Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Annex XV dossier proposing restrictions on

***N*,*N*-dimethylformamide**

ECHA/RAC/RES-O-0000006695-63-01/F

ECHA/SEAC/RES-O-0000006745-66-01/F

Compiled version prepared by the ECHA Secretariat of RAC's opinion (adopted 20 September 2019) and SEAC's opinion (adopted 5 December 2019)

20 September 2019

ECHA/RAC/RES-O-0000006695-63-01/F

5 December 2019

ECHA/SEAC/RES-O-0000006745-66-01/F

Opinion of the Committee for Risk Assessment

and

Opinion of the Committee for Socio-economic Analysis

on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation and the Committee for Socio-economic Analysis (SEAC) has adopted an opinion in accordance with Article 71 of the REACH Regulation on the proposal for restriction of

Chemical name(s):	***N*,*N*-Dimethylformamide**
EC No:	**200-679-5**
CAS No:	**68-12-2**

This document presents the opinions adopted by RAC and SEAC and the Committee's justification for their opinions. The Background Document, as a supportive document to both RAC and SEAC opinions and their justification, gives the details of the Dossier Submitter's proposal amended in response to information obtained from the consultation and other relevant information resulting from the opinion making process.

PROCESS FOR ADOPTION OF THE OPINIONS

Italy has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV dossier conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/21804/term on **19 December 2018**. Interested parties were invited to submit comments and contributions by **19 June 2019**.

ADOPTION OF THE OPINION

ADOPTION OF THE OPINION OF RAC:

Rapporteur, appointed by RAC: ***Sonja KAPELARI***

Co-rapporteur, appointed by RAC: ***Bert-Ove LUND***

The opinion of RAC as to whether the suggested restrictions are appropriate in reducing the risk to human health and/or the environment was adopted in accordance with Article 70 of the REACH Regulation on **20 September 2019**.

The opinion takes into account the comments of interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The opinion of RAC was adopted **by consensus**.

ADOPTION OF THE OPINION OF SEAC

Rapporteur, appointed by SEAC: ***Lars FOCK***

The draft opinion of SEAC

The draft opinion of SEAC on the proposed restriction and on its related socio-economic impact has been agreed in accordance with Article 71(1) of the REACH Regulation on **20 September 2019.**

The draft opinion takes into account the comments from the interested parties provided in accordance with Article 69(6)(a) of the REACH Regulation.

The draft opinion takes into account the socio-economic analysis, or information which can contribute to one, received from the interested parties provided in accordance with Article 69(6)(b) of the REACH Regulation.

The draft opinion was published at https://echa.europa.eu/restrictions-under-consideration on **25 September 2019**. Interested parties were invited to submit comments on the draft opinion by **25 November 2019**.

The opinion of SEAC

The opinion of SEAC on the proposed restriction and on its related socio-economic impact was adopted in accordance with Article 71(1) and (2) of the REACH Regulation on **5 December 2019**.

The opinion takes into account the comments of interested parties provided in accordance with Articles 69(6) and 71(1) of the REACH Regulation.

The opinion of SEAC was adopted **by consensus** of all members having the right to vote.

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OPINION OF RAC AND SEAC

The restriction proposed by the Dossier Submitter is:

Substance identity (or group identity)	Conditions of the restriction
– *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 dermal exposure of 0.79 mg/kg bw/day.

The Dossier Submitter proposes a two year transitional period.

THE OPINION OF RAC

RAC has formulated its opinion on the proposed restriction based on an evaluation of information related to the identified risk and to the identified options to reduce the risk as documented in the Annex XV dossier and submitted by interested parties as well as other available information as recorded in the Background Document. RAC considers that the proposed restriction on ***N,N*-dimethylformamide** is the most appropriate Union wide measure to address the identified risk in terms of the effectiveness, in reducing the risk, practicality and monitorability as demonstrated in the justification supporting this opinion, provided that the conditions are modified, as proposed by RAC.

The conditions of the restriction proposed by RAC are:

Substance Identity (or group identity)	Conditions of the restriction
– *N,N*-dimethylformamide – EC No 200-679-5 – CAS No 68-12-2	• Manufacturers, importers and downstream users of the substance on its own (regardless of whether DMF is a (main) constituent, an impurity or a stabiliser) 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 6 mg/m^3 and a worker

based harmonised DNEL for long-term dermal exposure of 1.1 mg/kg bw/day.

Note for the attention of the Commission: Similarly to the restriction on NMP (Annex XVII – entry 71), to enable biomonitoring, RAC recommends to derive a $DNEL_{(biomarker)}$ since DMF can be readily absorbed via exposed skin (see p. 18). RAC notes that biomonitoring is not needed for REACH enforcement.

THE OPINION OF SEAC

SEAC has formulated its opinion on the proposed restriction based on an evaluation of the information related to socio-economic impacts documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. SEAC considers that the proposed restriction on ***N,N*-dimethylformamide**[6] is the most appropriate Union wide measure to address the identified risks, as concluded by RAC, taking into account the proportionality of its socio-economic benefits to its socio-economic costs provided that the scope or conditions are modified, as proposed by RAC, as demonstrated in the justification supporting this opinion. SEAC proposes the same conditions for the restriction as proposed by RAC above.

JUSTIFICATION FOR THE OPINION OF RAC AND SEAC

IDENTIFIED HAZARD, EXPOSURE/EMISSIONS AND RISK

Justification for the opinion of RAC

Description of and justification for targeting of the information on hazard(s) and exposure/emissions) (scope)

Summary of proposal:

N,*N*-dimethylformamide (DMF) is an aprotic medium polar organic solvent classified as toxic to reproduction category 1B, acute tox. 4 (inhalation and dermal route) and as eye irritant 2. It is registered in the 10 000-100 000 t/a tonnage band and is used in a number of industrial applications and by professional workers. Therefore, occupational exposure to DMF is to be expected. Exposure to humans via the environment can be excluded since the substance is readily biodegradable and no potential for bioaccumulation exists. Thus, the restriction proposal is targeted at occupational exposure to DMF.

RAC conclusion(s):

RAC supports targeting the restriction proposal to occupational settings.

However, RAC notes that DMF has also been found in consumer products, such as soft foam toys (squishable toys) (Danish EPA, Survey 165).

Since the wording of the conditions of the restriction described in the Dossier Submitter's proposal is limited to the mono-constituent substance DMF (as such or in mixtures), other substances that contain DMF would inadvertently not be covered by the restriction. Therefore, RAC recommends that the wording of the conditions of the restriction is clarified to ensure that any substance containing DMF above the relevant concentration limit is subject to the proposed restriction, regardless of whether it is a (main) constituent, an impurity or a stabiliser (see "conditions of the restriction as proposed by RAC" above).

Key elements underpinning the RAC conclusion(s):

According to the registration dossier and the information provided by the Dossier Submitter, DMF is used at high volumes in the EEA for a broad range of industrial and professional uses. A large number of workers are, therefore, likely to be exposed and a targeted assessment of risk to workers is warranted.

The wording of the conditions of the restriction proposed by the Dossier Submitter is limited to the mono-constituent substance DMF (as such or in mixtures).

However, registrations for substances containing *N*,*N*-dimethylformamide at concentration ≥ 0.3 % are known. These would not be mono-constituent DMF. The Dossier Submitter's assessment also considered several contributing scenarios for DMF-containing substances at low concentrations.

Therefore, strictly following the Dossier Submitter's proposal for the conditions of the restriction would mean that certain DMF-containing substances would be inadvertently excluded from the scope of the restriction despite being included in the Dossier Submitter's assessment.

Therefore, RAC recommends that the wording of the conditions of the restriction is clarified to ensure that any substance containing DMF above the relevant concentration limit is subject to the proposed restriction, regardless of whether it is a (main) constituent, an impurity or a stabiliser.

Description of the risk(s) addressed by the proposed restriction

Information on hazard(s)

Summary of proposal:

DMF has a harmonised classification as a reproductive toxicant but the most sensitive target organ is the liver.

In the proposal from the Dossier Submitter, a chronic, systemic inhalation DNEL of 3.2 mg/m^3 was derived for workers based on decreased body weight, clinical chemistry changes and liver injury at the NOAEC of 80 mg/m^3 (25 ppm) in a two year study in rats (Malley *et al.,* 1994). A dermal chronic systemic DNEL of 0.79 mg/kg bw/day is derived based on reduced body weight, clinical chemistry changes and liver injury at the LOAEL in an oral 28-day repeated dose toxicity study, with a NOAEL of 238 mg/kg bw/day (BASF, 1977). The long-term inhalation and dermal DNELs cover also the respective short-term exposures.

These points of departure (PoDs) were used in DNEL calculations as shown below:

PoD inhalation DNEL	NOAEC 80 mg/m^3
Correction to human exposure	NOAEC × 6 h / 8 h × 6.7 m^3 / 10 m^3 = 40.2 mg/m^3
DNEL = human NOAEC / AFs (inter, intra)	NOAEC / ((1 × 2.5) × 5) = 3.2 mg/m^3

PoD dermal DNEL	oral NOAEL 238 mg/kg bw/day
Route to route extrapolation from oral to dermal NOAEL	NOAEL × 100 %/100 % = 238 mg/kg bw/day
DNEL = NOAEL / AFs (inter, intra, and duration)	NOAEL / ((4 × 2.5) × 5 × 6) = 0.79 mg/kg bw/day

The chronic, systemic inhalation DNEL of 3.2 mg/m^3 was derived by the Dossier Submitter for workers based on decreased body weight, clinical chemistry changes and liver injury at the NOAEC in a two-year study in rats (Malley *et al.,* 1994). The NOAEC was corrected to 40.2 mg/m^3, and by applying a total assessment factor of 12.5, a DNEL of 3.2 mg/m^3 was obtained. The long-term inhalation DNEL covers also short-term exposures.

A dermal chronic systemic DNEL of 0.79 mg/kg bw/day was derived based on reduced body weight, clinical chemistry changes, liver injury at the LOAEL in a 28-day repeated dose oral toxicity study with a NOAEL of 238 mg/kg bw/day (BASF, 1977) and using a total assessment factor of 300. The long-term dermal DNEL covers also short-term exposures.

RAC conclusion(s):

Long-term inhalation DNEL:

RAC agrees to an inhalation DNEL calculated based on liver effects in experimental animals (3.2 mg/m^3) but notes that there is extensive data on human exposure to DMF in workplaces and that these data should also be considered when setting the inhalation DNEL. For instance, a recent large epidemiology study (Kilo *et al.*, 2016) did not indicate any hepatic effects in

workers exposed to 6.2 ± 7.6 mg DMF/m^3 (mean ± S.D.) (range < 0.08-46.85 mg/m^3).

RAC notes that based on many epidemiological studies (and in consideration of animal studies) a limit value of 15 mg/m^3 has been proposed by, e.g., SCOEL (2006) and the German MAK commission (2010). The restriction proposal concludes that biomarkers of hepatic injury only indicate effects in workers at exposure levels exceeding 21 mg/m^3 (7 ppm) but considers that the human studies cannot be considered robust enough to be used for risk assessment. However, a meta-analysis of 21 human studies provided in the consultation (with 10 being used), indicates a LOAEC of ≥ 20 mg/m^3. RAC supports that 20 mg/m^3 is indeed an effect level but finds it difficult to set a NOAEC based on this analysis. This is because of the inconsistent grouping of studies and that the two most influential negative studies (Kilo *et al.*, 2016 and Wrbitzky *et al.*, 1999) have median exposure of 3.1 and 3.6 mg/m^3, respectively, indicating that a rather small proportion of workers were exposed to 10-20 mg/m^3 and that the power of the study in this range is therefore small.

However, RAC is of the opinion that a human NOAEC can be set based on the NOAEC of 6.2 mg/m^3 reported in the Kilo *et al.* study (2016) for hepatic effects in humans, resulting in a DNEL of 6 mg/m^3.

RAC further notes that DMF is a well-known reproductive toxicant and thus supports the inhalation DNEL for developmental toxicity in rabbits calculated to 6 mg/m^3 in the restriction proposal, based on a NOAEC of 150 mg/m^3 for malformations in a rabbit developmental toxicity study (Hellwig *et al.*, 1991).

Overall, RAC proposes a systemic long term DNEL of 6 mg/m^3 for the inhalation route based on a combination of human data and rabbit developmental toxicity data.

Long-term dermal DNEL:

Exposure to DMF is consistently reported to result in umbilical hernia in rabbit developmental toxicity studies, irrespective of exposure route (two studies reported by Hellwig *et al.* 1991 investigating dermal and inhalation routes, respectively, and an oral study reported in BASF 1976d). Whereas gallbladder agenesis and sternal malformations were only observed in the two most reliable studies (after dermal and inhalation exposure). Thus, based on this rather consistent malformation pattern, it seems that these three (types of) malformations are substance-related specific malformations in rabbits exposed to DMF.

RAC concludes that the lowest dose used in the dermal developmental toxicity study (i.e. 100 mg/kg/day) is a likely LOAEL, resulting in a dermal DNEL of 1.1 mg/kg bw/day based on a total assessment factor of 90 (2.4 for allometric scaling × 2.5 for remaining differences in sensitivity × 5 for intra-species variation in workers × 3 for LOAEL to NOAEL extrapolation). This DNEL is very close to the dermal DNEL proposed by the Dossier Submitter (0.79 mg/kg/day), but RAC prefers to use a dermal study as the basis for the DNEL rather than making a route-to-route extrapolation from an oral 28 days study, and therefore proposes to use the value of 1.1 mg/kg/day as the dermal DNEL.

Key elements underpinning the RAC conclusion(s):

There is no reliable dermal repeated dose toxicity study for DMF, whereas there are two dermal developmental toxicity studies (in rats and rabbits). The Background Document (Table 8) also mentions a dermal one-generation study in rats, which is not further described, either in the report or the annexes.

The Dossier Submitter has therefore used an oral repeated dose toxicity study as the basis

for the dermal DNEL. Limited information is available from this 28-day study, where rats were administered five doses a week via gavage. The Dossier Submitter considers the lowest dose as the NOAEL (20 doses of 238 mg/kg). RAC notes that an increased relative liver weight (magnitude unknown) and a decreased body weight (-8.6 %) were observed at this dose although it is not clear if the body weight decrease refers to a decrease in body weight gain or a decreased actual body weight relative to controls. Thus, this dose level may also be a LOAEL, if the body weight decrease is sufficiently adverse. RAC has no view on which dose level to choose as the LOAEL. Similar effects, albeit slightly more severe (body weight -15 %) were observed after 20 doses of 475 mg/kg. A 27 % decrease in body weight and histopathological as well as clinical chemistry evidence of adverse effects on liver were observed after 20 doses of 950 mg/kg. Thus, if considering liver toxicity, the clear effects at 950 mg/kg constitutes a LOAEL, and 475 mg/kg the NOAEL. If converting the dose of 475 mg/kg into a daily dose, the NOAEL becomes 339 mg/kg/day, thus higher than the NOAEL chosen by the Dossier Submitter (238 mg/kg). However, RAC concludes that too little information is available on this study to use it as the basis for a NOAEL.

Considering the uncertainties mentioned above, RAC considers that available dermal studies should be assessed as potential points of departure for the dermal DNEL. Only old dermal repeated dose toxicity studies are available, but they indicate that the liver is a target organ in rats, rabbits and guinea pigs after exposure of adult animals.

A NOAEL of 215 mg/kg/day after 30 day exposure of rats (Bainova and Antov, 1980, cited in OECD SIDS 2004) is mentioned in the restriction proposal. However, the description is too brief to allow it to be used to derive a reliable NOAEL. Dermal developmental toxicity studies reported in the scientific literature are therefore assessed below as an alternative basis for the dermal DNEL.

Developmental toxicity in rabbits

Dermal

In a dermal developmental toxicity study in Himalayan rabbits (Hellwig *et al.,* 1991), DMF was administered 6 hours/day under semi-occlusive conditions from gestation day (GD) 6-18. 400 mg/kg/day was a clearly teratogenic dose with limited maternal effects (5.6 % decrease in body weight; although it was not clear if this refers to absolute weight or body weight gain). Malformations included umbilical hernia (two in two different litters), gallbladder agenesis (five in two different litters) as well as many sternal malformations (not further defined, 15 in seven different litters). Although no malformations were observed in the group exposed to 200 mg/kg/day, one sternal malformation and two cases of gallbladder agenesis were observed at 100 mg/kg/day. The Dossier Submitter considered 400 mg/kg/day to be the LOAEL. However, considering the sternal malformation and gallbladder agenesis at 100 mg/kg/day (supported by higher incidences of these specific malformations at 400 mg/kg/day) it has to be further analysed whether these malformations can be chance findings or whether 100 mg/kg/day is the proper LOAEL.

Unfortunately, the Dossier Submitter does not provide historical control data (HCD) for the facility conducting the study. RAC has therefore looked for HCD for Himalayan rabbits and found a publication (Matsuo and Kast, 1995) from a laboratory in Japan that has used the strain of Himalayan rabbits originally coming from the German breeder also providing rabbits for the Hellwig (1991) study. The HCD comes from 40 studies conducted 1971-1991, representing 514 control litters. RAC acknowledges that although the HCD concerns Himalayan rabbits, this HCD does not fulfil the criteria as proper HCD, since the animals come from a different laboratory and the time period covered is too long. However, since there are

no proper HCD, the information is still interesting. The litter incidence of malformations in the Japanese colony of Himalayan rabbits was 5.25 % (27 litters with malformations among 514). For individual malformations, only the number of findings per 2 883 examined foetuses were reported. Seven malformations (fused sternebrae) and eight variations (split or asymmetry of sternebrae) concerning the sternal system were reported. Two foetuses were found to have umbilical hernia (malformation), and 14 foetuses small gallbladder (variation), but no lack of gallbladder (agenesis) was reported.

Thus, it seems to RAC that the findings in the 100 mg/kg/day dose in the study on DMF by Hellwig *et al.* (1991) may indeed be substance-related rather than chance findings. Rabbit developmental toxicity studies by other routes of exposure have therefore been assessed to see if the malformations observed in the dermal rabbit study possibly are found also in the inhalation and oral rabbit developmental toxicity studies, thereby supporting them as substance specific.

Inhalation

Hellwig *et al.* (1991) studied the developmental toxicity 0, 50, 150, or 450 ppm DMF in Himalayan rabbits exposed 6 hours/day during GD 7-19. No clinical signs or effects on maternal corrected body weight gain were observed. At the top dose, foetal body weight was decreased (-14 %) and there was a significant increase in occurrence of malformations (umbilical hernia in seven pups from four litters). One case of umbilical hernia was also observed at the mid dose, versus none in control and low dose. There were also three cases on missing “spleen and/or gallbladder” in top dose pups versus none in the other groups. Greatly increased incidences of sternal anomalies, split vertebrae and other skeletal variations were also observed at the top dose. Increased incidences of the malformation fused sternebrae (7.4, 2.8, 18.0 and 59.3 % of pups affected in control, low, mid and high dose, respectively) and skeletal variations were also noted in the mid dose group.

In the (inappropriate) HCD by Matsuo and Kast (1995), two cases of umbilical hernia (among 2 883 foetuses) and 14 cases gallbladder hypoplasia, but no gallbladder agenesis, were found in the 2 883 foetuses. Seven cases of fused sternebrae were found in the 514 litters, representing 0.24 % or the foetuses (7/2 883).

RAC supports the view of the Dossier Submitter that 50 ppm represents the NOAEC based on finding umbilical hernia and sternal malformations at the mid dose (150 ppm).

Oral

The developmental toxicity of orally administered DMF has also been studied in Himalayan rabbits (BASF 1976d, Merkle and Zeller 1980). DMF was administered by gavage at doses of 0, 44, 65 and 190 mg/kg/day on GD 6-18. Number of dams per group was not given. At the highest dose, maternal toxicity was indicated by significantly decreased body weight gain (magnitude not given, but likely high in light of the statement that “animals even lost weight”) and three abortions after the exposure period but before sacrifice on day 28. No maternal effects were noted in the mid or low dose groups. At the top dose, foetal weight was decreased (magnitude not given) and malformations were observed, with hernia umbilicalis as the most common malformation (seven foetuses). Other malformations included hydrocephalus internus (six foetuses), ectopia visceralis (three foetuses), exophtalmia (two foetuses) and one foetus with cleft palate. Three cases of hydrocephalus internus (in two litters) were found in the mid dose group, considered to be substance related. One case was found in the low dose group, but this incidence was stated to be in the range of control incidences. The number of litters or foetuses per group is not given, nor are control incidences described, so it is difficult to assess the power of this study and the effects observed. Besides being poorly

reported, other reasons for not using this study as the basis for the dermal DNEL are that using route to route extrapolation introduces uncertainties and that other rabbit studies have given a more consistent pattern of malformations with relatively similar (or lower) NOAELs.

Based on three cases of hydrocephalus internus (in two litters) in the mid dose group, the Dossier Submitter proposes the mid dose (65 mg/kg/day) as the LOAEL.

Conclusion on developmental toxicity in rabbits

Exposure to DMF resulted in umbilical hernia (protrusion of the navel because of a damaged abdominal wall) in all three available rabbit studies, representing three different exposure routes, whereas gallbladder agenesis and sternal malformations were observed in the two most reliable studies (after dermal and inhalation exposure). Thus, based on this rather consistent malformation pattern, it seems that these three (types of) malformations are substance-related specific malformations in rabbits exposed to DMF. The lowest dose levels where these malformations were found in the different rabbit studies are shown in the table below.

Table 1: Lowest dose levels causing malformations in rabbits exposed via three different routes

Malformation	Dermal (mg/kg/day)	Inhalation (ppm)	Oral (mg/kg/day)
Umbilical hernia	400	150 ppm	190
Gallbladder agenesis	100	450 ppm	-
Sternal malformations	100	150 ppm	-
Hydrocephalus internus	-	-	65

As to the relevance and adversity of umbilical hernia and gallbladder agenesis, RAC notes that they do occur in humans and in many cases require surgery. Umbilical hernia is defined as an abnormality in animals (Makris *et al.* 2009) whereas ECETOC report 31 defines gallbladder agenesis in rabbits as a variation.

Based on this analysis, RAC concludes that the lowest dose used in the dermal developmental toxicity study (i.e. 100 mg/kg/day) is likely to be a LOAEL, and that 150 ppm (roughly 0.45 mg/L) is the LOAEC after inhalation exposure (NOAEC 50 ppm).

The inhalation LOAEC has been transformed into an internal dose assuming a respiration rate of 39 litres/hour (mean of four published values as reported in Bide *et al.* 1997), a body weight of 2.6 kg for the Himalayan rabbits (Hellwig *et al.*, 1991) and 60 % inhalation absorption (as estimated in the restriction proposal). The 6 hour exposure to 0.45 mg/L leads to an internal exposure of 24 mg/kg/day (39 litres × 6 hours × 0.45 mg × 60 % / 2.6 kg). The dermal absorption is estimated in the dossier to be 40 %, so the internal exposure after dermal exposure of 100 mg/kg/day (the LOAEL) is about 40 mg/kg/day. Thus, both malformation profile and overall potency seem rather similar in the dermal and inhalation studies, while a slightly lower potency is noted in the oral study (perhaps related to a first pass effect in the liver).

For completeness and comparison, developmental toxicity studies in rats and mice have also been assessed by RAC, and this assessment is presented in the Background Document (Annex B.5.6). These studies do not affect the conclusion on developmental toxicity based on rabbit studies.

Overall conclusion on developmental toxicity

DMF seems to affect the skeletal system in all three species, with the rabbit as the most sensitive species. Relevance to humans must be assumed. The first signs of malformations in rabbits are seen at dermal doses of 100 mg/kg/day (sternal malformations and gallbladder agenesis) and following inhalation exposure to 150 ppm (umbilical hernia and sternal malformations). Although low incidences, and not always supported by clear dose-response, the malformations are rare, and the incidences exceed the only available (improper) HCD for Himalayan rabbits. Sternal malformations, umbilical hernia and gallbladder agenesis are serious effects supporting using 100 mg/kg/day as LOAEL for dermal developmental toxicity and 150 ppm as LOAEC for inhalation developmental toxicity (NOAEC 50 ppm = 150 mg/m^3).

DNEL derivation

If starting from a dermal study, no dose descriptor modification is needed as no route-to-route extrapolation is needed. As for dermal bioavailability, it is assumed to be high in both rabbits and humans, and a similar bioavailability in humans and rabbits is assumed as a worst-case assumption. The dermal rabbit study was conducted using six hours exposure/day under semi-occlusive conditions (during gestation days 6-18), resulting in a LOAEL of 100 mg/kg/day.

Human exposure could be eight hours/day, which would require a correction (by 6/8) of the LOAEL. However, eight hours exposure under semi-occlusive conditions seems to be an unrealistic worst-case assumption. Therefore, no correction is proposed and a LOAEL of 100 mg/kg/day will be used for DNEL derivation.

Concerning the application of assessment factors, RAC supports the use of 2.4 for allometric scaling (from rabbits to humans), 2.5 for remaining differences in sensitivity, and an intraspecies factor of 5 for workers. This latter has been set in line with REACH guidance, noting that there is no scientific reason to assume a different sensitivity to developmental effects in a working mother compared to a mother from the general population (for which an intraspecies AF of 10 would be used). In addition, an AF of three for the conversion of LOAEL to NOAEL is suggested, and the total AF then becomes 2.4 × 2.5 × 5 × 3 = 90.

A dermal DNEL of 1.1 mg/kg/day (100/90) is thus suggested by RAC to be used for dermal exposure. This DNEL is slightly greater than the dermal DNEL suggested by the Dossier Submitter (0.79 mg/kg/day).

Inhalation toxicity

For inhalation toxicity, the main question is whether animal or human data should form the basis for the DNEL.

Based on the repeated dose toxicity studies in experimental animals, RAC supports the use of 80 mg/m^3 (25 ppm) as the NOAEC for hepatic injury from the combined repeated dose toxicity/carcinogenicity studies in rats and mice. RAC supports the use of correction factors (6/8 × 6.7/10) and AFs (2.5 for remaining differences and 5 for intraspecies differences) suggested by the Dossier Submitter, thus resulting in a DNEL of 3.2 mg/m^3.

Based on the developmental toxicity studies by the inhalation route, RAC supports the use of 150 mg/m^3 (50 ppm) as the NOAEC based on finding umbilical hernia and sternal malformations in rabbits at the next higher dose (150 ppm). RAC supports the correction of the NOAEC (6/8 hours × 6.7/10 m^3) and the AFs (2.5 and 5) proposed by the Dossier Submitter, resulting in a DNEL of 6 mg/m^3. There is a rat study (TSCATS 1978) potentially giving a lower DNEL, but the study is too poorly reported to be considered by RAC as the basis for the DNEL.

However, there are many epidemiological studies available, and a limit value of 15 mg/m^3 has been proposed by, e.g., SCOEL (2006) and the German MAK commission (2017) based on human and animal data. Especially the data by Wrbitzky and Angerer (1998) and Wrbitzky (1999) seem important for SCOEL and MAK, but these studies are only briefly discussed in the restriction proposal. The publications show data for 126 male workers, divided in groups with different work tasks, which were exposed to median air concentrations of 0.7, 1.4, 2.3 and 2.8 ppm DMF. The range of exposure in these groups were < 0.1-13.7, 0.1-9.8, 0.8-36.9, and 0.3-37.9 ppm, but the distribution within these groups were not given, and no data were given for the 54 controls recruited from the same factory (or information on potential exposure of the controls to other chemicals). In the personal air sampling, 12 out of the 126 workers had air concentrations above 10 ppm, indicating a skewed distribution. The ranges above also indicate overlap between the different workstations. Liver effects were evaluated by calculating a liver index based on serum levels of the enzymes AST, ALT, and gamma-GT. Wrbitzky (1999) mentions that workers who had stopped work for reasons of poor health were not included, thus possibly leading to a "healthy worker" effect. For the analysis of the liver index, three groups of similar size were composed of workers (assumingly) not exposed to DMF (no data shown), workers in the finishing workplace with a median air concentration of 0.7 ppm, and the remaining workers with a (higher) median exposure to 2.3 ppm. Wrbitzky (1999) states that "the liver index correlates with both level of exposure to DMF and the amount of alcohol drunk". The data is only presented in box plots, and although an apparently increased liver index is observed in DMF-exposed workers not drinking alcohol, the difference is stated not to be statistically significant. For workers using alcohol (both < 50 g/day and > 50 g/day), the liver index was clearly increased although no statistical analysis was presented. However, alcohol consumption (> 50 g/day) seemed to affect the liver index more than median air concentrations of DMF up to 2.8 ppm.

Thus, the effect of DMF on liver index was indicated in spite of low median air exposure levels at the different workstations (0.7-2.8 ppm) (median 1.2 ppm; 3.6 mg/m^3). Also, only few measurements (12 out of 126) showed air concentrations above 10 ppm, indicating that the effects of DMF on the liver index were probably caused by rather low concentrations of DMF.

According to SCOEL, workers not consuming alcohol had no significant effects on the liver parameters (AST, ALT, GGT) in any group, whereas DMF affected the liver index in workers consuming alcohol. As alcohol consumption (average two beers/day) affected the liver index more than mean exposure to 7.3 ppm DMF (the work task with the highest exposure), SCOEL considered 7.3 ± 10.2 ppm (mean ± standard deviation) (22 mg/m^3) as a NOAEC. RAC notes that no specific analysis has been made for this group in the studies (Wrbitzky and Angerer (1998) and Wrbitzky (1999)), and that the data presented (only in box plots) refer to a combination of workers having three different work tasks with average exposure to 7.3, 6.4, and 2.5 ppm DMF. RAC notes that alcohol consumption is rather common among people in general, and that the mean alcohol consumption for the 180 workers participating in the study was 50 g/day. RAC further notes the clearly increased liver index (no statistical analysis provided in the paper) in workers consuming < 50 g alcohol/day and exposed to a mean concentration of 1.4 ± 2.2 ppm DMF (median 0.7 ppm) relative to workers not exposed to DMF but consuming alcohol. However, it is difficult to assess the adversity of the effects when the data is presented as a liver index. Based on the observation that alcohol consumption affects the liver index more than exposure to DMF, RAC is hesitant to accept 22 mg/m^3 as a human NOAEC for DMF, noting that alcohol consumption leads to real health problems. Because of rather poor reporting of data, RAC declined to set a DNEL based on these two studies.

SCOEL concluded that based on the human data (e.g. Wrbitzky and Angerer (1998) and

Wrbitzky (1999) described above) on liver enzymes, an OEL of 30 mg/m^3 (10 ppm), corresponding to 25 mg NMF/L urine is considered protective provided that excessive dermal uptake and alcohol consumption are avoided. However, taking into account the results from the effects on the liver in a long-term toxicity study in mice, for which a BMDL of 7.8 ppm and BMD of 14.7 ppm was calculated, an OEL of 5 ppm was proposed by SCOEL. The OEL of 15 mg/m^3 (5 ppm) was considered to also protect for developmental toxicity for which the NOEL had been calculated by SCOEL as 50 ppm.

As noted above, RAC does not find the data by Wrbitzky and Angerer (1998) and Wrbitzky (1999) that was used by SCOEL to be convincing enough for setting a DNEL because of poor reporting in the scientific publications and a low median exposure (3.6 mg/m^3). RAC has therefore put more emphasis on the new Kilo *et al.* study (2016, see below), the NOAEC from the rabbit developmental toxicity study corrected for worker exposure conditions (75 mg/m^3; 25 ppm), and using assessment factors in line with REACH guidance, resulting in a DNEL of 6 mg/m^3.

The restriction proposal also concludes that biomarkers of hepatic injury indicate effects in workers at exposure levels exceeding 21 mg/m^3 (7 ppm), but also notes that simultaneous dermal exposure are generally not considered in the epidemiological studies and that human studies cannot be considered robust enough to be used for risk assessment.

However, RAC specifically notes the latest and largest study so far investigating the effects on liver from occupational exposure to DMF (Kilo *et al.*, 2016; cited as IVC (2016) in the restriction proposal). The study included 220 exposed workers exposed to 6.2 ± 7.6 mg DMF/m^3 (mean ± S.D.) (range < 0.08-46.85 mg/m^3) and 175 controls. The extreme range of exposures, a median of 3.1 mg/m^3, and that 89 % of the workers were exposed to < 15 mg/m^3, indicate a skewed distribution. In addition, controls were recruited from plants with exposure to other chemicals (isocyanates and carbon disulphide at unknown concentrations), potentially affecting the liver.

Internal exposure was confirmed by measuring NMF (sum of *N*-methylformamide and *N*-hydroxymethyl-*N*-methylformamide) and AMCC (*N*-acetyl-*S*-(*N*-carbamoyl)cysteine) in urine and haemoglobin adducts of DMF (MIH) in blood (Kilo *et al.*, 2016). A further analysis of the data by Seitz *et al.* (2018) indicated a good correlation between DMF air levels and internal concentrations, but Seitz *et al.* (2018) noted that a correlation was also observed in workers using respiratory protection, suggesting that dermal uptake can also be important.

As pointed out by the Dossier Submitter, there is some uncertainty concerning a human NOAEC, as there are synergistic effects of ethanol and DMF, such that workers drinking alcohol are likely to be more affected by DMF than other workers. An even greater sensitivity (to alcohol and DMF) is expected in people carrying the gene ADH1B*2, an atypical allele leading to decreased activities of aldehyde dehydrogenases. This genetic polymorphism is found in 5 % of Europeans and in most people from Asia.

There were no indications of any effects of exposure to DMF on the four biomarkers for liver toxicity (AP, GGT, AST, ALT), but in consideration of the skewed distribution, that the controls potentially also were exposed to chemicals, synergism with ethanol, and polymorphism, RAC proposes that the mean exposure level of 6.2 mg/m^3 can be considered to be a human NOAEC. No assessment factor is used considering the large size of the study, the availability of other human studies, and that the NOAEC can be considered quite conservative.

Industry (Fedustria and IVC) provided in the consultation a meta-analysis of 21 studies where the effect of DMF exposure on liver function in workers was studied (#2005; a corrected and substantially revised version was later re-submitted as #2327 and #2337). The analysis found

10 studies fulfilling the pre-determined requirements for being useful and valid studies. The analysis gave the following odds ratios (OR);

Exposure	< 15 mg/m^3	OR 1.38 (0.80-2.39)
	< 20 mg/m^3	OR 1.43 (0.88-2.34)
	≥ 15 -< 20 mg/m^3	OR 1.65 (0.54-5.03)
	≥ 20 mg/m^3	OR 2.87 (1.92-4.30) (statistically significant)
	All studies	OR 2.17 (1.59-2.96) (statistically significant)

RAC notes that the grouping of the studies is based on the "midpoint value of DMF exposure", which in some cases is the median exposure (e.g. 3.1 mg/m^3 in Kilo *et al.*, 2016) and in other cases is simply calculated as the mean of the lowest and highest measured concentrations in a group (e.g. Wrbitzky *et al.* (1999) is put into the group with exposures ≥ 20 mg/m^3 while the median exposure is reported as 3.6 mg/m^3 by the author). RAC further notes that six of the 10 studies show effects of DMF on liver while four do not. Of the four negative studies, Kilo *et al.* (2016) and Wrbitzky *et al.* (1999) are given the greatest weight (26.4 and 11.5 % of total 100 %, respectively) in the analysis, while the median exposure in those studies are 3.1 and 3.6 mg/m^3, respectively.

All studies together suggest that DMF affects liver function in exposed workers, with the main contribution from studies with exposure > 20 mg/m^3, which clearly could be viewed as a human LOAEC. IVC proposes to set the NOAEC at 15 mg/m^3. The inconsistent grouping of studies makes it difficult to use the results of this meta-analysis for setting a NOAEC. RAC also notes that the greatest weight (26 %) of the 10 studies has been given to the Kilo (2016) study. The median exposure of 3.1 mg/m^3 in that study is thus strongly affecting the results of the meta-analysis, supporting using Kilo *et al.*, 2016 as basis for a (conservative) NOAEC.

In conclusion, in an approach combining human and animal data, RAC proposes to use for inhalation a DNEL of 6 mg/m^3 based on the NOAEC of 6.2 mg/m^3 (mean) in the Kilo *et al.* study (2016) for hepatic effects in humans and the DNEL of 6 mg/m^3 based on a NOAEC of 150 mg/m^3 for malformations in a rabbit developmental toxicity study (Hellwig *et al.*, 1991).

Biomarkers for exposure estimation to DMF

Comments in the consultation (#1957, #2033, #2036, #2038) have suggested that a biomonitoring DNEL is needed. However, no such DNEL was derived or proposed by the Dossier Submitter. Since there is no biomonitoring data used in the restriction proposal, there is no formal need for a biomonitoring DNEL in the assessment of the proposal. Nevertheless, RAC is of the view that combined exposure via the inhalation and dermal routes can only be assessed by proper biomonitoring.

RAC notes that at least three different biomonitoring approaches have been reported in the literature, focusing on different metabolites, with different half-lives, and therefore covering different exposure periods (Kilo *et al*., 2016, Seitz *et al*., 2018). Industry supports the need for a biomonitoring DNEL based on "DMF concentrations in the air may be poor indicators of internal exposure" (#1957, #2036). They suggest a biomonitoring DNEL of 20 mg NMF/L urine predictive of hepatic effects based on an analysis of the Kilo *et al.* data (2016) by Drexler *et al.* (2019), supported by a re-calculation of the OEL of 15 mg/m^3 to 19.3 mg NMF/L urine using an equation correlating air DMF with urinary NMF (Seitz *et al.,* 2018). NMF is defined as the sum of *N*-methylformamide and *N*-(hydroxymethyl)-*N*-methylformamide in urine, and is not creatinine-adjusted as creatinine-adjustment has not improved the relation between NMF and air DMF (Seitz *et al.*, 2018) or affected the urinary NMF-concentration in relation to dehydration/sweating (Miyauchi *et al.*, 2014).

Comments in the consultation (#2036, #2258) suggested that the DNEL of 6 mg/m^3 would correspond to a DNEL biomonitoring of 8 mg NMF/L urine based on equations provided by Seitz *et al.* (2018). RAC notes that the need for a biomonitoring DNEL comes from uncertainties as to how much exposure through the skin contributes to total internal exposure, and thus a high internal concentration of NMF in situations where a low air concentration of DMF has been measured indicate that the dermal exposure needs to be reduced. However, as a biomonitoring DNEL is calculated from the air DNEL for DMF, it is not directly related to a risk level.

Should a biomonitoring DNEL be set for DMF in the future, then a starting point for such discussions and further analysis could be the value of 8 mg NMF/L in urine which has been calculated from the DNEL of 6 mg/m^3. The urinary concentration of the DMF-metabolite AMCC (*N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine) is a biomarker for the assessment of cumulative whole-body exposure to DMF over a work-week and could be complementary to measuring NMF.

Furthermore, RAC notes that SCOEL (2006) has proposed a biological limit value of 15 mg *N*-methylformamide/L urine (post-shift an 8-hour work shift), corresponding to the OEL of 15 mg/m^3, and that the German MAK Commission uses the same value. This value needs to be adjusted, however, to take into account the DNEL values proposed by RAC. Thus, RAC recommends to set a DNEL$_{(biomarker)}$, which could be subsequently published in an addendum to the Guidance on "*How to comply with REACH Restriction 71, guideline for users of NMP (1-methyl-2-pyrrolidone).*

Information on emissions and exposures

Summary of proposal:

DMF is used in a variety of industrial sectors

- Manufacturing (20 000-30 000 tonnes/year),
- Formulation of substance (20 000-30 000 tonnes/year),
- Industrial use for the production of fine chemicals (2 000-3 000 tonnes/year),
- Industrial use for the production of pharmaceuticals (1 000-2 000 tonnes/year),
- Industrial use for the production of polymers (6 000-7 000 tonnes/year),
- Industrial use for the production of textiles, leather and fur (2 000-3 000 tonnes/year),
- Industrial use for the manufacture of non-metallic mineral products (500-1 500 tonnes/year),
- Industrial use for the manufacture of perfumes/fragrances (10-20 tonnes per year),
- Industrial use in the petrochemical industry (no information on volume used)

And

- Professional use as a laboratory agent (no information on volume used).

The exposure assessment by the Dossier Submitter was based on modelling using CHESAR v2.3 (released in 2014) with in-built ECETOC TRA v3.1. For two uses ("Industrial use for the manufacture of perfumes/fragrances" and "Professional use as laboratory agent") only modelled data are available whereas for all the other uses listed above, the Background Document also includes some air measurements.

The modelled exposure levels ranged from 0.021 to 4.568 mg/m^3 for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranges from 0.002 to 7.072 mg/kg bw/day (systemic, long-term).

The exposure assessment has shown that exposures resulting from processes under elevated

temperatures as well as processes requiring intensive manual applications and open processes, especially those described by PROC 19[1], are relatively high.

Since a worker can perform multiple tasks with potential exposure to DMF during a working day, combined (aggregated) exposure within a use was also assessed, but only for two sectors (e.g. "Industrial use for the production of fine chemicals" and "Industrial use for the production of textiles, leather and fur").

Exposure of humans via the environment can be excluded since the substance is readily biodegradable and there is no potential for bioaccumulation.

There is no information in the Annex XV dossier on consumer exposure.

RAC conclusion(s):

RAC notes that the Dossier Submitter considered mainly the uses listed in the Registration dossier by the lead registrant for the exposure assessment and requested all identified downstream users to provide specific information regarding their use pattern of DMF. Only the "Industrial use of DMF in the petrochemical industry" comes from another, not mentioned, source.

RAC acknowledges the variety of uses of DMF and, as the Dossier Submitter indicated, for several uses the number of sites may be significant (i.e. in the order of 1-100 according to the Registration dossier provided by the lead registrant) and therefore the number of occupational settings and the number of workers potentially exposed to the substance might be rather large.

RAC notes that the Dossier Submitter modelled individual tasks with multiple variation of operational conditions (OCs) and risk management measures (RMMs) – including personal protective equipment (PPE) – and provided the exposure modifying factors input data for the exposure modelling (e.g. for various substance concentrations, varying durations of activity, different efficiency of general ventilation and the assigned protection factors of the PPE (gloves, respiratory protective equipment (RPE)).

Since some comments provided during the consultation (#1957, #1986, #2295) questioned the selection of PROCs (e.g. the man-made fibre industry, the PU coatings and membranes sector and the fine chemicals industry sector), there might be some uncertainties with regard to the modelled data which cannot be easily solved since not all companies of these sectors might have expressed their view on this issue. However, according to information from the synthetic fibre industry, all companies were involved in the elaboration of the comments provided during the consultation. Therefore, there are no relevant uncertainties related to this sub-sector.

The relevance of PROC 19 was not addressed during the consultation. In addition, it is important to point out that while the PU coatings and membranes sector as well as the synthetic fibre industry claim that PROC 10[2] was not relevant for the production process, the Dossier Submitter stated that they have received information from Industry that both PROC 10 and 19 are used although these uses are "uses advised against" according to the Registration dossier[3].

Besides, industry clarified during the consultation that the synthetic fibre industry is covered

[1] PROC 19 – Manual activities involving hand contact;
[2] PROC 10 – Roller application or brushing;
[3] The registrants have identified PROC 10 for the "industrial use for the production of polymers" and PROC 19 for the "industrial use for the production of fine chemicals and pharmaceuticals" as "uses advised against".

under the section "Industrial use for the production of polymers" whereas according to information in the Background Dossier the synthetic fibre industry belongs to the sector "Industrial use for the production of textiles, leather and fur" (see table E7 – "Comparison of uses applied in the risk assessment and the SEA").

The fine chemicals sector stated that as the majority of processes are batch process, PROC 2[4] or PROC 5[5] might not be relevant.

The air monitoring data on DMF concentrations presented in the Background Document only provide limited support for the modelled data (for further information see "key elements underpinning the RAC conclusions") since the measurements were not performed under the same conditions (e.g. process temperature, concentration of the substance, use and rate of ventilation and/or LEV) as described for the modelled data. Whether the use of RPE was considered in the air monitoring data presented is not clear, for the modelled data the APF (assigned protection factor) is identified.

However, during the consultation, several companies, particularly related to the PU coatings and membranes sector[6] including both the textile and the synthetic fibre industry as well as their representatives and consultants provided information on air measurement concentrations. The latter presented the annual[7] 90th percentile in the synthetic fibre production: 12.1 mg/m^3 (2016), 12.4 mg/m^3 (2017), 8.5 mg/m^3 (2018) and in the PU coating of textile: 11.2 mg/m^3 for PU kitchen (2016-2019), 11.3 mg/m^3 for coating (2016-2019) while individual companies provided their individual data. Based on this information it is clear that the companies are able to comply with the current OEL of 15 mg/m^3 because they are using PPE for several tasks.

Concerning dermal exposure, both sectors point out that exposure estimates in the Annex XV dossier for dermal exposure might be on the one hand over conservative since local exhaust ventilation had not been taken into account. On the other hand, industry notes that the modelled exposure values might not consider the fact that DMF vapour is readily absorbed via exposed skin and might therefore be underestimated. However, both industry sectors confirm that manual transfer of DMF solutions might pose a risk.

In general, RAC concurs with the Dossier Submitter that the highest exposure levels might be expected for specific applications involving elevated temperatures, intensive manual applications and open processes that might narrow down the number of uses, or tasks in different uses, which might result in a health risk for workers.

Summing up, RAC points out that the Annex XV dossier would have been of much better quality if the information which was sent in during the consultation would have been provided to the Dossier Submitter at an earlier stage, i.e. before or during the preparation of the Annex XV dossier.

However, RAC is of the opinion that the exposure estimation presented in the Annex XV dossier can be used as basis for the risk characterisation because the modelling may sufficiently well represent the typical conditions and risk management methods (RMMs)

[4] PROC 2 - Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
[5] PROC 5 – Mixing or blending in batch processes;
[6] Industry states that the term "textile coating industry/sector" as used in the Annex XV dossier is imprecise since not only companies coating textiles but also papers (from which materials such as films and membranes are released) are covered in this sector. Reference to the "PU coatings and membranes sector", however, is intended to cover all of these activities, given similarities in the processes used.
[7] Why the 90th percentile was used on an annual basis and not on a daily basis to present exposure values is not completely clear to RAC. The reason might be that a long-term DNEL is considered to represent an annual value but this is definitely not the case. Long-term/chronic systemic DNELs are calculated for a shift-long exposure.

(including PPE) of different settings. RAC is aware of the uncertainties regarding the use of PROCs and highlights this issue in the subsequent section on "risk characterisation". RAC is also aware that dermal exposure modelling could result in underestimation with regard to dermal absorption of DMF vapours and overestimation due to exposure to splashes. However, RAC also acknowledges that overestimations are less likely in cases of tasks with high dermal exposure, where there is significant dermal contact with DMF.

Key elements underpinning the RAC conclusion(s):

In the Background Document, one professional and nine industrial uses of DMF are presented. The number of sites for some of these uses is reported to be 1-100 and therefore the number of potentially exposed workers might also be rather high but has not been provided for all of the sectors.

RAC notes that according to EASTMAN Chemical Company[8], U.S., DMF is used as carrier for inks and dyes in various printing and fibre-dying applications, in the production of high voltage capacitors, as a solvent, reagent and catalyst in the synthetic organic chemistry. It is also used as a cleaner (e.g. for hot-dip tinned parts), as industrial paint stripper, as a solvent in epoxy-based formulations, in the production of acrylic fibres and in the spinning of polyurethane based elastomers. Since there might be similarities between the USA and Europe regarding the use of DMF, RAC is of the opinion that some of the uses in the Background Document (e.g. "Industrial use for the production of polymers") could have been further differentiated by the Dossier Submitter in order to enhance the robustness of the exposure/risk assessment.

RAC acknowledges that the exposure assessment for DMF is based on a TIER 1 exposure model (ECETOC TRA v3.1) and that modelled exposure data, with a range of input parameters, were provided for all uses listed in the Background Document. However, RAC recognises some uncertainties with regard to the exposure assessment – besides the ones that are generally related to a TIER 1 model - since it is not clear if worst-case scenarios are considered with regard to different uses.

In addition, combined (aggregated) exposure resulting from several tasks a worker has to perform has only been assessed for the "Industrial use for the production of fine chemicals" and the "Industrial use for the production of textiles, leather and fur" scenarios. Besides, it is not possible to compare the measured data included in the Background Document (measurements are reported for all but for two uses, but for a very limited number of sites) with the modelled data. First of all, for most of the measured data contextual information is lacking (e.g. it is not even reported whether the data represent an 8-hour time weighted average (TWA) or whether they represent the air concentration for the task duration reported in the dossier). Secondly, the measured data cannot be easily compared to the modelled data since:

- there is not sufficient information about the RMMs implemented or
- OCs (e.g. process temperature) and RMMs related to measured data differ from those provided for the modelled data.

Further, the measured data provided through the consultation do not refer to specific PROCs in the Background Document.

With regard to the selection of PROCs, RAC notes that the Dossier Submitter did not provide information on how PROCs had been chosen for the exposure assessment. Therefore, it is not

[8] See https://www.eastman.com/Pages/ProductHome.aspx?product=71103587

clear to RAC whether all relevant PROCs are considered (for the different uses) in a specific sector. E.g. for the manufacture of fragrances/perfumes only two PROCs are provided and for the manufacture of non-metallic (mineral) products fewer PROCs are considered than for the production of pharmaceuticals. This raises some uncertainties since the production of pharmaceuticals is thought by RAC to be a closed, well contained, process which might be covered by a relatively small number of PROCs (definitely not including PROC 19).

Information provided through the consultation confirms RAC´s concern with regard to the selection of PROCs. It was pointed out that in the synthetic fibre industry PROC 2, PROC 4 and PROC 8b[9] do occur and that in the textile coating industry PROC 5, PROC 8a[10] and PROC 13[11] are relevant, but that in both sub-sectors PROC 10 does not occur. The other PROCs used for exposure modelling (e.g. PROC 4, PROC 8b, PROC 9[12]) might be relevant for other (sub-)sectors in the production of textiles, leather and fur but not for the textile coating industry. It was also clarified during the consultation (#2318, #2325) that in the fine chemicals sector PROC 2, PROC 8a, PROC 19 and PROC 5 might not be relevant. For the professional use as laboratory agent, in addition to PROC 15[13], also PROC 8b and PROC 9 might apply but since information on the choice of PROCs is lacking, there are some uncertainties related to this topic.

RAC notes that for maintenance and cleaning PROC 2, PROC 3[14], PROC 4 and PROC 8a were used in the modelling but not PROC 28[15] because neither the ECETOC TRA (nor CHESAR) provides separate exposure estimates for this activity. Since PROC 8a which is recommended (ECETOC Technical Report no 131, 2018) to be used is included in the exposure assessment, there are no significant uncertainties related to the exposure estimates for maintenance and cleaning activities.

Regarding dermal exposure estimates, it is noted that an evaluation by TNO (Marquart et al. 2017) showed that the ECETOC TRA dermal performance is generally consistent with a Tier 1 tool (over 80 % of predictions exceeded the 75th% of the measured values across all substance types) and has a clear bias towards severe overestimation (by up to two orders of magnitude) of dermal exposure at low measured exposure values (which may be linked to the closed or semi-closed processes) while all cases of apparent underestimation by the ECETOC TRA occurred at high measured exposure values (ECETOC Technical Report no 131, 2018), which may be linked to activities such as those described by e.g. PROC 19 and 10. That means that exposure during intensive manual contact described by those PROCs might be underestimated.

What might lead to a further underestimation of dermal exposure is that the model does not take into account the increasing dermal exposure to DMF with increasing concentration of DMF vapours[16]. That means that for semi-open processes with elevated temperature, the dermal exposure might be underestimated. This fact was addressed by Industry in the consultation (#1957, #1986). Industry pointed out that dermal exposure of the rather viscous DMF is mainly due to vapours and not due to splashes and direct contact. Therefore, the effect of the local exhaust ventilation should be taken into account in the modelling used for

[9] PROC 8b - Transfer of substance or mixture at dedicated facilities;
[10] PROC 8a - Transfer of substance or mixture at non-dedicated facilities;
[11] PROC 13 – Treatment of articles by dipping and pouring;
[12] PROC 9 – Transfer of substance or mixture into small containers;
[13] PROC 15 – Use as laboratory reagent;
[14] PROC 3 - Manufacture of formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
[15] PROC 28 - Manual maintenance or machinery;
[16] The operating temperature and the associated vapour pressure have only been taken into account for the inhalation route.

exposure calculation, since vapours can be managed with good local exhaust ventilation and as a result decrease the dermal exposure potential. In addition, Industry points out that dermal exposure estimated by the synthetic fibre sector and the textile coatings and membranes sector is lower compared to what was modelled in the Background Document. This relates to PROC 4 for the synthetic fibre industry and to PROCs 5 and 13 for the PU coating of textiles sub-sector. The dermal modelling for the latter was performed with a concentration of DMF of 100 % while Industry used a substance concentration of > 25 %, but RAC notes that the outcome of the modelling is not dependent on the percentage of DMF. However, since none of these PROCs is considered to pose a risk based on the DNELs proposed by RAC, this is not of relevance for the risk characterisation.

Characterisation of risk(s)

Summary of proposal:

In the Background Document, tasks/activities described by PROC 10, PROC 13 and PROC 19 result in a risk characterisation ratio (RCR) > 1.

A risk which is not adequately controlled for workers was identified for:

- Industrial use of DMF for the production of fine chemicals,
- Industrial use of DMF for the production of pharmaceuticals,
- Industrial use of DMF for the production of polymers,
- Industrial use of DMF for the production of textiles, leather and fur.

Besides, combined exposure to DMF related to performance of different tasks/activities by a worker within a working day presented by the Dossier Submitter also result in RCR > 1, as shown in the table below, summarising the result of the risk assessment provided in the Background Document.

While in 'Manufacture of substance' two tasks: 'Manufacture', PROC 2, and 'Charging and discharging', PROC 8b result in RCR > 1, the Dossier Submitter did not include them among those where the risk is not adequately controlled. The implementation of additional and/or more effective RMMs, such as use of RPE (with a higher APF), was not considered in the modelling. However, use of RPE would reduce the exposure. The Dossier Submitter therefore concluded that these tasks are not expected to be of concern for workers if additional RMMs are used.

Note, that the table only presents uses where the RCR > 1, calculated by the Dossier Submitter.

Table 2: Risk characterisation, based on the DNEL values proposed by the Dossier Submitter[17]

Identified use	Process Category (PROC)	RCRs[18]			Conclusion on risk
		Inhalation	Dermal	Combined	
Manufacture	PROC 2*; (condition 1: outdoor, process temp. ≤ 150 °C)	**0.999**	0.052	**1.052**	Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the manufacture of DMF is not expected to bear a safety concern for workers. Therefore, risks are adequately controlled if specific RMMs and/or OCs are applied.
	PROC 8b**; (condition 2: outdoor, process temp. ≤20 C)	**1.199**	0.521	**1.72**	
Industrial use for the production of fine chemicals	PROC 19; (indoor, process temp. ≤ 20 °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	**1.066**	**0.92**	**1.986**	Inhalation exposure may be decreased by adaptation 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. ≤ 20 °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.

[17] RAC did neither recalculate the modelled exposure data nor the risk characterisation ratios provided by the Dossier Submitter.

[18] Numbers in bold indicate a RCR close to but < 1 while numbers in bold with grey background clearly indicate a RCR > 1.

Identified use	Process Category (PROC)	RCRs[18]			Conclusion on risk
		Inhalation	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 below 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	**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.
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.

× RPE with an APF of 10 was considered in the modelling.

** No RPE was considered in the modelling.

RAC conclusion(s):

Based on the DNELs derived by RAC (1.1 mg/kg bw/day for the dermal route and 6 mg/m^3 for the inhalation route), using the CHESAR modelling tool (v2.3), there is a risk due to not adequately controlled exposure in the following sectors, linked to performing the tasks/activities described:

Table 3: Risk characterisation based on DNEL values calculated by RAC

Grey colour indicates uses where no risk is the conclusion, whereas bold RCR-numbers indicate a concern for high dermal or combined exposure.

Identified use	Process Category (PROC)	RCRs		
		Inhalation	Dermal	Combined
Manufacture of substance	PROC 8b; (condition 2: outdoor, process temp. ≤20 C)	0.640	0.373	**1.014**
Industrial use for the production of fine chemicals	PROC 19; (indoor, process temp. ≤ 20 °C)	0.305	**6.430**	**6.734**
	Combined exposure: PROC 2 and PROC 8b	0.569	0.661	**1.23**
Industrial use for the production of pharmaceuticals	PROC 19; (indoor, process temp. ≤ 20 °C)	0.03	**6.429**	**6.459**
Industrial use for the production of polymers	PROC 10; (indoor, process temp. ≤ 130 °C)	0.761	0.748	**1.500**
Industrial use for the production of textiles, leather and fur	PROC 10 (indoor, process temp. ≤ 200 °C)	0.533	0.748	**1.281**
	Combined exposure: PROC 9 and PROC 10	0.69	**0.935**	**1.625**

For two scenarios with RCRs > 1, no concern is assumed either (i) based on the fact that the RCR is close to 1 (RCR=1.014) and conservative exposure assessment ("Manufacture of substance") or, (ii) based on additional information provided in the consultation (PROC 19 for "Industrial use for the production of pharmaceuticals").

With regard to the RCRs presented in Table 3 above, RAC has serious doubts whether PROC 19 ("manual activities involving hand contact") occurs in the production of pharmaceuticals. In addition, the pharmaceutical industry stated that the OCs and RMMs applied for manufacturing of active ingredients allow the proposed exposure limits to be achieved.

RAC agrees with the Dossier Submitter's conclusion that risks might be adequately controlled in the following sectors, based on the modelled exposure/risk estimation:

- Manufacture of substance[19],

[19] Even though the RCR based on modelling indicates risk, measured data "Charging and discharging" (Table B93) seem to indicate that the modelled exposure assessment is very conservative and a conclusion of the Dossier Submitter that there is no risk could be supported.

- Industrial use for the manufacture of non-metallic mineral products,
- Industrial use for the manufacture of perfumes/fragrances,
- Industrial use in the petrochemical industry (including Industrial gases industry)[20],
- Professional use as laboratory agent.

These uses, as well as the result of the risk characterisation, are described in the Background document.

In addition, RAC is of the opinion that there might not be a risk in the industrial use for the production of pharmaceuticals for the reasons stated above.

RAC also notes that the risk characterisation for the formulation of DMF which is performed in different sectors (e.g. in the production of fine chemicals, pharmaceuticals, polymers, textiles and other products) and for maintenance and cleaning activities are not of concern based on the DNELs derived by RAC.

According to information provided through the consultation, the OCs and RMMs applied in the pharmaceutical industry for manufacturing of active ingredients (#1976) will allow the proposed exposure limits to be achieved. In addition, the fine chemical industry (e.g. the Spanish Association of Fine Chemicals Manufactures) stated that neither PROC 19 nor PROC 2 is relevant for their industry sector (#2295, #2303 and #2326). So, considering also the nature of the production of pharmaceuticals and fine chemicals, there might be no risk – based on the assumption that the information is representative for all downstream users from this sector.

The synthetic fibre industry and the PU coatings and membranes sectors pointed out that PROC 10 was not relevant for their uses. Both sectors stated that "the proposed DNEL for the inhalation route would be complied with when RPE is used". However, for the PU coatings and membranes sector (which belongs to the "Industrial use for the production of textiles, leather and fur") it is not clear if the statement (concerning PROC 10) is valid for all companies whereas for the synthetic fibre industry it is, according to information provided by industry at RAC-49.

Concerning dermal exposure, both sub-sectors point out that there is some uncertainty related to the exposure estimates in the Background Document (see section above). The textile coating sub-sector states (#1986) that the risk characterisation ratios for dermal exposure presented in the Annex XV dossier are a factor of five higher compared to calculations reflecting the real case situations.

Regarding combined/aggregated exposure RAC points out that the exposure resulting from the different tasks workers have to perform within one working day is not sufficiently well addressed in the Background Document. Only two different combinations (e.g. combination of PROC 2 and 8b in the "Industrial use for the production of fine chemicals" and PROC 9 and PROC 10 in the "Industrial use for the production of textiles, leather and fur", see table above) were considered in those two sectors. The limited consideration of potential combined exposure during a working day raises some uncertainties with regard to all other uses: there may be other combinations of tasks performed within a single shift in other sectors that may result in exposure leading to RCR > 1.

Summing up, RAC notes that the risks for workers are not adequately controlled (RCR > 1) in the

[20] RAC notes that the industrial gases industry (which might be a sub-sector of the sector "Industrial use of the petrochemical industry" confirmed that they are able to comply with the exposure concentrations recommended in the Annex XV restriction dossier.

- Industrial use for the production of fine chemicals,
- Industrial use for the production of polymers,
- Industrial use for the production of textiles, leather and fur.

In addition, particularly the synthetic fibre industry, the PU coatings and membranes sector and the fine chemical sector pointed out that they are not able to comply with the proposed inhalation DNEL without the use of RPE/PPE.

In addition, there might be an RCR > 1 for some combinations of tasks performed in some sectors.

Key elements underpinning the RAC conclusion(s):

There is no specific information for each sector on combined exposure from different tasks a worker performs during a working day. This leads to some uncertainties since there might be not adequately controlled risks related to some more (combined/aggregated) uses than the ones indicated in the Annex XV dossier.

Uncertainties in the risk characterisation

RAC notes that there is some uncertainty linked to the level of conservativeness of the TIER 1 model used for the assessment. While it is assumed, that the selection of presented PROCs originates from the registration Chemical Safety Reports (CSRs), specific information on how PROCs were chosen for the exposure assessment is lacking. Therefore, RAC is not sure if all relevant activities and tasks (expressed in PROCs) have been considered in the exposure/risk assessment, and if the tasks described by all presented PROCs are actually performed. These concerns are supported by the comments received in the consultation, since according to information provided, PROC 10 does not occur either in the synthetic fibre industry which is a sub-sector in the “Industrial use for the production of polymers” or in the PU coatings and membranes sector covered by the “Industrial use for the production of textiles, leather and fur” and PROCs 2 and 19 are not relevant for the “Industrial use of the production of fine chemicals”.

Thus, there may be no risk to be addressed in several sectors for which the Dossier Submitter concluded a RCR > 1, due to the inclusion in the exposure and risk assessment of the uses advised against by the registrant (namely PROC 10 for the “industrial use for the production of polymers” and PROC 19 for the “industrial use for the production of fine chemicals and pharmaceuticals”). However, RAC also notes that since the Dossier Submitter was made aware that these uses exist, RAC should not ignore that information without having evidence and therefore concludes that a risk may indeed exist.

Although the Dossier Submitter modelled identical processes with multiple variations of OCs and RMMs and provided information on the input data for the exposure modelling, resulting in exposure modifying factors, the representativeness of the modelled data for the different sites and uses remains uncertain, as also indicated by the statements above.

The lack of measured air concentrations in open processes (at elevated temperature) and the lack of contextual information on the (few) provided measured data do not decrease the uncertainty in the exposure/risk assessment.

Since risks have to be characterised based on combined exposure via the inhalation and the dermal routes, and modelled data are considered to overestimate low dermal exposure but underestimate high dermal exposure and exposure due to DMF vapours, RAC would have appreciated to receive information on biomonitoring data. Such data in combination with air measurements (e.g. personal sampling) would reduce uncertainty about the level of dermal

uptake related to specific tasks (PROCs) because measurements of dermal exposure are not available. Only the study by Kilo *et al.* (2016) provide some indication that dermal exposure due to direct contact might be of minor relevance since measured DMF concentrations in air and *N*-methylformamide (NMF) levels in urine correlate well. On the other hand, there is also a correlation in workers wearing RPE, strongly suggesting that DMF vapours are readily absorbed by skin.

It is not clear to RAC in which sectors combined/aggregated exposure due to different tasks/activities performed by a worker throughout a working day may occur. In the Background Document, aggregated exposure was assessed for the two sectors "Industrial use for the production of fine chemicals" and "Industrial use for the production of textiles, leather and fur". As pointed out by the Dossier Submitter, there might be other combined exposure scenarios in real workplace situations that result in uncontrolled risks for workers. Detailed information about the tasks performed in each sector would have been helpful on the one hand to be able to assess worker exposure and characterise risks properly and on the other hand to find out if RMMs are appropriate or if they could be improved.

Summing up, as pointed out by the Dossier Submitter, uncertainties occur due to the lack of data, shortcomings in models, choices and assumptions made and variability.

Whether the uncertainties taken together lead to under- or over-estimation of exposure is not clear to RAC. In the following table the direction of the uncertainties is indicated to provide some overview.

Table 4: Uncertainties in the risk characterisation according to RAC

Uncertainties	Effect on concern
Conservativeness of the TIER 1 model used for the assessment.	↓
The representativeness of the modelled data (use of PROCs) for the different sites and uses remains uncertain.	↓
The lack of representative measured air concentrations (personal sampling) for each (sub-)sector leads to some uncertainty with regard to the inhalation exposure.	↑↓
Exposure from dermal route is difficult to measure directly. Biomonitoring data would have been helpful in those assessments.	↑↓
Combined exposure, from different tasks during a workday is uncertain. Biomonitoring data would have been helpful in those assessments.	↑

Evidence whether the risk management measures and operational conditions implemented and recommended by the manufactures and/or importers are not sufficient to control the risk

Summary of proposal:

According to the Dossier Submitter, there is strong evidence that occupational exposure to DMF in some industrial settings results in a risk that is not adequately controlled (e.g.

"Industrial use for the production of fine chemicals", "Industrial use for the production of pharmaceuticals", "Industrial use for the production of polymers", "Industrial use for the production of textiles, leather and fur", where the RCR values were calculated to be > 1).

RAC conclusion(s):

RAC concludes that there is some evidence supported by the information provided during the consultation, particularly in the "synthetic fibre industry and the PU coatings and membranes sector", that the RMMs and OCs are not sufficient to control the risk for all exposed workers (RCR > 1). In addition, in other sectors there may be other combined (multiple tasks), shift-long exposures leading to RCR > 1 that were not identified by the Dossier Submitter.

Key elements underpinning the RAC conclusion(s):

In addition to RCRs > 1, based on modelling with some uncertainty concerning the PROCs used for the calculation of risks, some industry sectors, e.g. synthetic fibre industry, PU coatings and membranes sector, provided measured air concentrations showing that actual air concentrations are greater than the inhalation DNELs proposed by both the Dossier Submitter and by RAC (see section "Information on emissions and exposures").

Both sectors indicate that for some specific activities (e.g. activities covered under PROC 4[21] such as wet and dry spinning) it will not currently be possible to comply with the proposed DNEL for inhalation without the use of RPE. However, RAC notes that according to the data provided, both industry sub-sectors would be able to comply with the proposed DNELs by RAC by using effective PPE.

According to modelled exposure estimates in the Background Document, it is obvious that without taking RPE into account, the current OEL of 15 mg/m^3 would neither be achieved for PROC 3 in the "Industrial use for the production of polymers" nor for PROC 13 in the "Industrial use for the production of textiles, leather and fur" (see tables B100 and B102 in the Background Document, the use of PPE (RPE) is considered for 4 to 8 hours).

Besides, RAC notes that according to the study by Kilo *et al.* (2016), the range of inhalation exposure in two companies from the synthetic fibre sector is < 0.08-46.85 mg/m^3 i.e., there is already a need to use RPE for certain tasks to comply with the current OEL. Therefore, it seems that for the tasks where the measured air concentrations are above 6 mg/m^3 the use of RPE would need to be considered in order to adequately control the risk. Where there is a potential for dermal exposure, use of RPE may be necessary with even lower air concentrations, to achieve RCR < 1 for the combined dermal and inhalation exposure.

Evidence whether the existing regulatory risk management instruments are not sufficient

Summary of proposal:

The Dossier Submitter identified for which uses adequate control might not be achieved, based on the risk characterisation via modelling (CHESAR v2.3) but they did not provide any further evidence (such as measured data either related to the PROCs in question or for an 8 hour shift with sufficient contextual information to be sure how to interpret these data) that

[21] Based on the proposed DNELs by the Dossier Submitter (3.2 mg/m^3 for the inhalation route and 0.79 mg/kg bw/day for the dermal route), the RCR for PROC 4 calculated by the man-made fibre industry using CHESAR is 0.377 incl. RPE (APF 20) and gloves (APF 20).

the implemented RMMs are not sufficient.

RAC conclusion(s):

The use of DMF is currently not adequately controlled in all occupational settings, since occupational exposure might exceed the DNELs suggested by RAC, i.e., 6 mg/m^3 for the inhalation route and 1.1 mg/kg bw/day for the dermal route.

According to Commission Directive 2009/161/EU, the existing OEL for DMF is 15 mg/m^3. The dermal uptake of the substance is taken into account by a skin notation. In addition, SCOEL[22] recommended a biological limit value for DMF in September 2006 which is on *N*-methylformamide (15 mg/L urine, post-shift).

However, exposure below OEL is still not safe, as the DNEL value calculated by RAC for inhalation is lower than the established OEL. In addition, the contribution from dermal exposure also needs to be considered.

Key elements underpinning the RAC conclusion(s):

For detailed information, see section on hazards.

JUSTIFICATION IF ACTION IS REQUIRED ON AN UNION WIDE BASIS

Justification for the opinion of SEAC and RAC

Summary of proposal:

DMF is a high production volume substance registered with a total tonnage band of 10 000-100 000 t/a used in many industrial settings. It is produced in – and imported into – the EU. No direct exports have been reported. Based on the exposure assessment, risks on a Community-wide level are found to be present and need to be controlled. Secondly, according to the EU Treaties, the free movement of goods needs to be guaranteed in order not to distort the internal market. 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, providing a "level playing field" by preventing competition distortion and allows equal protection of human health across the EU.

[22] List of recommended health-based biological limit values (BLVs) and biological guidance values (BGVs), last update: June 2014

SEAC and RAC conclusion(s):

Based on the key principles of ensuring a consistent level of protection across the Union and of maintaining the free movement of goods within the Union, SEAC and RAC support the view that any necessary action to address risks associated with DMF should be implemented in all Member States. DMF is marketed and used throughout the EU and risks for workers have been identified. Therefore, action is required, and it should be taken on a Union wide basis.

Key elements underpinning the SEAC and RAC conclusion(s):

As stated by the Dossier Submitter and confirmed in the consultation, there is strong evidence that DMF is used in a large number of EU Member States. Therefore, the protection of human health from the adverse effects of DMF (e.g. reprotoxic effects) is needed on a Union-wide basis.

In the present opinion RAC concludes that for several uses the risks are not sufficiently controlled in workplaces (RCR > 1). The proposed restriction addresses manufacturing and use of the substance and would therefore prevent a possible trade and competition distortion and establish a level playing field for manufacturers and users.

The proposal follows the general principles for managing chemicals under REACH, except for the fact that the DNEL, derived on a regulatory science basis, is defined in the restriction rather than by registrants.

JUSTIFICATION WHETHER THE SUGGESTED RESTRICTION IS THE MOST APPROPRIATE EU WIDE MEASURE

Scope including derogations

Justification for the opinion of RAC

Summary of proposal:

The Dossier Submitter identified three different risk management options[23]:

- RMO1: Complete restriction (ban) of the substance:

  A total ban would eliminate any industrial and/or professional use of DMF. There would be no exposure anymore to this substance in the European Union and EAA countries but a shift to outside Europe.

- RMO2: The proposed restriction (imposing a harmonised systemic long-term DNEL[24] for the inhalation route and for the dermal route in an Annex XVII entry, for details see section below)

- RMO3: Authorisation: The risk reduction capacity is considered to be lower if the socio-economic-route would be brought forward under the REACH authorisation process. In case the adequate control route was be followed, the risk reduction capacity would be

[23] The Dossier Submitter compares three risk management options RMO1, RMO2 and RMO3 (Section 2.2), where the two first ones are restrictions and the last one is an authorisation. In the draft opinion, the authorisation is discarded as an option, and the main discussion concentrates on the two restriction options. To clarify the distinction and to follow a common practise in earlier restriction opinions, the restriction options are here called RO1 and RO2.

[24] Long-term/chronic systemic DNELs are calculated for a shift-long exposure. Therefore, they are to be used for the risk evaluation due to a daily exposure averaged over 8 hours.

the same as for RO2 since exposure is expected to be reduced below the proposed DNELs.

The Dossier Submitter has described the three alternatives more in detail in the Background Document.

The proposed restriction would address the identified risks for human health in the workplace on a Union wide basis. Although the substance will be further manufactured and used in several sectors, the risks linked to its use and subsequent exposure will be adequately controlled.

The Dossier Submitter rejected an option to list the substance on Annex XIV to REACH (RMO3) and thereby only allow authorised uses, as no feasible alternatives exist for a large number of uses. To control the risk the Dossier Submitter assessed two Restriction Options: RO1 and RO2. RO1 is a total ban for placing on the market and use of DMF for all applications in the EEA. Such a total ban would eliminate any industrial/professional exposure towards DMF.

The proposed restriction (RO2) is a combination of a harmonised DNEL for inhalation and for dermal exposure with a proposed concentration limit of 0.3 % for DMF. The level of harmonised DNEL for dermal exposure was set out to be 0.79 mg/kg bw/day in the original dossier. The inhalation DNEL implies that DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure[25] will remain below 3.2 mg/m^3.

The Dossier Submitter considers that RO1 and RO2 have substantially the same human health benefits as, applying the proposed DNELs and the necessary risk reduction measures, the risk will be adequately controlled. Due to the absence of suitable alternatives for a large number of uses, the total ban of DMF would have severe economic impacts.

The Dossier Submitter pointed out that the synthetic fibre industry and the PU coatings and membranes sector may not be able to comply with the proposed restriction without the use of PPE. While during the consultation the PU coatings and membranes sector asked for a transition period of 10 years in order to be able to substitute or upgrade plants, the synthetic fibre sector pointed out that not even a longer transitional period would help them to comply with the proposed DNELs.

The Dossier Submitter concludes that, except for the two sectors, the proposed restriction can be implemented without major costs. All the relevant sectors involved in the production of man-made fibres and 50 % of those involved in the production of PU coating and membranes, are expected to close down. The Dossier Submitter states that the estimated health benefits will outweigh the costs.

The Dossier Submitter proposes a transitional period of two years and has not proposed any derogation.

RAC conclusion(s)

RAC is of the opinion that the restriction is an appropriate measure to adequately control the risks for workers at all workplaces using DMF in the European Economic Area.

The scope of the restriction is clear. The concentration limit (0.3 %) of DMF under CLP is based on the generic concentration limit[26] (GCL) for substances toxic to reproduction.

[25] The "8-hour TWA" specifies what was meant by "long-term inhalation time" in the original proposal

[26] Specific and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance or in a mixture as identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous (CLP Regulation (EC) No 1272/2008).

RAC does not see a need for any derogations or a longer transitional period for any sectors (e.g. synthetic fibre industry and PU coatings and membranes sector) since according to the information provided during the consultation, the synthetic fibre industry as well as the PU coatings and membranes sector are able to comply with the proposed DNELs by using effective PPE and by implementing job rotation. The latter may be necessary for tasks which are not limited in their duration, where prolonged use of RPE is needed or where the background concentration of DMF is higher than the DNEL for workplace air concentration. Since the DMF is a threshold substance, daily exposures below combined DNEL levels would not result in an increase of the population at risk.

Although RAC is aware that hierarchy of control has to be followed, RAC notes that as long as the implementation of further technical RMMs is not feasible, organisational measures (e.g. job rotation) and the use of PPE are obligatory to protect workers and adequately control the risk. However, RAC assumes that, based on the hierarchy of control, the reliance on PPE will be reduced over the time and replaced by the implementation of technical RMMs.

Key elements underpinning the RAC conclusion(s):

According to the information provided during the consultation, RAC considers that all sectors will be able to comply with the proposed restriction although, particularly in the first years of the implementation of the restriction, the reliance on PPE will be an issue since the improvement of further technical measures to reduce exposure takes some time to be implemented.

Justification for the opinion of SEAC

SEAC conclusion(s):

SEAC focusses its assessment on the restriction options, RO1 and RO2. SEAC has not evaluated RMO3 (REACH Authorisation) in depth. However, SEAC can confirm that, according to the information available, no safer economically and technically feasible alternatives appear to be available for a number of uses, which could result in the scenario described by the Dossier Submitter where authorisation could be granted where adequate control is not demonstrated based on socio-economic considerations.

SEAC agrees with the conclusion of the Dossier Submitter that due to the manifested lack of feasible alternatives for a number of uses and considering that the risks can be sufficiently controlled by the proposed restriction, a complete ban (RO1) would be a less cost-effective restriction option than the proposed restriction (RO2).

SEAC does not find it necessary to consider whether other EU-wide measures could be more appropriate, as the proposal will ensure that all risks are controlled and it follows the general principles for managing chemicals under REACH, except for the fact that the DNEL is defined in a restriction under REACH rather than being derived by registrants.

SEAC notes that RAC has proposed higher DNEL values than that proposed by the Dossier Submitter, which will reduce compliance costs. Thereby, these higher DNEL values (further) improve the cost effectiveness of the restriction.

During the consultation the PU-coating sector requested transition period of 10 years from the time of entry into force of the restriction. Furthermore, the man-made fibre sector asked for gender specific DNEL values, as the liver effects are relevant for both men and women, while developmental effects are only relevant for women. This was reasoned by explaining

that in case the DNEL value for liver effects was higher than the DNEL value for developmental effects, higher exposure levels could be accepted for workers except women of childbearing age. Considering this, SEAC notes RAC's conclusion that the inhalation DNEL for the liver effect could possibly be higher than 6 mg/m^3, which is derived from a conservative NOAEC in the Kilo et al. (2016) study (cf. page 14 of the opinion for additional details).

However, SEAC concludes in line with the RAC conclusions[27] and responses[28] to consultation comments that the requests from the two sectors are not sufficiently justified. SEAC notes that the measured exposure currently is about twice the DNEL level derived by RAC and that RAC concludes that according to the information provided during the Annex XV consultation, the man-made fibre industry as well as the PU-coatings and membranes industry are able to comply with the proposed DNELs by using effective PPE and by implementing job rotation. This is further dealt with in the cost section below.

With regard to the length of the transitional period, RAC and SEAC agree with the Dossier Submitter proposal of a two-year transition period from the entering into force of the restriction understanding that the period also includes the implementation of the recommended and/or identified risk reduction measures. SEAC notes that Chemical Safety Reports, Safety Data Sheets, and information communicated down the supply chain shall be updated without delay as soon as new information potentially affecting the risk management measures becomes available or when a new restriction is imposed[29] (REACH Article 31 and 32).

Key elements underpinning the SEAC conclusion(s):

The proposal covers all professional and industrial uses of DMF. SEAC notes RAC's conclusion that the proposed restriction in combination with the cut-off value for reprotoxic substances of 0.3 % according to the CLP Regulation (EC) No. 1272/2008 (amending the Directive 1999/45/EC) will address all risk related to use of DMF[30].

SEAC acknowledges the general principle in REACH, where in the case that a supplier cannot identify relevant risk reduction measures to ensure that exposure will remain below the proposed DNEL values, the supplier has to advise against the use. However, REACH allows a downstream user to continue the use if the user can demonstrate safe use through a Downstream User Chemical Safety Assessment using the relevant DNELs. This might be possible since the user would have more specific information on further risk reduction possibilities. SEAC agrees that the proposed restriction conforms with the above-mentioned general principle.

With regard to RO1 (the ban) SEAC notes that RAC confirms that DMF is a threshold substance. Therefore, the risk is adequately controlled under the proposed restriction if the subsequent RCR is < 1. For a number of uses, it will still be possible to use DMF with an exposure below the proposed (safe) limits. Hence, SEAC agrees that the proposed restriction would be a more appropriate option than a complete ban.

[27] RAC conclusion on longer transitional period available on page 31.
[28] RAC rapporteurs response to consultation comment #2032
[29] SEAC notes that the Commission in the restriction on 1-methyl-2-pyrrolidone (NMP) (Annex XVII, entry 71) included a second paragraph to address the implementation of risk reduction measures. REACH Article 37(5) also covers the obligation for the down-stream user to apply the appropriate RMMs and OCs to adequately control the risks identified.
[30] According to REACH, Annex XVII, entry 30 DMF should not be placed on the market or used for supply to the general public when the individual concentration is equal or above 0.3 % (weight/weight) as substance, as constituent of other substance or in a mixture.

Effectiveness in reducing the identified risks

Justification for the opinion of RAC

Summary of proposal:

RAC conclusion(s):

The proposed restriction (RMO 2) defines mandatory inhalation and dermal DNELs, which would have to be used by current registrants in updating the CSRs, by new registrants and downstream users developing own CSRs. The OCs and RMMs required to reduce the inhalation and dermal exposure to levels below the DNELs would be listed in the exposure scenarios (ESs) and passed on with safety data sheets to downstream users. This option would be applicable to all uses, irrespective of how they are defined.

The proposed wording of the restriction also requires use of the RAC-proposed DNEL values for the inhalation and dermal exposure in safety data sheets by those, who do not have an obligation to develop CSRs.

RAC agrees with the Dossier Submitter that a total ban (RMO 1) would definitely reduce exposure for the European workforce and that authorisation (RMO 3) would be comparable to the risk reduction capacity of the proposed restriction in case the adequate control route would be followed but not if the socio-economic route would be followed.

Key elements underpinning the RAC conclusion(s):

The registrants have an obligation to provide updates to their registrations when the CSR is changed (Article 22 (g) of REACH). As a result of the incorporation of the DNEL values in the CSR, safe use (RCR < 1) will have to be described for all uses presented in the CSR. The risk reduction measures proposed by the registrants to protect against inhalation and dermal exposure are communicated in the exposure scenarios annexed to the safety data sheets – communication tools already being used for this purpose. While implementation of the recommended RMMs is not a requirement of the proposed restriction, it would be a result of it, and would bring along a desired risk reduction.

This option applies to manufacture, placing on the market (including import) and use of the substance.

Socio-economic impact

Justification for the opinion of SEAC

Costs

Summary of proposal:

The Dossier Submitter has calculated the cost impacts in a partly quantitative and partly qualitative manner for two restriction options: RO1 and RO2. The costs of these options were derived by comparing the costs of the baseline scenario with the cost impacts of the restriction. A quantitative assessment of the costs has not been found possible for all the sectors where workers can be exposed.

Currently, the main use of DMF (ca. 80 %) is as a solvent in chemical synthesis of pharmaceuticals, agrochemicals and fine chemicals, and in addition, in the electronic industry and as a solvent in the synthesis of artificial fibres 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 a laboratory chemical, as a cleaning solvent or in formulations. The substance is potentially used in all Member States. The baseline presented by the Dossier Submitter describes the current situation adjusted by expected growth in use.

Based on the registration dossiers and through consultation the Dossier Submitter has estimated the total production within the EU to be 20 000-30 000 tonnes. The following uses covering about half of the produced tonnage have been identified:

Identified uses	**Tonnage in t/a**
Production of fine chemicals	2 000-3 000
Production of pharmaceuticals	500-1 500
Production of polymers	5 000-7 500
Production of textiles, leather and fur	2 000-3 000
Manufacture of non-metallic mineral products	500-1 500
Manufacture of perfumes / fragrances	10-30

Note: Dossier Submitter indicates that the actual tonnages are expected to be higher than indicated in the table.

Through consultations with industry, the Dossier Submitter has gained information on the additional costs expected on certain industry sectors that the proposed restriction would impact (Figure E10 in the Annex E of the proposal):

1. Industrial gas industry: No significant impacts (below €5 M) are to be expected, as European producers are currently using DMF under conditions which comply with the proposed restriction;

2. Man-made fibre industry: Estimated impacts would over a 15-year period be €500-800 M. All costs are related to an indication in the questionnaire survey which states that the whole industry will close down the production of the man-made fibre production in the EEA;

3. Polyurethane (PU) coating and membranes industry: Estimated impacts would over a 15-year period be €365 - 690 M; 85% of the costs is related to an indication in the questionnaire survey that 50% of the production will close down the production in the EEA.

Where an industry sector has not made specific cost information available, it is assumed that the costs are moderate.

Total economic costs are estimated to be € 865-1 500 million over a 15-year period. The costs are claimed to be reduced by €185-345 million for the PU-coating and membranes sector if sufficient time (~10 y) is given for them to adjust to the restriction.

The Dossier Submitter has in principle considered the impacts on the different levels of the supply chain for the specific sectors: DMF producers, direct users in the sectors and downstream users. However, the Dossier Submitter has identified costs for DMF producers in case of the shut-down of production.

The Dossier Submitter has not calculated costs for the enforcement of the restriction.

SEAC conclusion(s):

SEAC finds the overall cost estimate developed by the Dossier Submitter to have shortcomings, to be very uncertain and to severely overestimate the costs. The overestimation is even more significant when applying the RAC derived DNELs, as the higher DNELs are expected to be less costly to comply with. SEAC acknowledges several uncertainties in the analysis.

Most importantly, SEAC does not find it likely that 50 % of the PU-coating and membranes sector as well as the complete[31] man-made fibre industry would close down due to the restriction. As this element represents about 90-95 % of the Dossier Submitter's cost estimate, this affects the cost estimate significantly.

SEAC has discussed the methodology for the way the Dossier Submitter has estimated societal loss due to close or relocation of the production in the Background Document. This is not included in the draft opinion as SEAC does not expect that the proposed restriction will result in major close down or relocation of the production.

Concerning the PU-coating and membranes sector, SEAC notes that a number of companies may be able to find substitutes for some of their uses. However, there will be no substitute for all uses. Investments planned in the industry may already reduce exposure to levels close to DNEL values recommended by RAC. However, further measures seem to be needed. SEAC and RAC find that in the short run companies may achieve the RAC DNELs by additional use of RPE and organisational measures (e.g. job rotation). This in turn gives more adjustment time for the companies to adopt any necessary technical measures, and it is expected to result in lower costs overall as companies can use the measures most suitable for them.

Furthermore, a new BREF[32] on Surface Treatment using Organic Solvents (STS) would cause parts of industry to face some of the similar measures in 4-5 years anyway. The extra costs due to the proposed restriction for these measures would then be in form of interests for the invested capital in the interim period. As there will be a transition period also with the restriction, this interim period will only be two or three years. SEAC notes a request by some industries for an extended transition period (up to 10 years). However, referring to the possibility to use PPEs etc., SEAC does not find this request to be justified.

SEAC notes representative consultation comments by the man-made fibre industry. Based on those comments, average exposure could be reduced close to or at the level of DNELs agreed by RAC by implementing different kind of risk reduction measures. This itself suggests, that the costs may be moderate, leading to the SEAC view that the costs reported in the Annex XV report are clearly overestimated. Industry has not convincingly demonstrated that the risks could not largely be adequately controlled by the use of PPE and administrative measures, like job rotation in cases where technical measures are not sufficient or feasible.

SEAC acknowledges the most recent comments received from organisations and individual companies in the consultation on the SEAC draft opinion, in which the man-made fibre sector and PU-coating sector still maintain that it would not be feasible for them to comply with the RAC DNEL values.

There is no overall estimation of costs for upgrading production facilities to be able to comply with the RAC DNEL values. SEAC notes that a preference for the principle of hierarchy of

[31] In the consultation of the SEAC draft opinion, the man-made fibre sector indicated that 50 % of the plants would close down the production

[32] BREF is a reference document for Best Available Techniques (BAT).

control[33] makes it difficult to estimate the overall least costs of reducing exposure, as it will be a case-by-case evaluation for each industrial user. The comments submitted by the man-made fibre industry in the consultation focus mainly on the costs of technical measures and consider the costs to be excessive. SEAC has a view that the additional use and the subsequent costs of personal protection equipment (PPE) and administrative measures could be a less expensive option.

During the consultation, the pharmaceuticals sector and industrial gas sector (petrochemicals) have indicated (Comments # 1976 and 1987, respectively) that they support the proposed restriction. According to the two sectors, the exposure is already at the level required in the original restriction proposal. For pharmaceuticals as well as other industries using DMF (production of fine chemicals, polymers, fine chemicals, phenolic resins, medical devices, sport equipment, chemical and pigment-dyes) no information on the need for further risk reduction measures and accompanying costs was provided.

SEAC agrees that the restriction will not impose further enforcement obligations and associated costs. This is further described in the section on practicalities below.

In the following sections, a specific evaluation for the PU-coating and membranes sector, impacts for the man-made fibre sectors and for other sectors using DMF are described.

Key elements underpinning the SEAC conclusion(s):

Based on the information available, SEAC agrees with the Dossier Submitter that safer alternatives are not available for all uses. As a polar aprotic solvent, DMF has specific properties.

Specific evaluation for the PU-coating and membranes sector

The Dossier Submitter analysed the ability of the PU-coating and membranes industry to substitute DMF in their activities. The Dossier Submitter's analysis has a high sectoral coverage (80-100%) given information that 30 firms represent the total turnover of the sector.

Based on the analysis, the Dossier Submitter concludes that it is not clear whether DMF can be completely substituted in the PU-coating sector. The use of DMF for the different types of coatings strongly depends on the polymer used for coating, the material to be coated and the properties to be achieved. In some applications DMF as coating solvent may be substituted by water or organic substances. However, some specific coatings will still require DMF. SEAC notes that this result has been confirmed by industry in the consultation (#1986).

Also for membranes, e.g. for osmosis or ultrafiltration, the choice of solvent is very important for the quality and a number of examples are presented for which DMF is not replaceable.

[33] Council Directive 89/391/EEC of 12 June 1989 'on the introduction of measures to encourage improvements in the safety and health of workers at work' establishes basic rules on protecting the health and safety of workers. The employer shall implement the measures on the basis of a number of general principles of prevention, among which: avoiding risks, combating the risks at source, replacing the dangerous substances by the non-dangerous or the less dangerous ones, and giving collective protective measures priority over individual protective measures. These principles have been further elaborated into a preferred hierarchy of control measures in article 6.2 of the Chemical Agents Directive: a) substitution, b) process design and engineering controls that prevent release of substances at source, c) collective protective measures at source, such as ventilation and organisational measures, and d) individual measures, such as personal protective equipment. The Carcinogens and Mutagens Directive defines requirements for carcinogenic or mutagenic substances. These substances should be replaced as far as technically possible, regardless of economic considerations (art. 4.1). If that is not possible, the company should use closed systems (art. 5.2), and if that is not possible as well, the employer should ensure that exposure is reduced to a level as low as technically possible by means of a combination of measures, including the limitation of the quantities of substances present and the number of workers exposed (art. 3 & 5). See https://oshwiki.eu/wiki/Hierarchy_of_prevention_and_control_measures

SEAC notes that this has also been confirmed in the consultation (#1975).

With regard to the costs of substitution, only limited information for the PU coating and membranes sector is available. Due to a lack of information on possible alternatives, the cost estimate only covers equipment required when substituting to alternatives and is listed as a one-time cost in the range of €60-100 million, as identified in the Dossier Submitter questionnaire survey. It is SEACs view that this information does not give a reliable picture of the possible costs, as no details on the equipment requirements nor estimates of the running costs are presented.

Based on information from the PU-coating and membranes industry, the Dossier Submitter indicates that the proposed restriction would result in companies representing 50 % of the turnover (in the part of the industry using DMF) substituting DMF with another substance. However, only very limited cost information for substitution is submitted. Companies were asked for information on costs for equipment, R&D, testing and variable costs, but no concrete alternative substances were identified, and the Dossier Submitter summarised the cost estimate to be a total amount of €50-110 million. Hence, SEAC considers the basis for the estimation to be non-transparent and therefore the estimate to be very uncertain. However, SEAC notes that according to the information submitted in the consultation several producers indicated that they have concrete plans for the substitution of DMF with alternatives on the short to medium term but did not provide further details. This is also driven by consumer demands for articles without DMF residuals.

SEAC further notes that a survey[34] submitted in the consultation indicates that with the on-going or planned investments, the inhalation exposure can meet an exposure level around halfway between the current OEL (15 mg/m^3) and the proposed DNEL (3.2 mg/m^3), which is quite close to the value recommended by RAC (6.0 mg/m^3). SEAC notes a consultation comment by Fedustria (#2327) that notes that the increase in the DNEL values by RAC will not fundamentally change the business case for the PU-coating companies as the investments industries have to make will be more or less the same whether they have to meet a DNEL for inhalation of 3.2 mg/m^3 or 6 mg/m^3. SEAC understands that 'lumpy investments' may sometimes cause such an outcome but notes that that more stringent limits tend to be progressively costlier to achieve, especially as any remaining need for risk reduction can be addressed by use of PPE and organisational measures.

The Dossier Submitter presented company level cost estimates for individual exposure reduction activities for reaching the required exposure level. The reduction activities range from minor interventions to more extensive investments and the subsequent costs reach several million Euros. The interventions cover activities like redesign of ventilation systems, retrofitting coating lines and use of automation. However, no aggregate cost estimate is presented. A specific analysis carried out for and reported by Fedustria[35] provides specific information on costs for different actions. However, no quantification for the sector has been performed.

SEAC acknowledges the hierarchy of control principle, which is generally to be followed in exposure control/risk management. The hierarchy of control principle makes it difficult to estimate the aggregated cost for risk reduction, as the decision on how to address the risks has to be done on a case-by-case basis. For instance, in some cases PPEs and administrative risk reduction measures, like job rotation can be implemented if higher level reduction

[34] Comment #1986. Fedustria is a Belgian federation of the textile, wood and furniture industry. The survey is based on individual discussions and meetings with 10 European companies using DMF (dimethylformamide) as a solvent for polyurethane (PU) for textile coating and film and membrane production.
[35] Information in note of 5 March 2018 on SEA on the PU coatings and Membranes sector (confidential).

measures, like substitution and further automation are too costly. SEAC notes that for tasks where the present exposure is above the safe level, increased use of personal protection equipment and possible extension of the staff to enable job rotation would also incur (case specific) additional costs. Therefore, the preferred activities may vary by individual company and as a result a mechanistic estimation of the aggregated cost for exposure reduction activities is not available.

In the consultation, several companies claimed that due to the need for rapid interventions in the production process and frequent changes in production it would not be possible for many of them to comply with the proposed limit. Fedustria (#1986) mentions that the use of RPE would theoretically be sufficient to decrease the calculated risk with regard to the proposed DNEL of 3.2 mg/m^3. However, Fedustria does not consider this practical nor comfortable since RPE should be worn continuously during eight-hour shifts, and as PPEs in many cases are not allowed to be worn for many hours. SEAC has a view that PPE and e.g. job rotations, optimising procedures and increased ventilation respecting environmental requirements may be used during adjustment periods when a company is adapting to new regulation and e.g. substitution or technical adjustments appear prohibitively costly in the short run.

Fedustria also notes that the release of a revised BREF on Surface Treatment using Organic Solvents (STS), which is expected in 2020, will impose a further reduction of the allowed diffuse emissions of DMF to the environment. A new mandatory emission level for diffuse emissions of DMF will be a factor of four lower than currently acceptable[36]. The companies will be obliged to comply with this new mandatary emission level at the latest four years after the publication of the revised BREF STS in the Official Journal i.e. potentially in 2024. SEAC takes this as an evidence that potential additional costs due to the proposed regulation may not be overly large as the revised BREF will cause the industry to move to the same direction within a few years, irrespective of the restriction.

SEAC further notes that it might be possible to use administrative measures in case there are practical issues hindering use of PPEs or other risk reduction measures.

SEAC notes that the PU-coating and membranes industry has indicated to the Dossier Submitter that “sufficient transition time” will decrease the socio-economic costs for this sector by 50 % (p. 434 in the XV *Annexes*). Furthermore, in the consultation (#1986, #2284, #2276 and #2282 and #2323) industries from the PU-sector requested a 10 year transitional period. This is generally reasoned by the time needed to identify and implement substitutes and possible risk reduction measures. SEAC does not see such a long transition period necessary as PPEs and administrative measures can be implemented within a short notice.

Impacts on the man-made fibre industry

DMF is used as a solvent in the production of polymeric (man-made) fibres. None[37] of the industry actors have identified alternative solvents that are technically and economically feasible (e.g. DMAC (having similar hazards as DMF), sodium thiocyanate, GBL, DPMrA and DMSO were reviewed). DMSO is discussed as the most promising potential alternative, but it does not have the same properties with regard to viscosity, tendency for coagulation and evaporation heat. Such technical feasibility aspects need to be solved before assessing the economic feasibility. SEAC notes the information about the use and lack of alternatives on the

[36] The acceptability in BREF is linked to the input volume and not directly related to the ambient air concentration.
[37] Although one company has identified one alternative for a smaller part of its production. (#2245)

man-made fibre sector and the sector's concern indicating that the whole sector would close down if DMF and aprotic solvents with similar characteristics (and hazards) are banned or if the DNEL values proposed by the Dossier Submitter were introduced.

During the consultation IVC[38], claiming to represent 100 % of the EU man-made fibre industries submitted further information (#1957, #2029, #2030, #2031, #2032 and #2245) concluding that at present, the industry cannot comply with the Dossier Submitter proposed DNEL of 3.2 mg/m^3 for inhalation for all workers as proposed in the Annex XV report, nor to level recommended by RAC. Furthermore, IVC stated that they would not be able to identify cost-effective technical measures that could further reduce exposure to DMF in the near future. However, exposure assessment made for IVC concluded that monitoring showed that the annual mean of exposure levels for the process with the largest exposure was 6.5 mg/m^3 in 2018 and the 90th percentile was 8.5 resulting in a risk characterisation ratio of 2.66 (based on originally proposed DNEL value). SEAC notes that using the RAC DNEL the RCR would be 1.5 for one activity (PROC10) for the combined route of exposure (inhalation and dermal). This RCR, potentially overestimated, is considered to be only slightly above 1 (1 is considered to be safe).

Based on information from one smaller producer, IVC indicated that the costs of new equipment for controlling exposures through increased ventilation would cost at least €150 million for the whole man-made fibre sector and would only result in an exposure level between the present OEL and the RAC DNEL. In addition, additional energy would be needed and there would be limited opportunity for recovery given the lower concentrations in gas stream.

SEAC notes the information submitted by IVC, which indicates that theoretically it would be possible to further reduce the exposure to the RAC DNEL by using administrative measures like job rotation and PPE. However, according to their analysis it is not desirable or practical, and they point out that increased use of PPE effects the welfare of workers would need to be balanced against the benefits from reduced DMF exposure (#2247).

In the consultation on the SEAC draft opinion IVC stated that the RAC DNELs would also impact other operations not only those with the highest concentrations and they would involve workers operating in the ambient conditions of the factories. Respiratory PPE is uncomfortable when used for an extended time especially in areas associated with high temperatures. Furthermore, it limits interaction with colleagues and makes work harder to do, thus significantly affecting the everyday working conditions. The RAC DNELs would require 30-40 % of those working with DMF to wear respiratory PPE (in addition to existing PPE use) for around 50 % of their working hours.

Overall, due to present exposure being close to the proposed levels, SEAC does not find it likely that the proposed restriction would result in the termination of the production of man-made fibres in the EU. However, SEAC recognises that the companies involved might need to make technical and operational adjustments. SEAC further notes that technical means alone could be costly and need some adjustment time. However, use of PPE and e.g. job rotation in the meantime may result in costs significantly lower than costs related to technical means. As in the case of the PU-coating and membranes sector, the preference for following the hierarchy of control principle makes it difficult to estimate the total cost of risk reduction. The decision on how to address the risks has to be done on a case-by-case basis and as a result, the estimation of the aggregated cost for required activities is not straightforward.

As no closing down of the production is expected, SEAC does not find it likely that the

[38] IVC is the association of the German, Austrian and Swiss Man-Made Fibres Industries.

proposed restriction will have a great impact on the man-made fibres supply chain. SEAC notes that in the case of termination of the production, the Dossier is not clear with regard to the impacts on industries which are depending on materials for which DMF has been used in the production (indirect users). In the argumentation for why the man-made fibre sector cannot increase the prices in order to transfer possible costs, the dossier says that fibres requiring DMF could still be imported and it does not matter whether DMF or DMF made fibres are produced locally or imported from outside the EU. This is not in line with the argumentation in social impacts where it is said that the termination of the fibre production could endanger several thousands of jobs. The Dossier Submitter indicates that this reflects inconsistencies in the information from industry. However, since termination of production of the man-made fibres are not envisaged, SEAC has not studied this aspect further.

Other sectors

For the industrial use of DMF, for the manufacture of non-metallic mineral products and for the manufacture of perfumes/fragrances no risks were identified by the Dossier Submitter with the originally proposed DNEL values and the outcome is even clearer in case of RAC derived DNELs. This has been confirmed by RAC.

During the consultation the pharmaceuticals sector and industrial gas sector (petrochemicals) have indicated in their comments (#1976 and #1987 respectively) that they support the proposed restriction. According to the two sectors, the exposure on their sectors is already at the level required in the original restriction proposal. This can probably be linked to fact that these sectors operate with rather closed systems. For pharmaceuticals as well as other industries using DMF (production of fine chemicals, phenolic resins, medical devices, sport equipment, chemical and pigment-dyes) no information indicated the need for further risk reduction measures (and accompanying costs). For the industrial gas sector, the Dossier Submitter, indicates that the current exposure level is already below the originally proposed DNELs, estimated costs to be between €0 and 5 million without giving details.

The only remaining use for which RAC has identified a certain risk[39] for industrial workers is the production of polymers[40]. However, except the man-made fibre sector, no information is available for that sector.

Hence, for other sectors it is not expected that the proposed restriction will cause any costs or at the most minor costs.

Overall cost estimate

Based on the above reasoning SEAC finds that the overall cost estimate presented by the Dossier Submitter severely overestimates the cost of the restriction.

For all uses where the risk is not yet adequately controlled it seems possible to implement PPEs and administrative risk reduction measures. In some cases, users will have the possibility to introduce further technical risk reduction measures over time. The costs of such measures are reduced with increased adjustment time; however, it is not possible for SEAC to give an estimate on the related costs. Furthermore, in some cases the same magnitude of risk reduction will be required due to other policies (e.g. BREFs), and additional costs due to the proposed restriction may be reduced significantly, in form of interests for advanced investments.

Benefits

[39] RCR for inhalation was found to be 1.4 and for dermal exposure 1.0 leading to a combined RCR of 2.4.
[40] IVC considers that the man-made fibre sector belongs to this sector. However, the impacts on this sector is described above.

Summary of proposal:

A quantification of health effects was possible for i) hepatotoxicity effects including alcohol intolerance and ii) carcinogenicity, while a qualitative assessment was given for iii) developmental effects.

Chronic DMF exposure might result in negative health effects for all workers, e.g. general loss of well-being, hepatic injury (elevated enzyme levels) and alcohol intolerance. When drinking alcohol after being exposed to DMF, workers suffer from effects such as face flushing, palpitation, headache, dizziness, body flushing and tremors. Even if not a disease itself, the symptoms cause discomfort and may be an early sign of liver damage. In relation to carcinogenicity, endpoints for further investigation in the health impact assessment are general loss of well-being and neoplastic lesions.

The most relevant affected human health endpoints of DMF are reproductive and developmental effects; however, there is no information available in the literature about cases of reproductive or developmental effects in humans after exposure to DMF.

The Dossier Submitter has used a quality-adjusted-life-years (QALY) approach and considered three types of cancer (prostate cancer, liver cancer and skin melanoma) and liver-related effects (liver cirrhosis) as a proxy. Using the lowest and highest gain in QALYs for each type of cancer and for liver cirrhosis, the total monetary value of health impacts is estimated to be €40-115 million per year and €760-1 330 million (NPV) calculated for a 15-year period (based on information from PU-coating, membranes and man-made fibres industries). No health impacts are expected from the industrial gases industry. Almost all of the quantified health impacts (99.7 %) were related to liver effects (cirrhosis).

The Dossier Submitter acknowledges that there exists significant uncertainty about a large number of parameters and assumptions in the benefits assessment and that the results must be interpreted with caution. In the qualitative description of the benefits, the Dossier Submitter identifies alcohol intolerance as the main effect for the proposed restriction as an early indicator of liver damage.

SEAC conclusion(s):

SEAC considers that the proposed restriction provides clear benefits. This is despite the conclusion that the quantitative benefits estimated by the Dossier Submitter are likely to be significantly less than the €77 million over the 15 years period initially estimated. The effectiveness of the restriction is supported by qualitative analysis, as many of the benefits can be qualitatively described. It is noteworthy that the main reason for the restriction is to avoid reprotoxic effects in form of developmental effects, however, the quantified benefit assessment is based on hepatotoxicity effects.

The RAC DNEL is derived on the reprotoxic endpoint. The identification of the development effect is based on reduced fertility and malformations in animals. Unfortunately, as mentioned above there is no quantification of the benefit available for these effects.

The DNEL for hepatotoxicity in humans is approximately at the same level as the reprotoxic effects. For alcohol intolerance[41] related to hepatotoxicity, SEAC considers that the quantified benefits are about €35-77 million over 15 years (NPV). However, the uncertainties related to this estimate are high and the estimate is most likely overestimated.

[41] The dossier submitter also sees alcohol intolerance as a “pre-marker” for a future liver disease.

With regard to carcinogenic effects, SEAC does not find it justified to conclude that the restriction will result in fewer cancer cases, even if IARC considers DMF as probably carcinogenic in class 2A. SEAC's view is based on the fact that the substance is not classified as carcinogenic, that the Dossier Submitter concluded that there is no basis for changing the classification and that the study which the Dossier Submitter used for the quantification did not find a causal relationship between exposure to DMF and cancer and especially not for testes cancer.

Hence, the restriction is estimated to provide quantitative health benefits, only related to liver effects (alcohol intolerance). This results in significantly lower benefits (vs. originally estimated by the Dossier Submitter) giving a range between €35 to 77 million over 15 years (NPV). This estimate, although an order of magnitude below the Dossier Submitter's estimate, suggests benefits from the restriction.

SEAC agrees with the Dossier Submitter that although the quantitative health effects are quite uncertain, qualitative results provide support for them. The numerous human and animal study results form a solid basis for the proposed restriction by means of reporting consistent adverse effects to human health. This is confirmed by RAC and further described in BD E.4.1.1.

As a whole, based on the assessment reported and accounting for both quantitative and qualitative evidence, SEAC finds the proposed restriction to provide clear benefits, which are (only) partly quantified.

Key elements underpinning the SEAC conclusion(s):

SEAC agrees to the general model used for calculating health benefits related to the restriction.

The benefits are estimated based on information on:

a) Number of exposed workers;
b) Incidence rate – based on studies of workers exposed to DMF;
c) Relationship between parameters and diseases;
d) Loss of QALY points due to disease;
e) Monetarisation of QALY points;
f) Calculation period – and discount rate.

These parameters are discussed below.

The number of exposed workers is limited to exposed workers in the PU-coating, membranes and man-made fibre sectors. Based on information on a questionnaire survey the Dossier Submitter estimated that between 1 300 to 2 500 workers will benefit from the restriction. The Dossier Submitter considers this as a rough estimate, and SEAC has no reason to challenge this estimate.

SEAC agrees that statistical data on incidences rates of a disease within a population can be used when a dose-response function is not available. SEAC notes that an assumption on how a change in exposure may change prevalence (or incidence) creates uncertainty in relation to the incidence rate, as the level of exposure itself has an influence on the result.

For the liver effect, the incidence rate is calculated based on a number of specific studies where exposed and non-exposed workers have been tested for liver related parameters. The

exposure levels[42] of the exposed workers seem to be not far above the present OEL value, and the studies are therefore considered to be relevant for the evaluation of the proposed restriction in relation to the baseline exposure. SEAC notes that the incidence rate values in different studies differ significantly (range 4-75 %)[43] and this adds to uncertainty. SEAC notes that this also reflects that the studies have not used the same liver parameters.

A major issue is how human monitoring data can be transposed into real number of specific diseases. For liver effects, the Dossier Submitter assumes that, in general, elevated levels of specific parameters always lead to cirrhosis. SEAC notes that no viable information is available which indicates higher incidence rate of cirrhosis in the exposed population, even if higher liver parameters are found for up to 75 % of workers in some studies.

Secondly, SEAC questions to what extent cirrhosis can be used as an appropriate proxy for the liver effect in the form of alcohol intolerance, i.e. whether the pain, discomfort etc. are comparable to cirrhosis symptoms. The symptoms registered by DMF users are e.g. face flushing, palpitation, headache, dizziness, body flushing and tremors. However, exposed workers can avoid these effects by not drinking alcohol. The question is whether alcohol intolerance is a disease[44] at all, but it can be considered as an early indicator of liver damage [toxicity] which might later result in other health impacts[45]. On the other hand, the symptoms due to DMF use can be seen to limit consumer behaviour and fulfilment (enjoyment of alcohol) and to cause decreased utility in that manner.

Thirdly, SEAC questions the longevity of the (hepatotoxicity) health effects noting that the Dossier Submitter originally assumed the effects to be chronic, implying that the welfare loss continues for the rest of a person's life. However, the Dossier Submitter elsewhere indicated that the hepatotoxic effects in form of alcohol intolerance are fully reversible. This is in line with a study mentioned in the report in the original dossier (p. 401) covering seven workers for which liver biopsies had shown abnormal high values, and which found that the liver values returned to normal after 4-22 months after absence from the working area. As a result, the Dossier Submitter later indicated that the estimation should be adjusted. In the Background Document the Dossier Submitter followed the advice from SEAC to assume that the effect of alcohol intolerance is for one year only. The assumption of one year is also somewhat ad hoc but appears to be an acceptable proxy and simplifies the estimation. Naturally, the estimated potential harm clearly decreases as the affected workers now suffer shorter time from the disease.

The originally calculated incidence rate was based on an assumption that the onset of the disease would be half of the observation period in the studies used for deriving the incidence rate. In average observation period was about 5.7 years implying that the time average period from exposure to onset was assumed to be 2.85 years. To be consistent with the assumption that the alcohol intolerance effect resulting from one year's exposure only last for 1 year, the estimated incidence rate ends up being higher than identified by the Dossier Submitter (40 %

[42] Cai et al. (1992) reported that in workers exposed to max. 21 mg/m^3 DMF, the levels of liver function indicators were similar to controls. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and authors suggested that a level at which no alcohol intolerance would occur is below that causing liver damage. Fiorito et al,: 21 mg/m^3; Redlich, Lou 9-75 mg/m^3.

[44] Even if the alcohol intolerance is not considered to be a disease at all, the impact of DMF exposure may be considered to cause a loss in welfare due to a person not being able to drink/enjoy alcohol. This approach has not been developed further.

[45] According to animal studies as well as human biomonitoring data, exposure to DMF influences the function of the liver, e.g. changes in liver function symptoms which is not directly linked to alcohol intolerance. The Dossier submitter indicates that this could imply lower body weight, probably combined with some loss in general well-being. The incidence rate for liver functions enzymes are much lower than the incidence rate for the alcohol intolerance.

compared to 14.9 %)[46].

The QALY approach provides a measure that integrates quantity of life with quality of life, i.e. a quality adjusted life year. An important issue is to determine the QALY score of individual diseases. The Dossier Submitter presents scores identified in different meta studies. For liver disease, the Dossier Submitter uses QALY scores of cirrhosis as a proxy, and finds values between 0.08 and 0.25. The 0.08 value is based on the Tengs and Wallace (RPA, 2015) and is recommended by RPA in a study for ECHA, while the 0.25 represents the highest range in the global burden of disease network. The central value of this study is 0.18 (see the Background Document, section E).

The symptoms for (decompensated) cirrhosis mentioned in global study are having a swollen belly and swollen legs, weakness, fatigue and loss of appetite.[47] However, as the effect is linked to alcohol consumption and therefore can be avoided, SEAC think it would not be appropriate to use the highest number of avoided QALYs per person (0.25)[48], but will base the further calculations on the lowest estimate 0.08 QALY loss per person per year[49].

The value for one life year of good health (1 QALY) is estimated to be €75 000. SEAC notes that the value of the QALY is debateable. The Dossier Submitters bases the value on a measure of value of a statistical lift (VoSL) of around €1.5 million for a 40-year-old person. SEAC finds this acceptable, although notes that the value used appears somewhat low as the value per statistical life referred by SEAC is generally between €3 million and €5 million. The QALY is monetised using a WTP-based value of a QALY through survey-based research. A survey[50] conducted in ten countries estimated an overall range of mean WTP per QALY to be between $18 000 and $77 000. Hence, the value per QALY used by the Dossier Submitter (€75 000) is just above this range[51]. Lastly, SEAC notes that QALYs only reflect disease burden due to direct changes in quality of life (well-being) and not direct health costs (medicines, hospitalisation), nor loss in productivity.

Using these assumptions, the exposure of 1 300-2 500 workers in the two sectors, as identified in the questionnaire survey, would imply that 520-1 000 workers would continuously have alcohol intolerance. The cost per case per year would be 0.08 × €75 000 = € 6 000 and hence the restriction would result in total benefits per year of €3.1-6.0 million. The total cost calculated over the 15 years period using a discount rate of 4% would result in an avoided loss of €35-68 million (NPV)[52]. SEAC notes that the original Dossier Submitter estimate was approximately 15 times higher[53] than the revised SEAC estimate.

SEAC further notes that the Dossier Submitter has used a discount rate of 4 % per year. Although SEAC consider this to be an often-used practice, SEAC note that this does not take into account the income elasticity of health. As the SEA guidance recommends using a declining rate for discounting of health effects it could have been justified to use 2 % for benefits before 30 years. SEAC notes that in that case the quantified benefit values would

[47] SEAC acknowledges that more generally, Liver cirrhosis is a serious, life-threatening disease.
[48] A score of 0 means death and a score of 1 means perfect health for one year. A QALY gain of 0.08 indicates that an individual who would have had the disease after exposure to DMF will now, due to the restriction, gain 0.08 QALY.
[49] If the score of 0.25 is used the estimated benefits (also monetarised) would be approximately 3 times higher.
[50] For SEAC info: The survey was conducted in 10 countries (Netherlands, UK, France, Spain, Sweden, Norway, Denmark, Poland, Palestine and Hungary) and in total 39 922 people completed the survey (overall response rate was about 60 %).
[51] The value of $18 000-$77 000 in 2010 is approximately €15 000-€65 000 in 2018 prices (inflation 12.3 % from 2010 to 2018).
[52] To the extent the BREF process would result in similar risk reductions as the proposed restriction, only the benefits for the interim period should be included in the benefit assessment.
[53] Compared to the Dossier Submitter's low level of a QALY value of 0.08, the central value was €567. Estimating for 1 300 and 1 700 workers respectively the benefit related to cirrhosis is €500 million and €650 million.

have been estimated to €40-77 million.

Table 5. Monetarised benefits of the restriction for workers in PU-coating sector and man-made fibre sector, assumptions and estimation (15 years)

Number of exposed workers	1 300-2 500
Incidence rate – studies of workers exposed to DMF (liver effects)	40 %
Relationship between measured parameters and disease	1-1
Length of disease	1 year
Lost QALY point due to disease	0.08
Monetarisation of 1 QALY point, €	75 000
Calculation period and discount rate	15 years; 4 % (2 %)
Calculated health benefits, million €	35-68 (77)

Carcinogenicity

For carcinogenicity, the Dossier Submitter notes that DMF is not classified as carcinogenic. SEAC further notes that the study by Walrath (1989), on which basis the Dossier Submitter performed the quantification, concluded that there was no causal relationship between exposure to DMF and cancer effect. IARC[54] has classified DMF as probably carcinogenic to humans (group 2A) but even if this conclusion was based on "sufficient animal data", the evidence in humans was considered to be only limited as a positive association between exposure to *N*,*N*-dimethylformamide and cancer of the testes had been observed. However, in the Walrath (1989) study a (non-significant) negative association between exposure for DMF and cancer of the testes was found. Therefore, SEAC does not find it appropriate to include the quantification of the carcinogenic effects in the overall estimation of benefits.

Overall, SEAC concludes that the health benefit from the restriction in the PU-coating and man-made fibre industry, based on the QALY approach would be around €35-77 million (NPV) over a 15-year period. This is solely based on liver effects. SEAC acknowledges that the estimation includes large uncertainties.

Overall benefit estimation

SEAC notes that the benefits may occur also in other industries using DMF. RAC identified possible DMF related risks not to be adequately controlled for workers in the production of fine chemicals, pharmaceuticals and polymers.

Furthermore, as the QALY approach is used, neither benefits in the form of direct health costs (medicines, hospitalisation) nor in loss of productivity are taken into account.

Finally, and most importantly, SEAC underlines that any developmental impacts, although thought to be the most relevant affected human health endpoints, are left out from the quantification as there is no information on them available in the literature.

Other impacts

[54] https://monographs.iarc.fr/wp-content/uploads/2018/06/mono115-04.pdf

Summary of proposal:

The Dossier Submitter indicates that due to the termination of 50 % of PU-coating, 500-1 000 jobs will be lost and due to the termination of all production of man-made fibres, 1 000-2 000 jobs will be lost. Furthermore, the restriction could endanger additional 1 000-2 000 jobs employed by the suppliers to the man-made fibre industry.

SEAC conclusion(s):

As mentioned above, SEAC considers it unlikely that the proposed restriction will result in termination of production in the EEA. Actually, if administrative measures should be needed to reduce the time where individual workers are exposed to DMF, this could result in principle in further jobs (albeit with reduced efficiency, which in turn would be reflected in higher costs and potentially reduced competitiveness).

Due to (international) competition it will not be possible for DMF users in all sectors to transfer costs of further risk reduction measures (by increasing the prices) to their customers. However, for some products this may be possible. For instance, the man-made fibre industry has indicated that companies operating in specialised markets, for which alternative suppliers are not readily available it might be possible to transfer the (compliance) costs to their customers.

SEAC agrees, that for RO1 (the ban) impacts on costs and wider effects can be expected to be large. This is described in detail in the background document and supported by comments received via the consultation regarding the industrial gas sector (e.g. #1986), the man-made fibre sector (e.g. #2245) and PU-coating and membranes sector (e.g. #1986).

Overall proportionality

Summary of proposal:

The Dossier Submitter concludes that RO2 is proportional. The conclusion is based on a comparison of the monetised costs and benefits. The costs of the restriction proposed are described to be limited and even further reduced from the presented values in case an adjustment time is extended. The quantified benefits alone cover the costs, and non-quantifiable benefits give further support to the benefit estimation.

Alternative RMOs discussed in the proposal have been assessed to be less (or even non-) proportional.

The Dossier Submitter acknowledges, that “There exists significant uncertainty about an important number of parameters and assumptions that may affect the balance of costs and benefits” and that the results of the calculations presented therefore must be interpreted cautiously.

A complete restriction (RO1) is not considered to be proportionate by the Dossier Submitter as most of the users of DMF will be forced to relocate or even terminate their business. The risks of the use would not disappear, rather they would be shifted outside the European Union.

Since there is a lack of alternatives, authorisation (RMO3) is considered to be less proportionate than the proposed restriction (RO2). In addition, it is costly and time-consuming, for industry and for authorities and there is an uncertainty how industry would respond to RMO3.

RAC and SEAC conclusions:

RAC agrees that since there seems to be still a lack of adequate alternatives (see Background Document), RO2 is the most appropriate option for the time being to adequately control the risks.

There are several uses and occupational settings that can already use DMF in a safe way (RCR < 1). A total ban (RO1) would not differentiate between workplaces on the basis of risk and so is unlikely to be proportionate.

The implementation of ESs developed under the RO2 would direct the efforts onto the specific uses / PROCs for which adequate control is not yet achieved.

Concerning authorisation (RMO3), DMF is on the candidate list what means that DMF would have to be prioritised by ECHA and that approval of the Member States and Commission would be needed to be included in Annex XIV. This takes time and would delay the process to achieve adequate control for all uses / at all workplaces. As there are only limited PROCs / uses where adequate control cannot be demonstrated, the risk-reduction of the authorisation requirement would be limited.

Regarding effectiveness, RAC is of the opinion that the proposed restriction would be effective in risk reduction. It would address all the existing uses which are still not adequately controlled (RCR > 1) and all future uses.

For currently not adequately controlled tasks/PROCs, further RMMs have to be implemented. RAC notes that effective PPE can be used without any further delay whereas the implementation of organisational measures (e.g. job rotation) would take some time and introducing technical measures can be rather time-consuming.

SEAC notes the benefits of the restriction: 1 300-2 500 workers, that are currently exposed to DMF at their workplaces at a level which might cause (i) developmental effects to children of female workers, or (ii) liver effects, would be able to continue their work while reducing the risk for their health.

SEAC notes that one of the main benefits – avoiding reproductive and development effects - is not quantified, nor monetised.

Related to liver effects, SEAC has quantified health benefits arising from the restriction in the PU-coating, membranes and man-made fibre industry of €35-77 million (NPV) over a 15-year assessment period. Although the benefits of the restriction are evident, their quantification is uncertain. Specifically, SEAC acknowledges that the quantified benefits are likely to have been overestimated meaning that, in reality, the benefits are more likely to be towards the lower end of the range than the upper end of the range.

SEAC further notes that the restriction will also avoid exposure in other sectors where exposures might be higher than the considered DNELs.

With regard to the costs estimate, only limited information on the aggregated cost for compliance is available. The use of technical measures alone to reduce the exposure, e.g. retrofitting ventilation systems can, according to industry information, cost several million Euros. However, PPEs and administrative risk reduction measures can be implemented at relatively low cost, and more advanced/higher tier risk reduction technologies can be implemented gradually.

SEAC notes that the proposed restriction in principle follows the conventional way of ensuring that chemicals are used safely (REACH Regulation, Titles II-V). The DNEL is a calculated based on hazard data combined with factors to address variations and uncertainties for when an exposure can be considered safe. As a result, the Dossier Submitter disagrees with the

registrants on the level of exposure that can be considered safe. Hence, the proposal is developed to bring the exposure to the safe level.

Overall SEAC finds the RAC modified proposal to be proportionate, as the benefits are clear and the minimum cost estimates appear moderate.

With regard to the transitional period for implementing technical measures, SEAC notes information from the PU-coating sector that upgrading of plants to conform to the new BREF on Surface Treatment using Organic Solvents (STS) is expected in 2024. SEAC further notes potential synergies and cost savings in combining RMMs updates to reduce both external and internal exposure to DMF.

Uncertainties in the proportionality section

The overall conclusion that sufficient risk reduction can be achieved, by accepting use of PPEs and administrative measure as last options, has not been confirmed by the PU-coating and membranes nor the man-made fibre industry.

Uncertainties in RACs risk assessment regarding the present exposure are relevant for the evaluation of need to reduce exposure as there might still be other uses of DMF where risks are not adequately controlled.

As discussed in the RAC section on characterisation of risks, it is not clear whether risks actually exist in all areas covered by the risk assessment. E.g. industry organisations for PU-coating, membranes and man-made fibre industries have submitted information in the consultation that roller or brushing application (PROC 10) and hand mixing with intimate contact (PROC 19) for which the highest risk levels were identified in the considered exposure scenarios, are not current industrial practices. This causes some uncertainty to the benefit estimation; but obviously if no risks exist, no further risk reduction measures are needed, and hence no cost will occur.

It is not clear how representative the estimated avoided health effects are. For instance, it is unclear whether cirrhosis is an appropriate proxy for liver effects, what the exposure in case of no restriction would be, and what the number of diseases related to different exposure levels are and to which extent the changes in liver parameters will result in real diseases. Industry has indicated that respecting the inhalation OEL of 15 mg/m^3 they have not observed cases of diseases, apart from alcohol intolerance. These issues cause significant uncertainty to the benefit estimation. Furthermore, as mentioned above, although the main reason for the restriction is to avoid reprotoxic effects in form of developmental effects, the benefit assessment is only based on hepatotoxicity effects.

Practicality, incl. enforceability

Justification for the opinion of RAC and SEAC

Summary of proposal:

According to the Dossier Submitter, the proposed restriction is the most appropriate option with regard to implementability due to the absence of suitable alternatives for most of the uses.

According to the Dossier Submitter, based on the information received from industry, the industrial gases industry would face no difficulty under the proposed restriction because the current exposure levels are well below the proposed DNELs. However, the Dossier Submitter

states that the proposed restriction is not implementable for the man-made fibre industry neither the PU-coating industry.

Both industries currently comply with the occupational exposure limit (IOEL) of 15 mg/m³. The Dossier Submitter proposes to set a long-term inhalation DNEL of 3.2 mg/m³, which would not be economically feasible for those industries. In order to meet the proposed DNEL value, exponentially increasing investments and costs are needed according to the industry. Furthermore, both industries face fierce international competition and would not be able to pass on the increased costs on customers.

The restriction proposed is considered to be enforceable.

RAC and SEAC conclusion(s):

The current restriction proposal is limited to checks of the exposure scenarios in the safety data sheets and to check, if the site conditions (e.g. RMMs) are consistent with relevant exposure scenarios by the National Enforcement Authority. There is no new procedure related to the restriction proposal, but the same type of verification that would be done for any other substance for which there are exposure scenarios provided. From this point of view, practicability is ensured.

SEAC considers that, with the DNEL values agreed by RAC, it is likely that the proposal will be implementable for all sectors including the PU-coating and membranes and man-made fibre industries.

The costs for upgrading plants and substitution may be significant for some sectors. However, the adequate control can be achieved in the short term using PPEs and administrative measures, if higher levels measures in the hierarchy of control regime under OSH are not technically and economically feasible.

Furthermore SEAC (and RAC) find the restriction to be enforceable and monitorable. SEAC considers that there is no need for additional enforcement activities than those to be performed under the “normal REACH enforcement scheme”.

Key elements underpinning the RAC and SEAC conclusion(s):

In their advice Forum state that “… it is unclear what the companies must do to comply, and how to enforce the restriction…”. The advice focusses on new needs to measure worker exposure and DMF content in mixtures, and highlights that no analytical methods are described. Forum also state that a monitoring programme needs to be included in the restriction, in line with what was decided in the NMP-restriction.

In contrast, RAC understands that the restriction only requires using lower DNELs in the CSR, and if needed, to adjust the RMMs, and OCs, accordingly in order to meet these new DNELs. Thus, no sampling, measuring, monitoring programme, or analytical methods are needed in relation to the restriction. It is the responsibility of employers to decide within their workplace risk assessment whether also measurements are necessary to demonstrate compliance with the new DNELs.

RAC is thus of the view that the proposed restriction is as practical and enforceable as any REACH enforcement activity of exposure scenario with risk reduction measures described in the CSR and communicated by the safety data sheet. The enforcement of this restriction is the same as for any other REACH-registered substance: e.g. enforcement of REACH Article 14, Article 31 (Safety Data Sheet (SDS) content and duty for a supplier to update SDS), and Article 37 (A duty for a downstream user to identify, apply and recommend risk reduction measures if needed).

Due to the proposed restriction registrants of DMF would have to review their registration dossiers, including the Chemical Safety Reports (CSRs), and include relevant toxicological information in line with the mandatory DNEL levels. The exposure scenarios (ESs) generated have to be updated, to present safe use conditions when the DNEL values proposed in the restriction are used. Following the update of the CSR, SDSs have to be updated, to make them consistent with the CSR.

Formulators will have to update their SDSs, to include the relevant information from the CSR for the substance, including DNEL values and ESs and suppliers will have to update the SDS 'without delay'.

The end-users must identify and apply accordingly the appropriate measures to control risks. These measures are normally communicated to Downstream Users by the supplier via the SDSs. Should their use be outside the conditions described in an exposure scenario attached to SDS or for any use his supplier advises against – according to Art 37 (4) they must prepare a chemical safety report in accordance with Annex XII to REACH.

As indicated in the cost section above, SEAC and RAC find it feasible for all industries involved to reduce the exposure to the proposed level.

According to Fedustria (#1986) the coating industry is testing different options to improve the ventilation and decrease the diffuse emissions to further reduce the exposure to DMF in the near future. Measures, like fully enclosing of the head of the coating line, cleaning of the pumps in separate rooms equipped with ventilation, increasing and improving the ventilation efficiency at several places and introduction of pneumatic closed covers, are thought to look promising but will require more time to be implemented by the whole industry. However, it is expected that the combination of all the separate measures currently under investigation will bring the exposure concentrations of DMF below the proposed DNEL of 3.2 mg/m^3. SEAC understands that the described measures can be both costly and time consuming but notes that in the meantime PPE and administrative measures should be sufficient to comply with the RAC derived DNEL values.

It will for some uses also be possible to substitute DMF with another less dangerous substance. However, there is no indication on a number of users who in the short run could rather replace DMF and what the related practicalities would be.

For the man-made fibre sector, IVC has described several risk reduction measures, but indicates that most of them, e.g. automation, enclosure and increased ventilation have already been implemented in the industry. Therefore, wider use of PPE and job rotation is mostly considered.

SEAC considers that there is no need for additional enforcement activities than those to be performed under the "normal REACH enforcement scheme"[55]. The only difference is the level of the DNEL value, which is to be used in the risk assessment and which has to be communicated to downstream users. The level of the DNEL value itself does not imply changes in enforcement.

The Dossier Submitter indicated that manufacturers, formulators, industrial users and

[55] According to Article 31, and 32, a supplier of a DMF shall provide the recipient with a safety data sheet including a chemical safety report with relevant exposure scenarios (or relevant information about the substance that is necessary to enable appropriate risk management measures to be applied to ensure safe use of chemicals in case a safety data sheet is not required) which makes it possible for downstream users to identify, apply and recommend the relevant measures further downstream (Article 37). Downstream user obligations are to be enforced. Note, if use is covered by exposure scenarios set up in the safety data sheep the obligation is to apply appropriate risk management measures (RMMs) and operational conditions (OC) proposed in (extended) safety data sheet or other information received from the supplier to adequately control the risks identified.

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. In the Forum's opinion, having a monitoring program must be also part of the proposed restriction. SEAC notes, that REACH does not require monitoring programme for other substances with similar risk profiles and that setting this requirement would result in further costs.

Forum notes that in some countries the proposed restriction poses some organisational difficulties. In several Member States the responsibility for the enforcement of workplace safety and the environmental protection are split between different authorities. Thus, this workplace related restriction in REACH may lead to mixed competencies. SEAC finds that this issue is not specific for the proposed restriction, as it applies to all industrial and professional use of chemicals where workers might be exposed and SEAC does therefore not evaluate this further.

Monitorability

Justification for the opinion of RAC and SEAC

The restriction as it is proposed by the Dossier Submitter with the revised DNELs by RAC could be enforced by checks of the amendments in the registration CSR and in the extended safety data sheets.

Preparations/mixtures containing > 0.3 % DMF should be labelled as reproductive toxicants, and the labelling should thus provide information that the concentration exceeds 0.3 % and that the restriction therefore applies. However, should further verification on the concentration be needed, there are analytical methods available that are currently used for measuring DMF.

Since Registrants should provide updates to their Registration dossiers when the CSR is changed (Article 22 (g) of REACH) – as already mentioned above - it would be relatively easy to identify if this has been done by current registrants. The DNEL levels used in the new Registrations could also be easily checked.

Downstream users developing their own CSRs have an obligation to notify ECHA that their use is not covered by the CSR of the registrant (REACH Article 38 obligation). Therefore, they will be known, and their CSR can also be examined by the National Enforcement Authority.

The compliance with the requirement to include relevant DNEL values in the safety data sheets could be verified by the Member State National Enforcement Authorities, who could also verify the compliance of the downstream users with the use conditions described in the exposure scenarios attached to the safety data sheets. The evaluation of compliance with the provisions of the restriction would not differ from the verification of the compliance of the downstream users with the applicable provisions of REACH.

Summary of proposal:

Regarding the 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 in case of the proposed restriction.

RAC and SEAC conclusion(s):

SEAC notes that the proposed restriction in principle follows the traditional way of ensuring

that chemicals are used safely. Commonly applied procedures can be used.

UNCERTAINTIES IN THE EVALUATION OF RAC AND SEAC

RAC

Summary of proposal:

RAC supports the Dossier Submitter´s uncertainty analyses in the Background Document (see table below) concerning the exposure assessment.

Table 6.

	Source of uncertainty		Direction and Magnitude
Exposure Assessment	Scenario uncertainty	Descriptive errors	++
		Errors of assessment	+
		Emission sources	++
		Exposed population	+/-
		Exposure events Magnitude and frequency	+
		Efficacy of RMMs	--
	Model uncertainty	Validity domain	+/-
		Oversimplification	++
	Input parameter uncertainty	QSAR	+/-
		Vapour pressure at process temperature	++
		Effectiveness of RMMs	-
		Choice of exposure concentration	+
		Choice of PPE: gloves	+/-
		Choice of PPE: respirator	+/-
		Duration of activity	+

Legend: +, ++, +++: low, medium and high overestimation of the exposure; -, --, ---: low, medium and high underestimation of the exposure.

Besides, the Dossier Submitter noted that since there might be some overestimation of exposure, particularly in PROCs for which the RCR for combined exposure is only slightly > 1, those cases might be borderline adequately controlled.

RAC conclusion(s):

RAC notes that there are some minor to moderate uncertainties related to:

- the use of the Tier 1 model and

rather significant uncertainties related to:

- descriptive errors (including the use of PROCs which was questioned in the consultation) as well as:
- incomplete information provided by Downstream Users (e.g.:
    - the use of PROCs 10 and 19, which are according to the Registration dossier "uses advised against" as well as:
    - lack of measured workplace air concentrations for each (sub)-sector with sufficient contextual information on OCs and RMMs,
    - lack of measured dermal uptake (e.g. via biomonitoring),
    - lacking information on combined/aggregated exposure due to different tasks/activities workers have to perform throughout a working day).

However, based on the statements and measurements provided during consultation, it is quite clear that particularly the synthetic fibre industry and the PU coatings and membranes sector cannot actually comply with the proposed DNELs. Further RMMs have to be implemented (see above).

SEAC

Summary of proposal:

The major uncertainties are related to the parameters of human studies that do not allow establishing of a consistent pattern of exposure and dose-response for the increase in incidence of critical health effects. Therefore, instead of going for quantitative impacts, an (extensive) qualitative description was given along with 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 non-health-related socio-economic impacts may be subject to three types of uncertainty. First, quantitative results are only presented for the industrial gas sector, the fibre sector and the PU-coating and membranes sector. No quantitative assessment is made for other industries. Hence, presented results concern only a part of affected actors.

Second, the lack of accuracy in collected data and in the robustness of the adopted methodology introduce uncertainty. In particular, estimation of market growth rates, total market size, as well as margins, turnovers and closing costs may be subject to uncertainty. Furthermore, there is naturally uncertainty concerning the firms' reactions.

Third, received answers from companies or associations representing (inherently uncertain response of) a given industry were extrapolated to all uses, which poses uncertainty, as the exact data for non-responding companies are not known.

SEAC conclusions:

SEAC agrees that as a whole, there are very large uncertainties related to the Dossier Submitter's estimation of the socio-economic impacts of the restriction, both with regard to benefits and costs. Based on industry information RAC considered it to be possible to address the risks by use of PPEs and administrative measures. This would severely reduce the cost estimates.

SEAC notes that the PU coating sector and the man-made fibre sector continue to hold a view in the recent consultation of the SEAC draft opinion that the RAC agreed DNEL values are still challenging for the industry. Based on this view they stress the need for a higher DNEL level

(10 mg/m^3, the PU-coating sector) and for a longer (5-10 year) transitional period (the PU-coating sector) or an exemption[56] (the man-made fibre sector).

SEAC cannot judge impacts on the proportionality of allowing higher exposure than the RAC agreed DNEL values.

Key elements underpinning the SEAC conclusion(s):

The most important uncertainty is related to the possible reaction by industry, especially whether it is possible for the PU-coating sector and the man-made fibre sector to introduce further risk reduction measures and thereby avoid close-down of the production in EEA.

Moreover, the cost estimate is very uncertain, and the question of scaling from companies that have answered the questionnaire is drowning in uncertainty about cost figures for those who submitted information and for parameters which have not been taken into account.

Regarding information from other industries, SEAC notes that the cost of implementing further measures to reduce the exposure to the proposed DNEL values is summarised as it is not known which industries, and how many plants have to implement further risk reduction measures. However, as indicated above PPEs and administrative measures which can be characterised as low-cost measures can be used if other measures are not feasible to implement, especially in the short run. In the consultation of the SEAC draft opinion the man-made fibre industry repeated their original position (their comment in the consultation of the Annex XV report) that a large part of this industry would not be able to reduce the exposure to the proposed level.

Given this uncertainty, SEAC underlines that the man-made fibre sector produces a number of strategically important products, like carbon fibres for wind turbines and light weight composites for transportation.

The sector did not submit further cost information on what the costs would be due to the extended use of PPEs in combination with job rotation, however, noted that the extensive use of PPEs is not possible in practise. Similarly, part of the PU-coating industry indicated that shifts shorter than 8 hours are not acceptable for workers and PPEs like total mask and disposable clothes are uncomfortable.

In addition to the above, the quantified health benefits are also characterized by significant uncertainty. The following elements can be listed:

- Number of workers with exposure at the OEL level or higher
- Incidence rate for exposed workers due to limited information on odds ratios and exposure levels in studies used for the estimation
- Whether cirrhosis is an appropriate proxy for the effect (alcohol intolerance or elevated liver parameters). Approximately 15 % of the workers in the studies mentioned in the background document had changes in other liver parameters (elevated liver enzymes). However, it is still unclear whether measured changes in liver parameters can be interpreted as disease.

During the consultation on the SEAC draft opinion the man-made fibre industry indicated that the level of alcohol intolerance is very low, and not at all in the range of 40 % of the exposed workers as assumed in the benefit estimation. SEAC agrees that this assumption is very

[56] Actually the two sectors disagree with the proposed DNEL values. However, it is outside of SEACs remit to assess the correct level of no exposure. Therefore, only an exemption on the implementation of the necessary risk management measures is a relevant option to consider.

uncertain. It was based on average values for a number of studies which found alcohol intolerance between 11 % and 74 %, and the actual exposures were not always very clear. With the baseline of 15 mg/m^3, the incidence rate is most likely significantly lower than the 40% used in the estimation.

SEAC acknowledges that as the alcohol intolerance is an acute effect it is not expected to last for several days when there is no further exposure to DMF. If the exposure continues the effect is expected to remain.

Furthermore, following elements have not been taken into account:

- Developmental effects for exposed female workers;
- 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 have not be evaluated;
- Health benefits for DMF exposed workers outside the PU-coating, membranes and man-made fibre industry;
- Direct costs savings related to avoided health effects, e.g. in hospitals and loss of productivity.

REFERENCES

Detailed references can be found in the Background Document and its associated annex. Only new references, not indicated in the Background Document and its associated annex, are indicated below.

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