Committee for Risk Assessment (RAC)

Opinion

on an Annex XV dossier proposing restrictions on

1-Methyl-2-pyrrolidone

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

Adopted

5 June 2014

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Opinion of the Committee for Risk Assessment

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 on the proposal for restriction of

Chemical name(s):	***1-Methyl-2-pyrrolidone***
EC No.:	212-828-1
CAS No.:	872-50-4

This document presents the opinion adopted by RAC, while the Background Document (BD) supports both the RAC and SEAC opinions, providing further details.

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV report conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at ***http://echa.europa.eu/web/guest/restrictions-under-consideration*** on ***18 September 2013***. Interested parties were invited to submit comments and contributions by ***18 March 2014***.

ADOPTION OF THE OPINION OF RAC:

Rapporteur, appointed by RAC: **Bert-Ove Lund**

Co-rapporteur, appointed by RAC: **Thomasina Barron**

The RAC opinion as to whether the suggested restrictions are appropriate in reducing the risk to human health and/or the environment has been reached in accordance with Article 70 of the REACH Regulation on 10 December 2013.

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

The RAC opinion was adopted by consensus.

OPINION

RAC has formulated its opinion on the proposed restriction based on information related to the identified risk and to the identified options to reduce the risk as documented in the Annex XV report 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-methylpyrrolidone*** is the most appropriate EU wide measure to address the identified risks in terms of the effectiveness in reducing the risks provided that the scope and conditions are modified.

The conditions of the restriction proposed by RAC are:

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

The Forum has noted the amended proposed text of the restriction, and suggested some refinements. However, as the RAC opinion presents only the conditions of the proposed restriction (see above), the suggested refinements were not introduced. Instead, the Forum advice will be made available to the Commission.

JUSTIFICATION FOR THE OPINION OF RAC

IDENTIFIED HAZARD AND RISK

Description of and justification for targeting of the information on hazard and exposure

According to the dossier submitter, the restriction proposal is focused on occupational health, as a harmonised classification proposal[1] (which was adopted by RAC at its 29th meeting[2]) is thought by the dossier submitter to result in the cessation of all consumer use because of the proposed lowering of the specific concentration limit to a level that would then make it a subject of entry 30 of Annex XVII of REACH.

Restriction Description of the risk to be addressed by the proposed restriction

Information on hazard(s)

The toxicological data base for NMP is rather extensive even if focused on the two endpoints with relevance for this restriction proposal. There are twelve repeated dose toxicity studies described in the report (7 oral, 4 inhalation, and 1 dermal). For the assessment of developmental toxicity, the report describes four 2-generation studies (3 oral and 1 inhalation), as well as 7 developmental toxicity studies (3 oral, 2 inhalation, and 2 dermal). Most studies are conducted on rats, but there are a few on mice, rabbits, and dogs as well.

RAC agrees with the dossier submitter on the choice of the key studies, for which DNELs were derived. The overall conclusion based on the 17 rat studies is that the most sensitive effect of NMP concerns a decreased body weight gain, both in adults and offspring.

The key studies, for which the 'leading' DNELs were calculated, are described below, based on the summaries in the restriction proposal. These summaries are followed by the RAC assessment of the studies.

The 90 days inhalation study in rats as the basis for the worker inhalation DNEL (BASF AG 1994 (also referenced as Lee 1987 in the report)

RAC assessment: A NOAEC at 500 mg/m^3 was determined based on a statistically non-significant decrease in body weight gain of 4.8% in male rats at 1000 mg/m^3 at day 33 in a 90 days study (BASF, AG 1994). Although the decreased body weight gain was only statistically significant on day 33 (-9%) at 3000 mg/m^3, an apparent dose-response for the reduced growth rate was indicated at the time points studied (day 12, 33, 61 and 96). However, there were no signs of effects on the body weight gain of females, which perhaps could be interpreted as an inconsistency. However, also in the 2 year inhalation study (Lee et al, 1987), body weight was affected only in the males (a 6% reduction in body weight gain at 400 mg/m^3). There is no information given on body weight in the reporting of the 28 days inhalation study (Lee et al, 1987), but it is noted that excessive mortality was observed at 1000 mg/m^3. The effect on male body weight gain thus seems consistent and substance-related, although slight. Of these studies, the 90 days study is the most, and perhaps only, reliable study, as it used head-nose exposure, whereas the others used whole-body exposure, thus resulting also in oral exposure via grooming. The suggested

[1] Classification, Labelling & Packaging Regulation (EC) 1907/2006

[2] Subject to a decision to implement by the Commission

NOAEC of 500 mg/m^3 is very conservative, and a more robust, alternative NOAEC from this study would be 1000 mg/m^3, based on the statistically significant 9% decrease in body weight at 3000 mg/m^3. It is noted that when the NOAEC of 500 mg/m^3 is not used a study with inhalation exposure of human volunteers (local irritation at 80 mg/m^3) would give a DNEL lower than the one calculated based on the 'new' NOAEC of 1000 mg/m^3. However, since the pregnant worker DNEL is the overall lowest DNEL and the one used in the RAC risk characterisation, other DNELs were not calculated.

The 28 days dermal study in rabbits as the basis for the worker dermal DNEL (GAF Corp. 1986)

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

The inhalation developmental toxicity study in rats as the basis for the pregnant worker inhalation DNEL (Sallenfait 2001)

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

The dermal developmental toxicity study in rats as the basis for the pregnant worker dermal DNEL (FDRL 1979)

RAC assessment: The rat dermal developmental toxicity study showed clear evidence of

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

Discussion of relevance of health effects observed

It is quite clear that one of the most sensitive endpoints of NMP in all species and all studies is a decreased body weight (of males, females, and pups). Therefore, it is difficult to assess the contribution of maternal toxicity in the evaluation of developmental toxicity. The maternal effect in the Saillenfait studies is described in the BD as a "transient decrease in body weight gain and food consumption". Body weight gain GD 6-21 minus gravid uterine weight is the most representative measure considering the decreased pup body weights, and although there is a decrease, it is not statistically significant. Thus, the rats weighed roughly 235 g at day 0, and whereas the controls gained 32 grams, the high dose dams gained 26 gram. It seems very unlikely that this small difference could explain the decreased pup body weights, and the pup effect is therefore not likely to be a secondary unspecific effect of maternal toxicity. In the second key inhalation study, Solomon et al 1995, a similar decrease in pup body weight (as in Saillenfait 2001) is observed at a similar exposure level. However, in this case without any effects on the maternal body weight, supporting that the effects on the pups are a direct effect and not a secondary unspecific effect of maternal toxicity. There is also one oral developmental study (TSCAT 1992a) with effects on pup body weights without statistically significant effects on the dams.

As regards the human relevance of the experimental animal data, it has to be assumed that the animal data is relevant for extrapolation to humans, and there is no data to contradict this assumption. Thus, an effect on fetal growth is expected to be the most sensitive endpoint in humans, and perhaps also the only relevant effect at the exposure values presented below. An average decreased birth weight of 5%, remaining at least until weaning, was observed in the rats at the LOAEC, which in general represents a distribution among the affected animals with some not affected at all and some affected more than 5 %. A low birth weight, defined as a weight <2.5 kg at birth, has in humans been correlated to impaired development (of e.g., the neurological or immune system) and with adult conditions such as type 2 diabetes and hypertension. However, it is generally difficult to draw firm casual links between a low birth weight and a subsequent condition. Thus, it is not possible to translate the decreased birth weight observed in the animal studies into an expected outcome in humans, but rather conclude that a decreased birth weight in general may be a disadvantage for the later development of the baby and/or adult health of the individual concerned. More severe effects can occur in animals at higher NMP exposure levels, but these exposure levels would likely represent rather unusual human exposure situations such as; oral ingestion of NMP; perhaps spraying 180 degree warm NMP (which is advised against in the registration); or by continually contaminating hands and arms with liquid NMP. Thus, at the observed exposure levels, the risk most likely concerns a decreased birth weight.

Calculation of DNELs

Based on the above NOAELs and NOAECs, long-term DNELS were calculated by the dossier submitter using assessment factors for:

Interspecies differences – factors were set according to the REACH guidance (Guidance on information requirements and chemical safety assessment – Chapter R8: Characterisation of dose [concentration]-response for human health, 2012). A factor of 2.5 was used for remaining differences (toxicodynamics), both for the inhalation and dermal routes. A factor of 4 was used for allometric scaling (toxicokinetics) in the calculation of the dermal DNEL, whereas no allometric scaling is needed according to the guidance for the inhalation DNEL.

However, if substance-specific data is available, the default assessment factors may be adjusted. Toxicokinetic studies indicate that humans do not show higher plasma NMP levels than rats following inhalation exposure. On the contrary, there are indications that the levels in humans would actually be lower than in rats, which potentially could justify a reduction in the inter-species factor for differences in kinetics. However, quantification of this difference is difficult, because of e.g., large individual differences among humans as well as rats, and that the plasma concentration in the low dose rat study represents NMP and metabolites whereas human plasma levels only represent NMP (and not metabolites). The RAC supports the interpretation of the data made by the dossier submitter, and concludes that there might be an additional margin of safety for humans caused by differences in kinetics, but that this difference cannot be quantified and translated into an adjusted assessment factor.

Intraspecies differences – the factor for workers (5) was set in line with the REACH guidance. The guidance does not specifically mention pregnant workers, but the dossier submitter used a specific assessment factor for pregnant workers based on the argument that the children whom the restriction is meant to protect belong to the general population rather than to the workers. Therefore, for pregnant workers the assessment factor normally used for the general population (i.e., 10), was used. As mentioned above, there is no specific guidance concerning pregnant workers, and although many RAC members were sympathetic towards the line of reasoning proposed by the dossier submitter, it was noted that a strict interpretation of the guidance would lead to using an assessment factor of 5 also for pregnant workers. Deviating from the guidance without having a scientific basis for doing so would not be justified and could lead to inconsistencies between opinions For reference purposes, the DNELs and RCRs representing both the dossier submitter's and RAC's recommendation are presented in the opinion but only those of RAC are used.

Study design versus human exposure situations – modification of the dose descriptors and corrections of study durations were done in line with the REACH guidance.

Inhalation exposure
The Dossier Submitter has proposed to use for derivation of DNEL a NOAEC of 500 mg/m^3 based on the 90 day inhalation study, with decreased body weight gain as a relevant effect. The resulting DNEL value would be 10 mg/m^3. The RAC notes that this NOAEC is a very conservative one, because the effect at the next higher concentration (1000 mg/m^3) was very slight and not statistically significant.

The RAC proposes that a more robust worker inhalation NOAEC based on this study would be 1000 mg/m^3 (based on a statistically significant effect on the body weight at the next higher concentration), resulting in a DNEL of 20 mg/m^3. This DNEL was used in calculating RCRs in table 2 below. It is noted that the local irritation observed at 80 mg/m^3 in human volunteers in the Bader et al (2007) inhalation study would give a DNEL (16 mg/m^3) similar to, although slightly lower than, the one calculated based on the selected NOAEC of 1000 mg/m^3. No RCR-calculations were, however, performed using this DNEL as the RAC was of the view that the 'pregnant' worker DNEL should be used for all workers.

The NOAEC proposed for pregnant workers (247 mg/m^3), based on developmental toxicity study demonstrating decrease of the fetal body weight, is supported by the RAC, but the RAC has re-calculated the DNEL for pregnant workers based on an assessment factor of 5 for intraspecies differences (rather than 10 as proposed by the dossier submitter), resulting in an inhalation DNEL of 10 mg/m^3 rather than the proposed DNEL for pregnant workers of 5 mg/m^3.

Dermal exposure
The dossier submitter proposes a NOAEL on 826 mg/kg/day for workers based on a dermal 4 weeks study in rabbits, where 1 out of four rabbits died at the next higher (i.e., the top) dose. For pregnant workers a NOAEL on 237 mg/kg/day (based on a dermal developmental toxicity study demonstrating fetal toxicity and malformations) is proposed based on a

dermal developmental study in rats with clear toxic effects at the next higher (i.e., the top) dose. Based on these NOAELs, DNELs on 4.6 and 2.4 mg/kg/day were calculated.
The RAC supports the NOAELs as such, but has re-calculated the DNEL for pregnant workers based on an assessment factor of 5 for intraspecies differences (rather than 10 as proposed by the dossier submitter), resulting in a dermal DNEL for pregnant workers of 4.8 mg/kg/day (using assessment factors of 2.5x4x5). It is noted that the dermal DNELs for workers and pregnant workers are almost identical, but considering the uncertainty concerning the rabbit study that is the basis for the worker DNEL (the substance-relationship for the single death can be questioned by the lack of signs of toxicity on the three surviving animals), RAC is of the opinion that the dermal DNEL of 4.8 mg/kg/day is the more robust DNEL.

In the opinion of RAC, the DNELs calculated for pregnant workers should be used for all workers. Thus, the alternative DNELs supported by the RAC can be seen (in bold) in the right hand column in table 1 below, i.e., an inhalation DNEL of 10 mg/m^3 and a dermal DNEL of 4.8 mg/kg/day.

Table 1. Long term inhalation and dermal DNELs for workers and pregnant workers, as proposed by the dossier submitter and calculated by the RAC, respectively.

	Dossier proposal		DNEL based on AF=5	
	Workers (AF=5)	Pregnant workers (AF=10)	Workers	Pregnant workers
Inhalation DNEL (mg/m^3)	10	5.0	20	**10**
Dermal DNEL (mg/kg/day)	4.6	2.4	4.6	**4.8**

Considering that the leading health effect is related to reprotoxic properties of the substance, RAC did not consider it as necessary to develop DNELs for short-term exposure.
In addition, even though the substance is volatile, it does not have significant acute toxicity that would justify such a short term value.

The equivalent DNELs used in the registration dossiers by Industry were 40 mg/m^3 for inhalation (based on the iOEL recommended by the SCOEL, 2007) and 19.8 mg/kg/day for the dermal route.

The iOEL recommended by the SCOEL is set based on NOAECs for developmental toxicity in the range of 206-500 mg/m^3. The SCOEL applied an uncertainty (assessment) factor of 5 on the lowest NOAEC of 206 mg/m^3 (Solomon et al 1995), giving an iOEL of 40 mg/m^3. The reasons for choosing the factor 5 were not given. The inhalation DNEL proposed by the RAC is based on the same studies, but using the Saillenfait study (2001) as the starting point (NOAEC 247 mg/m^3). Assessment factors (2.5x5) and dose corrections ((6/8)x(6.7/10)) as recommended by the REACH guidance have been applied. The assessment factors are for remaining differences in sensitivity (2.5) and for intraspecies differences (5). The NOAEC is corrected for the animal exposure being 6 hours per day in contrast to an 8 hour working day, and for different inhalation volumes for rats at rest (6.7 m^3) and humans at light work (10 m^3).

Under the provisions of worker protection legislation, dermal occupational exposure limits are not established. A skin notation is included with the OEL for NMP.

Information on emissions and exposures

There is a significant variety of uses of NMP, and the number of occupational settings where NMP is used is therefore very large, as is the number of workers potentially exposed to NMP.

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

It is impossible to get detailed exposure information from all these, possibly, thousands of occupational settings, covering all workers. Therefore, the Background Document is based on the registration dossiers using modelled data, developed with first tier assessment tool EasyTRA 3.5. The use of modelled data may better reflect the exposures resulting from use of a substance in a wide variety of industrial and professional settings, in many countries. The registration dossiers demonstrate safe use in most scenarios with the 1st tier exposure modelling tool, and refinement using more detailed, higher tier models was pursued in very few cases (Table B.70 – non-wire coating and Table B.80 – agrochemicals). Some measured data is available and discussed in the restriction dossier, but it is difficult to know how representative measured data are for such a widely used substance.

The most reliable exposure estimates available are those from the registration dossier. According to the registration information referred to in the Annex XV restriction dossier, local exhaust ventilation (80, 90, or 95% efficiency) is used in some scenarios but not in others. The duration of exposure varies between 1 and 8 hours. The concentration (weight fraction) is normally set at 1, but in a few cases 0.5 or 0.25 was used (where mixtures would be used). Gloves with either 80 or 95% protection efficiency are used in some exposure scenarios, but there are also scenarios where gloves are not used. Respiratory protective equipment is not used in any of the scenarios. Overall, the impression is that the registrants have tried to describe the exposure scenarios reflecting current working practices as far as possible.

For industrial uses, the inhalation exposure levels ranged from 0.04 to 20.65 mg/m^3 and dermal exposure ranged from 0.03 to 5.49 mg/kg bw/day. For professional uses, the exposure levels ranged from 2.97 to 20.65 mg/m^3 for inhalation and from 0.14 to 5.38 mg/kg bw/day for dermal exposure.

Some information on exposure and working conditions has been provided during the public consultation, especially from a few companies in the wire coating and battery sectors, but the information does not in general contradict the current exposure assessment. However, some comments indicate routine use of respiratory protective equipment. It is noted that the wire coating sector is considered to use a very large share of the total volume of NMP in Europe. This sector claimed to have significant difficulties with reducing exposure to the DNEL levels.

The RAC is of the opinion that the exposure estimates presented in the restriction dossier can be used as the basis for the risk characterisation, because the modelling seems sufficiently adequate and may acceptably represent the average conditions of a high number of occupational settings.

The substance evaluation process may provide an opportunity to collect measured exposure data from a number of occupational settings. This data may provide a basis for a better risk

assessment, but is not a risk management option as such.

Characterisation of risk(s)

Based on the DNELs presented above, calculated by the dossier submitter and the RAC, respectively, and the exposure estimates from the registration dossier, RCRs are calculated and presented below in table 2. It is concluded that the RCR values for workers and pregnant workers are >1 for most scenarios. More specifically, using the DNELs calculated by RAC, 12 and 13 out of 15 scenarios for workers and pregnant workers, respectively, have RCRs>1. The contribution from the inhalation route is generally higher than that from the dermal route, and the combined exposure gives RCR that range between 0.3 and 2.6 for pregnant workers, with the majority of them above or around 2. For workers, and using the alternative inhalation DNEL proposed by RAC, the combined exposure gives RCR that range between 0.2 and 1.6, with 12 of 15 scenarios exceeding an RCR of 1.

The higher alternative RCRs (based on the standard AFs) for pregnant workers than for workers is a result of getting lower NOAELs/NOAECs in reproductive toxicity studies than in conventional long term studies. **In the opinion of RAC, the DNELs calculated for pregnant workers based on developmental toxicity studies should be used for all workers.** This is also the approach used by SCOEL in setting their inhalation iOEL for NMP based on developmental toxicity studies.

Table 2. RCRs as calculated in the restriction proposal and RCRs calculated by the RAC. In both cases, the RCRs represent combined exposure via inhalation and the dermal route.

	Combined RCRs in DS proposal		**RAC derived RCRs**	
	Workers	**Pregnant workers**	**Workers**	**Pregnant workers**
Industrial uses				
Manufacturers	1.39	2.77	0.77	1.38
Charging and discharging	2.33	4.61	1.47	2.31
Chemical industry processes	2.22	4.42	1.18	2.21
Formulation	2.66	5.27	1.63	2.64
Coating processes	2.25	4.46	1.32	2.23
Cleaning processes	2.25	4.46	1.32	2.23
Laboratory use	0.28	0.56	0.17	0.28
Functional fluids	2.02	3.94	1.60	1.97
Construction chemicals	1.61	3.18	1.40	1.59
Professional uses				
Charging and discharging	2.33	4.61	1.47	2.31
Formulation	2.33	4.61	1.47	2.31
Coating process	1.74	3.46	1.02	1.73
Agricultural chemical industry	1.70	3.30	1.44	1.65
Laboratories	0.49	0.97	0.28	0.48
Functional fluids	2.44	4.84	1.40	2.43

In some cases, according to the modelling being used, the RCRs could be reduced below 1 by considering additional RMMs (such as extraction ventilation or respiratory protective equipment), or change of duration of exposure (currently assumed to be 8 hours a day in most scenarios).

While it is noted that the modelling used is likely to be of a conservative nature (a first tier modelling tool is used) and may have overestimated the exposure, there is a significant number of occupational settings using NMP, therefore the exposure assessments are likely to be relevant for some, or even many, of these settings.

The DNELs for the pregnant workers are robust, and the concern for (pregnant) workers is hence supported by RAC.

It is therefore concluded that the risk characterisation shows that risks for (pregnant) workers are not sufficiently controlled, and that the risk assessment shows that further risk management measures (than those expressed to be used in the registration dossier) are needed.

JUSTIFICATION THAT ACTION IS REQUIRED ON AN EU WIDE BASIS

The large number of different uses of NMP, the large number of occupational settings in many different EU member states where NMP is used, and the large number of workers potentially exposed to NMP are reasons for community-wide action. Furthermore, it is noted that although there is an indicative occupational exposure limit (iOEL) proposed on the EU level, the national OELs vary greatly (10-fold) indicating varying levels of protection among workers in the EU, as described in the Background Document. Conditions as proposed in the restriction would be identical and applicable in all Member States, ensuring uniform level of protection to the population at risk through the European Union.

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

The baseline

The baseline with which to compare the Risk Management Options (RMOs) below is that no restrictions on the use of NMP would be implemented. This would mean that the national OELs, implementing the EU iOEL of 40 mg/m^3, would remain as the main risk management measure. However, they vary between 20 and 200 mg/m^3, which can be compared with the DNEL of 10 mg/m^3 as proposed by the RAC.

No additional enforcement or monitoring would be conducted and no further risk management measures would be introduced. When compared to the RAC DNEL, based on the REACH methodology, the current OELs set in Member States are not sufficient to protect workers.

The baseline situation is therefore that the existing legislative framework, does not require further reduction of exposure of workers and considering that most RCRs are >1, the baseline situation will not be effective in reducing the risks (zero effectiveness). It is possible that some registrants would voluntarily introduce the RAC DNEL. However, as it would not be a mandatory requirement, this cannot be taken into account.

Risk Management Option (RMO) analysis

The Background Document discusses several different risk management options. A brief analysis of these options, presenting their effectiveness, enforceability and monitorability is given in Annex I.

It should be noted that of all the options presented, the RAC is of the view that the DNELs proposed by the dossier submitter should be replaced with an inhalation DNEL of 10 mg/m^3 and, where applicable, a dermal DNEL of 4.8 mg/kg/day should be used.

The following is therefore an analysis of the dossier submitter's proposal and the amended RMO 3, recommended by the RAC.

The restriction proposed by the dossier submitter

The restriction proposed by the dossier submitter is based on imposing a harmonised inhalation exposure limit and a general requirement to protect against dermal exposure in the annex XVII entry.

Advantages

The inhalation exposure limit should be applied in all sectors and for all uses, and is expected to be effective, although only after the proposed 5 years delay of entry into force. Enforcement will focus on compliance with the air concentration limit (as this is included in the wording of the proposed restriction) and is to be established by air monitoring. The obligation imposed by the restriction (to have exposure below the exposure limit) is on the users of NMP, not the registrants.

Article 31(9) of REACH requires updating of safety data sheets (and their annexes containing exposure scenarios) once a restriction has been imposed by clearly stating the new exposure limit.

In addition, Annex I, paragraph 0.5, states that the registrants have to take into consideration 'where available and appropriate, an **assessment** carried out under Community legislation (…)', and reflect it in the CSR.

With reference to Annex I, the RAC opinion and the DNELs proposed therein can be considered to represent an assessment, and registrants therefore have to take the DNELs into consideration in their CSR. This may result in registrants amending the DNEL used in their CSRs (by choosing the RAC DNELs for inhalation and dermal effects), or providing a justification as to why they do not consider it appropriate to do so. If they would use the DNEL derived by RAC, it may lead to recommendation of enhanced (compared to currently used) risk management measures in the exposure scenarios annexed to the safety data sheets. This would not directly aid the enforcement of the restriction itself (an exposure level) but would likely assist the users to comply with the exposure level and lead to a human health benefits.

Disadvantages

The Forum has identified some issues concerning air monitoring and chemical analysis, both with regard to defining methods (different methods are available) and with regard to a perceived lack of experience in enforcement of OELs among REACH enforcers.

The DS proposed to include a general requirement to protect against dermal exposure, similar to the requirements under the chemical agents directive. Thus, dermal exposure should be avoided according to the proposal, but the Forum has pointed out that this may cause enforceability problems as it is unclear what avoidance means (using gloves, zero dermal exposure, or other limit values?).

In addition, it is noted that binding OEL values are developed under worker protection legislative framework, as discussed in Annex I, thus imposing effectively a REACH-equivalent to a binding OEL in contradiction to an existing OEL (under OSH legislation) could cause confusion amongst the users of the substance.

The modified RMO 3 proposed by RAC

The RAC has modified RMO3[3]. According to this modification, the entry in Annex XVII would state that the inhalation and dermal DNELs set by RAC shall be used by existing registrants (requiring updating of their CSRs), by new registrants, and by downstream users in their CSRs.

Advantages

In contrast to the restriction proposed by the dossier submitter and other RMOs proposing use of an inhalation DNEL (RMO2b and RMO3), RAC proposes to also include the dermal DNEL in the restriction wording. It would high-light the need to protect against dermal exposure and the exposure scenarios would then have to suggest concrete and use-specific risk management measures to reduce the dermal exposure (e.g., engineering controls or type and thickness of gloves limiting exposure potential). While the dermal risk management measures recommended may not be different than those used when applying the chemical agents directive (or requiring avoiding dermal exposure), it is an advantage from a risk and enforcement point of view to assess the risk in a quantitative manner and have the dermal risk management measures specified in the exposure scenarios.

Additional advantages are that:

- the use of RAC-developed DNELs in updating of the CSRs should ensure that risk management measures, for inhalation and dermal exposure, defined on the basis of a quantitative assessment, are introduced / recommended for all uses until the RCR is below one,

- this option will not require other enforcement approaches than those currently in place for enforcing registration requirements related to CSRs and implementation of ESs in different member states, and

- that monitorability can be ensured by primarily, checking by ECHA and / or National Enforcement Authorities (NEA) that registration dossiers were updated, and checking of the Safety Data Sheets by the Member State National Enforcement Authorities.

Disadvantages

A disadvantage is that effective RMMs would be recommended only for import and manufacture requiring a CSR, i.e. $\geq$10 tonnes/year, so triggering the development of exposure scenarios. However, according to an analysis of information provided in registrations, the volume of substances manufactured or imported between 1 and 10 tonnes constitutes <1% of the total volume of NMP used in the EU. The SDSs issued by those registrants would have to include the DNEL value proposed in the restriction, even though exposure scenarios would not be included. It is expected that the lowest benchmark level is applied, in this case the DNEL. In the worst case - the workplaces where these volumes are handled would still have to apply the provisions of the current national worker protection legislation, including the national OEL.

[3] Option 3 proposed by the DS (see also Annex 1) defines a mandatory inhalation DNEL, which in combination with protection measures for dermal exposure would have to be used by current registrants in updating the CSRs and by new registrants. The RMMs required to reduce the inhalatory exposure to below the DNEL level 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 registered uses, irrespective of how they are defined.

Conclusion of the RMO Analysis

All of the RMOs presented in Annex I and the Background Document have their advantages and disadvantages. However, this analysis indicates that the RMO3 with the modifications proposed by the RAC may be the best of the options considered.

Based on the assumption that the 'RAC's DNEL' will be used, the restriction proposed by the dossier submitter as well as RMO 3 could be good ways forward, as they apply to all uses. However, in the Dossier Submitter's proposal, the dermal exposure would not be meaningfully addressed, and there could be issues concerning enforceability. If it would be possible to clearly define which uses/sectors to include or exclude, option 2B could also be considered as a starting point for a restriction. A binding OEL has some advantages, but as it would be developed under a different legislative framework, it seems not realistic at present.

Of all the options considered it would seem to the RAC, that the modified RMO 3 has the most advantages, as it is based on normal REACH approaches.

The RAC therefore recommends that the modified RMO 3 is an appropriate EU wide measure to be implemented in order to reduce the risk posed by NMP in the workplace. The modified RMO 3 requires use of DNEL for dermal and inhalatory exposure to be included in the chemical safety assessments and in the safety data sheets by all relevant actors (manufacturers, importers and downstream users). This restriction is expected to affect all uses and sectors where the RCR is currently above 1, by requiring introduction of additional risk management measures, communicated in exposure scenarios, until worker exposure is below the inhalation and dermal DNELs. Safety Data Sheets provided for users relaying on the suppliers not developing CSR (manufacture or import <10t), will include DNEL levels for both inhalation and dermal exposure. It is expected that they will be used in the evaluation of exposure.

The following sections (effectiveness, practicability and monitorability) reflect that recommendation.

In addition, RAC would suggest that ECHA, 1 year after entry into force of the restriction, initiate a targeted compliance check to verify that the DNELs introduced in the Annex XVII entry were used in development of the Exposure Scenarios in the registration dossiers of NMP, as due to the implementation of RMO 3 (modified), registrants will have to update and resubmit their registrations for the substance under Article 22 of REACH.

Effectiveness in reducing the identified risks

The proposed restriction 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 operational conditions and RMMs required to reduce the inhalatory and dermal exposure to levels below the DNEL 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 DNELs for inhalation and dermal exposure in safety data sheets by those, who do not have an obligation to develop CSRs.

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 about a desired risk reduction.

This option applies to manufacture, placing on the market (including import) and use of the substance (as in the option proposed by the dossier submitter).

The Forum has noted that the enforcement of this restriction proposal would lead to compliance with an update of the registration documentation related to the use of substance as such and in mixtures. However, as also noted by RAC, the risk reduction will not be directly achieved through compliance with the restriction. As pointed out by RAC, the identified risks will be reduced through the implementation of the conditions of use described in the updated exposure scenarios by downstream users.

Practicality, including enforceability

Modified RMO 3 is similar to the restriction wording proposed by the dossier submitter, but with the important difference that it would require enforcers to enforce the provisions related to CSRs and verify implementation of conditions presented in exposure scenarios rather than focusing on enforcing compliance with an air concentration limit (as presented in the proposed wording of the restriction), to be established by air monitoring. In addition, dermal exposure would be evaluated quantatively in the CSR and specific RMMs would be proposed in the ESs. It seems to be an advantage from an enforcement point of view.

The compliance with the proposed restriction could be verified at two levels. The registration dossiers and CSRs would have to be amended, to include proposed DNEL levels (a requirement under Art 22.g REACH). This requirement would also apply to downstream users developing own CSRs (Art 37 of REACH). Therefore, exposure scenarios will have to be modified to describe conditions of safe use (RCR<1). Then, the conditions described in the exposure scenarios would have to be communicated to and implemented at the use sites. The manufacturers and importers that do not have to develop CSR will have to include relevant DNELs in their SDSs.

The compliance with the restriction requirement could be assessed by checking of the registration dossiers (ECHA and NEA), and by checking that the DNELs are stated in the SDS.

The enforcement of exposure scenarios (attached to the SDS), based on the implementation of set DNELs, by Member State National Enforcement Authority would not differ from enforcement of general provisions of REACH related to implementation of conditions presented in the exposure scenarios, and would not be a part of the enforcement of the restriction. Nevertheless, the implementation of RMMs presented in the Exposure Scenarios is essential to achieve the risk reduction by this restriction.

Including a dermal DNEL in the restriction proposal removes for the user and enforcement agency any ambiguities related to the type of RMMs needed to establish safe level of dermal exposure (compared to the option proposed by the dossier submitter).

The Forum did not raise any issues with practicability or enforcement of this restriction proposal.

Monitorability

Registrants should provide updates to their registrations when the CSR is changed (Article 22.g of REACH); 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. Therefore, they are known, and their CSR can also be examined by the NEA.

The compliance with the requirement to include relevant DNEL values in the SDSs could be verified by the Member State National Enforcement Authorities.

It is noted that there is currently limited experience on how well enforcement of registrations and exposure scenarios works in practice. It is therefore suggested to have an EU-wide enforcement project on NMP 3 years after entry into force, focusing on verification of the DNEL values used in SDSs and implementation of exposure scenario conditions by users of the substance.

BASIS FOR THE OPINION

The Background Document provides the detailed grounds for the opinion.

Basis for the opinion of RAC

The main change(s) introduced in restriction(s) as suggested in this opinion compared to the restrictions proposed in the Annex XV restriction dossier submitted by the Netherlands are:

- that the proposed inhalation DNEL has been revised (10 rather than 5 mg/m^3),
- that a dermal DNEL has been introduced to the restriction text proposal,
- that rather than stating an air concentration limit to be established by air monitoring (analogous the iOEL), the proposed restriction defines mandatory DNELs, which would have to be used by current registrants in updating the CSRs and by new registrants, as well as by downstream users, preparing their own CSRs. The RMMs required to reduce the inhalatory and dermal exposure to below the DNEL levels would be listed in the exposure scenarios (ESs) and passed on with safety data sheets to downstream users.
- that a requirement to include the proposed RAC DNEL values for inhalation and dermal exposure to Safety Data Sheets prepared by all relevant actors (manufacturers, importers and downstream users) is added

The basis for these changes is

- That the RAC has chosen to use assessment factors as proposed in the REACH guidance.
- A dermal DNEL is already used in the current CSR and its inclusion in the restriction would highlight the need to protect against dermal exposure; the exposure scenarios would then have to suggest concrete and use-specific risk management measures to reduce the dermal exposure, removing the ambiguities present in the original proposal.
- The approach for producing the CSR and ESs is well known; risks have to be dealt with when encountered (such as when RCRs >1) by introducing further risk management measures or adjusting operational conditions. The risk reduction measures proposed are easy to communicate to the users in the supply chain as they have to be included in the exposure scenarios annexed to the safety data sheets, which are communication tools already being used currently for this purpose.
- To ensure that even when there is no requirement to prepare a CSR, proposed in the

restriction DNEL values are included in the SDSs (e.g.: registrations <10t, substance recycling)

Annex I: Risk Management Option Analysis for 'other' RMOs

RMO 1

This RMO proposes a total ban on the use of NMP (option 1).

Advantages

This RMO would be the most effective measure in terms of reducing the exposure, ease of enforcement and monitoring.

Disadvantages

The calculated RCR values would indicate that less severe measures could adequately address the concern. There are some uses and occupational settings that can already use NMP in a safe way (that is, RCR is <1). A total ban would not differentiate between workplaces on the basis of risk and so is unlikely to be proportionate related to the risks.

RMO 2

The dossier discusses three different versions of this RMO proposing restriction of some uses/sectors where alternatives seem to be available (options 2A, 2B, and 2C), while derogating other uses.

In options 2A and 2B, the derogated uses/sectors are listed. These derogated uses are allowed only if they occur in controlled closed systems or with best available techniques (BAT) implemented (option 2A) or if a CSR based on the proposed inhalation DNEL can demonstrate safe use (option 2B). Uses/sectors not derogated are banned, which includes six applications discussed in the dossier (non wire coating, professional cleaning, agrochemical formulation, construction materials, functional fluids, and laboratory uses) as well as uses/sectors which were not identified by the dossier submitter in their analysis or 'new' uses that could become desirable in the future. It is noted that the risk assessment indicates no concern for laboratory settings (RCR<1), so it may be a mistake in the dossier not to include laboratory uses among derogated uses.

Option 2C is a targeted restriction on four specified uses/sectors where alternatives are thought to be available (non wire coating, professional cleaning, agrochemical formulation, and construction materials), with all other uses allowed irrespective of RCRs (including those with RCR>1). Based on volume, the allowed uses would make up the majority of the total tonnage.

Advantages

Partial bans in options 2A-2C would be efficient measures, assuming that the banned and derogated uses/sectors could be properly defined.

Option 2B would be easy to implement as enforcement of the CSR would rely on approaches currently being used to enforce REACH registrations (see also option 3 below) and the introduction of additional risk management measures will be risk based, i.e., only needed when RCRs are >1.

Disadvantages

The main drawback with option 2A is that the "BATs to reduce inhalation and dermal exposure" are not defined, which is likely to affect enforceability. Also, since BATs are not defined, it is difficult to assess the effectiveness of the control of the risk in the allowed uses, although banning the other uses is clearly an effective measure. BATs could be developed, but it is not clear how fast and for which sectors they can be agreed on.

Technological progress would require periodical revisions of the BATs.

Option 2B only focuses on limiting the inhalation exposure (just as the iOEL) and as dermal exposure can contribute significantly to the exposure to NMP, this is a disadvantage from an effectiveness perspective; the need for risk management measures would be quantitatively assessed only for inhalation exposure. In addition, only import and manufacture requiring a CSR, i.e. ≥10 tonnes/year, would be affected by the restriction. However, according to an analysis of information provided in registrations, the volume of substances manufactured or imported between 1 and 10 tonnes constitutes <1% of the total volume of NMP used in the EU. The SDSs issued by those registrants would have to include the DNEL value proposed in the restriction (REACH, Art. 31, 9c), even though exposure scenarios would still not need to be included. It is expected that the lowest benchmark value would be used for exposure assessment by the user. In the worst case scenario, the provisions of the current national worker protection legislation, including the national OEL would be used.

It is difficult to properly define the uses/sectors to be included in the ban or derogated as proposed in RMO2c. For example, a restricted use such as professional cleaning may occur in all different sectors, including allowed sectors, making enforcement difficult unless the banned uses can be defined very clearly. This uncertainty makes it difficult to estimate the effectiveness, both with regard to volumes affected and number of workers affected. Professional cleaning on the one hand represents a very small part of the total volume of NMP (approx. 5%, annex III of the background document), but on the other hand a very significant proportion (more than 50%, Table F.05A of the background document) of workers potentially exposed to NMP belong to the use category 'professional cleaning', especially if cleaning in the automotive sector is also included. The efficiency of this RMO will depend on the extent to which cleaning is included in the ban, which at present is unclear as it occurs also in allowed sectors.

Therefore, the main problem with these three options (2A-C) is that it is difficult to clearly define the uses/sectors to be included or derogated, and as mentioned above, a use such as professional cleaning may occur in many different sectors. This will affect both the enforceability and the monitorability. These three alternative options may result in risk reduction in some uses/sectors, and not in others, but the reduction will depend on the availability of alternatives and not on whether there is a concern or not for a particular use/sector (e.g. 2C). The effectiveness in reducing the identified risks could, therefore, be challenged. Giving consideration to the possibly conservative nature of the exposure estimates and the limited specific data on exposure for the wide variety of uses of NMP, a total ban for some uses/sectors may also be considered unnecessarily strict, if instead introduction of additional risk management measures could reduce the RCRs below one.

RMO 3

Option 3 proposes to define an inhalation DNEL, which in combination with protection measures for dermal exposure would have to be used by the registrants in updating the CSRs and by new registrants. The RMMs required to reduce the inhalatory exposure to below the DNEL level 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 registered uses, irrespective of how they are defined.

Advantages

Option 3 is the basis of the restriction wording proposed by the dossier submitter, as discussed in the opinion. However, the important difference is that in this option it would be required to enforce the provisions related to CSRs and conditions presented in exposure scenarios rather than focusing on enforcing compliance with an air concentration limit (as presented in the proposed wording of the restriction), to be established by air monitoring.

The approach for producing the CSR and ESs is well known. Registrants are obliged provide

updates to their registrations when the CSR is changed (Article 22.g of REACH); it would be relatively easy to identify if this has been done for current registrants, thus easing enforcement. The risk reduction measures proposed have to be included in the exposure scenarios annexed to the safety data sheets that are communication tools already being used currently for this purpose. The enforcement of the application of conditions of exposure scenarios generated due to restriction process would be the same as for any other registration.

Another advantage is that this option covers manufacture, placing on the market (including import) and use of the substance (as in the option selected by the dossier submitter).

Disadvantages

A drawback of option 3 is that only import and manufacture requiring a CSR, i.e.>10 tonnes/year, would be affected by the restriction. The possible ramifications *of this limitation* are already described in presentation of negative aspects related to RMO2B.

It is noted that there is currently limited experience on enforcement of registrations and exposure scenarios, however, experience will be gained over the next 5 years (the expected transition period for the measure). Another limitation of this RMO is that it deals with the issue of dermal exposure only in qualitative way, as the DS proposes to include a general requirement to protect against dermal exposure. However, the Forum has pointed out that it is unclear what avoidance means (using gloves, zero dermal exposure, other limit values?) which may cause enforceability problems.

RMO 4

Risk management option 4 is authorisation. NMP is on the candidate list. For the substance to be subject to authorisation, this would require that NMP is prioritised (by ECHA in the future), and that it would gain approval of the MSs and Commission. If this was the case - the substance would be included in annex XIV.

Advantages

Advantages are that each sector (or even company) has to evaluate its uses thoroughly, and either show safe use via a risk assessment (adequate control) or use socio-economic arguments for a continued use of the substance, in the absence of technically and economically viable alternatives. All uses have to be approved and well described in the exposure scenarios, making it easy to enforce and monitor the use. The DNEL developed by RAC in the evaluation of the restriction proposal could be used as the reference DNEL for the substance.

In addition, authorisation would cover all tonnages placed on the market (as compared to option 3 and uses covered by restriction in 2B).

Disadvantages

One of the disadvantages of the authorisation system is that it may seem a resource intensive process: there are very many varied uses, that authorisation would have to be applied and considered for.

While authorisation covers the use of the substance it does not cover the manufacture of the substance (as specified in the original dossier submitter's proposal).

Other potential measures based on RMOs discussed in the DS proposal

A binding OEL

The proposed by the dossier submitter restriction could be seen as a harmonised, binding "OEL", even though it would reflect the DNEL, and so setting a binding OEL (BOELV) under the worker protection legislation could be an option to consider.

Advantages

An advantage of this option is that a new binding OEL would be used and enforced in the same way as other binding OELs under the worker protection legislation.

This option would also avoid perceived conflict between REACH and the worker protection legislation.

BOELVs take account of socio-economic and technical feasibility factors as well as the hazard and risk – similarly to restricition opinions.

Disadvantages

Binding OELs are developed under workers protection legislative framework. It is a difficult and lengthy process initiated when policy considerations require it; there are only binding OELs for 5 substances so far. It also should be considered that it cannot be predicted what would be the numerical value of such binding OEL.