



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

Risks of systemic effects after dermal exposure for workers

Part A: Proposed approaches for risk evaluation

RIVM letter report 320041001/2011

W. ter Burg | J.J.A. Muller | W.P. Jongeneel



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W ter Burg, JJA Muller, WP Jongeneel.

Contact:

Wouter ter Burg

Centre for Substances and Integrated Risk assessment (SIR)

wouter.ter.burg@rivm.nl

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Abstract

Risks of systemic effects after dermal exposure for workers – Part A: Proposed approaches for risk evaluation

A simple approach is suggested to evaluate risks of systemic effects after occupational dermal exposure to chemical substances. Legislation requires that employers provide a safe and healthy workplace for their employees and moreover that employers should be able to prove that the occupational exposure is safe. However, up till now an evaluation of risks associated with occupational dermal exposure is rarely included.

The approach, which is represented in a flowchart, is based on available information on the substance's properties. To assess or exclude possible risks from occupational dermal exposure two methods were described. The first method describes how the dermal exposure and/or dermal absorption of a substance can be excluded. In the second method is described how exposure estimates and limit values can be obtained and compared to each other to assess the risk. If the data is considered insufficient, alternative methods are suggested, which however require more toxicological assessment skills.

Keywords:

chemicals, employee, risk assessment, dermal exposure

Rapport in het kort

Risico's op systemische effecten na huidblootstelling – Deel A: voorgestelde aanpakken voor risico-evaluaties

Een eenvoudige aanpak is voorgesteld om risico's op systemische effecten na huidblootstelling in arbeidssituaties aan chemische stoffen te kunnen beoordelen. De wetgeving vereist dat werkgevers hun werknemers veilig en gezond laten werken en dit ook aan kunnen tonen. Op dit moment worden systemische effecten na huidblootstelling vaak niet meegenomen in Risico Inventarisatie en Evaluatie (RI&E) door een werkgever.

De eenvoudige aanpak is gebaseerd op beschikbare stof- en toxiciteitsgegevens en samengevat in een werkschema. Om risico's te beoordelen of uit te sluiten worden twee methoden beschreven. De eerste methode houdt in dat wordt aangetoond dat er geen huidblootstelling of huidopname van een stof is. In de tweede methode, wordt beschreven hoe huidblootstelling en normen van een stof kunnen worden verkregen. De verkregen huidblootstelling en norm kunnen dan met elkaar vergeleken worden om een risico te kunnen beoordelen. Als onvoldoende gegevens beschikbaar zijn, dan worden aanbevelingen gedaan voor een alternatieve aanpak, die meer toxicologische kennis vereist.

Trefwoorden:

gevaarlijke stoffen, werknemer, risicobeoordeling, RI&E, huidblootstelling

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Summary

In the workplace, workers are often exposed to a range of substances.

According to article 5 of the Working Conditions Act

((Arbeidsomstandighedenwet) the employer should have a Risk Inventory and Evaluation (RI&E), in which safe use of those substances is described. Focus has predominantly been on assessment of health risks after inhalation exposure, to which end 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. In practice, a safe value will not be available for dermal exposure and thus the RI&E might be considered incomplete and not compliant with regulations. In this report, methods for showing safe use of substances are explored and a first tier approach to assess the risks of systemic effects after dermal exposure will be proposed.

In the first tier approach, three scenarios were described, including several methods:

- 1) determining that exposure can be considered negligible,
- 2) determining that the toxicity can be considered negligible, or
- 3) determine that the exposure is below the toxicological reference value (OEL).

In case a substance will not be absorbed by the skin or will not come into contact with the skin, the internal exposure can be considered negligible. Multiple criteria, to be used in a weight of evidence approach, are given to determine whether dermal absorption is sufficiently low to conclude that exposure is negligible. The use of substances in 'closed' systems will be sufficient to conclude negligible external exposure if the closed system meets high standards. Since negligible exposure relates to the toxicity of a substance, in case of extremely toxic substances this approach should therefore not be used as low exposures may still cause effects.

There are no lists of substances with sufficiently low human toxicity. Also there are no criteria to determine such substances. Therefore, it cannot be concluded that a substance has such a low toxicity that no risk assessment is required. In most cases, the third approach will have to be followed where one should derive a dermal exposure estimate and obtain a dermal OEL. Based on a brief evaluation of exposure models it is recommended to use the RISKOFDERM model to determine the dermal exposure. Two options are given to obtain a dermal OEL, i.e. apply route-to-route extrapolation from existing (inhalatory) OELs or use the dermal DNEL from REACH or another toxicological reference value. Alternatively the Toxicological Threshold of Concern concept can be used. The three scenarios are summarized in a flowchart and information sources to obtain toxicological information are given.

The safe use of a substance can be shown following one of the suggested approaches, provided conditions are met. It is preferred to follow the third approach, because in this approach the risks are characterized and therefore the result provides more confidence. Possibly the third approach needs refinement steps (iteration) to determine safe use of the substances or the user could consider higher tier approaches. It remains the responsibility of the employer to take sufficient measures to control the risks.

1

Introduction

In the workplace employees can be exposed to hazardous chemicals. The use of such chemicals may lead to possible health risks. Therefore a Risk Inventory and Evaluation (RI&E) is required for employers according to article 5 of the Working Conditions Act (Arbeidsomstandighedenwet). According to article 4.2 of the Occupational Safety and Health Decree (Arbeidsomstandighedenbesluit) this includes exposure and risk assessment of dangerous substances they either produce, store, transport or use. Current RI&Es focus predominantly on inhalation exposure and risks. To this date, the Dutch occupational exposure limits (OELs) are based on inhalation exposure, resulting in occupational exposure limits for the duration of an eight hour work shift for a work life-time exposure (40 years, 8h-time weighted average; TWA) or for 15-min. A skin notation is given to an OEL if dermal exposure or dermal toxicity is considered relevant (www.ser.nl), but no quantitative dermal OELs have been derived. In general, local skin effects as a result of dermal exposure, such as irritation, corrosion, and sensitisation, are covered in safety data sheets (SDS). However, systemic effects caused by dermal exposure, may be overlooked in the RI&E.

At this moment the extent of the possible risks associated with occupational dermal exposure related systemic toxicity is unknown. Additionally, as there is less focus on systemic effects after dermal exposure compared to other routes of exposure, the Labour Inspectorate has not paid attention to inspecting the measures taken against those possibly risky work scenarios. In practice, a safe value will not be available for dermal exposure and thus the RI&E might be considered incomplete and not compliant with regulations. Currently, there are limited 'prefab' methods available that can be used to set up a RI&E for systemic effects after dermal exposure. Therefore, a more in depth exploration of methods is made that should provide methods to determine risks of systemic effects after occupational dermal exposure. Methods used for a quantitative or qualitative risk assessment of systemic effects after dermal exposure used in REACH and in several surrounding countries were explored to this end. Short descriptions of these methods are provided in Appendix I. In addition, approaches developed within the European 6th framework project OSIRIS on integrated testing strategies were considered. Further, some methods used for the derivation of inhalation OELs were looked upon.

The explored methods and approaches will be described in this letter report, following scenarios of the availability of information, i.e. the scenario negligible exposure of a substance, scenario negligible toxic properties of a substance, or the scenario where exposure and toxicity are compared (chapters 2, 3 and 4, respectively). Attention is given to the applicability and data requirements associated with the methods and/or approaches. The advantages, disadvantages, consequences and actions for users in those scenarios will be described. The preferred scenario, which an assessor should strive after, is the scenario where an exposure assessment is compared to the toxic properties of a substance.

In this report, a first tier approach will be suggested and additional options for a higher tier approach will be indicated where possible. The entire first tier approach including all three scenarios is visualized in a flowchart (chapter 5). A medium level of experience in the field of exposure assessment, toxicology and

risk assessment is required. The approaches should be workable for people like occupational toxicologists and occupational hygienists.

This report is part of an integral project on dermal exposure and systemic health effects in workers. This project consists of two parts; the first part (A) focuses on the exploration of methods to estimate the risk of systemic health effects after dermal exposure; the second part (B) is to identify two or three examples of working conditions relevant for the small and medium enterprises (SME, Midden- en Kleinbedrijf in which systemic health effects could be expected after dermal exposure to substances. At a later stage, the derived first tier approach may be applied to the selected substances.

2 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. The user, i.e. the employer at SME, expert from branch organization or a consultant with sufficient knowledge on exposure and risk assessment, can indicate that the dermal exposure is without appreciable risk if exposure is non-existent, or considered to be negligible or not relevant.

Indicating that an exposure is negligible with sufficient reliability is difficult or perhaps impossible, because an exposure may be very low, but in combination with a very highly toxic substance may still be cause for concern. Whether or not an exposure is negligible is therefore based on weight of evidence in combination with expert judgment in this approach. Preferably, the exposure is quantified and compared to a toxicological reference value, where possible.

For example: the use of substances in closed systems may seem to be without any exposure. Although the term closed system may indicate otherwise, a closed system is never fully closed because of joints in the installations, valves and must be opened every now and then for maintenance. Dermal exposure may therefore be possible. Even short infrequent exposures can lead to systemic effects if the substance is absorbed. In the situation where dermal exposure cannot be excluded, systemic exposure can be considered negligible when a substance is not taken up dermally, in other words is not absorbed.

In this chapter first an overview will be presented of situations where internal dermal exposures can be excluded or can be considered negligible and second when external dermal exposure can be considered negligible.

2.1 Exclusion of internal exposure after dermal contact

This section describes when and how internal exposure after dermal contact can be considered negligible. Key element in this approach is the assessment of dermal absorption of a substance.

2.1.1 Negligible dermal absorption

Dermal absorption is necessary before a substance becomes systemic available and can cause systemic effects. The literature on dermal absorption of substances is extensively discussing methods to measure dermal absorption using human skin, animal skin (*in vivo* and *ex vivo*), skin cultures, amongst others, and discussing methods to estimate absorption by mathematical models. For dermal absorption, a validated OECD *in vitro* study already exists (OECD 428).

In order for a substance to be absorbed, it must be able to cross biological membranes. According to and based on the Technical Guidance Document (EC, 2003; EC, 2007), absorption of compounds by dermal route is likely to be impaired when some of the following criteria are valid:

"Substances that can potentially be taken up across the skin include gases and vapours, liquids and particulates. Dermal absorption is influenced by many

factors, e.g. physico-chemical properties of the substance (i.e. molecular mass and lipophilicity), its vehicle and concentration, and the exposure pattern as well as the anatomical site of the exposed skin. For the following, preliminary indications can be identified.

- Dry particulates are not readily absorbed by the skin. These dry particulates will have to dissolve into the surface moisture of the skin. Absorption of volatile liquids across the skin may be limited by the rate at which the liquid evaporates off the skin surface. A criterion could be:
 - Full evaporation of high levels of contamination can be expected in a matter of minutes (say < 10 minutes). The vapour pressure of the substance or product as a whole plays a role. And,
 - Duration of exposure is not more than 10 minutes consecutively and frequency not more than four times per day.
- MW > 500 may impair dermal absorption.
- For substances with $\log K_{ow} < 0$ (poor lipophilicity), dermal absorption is limited. When $\log K_{ow} < -1$, the substance is not likely to be absorbed. For $\log K_{ow} > 4$, the rate of penetration may be limited by the transfer between stratum corneum and the epidermis. When $\log K_{ow} > 6$, the rate of transfer between the stratum corneum and the epidermis will be slow and will limit absorption across the skin.
- If water solubility is below 1 mg/l, dermal uptake is likely to be low. Between 1-100 mg/l, absorption is anticipated to be low to moderate and between 100-10000 mg/l moderate to high. If water solubility is >10000 mg/l and $\log K_{ow} < 0$, the substance may be too hydrophilic to cross the lipid rich environment of the stratum corneum and dermal uptake will be low.”

It is suggested that when a combination of two or more of the criteria above are such that they indicate very low dermal absorption, the absorption can be considered to be very low (a similar approach was considered in the European 6th framework project OSIRIS). However, this rule is not based on an exhaustive database and thus lacks scientific justification. From the results shown in Table 1, one can conclude that even though a single criterion is unfavourable for absorption (i.e. a molecular weight of 600) the absorption can still be relatively high when other criteria are favourable for absorption. Setting strict quantitative boundaries for a single parameter is difficult and the above mentioned values are mere guidance values. Many mathematical models have been developed, where such parameter values serve as input for estimating dermal absorption. However, in most cases at most two criteria are taken into account, i.e. the molecular weight and Log K_{ow} . The criterion considering fast evaporation of the skin is for instance very difficult to quantify, because guidance does not exist as to what vapour pressure ensures fast evaporation. If gases or very volatile liquids are considered one can assume that skin contact is brief, but absorption may still occur. Currently, there is one model, which takes this specific scenario into account, that can be used, i.e. IndusChemFate (see brief description in section 2.1.2). This model calculates internal exposures and air concentration after a dermal exposure, from which can be concluded that evaporation was sufficiently rapid in cases where more than 99.9% of the initial substance is found in the air.

The Health Council of the Netherlands (Gezondheidsraad) stated in 2001 that a mathematical model alone is not sufficient to estimate the dermal absorption, since influencing factors that might enhance dermal absorption are not taken

into account. Such factors may be occlusion, skin penetration enhancers (e.g. irritants), skin or environmental temperature, transpiration, and the way of contact with the skin.

2.1.2 *Determining dermal absorption of substances*

In practice, it is not possible to say that a substance will not be absorbed at all. At best, one can determine that the dermal absorption is very low. Basically, there are three ways to 'determine' the dermal absorption and thus the internal exposure:

- 1) Assume a dermal absorption fraction,
- 2) Determine the dermal absorption fraction by using the flux (rate at which a substance diffuses through a barrier per unit time), or determine the skin permeation, and
- 3) Measure the dermal absorption in animal studies.

Many frameworks opt for the first, whether or not supported by *in vitro* or *in vivo* measurements. As a default often 100% is assumed or 10% if there are reasons to believe that a substance will be absorbed poorly. Both defaults are considered to be worst case in many situations. In case that measurement data are available, however, care must be taken that the measurements mimic the actual exposure situation.

The flux or skin permeation (option 2) can be determined experimentally or by the use of QSARs. QSARs are mathematical relationships, which based on substance properties as mentioned above, estimate, in this case, the flux or skin permeation. In general, the QSARs are derived for subsets of substances (domain). The validity and predictiveness are therefore limited to their domain. Many QSARs for dermal absorption exist and have been evaluated by Bouwman et al., (2008) and Van Ooijen et al. (2008), which evaluation will not be reproduced here. Their conclusions were that the uncertainty in the outcome may range several orders of magnitude, erring in general on the conservative side. Out of in total 34 QSARs, Bouwman et al. selected 4 which were up to their preset criteria that are based on OECD principle to evaluate QSARs (OECD, 2007). The criteria included goodness of fit, non-complex algorithms, defined and broad applicability domain, amongst other. Bouwman et al. selected the QSARs of Magnusson et al. (Magnusson et al., 2004), McKone and Howd (McKone and Howd, 1992), Moss and Cronin (Moss and Cronin, 2002) and Ten Berge (as published in Wilschut et al. 1995a, represented as SKINPERM) (Table 1). Van Ooijen mentions that the QSAR by Magnusson et al. is the only one that estimates the flux¹, known to have higher reliability than estimates of the skin permeation (Van Ooijen et al., 2008).

A preferable approach, according to OECD, is to express predicted dermal absorption in terms of the amount absorbed over a given time period and for a given area, recognizing that this can be predicted from maximum flux data and it is the amount that is most applicable for toxicity assessment. As example, OECD showed a table based on Magnusson et al. (2004) (Table 2). A similar table can be presented using the skin permeation coefficient as input, instead of the maximum flux. For worker exposure an 8 hour exposure may be considered,

¹ The maximum flux through the skin (mol/cm²/h) is estimated by the product of the skin permeation coefficient and the measured or estimated solubility of the substance in its vehicle, usually water.

which would reduce the absorption percentages, provided that the workers clean themselves after work shifts.

Table 1: The four selected QSARs and their applicability domains by Bouwman et al. (Bouwman et al., 2008)

	Endpoint	Applicability domain		External evaluation indicated by correlation coefficient r^2 (n)		
		Vehicle				
		MW	$\log K_{ow}$	All compounds	Water	None
Magnusson et al.	$\log J_{max}$ (flux)	50 < 500	-2 to 5	0.57 (109)	0.50 (88)	0.75 (21)
McKone and Howd	k_p	50 – 200	0 to 4	< 0.3 (101)	< 0.3 (80)	< 0.3 (21)
Moss and Cronin	$\log k_p$	50 < 350	-1 to 4	< 0.3 (101)	< 0.3 (80)	< 0.3 (21)
SKINPERM	k_p	50 < 450	0 to 4	< 0.3 (101)	< 0.3 (80)	< 0.3 (21)
Test set		100 - 400	-1 to 4			

Table 2: Estimations of amounts and % absorbed over 24 hr, applying the upper limit for maximal flux versus molecular weight (Magnusson et al, 2004).

Molecular weight	Maximum flux upper limit (mol/cm ² hr)	Amount absorbed over 24 hr g/cm ²	% absorbed if 1 g applied	% absorbed if 1mg applied	% absorbed if 1µg applied
100	$10^{-3.5}$	0.76	76	100	100
200	10^{-5}	0.048	4.8	100	100
300	$10^{-6.5}$	0.0023	0.23	100	100
400	10^{-8}	0.00010	0.01	10	100
500	$10^{-9.5}$	3.8E-06	0.0004	0.38	100
600	10^{-11}	1.4E-07	1.44E-05	0.014	14.4
800	10^{-14}	1.9E-10	1.92E-08	1.92E-05	0.019

Although the use of a QSAR is not difficult, the interpretation of the results and validity can be complex. The outcome, a flux or skin permeation, denotes a velocity with which the substance may cross a skin barrier. To get a feeling for the internal exposure, calculations must be made to determine which fraction of the dermal load over time was absorbed. A major deficit of QSARs is that no account is taken for the external exposure situation. The dermal load (amount per surface area skin) and evaporation from the skin influence the dermal absorption process. A recently developed model, IndusChemFate (developed by ten Berge, funded by CEFIC-LRI project), does take these steps into account. IndusChemFate calculate the dermal absorption by a QSAR (SKINPERM) and the evaporation process simultaneously. Dermal absorption of gases is included in this model, where most models do not consider this. The model, however, does not provide the amount that will be absorbed, but provides concentrations in

exhaled air, in urine and in blood. By back calculating the outcome of the model to an internal concentration makes it possible to determine the dermal absorption (assuming that dermal exposure was the only route of exposure). Note that inclusion of evaporation off the skin is a major advantage, but that the estimation of the skin permeation is still relatively uncertain, especially when substances outside the test domain are considered.

Van Ooijen et al. (2008) note that mechanism-based models, especially when probabilistic data are used, provide the highest tier of dermal absorption modeling. These models, based on the underlying mechanisms, relate dermal absorption to physico-chemical parameters, such as diffusion and partition coefficients that depend solely on the given substance and vehicle. They are not based on a assumed relationship (with no underlying mechanisms, such as QSARs). These models are however not common available and require various substance specific data, which have to be experimentally determined.

2.1.3 Qualitative approach to determine negligible dermal absorption

Preferably, measurement data are used to establish the dermal absorption of a substance, which were either obtained in animal studies or from *in vitro* studies according to OECD 428. From the Toxicological Threshold of Concern (TTC) approach it can theoretically be calculated that a dermal absorption percentage of 0.0001%² (see footnote for calculation) or lower is considered to result in a negligible internal exposure. However, dermal absorption measurements and QSARs cannot estimate dermal absorption in such low ranges with sufficient reliability. Remarkably, none of the cited QSARs and their associated applicability domain by Bouwman et al. (2008) includes the criteria set for molecular weight and $\log K_{ow}$ indicative for very low dermal absorption (see Section 2.1.1). Therefore, it can be concluded that QSARs should not be used to determine very low dermal absorption at all.

Therefore, it is suggested to use a weight of evidence approach to determine whether or not dermal absorption of a single substance can be considered very low. The criteria mentioned in section 2.1.1. are used as input. Basically, it was considered that either 3 conditions are met or at least two conditions are met where at least one criterion is far beyond the set boundary (indicated by << or >>). Note that the criteria of physical state and fast evaporation are not quantified below. These criteria can be used as additional weight of evidence increasing the reliability of one's conclusion. Dermal absorption is considered to be very low when one of the following conditions are 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

Absorption enhancing conditions, such as damaged skin, occlusion, combined exposure, amongst other, must be taken into account and if they cannot be ruled out, dermal absorption cannot be considered to be very low, and consequently not be used as exclusion criterion.

² The boundary of 0.0001% was derived based on an assumed maximal dermal load on both hands per day (860 cm²) with a 1mm layer (both hands would be immersed in a liquid) resulting in a total dose on the skin of 86 g pure substance (assuming 1mL equals 1 g). For a subject with a body weight of 60 kg this results in a maximal exposure of 1433 mg/kg bw/d. Comparing this value with the external Toxicological Threshold of Concern (TTC, section 4.2.7) for Cramer class III, i.e. 0.0015 mg/kg bw/d, shows that this TTC will already be exceeded at an absorption percentage of 0.0001%, which thus can be considered sufficiently low.

2.2

Negligible external dermal exposure

Since a negligible exposure cannot be defined without having adequate toxicological knowledge, it is decided to focus on strictly controlled conditions as stated under REACH. The application of controlled conditions generally result from either a physiological or toxicological necessity to be able to work with certain substances and are therefore considered as higher tiers of controlling risks. However, it is considered that in a scenario where there is no likelihood of exposure, as described below, would fit in a first tier approach.

2.2.1 Strictly controlled conditions

Under REACH (article 17.3 and 18.4, see also REACH guidance on intermediates, ECHA 2010)), strictly controlled conditions are considered as "(a) the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage; (b) procedural and control technologies shall be used that minimise emission and any resulting exposure; (c) only properly trained and authorised personnel handle the substance; (d) in the case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered; (e) in cases of accident and where waste is generated, procedural and/or control technologies are used to minimise emissions and the resulting exposure during purification or cleaning and maintenance procedures; (f) substance-handling procedures are well documented and strictly supervised by the site operator". The above mainly concerns the handling of intermediates in chemical industries, but might also apply to other occupational environments.

In chapter R.12 on the 'Use Descriptor System' of the Guidance on Information Requirements and Chemical Safety Assessment, the following was stated: A high integrity closed system is the type of system described by Process Category 1 (PROC1). 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. PROCs with higher assigned numbers indicate an increased possibility of exposure. Below the first four PROCs are shown, which describe processes that are more or less closed systems with increasing likelihood of exposure (Figure 1, adopted from chapter R.12).

Process categories [PROC]		
	Process categories	Examples and explanations
PROC1	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
PROC2	Use in closed, continuous process with occasional controlled exposure	Continuous process but where the design philosophy is not specifically aimed at minimizing emissions It is not high integrity and occasional expose will arise e.g. through maintenance, sampling and equipment breakages
PROC3	Use in closed batch process (synthesis or formulation)	Batch manufacture of a chemical or formulation where the predominant handling is in a contained manner, e.g. through enclosed transfers, but where some opportunity for contact with chemicals occurs, e.g. through sampling
PROC4	Use in batch and other process (synthesis) where opportunity for exposure arises	Use in batch manufacture of a chemical where significant opportunity for exposure arises, e.g. during charging, sampling or discharge of material, and when the nature of the design is likely to result in exposure

Figure 1: process categories (PROCs) 1 to 4 with visualization of the process.

In many situations occasional breaching of the system is likely to occur as a result of maintenance, quality control or sampling tasks, e.g. for quality control sampling or for removal/disposal. If exposure can occur incidentally it is unknown whether or not systemic effects are relevant without knowing the chemical characteristics (see section 2.1) or toxicity. In practice, closed systems, that ensure lack of exposure, are more relevant for larger industries and generally do not describe the use of substances in Small and Medium Enterprises (SMEs). Although PROCs 2 to 4 describe conditions where exposures are expected to be low, they do not describe a strictly controlled condition. It is concluded that PROC1 does describe a strictly controlled condition.

If indeed exposures may occur, (dermal) exposure may be prevented by the use of risk management measures, however in that case the exposure can no longer be considered as negligible. In higher tier assessments the use of RMM can be considered to determine whether or not the exposure is sufficiently controlled. This means that in higher tiers either the exposure is expected to be reduced to an order that it may be considered to be negligible or the exposure is reduced to below a toxicological reference value.

2.2.2 Measurements of dermal external exposure

Several methods exist to measure the dermal exposure during tasks at the work place. If the external exposure is considered to be low, measuring the dermal exposure may provide sufficient evidence to determine that the exposure is negligible. Measuring the exposure often provides more confidence in real-time exposure as exposure assessments using models have to take into account uncertainties, which often involves taking worst case assumptions. To determine if exposures are negligible using models is advised against due to these uncertainties. Measurement data can be used as complementary data in a weight of evidence approach in cases where the exposure is expected to be low, but not yet proven. Measuring the exposure, however, is not a first tier approach as it may be very time consuming and involve high costs to obtain a sufficiently reliable exposure measurement.

Discussing the several methods to measure dermal contact and in what way goes beyond the scope of this report. Briefly, three categories of dermal exposure measurements exist, i.e. use of surrogate skin, tracer techniques, and

removal techniques (Fenske, 1993). Surrogate skin techniques involve placing a substance collection medium on the skin. Whole-body garments and patches can be used to this end. Removal techniques involve wiping and wash off/rinse off methods. Tracer techniques often involve the use of fluorescence materials as tracer added to the process. Recently, a vacuuming technique was developed to determine dermal exposure to dust and particles (Lundgren et al. 2005). Biomonitoring can be used to determine whether or not exposure to the skin has occurred, but will not provide a dermal exposure estimate.

2.3

Suggested approach to determine negligible exposure

The advantages of the approach using exposure information only are that the risks of systemic effects after occupational dermal exposure of substances can be determined without the use of toxicological data. In that case, an incomplete dataset on toxicology will in no way affect the outcome. It is, however, anticipated that this approach cannot be used in most cases in the first tier.

In a qualitative weight of evidence approach, the user should determine whether the internal exposure can be considered negligible (see criteria under 2.1.3). If a substance is used under conditions described in PROC1 the exposure can be considered negligible. In all other cases, additional evidence is required that the exposure is sufficiently low. Additional evidence can be found using higher tier approaches such as taking into account the effects of RMM or exposure measurement data.

Negligible exposure, however, relates to the toxicity of a substance. In case of extremely toxic substances (based on for instance acute toxicity studies), this approach should not be used as low exposures may still cause effects.

If the process category, external exposure profile and dermal absorption information cannot rule out that internal exposure after dermal exposure is likely, then the exposure must be quantified and compared to a toxicological reference value (see Chapter 4), unless the substance is not considered toxic (Chapter 3).

3 Scenario 2: substance is not considered toxic.

There are no criteria for when a substance can be considered to cause no risk merely due to its low toxicity and independent of the exposure level. This holds equally for substances included in Annex IV of REACH (EC, 2006) which are exempted from registration (REACH article 2.7(a)). Exposure to these substances under occupational conditions may be a concern for the health of workers. For example, water in this Annex IV, of which it is known that it plays a role in the onset of skin problems in an occupational setting. In addition, working under wet conditions increases the skin permeability for other substances that can cause systemic effects. In other words, the appearance of water in Annex IV of REACH cannot automatically lead to the exclusion of water from the RI&E. This indicates that this list may not be an appropriate instrument for showing the absence of risk under occupational conditions given the rationale of the RI&E. Therefore, Annex IV of REACH will not be used as a source of non-toxic substances for which safe use can be assumed independent of the level of exposure within a RI&E.

Some criteria such as the classification criteria for systemic effects after repeated exposure (STOT-RE) and the upper limit in the testing guidelines have been investigated (See appendix 4). It is concluded that these criteria cannot be used to conclude that the toxicity of a substance is so low that safe use can be assumed

In conclusion, safe use based on absence of toxicity cannot be used.

4 Scenario 3: comparison of exposure and toxicological data

4.1 **Exposure assessment**

Assessing dermal exposure can be done in several ways. Measurements can be performed at the workplace showing the dermal load during work shifts (see section 2.2.2). Biomonitoring has gained much interest in recent years. Biomonitoring is very valuable when systemically acting substances are considered because the internal dose is measured. However, with focus on this framework, it remains difficult to exclude possible confounders such as historical exposure, other routes of exposure or other non-occupational sources of exposure if one is interested only in the contribution of dermal exposure to the total exposure.

In practice more feasible is the use of models to estimate the dermal exposure or the risks after dermal exposure. Some, of many, models have been briefly evaluated. For each model the pros and cons are given (Table 3). Please note that the overview of dermal models is not complete or perhaps not up to date as some models are continuously updated or new models become available.

The 'risk' models in the overview are the RISKOFDERM toolkit (which is implemented in Stoffenmanager), EMKG and COSH Essential models. In the COSHH Essential, EMKG, and RISKOFDERM toolkit models the dermal exposure (qualitative or quantitative estimated) is placed in exposure bands. The toxicity is semi-quantified by using the classification and labeling system of substances and placed in hazard bands. Using a risk matrix which combines the exposure and hazard bands indicates whether or not there might be a risk. This approach is relative simple and crude due to relatively large bands, and as a consequence provides results with low precision. For this reason, the models do not use the risk matrix to determine safe use, but uses it to determine what actions are in place to lower the exposure or to prioritize on which tasks to act first. With that goal in mind, the models can be very useful to setup risk control strategies in SMEs.

In the ECETOC TRA model, a first tier risk model, the user is requested to fill in a toxicological reference value for the most critical endpoint, which is compared to the quantitative dermal exposure estimate to determine the risk. The ECETOC TRA uses the categorization according REACH in PROCs and activities, which have to be selected by the user. The ECETOC TRA is therefore process based rather than task based. Different tasks may belong to the same PROC for which only one exposure estimate is given. This way of approaching the exposure may be crude and may need refinement to tailor-make the assessment for specific tasks, which can be achieved by adjusting input or to consider higher tier models.

The other models are aimed at dermal exposure specifically or at exposure in general, i.e. DREAM, EASE, RISKOFDERM model, BEAT and IndusChemFate, amongst other. DREAM, RISKOFDERM model and BEAT are specifically aimed to determine the dermal exposure and are preferred over the more generic exposure or risk models. The models are task based and, except for DREAM include input from measurements. DREAM is the only model which has been validated, but only for exposures to liquids.

In addition, many algorithms that have been developed for specific purposes may be used for higher tier assessments. Exposure assessment models that have been collected for the exposure assessment of biocides (TNsG) and pesticides (EUROPOEM and others) can be applied for some worker exposure assessments. Such algorithms are generally very task specific.

Currently, under REACH as first tier the ECETOC TRA model is recommended and as higher tier model the RISKOFDERM model. It is anticipated that these models will be used more often. In this framework, the recommendation to use the RISKOFDERM model (freely available from www.tno.nl) is adopted even though under REACH it is considered as a higher tier. The RISKOFDERM model is aimed specifically at dermal exposure, provides quantitative dermal exposure ranges (it is suggested to take the 90th percentile as outcome) based on measured data, and as more practical reason, is task based. The fact that RISKOFDERM is task based 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.

Table 3: Overview of dermal exposure and risk models

Model	Pros	Cons
DREAM	Easy to use Task specific Ranking of tasks Semi quantitative estimates	No internal exposure Lacks discriminative power within tasks Validated for exposure from liquids only
EASE	Tasks are ranked based on a decision tree Task specific	(Semi-)quantitative estimates reduced to crude classes
BEAT	Task specific Includes measurement data Quantitative estimate	Complex model, largely consisting of default values from specific measurement sets Limited to tasks with measurements Only external exposure
IndusChemFate	Generic PBPK model which can determine internal systemic exposure	Dermal load must be predefined separately Complex model with generic metabolism data
ECETOC TRA	Focused on REACH PROCs (process descriptors) Quantitative estimate Risk characterization included	Applicable for PROCs, making it difficult to link the exposure to activities. May be too worst case
RISKOFDERM	Model: Question based Quantitative exposure estimates Risk characterization included Includes measurement data Task specific Toolkit: as model, but simplified to qualitative estimates based on default values Aimed at SME, easier to use	Model: Relatively complex Gases and vapours not taken into account Only external exposure PPE not taken into account. Toolkit: Not quantitative Imprecise Substance needs to be classified
COSHH essentials	Task and process specific Easy to use Hazard banding	Mainly for inhalation No dermal exposure estimate is generated Substance needs to be classified
EMKG	Easy to use Hazard banding	Mainly inhalation Qualitative approach of exposure and hazard Substance needs to be classified

4.2 Determination of a dermal OEL

The dermal OEL can be available or determined using several different models as described below.

4.2.1 Data requirements

There is currently no defined minimum toxicological dataset for the derivation of a dermal OEL within a RI&E. Some considerations on a minimum toxicological dataset are provided in Appendix V. According to SCOEL a 90-day repeated dose study is in most cases advisable for an inhalatory OEL. Further, information on mutagenicity/carcinogenicity and reproduction toxicity is required. These data requirements are roughly comparable to the REACH requirements above 100 tons per year. For substances below the 100 tons per year the REACH requirement do not suffice. According to REACH a DNEL can be derived already based on the data that should accompany the registrations of substances in the tonnage of 10 tons per year. For lower tonnage levels even less information comes out of REACH. For such substances REACH requires a minimum data package or even no data. This shows that deviation from the REACH requirements is needed for determining a dermal OEL for the RI&E. In conclusion, following the principals that underline the derivation of OELs, the data set corresponding to the REACH requirements for the tonnage of minimal 100 tons per year data should be used when a dermal OEL is derived for a RI&E. Please note that some groups of substances are exempted from data requirements or have limited data requirements even above 100 t., e.g. intermediates (REACH articles 17 and 18.). For such group of substances, no reliable DNEL can be derived.

4.2.2 Route to Route extrapolation

In the risk characterization, toxicological data is needed for the specific route of exposure to assess a potential health risk. For the dermal route of exposure these data are often not available and route-to-route extrapolation is an alternative. This section will briefly describe the criteria for applying route-to-route extrapolation (oral => dermal and respiratory => dermal) and the validation of route-to-route extrapolation. Furthermore, the practical feasibility of extrapolating existing limit values to specific dermal limit values will be discussed.

4.2.2.1 Guidance on extrapolation existing limit values

Although limited, there are existing limit values which could be used for route-to-route extrapolation to a dermal limit value. If all of the criteria for route-to-route extrapolation are met route-to-route extrapolation is scientifically acceptable.

When applying route-to-route extrapolation the following set of criteria need to be fulfilled (Wilschut et al. 1998; Rennen et al. 2004):

- the available toxicity data are considered adequate and reliable
- 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
- the considered toxic effect is independent of the route of exposure.
- the absorption efficiency is the same between routes or the difference is known and can be quantified
- hepatic first pass effects are minimal

- there is no significant chemical transformation by oral, gut or skin enzymes or in pulmonary macrophages
- the chemical is relatively soluble in body fluids.

More in depth guidelines and evaluation of route-to-route extrapolation can be found in reports from IGHRC and TNO (Wilschut et al. 1998; IGHRC 2006).

However, it might be possible to extrapolate using default worst case assumptions (see below).

Extrapolating from an ADI (Acceptable Daily Intake).

The ADI is derived from oral studies for the general population. Usually, the ADI is derived within the framework of pesticides and the underlying toxicological datasets are more than sufficient. ADI's derived by international scientific institutions can be used without further scrutiny.

On the assumption that, in general, dermal absorption will not be higher than oral absorption, no default factor (i.e. factor 1) should be introduced when performing oral-to-dermal extrapolation unless specific information is available that shows otherwise. As the ADI is derived for the general population, and therefore more stringent in applying safety factors, no additional uncertainty factors for the use of route-to-route extrapolation has to be applied.

The dermal limit value can than be derived as follows:

$$(1) \text{OEL}_{\text{human,dermal}} = \text{OEL}_{\text{human,oral}} \times \frac{\text{absorption}_{\text{oral}}}{\text{absorption}_{\text{dermal}}} \text{ (default=1)}$$

(mg/kg bw/day)

As a default 100% dermal absorption is assumed. If there are reasons to believe that a substance will be absorbed poorly (see paragraph 2.1.1 and 2.1.2) 10% dermal absorption can be assumed. It is to be noted that route-to-route extrapolation is associated with a high degree of uncertainty and should be conducted with caution relying on expert judgment

Extrapolating from a respiratory occupational limit value) (grenswaarde)

The OEL, especially the non-legal ones, may only be based on local irritant effects on eyes or lungs, so one should carefully examine the derivation to see whether all criteria for applying extrapolating are met. Furthermore, with non-legal limit values one should look into to the underlying toxicological data set to determine whether the limit value is derived from sufficient toxicological data (for data requirements, see paragraph 4.2.1).

If the limit value is based on an oral study and then extrapolated into a respiratory limit value, one should use the oral study as starting point for extrapolating and continue as described above. If the limit value is based on a respiratory study, route-to-route extrapolation to a dermal limit value can also be done.

Respiratory to dermal extrapolation should be handled on a case-by-case basis. In the TNO report of Wilschut et al. 1995 the following equation is proposed, where the NOAELs are replaced by limit values in this representation of the equation (Wilschut et al. 1995b):

$$(2) OEL_{human,dermal} = OEL_{human,respiratory} \times V_{rate} \times T \times \frac{absorption_{inhalation}}{absorption_{dermal}} \times \frac{1}{bodyweight}$$

(mg/kg bw/day)

V_{rate} = human adult ventilation rate

T = exposure duration

A ventilation rate of 6.7 m³ per 8 hours for base level and of 10 m³ per 8 hours for light activities can be assumed (REACH guidance, 2008). The default body weight is 70 kg. Respiratory bioavailability is assumed to be 75%. As a default often 100% dermal absorption is assumed. If there are reasons to believe that a substance will be absorbed poorly (see paragraph 2.1.1 and 2.1.2) 10% dermal absorption can be assumed by default.

4.2.2.2 Validation of route-to-route extrapolation

In the study conducted by Wilschut *et al.* (1998) the route-to-route extrapolation was evaluated based on known repeated dose data from different routes of exposure of one substance. Both experimental as different default values for absorption were used to calculate an extrapolation factor. The calculated extrapolated no effect level for one route was then compared with the experimental data for that route. A summary of the results of this study is given in appendix II.

The results showed that for oral to dermal extrapolation, even if full dermal absorption is anticipated for every single substance, some substances will still have an unsafe estimated no effect level for dermal exposure. Further analyses showed the uncertainty was about a factor of 3. The respiratory to dermal route-to-route extrapolation was not possible to evaluate due to a too limited number of data.

4.2.2.3 Conclusion

In conclusion, it is important to determine on what toxicological basis the OEL was derived, i.e. oral, inhalation, or dermal toxicity studies, and whether the critical effect concerns a local or systemic effect. Also the applied uncertainty factors may provide more confidence that an extrapolation would err on the safe side. Although the route-to-route extrapolation of systemic effects is scientifically acceptable in comparison to local effects, again one would err on the safe side as an extrapolation in that case would be worst-case. If one considers that the derived dermal limit value will be compared to a 90th percentile exposure estimate, the approach altogether may be considered worst case.

4.2.3 DNEL from registration

REACH requires the determination of a dermal DNEL for substances imported or produced at 10 tons or more per year if there is dermal exposure. The method for the determination in REACH as described in the REACH guidance (ECHA, 2008) is in general acceptable. The data requirements at the 100 ton level are considered minimal (see 4.2.1). The dermal DNEL is therefore considered acceptable as an OEL if the data requirements are fulfilled and in case the dermal DNEL is based on route-to-route extrapolation performed within the set

criteria. If the dermal DNEL was derived based on oral or inhalation data, the route-to-route extrapolation described in this report (4.2.2) could also be considered.

4.2.4 Determining a dermal OEL using available toxicological data

A dermal OEL can be determined using the available toxicological data if the available data fulfill the requirements as described in chapter 4.2.1. The method described in the REACH guidance (ECHA, 2008) can be used. Sources for toxicological information are described in chapter 5. However, this requires a high level of toxicological knowledge. Therefore, this is considered to be a higher tier approach.

4.2.5 Grouping and read-across

In the REACH guidance on QSARs and grouping of chemicals (ECHA, 2008), the terms category approach and analogue approach are used to describe techniques for grouping chemicals, whilst the term read-across is reserved for a technique of filling data gaps in either approach. A chemical category is a group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic). In principle, more members are generally present in a chemical category, enabling the detection of trends across endpoints. As the number of possible chemicals being grouped into a category increases, the potential for developing hypotheses for specific endpoints and making generalisations about the trends within the category will also increase, and hence increase the robustness of the evaluation. The term analogue approach is used when the grouping is based on a very limited number of chemicals, where trends in properties are not apparent.

Categories of chemicals are selected based on the hypothesis that the properties of a series of chemicals with common structural features will show coherent trends in their physico-chemical properties, and more importantly, in their toxicological (human health/ecotoxicity) effects or environmental fate properties. Common behaviour or consistent trends are generally associated with a common underlying mechanism of action, or where a mechanism of action exhibits intensity changes in a consistent manner across the different members of a category.

The use of a category approach will mean that it is possible to identify properties which are common to at least some members of the category. The approach also provides a basis on which to identify possible trends in properties across the category. As a result, it is possible to extend the use of measured data to similar untested chemicals, and reliable estimates that are adequate for classification and labelling and/or risk assessment can be made without further testing. In addition, knowledge of the expected effects of the category together with information on use and exposure will help in deciding not only whether additional testing is needed, but also the nature and scope of any testing that needs to be carried out.

REACH (EC, 2006) provides some criteria and the guidance on QSARs and grouping of chemicals can be used. The reliability of grouping and read-across depends strongly on the presence of toxicological data on similar substances. Therefore, no general conclusion can be drawn on the reliability of grouping and read-across. In practice, grouping and read-across is used frequently. For

example for different soluble salts of a toxic metal it is reasonable to assume that the anion does not affect the toxicity once the salt reaches the systemic circulation. However, the anion may affect the absorption and affects the toxicity expressed as mg/kg bw/day due to possible differences in molecular weight. The correctness of read-across has been shown for several groups including 1-methoxypropan-2-ol (Vink et al., 2010). However, read-across can result in an incorrect prediction of the toxicity, for example for substances for which the group shows a specific toxicity based on the reactivity of a specific group present within all members of the group but the substance to be predicted has an additional effect due to the binding to a specific receptor. In practice, grouping and read-across has been used by industry and regulatory authorities in many cases. Grouping and read-across has been used and accepted within REACH in several but not all cases depending on the justification.

The OECD has developed a toolbox which contains instruments for the grouping of substances and read-across. This tool is freely available at <http://www.qsartoolbox.org/index.html>. Also a guidance document is available on using the OECD (q)sar application toolbox (OECD, 2009).

Overall, grouping and read-across can be used as a stand alone method for hazard assessment of substances after very careful consideration of the available toxicological data. This can be done for all endpoints or for some endpoints in addition to toxicological data. The reliability of the resulting OEL strongly depends on the availability of toxicological data of similar substances. The criteria and guidance provided for REACH can be used to justify the resulting dermal OEL. However, this approach requires a high level toxicological expertise. Therefore, this approach should only be considered in a higher tier.

4.2.6 QSARs

SARs and QSARs, collectively referred to as (Q)SARs ((quantitative) structure-activity relationships), are theoretical models that can be used to predict in a qualitative or quantitative manner the physico-chemical, biological (e.g. toxicological) and environmental fate properties of compounds from a knowledge of their chemical structure.

The potential applicability of computational methods in the evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances was recently evaluated by Computational Toxicology Group of the Institute for Health and Consumer Protection on request of the European Food Safety Authorities (CTG, 2010) REF <http://www.efsa.europa.eu/de/scdocs/doc/50e.pdf>. The results of this study are also relevant for the use of (Q)SARs for substances used by workers. The study looked at the availability and applicability of (Q)SARs for several endpoints. (Q)SARs for repeated dose toxicity, reproductive toxicity, mutagenicity and carcinogenicity, as the endpoints relevant for systemic effects, were mainly limited to predictions of the presence or absence of a certain type of effects with a limited accuracy. When quantitative predictions were provided, the predictions were correct for only a limited percentage of substances.

ECETOC concluded (ECETOC, 2006) that (Q)SARs are insufficiently reliable for predicting toxicity and therefore are of limited value for setting OELs. (Q)SARs can be used within REACH (EC, 2006) when a number of conditions are met. However, the use of (Q)SARs by industry for REACH is very limited. SCOEL states in their key documentation number 6 (SCOEL, 2009) that the use of 'structure-activity relationships' is generally not regarded as a reliable method

for predicting toxicological properties, except where there is a dominant common dominator of toxicological significance.

Overall, the use of (Q)SARs for the prediction of the overall toxicity or certain toxicological endpoints like repeated dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity is not considered to be sufficient for the protection of workers.

4.2.7 *Toxicological Threshold of Concern*

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 levels are determined by deriving a 'safe level of exposure' from an extensive database in which individual safe levels of exposure for substances were gathered using 5th percentile of No Observed Adverse Effect Levels (NOAELs) in the database, a body weight of 60 kg and an assessment factor of 100 (for workers perhaps an assessment factor of 50 may suffice). TTCs have been derived from oral (sub)chronic studies, and also for the inhalation and dermal route TTCs have been proposed.

The TTC concept is characterized by the classification of substances into three classes by Cramer, i.e. the Cramer classes I-II-III (Cramer et al. 1978). The classes are based on chemical structure and one can allocate a substance to one of the classes by a decision tree approach. Toxtree is a software program that assigns substances to a certain Cramer class (downloadable at <http://sourceforge.net/projects/toxtree/> last visited on July 14th, 2011). The classes were expanded with additional classes for neuro-toxicants, immunological toxicants and carcinogens. Inorganic compounds, heavy metals, proteins, polymers, polyhalogenated ring structured compounds, and substances with long half-lives were excluded (Munro et al. 1996; 2008; Kroes et al. 2004).

Van de Bovenkamp and Buist (2010, within the 6th framework project OSIRIS) studied the possibility of deriving a dermal TTC. Since information is lacking on oral absorption of substances versus dermal absorption by the same substances, no modification for absorption differences between oral and dermal exposure is used. The relevant values for dermal exposure are:

- Cramer class 1: 30 µg/kg BW/day = 0.030 mg/kg BW/day
- Cramer class 2: 9 µg/kg BW/day = 0.009 mg/kg BW/day
- Cramer class 3: 1.5 µg/kg BW/day = 0.0015 mg/kg BW/day

At present the TTC concept is adopted by the Joint FAO/WHO Expert Committee (JECFA) on food additives, except for carcinogens. The European Medicines Agency (EMEA) and a guidance document by DG SANCO mention the use of TTC for impurities and contaminants, respectively. Under REACH the TTC concept is considered for application in cases where there are only a few number of exposure scenarios that allow good characterization. The TTC approach could be used to waive tests (EFSA, 2010 in draft). Currently, the European Food and Safety Authority and the Scientific Committee on Consumer Products are evaluating the TTC concept and its applicability in the field. It is suggested to await the finalization of these evaluations and then apply it to worker safety assessments as well.

Obviously, an exposure assessment needs to be performed to assure that the TTC levels will not be reached under working conditions. Current available models can be used for this purpose. Using the default worst case values in exposure estimation will generally lead to higher exposure estimates than the

TTC levels (Table A of appendix III). As an example, exposure estimates derived with RISKOFDERM using default values were compared to the dermal TTC for Cramer class 1 (see appendix III). This approach is in conformity with the recommendation in paragraph 4.1 to use RISKOFDERM as preferred exposure estimation model.

4.2.8 *Estimating toxicity based on a limited dataset.*

For substances with a limited data set, an OEL could be estimated using the available limited data. There are some proposals for such an approach for the inhalation route (ECETOC, 2006), however most proposals have not been judged at their merits. One method is the prediction of the OEL based on the results of the acute toxicity studies. However, as far as known no such proposals are available for the dermal route. Further, acute toxicity studies do not provide information on the mutagenicity and reproductive toxicity of a substance. Acute toxicity data are not suitable for the derivation of a dermal OEL value. Another method is banding of the OEL based on the classification. In principle, classification is based on data. It is therefore better to use the available data direct for the determination of an OEL. However, the data used for classification may not always be available. In such cases an estimate could be made based on the classification. However, as far as known no validated scheme's are available for the dermal route. Development and validation of such scheme's for the dermal route is required before a conclusion on this method can be drawn. At this moment, estimating toxicity based on a limited dataset is advised against.

4.2.9 *Conclusion on the methods for determining a dermal OEL.*

There are three methods that can be used in a first tier approach to determine a dermal OEL for a RI&E. The dermal DNEL as determined for REACH can be used as a dermal OEL if the data requirements and the route-to-route requirements are fulfilled. 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 are fulfilled and the limit value is based on sufficient data. However, the direct determination of a dermal OEL from the data base is advised in such cases especially if inhalation OELs are based on oral NOAELs. A Dutch legal inhalation OEL fulfils the data requirements. The dermal 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, and if not successful subsequently use the TTC approach. 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 lack proper scientific foundation.

Higher tier options, requiring expert toxicological knowledge, are determining the dermal OEL using the method as described for the DNEL using the available toxicological data if the data fulfill the minimal data requirements. Where such data or parts of it is missing, read-across can be used if structurally similar substance with sufficient data are available.

4.3 Conclusion on the comparison of exposure and toxicological data

Comparison of the measured or estimated exposure with a dermal OEL based on sufficient data is expected to be possible in many cases. For the estimation of

the dermal exposure, the RISKOFDERM model using the 90th percentile is advised. The first tier options for determining a dermal OEL are described in chapter 4.2.9. When the estimated dermal exposure is below the dermal OEL it can be concluded that the dermal exposure does not result in a risk. However, when the dermal exposure is equal or above the dermal OEL, a risk cannot be excluded. In such cases the risk assessment could be refined or the working conditions should be adapted to decrease the exposure to a level below the dermal OEL.

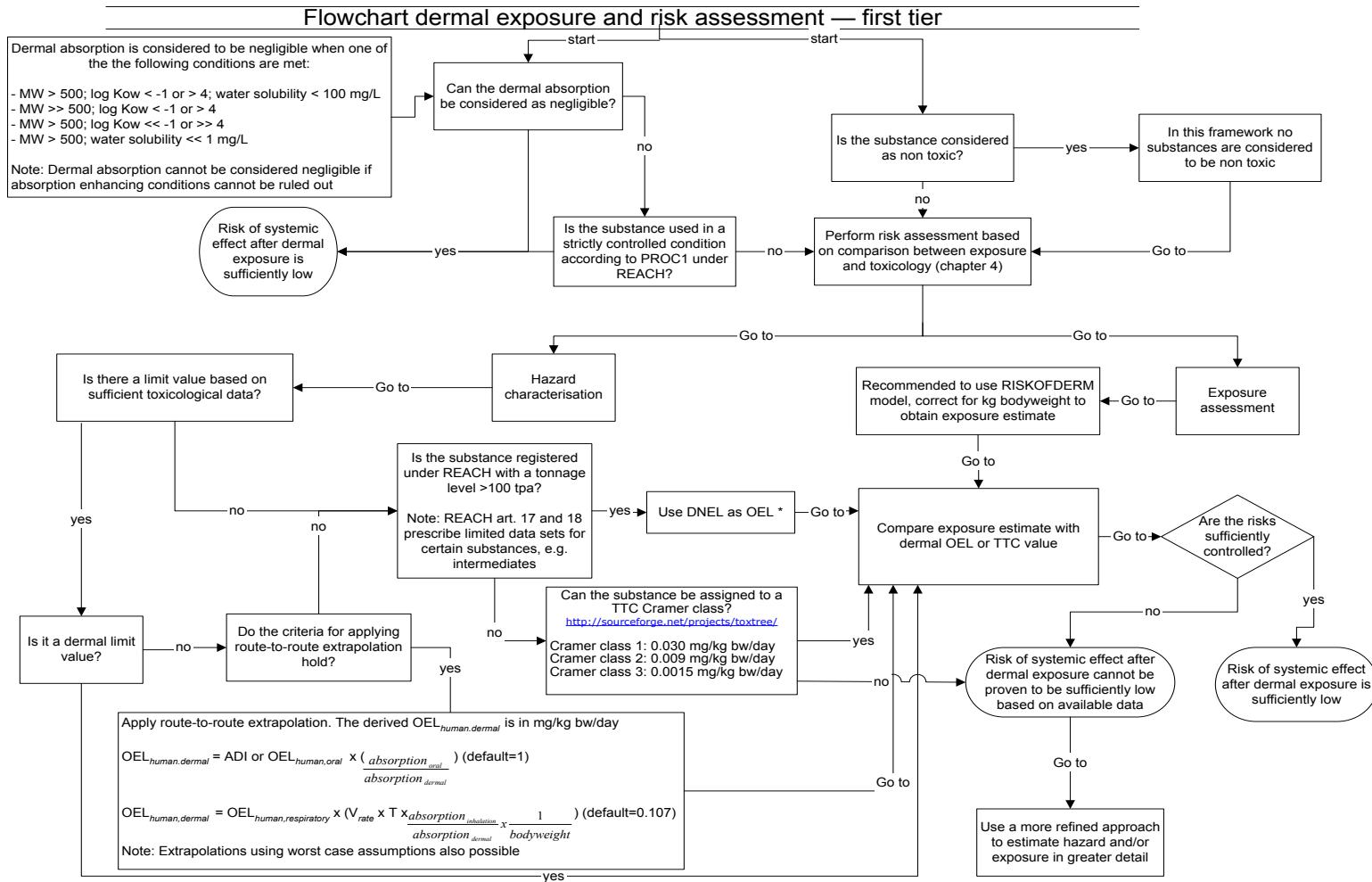
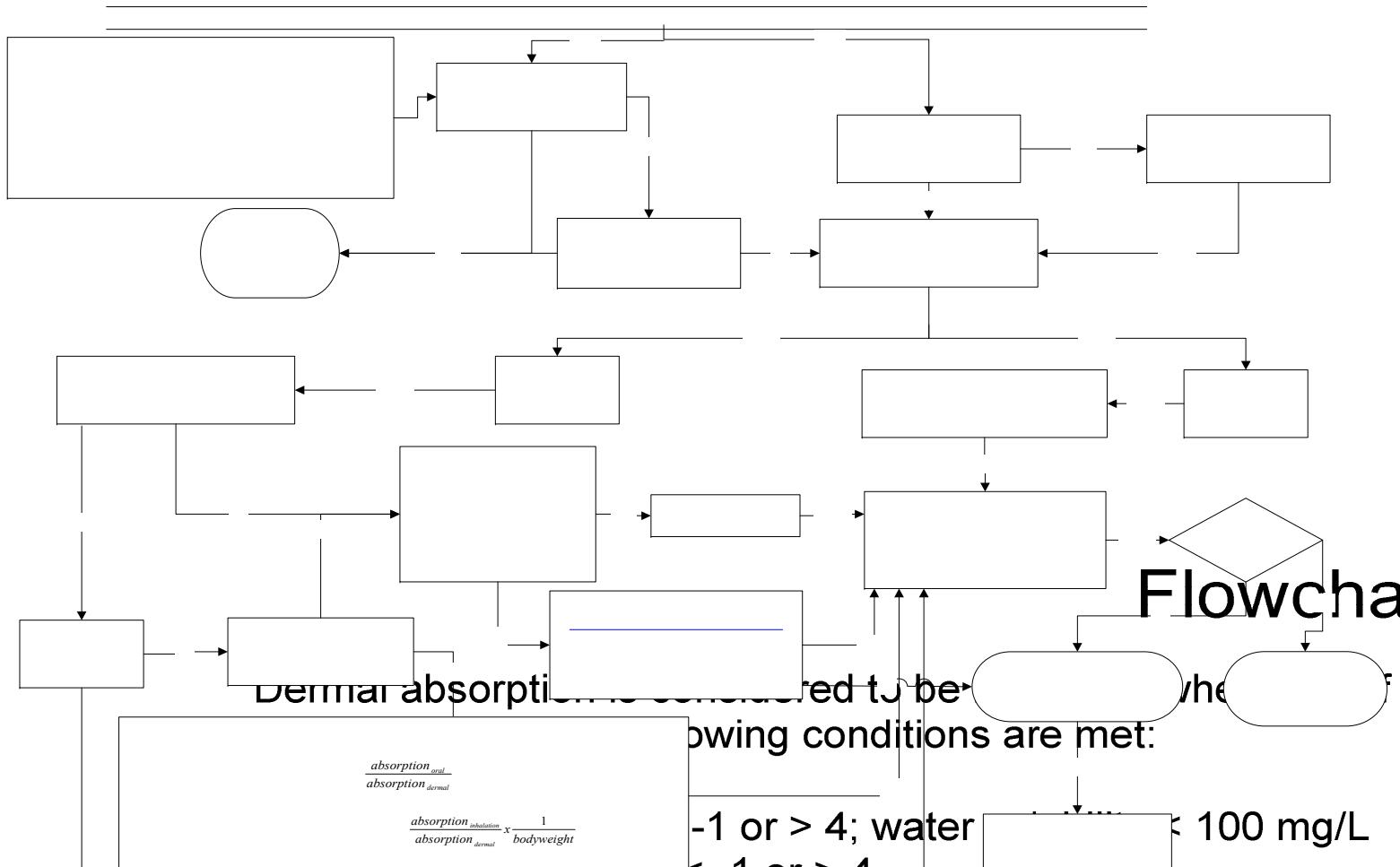


Figure 2:
Flowchart dermal
exposure and risk
assessment.

* In case under REACH a dermal DNEL was derived it should be checked if the route-to-toute 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 consider the DNEL, although both are equally accepted.



- MW > 500; log Kow << -1 or >> 4
- MW > 500; water solubility << 1 mg/L

Note: Dermal absorption cannot be considered negligible if absorption enhancing conditions cannot be ruled out

Figure 2:
Flowchart dermal
exposure and risk
assessment.

* In case under REACH a dermal DNEL was derived it should be checked if the route-to-toute 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 consider the DNEL, although both are equally accepted.

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6 Toxicological data sources

The information sources presented in this chapter (non limitative) could be consulted for information on substances.

The extended safety data sheet (eSDS) provides all available data on a substance including the toxicological data. For substance registered under REACH, the eSDS contains DNELs for all relevant routes of exposure if the substance is produced at levels above 10 tons per year. No DNEL is required for substances below 10 tons per year. However, toxicological data has to be provided in the eSDS. If the substance is registered under REACH, study summaries are available at the ECHA website. For mixtures, the eSDS contains the ingredients depending on the concentration and the classification of the ingredients.

For substances without toxicological data a computer search could be performed. Summaries of existing toxicological studies can be searched via echemportal (www.echemportal.org). This is not recommended unless one is skilled in this work.

DG Sanco publishes the results of the registration of plant protection products on the website: http://ec.europa.eu/sanco_pesticides/public/. Via active substance, a substance can be selected. The resulting website of the substance provides the internal Acceptable Operator Exposure Level (AOEL) of the substance in mg/kg bw/day. Correction for the percentage of dermal absorption is required to obtain a dermal OEL. Information on the dermal absorption is sometimes provided in the review report available on the same page.

DG Environment published the results of the registration of biocides on the website: http://circa.europa.eu/Public/irc/env/bio_reports/library. Active substances have to be searched within this part of circa. The final assessment reports provide AEL values. These are internal OEL values requiring correction for the dermal absorption. This information may be available in the final assessment.

Inhalation OELs are available at the website:
<http://www.ser.nl/nl/taken/adviserende/grenswaarden/overzicht%20van%20stoffen.aspx> and on the website
<http://www.veiligwerkenmetchemischestoffen.nl/default.aspx>
The background of the OEL can be found following the provided references.

The RIVM publishes limit values on the "Risico van stoffen website" (<http://www.rivm.nl/rvs/normen/>). The limit values are partly the same as in the other sources above.

A list of carcinogenic, mutagenic and reproduction toxic substances issued by the Ministry of Social Affairs and Employment, according to article 4.11 of the Occupational Safety and Health Decree, can also provide information and directions on how to deal with those substances.

7 Discussion and conclusions

In general, the safe use of substances by workers can be shown by either showing that exposure or the toxicity 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 characterized, instead of that risks are considered to be sufficiently low. These approaches also apply to systemic effects after dermal exposure for workers.

Criteria have been mentioned that are indicative of very low absorption through the skin. Dermal absorption is complex involving several factors that may play a role. Therefore, multiple criteria must be fulfilled to conclude very low absorption. Theoretically, with very high external exposures the internal exposure may in the case of very low absorption still become a concern for systemic effects. However, extremes such as long-term immersion in fluids should always be avoided in setting occupational health strategies for workers. Therefore, it is considered that negligible dermal absorption according to the provided criteria is sufficient to exclude risks of having systemic effects. If internal exposure cannot be ruled out because the substance is expected to be absorbed, the exposure may still be considered negligible when the external exposure is absent. Showing that the external exposure is absent is, in principle, impossible. Many closed systems are never fully closed because of joints in the installations, valves etc. and are sometimes opened for maintenance and thus may lead to exposure. Closed systems according to PROC1 definitions only allow the conclusion that exposure is considered negligible.

The weight of evidence approach as a first tier, as described in chapter 2, is aimed to be on the safe side. Higher tier options are evaluating the exposure reducing effects of personal protection or performing exposure measurements. Since exposure measurements can be quite expensive and the use of personal protection is not desirable and requires (toxicological) substance information, it is advised continuing to performing a risk assessment as described in chapter 4.

Presently, there are no lists of substances with sufficiently low toxicity that apply specifically to workers. Also there are no criteria to determine such substances. Therefore, it cannot be concluded that a substance has such a low toxicity that no risk assessment is required.

The third method, risk assessment, is probably required for most substances. Risk assessment requires the comparison of the measured or estimated exposure with the estimated toxicity of a substance, where measurements are preferred over models. If measurement data are not available, it is proposed to use the RISKOFDERM model using the 90th percentile of the exposure distribution for estimating the exposure. This model is specific for the dermal route, based on measured data and the uncertainty is (partially) quantified by the used percentile of the exposure distribution. This results in a reasonable worst case estimate of the exposure. The dermal OEL can be determined from existing inhalatory OELs, DNELs derived according to REACH or other existing toxicological reference values by applying route-to-route extrapolation if needed and justified, provided that data requirements as proposed in this report are fulfilled by toxicological studies. Although, the abovementioned options are equally accepted, preference have been given to use existing limit values as starting point, because those limit values have been peer-reviewed. As

alternative in the first tier the TTC concept may be used as well. Deriving a dermal OEL based on toxicological data is considered a higher tier. The currently ongoing validation of the TTC and the increasing use in several regulatory methods provides sufficient justification to apply the TTC also in the safety assessment for workers. If a TTC can be accepted, preferably at an international level, it can be used as a practical limit to judge the estimated exposure in view of possible risks. Therefore, it is proposed to await the finalization of the validation of the TTC concept by EFSA and SCCP and to apply it also to worker safety assessment.

Comparison of the estimated exposure with the dermal OEL shows whether there is safe use or not. In case of safe use, this can be documented for the RI&E. In case there is no safe use there are several options. The risk assessment could be refined using higher tier exposure assessments, such as exposure measurements at the workplace or use of more complex internal exposure models such as IndusChemFate or generating additional toxicity data. Alternatively, the exposure could be reduced. Several options are available such as replacement of the substance, reduction of the concentration of the substance in a mixture, reduction of the exposure period and other working conditions. This will affect the estimated exposure level. There will be a number of substances for which all the proposed methods will not work because based on the exposure, the dermal absorption and presence or absence of data, the safe use cannot be shown. It remains the responsibility of the employer to take sufficient measures in such cases to assure the safety of the workers. It is anticipated that in the future the information requirements of REACH will result in additional data on many the substances frequently used.

In case of extremely toxic substances, based for instance on acute toxicity studies that are mostly available, it is not possible to base safe use solely on negligible exposure or a first tier risk assessment. In that case, it is suggested to either replace the use of the substance or characterize the risk more thoroughly.

Employers are responsible for proving the safe use of chemicals including determination of dermal OELs.

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9

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10

Appendix I: Short description of methods used by others.

TRGS 401

The German method for the assessment of risks for systemic effects after dermal exposure is part of TRGS 401 (BAUA 2008a,b). TRGS 401 also describes local skin effects including wet work but this will not be included in this description of the method as the focus is on systemic effects.

The potential for systemic effects after dermal exposure of a substance is based on the classification, H-notation in the OEL lists and some specific lists included in the TRGS-401. If there is no classification or data indicating the presence or absence of dermal absorption, it should be checked whether this is based on sufficient data. If no data is available, a certain risk should be assumed. A list of substances for which the dermal absorption is also considered relevant when the substance is present as a vapour is provided. The assessment of the dermal exposure is based on the contact area and the contact duration. Based on hazard, exposure and working conditions the risk is classified in three classes. Protective measures are provided in a general way for each class. Medical examination should be offered to workers for some listed substances with systemic effects after dermal exposure. Further, there are a number of activity-related and sector-related requirements that should be followed.

According to TRGS 400, can a risk-assessment provided by the producer or importer be used if certain requirements are fulfilled. However, the responsibility remains with the employer.

TRGS 401 is combined with other guidelines in the "Einfaches Maßnahmenkonzept Gefahrstoffe" (EMKG) (BAUA, 2008a,b). This is a user friendly version for small and medium size enterprises.

Guidance for setting Occupational exposure limits: Emphasis on Data-poor substances

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) published a report in which six methods for setting OELs for data-poor substances were proposed and evaluated (ECETOC, 2006). These OELs related to inhalatory exposure but the methods may also be applicable to dermal OELs with some modifications. The proposed methods and the ECETOC conclusions are:

- Hazard banding seems to be a promising method to set OELs for data-poor substances with EC risk phrases. These risk phrases are grouped following ECETOC criteria into four categories or hazard bands for gases/liquids and solids, each corresponding to a specific OEL range.
- The maximum tolerated dose in long-term studies can be used to derive an OEL. If not known, the maximum tolerated dose can be predicted from the acute oral toxicity (lethal dose in rats) and the octanol-water partition coefficient.
- Four-hour lethal concentrations from rat inhalation studies can be used directly for calculating OELs.

- Current (quantitative) structure-activity relationships for predicting toxicity are insufficiently reliable, and therefore of limited value for setting OELs. It is recommended to search for substances with similar structures and known toxicity, and then read the data across.
- If an OEL is to be based on sensory irritation, it can be predicted from the so-called respiratory dose, i.e. the concentration in air which reduces the breathing rate of mice by 50%. If not available, the respiratory dose can be calculated from the octanol-air partition for substances from a homologous series.
- Finally, the principle of threshold of toxicological concern (normally for food contaminants) can be used for deriving OELs if less conservative safety factors are applied.

Overall, ECETOC concluded that for certain substances none of the proposed methods will be applicable. For others, one or more of the methods might be appropriate, but could lead to different results. In conclusion, therefore, it is proposed that an integrated approach based on the six methods proposed can be used to set a provisional OEL for the data-poor substance concerned. However, for the value to be reliable, experienced toxicological expertise is required in the interpretation of the results.

COSSH essentials

The UK provides advice to employers on controlling the use of chemicals via an online program. This method takes into account inhalation exposure and local and systemic effects after dermal exposure. Direct advice is provided for some processes, tasks and services. For other uses, the hazard is assessed using banding based on the classification. For local and systemic effects after dermal exposure only one band is used (Hazard group S). The exposure is estimated based on the task, dustiness of solids or volatility of liquids, the amount used and in some instances the duration of the task. Combining hazard and exposure a conclusion is drawn on which level of control applies and guidance sheets are provided in which it is described how that level of control can be achieved.

Leidraad Veilig werken met chemische stoffen.

The SER (Sociaal Economische Raad) has developed guidance for fulfilling the ARBOwet. The website provides two options namely validated safe working conditions and branch specific OELs. A webpage asking several questions guides the user through the different options. The availability of inhalation OELs is based upon using public OELs, health based OELs determined by SCOEL or GR or OELs determined in other countries. After 2010, the DNELs from REACH could be used. If no OEL is found, this can be determined. For the determination of OELs three different methods are proposed. Two methods are based on the NOAELs from animal studies and the third is based on banding using the classification. A minimal data set for determination of a OEL is not mentioned (Consortium, 2008).

Referentie: Consortium, 2008, Beslisschema grenswaarde keuze,
9S2119.01/N0009D/Nijm
(<http://www.veiligwerkenmetchemischestoffen.nl/default.aspx>)

11

Appendix II: Route to Route extrapolation validation

Validation of route-to-route extrapolation

In the study conducted by Wilschut *et al.* (1998) the route-to-route extrapolation was evaluated based on known repeated dose data from different routes of exposure of one substance. Both experimental as different default values for absorption were used to calculate an extrapolation factor. The calculated extrapolated no effect level for one route was then compared with the experimental data for that route. This results in a 'eo' ratio, meaning the ratio between the no effect level estimated and the no effect level observed. In case the $eo \leq 1$ the extrapolation is assumed to be 'safe'. This eo is calculated for different route-to-route extrapolations and various substances.

Oral to dermal route-to-route extrapolation

The following default values were used for oral to dermal route-to-route extrapolation (Table II-1):

Table II-1: default values for oral to dermal extrapolation

Starting route: oral	Extrapolation route: dermal		
Definition	Oral absorption (%)	Dermal absorption (%)	Remark and assumptions
1	100	100	Oral absorption is equal to dermal absorption
2	100	100/10*	Dermal absorption is equal to oral absorption or 10%
	50	50/10*	Dermal absorption is equal to oral absorption or 10%
4	experimental data or, if not available, 50	experimental data or if not available - $LD_{50}\text{-oral} \leq LD_{50}\text{ dermal}$: dermal absorption is equal to oral absorption or 10%* - $LD_{50}\text{-oral} \geq LD_{50}\text{ dermal}$ or no data available on acute toxicology: dermal absorption is 100 or 10%*	

* if molecular weight > 400 or a partition coefficient octanol-water <-1 or >4 dermal absorption is assumed to be 10%.

With these different default values the following eo's were obtained (Table II-2):

Table II-2: Number of eo ratios

Estimated no effect level using:	$eo \leq 1$ (safe)	$eo > 1$ (unsafe)	Total number
Definition 1	23	2	25
Definition 2	20	5	25
Definition 3	21	4	25
Definition 4	21	4	25

Numbers in table represent the number of eo ratios, not the eo ratio itself

The result show that even if full dermal absorption is anticipated some substances will still have an unsafe estimated no effect level for dermal exposure based on extrapolation of oral repeated dose toxicity data.

After further analyses of the data the authors suggest an additional uncertainty factor of at least 2.7 when assuming no differences in oral and dermal absorption (definition 1) when applying route-to-route extrapolation from oral to dermal no effect levels. This additional uncertainty factor of 2.7 is based on the 95-percentile of the log-normal distribution of eo to get an estimated no effect level which is equal or lower the observed no effect level for the dermal route.

Respiratory to dermal route-to-route extrapolation

The following default values were used for respiratory to dermal route-to-route extrapolation (Table II-3):

Table II-3: Default values for respiratory to dermal extrapolation

Starting route: Respiratory		Extrapolation route: dermal	
Definition	Respiratory absorption (%)	Dermal absorption (%)	Remark and assumptions
1	100	100	Respiratory absorption is equal to dermal absorption
2	100	100/10*	Dermal absorption is equal to respiratory absorption or 10%
3	75	100/10*	Respiratory absorption is 75% and dermal adsorption is 100 or 10*
4	75	75/10*	Dermal absorption is equal to respiratory absorption or 10%

* if molecular weight > 400 or a partition coefficient octanol-water <-1 or >4 dermal absorption is assumed to be 10%.

With these different default values the following eo 's were obtained (Table II-4):

Table II-4: Number of eo ratios

Estimated no effect level using:	$eo \leq 1$ (safe)	$eo > 1$ (unsafe)	Total number
Definition 1	8	2	10
Definition 2	8	2	10
Definition 3	8	2	10
Definition 4	8	2	10

The small database did not allow any further analysis and it was concluded that it was not possible to evaluate respiratory to dermal route-to-route extrapolation due to a too limited number of data.

Feasibility of extrapolating existing limit values

Existing inhalation limit values are usually not based on dermal exposure; but on oral or respiratory exposure. Therefore, the feasibility of extrapolating these existing limit values to dermal limit values is discussed. As mentioned above, there are several criteria that need to be fulfilled before applying route-to-route extrapolation. Even if these criteria are met, the validity of route-to-route extrapolation is doubtful, especially for respiratory to dermal route-to-route extrapolation.

The existing public limit values for worker exposure (OELs, "grenswaarden") are mostly based on local irritation as most sensitive endpoint. It would go beyond the scope of this report to fully quantify how much and which of these limit

values is based on local irritation as no overview exists so far. One would have evaluate all relevant reports from the Health Council of the Netherlands (Gezondheidsraad) or the Scientific Committee on Occupational Exposure Limits (SCOEL) for these substances to review the limit value derivative. Instead, reference is made to a limited screening on the basis of TLVs derived by the American Industrial Hygiene Association (AIHA).

A summary of the TLV's (in 2005) was made for previous projects. From this summary a total of 52% limit values was based on only local irritation. Another 20% was based on local irritation and systemic effects. A limited screening of some of the substances with both local irritation and systemic effects for which Dutch public limit values exist (allylalcohol; ethylamine; ethyl benzene; 2-butanone) reveals that all derivations were based on inhalation studies and that in half of the cases local irritation was the most sensitive endpoint. For the remaining substances with only systemic effect, about 30% of the limit values were based on oral studies.

Further, existing inhalation limit values were not always based on a minimum toxicological database as indicated by the SCOEL Key document (SCOEL, 2009) and by the Health Council of the Netherlands (2000). Especially data on reproductive toxicity were regularly missing.

12 Appendix III: Comparison RISKOFDERM default outcome and TTC value

In RISKOFDERM there are six models for six different types of exposure process. Each has its own set of determinants. Some models provide results for hands/forearms and for the remainder of the body. All results are for potential dermal exposure, *i.e.* the amount that reaches the skin or any (protective) clothing or gloves covering the skin. In risk assessments in general only the potential exposure to the hands and forearms is taken into account, because the other body parts should be covered by (working) clothing. Therefore, in this evaluation also only the potential exposure to the hands is taken into account. For RISKOFDERM the 90th percentile is considered to be the reasonable worst case value. RISKOFDERM leads to results in μL for liquids and mg for solids. For ease of calculation it is assumed here that 1 μL liquid is equal to 1 mg.

Not all combinations of type of product and type of activity can be estimated using RISKOFDERM, because several combinations are not covered sufficiently by the measured data used to build the model.

In Table III-1 the lowest exposure levels (potential dermal exposure) of product are presented that are calculated using RISKOFDERM with the lowest use rates in data on which the model was based and worst case inputs for other parameters.

Table III-1. Lowest exposure levels related to lowest amounts in RISKOFDERM and worst case conditions

Type of product and activity	Parameters leading to lowest estimate	Estimated exposure level (mg/kg bw/day) ^a	Remarks
Filling, mixing and loading – liquids	Use rate 0.008 L/min, duration 1 min → amount 0.008 L	0.14	
Filling, mixing and loading – low or moderately dusty solids	Use rate 0.56 kg/min, duration 1 min → amount 0.56 kg	0.25	A low or moderately dusty solid either does not produce clearly visible dust in the air, or the dust can be seen only briefly
Filling, mixing and loading - high dusty solids	Use rate 0.56 kg/min, duration 1 min → amount 0.56 kg	1.90	A highly dusty solid emits a clearly visible dust cloud that lingers in the air
Wiping – liquids	Use rate 0.0017 L/min, duration 1 min → amount	6.07	Whether the relation between duration and exposure holds for

Type of product and activity	Parameters leading to lowest estimate	Estimated exposure level (mg/kg bw/day) ^a	Remarks
	0.0017 L		wiping for only one minute is very uncertain, since the lowest duration was 5 minutes.
Dispersion with a hand-held tool	Use rate 0.0001 L/min, duration 1 min → amount 0.0001 L	<i>0.0047</i>	Estimate with highest viscosity category as worst case. Values are lower with lower viscosity categories.
Spraying – liquids	Use rate 0.04 L/min, duration 1 min → amount 0.04 L	6.31	Estimate for highly volatile carrier liquids. Values are lower for not highly volatile carrier liquids, but still far above the suggested dermal TTC for Cramer Class 1 substances.
Spraying – powders	Use rate 0.02 kg/min, duration 1 min → amount 0.02 kg	2.67	
Immersion of objects in liquid baths	Amount or use rate are no parameters in this model. Duration 1 minute	64.3	

^a 90th percentile of RISKOFDERM output distribution. RISKOFDERM delivers results in µL for liquids and mg for solids. For simplicity it is assumed that 1 µL of a liquid has a weight of 1 mg (i.e. density is 1 mg/µL). The resulting values are divided by 60, which is the default weight of workers used in risk assessments, to calculate values in mg/kg bw/day. Values in *italics* are below the suggested dermal TTC for Cramer Class 1 of 0.030 mg/kg bw/day.

The only type of dermal exposure situation where RISKOFDERM can calculate amounts that lead to potential hand exposures below the suggested dermal TTC for Cramer Class 1 of 0.03 mg/kg bw/day is for dispersion of products with a hand-held tool. Very low amounts (grams) can be used on a day for different viscosities of products according to RISKOFDERM before the potential dermal exposure is above the value of 0.03 mg/kg bw/day.

13 Appendix IV: Substances of low toxicity

Some criteria that could be used to determine whether the toxicity of a substance is so low that no risk is expected, independent of the exposure, have been investigated.

REACH does not require a risk assessment for substances that are not classified. In the case that the conclusion for no classification is based on sufficient data, this means that for systemic effects after dermal exposure, the substance is not mutagenic, carcinogenic or toxic to reproduction and that no specific-target organ-toxicity was observed after repeated exposure below certain dose levels. For an oral 28-day study this dose level is 300 mg/kg bw/day (EC, 2008). In practice, this means that effects occur at dose levels higher than 300 mg/kg bw/day, but the exact NOAEL cannot be derived from the classification. It can only be stated that the LOAEL will be higher than 300 mg/kg bw/day. The average difference in dose spacing is a factor of 3 and thus the NOAEL will be approximately a factor 3 lower than the LOAEL, i.e. 100 mg/kg bw/day or higher. Extrapolating to chronic exposure with a default factor of 6 and additional default factors of 5 and 10 for interspecies and intraspecies, respectively, would result in an oral DNEL of 0.33 mg/kg bw/day. The dermal DNEL may become higher when the dermal absorption is lower than the oral absorption. For dermal studies, the guidance value is 600 mg/kg bw/day resulting in the case of no classification in a DNEL of 0.66 mg/kg bw/day. Both values are in a range at which dermal exposure can occur (see for instance the calculation in footnote 2 on page 13). The absence of a classification even when based on sufficient data using worst case assumptions is therefore no justification within a RI&E for not performing a risk assessment or for assuming safe use.

Test guidelines contain an upper limit above which exposure is considered to be unlikely. For most test guidelines the upper limit is 1000 mg/kg bw/day. Note that this exposure level is below the estimated maximal dermal exposure of 1433 mg/kg bw/day (see footnote 2). If a substance shows no effect in all required tests including mutagenicity / carcinogenicity, toxicity to reproduction and repeated dose toxicity at the limit dose of 1000 mg/kg bw/day, then it could be assumed that there is no risk for systemic effects after dermal exposure. A reasonable worst case estimate for dermal exposure is 20000 to 40000 mg/person/day (Schneider et al, 2007). Taking into account the protective effect of clothing of 90% and excluding spraying activities, the reasonable worst case dermal exposure is estimated at 2000 to 4000 mg/person/day or 30 to 60 mg/kg bw/day. Using a NOAEL of 1000 mg/kg bw/day in a 28-day study and the safety factors described above results in a DNEL of 3.3 mg/kg bw/day. This means that for pure substances, the absence of toxicity at the limit dose is not sufficient to show safe use.

It can be concluded that there are no criteria available that can assure that the toxicity of a substance is so low that there is no risk independent of the exposure.

14 Appendix V: Data requirements

There is currently no defined minimum toxicological dataset for the derivation of a dermal OEL within a RI&E. We looked at the data requirements for inhalation OELs to determine which studies would also be relevant for a dermal OEL.

SCOEL published a description of the methodology for the derivation of occupational exposure limits: key documentation version 9 (SCOEL, 2009). This document sets out the general principles and approaches taken by SCOEL in dealing with the general issues arising in relating to its work. For repeated dose toxicity, the SCOEL key document states that such data is required to provide information on possible adverse effects arising from long term exposure.

Adequate study duration will depend on the nature of the effects; in some cases a 28-day study may be sufficient, but in most cases an exposure duration of 3 to 6 months, or even longer, may be required. However, no criteria are provided for assessing the required study duration. Data on reproduction toxicity will be taken into account with all other aspects of toxicity but will normally not be a factor in determining the size of an "uncertainty factor". However, the absence of reproduction studies is in such cases mentioned in the summary and documentation document. The key document of SCOEL contains a scheme for the evaluation of carcinogens and mutagens but no statement on the data requirements for OEL derivation. SCOEL uses uncertainty factors to extrapolate from the NOAEL/LOAEL for the animal study database to an OEL. Based on the quality of the database (SCOEL discriminates between four levels of database quality), an uncertainty factor is applied.

Overall, SCOEL does not provide strict data requirements and rigid safety factors for deriving OELs. In most cases a repeated dose study of 3-months or longer is required. However, it is clear that there is no requirement to provide a complete data set.

The derivation of private OELs is one option in the case that public OELs are not present. The SER has developed a guideline for safe working with chemicals (<http://www.veiligwerkenmetchemischestoffen.nl/default.aspx>). This contains a decision tree which could result in the conclusion that an inhalation OEL is not present and has to be derived. Several options for determination of an inhalation OEL are provided including calculation based on the NOAEL and banding but no criteria for data requirements are provided.

REACH requires the presence of toxicological data for registered substances depending on the tonnage imported or produced per year per company (EC, 2006). Between 1 and 10 tons per year, no repeated dose toxicity studies are required. Besides local effect studies only an acute oral toxicity study and an Ames test has to be provided. Between 10 and 100 tons per year, a 28-day study, a reproductive screening study and an additional in vitro mutagenicity study is required. Between 100 and 1000 tons per year, a 90-day study is required plus additional reproductive toxicity studies and in vivo mutagenicity studies in case of positive in vitro tests. Above 1000 tons per year there are some additional requirements. A risk assessment is required for hazardous substance above 10 tons per year.

Route of exposure

Studies using the dermal route could be considered as optimal for derivation of a dermal OEL. However, for most substances only one route is tested. The best route for the overall risk assessment therefore depends on the exposure to the substance. Further, it should be taken into account that the test guidelines for dermal repeated dose toxicity originate from 1981. Some observations required for the inhalation and oral route are not required for the dermal route.

Conclusion

The data requirements for the derivation of an inhalation OEL are not specified at the national and the European level. This is probably intentional to allow a more flexible approach depending on the available data for expert committees of scientific and governmental experts. However, this should be different in the case that an OEL is derived by the employer or their representatives. As a minimum, information on repeated exposure (90-days) is required, mutagenicity tests capable of detecting gene and chromosomal mutations and reproduction toxicity studies relevant for an effect on development and on fertility. This data requirement is comparable to the REACH requirements above 100 tons per year.

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