



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

**Risks of systemic effects after dermal  
exposure for workers**

*Part C: N-methylpyrrolidone as case study*

RIVM Letter Report 320002002/2012

W.P. Jongeneel



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## Colophon

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This investigation has been performed by order and for the account of Ministry of Social Affairs and Employment, within the framework of chemical safety

## Abstract

### **Risks of systemic effects after dermal exposure for workers - Part C: N-methylpyrrolidone as case study**

A newly developed methodology was found to be applicable to perform a health risk assessment. This methodology estimates the risk of systemic effects after occupational dermal exposure to chemical substances.

N-methylpyrrolidone (NMP), as constituent in paint removing agents, was chosen to evaluate the proposed methodology. The applied methodology requires information on the physico-chemical and toxicological characteristics of NMP. Three different levels of information availability (worker, branch organization and professionals) were identified and for each level the methodology was applied.

Using NMP as example, the methodology can be applied without problems if sufficient information sources are available. When only the (extended) Safety Data Sheet ((e)SDS) is available, information is too limited to be of use in the proposed methodology.

Key words:

N-methylpyrrolidone (NMP), employee, risk assessment, dermal exposure

## Rapport in het kort

### **Risico's op systemische effecten na huidblootstelling – Deel C: N-methylpyrrolidon als voorbeeld casus**

Uit dit rapport blijkt dat een nieuw ontwikkelde werkwijze toepasbaar is om een gezondheidskundige risico beoordeling uit te voeren. Deze werkwijze schat het risico in van systemische gezondheidseffecten voor werknemers als gevolg van huidblootstelling aan chemische stoffen.

N-methylpyrrolidon (NMP), als ingrediënt in verf afbijtmiddelen, is gekozen om de ontwikkelde werkwijze te testen. Hiervoor is informatie nodig over de fysisch-chemische en toxicologische eigenschappen van NMP. De beschikbaarheid van informatiebronnen kan in drie verschillende niveaus worden ingedeeld (werknemer, branche organisatie en professionals). Voor elk informatieniveau is de werkwijze toegepast.

Met NMP als voorbeeld, kan de werkwijze zonder problemen toegepast worden wanneer er voldoende informatiebronnen beschikbaar zijn. In het geval dat er alleen toegang is tot het veiligheidsinformatieblad (VSB), is de beschikbare informatie te beperkt om tot een bruikbare risicoschatting te komen met de voorgestelde werkwijze.

Trefwoorden:

N-methylpyrrolidon, werknemer, risicobeoordeling, RI&E, huidblootstelling

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## 1 Introduction

Employees in small and medium enterprises (SME) can be exposed to various chemicals during their daily working activities. Exposure can occur via different routes, such as inhalation or via the skin (dermal) and might result in local or systemic adverse health effects. Local effects take place at the point or area of contact, the site may be skin, the respiratory tract, gastrointestinal system, eyes, etc, often leading to signs of irritation. A systemic effect generally refers to an adverse health effect that takes place at a location distant from the body's initial point of contact and presumes absorption and systemic availability. Systemic health effects can range from mild and reversible to irreversible and even fatal effects.

According to article 5 of the Working Conditions Act (Arbeidsomstandighedenwet) the employer should make a Risk Inventory and Evaluation (RI&E) in which safe use of substances is described. Focus has predominantly been on assessment of health risks of inhalation exposures for which purpose occupational exposure levels (OELs) have been derived. Risk assessment of health effects after dermal exposure up to now has focused on local effects. The assessment of systemic effects after dermal exposure has had less attention to date. Instead, if dermal exposure could contribute substantially to the total body burden and consequently to concern, a skin notation is assigned in addition to the OEL. 'Substantial contribution' to total body burden will usually be established on a case-by case basis but may in general be of the order of 10% or more compared to the uptake from 8-hour respiratory exposure to the OEL. In practice, a quantitative limit value for the assessment of systemic health effects from dermal exposure will not be available and thus the RI&E might be considered incomplete and not compliant with regulations.

In contrast to the more acute local effects, such as irritation, it is unclear in what kind of branches systemic effects due to dermal exposure might be a serious health problem. The Labour Inspectorate has broad experience with the enforcement of respiratory OELs but only limited experience with dermal exposure. Therefore, there is a need to gain more insight on the incidence and seriousness of systemic health effects following dermal exposure.

The present report is part of an integral project on dermal exposure and systemic health effects in workers. This project consists of three parts; the first part (A) focused on the development of a methodology for employers and/or employees to estimate the risk of systemic health effects after dermal exposure (ter Burg et al. 2011); the second part (B) identified three examples of occupational scenarios where systemic health effects could be expected after dermal exposure (Jongeneel and ter Burg 2011). The present report describes the third and last part (C) in which the applicability of the developed methodology (part A) will be verified using one of the examples from part B.

## 2 Methods

The selection of the substance and a relevant occupational exposure scenario was made after consultation with the Ministry of Social Affairs and Employment (SZW). The scenario of choice was graffiti removal using paint removing agents containing N-methylpyrrolidone (NMP). Figure 1 describes the flowchart as developed in part A that will be applied to this scenario. The methodology as described in part A is based on a tiered approach where the flowchart is the first tier. If a risk for systemic health effects after dermal exposure can not be excluded, a more refined i.e. higher tier approach need to be undertaken. In such a higher tier, the exposure assessments can be refined.

### 2.1 Description of use

Graffiti removal using paint removing agents includes the application of graffiti remover (containing 50-100% NMP) onto a wall using a trigger spray and to actively disperse and brush the graffiti remover on the surface. It was assumed that during an 8-hour shift, these types of activity would occur about 1/3 of the time, i.e. approximately 160 minutes equally divided in 80 minutes of application and 80 minutes of brushing. This assumption is based on the fact that somebody does neither sprays or brushes graffiti remover onto a surface for a complete 8-h working shift. Instead, time will be spend on other activities like rinsing and hosing down the surface with water and the movement from one graffiti spot to another.

### 2.2 Substance information and information sources

Some relevant specific physico-chemical characteristics of NMP could be found in different information sources. This information could relate to the specific dermal absorption or toxicology. Three relevant information levels are identified:

Level 1: The (extended) safety data sheet ((e)SDS) of the used product.

Level 2: The public REACH registration dossier of NMP and some of the information sources as described in chapter 6 of part A:  
[http://ec.europa.eu/sanco\\_pesticides/public](http://ec.europa.eu/sanco_pesticides/public);  
[http://circa.europa.eu/Public/irc/env/bio\\_reports/library](http://circa.europa.eu/Public/irc/env/bio_reports/library);  
[www.ser.nl/nl/taken/adviserende/grenswaarden/overzicht%20van%20stoffen.aspx](http://www.ser.nl/nl/taken/adviserende/grenswaarden/overzicht%20van%20stoffen.aspx);  
[www.veiligwerkenmetchemischestoffen.nl/default.aspx](http://www.veiligwerkenmetchemischestoffen.nl/default.aspx);  
[www.rivm.nl/rvs/normen](http://www.rivm.nl/rvs/normen).

Level 3: [www.echemportal.org](http://www.echemportal.org);  
 other sources ((open) literature).

It is anticipated that every user has access to level 1 information, the safety data sheet (SDS), and can use the information provided. In practise this will be the SDS provided by the supplier of the mixture. However, for this verification of the applicability of the method, publicly available SDS's had to be retrieved. Exemplary SDS's of graffiti removal products available in the Netherlands containing NMP were collected via a desktop research using Google (keywords: '872-50-4 sds graffiti' and '872-50-4 veiligheidsinformatieblad graffiti', only looking at pages originating from the Netherlands). Eight SDS's were retrieved using this methodology and used to determine which information is available on the product SDS. No extended SDS containing relevant exposure scenarios was found. All SDS's were last updated between August 2007 and December 2008.



Larger branch organisations usually can interpret and use level 2 information. Only professionals will probably have access to, and knowledge to interpret level 3 information. When the applied methodology requires information on the physical, chemical or toxicological characteristics of NMP the information level at which this information is available will be stated.

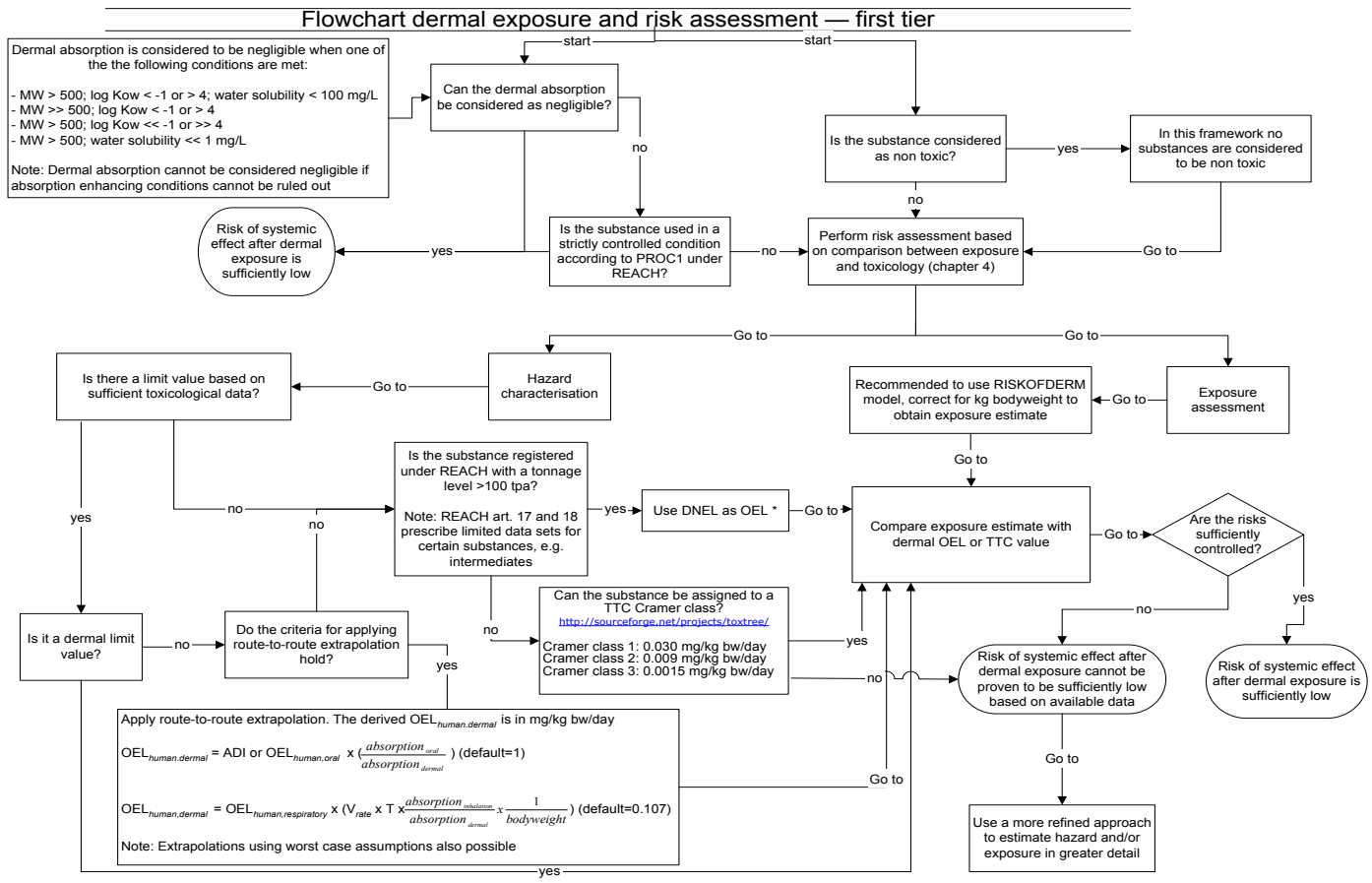


Figure 1: Flowchart dermal exposure and risk assessment.

\* In case under REACH a dermal DNEL was derived it should be checked if the route-to-route criteria were met. If the dermal DNEL was derived based on oral or inhalation data, the route-to-route extrapolation described in this report could be considered as well.

Note that the recommended route is displayed in the scheme, i.e. use existing limit values first, prior to considering the DNEL, although both are equally acceptable.



## 3 Results

Using the flowchart described by ter Burg et al. 2011 (Figure 1) three scenarios are considered: negligible exposure, negligible toxicity and the comparison between exposure and toxicological data. In part A it was concluded that only absence of toxicity was not an applicable criteria to ascertain safe use. Therefore, in this chapter only the scenarios concerning negligible exposure and the comparison between exposure and toxicological data will be discussed.

### 3.1 Scenario 1: Negligible exposure

Starting point in this scenario is that the information on exposure (taking into account the properties of substance, products and processes) may suffice to conclude safe occupational use if exposure is non-existent, or considered to be negligible or not relevant. This evaluation will be performed by for instance the employer at SME, expert from branch organization or a consultant with sufficient knowledge on exposure and risk assessment.

#### 3.1.1 *Exclusion of internal exposure after dermal contact*

This section describes the information needed and how it can be used to verify whether internal exposure after dermal contact can be considered negligible. Key element in this approach is the assessment of the dermal absorption potential of a substance and to assess whether it is sufficiently low to conclude negligible internal exposure.

##### 3.1.1.1 Level 1 information:

No data on dermal absorption or relevant physico-chemical characteristics was found on the exemplary SDS's. Preferably, measured data are used to establish the dermal absorption of a substance. However, this kind of information is not obligatory for an SDS. Instead, the SDS contains information on some physico-chemical characteristics of the end product, usually a mixture, and not of the individual components. Essential information, such as the molecular weight and the log  $K_{ow}$ , that are needed to determine the dermal absorption, are not included in the SDS. Therefore, users having only access to the SDS will not have sufficient information to evaluate the potential dermal absorption.

##### 3.1.1.2 Level 2 information

The information sources available at level 2 leads, among other, to the derivation of the occupational exposure limit for NMP by the SCOEL ([www.ser.nl/en/oel\\_database.aspx](http://www.ser.nl/en/oel_database.aspx)). The background document ([www.ser.nl/documents/43948.pdf](http://www.ser.nl/documents/43948.pdf)) provides measured data for the dermal absorption of NMP. Human volunteer studies have shown that NMP is rapidly absorbed following exposure by the inhalation, dermal or oral route. Ligocka et al. demonstrated a mean 68% absorption of NMP through the skin in 12 human volunteers exposed for 6 hours to 300 mg 100% NMP via a skin patch (filter paper, 5 cm diameter) (Ligocka et al. 2003).

Additionally, Bader et al. have reported dermal absorption of NMP from the vapour phase, equivalent to approximately ~ 30 % of the total inhalation dose in an experimental study in human volunteers, the design of which included a phase in which inhalational uptake was prevented by face shields (Bader et al. 2008). Dermal absorption can therefore contribute significantly to the body

burden and therefore negligible dermal absorption is excluded based on measurement data.

The [public registration dossier](http://echa.europa.eu/) of NMP contains several *in vitro* en *in vivo* studies in rat and *in vitro* on the human skin (<http://echa.europa.eu/>). NMP was administered via both occlusive as non-occlusive methods in several dilutions with water and limonene. Absorption ranged from 15-98% depending on the species, dilution of NMP, carrier and type of application. Although these studies provide more insight in the toxicokinetics of NMP, the human volunteer study by Ligocka *et al* is believed to be more relevant to assess the dermal absorption of NMP in humans.

Although in this case not necessary for NMP, an evaluation based on physico-chemical properties is made for illustrative purposes. Dermal absorption is considered to be very low if one of the following conditions is met:

- MW > 500; log  $K_{OW}$  < -1 or > 4; water solubility < 100 mg/L;
- MW >> 500; log  $K_{OW}$  < -1 or > 4;
- MW > 500; log  $K_{OW}$  << -1 or >> 4;
- MW > 500; water solubility << 1 mg/L;

In Table 1 the relevant physico-chemical properties of NMP are given. From the chemical-physical properties of NMP and the criteria for low dermal absorption set out above, it follows that the dermal absorption of NMP can not be considered to be very low.

Table 1: Chemical and physical properties of NMP (source: SCOEL 2007)

	<b>Molecular weight</b>	<b>Log <math>K_{OW}</math></b>	<b>Water solubility</b>
NMP	99.13	-0.38	100% at 25°C

Both the *in vivo* experimental data as well as the physico-chemical properties of NMP indicate a relevant dermal absorption potential. Therefore, the criteria for exclusion of internal exposure after dermal contact are not met.

#### 3.1.1.3 Level 3 information

The information gathered from level 2 sources is sufficient for evaluation of the dermal absorption potential and there is no need to access level 3 sources.

#### 3.1.2 Negligible external dermal exposure

Negligible exposure cannot be defined without having adequate toxicological knowledge, that is: as substances are more toxic, a lower exposure is required to induce adverse health effects. Therefore, it was decided in part A to focus on strictly controlled conditions as stated under REACH. If a substance is used under conditions described in Process Category 1 (PROC 1) of the REACH Guidance on Information Requirements and Chemical Safety Assessment, then the exposure can be considered negligible.

PROC1 is described as follows: 'Use in closed process, no likelihood of exposure. Use of the substances in high integrity contained system where little potential exists for exposures, e.g. any sampling via closed loop systems'. The most important criterion is that the design and quality of the closed system should be such that any contact with the substance is prevented. This means no leakage or release of the substance should occur at any moment, no transfer activities or other activities that could result in contact should occur.

From the work description, as mentioned in the introduction, it is clear that the use specified does not fulfil the description of PROC 1. Therefore, the criteria for negligible external dermal exposure are not met.

### 3.1.3 *Conclusion on scenario 1*

In conclusion, the external dermal exposure to NMP is not negligible in the present exposure scenario and internal exposure after dermal contact can not be excluded.

## 3.2 **Scenario 2: comparison of exposure and toxicological data**

### 3.2.1 *Exposure assessment*

The assessment of dermal exposure can be done in several ways. Measurements can be performed at the workplace showing the dermal load during work shifts. Biomonitoring has gained much interest in recent years. More feasible in practice is the use of models to estimate the dermal exposure or the risks after dermal exposure.

In part A it was recommended to use the RISKOFDERM model (freely available from [www.tno.nl](http://www.tno.nl)). The RISKOFDERM model is aimed specifically at dermal exposure, provides quantitative dermal exposure ranges based on measured data, and as more practical reason, is task-based. The latter is a major advantage in assessing the risks of several tasks within a company and moreover is very helpful in setting up risk control strategies. It is highly recommended to at least obtain quantitative exposure estimates as the estimate can directly be compared to an OEL.

A basic internet research focusing on the keywords 'graffiti removal' or 'graffiti remover' gave the following insights about the routine of graffiti removal. The paint removing agent can be applied onto the smirched wall using a trigger spray. Some instructions mention the use of a brush to actively disperse and brush the paint removing agent onto the wall. Usually, the paint removing agent needs to soak on the surface for approximately 5 to 10 minutes before the wall is rinsed or pressure hosed off with water. For the exposure assessment, the application of the paint removing agent and the brushing on the wall are identified as the most relevant tasks for dermal exposure. The rinsing or pressure hosing with water is considered less relevant.

The application rate of the product for both tasks is estimated to be 0.009 liter/minute. This rate is chosen from measured mass generation rates of trigger spray cans used in ConsExpo (Delmaar and Bremmer 2009). It corresponds to the mass generation rate of a plant spray with the nozzle set at coarse droplets. In practice, user info can be used. Furthermore, it is anticipated that the dispersion and brushing of the paint removing agent on the surface is done with a hand held brush, capable of applying more strength and therefore enabling more actively forced brushing.

In Table 2 the task specific input assumptions for the work description of the application of the paint removing agent are given. Table 3 provides the task specific input assumptions for brushing and dispersion of the paint removing agent. These assumptions are used to generate the exposure estimate. The output of the RISKOFDERM model for both tasks is depicted in Table 4.

Table 2: Input parameters in the RISKOFDERM model for the work description of the application of the paint removing agent

<b>RISKOFDERM model description</b>	<b>Input for task specific application of graffiti remover</b>
Relevant process for the assessment	Spraying: <i>Spray application of products such as paints, glues, cleaning products.</i> <i>Hosing down with water using a normal water line under normal pressure is <u>not</u> included</i>
Where is the spray application done?	Outdoors
Is application done downward or level or overhead?	Level
What is the direction of airflow that comes from the source?	Away from the worker
Is the worker segregated from the source?	No
How far is the source from the worker?	Up to 1 meter
What is the volatility of the carrier liquid?	Highly volatile
Is the product sprayed a liquid or a solid	Liquid
What is the application rate of the product?	0.009 liter/minute
Percentile for the exposure rate distribution to be assessed?	90% percentile
What is the cumulative duration of the scenario during a shift?	80 minutes

Table 3: Input parameters in the RISKOFDERM model for the work description of the brushing of the graffiti remover on the surface

<b>RISKOFDERM model description</b>	<b>Input for task specific brushing of graffiti remover</b>
Relevant process for the assessment	Dispersion with handheld tools: <i>Dispersion of products of substances by using a brush, comb, rake, roller or other tool with a handle; the purpose is to spread the product over a surface.</i>
Is application done downward or level or overhead?	Level or overhead
What is the viscosity of the product applied?	Viscosity like water
What is the application rate of the product?	0.009 liter/minute
What kind of tools are used for the application?	Tools with handles <30 cm in lengths
Percentile for the exposure rate distribution to be assessed?	90% percentile
What is the cumulative duration of the scenario during a shift?	80 minutes

Table 4: Output (in mg per daily 8-hr shift) of the RISKOFDERM model for the work description of the application (spraying) and dispersion (brushing) of the paint removing agent.

	<b>Spraying</b>	<b>Brushing</b>
<b>Results percentiles</b>	<b>Hands loading (mg*)</b>	<b>Hands loading (mg*)</b>
10%	11	3
20%	24	8
30%	42	16
40%	68	32
50%	106	58
60%	168	107
70%	272	207
80%	481	445
<b>90%</b>	<b>1057</b>	<b>1288</b>
95%	2027	3098
99%	6874	16072 (may be unrealistic)

\* The RISKOFDERM model assumes a density of 1. In practice, the density of NMP is 1.03 g/cm<sup>3</sup> and the density of a NMP containing (50-100%) graffiti remover is 0.97 g/cm<sup>3</sup>.

It is suggested in part A to take the 90<sup>th</sup> percentile as outcome for the exposure assessment. When adding hands loading values (90% outcomes) for both activities the total exposure on the hands is estimated to be 2345 mg per day. When assuming a default bodyweight of 70 kg, the total external exposure would be 33.5 mg/kg bw/day. This loading assumes 100% NMP as the graffiti remover. Specific information on the percentage of NMP in the graffiti remover could lower the total exposure. Furthermore, in this exposure scenario only the potential exposure to the hands and forearms is taken into account, assuming that the other body parts should be covered by (working) clothing.

### 3.2.2

#### *Determination of a dermal occupational exposure limit*

A dermal occupational exposure limit (OEL) can be available or determined using several different methods. There are three methods that can be used in the first tier approach:

- For substances with an existing limit value, such as an inhalation OEL or an oral ADI, the dermal OEL can be determined using route-to-route extrapolation if the requirements for this extrapolation (as specified in ter Burg *et al.*, 2011) are fulfilled and the limit value is based on sufficient data. A Dutch legal inhalation OEL fulfils these data requirements. However, the direct determination of a dermal OEL from the original data base is advised in such cases especially if inhalation OELs are based on oral NOAELs.
- Use the dermal DNEL as determined for REACH as a dermal OEL if the data requirements and the route-to-route requirements are fulfilled.
- The dermal toxicological threshold of concern (TTC) can be used as a remaining option for all substances.

It is recommended, but not legally obliged, to first evaluate the option of using an existing limit value, prior to continue the DNEL option. The TTC approach should only be used as a last option. The reason for this recommendation is that existing limit values have been derived by governmental agencies and have been subject to peer review, whereas DNELs are set by industry and may not be peer reviewed. For NMP, as exemplary case, all three methods will be explored.



### 3.2.2.1 Level 1 information

#### **Using an existing limit value**

In two exemplary SDS's a respiratory occupational exposure limit value (OEL) was given for NMP. Limit values were given for peak (STEL, 15-min TWA) and long term (8-h TWA) exposure. The source of the limit values was not traceable. The OEL stated in the SDS is an inhalation OEL and should therefore be extrapolated to a dermal OEL. When applying route-to-route extrapolation the following set of criteria need to be fulfilled:

- a) the available toxicity data are considered adequate and reliable;
- b) the critical effect(s) for the routes of exposure under consideration are systemic, and the absorption and expression of toxicity are not influenced by possible local effects;
- c) the considered toxic effect is independent of the route of exposure;
- d) the absorption efficiency is the same between routes or the difference is known and can be quantified;
- e) hepatic first pass effects are minimal;
- f) there is no significant chemical transformation by oral, gut or skin enzymes or in pulmonary macrophages;
- g) the chemical is relatively soluble in body fluids.

From the information on the SDS most of the above mentioned criteria can not be evaluated. Therefore, users having only access to the SDS will not have sufficient information to transpose an inhalation OEL to a dermal OEL.

#### **Using the dermal DNEL**

None of the exemplary SDS's contained dermal DNEL's as the latest update of the SDS was in 2008, some years before the REACH registration of NMP. Updated SDS's might contain a dermal DNEL, but in any case its toxicological basis should be checked. Only if the substance is registered with a tonnage level >100 tpa, the toxicological basis is considered to be sufficient. Furthermore, a dermal DNEL will often be derived using route-to-route extrapolation in which case the criteria set above for route-to-route extrapolation should apply. From the SDS information only, most of these criteria can not be evaluated. Therefore, users having only access to an SDS with a dermal DNEL will not have sufficient information to evaluate the applicability of this dermal DNEL in a first tier approach as described in part A.

#### **Using the dermal TTC**

As a last option, the substance might be assigned to a TTC Cramer class (<http://sourceforge.net/projects/toxtree/>). The toxicological threshold of concern (TTC) is a level below which toxicological effects are not expected for a specified class of substances, even though the substance itself has not been tested for its toxicity. The TTC concept is characterized by the classification of substances into three classes by Cramer, i.e. the Cramer classes I-II-III. The classes are based on chemical structure and one can allocate a substance to one of the classes by a decision tree approach. For the assignment of a substance in a Cramer class, the SMILES notation and some common knowledge on the chemical structure is needed. This information is not stated on the SDS, therefore the substance can not be assigned to a Cramer class.

In conclusion, the information provided at level 1, the SDS, is not sufficient to determine a dermal OEL or TTC value. Even if an SDS provides a dermal DNEL it can not be evaluated as to its applicability in the present approach. Therefore,

risk of systemic effects after dermal exposure cannot be proven to be sufficiently low based on available level 1 data.

### 3.2.2.2 Level 2 information

#### **Using an existing limit value**

Preferably, an existing limit value is to be used. The social economic council (SER) of the Netherlands ([www.ser.nl](http://www.ser.nl)) has published a public inhalation limit value for NMP of 40 mg/m<sup>3</sup>, corresponding to 10 ppm. This limit value is adopted from the Scientific Committee on Occupational Exposure Limits (SCOEL) of the EU. Also a skin notation is assigned to NMP by the SCOEL as '*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*'. The underlying SCOEL report can be consulted on the website of the SER ([www.ser.nl/documents/43948.pdf](http://www.ser.nl/documents/43948.pdf)).

The inhalation OEL is based on developmental toxicity and some effects on fertility in reproductive toxicity studies in rats, rabbits and mice following exposure to NMP at maternally toxic doses. The SCOEL states the following regarding the derivation of the inhalation OEL:

*'In relation to the reproductive toxicity seen in studies with NMP in rats, rabbits and mice, changes seen at exposure levels of 250 - 500 mg/m<sup>3</sup> by the inhalation route were minor (decreased pup weight and pup weight gain in the presence of maternal toxicity). NOAELs lay in the range 206 - 500 mg /m<sup>3</sup>. Application of an Uncertainty Factor (UF) of 5 to the lowest figure in this range provides an OEL of 40 mg/m<sup>3</sup>. 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.'*

*'Taking into consideration the potential of NMP to produce respiratory irritation and chemosensory effects, both in humans and animals, and systemic toxicity, in particular reproductive toxicity in studies in experimental animals, a health-based OEL (8-hour TWA) of 10 ppm (40 mg/m<sup>3</sup>) is recommended. A STEL (15 mins) of 20 ppm (80 mg/m<sup>3</sup>) is proposed, in order to limit peaks of exposure which could result in irritation. This recommendation is supported by the results of inhalation studies in animals.'*

The OEL of the SCOEL is based on inhalation studies. To transpose an inhalation OEL to a dermal OEL, route-to-route extrapolation need to be applied. When applying route-to-route extrapolation the following set of criteria need to be fulfilled:

- a) the available toxicity data are considered adequate and reliable;
- b) the critical effect(s) for the routes of exposure under consideration are systemic, and the absorption and expression of toxicity are not influenced by possible local effects;
- c) the considered toxic effect is independent of the route of exposure;
- d) the absorption efficiency is the same between routes or the difference is known and can be quantified;
- e) hepatic first pass effects are minimal;
- f) there is no significant chemical transformation by oral, gut or skin enzymes or in pulmonary macrophages;
- g) the chemical is relatively soluble in body fluids.

For the extrapolation of the inhalation OEL of NMP all these criteria are met.

(a) Recommendations from the SCOEL that are adopted by the SER are considered to be based on adequate and reliable data. (b) Although NMP causes some respiratory irritation and chemosensory effects as well, the 8-hour TWA OEL is based on systemic effects (developmental and fertility effects). (c) Developmental effects were seen after oral, inhalation and dermal exposure in rats and rabbits. (d) Toxicokinetic studies in human volunteers and in animals show readily absorption of NMP after oral, dermal and inhalation exposure. Total absorbed doses are estimated at 100% for inhalation, 68% after dermal exposure and 65% after oral exposure. (e) Although this is less relevant for the extrapolation of an inhalation OEL to a dermal OEL, there are no indications of significant hepatic first pass effect altering the systemic toxicity seen after NMP exposure. In fact, the SCOEL background document states that the minor metabolite 2-pyrrolidone, formed after NMP exposure, might be responsible for the reproductive effects seen in animal studies with NMP. (f) There are no indications of significant chemical transformation by oral, gut or skin enzymes or in pulmonary macrophages. (g) The substance has a log  $K_{ow}$  of -0.38 and is 100% soluble in water at 25°. It is therefore assumed that NMP is also relatively soluble in body fluids.

For the route-to-route extrapolation from an inhalation OEL to a dermal OEL the following equation is proposed in part A:

$$OEL_{human,dermal} = OEL_{human,respiratory} \times V_{rate} \times T \times \frac{absorption_{inhalation}}{absorption_{dermal}} \times \frac{1}{bodyweight}$$

The following parameters are used:

- a default worker ventilation rate of 1.25 m<sup>3</sup> per hour for light activities;
- a default exposure time of 8 hours per work shift;
- a respiratory absorption of 100%;
- a dermal absorption of 68%;
- a default bodyweight of 70.

Using the equation above, the inhalation OEL of 40 mg/m<sup>3</sup> can be extrapolated to a dermal OEL of 8.4 mg/kg bw/day.

### Using the dermal DNEL

On the website of the European Chemical Agency (ECHA) (<http://echa.europa.eu/>) NMP has been registered with a [registration dossier](#). A dermal DNEL for workers of 19.8 mg/kg bw/day is given for systemic effects after long term exposure. It should be checked what the toxicological basis of this dermal DNEL is. Only if the substance is registered with a tonnage level >100 tpa, the toxicological basis can be considered sufficient. The dossier contains the necessary toxicological data associated with >100 tpa dossiers and an additional reproduction study is available. This means the toxicological data requirements are fulfilled.

It is not known whether this dermal DNEL is derived via extrapolation of the inhalation DNEL. The dossier contains a dermal developmental study in rats with a NOAEL of 237 mg/kg bw/day. The derived DNEL is almost exactly 12 times lower than the NOAEL in the dermal study. Therefore, it is plausible that the REACH DNEL is based on the dermal developmental study using a total assessment factor (AF) of 12 (probably an AF of 4 for allometric scaling and an

AF of 3 for differences within the working population conform the ECETOC Guidance (available at [www.ecetoc.org](http://www.ecetoc.org))).

### Using the dermal TTC

The toxicological threshold of concern (TTC) is a level below which toxicological effects are not expected for a specified class of substances, even though the substance itself has not been tested for its toxicity. The TTC concept is characterized by the classification of substances into three classes by Cramer, i.e. the Cramer classes I-II-III. The classes are based on chemical structure (using the SMILES notation) and one can allocate a substance to one of the classes by a decision tree approach. The SMILES notation of NMP can be calculated using its CAS number at <http://cactus.nci.nih.gov/chemical/structure> Using Toxtree (<http://sourceforge.net/projects/toxtree/>), a free software program, NMP was assigned as Cramer class III. The corresponding value for dermal exposure is 0.0015 mg/kg bw/day.

In conclusion, the information provided at level 2 is sufficient to determine a dermal OEL from an existing limit value or TTC value. Furthermore, a dermal DNEL is provided from the REACH registration dossier, although it is unknown how this DNEL has been derived.

#### 3.2.2.3 Level 3 information

The information gathered from level 2 sources is sufficient for the determination of a dermal OEL and there is no need to access level 3 sources.

#### 3.2.3 Comparison of estimated exposure with the derived dermal OEL's

In this section a comparison is made between the exposure estimate (the 90<sup>th</sup> percentile using RISKOFDERM) and the dermal OEL's discussed in section 3.2.2. A risk characterisation ratio (RCR) is calculated as a comparison between the estimated exposure and the respective dermal OEL's. This RCR can be used to estimate whether the dermal exposure could result in a health risk. If the RCR is equal to or smaller than 1, it can be concluded that dermal exposure will not result in a health risk. However, when the dermal exposure is higher than 1, a health risk can not be excluded. In such cases the risk assessment could be refined or the working conditions should be adapted to reduce the exposure to a level below the dermal OEL. In Table 5 the results of the comparisons are shown.

Table 5: Comparison between the estimated exposure and the different derived dermal OEL's.

	Exposure (mg/kg bw/day)	Risk characterisation ratio
<b>Dermal exposure estimation</b>		
RISKOFDERM 90 <sup>th</sup> percentile	33.5	
	<b>OEL (mg/kg bw/day)</b>	
<b>Dermal OEL derivation</b>		
Existing legal limit value	8.4	4.0
REACH dermal DNEL	19.8	1.7
TTC	0.0015	>20.000

#### 3.2.4 *Conclusion on scenario 3*

For users only having access to level 1 information, the SDS, the information is not sufficient to derive a dermal OEL. Therefore, risk of systemic effects after dermal exposure cannot be proven to be sufficiently low based on the available data at level 1

For users having access to level 2 information, dermal OEL's can be derived. As can be seen from Table 5, for all derived dermal OEL's the exposure is higher than the derived dermal OEL. Therefore, a risk of systemic health effects given the specified working conditions can not be excluded.

## 4 Discussion and conclusion

In general, the safe use of substances by workers can be confirmed by either showing that exposure is negligible or by showing that the exposure is below a relevant toxicological limit value. Preferably, the latter approach is aimed for as possible risks are quantitatively characterized which makes it possible to evaluate possibilities for and effectiveness of risk reduction measures. These approaches also apply to systemic effects after dermal exposure for workers.

In this report, a health risk assessment following dermal exposure is conducted for the use of NMP-containing paint removing agents by workers who remove graffiti outdoors. The risk assessment is based on the methodology as developed in part A of this project. Using this methodology, both internal as well as external exposure to NMP could not be considered negligible for this scenario. Subsequently, a dermal exposure estimate was generated with the RISKOFDERM model and compared with dermal occupational exposure limits derived from different information sources. The estimated exposure is in all instances higher (range 1.7 - >20.000) than the respective limit values. Therefore, a risk of systemic health effects due to dermal exposure of NMP when removing graffiti outdoors can not be excluded

Three levels of available information sources were created reflecting the available information and interpretation at worker, branch and professional level. It can be concluded that the available information at worker level, only having access to the (e)SDS, is insufficient to perform a health risk assessment following dermal exposure in this first tier approach. At level two, sufficient information is available to perform a risk assessment based on the considered methodology. A higher level of information sources was not necessary in the first tier and is expected to be only useful in a higher, more refined, tier. In such a higher tier the exposure assessments can be refined by actual exposure measurements at the workplace or through use of more complex internal exposure models such as IndusChemFate.

The methodology as proposed in part A was found to be applicable for a first tier approach to perform a health risk assessment following dermal exposure. Using NMP as example the methodology can be applied without problems if sufficient information sources are available. For workers having only access to the (e)SDS, the available information is too limited to be of use in the proposed methodology.

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