

ECHA Committee for Risk Assessment (RAC)
and
**Scientific Committee on Occupational Exposure
Limits (SCOEL)**

Joint Opinion
**to resolve differences in scientific opinion as
regards exposure levels for**

N-Methyl-2-Pyrrolidone

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JOINT OPINION OF THE COMMITTEE FOR RISK ASSESSMENT (RAC) AND THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS (SCOEL) FOR N-METHYL-2-PYRROLIDONE (NMP)

Introduction

In accordance with Article 95(3) of REACH as implemented through ECHA Management Board Decision 22/2013 and in accordance with Article 2(9) of Commission Decision 2014/113/EU the Commission Services (April 2015) requested ECHA and the Scientific Committee on Occupational Exposure Limits (SCOEL) to resolve the differences in scientific opinions between the two Committees, the Risk Assessment Committee (RAC) of ECHA and SCOEL, as regards exposure levels for 1-methyl-2-pyrrolidone (NMP). The two Committees were requested to work together to discuss the application of their differing methodologies in the case of NMP and to prepare a joint opinion, taking into account and evaluating all available scientific information, and to recommend a common health based reference value. The Commission services requested to:

- a) Develop and provide a joint opinion together with the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) on a recommendation for a limit value for worker protection for NMP related to inhalation exposure and/or
- b) Develop and provide an opinion on the recommendation for a limit value for worker protection for NMP related to inhalation exposure highlighting all issues, for which a common view between RAC and SCOEL could not be presented including methodology and/or
- c) Propose the publication of Recommendation(s) and/or scientific Opinion(s) provided in accordance with the described tasks.

1. Process for Adoption of the Joint Opinion

1-methyl-2-pyrrolidone (N-methylpyrrolidine; NMP) is a widely used aprotic solvent.

The Commission adopted (Directive 2009/161/EU) an indicative occupational exposure limit (OEL) value (IOELV) of 40 mg/m³ for exposure (over 8 hours, time weighted average) together with a short-term exposure limit of 80 mg/m³ and with a 'skin' notation for NMP in 2009. These limit values were based on a 2007 recommendation by the SCOEL¹.

On 5 June 2014, RAC adopted their opinion² on a proposal from the Netherlands to restrict the marketing and use of NMP³. The proposed restriction is based on a harmonised inhalation exposure limit and a general requirement to protect against dermal exposure in the REACH Annex XVII entry; the inhalation exposure limit should be applied in all sectors and for all uses. In their opinion (2014), RAC agreed with the Netherlands that those conducting a REACH chemical safety assessment in the workplace should use long term 'Derived No Effect Levels'

¹ Recommendation from the Scientific Committee on Occupational Exposure Limits for N-Methyl-2-Pyrrolidone. SCOEL/SUM/119. August 2007.

² Committee for Risk Assessment (2014) Opinion on an Annex XV dossier proposing restrictions on 1-Methyl-2-pyrrolidone: <http://echa.europa.eu/documents/10162/b62accae-9ff6-423e-9db4-1c1ea3fa4a71>.

³ Proposed restriction text as amended by RAC: 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/m³ and a long term DNEL for workers dermal exposure of 4.8 mg/kg/day.

(DNELs) of 10 mg/m³ for inhalation exposure and 4.8 mg/kg/day for dermal exposure for workers as the basis for their risk characterisation.

In their request to resolve the differences in scientific opinion between the two Committees, RAC and SCOEL, the Commission raised a concern that in practice, the inhalation DNEL could be seen as being equivalent to an OEL but with a lower numerical value than the existing IOELV.

Through earlier discussions, it had been established that both Committees consider the same data-set for NMP but select the point of departure differently and use different assessment factors to derive their respective limit values.

In the sense of Art. 95 of REACH, there is therefore a difference of opinion between RAC and SCOEL regarding which critical adverse health effect should be used as the basis to derive an exposure value or their recommendations for limit values for worker protection for NMP related to inhalation exposure.

In accordance with Article 95(3) of REACH, as implemented through ECHA Management Board Decision 22/2013, and in accordance with Article 2(9) of Commission Decision 2014/113/EU, the Commission services request that the two Committees address this issue and work together to resolve this difference.

In that regard, the Commission services requested that the ECHA and SCOEL secretariats make the necessary practical arrangements for RAC and SCOEL members respectively to work together to discuss the application of their differing methodologies in the case of NMP and in particular:

- the choice of critical adverse health effect(s),
- the use of a weight of evidence approach,
- the appropriate use of assessment factors and their scientific relevance,

with the objective to agree, if possible, on these parameters for the specific case in order to recommend a common health-based reference value. Any identified differences of approach should be duly justified.

On 4 May 2015 and on 8 September 2015, respectively both RAC and SCOEL received their mandates to draw up a joint opinion on differences between the Derived No Effect Level (DNEL) and the Occupational Exposure Limit (OEL) for NMP (Annexes 1 and 2). The mandate for SCOEL was renewed by the Commission on 14th of December 2015 to align the March 2016 reporting data for both Committees.

2. Adoption of the Joint Opinion of ECHA/RAC and SCOEL

Firstly, both RAC and SCOEL independently reviewed their original opinions in the light of the most recent information available (Appendix 1 and 2), coming to somewhat different conclusions in each case. However, the changes were not sufficient to resolve the observed difference in reference values.

The joint ECHA/RAC-SCOEL Working Group on NMP then held three joint meetings⁴ to resolve the differences as regards the choice of critical adverse health effect(s), the use of a weight of evidence approach, and the use of assessment factors and their scientific relevance.

RAC and SCOEL have different tasks as set out in the relevant legislation that underpins their regulatory role. Correspondingly, both entities have different approaches to fulfil their tasks. However, it is recognised that there are similarities between the two approaches in both underlying methodology and their application.

RAC: The inhalation DNEL proposed by RAC was 10 mg/m³ and this was revised to 14.4 mg/m³ following the aforementioned review by RAC; the dermal DNEL proposed is 4.8 mg/kg/day.

⁴ October 2015, July 2016 and August 2016.

SCOEL: The OELs and notations, as recommended:

8-hour TWA:	10 ppm (40 mg/m ³)
STEL:	20 ppm (80 mg/m ³)
BLV:	20 mg/g creatinine 2-hydroxy-N-methylsuccinimide (2-HMSI) in urine, monitored morning-after-shift (18 h), or 70 mg/g creatinine 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) in urine, monitored 2-4 h after exposure/shift
Additional categorisation:	-
Notation:	"skin"

3. Summary of Key Points from Joint ECHA/RAC and SCOEL Discussions

NOTE TO THE READER: SCOEL requested section 3 to be moved to the Appendix 1 (RAC agreement and Scientific Grounds for the RAC opinion). This was not agreed by RAC.

Critical effects

SCOEL regards an OEL of 40 mg/m³ (8h-TWA) as a health-based reference value supported by scientific evidence as outlined in SCOEL/REC/119. SCOEL does not see clear scientific evidence that a value lower than 40 mg/m³ (8h-TWA) will be more protective for workers' health.

Following the re-analysis of the short term and systemic effects of NMP, RAC's opinion is that a health based inhalation DNEL level of 14.4 mg/m³⁵ combined with a dermal DNEL of 4.8 mg/kg/day (to manage systemic effects from combined exposure) is suitable. It is also the opinion of RAC that a higher value would not be protective of pregnant workers health.

The RAC-SCOEL Joint Working Group agreed that respiratory irritation, (as evidenced by chemosensory effects) is in principle suitable as a PoD for deriving workplace DNEL's and OEL's; likewise, developmental effects can also be used. In the case of NMP however, as documented in their respective opinions, RAC and SCOEL place a different emphasis on the importance of each of these effects as a PoD. SCOEL clearly favours respiratory irritation, while RAC favours developmental effects as the leading PoD.

Where irritation is concerned, the workplace conditions in the microchip industry of the early 1990's such as described in Beaulieu et al. (1991) were the original cause of concern, triggering further research into exposure to NMP in the workplace. The van Thriel et al. (2007) human volunteer study showed clearly that at concentrations of 80/160mg/m³, (the maximum allowed on medical ethical grounds (based on the MAK value), no irritative effects were observed. RAC understands that SCOEL used this in a pragmatic way to set a conservative/protective OEL. However, the lack of any dose-response relationship prevented RAC from taking this forward as a PoD. It is noted that the broader scientific consideration of chemosensory irritation contrasts with the (classification driven) division into eye, skin and respiratory irritant generally used by RAC.

With regards to developmental effects (retardation of foetal and pup body weights) observed in the animal studies following different routes of exposure, RAC and SCOEL differed in their views with regards to adversity. RAC considered that these effects were consistent across the animal studies and even if the retardation was slight (around 5%), the later malformations with increasing dose and the potential relevance in later life for humans meant that they could

⁵ RAC considered that its original proposal of 10 mg/m³ [reference in footnote 1] for inhalation exposure is also valid in terms of applying the relevant REACH guidance.

not be dismissed⁶. SCOEL on the other hand considered that the effects were of borderline adversity, of marginal severity and that they were fully reversible. The issue of maternal toxicity was also considered in this context by both Committees.

Regarding the reproductive effects of NMP, Poet et al (2007, 2016) used PBPK modelling to calculate human equivalent concentrations from rats, corresponding to the internal dose point of departure values (thus, partly avoiding the use of default assessment factors and resulting in a human point of departure calculated using substance-specific data); this was considered as a possible way forward by the SCOEL members. However, RAC noted that while the model had been improved, the quality of the input data had not. The human kinetic data used was from male volunteers only (to assess effects in females) and the rat data had a high variability making its use questionable. The modelling indicates that the human PoD is higher than the rat PoD, and that use of the rat PoD therefore would be too precautionary. Using the human PoD was considered as the preferred way forward by the SCOEL members.

The issue of relevance for the workplace was briefly touched on but it was clear that SCOEL members considered, for the above reasons, that the developmental effects were of little relevance, hence leaving them behind in favour of respiratory irritation. RAC members considered that they were of central relevance and hence took them forward as the main PoD to derive an inhalation DNEL.

Taking the above into account, an agreement on the science reflecting the hazardous properties of NMP (such as the critical effect underpinning the DNEL and the OEL) could not be reached. The specific methodology applied by each Committee leads to different outcomes with regard to the objective formulated in the request of the Commission services, namely a 'common health-based reference value.' The reviews undertaken by each Committee have reconfirmed the derivation of the relevant limit values

4. Joint Conclusions of ECHA/RAC and SCOEL

1. It was recognised that the respective assessments have relied on the same extensive database, which included both animal studies and human data;
2. It was agreed that chemosensory irritation⁷, is in principle suitable as a **point of departure** for deriving workplace DNEL's and OEL's; likewise, developmental effects can also be used;
3. The same point of departure for deriving limit values for NMP was not agreed; RAC and SCOEL placed a different emphasis on the importance of the effects. SCOEL favoured respiratory/chemosensory irritation, whilst RAC favoured developmental effects as the point of departure.
4. Considering point 3 above, RAC and SCOEL agreed that there was no benefit in reviewing the differences in their respective methods of **accounting for uncertainty** in extrapolating from animal studies or human volunteers to workers.
5. It was agreed that the methodological differences highlighted in this joint opinion should be considered further on a higher and more generic level under the related Art. 95 mandate to RAC and SCOEL on OEL/DNEL methodology.

⁶ This is further supported by OECD, 2007; US-EPA, 2015 and Poet et al. (2007, 2016)

⁷ It is recognised that Poet et al. (2007) considered chemosensory irritation in broad terms in their human volunteer study. However as the chemical is classified under CLP as a respiratory irritant, this term is used.

Appendix 1. RAC agreement and Scientific Grounds for the RAC opinion

Agreement on the Opinion of RAC

The RAC-members of the joint RAC-SCOEL working group on NMP developed a draft review paper. RAC agreed on the draft review paper on 4 March 2016 at its 36th Meeting.

The draft re-analysis, taking into account the SCOEL recommendation on NMP of March 2016⁸, was reconfirmed at its 37th meeting⁹.

The final draft opinion of RAC-members of the Joint RAC-SCOEL Working on NMP was agreed at its 39th meeting in December 2016.

Scientific Grounds for the RAC Opinion

The Netherlands submitted their Annex XV restriction proposal¹⁰ on NMP on 9 August 2013 proposing a HBLV of 5 mg/m³.

NMP is classified in Regulation 1272/2008 (CLP)¹¹ as: Repr. 1B H360D, Skin Irrit. 2 H315, STOT SE 3 H335, Eye Irrit. 2 H319.

In the case of restrictions, RAC evaluates the proposal of the Dossier Submitter and may as part of its evaluation, critically review any Derived No Effect Levels (DNEL) proposed.

DNELs are purely health based, scientifically derived Health Based Limit Values (HBLVs). DNEL values are calculated by applying assessment factors to the relevant PoD obtained from the assessment of (usually) animal studies (where possible carried out to an agreed test guideline¹² and under GLP). The assessment factors are applied to cover uncertainty in the estimates and have been agreed on in a transparent manner through a process involving Member States, Industry and other Stakeholders; they are set out in the relevant guidance¹³. These DNEL values are used under the REACH regulation to compare with measured or modelled exposure levels, in order to determine if there is a risk from the manufacture and/or use(s) of a substance.

In (preparation of) their proposal, the Netherlands undertook a comprehensive assessment of all available data. This led the Dossier Submitter to conclude that developmental toxicity was the key endpoint to take forward in the Risk Assessment and Risk Characterisation. From an analysis of the available studies they derived a DNEL of 5 mg/m³ that was compared to the available exposure information. The resulting risk characterisation ratios indicated a risk for a number of uses of NMP.

RAC in their opinion of June 2014 critically evaluated the Annex XV restriction report, submitted by the Netherlands. Their assessment differs from that of the Dossier Submitter: RAC used an assessment factor of 5 for intraspecies differences (as recommended in the guidance for workers) instead of the assessment factor of 10 (recommended for use for the

⁸ CircaBC/empl/Scientific Committee on Occupational Exposure Limits for Chemical Agents - SCOEL (public access)/Library/Published Recommendations and Opinions ; <https://circabc.europa.eu/w/browse/373d5906-e1b3-4444-bb93-a16b2165c673>

⁹ /CircaBC/echa/RAC and SEAC Committees/Library/RAC and SEAC restricted/RAC meetings/RAC-37-1/Documents (restricted access)

¹⁰ Annex XV restriction report is available from <http://echa.europa.eu/documents/10162/ee4c88a9-d26f-4872-98fd-fb41646cc9e1>

¹¹ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1)

¹² Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (Text with EEA relevance)

¹³ Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health available from http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

general population) applied by the Dossier Submitter. After applying the relevant assessment factors RAC proposed a DNEL of 10 mg/m³.

RAC agreed as within the proposed restriction proposal for NMP that a reduction in foetal/pup body weight as the most sensitive adverse effect for exposure via inhalation. This effect was consistently observed across studies and routes of administration, with a developmental toxicity study by Saillenfait et al. (2003) resulting in the overall lowest inhalation DNEL. The NOAEC of 247 mg/m³ [60 ppm] from this study served as PoD, based on a 5% decrease in foetal body weight observed at the next higher concentration of 494 mg/m³ [120 ppm].

RAC also derived a DNEL for workers in general, of 20 mg/m³, based on a 90 day inhalation study (Lee et al. (1987)) with decreased body weight as the relevant effect. This DNEL is relevant for all workers and not just pregnant workers but may not be effective in controlling the risk to the latter vulnerable group.

In addition to the inhalation DNEL, RAC also determined a dermal DNEL of 4.8 mg/kg bw/day. This DNEL is an important element in evaluation of the combined (systemic) effects from inhaled and dermally absorbed NMP.

Choice of critical adverse health effect / Point of departure (PoD)

In its original opinion (2014), RAC has selected developmental toxicity as the critical effect. In choosing its relevant adverse effect, SCOEL has chosen local irritancy/chemosensation as the primary critical adverse effect.

Local irritancy/chemosensation

RAC has a number of concerns related to local irritancy/chemosensation as an adverse effect for NMP even though the substance is classified for respiratory irritation. Van Thriel et al (2007) acknowledges that 'due to conflicting results, there is a debate whether NMP causes irritations of the upper airways/eyes or not' and reports the absence of any effect (let alone adverse) in the human volunteer study. RAC prefers human data when available as opposed to animal data, however in the opinion of RAC the absence of any effect in the human volunteer study precludes this study to be seen as the most relevant study for setting the HBLV. In addition, the experimental animal data for respiratory tract irritation (slight effects in the URT at 1000 mg/m³ in the 90d-inhalation study, no relevant effects in the lower respiratory tract) supports the view that this is not a key effect. Furthermore, the OECD SIAR (2007), states that NMP is not irritating to the eyes or the upper respiratory tract.

In the Annex XV restriction dossier submitted by the Netherlands to ECHA for RAC's evaluation, this endpoint was assessed and a NOEC of 80 mg/m³ was proposed based on moderate annoyance observed at peak exposures but not for respiratory irritation as such.

Reduction in foetal/pup body weight

In the RAC opinion on NMP (2014) a study from Saillenfait et al, 2001, 2003, was used as the key study related to a decrease in rat pups' weight.

RAC assessed this as a relevant effect as it was supported by findings of body weight reductions of a similar magnitude in Solomon et al 1995.

It is generally accepted that the reproductive effects are the primary adverse effect of NMP (Torka et al (2010); Poet et al (2016)). It is further noted that also US EPA (2015) based their recent risk assessment of NMP on this effect.

It is also generally accepted that a decreased birth weight may be a disadvantage for the later development of the baby or adult health of the individual concerned. So, for pregnant workers exposed to NMP, this is considered to be a relevant adverse effect. There is consistent evidence in various reproductive toxicity studies that the reduction in foetal/pup body weight is the key toxic effect. A study on developmental neurotoxicity by Hass et al (1994) may suggest impairment of complex neurobehavioral endpoints in NMP-exposed rat offspring and other known potential effects caused by a low birth weight are cardiovascular disease and diabetes but such endpoints have not been studied for NMP. In addition to this, the USE-EPA, in considering the same dataset (EPA-TSCA workplan 2015) went further and considered that the fetal and pup body weight effects, along with delayed ossification, skeletal malformations and increased fetal and pup mortality form part of a continuum of reproductive and developmental effects. They considered reduced fetal body weight is a sensitive endpoint that is considered a marker for fetal growth restriction, which is often assumed representative of chronic rather

than acute exposures. RAC considers that the dose response data in these studies fit together rather convincingly.

RAC acknowledges that it is unclear what the critical decreased birthweight percentage is and that a 5% decrease might not be that big an effect. On the other hand, the treatment relationship is supported by findings of decreased foetal/pup body weights of similar magnitude at similar exposure levels in various inhalation studies (see Table 1: Overview of inhalation studies (RAC opinion)), as well as in dermal and oral studies.

Table 1: Overview of inhalation studies (RAC opinion)

Route	Dose / effects									References
Inhalation (mg/m³) [ppm]	206 [51]	247 [60]	360 [87]	478 [116]	494 [120]	500 [122]	618 [150]	680 [165]	1000 [243]	
Rat (dev.tox)	---	No effects	---	---	Fetal Bw↓ - 5%	---	---	---	---	Saillenfait et al., 2001, 2003
Rat (dev.tox)	---	---	No effects	---	---	---	---	---	---	Lee et al., 1987
Rat (dev.tox)	---	---	---	---	---	---	---	Fetal Bw↓ - 4-5%; Delayed ossification	---	Hass et al., 1994
Rat (dev.tox)	---	---	---	---	---	---	Fetal/Pup Bw↓ - 6-7% day 1-22; Delayed physical development	---	---	Hass et al., 1995
Rat (2-gen)	No effects	---	---	Fetal/Pup Bw↓ - 10.8% day 1 - 4.5% day 21	---	---	---	---	---	Solomon et al., 1995
Rabbit (dev.tox)	---	---	---	---	---	No effects	---	---	Skeletal variations (extra rib in 32 vs 6% of foetuses)	BASF AG 1991c, BASF AG 1993b

Conclusion of RAC: Reproductive toxicity is the key effect to take forward in derivation of any HBLV.

Point of Departure

In the RAC opinion on the proposed NMP restriction (2014), a PoD of 247 mg/m³ from Saillenfait et al, 2001, 2003 was used also taking into account the results of the study of Solomon et al 1995. Other inhalation studies available were not considered, as they were performed using only one dose level, thus not permitting the setting a NOAEL.

In the current mandate RAC re-assessed all the available information and, to take into account all five inhalation studies available in rats (6 studies overall), including the single dose studies, considers that a new, overall PoD of 360 mg/m³ would be representative. This value is the NOEAC in the Lee study (1987), which is below the lowest LOAEC of 478 mg/m³ in the Solomon study and below the LOAEC (618 mg/m³) of the Hass study (1995), where there is some delayed physical development at this concentration, and about 6-7% reduction of foetal body weight.

Conclusion of RAC: A Point of Departure of 360 mg/m³ could be appropriate to take forward for HBLV derivation based on an alternative approach were all available studies are considered. However, in the view of RAC the original proposal is also valid in terms of applying the relevant REACH guidance.

The appropriate use of assessment factors and their scientific relevance

The assessment factors used by RAC

Corrections to NOAEL for exposure conditions:

- 6.7/10 for respiratory volume of animal vs worker and 6/8 for duration of daily exposure.
- Interspecies differences: A factor of 2.5 was used for remaining differences (toxicodynamics).
- Interspecies differences: A factor of 1 was used for toxicokinetics.
- Intraspecies differences: a factor of 5 for workers was set in line with the REACH guidance.

These factors were used in accordance with the description of their applicability and methodology as described in Guidance document R8. However, RAC did give special consideration if deviation from the standard assessment factor for interspecies differences was warranted but concluded 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.

PBPK modelling

In 2010, Poet and co-workers published a PBPK model describing the pharmacokinetics of NMP in rats and humans. The rat model was used to determine the relationship between NMP concentrations in maternal blood and decrements in foetal/pup body weights following exposures to NMP vapour. Benchmark dose (BMD) modelling was used to better define a PoD for foetal/pup body weight changes based on dose-response information from two inhalation studies on developmental toxicity in rats; a benchmark response (BMR) corresponding to 1 SD decrease in foetal body weight was used. The PoD and human PBPK model were then used to estimate the human equivalent concentrations (HECs). As to the use of uncertainty factors (UF) in establishing OELs, Poet et al. (2010) concluded that “the use of the PBPK model reduces, or eliminates, the need for an UF describing uncertainty in interspecies extrapolation. The use of the PBPK model does not, however, replace the interhuman variability UF.”

US EPA (2015):

In their risk assessment of NMP, US EPA used the PBPK model as published by Poet et al. in 2010, but adapted and validated it for their own use, in cooperation with Poet. US EPA also applied BMD modelling to the developmental toxicity studies to calculate the BMDL5 and PoDs, using a 5% benchmark response for decreased fetal body weight.

The PoD selected for risk assessment was 411 h.mg/L, the BMDL5 from the Saillenfait et al. 2003 study:

Table 2: Table showing dose vs Area Under Curve for calculation of BMDL₅

Reference	Dose (ppm)	Dose AUC (h.mg/L)	BMDL ₅ (h.mg/L)
Saillenfait et al. 2003	0	0	411
	30	158	
	60	323	
	120	668	

This PoD was compared to the estimated human exposure levels, recalculated by EPA into internal doses by means of the human part of the PBPK model. For risk assessment a benchmark Margin of Exposure (MOE) of 30 was selected, with MOE’s <30 presenting a risk. The benchmark MOE of 30 comprises an interspecies factor of 3 (for TD differences) and an intraspecies factor of 10 (for TK and TD differences).

In 2016 an updated version of this PBPK model was published. The update presented a further calibration of the same data and validation of the model following US EPA’s review of the

original model, along with BMD modelling¹⁴. Poet and co-workers suggested the following UFs in establishing an OEL for NMP based on the calculated HEC of 490 ppm:

- no factor for interspecies toxicokinetic (TK) differences, due to use of the PBPK model;
- a default factor of 3.16 for interspecies toxicodynamic (TD) differences;
- a data-derived extrapolation factor of 2.1 for intraspecies TK differences, based on the human PBPK model;
- a default factor of 3.16 for intraspecies TD differences,

resulting in a total UF of 21.

When taking into account the various models described above, the following can be concluded:

Compared to the benchmark MOE of 30 (as proposed by US EPA), it is clear that RAC has not been overly conservative in applying a total assessment factor (AF) of 12.5 in deriving the DNEL, following the adjustment of PoD for exposure conditions. The factor of 21 used by Poet et al. is also in the same range, however with a notable difference: this factor was applied to the HEC rather than to the rat PoD, the former predicted by the PBPK model to be almost 6-fold higher than the rat PoD.

The fact that both US EPA and Poet et al. still propose a factor to be applied for toxicokinetic differences within the human population indicates that the human PBPK model does not (or not sufficiently) account for these differences. Concern related to this issue was previously expressed by RAC, given various uncertainties in the data sets for the PBPK model (including the human variability, the limited number of only male volunteers involved, the large variations in CYP2E1, which is involved in the metabolism, and big variations in rat inhalation data). For that reasons RAC does not consider the human PBPK model sufficiently robust for deriving human equivalent concentrations (HEC) as POD for the NMP DNEL derivation. Correspondingly RAC prefers to directly use the rat developmental toxicity data as starting point for the DNEL derivation.

Conclusion of RAC: *The assessment factors used by RAC are set out in the ECHA R.8' Guidance on Information Requirement and Chemical Safety Assessment' and whilst it is possible to deviate from them using chemical specific data, there needs to be a scientific justification to do so. On further examination, accounting for the uncertainties in the robustness of the human PBPK model, RAC does not see such a sufficiently valid justification for the HEC approach.*

Overall RAC conclusion

Reproductive toxicity is the key critical endpoint of concern; there is no evidence that respiratory irritation occurs following exposure to NMP (despite its classification for that endpoint). The revised NOAEL can be supported as a PoD and the assessment factors used to obtain the DNEL are scientifically justified and in line with other regulatory systems.

Taking reproductive toxicity as the key effect and a PoD of 360 mg/m³, the resulting HBLV would become $(360 * 6.7/10 * 6/8)/(2.5 * 5) = 14.4 \text{ mg/m}^3$.

However, it should be noted that the original DNEL of 10 mg/m³ based on the PoD of 247 mg/m³ from Saillenfait et al, 2001, 2003 remains a valid conclusion in the opinion that is still fully justifiable.

All available NOAECs and LOAECs for the developmental effects including those related to single dose studies (which had been previously excluded) were re-assessed. It was proposed to keep with the Assessment Factors used in this case and at this stage.

List of new references, not included in the previous RAC- opinion

Poet, T., Kirman, C., Bader M., van Thriel, C., Gargas, M., and Hinderliter, P. Quantitative Risk Analysis for N-Methyl Pyrrolidone Using Physiologically Based Pharmacokinetic and Benchmark Dose Modeling Toxicological Sciences (2010) 113(2): 468–482.

Poet, T., Schlosser, P., Rodriguez, C., Parod, R., Rodwell, D., Kirman, C., Using Physiologically Based Pharmacokinetic Modeling and Benchmark Dose Methods to Derive an Occupational

¹⁴ This further calibration and validation was done with the same dataset as available before, as far as can be seen.

Exposure Limit for N-Methylpyrrolidone, Regulatory Toxicology and Pharmacology (2016) 76: 102-112

STATE OF CALIFORNIA - DEPARTMENT OF INDUSTRIAL RELATIONS OCCUPATIONAL SAFETY AND HEALTH STANDARDS BOARDS INITIAL STATEMENT OF REASONS CALIFORNIA CODE OF REGULATIONS Title 8: Division 1, Chapter 4, Subchapter 7, Article 107, Section 5155 of the General Industry Safety Orders Airborne Contaminants: N-Methylpyrrolidone (NMP):

[http://www.dir.ca.gov/oshb/Airborne_contaminants_N - Methylpyrrolidone ISOR.pdf](http://www.dir.ca.gov/oshb/Airborne_contaminants_N_-_Methylpyrrolidone_ISOR.pdf)

Appendix 2. SCOEL Opinion

SCOEL/OPIN/2016-119-2 Joint Opinion on N-methyl-2-pyrrolidone (NMP) from the Scientific Committee on Occupational Exposure Limits (SCOEL) and the European Chemicals Agency Committee for Risk Assessment (RAC)

1. Summary outcome of scientific discussion

NOTE TO THE READER: This section is SCOEL's interpretation of RAC's considerations and have not formed part of the joint ECHA/RAC-SCOEL review: they do **not** reflect RAC's views, considerations or conclusions which are correctly presented in the beginning "joint section", in Appendix 1 and in the minutes of the two meetings.

Critical effects

1. SCOEL and RAC agree that developmental toxicity is in general a critical adverse effect that if observed and justified by scientific evidence is relevant for derivation of a DNEL or OELs.
2. SCOEL and RAC agree that chemosensory irritation is in general a critical adverse effect that if observed and justified by scientific evidence is relevant for derivation of OELs and possibly also for a DNEL.

Developmental effects

For NMP RAC considers developmental effects to be the most critical possible health effect and derives a long-term inhalation DNEL based on the database for this endpoint. RAC agrees that the data provide evidence for no or low adversity and that the effects described are borderline. RAC agrees that there can be no plausible mechanistic (Mode of Action) of such an effect be proposed. RAC agrees that the data presented for fetal effects and for reduced body weight are generally associated with toxic effects on the dams. RAC confirms that for calculation of the DNEL value the 'severity and adversity' of the effect were not accounted for. RAC re-confirms that the default assessment factors were applied. RAC reconfirmed that the factor for the human equivalent effective concentration presented in the PBPK modelling was not taken up for the calculation of the DNEL. The DNEL derived for long-term inhalation exposure is 10 mg/m³ or by alternative calculation is 14,4 mg/m³. Both are regarded by RAC as being equally valid. The dermal DNEL derived is 4,8 mg/kg/day. The values were derived based on the considerations for pregnant workers, but are proposed to be applied for workers in general.

SCOEL fully considers developmental effects for NMP, but does not regard developmental effects to be critical based on the evidence:

- For SCOEL the overall evidence confirms that developmental effects are only observed together with toxic effects on the dams, which invalidates the observations as being qualified as substance-specific adverse effects.
- Even if taken into account, the observed findings are fully reversible regarding the manifestation of a possible and predicted adverse health effect.
- Also the observed findings are of borderline severity. The level of 5% applied as decision level and cut-off value for evidence is arbitrary. Though being partly statistically significant, the biological relevance and, thus adversity, is questionable.
- The intense bad smell of NMP and its irritation effects are plausibly explaining stress observations on animals and reduced food uptake or reduced uptake of mother milk. This could plausibly explain the observations reported.
- The experimental conditions, under which tests in animals were performed, addressed a different physical state of NMP above vapour saturation concentration.

The concentrations at which effects are suggested by RAC are by a margin of exposure (factor) of 5 below the OEL TWA recommended by SCOEL and already implemented and in place. If the correction factor for the human equivalent effect concentration from the PBPK assessment is taken into account, the margin would be in the range of 35 to 240. The margins indicate that even if there was an effect and even if the scientific evidence and plausibility would be assumed in contradiction to the listed findings above, the level of exposure is covered by the OEL recommended by SCOEL and implemented.

In addition, within the OSH legislative framework, the Pregnant Workers Directive (PWD) 92/85/EEC as amended by 2014/27/EC applies. In particular, Article 4 of the PWD requires the employer to assess and take appropriate management action to prevent pregnant workers from being exposed to a whole range of harmful chemicals as defined in PWD Annex I. NMP falls within the criteria defined in this Annex. As a result and together with the existing OSH OEL and general requirements of CAD, in practice no workplace exposures that could cause harm to pregnant workers or their offspring are expected. This collective consideration of both the scientific aspects and the regulatory risk management aspects are of key importance.

On this basis the risk, if assumed to exist, is sufficiently controlled. Similarly, the concern as raised for pregnant workers and generalized to concern all workers is addressed.

Chemosensory irritation effects

Regarding NMP SCOEL considers the chemosensory irritation effects as being adverse and local irritation as the most critical effects.

- Observations are made in humans and specifically at workplaces, supported by human case reports and by a controlled study in humans.
- The effects observed reported are of severity and clear adversity. They are based on a number of empirical objective and subjective symptoms.
- The underlying pathophysiological mechanisms are known and explained. They are specific for humans and of clear relevance for workplaces.
- The experimental conditions, under which tests in humans were performed, addressed the physical state of NMP at the level of the derived OEL below vapour saturation concentration, which is relevant for the workplace.
- The human controlled study was performed at concentrations with peak exposures and with participation of young male volunteers. Young humans are the most sensitive group.
- In the human volunteer study and for ethical reasons the maximum exposure concentrations both for TWA and for peak concentrations were limited to twice as high the concentration of the recommended OELs: 80 mg/m³ and 160 mg/m³. This study provided evidence that no adverse health effects are observed at the corresponding levels of concentration.

On the basis of the above described scientific evidence, SCOEL recommended within the set of OELs a TWA of 40 mg/m³ and a STEL of 80 mg/m³. The additional 'skin notation' as recommended by SCOEL points at a possible significant uptake through the skin. This is of immediate workplace relevance and inform about the consideration of corresponding protective measures. Direct analytical measurements of skin exposure are not reasonably feasible.

The additional Biological Limit Value for the urinary excretion of the two main NMP metabolites (20 mg 2-HMSI/g creatinine; 70 mg 5-HNMP/g creatinine) is recommended by SCOEL. It enables exposure monitoring.

For NMP RAC considers chemosensory irritation effects, but does not regard chemosensory effects to be the critical health effect. DNELs based on the database for this endpoint are not derived.

- For RAC irritation effects are not demonstrated in animal studies.
- RAC deems the observations reported in the case studies and at the workplace to be of insufficient quality. For example it was not sufficiently clear, what the active compound was, if symptoms by workers were reported that worked near a bath of NMP with an NMP temperature of 80 °C.
- The symptoms of workers reported included 'severe eye irritation and headaches'. Exposure was described for a certain level as 'immediately unbearable'. For RAC the observations reported are not providing suitable information supporting an adverse effect. The early stages of chemosensory irritation effects themselves are manifested, observationally described and empirically apparent. The early and mild stages are transient, but higher or more prolonged exposure leads to irreversible neurogenic inflammation and tissue damage.

RAC does not see that these effects were induced by NMP in the controlled human study and specifically induced by NMP in the case reports and questions therefore local irritation for workers as a critical health effect.

For details of the scientific argumentation of RAC and SCOEL on both developmental toxicity and chemosensory irritation see Annexes and the minutes of the meetings 2016-07-22 and 2016-08-23.

Taking the above into account, an agreement on the science reflecting the hazardous properties of NMP (such as the critical effect underpinning the DNEL and the OEL) could not be reached. The specific methodology applied by each Committee leads to different outcomes with regard to the objective formulated in the request of the Commission services, namely a 'common health-based reference value.' The reviews undertaken by each Committee have reconfirmed the derivation of the relevant limit values.

2. Joint conclusions of RAC and SCOEL:

1. It was recognised that the respective assessments have relied on the same database, which included both animal studies and human data;
2. It was agreed that chemosensory irritation, is a valid endpoint suitable as a point of departure for deriving workplace DNELs and OELs;
4. Considering point 3 above, RAC and SCOEL agreed that there was no benefit in reviewing the differences in their respective methods of accounting for uncertainty in extrapolating from animal studies or human volunteers to workers, i.e. the differences in deriving DNELs and OELs cannot be scientifically resolved.
5. The substance specific differences highlighted in this joint opinion should be considered further on a higher and more generic level under the related Art. 95 mandate to RAC and SCOEL on OEL/DNEL methodology.

Though the differences in deriving DNELs and OELs cannot be resolved from a scientific point of view, a scientific conflict as such does not exist, even if two numerical values are taken out of context and presented next to each other. The respective values are scientific answers to different scientific questions asked and derived for a different purpose. The congruency that the two sides of policy-related scientific analysis have shown is rather convincing and can be used in synergy. Scientific-technical comparisons and convergence of aspects of scientific methodologies can certainly be performed for comparable elements. However, full synergies will most probably be developed by taking advantage of the strengths of both in terms of workplace –specific approaches under the OSH framework and general harmonised toxicological predictive considerations under REACH.

The legislative framework of OSH and the REACH regulation themselves in their purpose, tools, intended use and the users are decisively defining how scientific-technical assessments are performed for the respective policy need. This applies also to DNELs and OELs in their respective context for the intended purposes and use by the different tools.

In the OSH framework, the SCOEL OELs, 8-h time weighted average (TWA) and short-term limits/excursion limits (STEL) are defined and both required for implementation at the workplace as minimum requirements together with a notation 'skin'. This notation 'skin' points at the fact that it can be taken up via the skin and therefore skin exposure should be prevented. In contrast, a DNEL for skin exposure is contradicting the concept of the notation 'skin' by SCOEL in the mentioned sense of prevention of exposure and the minimum requirements. In addition, a skin exposure cannot be reasonably quantified by measurements at the workplace. In addition, the Biological Limit Value as recommended by SCOEL provides a meaningful component for exposure monitoring and minimization at the workplace. This component is currently not legally implemented under OSH. However, it is recommended, known to the stakeholders and might be used in practice.

In addition, within the OSH legislative framework, the Pregnant Workers Directive (PWD) 92/85/EEC as amended by 2014/27/EC applies. In particular, Article 4 of the PWD requires the employer to assess and take appropriate management action to prevent pregnant workers from being exposed to a whole range of harmful chemicals as defined in PWD Annex I. NMP falls within the criteria defined in this Annex. As a result and together with the existing OSH OEL and general requirements of CAD, in practice no workplace exposures that could cause harm to pregnant workers or their offspring are expected. This collective consideration of both the scientific aspects and the regulatory risk management aspects are of key importance.

3. Considerations on the underlying frameworks

The **REACH Regulation** requires 'adequate control' of risks to workers from exposure to chemical substances (and also 'mixtures') which are 'placed on the market' in the EU. There is no fundamental conflict between the concept of 'adequate control' as set out in the articles of the REACH Regulation and other EU legislation applying to worker protection from chemical risks (namely the OSH Directives).

However, Annex I to the REACH Regulation goes on to define 'adequate control' in a way that does fundamentally conflict with the OSH Directives.

Specifically, REACH Annex I Section 6.4 states that (for worker protection inter alia) 'adequate control' means exposure below 'levels of exposure to the substance above which humans should not be exposed' – and identifies the latter as 'Derived No-Effect Levels', or DNELs. The default approach to 'characterisation' of risk under REACH Annex I (in a REACH 'Chemical Safety Assessment') is to 'derive' a DNEL, estimate exposure levels, and compare the two. This 'fully quantitative' comparison results in a 'risk characterisation ratio' (RCR) of exposure vs. DNEL. According to REACH the risk to workers in any given exposure scenario can be considered to be 'adequately controlled' if exposure does not exceed the appropriate DNEL – i.e. if the $RCR \leq 1$. **DNELs are therefore the central element in the REACH approach to chemicals risk management; however, the DNEL is not defined with respect to its implementation at the workplace.**

The REACH model for worker protection is based on certain fundamental assumptions:

- i) risk assessment not only CAN but SHOULD be quantitative (the RCR),
- ii) for the vast majority of chemical substances there are individual thresholds per exposure route which should not be crossed and which need to be identified,
- iii) that the DNEL represents such a threshold (and that exposure beyond this is harmful), and
- iv) that these thresholds SHOULD be 'derived' according to a detailed, standardized methodology which is intended to produce very conservative (precautionary) outcomes based on default 'assessment factors', test results, and predictive modelling to address a single 'critical health effect'.

These assumptions are carried over from environmental sciences and do not align with established (robust and highly-evolved) approaches in both the OSH Directives or otherwise in OSH best practice.

In order to resolve this misalignment, and to improve the effectiveness and proportionality of the REACH system for protecting workers, REACH risk characterisation should be made more flexible and proportionate than the current (very precautionary) 'fully quantitative RCR' default approach. In particular 'adequate control' of chemicals risks to workers according to REACH should be conceptually aligned with existing OSH good practice such as 'control banding' and the Chemical Agents Directive 'hierarchy of control'.

The REACH text provides the flexibility for this to be achieved as a policy initiative without changes to the legal text. Specifically, REACH Annex I Section 0.12 provides for use of an alternative methodology for worker protection in undertaking a REACH Chemical Safety Assessment where the default REACH methodology is 'not appropriate'.

4. Scientific Grounds for the Opinion of SCOEL

NMP shows intrinsic hazardous properties with respect to local and systemic effects. The following key effects were considered as being especially relevant for the protection of workers and in particular the OEL derivation:

- (a) the potential of the substance to produce respiratory irritation and chemosensory effects, both in humans and animals, and
- (b) the systemic toxicity of NMP, in particular reproductive toxicity in studies in experimental animals.

Outcome Considerations

Following SCOEL's Methodology for the Derivation of Occupational Exposure Limits (version 7, June 2013), the existing human data are considered highly relevant for OEL derivation.

(a) Local irritancy/chemosensation

Subchronic studies in rats point to local nasal irritation by upon NMP exposure, with an NOAEL of 125 ppm (7.3.2.1.). There were no indications of respiratory irritation or other health effects of NMP in a study involving exposure of human volunteers to 10, 25 or 50 mg/m³ [2.5, 6.2 or 12.5 ppm] over an 8 hour period (Åkesson and Paulsson, 1997). Workers exposed to levels of up to 280 mg/m³ [70 ppm] reported severe eye irritation and headache, but no dose-response relationship could be established (Beaulieu and Schmerber, 1991). In a comprehensive experimental study (van Thriel et al., 2007) on 15 healthy young male volunteers exposed to 10 mg/m³ [2.5 ppm], 40 mg/m³ [10 ppm], 80 mg/m³ [20 ppm] and 25/160 mg/m³, the latter including peak exposures up to 160 mg/m³ [40 ppm], NMP could be smelled by the subjects, and it was reported to be slightly annoying. For these olfactory symptoms a strong adaptation was observed, especially during the first 4 hours of exposure. SCOEL does not consider such symptoms as being adverse for workers (see 7.9). Symptoms indicative of an irritant potential, especially trigeminal sensations, were not elicited by NMP. The conclusion from this well executed and documented study was that NMP is an odorous substance, but without sensory irritation potency up to 80 mg/m³ [20 ppm] and under conditions of 15-min peak exposures to 160 mg/m³ [40 ppm]. Therefore, for local irritancy in humans a NOAEC of 20 ppm (highest concentration tested by van Thriel et al., 2007), is well established. The study of van Thriel et al. (2007) also considered possible influences of physical workload, which was simulated by six 10 min periods of exercise on a bicycle ergometer at 75 W.

Regarding NMP SCOEL considers the chemosensory irritation effects as being adverse and local irritation as the most critical effects.

- a. Observations are made in humans and specifically at workplaces, supported by human case reports and by a controlled study in humans.
- b. The effects observed reported are of severity and clear adversity. They are based on a number of empirical objective and subjective symptoms.
- c. The underlying pathophysiological mechanisms are known and explained. They are specific for humans and or clear relevance for workplaces.
- d. The experimental conditions, under which tests in humans were performed, addressed the physical state of NMP at the level of the derived OEL below vapour saturation concentration, which is relevant for the workplace.
- e. The human controlled study was performed at concentrations with peak exposures and with participation of young male volunteers. Young humans are the most sensitive group.
- f. In the human volunteer study and for ethical reasons the maximum exposure concentrations both for TWA and for peak concentrations were limited to twice as high the concentration of the recommended OELs: 80 mg/m³ and 160 mg/m³. This study provided evidence that no adverse health effects are observed at the corresponding levels of concentration.

(b) Developmental effects

The central studies are three rat developmental toxicity studies upon inhalation. Slight retardation in foetal and pup weight gain was reported in two studies (Solomon et al., 1995; Saillenfait et al., 2003; 7.8.2), but not in a third study (Lee et al., 1987):

- (1) Saillenfait et al. (2003) reported on reduced food consumption, reduced maternal body weight gain, and reduced foetal weight at 120 ppm [480 mg/m³]. At 60 ppm [240 mg/m³] there was only a slight reduction in maternal body weight gain on days 6-13 of gestation, but no significant later reduction on days 13-21.
- (2) Solomon et al. (1995) reported a very slight decrease in foetal weight in the F1 offspring at 116 ppm [464 mg/m³], with NOAEC being 51 ppm [204 mg/m³]. This slight effect also appeared at birth among the pups of the reproductive phase where it persisted for 21 days after birth, when NMP inhalation of the mother ceased. Thereafter, the body weight of the offspring was within the range of the control values. [A low palatability of the mother's milk might be a factor contributing to this effect.] Again, no developmental effects appeared in the 10 ppm [41 mg/m³] or 51 ppm [210 mg/m³] groups.
- (3) In the rat developmental toxicity study by Lee et al. (1987) exposure to 100 [24 ppm] or 360 mg/m³ [87 ppm] (6 h/d on days 6 through 15 of gestation) did not affect either the outcome of pregnancy or the embryonal growth rate.

Thus, the results of all these three developmental toxicity studies show only very slight or no effects at doses up to 120 ppm. Considering the overall weight of evidence, there might be a tentative, borderline and transient and reversible effect on the pup weight, with a NOAEC of 51 ppm, based on the study of Solomon et al. (1995). However, if such an effect would be assumed to exist, the degree of adversity for humans appears to be very low, as the effect is slight/borderline and fully reversible. It is not supported by all inhalation studies performed. In the study by Saillenfait et al, there was some decrease in foetal BW at 120 ppm, but in the presence of reduced maternal food consumption and small reductions in maternal body weight. As the studies by Lee et al (1987) and by Solomon et al (1995) were performed at the same laboratory, one would expect no relevant methodological differences between these studies.

Thus, developmental toxicity and minor effects on fertility have been reported in reproductive toxicity studies in rats, rabbits and mice, following exposure to NMP by the inhalation or the oral route at maternally toxic doses. NOAELs for reproductive effects range from 206 to 500 mg/m³ [51 – 125 ppm] in inhalation studies (see 7.8.2). As discussed in chapter 7.9, a NOAEC of 51 ppm (Solomon et al., 1995) is related to a borderline and transient and reversible effect on rat pup body weight gain. The degree of adversity of this effect for humans is considered to be borderline, as the effect seen at the next higher concentration of 116 ppm was borderline, fully reversible and of limited severity. In addition, in other inhalational developmental toxicity studies effects were seen not seen or were seen only in the presence of reduced food consumption and slight effects on maternal body weight. The consideration of this effect as being borderline is supported by oral studies, as even doses up to a level of 250 mg/kg did not show this effect.

For NMP SCOEL fully considers developmental effects, but does not regard developmental effects to be critical based on the evidence:

- a. For SCOEL the overall evidence confirms that developmental effects are only observed together with toxic effects on the dams, which invalidates the observations as being qualified as adverse effects.
- b. Even if taken into account, the observed findings are fully reversible regarding the manifestation of a possible and predicted adverse health effect.
- c. Also the observed findings are of borderline severity. The level of 5% applied as decision level and cut-off value for evidence is arbitrary. Though being in part statistically significant, the biological relevance and, thus adversity, is questionable.
- d. The intense bad smell of NMP and its irritation effects are plausibly explaining severe stress observations on animals and reduced food uptake or reduced uptake of mother milk. This could plausibly explain the observations reported.
- e. The experimental conditions, under which tests in animals were performed, addressed a different physical state of NMP above vapour saturation concentration.

The concentrations at which effects are suggested by RAC are by a margin of exposure (factor) of 5 below the OEL TWA recommended by SCOEL and already implemented and in place. If the correction factor for the human equivalent effect concentration from the PBPK assessment is taken into account, the margin would be in the range of 35 to 240. The margins indicate that even if there was an effect and even if the scientific evidence and plausibility would be assumed in contradiction to the listed findings above, the level of exposure is covered by the OEL recommended by SCOEL and implemented.

In conclusion, the derivation of an OEL considers both (a) acute local irritation effects, for which solid human data are available, and (b) the developmental effects (lower weight gain) upon repetitive dosing, as established in rats. For (a) local irritation, the conditions of the study of van Thriel et al. (2007) of 20 ppm provide a valid and well-defined point of NOAEC for the critical effect.

The study of van Thriel et al (2007) was a controlled human exposure study assessing especially sensitive and objectively verifiable effects. The study included experimental conditions of physical workload. It was performed in young male volunteers, which are considered as being highly susceptible to chemosensory effects (Brüning et al. 2014). Available data indicate that an intra-species uncertainty factor >1 may not be needed whenever good exposure studies with human volunteers are available (Brüning et al. 2014). Moreover, case studies have led to the conclusion that human acute experimental NOAECs for chemosensory effects are similar to NOAECs derived from exposures at the workplace (Brüning et al. 2014).

Therefore, the overall uncertainty factor applied by SCOEL considers possible differences due to gender and any possible remaining uncertainties. A factor of two appears adequate to account for the identified and remaining uncertainties.

An OEL (TWA) of 10 ppm and a STEL (15 min) of 20 ppm is therefore considered protective for workers. The study by van Thriel et al. revealed that peak concentrations of 40 ppm were also without effect, thus supporting a STEL of 20 ppm.

NMP is well absorbed through the skin, both in humans and in animal studies and some systemic toxicity (including developmental toxicity) is seen following dermal uptake. A "*skin*" notation is therefore considered necessary.