# 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/[reference code to be added after the adoption of the SEAC opinion]**

**Adopted**

20 September 2019

**20 September 2019**

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

**20 September 2019**

**[SEAC opinion number[reference code to be added after the adoption of the SEAC opinion]**

# 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 public 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 **[date of adoption of the opinion]**. **[**The deadline for the opinion of SEAC was in accordance with Article 71(3) of the REACH Regulation extended by **[number of days]** by the ECHA decision **[number and date]]**[1].

**[**The opinion takes into account the comments of interested parties provided in accordance with Article[s 69(6) and][5] 71(1) of the REACH Regulation.**]** **[**No comments were received from interested parties during the public consultation in accordance with Article[s 69(6) and][3] 71(1)**]**[6].

The opinion of SEAC was adopted **by [consensus.][a simple majority]** of all members having the right to vote. [The minority position[s], including their grounds, are made available in a separate document which has been published at the same time as the opinion**.]**[6].

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[1] Delete the unnecessary part(s)

## Contents

{to be added in the final consolidated opinion}

# 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<br>– EC No 200-679-5<br>– 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 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<br>– EC No 200-679-5<br>– 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), RAC recommends to derive a $DNEL_{(biomarker)}$ since DMF can be readily absorbed via exposed skin (see p. 16). RAC notes that biomonitoring is not needed for REACH enforcement.

## THE OPINION OF SEAC

See the opinion of SEAC

# 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 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 a 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 repro-toxicant but the most sensitive target organ is the liver.

In the proposal from the Dossier Submitter, an chronic, systemic inhalation DNEL of 3.2 mg/m$^3$ is derived for workers based on decreased body weights, 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 weights, 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 public consultation (with 10 being used), indicate 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 decreased 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 the liver toxicity, the clear effects at 950 constitutes a LOAEL, and 475 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). 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 dermal exposure of adult animals.

A NOAEL on 215 mg/kg/day after 30 days 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 setting 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 it covers a too long time period. 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 the

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 top 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 a likely 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 to 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 to 100 mg/kg/day (the LOAEL) is about 40 mg/kg/day. Thus, both malformation profile and overall potency seems 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**

Dermal toxicity

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 DS (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 overlapbetween the different work stations. 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 work stations (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 2 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$^3$, show 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 also was 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) has, provided a meta-analysis of 21 studies in the public consultation, where the effect of DMF exposure on liver function in workers has been studied (#2005; later corrected and a substantially revised version was 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 simply is 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 public 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, RACis 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 public consultation (#2036, #2258) have 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)*"[2].

**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

[2] https://echa.europa.eu/de/-/advice-on-how-to-comply-with-nmp-restriction

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[3], 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 public 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 public consultation. Therefore, there are no relevant uncertainties related to this sub-sector.

The relevance of PROC 19 was not addressed during the public 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[4] 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

[3] PROC 19 – Manual activities involving hand contact;
[4] PROC 10 – Roller application or brushing;

Registration dossier[5].

Besides, industry clarified during the public consultation that the synthetic fibre industry is covered 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 the majority of processes is batch process, PROC 2[6] or PROC 5[7] 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 public consultation, several companies, particularly related to the PU coatings and membranes sector[8] 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[9] 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 of 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 public consultation would have been provided to the Dossier Submitter at an earlier stage, i.e. before or during the preparation

[5] 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".
[6] PROC 2 - Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
[7] PROC 5 – Mixing or blending in batch processes;
[8] 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.
[9] 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.

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 RMMs (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[10], 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.

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

Further, the measured data provided through the public 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 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 public 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[11] do occur and that in the textile coating industry PROC 5, PROC 8a[12] and PROC 13[13] 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[14]) 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 public 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[15], 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[16], PROC 4 and PROC 8a were used in the modelling but not PROC 28[17] 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

[11] PROC 8b - Transfer of substance or mixture at dedicated facilities;
[12] PROC 8a - Transfer of substance or mixture at non-dedicated facilities;
[13] PROC 13 – Treatment of articles by dipping and pouring;
[14] PROC 9 – Transfer of substance or mixture into small containers;
[15] PROC 15 – Use as laboratory reagent;
[16] PROC 3 - Manufacture of formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
[17] PROC 28 - Manual maintenance or machinery;

DMF vapours[18]. That means that for semi-open processes with elevated temperature, the dermal exposure might be underestimated. This fact was addressed by Industry in the public 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 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.

[18] The operating temperature and the associated vapour pressure have only been taken into account for the inhalation route.

**Table 2: Risk characterisation, based on the DNEL values proposed by the Dossier Submitter[19]**

| Identified use | Process Category (PROC) | RCRs[20] | | | 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.<br><br>Risks may not be sufficiently controlled. |
| | Combined exposure:<br><br>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.<br><br>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.<br><br>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.<br><br>Risks may not be sufficiently controlled. |

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

[20] 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[20] | | | 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.<br><br>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.<br><br>Risks may not be sufficiently controlled. |
| | Combined exposure:<br><br>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.<br><br>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.<br>Since no information on combined exposures has been made available, unacceptable risks may be relevant.<br><br>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:<br><br>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:<br><br>PROC 9 and PROC 10 | 0.69 | **0.935** | **1.625** |

For two scenarios with RCRs > 1, no concern is assumed either based on a low RCR and conservative exposure assessment ("Manufacture of substance") or additional information provided in the public consultation ("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[21],

[21] 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)[22],
- 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 public 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 in the RAC-49 meeting.

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 a 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.

[22] 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.

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

- 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 a 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 public 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 than these in real workplace situations resulting in not adequately controlled 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 and 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 work day is uncertain. Biomonitoring data would have been helpful in those assessments. | ↑ |

## Evidence if 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 public 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[23] such as wet and dry spinning) not being able to comply with the proposed DNEL for the inhalation route 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 if 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 on 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 reach adequate control of 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 if 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

[23] 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).

an 8 hours shift with sufficient contextual information to be sure how to interpret these data) that the implemented RMMs are not sufficient.

**RAC conclusion(s):**

The use of DMF is currently not adequately controlled in all occupational settings, since according to RAC occupational exposure might exceed the DNELs for reproductive toxicity 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[24] 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:**

According to the Dossier Submitter, there is strong evidence that DMF might be used in all EU Member States. Therefore, the protection of human health from the adverse effects of DMF (e.g. reprotoxic effects) is needed on Union wide basis.

**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 are 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 also confirmed in the public 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 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

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

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

### Justification for the opinion of SEAC and RAC

### Scope including derogations

### Justification for the opinion of RAC

#### Summary of proposal:

The restriction proposed by the Dossier Submitter is based on imposing a harmonised systemic long term DNEL[25] for the inhalation route and a harmonised systemic long term DNEL for the dermal route in an Annex XVII entry (RMO 2).

This entry would address the identified risks for human health in the workplace on 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 did not foresee any derogations but they 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 public consultation the PU coatings and membranes sector asked for 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.

In general, a transition period of two years is recommended. The concentration limit of DMF should be 0.3 %

#### 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.

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 public 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.

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[25] 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.

[26] Specific concentration limits 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 an identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous.

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 is obligatory to protect workers and adequately control the risk (RCR < 1). 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 public consultation, RAC has the impression 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 take some time to be implemented.

**Justification for the opinion of SEAC**

**Summary of proposal:**

Add summary of Dossier Submitter proposal from the Impact Assessment section of the Annex XV restriction report.

**SEAC conclusion(s):**

Add conclusion of SEAC

**Key elements underpinning the SEAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

## Effectiveness in reducing the identified risks

## Justification for the opinion of RAC

**Summary of proposal:**

The Dossier Submitter identified three different risk management options:

- RMO 1: 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.

- RMO 2: The proposed restriction (see section above)
- RMO 3: Authorisation:

  The risk reduction capacity is considered to be lower if the socio-economic-route will be brought forward. In case the adequate control route will be followed, the risk reduction capacity will be the same as for RMO 2 since exposure will be reduced below the proposed DNELs.

**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

| Guidance[11] |
| --- |
| Give an evaluation of the socio-economic impacts of the proposed restriction and of the other restriction options. This evaluation takes into account the available information on availability and technical and economic feasibility of alternatives and available socio-economic assessment of the proposed restriction documented under the Impact Assessment section of the Annex XV restriction report. |

### Justification for the opinion of SEAC

#### Costs

**Summary of proposal:**

Add summary of Dossier Submitter proposal from the Impact Assessment section of the Annex XV restriction report.

**SEAC conclusion(s):**

Add conclusion of SEAC

**Key elements underpinning the SEAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

**Benefits**

**Summary of proposal:**

Add summary of Dossier Submitter proposal from the Impact Assessment section of the Annex XV restriction report.

**SEAC conclusion(s):**

Add conclusion of SEAC.

**Key elements underpinning the SEAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

**Other impacts**

**Summary of proposal:**

Add summary of Dossier Submitter proposal from the Impact Assessment section of the Annex XV restriction report.

**SEAC conclusion(s):**

Add conclusion of SEAC.

**Key elements underpinning the SEAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

**Overall proportionality**

**Summary of proposal:**

DMF is a high tonnage substance, with a registered tonnage band of 10 000 to 100 000 tonnes used per year in the EU. DMF is used primarily as a solvent in the production of fine chemicals, pharmaceuticals, polymers, textiles, leather and fur, in the manufacture of non-metallic mineral products, perfumes/fragrances, in the petrochemical industry and as a laboratory agent.

A complete restriction (RMO 1) is not considered to be proportional by the Dossier Submitter as most of the user of DMF will be forced to relocate or even terminate their business. Besides, the risks will be shifted outside the European Union.

Since there is a lack of alternatives, authorisation (RMO 3) is considered to be less proportional than the proposed restriction (RMO 2). In addition, it is costly and time-consuming, for industry and for authorities and there is an uncertainty how industry will respond to RMO 3.

The Dossier Submitter concludes the (proposed) RMO 2 to be proportional.

**RAC and SEAC conclusion(s):**

RAC agrees that since there seems to be still a lack of adequate alternatives (see Background Document), RMO 2 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 (RMO 1) would not differentiate between workplaces on the basis of risk and so is unlikely to be proportionate.

The implementation of ESs developed under the RMO 2 would direct the efforts onto the specific uses / PROCs for which adequate control is not achieved yet.

Concerning authorisation (RMO 3), 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 few PROCs / uses where adequate control cannot be demonstrated, the risk-reduction of the authorisation 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.

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

N.A.

**Uncertainties in the proportionality section**

N.A.

### 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.

**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.

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

In their advice FORUM states that *"… it is unclear what the companies must do to comply, and how to enforce the restriction…".* The advice focus 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 other exposure scenarios 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 (SDS content and duty for a supplier to update SDS), and Article 37 (Duty for a downstream user to identify, apply and recommend if needed risk reduction measures).

### 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 can 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 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 are 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:**

Add summary of Dossier Submitter proposal from the Impact Assessment section (Other impacts, practicality and monitorability) of the Annex XV restriction report.

**RAC and SEAC conclusion(s):**

Add conclusion of RAC and SEAC.

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

Add analysis that justifies the conclusion given above[12], including relevant elements from the Forum's advice.

## 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 XXX:**

| | 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 PROCs for which the RCR for combined exposure is slightly > 1, might be 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 public 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 public 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).

**Key elements underpinning the RAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

**SEAC**

**Summary of proposal:**

Add summary of Dossier Submitter proposal from the uncertainties section of the Annex XV restriction report.

**SEAC conclusion(s):**

Add conclusion of SEAC.

**Key elements underpinning the SEAC conclusion(s):**

Add analysis that justifies the conclusion given above[12]

## 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.*

Bide *et al.*, 1997, Estimation of human toxicity from animal inhalation toxicity data: Minute volume-body weight relationships between animals and man. Defence research establishment Suffield, Ralston, Alberta, Canada. Suffield report 673.

ECETOC TRA, 2018, Technical report No. 131, Targeted Risk Assessment: Further Explanation of the Technical Basis of the TRA v3.1, Brussels, February 2018, ISSN-2079-1526-131.

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