.10).

The potential adverse human health effects of DMF are mainly based on results from animal studies. A qualitative description of these potential effects is given, followed by a description of attempts to quantify the effects (fully reported in the Annex E: Impact Assessment). The analysis is performed taking the EEA as a geographical scope. As such, potential changes in human health effects outside the EEA are not addressed.

The dossier submitter explored methodology for a Health Impact Assessment for chemicals within REACH using RPA report (2011). Four options are provided to quantify "key elements" (RPA report, 2011; Chapter 6.1.2):

- "dose-response functions";
- attributable fractions;
- prevalence or incidence;
- the Risk Characterization Ratio (RCR) together with the margin of safety (MOS).

A thorough analysis of the four routes led to a conclusion that the quantification of health effects was possible for hepatotoxicity effects including alcohol intolerance and carcinogenicity, while a qualitative assessment is more appropriate for developmental effects. Despite the uncertainties surrounding quantifiable health effects of DMF in humans, an evaluation of the proportionality of the proposed restriction, in absolute value, by comparing costs and benefits for each sector could be made.

Qualitative description of health effects of DMF

1) Systemic health effects after chronic exposure (hepatotoxicity and alcohol intolerance)

Chronic DMF exposure might result in negative health effects for all workers (female and male). In repeated-dose animal studies, the adverse systemic effects found were changes in body weight, changes in food consumption, hepatic injury and increased kidney weights. In an inhalation repeated dose toxicity study, minimal to mild hepatocellular hypertrophy was observed at all concentrations tested. In the oral exposure study, hepatic injury was further characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Similarly, with developmental effects, AMCC metabolite is assumed to be responsible for the occurrence of hepatotoxic effects.

At very high dose levels of DMF, exceeding MTD (Annex - Information on hazard, exposure/emission and risk, section B.5.8), DMF produced neoplastic lesions in two rodent species. There were increased mortalities and increased incidences of benign and malignant neoplasms, hepatocellular adenomas and carcinomas and hepatoblastomas. These effects

were seen only in two two-year inhalation studies, while no such effects were observed in the third two-year inhalation study in two rodent species or in any other long-term study. The incidences of testicular tumors in rats and mice were similar to control values.

In general, the most critical effect in the animal studies is based on hepatotoxicity.

Relevancy for humans

The extrapolation of the chronic systemic effects of DMF described in animals to humans could imply that a person would eat less and loose some body weight, probably combined with some loss in general well-being. The hepatotoxicity effects of DMF found in animal studies seem to be easily to extrapolate to human health effects. In this regard, different publications exist referring to medical surveillance data and human health effects associated with DMF exposure in different industry branches. The obtained results mainly refer to a chronic DMF exposure (workers exposed to DMF for several years). In one study among workers in an acrylic fibre factory, exposure to DMF vapour (< 30 mg/m³) for 5 years did not seem to entail a risk of liver cytolysis. Similar findings were indicated by two studies among workers exposed to DMF in a synthetic leather manufactory (0 – 5.13 ppm) and in a factory for the production of polyurethane (up to 7 ppm). However, DMF-induced liver damage was found in another study among synthetic leather workers exposed to high DMF concentrations (i.e. 20 – 60 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase levels. Further symptoms such as epigastric pain, nausea and loss of appetite have occurred at DMF levels of 10 – 60 ppm. Besides hepatotoxicity, less tolerance to alcoholic beverages was determined in these cases. Reduced alcohol tolerance is one of the earliest manifestations of excessive exposure to DMF. The workers had flushing symptoms including abdominal pain, flushing of skin on face, and arms, reddening of eyes, stomach ache, nausea etc ("loss of wellbeing" effects). Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance.

The effects of DMF found in other organs (kidney) 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 for humans. Thus, effects to other organs will not be evaluated. Based on this information, potential endpoints for further investigation in the health impact assessment are:

- general loss of well-being;
- hepatic injury (elevated enzyme levels);
- alcohol intolerance.

2) Carcinogenicity effects

Regarding carcinogenic effects observed in two animal studies, there are predominantly hepatic, testicular and mammary gland tumors reported in animals.

Relevancy for humans

Cases of testicular, prostate, oral cavity, throat, liver and skin cancers in workers of aircraft repair and leather tannery facilities exist. Moreover, the cases of these types of cancer failed to be confirmed in further studies. Additionally, confounders like smoking and co-exposure to other chemicals have not always been considered.

Based on this information, potential endpoints for further investigation in the health impact assessment are:

- general loss of well-being;

- neoplastic lesions.

3) Reproductive / Developmental effects

As described in Annex - Information on hazard and risk, the most relevant affected human health endpoints of DMF are the reproductive and the developmental effects. It is concluded from the results of the continuous breeding study in mice that DMF exposure causes significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index, reduced no. of litters and litter size) in the presence of general toxicity in females (increased liver weights, hepatocellular hypertrophy and decreased body weights). Moreover, reproductive toxicity of DMF resulted in affected prostate weight and epididymal spermatozoa concentration in the F1 parental males. Furthermore, it is concluded from several animal developmental studies performed via different exposure routes (dermal, oral and inhalation) that DMF exposure during gestation causes developmental toxicity, including embryo-/fetotoxicity and teratogenicity without overt maternal toxicity, pointing to a clear specific effect of DMF as developmental toxicant. Embryo- and fetotoxic effects were manifested by decreased number of liveborn pups, decreased number of litters, litters' size, and decreased foetal body weights. Teratogenic effects included external, skeletal and visceral malformations as well as increased incidence in variations and retardations was observed. In rats, embryo-/fetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Relevancy for humans

There is no information available in literature about cases of reproductive or developmental effects in humans after exposure to DMF. As described in the toxicokinetic section (Annex - Information on hazard, exposure/emission and risk, section B.5.1), ADME characteristics in animals and humans are similar. Furthermore, specific metabolite such as N-acetyl-S-(N-methylcarbamoyl) -cysteine (AMCC) is expected to be responsible for developmental toxic effects. Since this metabolite has also been identified in humans, the relevant reproduction and developmental effects demonstrated in rodents could also be relevant for humans. Furthermore, accumulations of AMCC in human body or rather high proportions of this metabolite in humans in comparison to rodents have been described. Based on this information, potential endpoint for further investigation in the human health impact assessment is:

- increase in AMCC metabolite

Possibility of quantification of the health effects of DMF in humans

Possible approaches to quantify health effect in humans are elaborated by RPA and summarized as follows:

According to Part 1 of the RPA (2011), the extent to which Risk Characterisation Ratios (RCRs) provide information with which to inform a SEA is limited, as they provide no information on the severity or extent of effects that might be anticipated to occur in an exposed population. Consecutively, the document lists different approaches how to appropriately quantify 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."

The Dossier Submitter sees in theory two possible routes for quantitative health impact assessment (the options 1 and 3 as mentioned above). In the Annex E is reported an in deep analysis of these options. Although hepatotoxicity effect levels in animals well correlate with effect levels in humans, the calculated MOS of 1.85 and 25 are not sufficient to demonstrate efficiency of the proposed restriction following this calculation approach. Specific mathematical models are necessary to derive odds ratios, incidence ratios in persons-years or other "health metrics" from the effect-exposure regression line in order to proceed with the valuation of health impact assessment. Thus, the above described Option 3, even though with very rough assumptions, is also used to valuate hepatotoxicity effects including alcohol intolerance (see section 4). For developmental effects, no quantification is possible since the

relevant effects have not been observed in human. Risk reduction of developmental effects in humans is however will be reduced to a negligible risk in case of the proposed restriction. For carcinogenicity effects, Option 3 (prevalence/incidence) is more appropriate since odds ratios for several types of cancers probably attributed to DMF exposure exist in the literature.

Calculation based on prevalence and incidence studies on hepatotoxicity including alcohol intolerance and carcinogenicity caused by DMF (Option 3)

This approach includes the use of incidence 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

Various types of cancer are reported in workers exposed to DMF. However, there was no relationship with duration of exposure in several studies or the incidence cases were not linked to duration of exposure at all (no data about duration of exposure). Moreover, exposure levels were characterized as low (1<2 ppm), moderate (2<10 ppm) or high (>10 ppm). No significant increase in the incidence of tumors could be established for higher exposure levels. Therefore, no exposure-response correlation could be established based on these human data. Taking into account very high exposure levels (exceeding MTD) in laboratory animals at which increased incidence of tumors was observed, and, probably, very high (> 10 ppm) exposure levels in humans, a rough semi-quantitative estimation can be made for carcinogenicity: tumors can occur in humans exposed to only very high dose levels to DMF during many years.

Proposed methodology: using QALYs for monetizing health impacts

Quantifying health benefits of the proposed restriction requires choosing among several tools for valuing specific health states and translating them into monetary values. In this report, we propose to focus on one of two widely used metrics, namely Quality-Adjusted Life Year (QALY) and Disability-Adjusted Life Year (DALY).

From the QALY perspective, health is defined in terms of the value-weighted time (i.e. life-years weighted by their quality) which is accumulated over a relevant time horizon[1]. Conversely, DALY is a time-based measure considering years of life lost due to premature mortality and years of life lost due to time lived in health states reflecting less than ideal health.

RPA (2015) provides detailed information about the definition and derivation of QALYs and DALYs, utility and disutility weights existing in the literature and discussions about methodological issues arising from their use. Our analysis builds mainly on information provided in that study and does not intend to develop or deepen any related debates. For simplicity reasons, we select the QALY metric for our assessment analysis. The steps undertaken for monetizing the health benefits of the proposed restriction are the following:

1. identification of health effects related with DMF exposure (diseases/health outcomes relevant for humans);

2. identification of the number of people potentially affected by DMF (benefited by the proposed restriction);

3. for each disease, calculation of gains in terms of QALYs or DALYs. This phase requires defining the following assumptions:

[1] See RPA (2015) for a more detailed exposition.

a. utility and/or disutility weights

b. life expectancy

c. disease onset

d. life expectancy conditional on the disease (or duration of the disease)

4. based on outcomes from steps 2 and 3, estimation of the total number of QALY/DALY gains;

5. using the value of a life year, monetization of health impacts.

Step one here above has been already undertaken in Annex B of the restriction report. The main health impacts related to DMF exposure identified in the analysis included developmental effects, carcinogenicity effects, hepatotoxicity and alcohol intolerance.

The details of the procedure are reported in Annex E.

Aggregation and monetization of health impacts

The three types of cancer identified as related to positive attributable proportions of affected people have been considered, namely prostate cancer, liver cancer and skin melanoma and liver-related effects using liver cirrhosis as a proxy. On the other hand, the proportion of exposed workers is accounted who will likely develop each of the diseases across the two industries where health benefits from the restriction are expected: coating textiles and man-made fibers.

The following Table 11 presents the monetary value of health gains expected in one year for each type of cancer and liver cirrhosis and utility weight considered, by industry.

Table 11 - Monetary value of expected health gains by industry

	Gain in QALYs considered	Coating textiles industry	Man-made fibers industry
	X = (1-W)	L = K * 75,000	
Liver cancer	0,51	159 028 €	49 519 €
	0,27	153 072 €	47 665 €
Prostate	0,23	38 607 €	12 022 €
	0,31	51 862 €	16 149 €
	0,42	69 592 €	21 670 €
Skin cancer - melanoma	0,21	108 217 €	33 697 €

	0,30	123 499 €	38 456 €
	0,35	132 281 €	41 191 €
Liver cirrhosis	0.08	37 100 457 €	11 552 633 €
	0.18	83 476 028 €	25 993 425 €
	0.12[2]	57 041 953 €	17 762 174 €
	0.25[3]	115 938 928 €	36 101 979 €

Taking the lowest and highest gain in QALYs (X) for each type of cancer and for liver cirrhosis, the following Table 12 presents the total monetary value intervals of health benefits expected from the proposed restriction by industry in one year.

Table 12 - Monetary values of health benefits expected from the proposed restriction in one year (million euros)

Coating textiles industry[4]	**Man-made fibers industry[5]**	**Total**
37.4 M€ - 116.3 M€	11.6 M€ - 36.2 M€	49.0 M€ - 152.5 M€

The total health benefits estimated for one-year amount around 49.0 and 152.5 million euros. Considering a fifteen-year time horizon and a discount rate of 4%, as done for the estimation of economic impacts[6], the total current and discounted health benefits expected from the restriction for each industry have been calculated (Table 13).

Table 13 - Total monetary values of health benefits expected from the proposed restriction (Millions of Euros)

	Coating textiles	**Man-made fibers**	**Total**
Current value	561.0 – 1 744.5 M€	174.7 – 543.2 M€	735.7 – 2 287.7 M€

[2] Disutility weight
[3] Disutility weight
[4] (85162 + 29131 + 84963 = 199256). Reported results are rounded to the nearest integer. Calculations include all decimals.
[5] (26518 + 9071 + 26456 = 62046). Reported results are rounded to the nearest integer. Calculations include all decimals.
[6] See Annex – Impact Assessment, section E.4.2.5

Net present value	432.5 – 1 344.8 M€	134.7 – 418.8 M€	567.1 – 1 763.5 M€

The total health benefits from the proposed restriction are estimated at least between 567.1 and 1763.5 Million Euros. This does not include the health benefits from the other sectors, which could not be specified, but would have to be added on top of it.

Overview of limitations and uncertainties

A combination of explicit and implicit assumptions made in this report represents an effort to assess health effects related to DMF. Nonetheless, it is important to acknowledge the uncertainty introduced by the lack of information regarding certain health outcomes further to the methodological issues discussed in the literature. The results of the calculations presented here must be interpreted therefore cautiously. There exists significant uncertainty about an important number of parameters and assumptions that may change the balance of costs and benefits. A sensitivity analysis is reported in Annex F.

It is obviously from the summarized important limitations and uncertainties of the health impact assessment that quantified health gains should be regarded only as a rough estimation.

Qualitative description of health benefits

Although the quantitative health impacts seem so uncertain and the numbers may not have an actual meaning, using a lot of assumptions and some quantitative proxies a quantification of the potential health impacts effects provide insight in the magnitude of the potential effects. The numerous human and animal study results form a solid basis for the proposed restriction by means of reporting consistent potentially adverse effects to human health. Even if these non-quantified effects cannot be assessed – in any case they are additional benefits and come to the top of the benefits described above and in that way support the proportionality assessment.

An important finding of this health impact assessment is that the probability of alcohol intolerance effects is very high at exposure levels to DMF associated with still normal liver enzyme levels. As can be seen in the above calculations, odds ratios for alcohol intolerance effects were many folds higher than those for the enzyme levels. Since alcohol intolerance is an early indicator of liver damage, this effect should be considered as the main effect for the proposed restriction. Pronounced alcohol intolerance effects accompanied with loss of general "well-being" i.e. headache, nausea, vomiting, epigastric and hepatic pain, flushing of face and neck etc. are reported exactly at this airborne concentration of DMF and lower in many human studies with European and Asian populations. A long-term exposure to DMF, even at current OEL, can result in adverse effects especially in sensitive persons and with hepatic diseases. Even though hepatic toxicity, as described in the Hazard Assessment (Part B) is not a chronic disease, it would result in high medical costs in the EU.

The estimated health benefits are likely to be larger in practice when considering the following arguments related to shortcomings of the published studies:

- some health endpoints are not considered at all because the results are not quantifiable (please see Annex E: Impact Assessment): cardiovascular complaints, irritation;
- there are no extensive studies dealing with investigation of reproductive and developmental effects due to DMF exposure in humans. However, the effects seen in animals cannot be ignored; thus, a certain risk exists also for humans, especially taking into account the metabolism pathway of DMF leading to higher levels of AMCC metabolite. This metabolic route is known to be more relevant for humans and because

it was thought to be linked to developmental effects in rodents, the risk of developmental toxicity in humans cannot be ruled out;
- there are a lot of cases reporting severe health effects especially at high peaks of exposure that could not be avoided in the past, like for example by cleaning of production lines, where dermal contact, which contributes significantly to body burden to DMF, cannot be ruled out;
- a lot of studies reporting alcohol intolerance symptoms in the exposed group do not contain control group, so that odds ratios cannot be calculated and therefore they could not be used further for the valuation of health impacts (please see Annex E: Impact Assessment);
- in several studies investigating damage of liver caused by exposure to DMF, alcohol intolerance effects were not reported at all. Since this effect occurs at exposure levels of the current OEL of 5 ppm, it is mostly relevant for the evaluation. Similarly, studies dealing only with investigation of alcohol intolerance do not report influence of DMF exposure on liver enzymes.

Other impacts, practicability and monitorability

According to the received information from industry representatives, the industrial gases industry would face no difficulty under the proposed restriction because the current exposure levels are well below the proposed DNELs. The proposed restriction is however not implementable at the moment for the man-made fiber industry and the textile coating industry. Both industries currently operate under the occupational exposure limit (IOEL) of 15 mg/m³. The proposed restriction would require a reduction from 15 mg/m³ to 3.2 mg/m³, which would not be economically feasible for both industries. In order to meet more severe DNEL values, exponentially increasing investments and costs would be needed. Both industries face fierce international competition and would not be able to pass on the increased costs on customers.

RMO 2 would actually not be manageable for the man-made fiber industry and the textile coating industry. Both industries claim that the proposed DNEL levels are not achievable. The implementation of the proposed restriction would hence not be clear for the actors present in these industries, as it is not obvious how to reduce the exposure to the required levels. However, it appears likely that the proposed DNEL levels can be achieved in the future due to the development of new technologies in terms of risk reduction and especially process optimation. Measures for process optimation could encompass automatisation procedures, increased levels of containment and segregations of emitting processes. Since such technical implementations are generally time-consuming allowing sufficient research and proper development, a derogation in terms of time for the proposed restriction would permit those industry sectors to comply with the proposed restriction.

The restriction proposed is deemed to be enforceable:

1. analytical monitoring of DMF in workplace air and biological media is already widely performed using different standardised methods. For workplace air, methods of choice are high-performance liquid chromatography (HPLC), gas-liquid chromatography (GLC) or gas chromatography – mass spectrometry (GC-MS). Furthermore, detector tubes certified by US NIOSH, or other direct-reading devices calibrated to DMF can be used to easily determine workplace concentrations of the substance.
2. for biological media, the metabolite most often analysed is N-methylformamide which can be determined by using several GC methods.

Regarding monitorability, there are no specific concerns as this can be done through enforcement. Further, monitoring of exposure levels is already carried out under worker protection legislation and hence, it should be no problem to adopt similar activities.

Proportionality

Effectiveness is defined such as the RMO must be targeted at the effects or exposures that cause the identified risks, capable of reducing these risks to an acceptable level within a reasonable period of time, and proportional to the risk (ECHA, 2007). Due to the fact that there are no alternatives available that can replace DMF for all its uses (see Annex E: Impact assessment), the proposed restriction is considered to be the most appropriate measure from a risk reduction capacity perspective, as it is clearly targeted to the identified risks.

The analysis presented in this report allowed for assessing and monetizing expected health impacts of the proposed restriction. A quantitative assessment of the costs was not possible to the other sectors mentioned above. It is assumed that the costs are moderate, as industry sector has not made specific cost information available. The Table 14 compares them to the economic impacts estimated in Annex E: impact assessment.

Table 14 - Overview of estimated socio-economic impacts of the proposed restriction (in M€)

	Economic impacts	**Health impacts of risk reduction**
Coating textiles / PU membranes sector	380 to 720 M€	473.8 – 1473.9
Industrial gases	0 to 5 M€	0
Man-made fibers	500 to 800 M€	147.5 – 458.9
Total	880 to 1515 M€	567.1 – 1 763.5

A restriction on DMF will result in a reduction in systemic health risks. The total health benefits (not including the other sectors) from the proposed restriction are estimated between 567.1 and 1 763.5 Million Euros. This means that the economic impacts of the proposed restriction and the expected quantifiable health benefits are on an equal level. Provided costs from a new socio-economic study on the continuation of DMF use in the PU Coatings Textile sector shows, that if sufficient transition time is provided, upgrading and retrofitting of plants for continued use of DMF is possible. In addition, a combination of measures of using PPE and rotation of staff and other management measures in workplaces with potential exposure, will further reduce the socio-economic costs. It is assumed, that the costs for the PU Coating Textiles sector could be reduced with these measures by 50%, resulting in costs for RMO2 of 190 to 360 M€.

Moreover, non-quantifiable health benefits will further move the ratio towards the social benefit, which means that in sum, the social benefits (reduction in health costs) will outweigh the socio-economic costs.

In summary, this option provides more legal certainty and is expected to result in a complete risk reduction of DMF.

Overall assessment of RMO 2

All criteria used in the assessment of this RMO are fulfilled; all identified risks have been addressed. Although the risk is not completely removed as DMF will continue to be manufactured / used, it will be adequately controlled and all uses will be safe.

2.2.3 RMO 3 - Authorisation

Economic impact

According to the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section D of Annex E: Impact assessment):

1. industrial gas industry: The estimated impact would be 260 to 310 M€ in the best case and more than 310 to 400 M€ in the worst case;

2. fiber industry: The estimated impact would be 501 to 610 M€ in the best case and 703 to 811 M€ in the worst case;

3. coating textile industry: The estimated impact would be 358 to 472 M€ in the best case and 572 to 690 M€ in the worst case;

4. other industries: For some industries (pharmaceuticals sector, agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. In general, the pharmaceutical industry would take authorisation on a case by case basis, namely by applying for an Authorisation and, if granted, working towards substitution of DMF as required by the Authorisation. However, if a substitute was not found and a re-authorisation was not granted, then operations using DMF for this sector would be forced to move to non-EU countries and/or outsource the work to companies outside the EU.

Human health and environmental impacts

Risk reduction capability of RMO 3 is less than RMO 2. Risk reduction in case of an authorisation based on adequate control route is expected to be comparable to restriction route, because in case authorisation is granted exposure will be reduced to a value below the DNEL for the authorized uses and no risks will remain. In the same way in case of restriction only the uses with exposure below the DNEL imposed would be allowed. However, based on the socio-economic route some (uncontrolled) risks may remain with the authorisation route. Health effects of DMF can, therefore, not completely ruled out.

Other impacts, practicability and monitorability

The actors involved have to be capable in practice to comply with the Risk Management Measure. To achieve this, the necessary technology, techniques and alternatives should be available and economically feasible. For many applications, it is very difficult to substitute DMF and alternatives or techniques for these uses are currently not known. Furthermore, many other available aprotic solvents have the same intrinsic properties with regards to reproductive toxicity as DMF (e.g. DMAC and NMP). From a risk management point of view polar aprotic solvents should be treated in a consistent way. The demand to substitute the substance due to its toxicological properties is already included in existing regulations and looking for alternatives to aprotic solvents of medium polarity has been rather unsuccessful, even after 20 years of research work. In general, it can be stated that industry supports substitution of DMF by other solvents, except the pharmaceutical industry. DMF plays a crucial role in the manufacturing and sterilisation of pharmaceuticals and in quality control applications.

Authorization route would be implementable for sectors that are able to demonstrate an adequate control, but this option would entail costs for those sectors that are already operating below the DNELs.

RMO3 wouldn't be implementable for sectors that aren't able to have an adequate control and should apply based on the socio-economic route. In this case an authorization use could not be granted and the related activities would be moved to non-EU countries and/or outsourced. For processes and applications that have been validated with DMF, it's much more practical to move the activities to outside the EU than to try to revalidate with solvents of unknown utility and with the uncertainty whether the new solvent may itself become authorised. The compliance of relevant actors can be checked but will be specific for the different sectors as authorisation applications will be tailor-made.

Regarding enforceability there are no substantial differences between RMO2 and RMO3.

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.

Regarding monitorability, there are no specific concerns as this can be done through enforcement.

Proportionality

Risk reduction capability of RMO 3 is less than RMO 2. Risk reduction in case of an authorisation based on adequate control route is expected to be comparable to restriction route, because in case authorisation is granted exposure will be reduced to a value below the DNEL for the authorized uses and no risks will remain. In the same way in case of restriction only the uses with exposure below the DNEL imposed would be allowed. However, based on the socio-economic route some (uncontrolled) risks may remain with the authorisation route. Health effects of DMF can, therefore, not completely ruled out.

The compliance costs are expected to be comparable to RMO2, but the administrative costs (especially the preparation of application for authorisation, fee for application, research activities to find an alternative, the need to re-apply for authorization after a few years) are expected to be much higher than other RMOs; wider socio-economic effects are expected to be comparable to RMO1.

Total economic effects of authorisation are expected to be larger than those of RMO2 but smaller than RMO1.

Requesting Authorisation is usually a great effort both for industry and for authorities. Economic disadvantages for EU users of DMF will emerge if comparable measures for safe DMF uses are not introduced outside of the EU. Due to a lack of alternatives, the outcome might be that the DMF using industry is leaving the EU. A restriction is considered more proportionate than authorisation, as risk of use can be excluded by implementing restrictions for "risky" applications not unnecessarily harming clearly safe uses by inappropriate authorisation costs and phase-outs.

Overall assessment of RMO 3

The risk reduction capacity of this RMO is limited compared to the other RMOs, as. some uncontrolled uses could continue because the socio-economic analysis could be sufficient to grant authorization. As application for authorisation is costly and time-consuming, instead a lot of companies will relocate their business to non-EU countries.

Regarding enforceability and monitorability there are no substantial differences, but the practicability of the authorisation route is lower compared to the other RMOs, as implementability is limited, for the absence of suitable alternatives.

2.3 Comparison of the risk management

In Table 15 below provides an overview of the different RMOs compared against the key criteria effectiveness (risk reduction capacity & proportionality), practicality and monitorability. According to this, the proposed restriction (RMO 2) would be the most appropriate risk management option.

Risk Reduction Capacity

The risk reduction of complete restriction (RMO 1) is expected to be substantial and more or less equal to the risk reduction of the proposed restriction (RMO 2). The risk reduction of authorisation (RMO 3) is considered to be slightly decreased compared to RMO 1 and RMO 2. With regard to the social-economic route within authorisation procedures under REACH, DMF may be used without adequate control still bearing a safety concern for workers.

Monitorability

Regarding monitorability, there are no specific concerns for any of the RMOs.

Proportionality

In case of complete restriction (RMO 1), this option is considered not to be proportional as most of the users of DMF will find themselves forced to relocate or even terminate their business in case of a full ban of DMF. Respective risks will only be shifted outside EU. In case of authorisation (RMO 3), there is a great uncertainty how industry will respond. The costs (compliance costs and administrative costs) and wider socio-economic effects are expected to be very significant. Requesting for authorisation is costly and time-consuming, both for industry as for authorities. Moreover, there is a clear lack of alternatives. Therefore, RMO 3 is considered to be less proportional than RMO 2 because the existing risks can be managed by more appropriate risk management options and the administrative costs of RMO 3 are expected to be higher than other RMOs.

Practicality

With regard to practicality, the proposed restriction (RMO 2) is the most appropriate option. In case of complete restriction (RMO 1), it is very difficult to substitute DMF and alternatives or techniques for these uses are currently not known (Table 15). Due to the absence of suitable alternatives implementability is clearly lacking. Due to these circumstances (lack of alternatives and respective technology and techniques), the authorisation route (RMO 3) is clearly lacking implementability as well.

Table 15 - Comparison of the identified RMOs against the key criteria

Criterion	RMO 1: Complete Restriction	RMO 2: Proposed restriction	RMO 3: Authorisation
Risk Reduction Capacity	+	+	+
Proportionality	-	+	-
Practicality (implementability, enforceability, manageability)	-	+	-
Monitorability	+	+	+

3. Assumptions and uncertainties

Assumptions

Human health and economic impacts

The main assumption of the proposed restriction is a ban of particular (critical) applications of DMF that is assumed to result in a reduction of exposure to workers and consequently a reduction in negative health effects. The differences between health impacts of the proposed restriction and the baseline scenario have been discussed with regard to the leading health effects induced by DMF: hepatotoxicity and alcohol intolerance as consequence thereof, and probability of developmental and carcinogenicity effects in humans under the long-term exposure conditions. The potential adverse human health effects of DMF are mainly based on its high bioavailability to human body via all exposure routes during a very short period of time.

The analysis is performed taking the EEA as a geographical scope and the time period of analysis is set to 15 years. An attempt was undertaken to quantify the health impacts. The methodology of quantification used was based on key elements described in the RPA report (2011). The most suitable two approaches were exercised: using “dose-response relationship” (option 1; the point 1 from the RPA Report) and “Starting point is prevalence” (option 3; point 3 from the RPA report). Option 1 is mostly relevant for hepatotoxicity and alcohol intolerance effects, since NOAEL and LOAEL exist for these effects for humans. However, no sufficient level of certainty to do this exists for the developmental and carcinogenicity endpoints, due to the absence of dose-response relationship in humans for these endpoints.

A possibility to quantify hepatotoxicity and alcohol intolerance effects following option 1 did not result in a sufficient level of efficiency of the proposed restriction. The extrapolation steps did not allow to derive odds ratios, incidence ratios in persons-years or other “health metrics” from the effect-exposure regression line in order to proceed with this calculation approach and further with the valuation of health impact assessment.

For developmental effects, no quantification is possible since the relevant effects have not been observed in human. Risk of developmental effects in humans however will be reduced to a negligible risk in case of the proposed restriction.

For carcinogenicity effects, option 3 (prevalence/incidence) is more appropriate since odds ratios for several types of cancers probably attributed to DMF exposure exist in the literature. Using rough assumptions, quantification of hepatotoxicity and alcohol intolerance effects was possible also by option 3 because literature data allowed to derive odds ratios and incidence ratios in persons-years. QALY and DALY metrics were used to translate health effects into monetary values.

Additionally, a fourth option to assess in some quantitative way the effectivity of the various RMOs on human health risks was to assess their risk reduction capacity. An assumption was made that the decrease in exposure caused by the implementation of a RMO will lead to a change, a decrease, in the RCRs. This approach (please refer to RPA report) is not a human health impact assessment, but merely a quantification of the effect of an RMO on RCRs (please see Annex E: Impact assessment section E 4.1 Human health and environmental impacts). As result of this analysis, the quantification of health effects was possible even though a number of rough estimations were made due to uncertainties in the published human studies. As the consequence, monetary estimates of benefits of the proposed restriction have been calculated. Additionally, qualitative estimates of positive health impacts are given:

- developmental effects are not expected to occur in humans since dermal and inhalation exposures will be considerably reduced and, therefore, increased levels of AMCC metabolite, which is thought to be involved into the manifestation of developmental effects, could be ruled out;

- carcinogenicity effects: development of tumors in workers exposed to DMF could not be attributed to DMF exposure in the baseline scenario, since standardized incidence rates (SIR) (observed versus expected from company rates) were not significant in several case-control studies on the one hand, and there was no relationship with duration and levels of exposure on the other hand. Moreover, if activities related to high inhalation and dermal exposure are eliminated as the result of this restriction, a possibility to estimate the proportion of cancer cases attributable to exposure to DMF will be expected much lower;

- as a result of this restriction, the proportion of cases attributable to exposure to DMF related to incidences of hepatotoxicity and alcohol intolerance described in literature will be theoretically much lower because excluding activities with an uncontrolled risk, high exposure processes will be excluded and the percentages of incidence of hepatic injury and alcohol intolerance will be significantly lower;

- the estimated health benefits are likely to be larger in practice only when taking into account the following arguments related to shortcomings of the published studies;

- some health endpoints are not considered at all because the results are not quantifiable (please see Annex E: Impact assessment): cardiovascular complaints, irritation;

- there are no extensive studies dealing with investigation of reproductive and developmental effects due to DMF exposure in humans. However, the effects seen in animals cannot be ignored; thus a certain risk exists also for humans, especially taking into account the metabolism pathway of DMF leading to higher levels of AMCC metabolite. This metabolisation route is known to be more relevant for humans and because it was thought to be linked to developmental effects in rodents, the risk of developmental toxicity in humans cannot be ruled out;

- there are a lot of case reports reporting severe health conditions especially at high peaks of exposure that cannot be avoided like for example by cleaning of production line, where dermal contact, which contributes significantly to body burden to DMF, cannot be ruled ou;

- a lot of studies reporting alcohol intolerance symptoms in the exposed group do not contain control group, so that odds ratios cannot be calculated and therefore they could not be used further for the valuation of health impacts (please see Annex E: Impact assessment);

- in several studies investigating damage of liver caused by exposure to DMF, alcohol intolerance effects were not reported at all. Since this effect occurs at exposure levels of the current OEL, it is mostly relevant for the evaluation. Similarly, studies dealing only with investigation of alcohol intolerance do not report influence of DMF exposure on liver enzymes.

Two sources of information were used for evaluating the economic impacts of the total restriction and the authorization route: responses to the questionnaire, which is presented in the Annex G: Stakeholder information during the preparation of the Annex XV dossier. The questionnaire was used to collect the information regarding the use of DMF and possible reactions to the complete DMF restriction and the REACH authorization route. The data from the Structural Business Statistics of Eurostat were also used. More precisely, data were taken from the Annual detailed enterprise statistics for industry (NACE Rev. 2, B-E) as the new activity classification (NACE Rev 2) allows for identifying very close sectors to the ones studied. The Table 16 presents the NACE codes and labels corresponding to the analysed industries.

Table 16 - NACE codes used in the SEAH

Industry	NACE code	Label
Fiber	C2060	Manufacture of man-made fibres
Industrial gases	C2011	Manufacture of industrial gases
Textile-polyurethane	C1330	Finishing of textile

The Eurostat data were used only when essential information concerning the industry's situation was not available in the questionnaires. Concretely, the ratio of personnel cost to turnover was taken from this source for all the industries and the ratio of gross operating surplus to turnover was used in the case of the man-made fiber industry as information on the operating margin was not available from the questionnaire.

Additionally, questions concerning the proposed restriction were asked to the identified industry experts in order to evaluate impacts of the proposed restriction.

Impacts are evaluated by comparing a given RMO to the baseline scenario. The latter describes the outcome that would take place if the use of DMF was not restricted in any way. It is forecasted using the information about the actual use of DMF.

All the impacts are evaluated for two cases: the best case and the worst case. There are two distinguishing factors between the two cases. The first factor concerns the considered reaction. For example, if a potential substitution for the use of DMF is currently unknown but could be discovered in the future, the substitution is only considered in the best case. The second factor is related to parameters used in the evaluation. For example, if a questionnaire indicates that 30-100% of business will be terminated, 30% is taken into account for the best case and 100% for the worst case.

The focus of the socioeconomic assessment is on the European Economic Area (EEA). Consultation of firms and quantitative impact assessment were drawn on a European basis.

Analysed reactions

The collected data allowed to analyze three RMOs (a complete restriction, the proposed restriction and the authorisation route). For each RMO, the following reactions were considered:

1. business termination;
2. business relocation;
3. use of an alternative substance (substitution).

For a full discussion of the analysed reactions on the economic impacts see Annex F: Assumptions, uncertainties and sensitivities.

Uncertainties

Human health and economic uncertainties

The major uncertainties are related to the following parameters of human studies that do not allow establishing a consistent pattern of exposure and dose-response for the increase in incidence of critical health effects:

1. limited size of investigated human populations;
2. magnitude and duration of exposure are very different in different studies;

3. extent of exposure to other substances;
4. confounding factors like cigarette smoke;
5. adequacy of reporting in these investigations;
6. absence of developmental toxicity effects due to DMF exposure in humans;
7. available animal data showed effects only in case of exceeding MTD and available human data showed no significant differences between exposed group and controls (carcinogenicity);
8. high uncertainties exist by calculation of incidence rates of hepatic injury and alcohol intolerance in case of eliminating critical applications associated with a high risk for human health.

Therefore, the available information from animal studies and few human data could not serve as a basis to establish a reliable dose-response function for humans and to quantify the health impacts. Moreover, quantitative impacts would be quite uncertain so that the calculated 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.

The assessment of socio-economic impacts may be subject to three types of uncertainty. First, the quantitative assessment is not made for all the potentially affected industries. Quantitative results are only presented for industrial gas sector, fiber sector and textile sector, as too few answers were received for the other potentially affected industries. When reading results, one hence should bear in mind that presented results concern only a part of affected actors.

Second, received answers from companies or associations representing a given industry were extrapolated to entire industries. This poses uncertainty, as the exact data for non-responding companies are not known. In order to account for this type of uncertainty the turnover of companies which provided answers to the questionnaire was compared to the total market size. As the following Table 17 illustrates, answering companies and associations correspond to the majority of the concerned turnover. Potential extrapolation of the results hence does not seem to pose too much problem.

Table 17 - Comparison of the turnover covered by the questionnaire with the estimated market size

Industry	Total estimated market size (in M€)	Turnover covered by the questionnaire (in M€)	%
Industrial gases	10-50 M€	10 to 50 M€	75 – 100 %
Fibers	250 to 350 M€	200 to 300 M€	75 – 100 %
Textiles	350 to 500 M€	350 to 500 M€	80 – 100 %

Third, the accuracy of collected data and the robustness of the adopted methodology introduce uncertainty. In particular, estimations of market growth rates, estimations of total market size, as well as not declared margins, turnovers and closing costs may be subject to uncertainty. Furthermore, there is uncertainty concerning the firms' reactions. In order to deal with this type of uncertainty, two cases including best case and the worst case were studied.

A full analysis of the assumptions used and of the decisions made during the analysis is avalaible in the following:

1. Annex B: Information on hazard, emission/exposure and risk Section B.9 (Exposure assessment), B.10 (Risk characterisation) and B.11 (Summary on hazard and risk);

2. Annex E: Impact assessment: information on alternatives;

3. Annex E: Impact assessment: qualitative and quantitative assessment of the health impacts and the Economic Impact.

4. Conclusion

The analysis of the different identified RMOs – total ban (complete restriction), proposed restriction and authorisation – against the key criteria demonstrates that the proposed restriction route should be the most appropriate risk management option. In the case of a defined risk, as identified through the available exposure data, a restriction should be the preferable regulatory measure and consequently should be chosen as risk management option according to REACH. In contrast to a total ban, the proposed restriction won't force the users to relocate or even terminate their business, as in the case of total restriction, but with adequate risk management measures some uses will continue. In contrast to the authorisation process, the proposed restriction with the conditions as defined in Section B of this report would address all identified risks. According, the proposed restriction (RMO 2) would be the most appropriate risk management option. The exposure control (inhalation) via a harmonised national OEL might not be optimal, as it is the only exposure limit that is outside the scope of REACH and the Scientific Committee on Occupational Exposure Limits (SCOEL) has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. Therefore, a harmonised DNEL for inhalative exposure is proposed instead. The advantage here would be that no further enforcement activities are required due to the implementation of such a restriction. Concluding, the restriction proposed comprises the conditions as set out in the Table 18.

Table 18 - Proposed Restriction

	Conditions of Restriction
XX. N,N-dimethylformamide EC No.: 200-679-5 CAS No.: 68-12-2	• 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.zzzz] a worker based harmonised Derived No Effect Level (DNEL) value for long-term inhalation exposure of 3.2 mg/m^3 and a worker based harmonised DNEL for long-term DNEL dermal exposure of 0.79 mg/kg bw/day..

The proposed restriction aims to restrict the uses of the substance on its own or in mixtures in a concentration equal or greater than 0.3%. A transitional period of two years is recommended.

The main reason for acting on a Community-wide basis is the protection of human health from the adverse effects of DMF due to its reprotoxic (Category 1B) properties. There is strong evidence, that in some industrial settings occupational exposure exists which is above the derived threshold values. According to the EU's Treaty, free movement of goods need to be guaranteed in order not to distort the internal market. Therefore, acting on a Community-wide basis ensures equal treatment of both - EU producers and importers, gives a clear message to non-Community suppliers and provides a "level playing field" and equal protection of human health across the EU.

The proposed restriction would eliminate all critical applications with RCRs > 1 and which have been assessed to bear a certain risk for industrial (or professional) worker. In the case of a mandatory harmonised DNEL, the exposure to DMF in all workplaces needs to be lower than the reference value. Therefore, all RCRs will be lower than 1. For many applications bearing an acceptable risk, RCRs will probably remain the same. RCRs for applications bearing a certain (unacceptable) risk would decrease to a level of at least below 1. If RCRs could not be decreased to < 1 by strict RMMs and/or OCs, the respective applications would not be performed anymore within the EEA. Therefore, some risks will be eliminated because uses for which the exposure reduction is not feasible are abandoned. In the end, risks will be sufficiently controlled for all identified uses and no health effects of DMF would occur anymore.