Proposal for the assessment of quantitative dermal exposure limits in occupational environments: part 1. Development of a concept to derive a quantitative dermal occupational exposure limit

P M J Bos, D H Brouwer, H Stevenson, P J Boogaard, W L A M de Kort, J J van Hemmen

Abstract

Dermal uptake of chemicals at the workplace may contribute considerably to the total internal exposure and so needs to be regulated. At present only qualitative warning signs—the “skin notations”—are available as instruments. An attempt was made to develop a quantitative dermal occupational exposure limit (DOEL) complementary to respiratory occupational exposure limits (OELs). The DOEL refers to the total dose deposited on the skin during a working shift. Based on available data and experience a theoretical procedure for the assessment of a DOEL was developed. A DOEL was derived for cyclophosphamide and 4,4-methylene dianiline (MDA) according to this procedure. The DOEL for MDA was tested for applicability in an actual occupational exposure scenario. An integrated approach is recommended for situations in which both dermal and respiratory exposures contribute considerably to the internal exposure of the worker. The starting point should be an internal health based occupational exposure limit—that is, the maximum dose to be absorbed without leading to adverse systemic effects. The proposed assessment of an external DOEL is then either based on absorption rate or absorption percentage. The estimation of skin penetration seems to be of crucial importance in this concept. If for a specific substance a maximal absorption rate can be estimated a maximal skin surface area to be exposed can be assessed which may then serve the purpose of a DOEL. As long as the actual skin surface exposed is smaller than this maximal skin surface area the internal OEL will not be exceeded, and therefore, no systemic health problems would be expected, independent of the dermal dose/unit area. If not, the DOEL may be interpreted as the product of dermal dose/unit area (mg/cm²) and exposed skin surface area (cm²). The proposed concept for a DOEL is relevant and can be made applicable for health surveillance in the occupational situation where dermal exposure contributes notably to the systemic exposure. Further research should show whether this concept is more generally applicable.

Keywords: dermal exposure; occupational exposure limits; industrial hygiene

BACKGROUND FOR DERMAL OCCUPATIONAL EXPOSURE LIMITS

At the workplace toxic substances may enter the body through the respiratory tract, through the gastrointestinal tract, and through the skin. It is assumed that the major routes of entry are the airways and the skin, although the intestinal route may not be negligible due to the so-called hand-mouth shunt and, secondary ingestion after respiratory exposure.

To protect people from detrimental effects due to exposure to chemicals, several limit values have been developed. For oral exposure acceptable daily intake values (ADIs) have been adopted for the general population, but these are of limited value to workers. Several types of quantitative occupational exposure limits (OELs) have been derived to protect workers from adverse health effects of toxic substances at work. Basically, if exposure is kept below the limit, no adverse health events are expected in the workers (table 1). For respiratory exposure, the threshold limit value (TLV, set by the American Conference of Governmental Industrial Hygienists (ACGIH)) is most often adopted worldwide. In the Netherlands, maximum accepted concentrations (MAC values) are in use.

As well as external exposure limit values, internal values exist for several xenobiotics for systemic exposure, known as biological limit values (BLVs). Examples are the biological exposure index (set by the ACGIH) and the German “BAT-Werte” (set by the “Deutsche Forschungsgemeinschaft”). Recently, the Health and Safety Executive in the United Kingdom has introduced biological monitoring guidance values for six substances. The main advantages of a BLV relate to (a) its independence of the route of entry, and (b) its use in assessing an overall health risk, as monitoring of

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### Table 1 Some characteristics of available exposure limits

<table>
<thead>
<tr>
<th>Qualitative or quantitative</th>
<th>Target population</th>
<th>Monitoring methods</th>
<th>Route of entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold limit value (TLV)</td>
<td>mg/m³</td>
<td>Environmental monitoring (EM)</td>
<td>Respiratory tract</td>
</tr>
<tr>
<td>mg/kg food</td>
<td>General population</td>
<td>No specific worker monitoring method</td>
<td>Acceptable daily intake (ADI)</td>
</tr>
<tr>
<td>mg/kg body weight</td>
<td>General population</td>
<td>Personal air sampling (PAS)</td>
<td>Skin</td>
</tr>
<tr>
<td>mg/m³</td>
<td>General population</td>
<td>Personal air sampling (PAS)</td>
<td>Miscellaneous or combined</td>
</tr>
<tr>
<td>mg/l blood, mg/l urine, mg/m³ exhaled air</td>
<td>Workplace</td>
<td>No specific worker monitoring method</td>
<td>Biological limit value; (BEI, BAT-Werte, biological monitoring guidance value)</td>
</tr>
<tr>
<td>mg/kg food</td>
<td>Workplace</td>
<td>Personal air sampling (PAS)</td>
<td>Quantitative</td>
</tr>
<tr>
<td>mg/kg body weight</td>
<td>Workplace</td>
<td>Personal air sampling (PAS)</td>
<td>Qualitative</td>
</tr>
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<td>Quantitative</td>
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<td>mg/kg food</td>
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<td>Qualitative</td>
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<td>mg/kg body weight</td>
<td>Workplace</td>
<td>Personal air sampling (PAS)</td>
<td>Qualitative</td>
</tr>
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</table>

At the request of the Dutch Ministry of Social Affairs and Employment a concept was developed for a more quantitative health based dermal occupational exposure limit (DOEL). A practically applicable DOEL may serve as a useful tool in the policy of protecting workers’ health and provide the government with a valuable and applicable instrument for the regulation of skin exposure at the workplace as well as other OELs. The process was divided into three phases, (a) the development of such a concept, (b) assessment of a DOEL for two substances according to this concept, and (c) testing the applicability of one of these DOELs in an actual occupational environment. The present report describes the first two phases. The third phase is presented in an accompanying paper. The present reports are considered to serve as a starting point for the development of DOELs, and are not meant to be the final guidance for the derivation for a DOEL.

### PRIORITY SETTING FOR THE ASSESSMENT OF DERMAL OCCUPATIONAL EXPOSURE LIMITS

A DOEL, in combination with other types of standards, may provide a more complete set of exposure limits, which together allow for a risk assessment of a workers’ health relative to chemical exposure at work (fig 1). It will be neither possible nor necessary to assess a DOEL for every possible substance. Assessment of a DOEL will be useful for all chemicals for which adequate protection of the worker demands...
monitoring skin exposure on a regular basis. Therefore, criteria should be developed to set a priority list of chemicals. Priority setting may be based on data obtained from different viewpoints and sources. Chemicals for which a skin notation could be assessed as well as an OEL for respiratory exposure may be selected. For example, Fiserova-Bergerova et al proposed the comparison of rates of skin penetration and pulmonary uptake at the level of an OEL as a criterion for relevant dermal uptake. However, these chemicals are generally selected according to criteria for priority setting for respiratory exposure—for example, based on the prevention of respiratory tract irritation—which are not necessarily applicable to dermal exposure.

The ECETOC and the US Environmental Protection Agency (US EPA) published documents that may provide some useful information on this topic. Further, specific groups of substances related to either structure or effect may be identified for which a DOEL is either necessary or unnecessary. Examples of substances related to structure are the glycol ethers, whereas examples of those related to effect are defatting agents which may either be taken up quickly themselves, or increase skin uptake of defatting agents which may either be taken up even after the external exposure has ended. Occupational exposure may be due to contact with contaminated surfaces, gases, aerosols, liquids, and dusts. Two expressions of dermal exposure have been defined. Firstly, potential dermal exposure, which is defined as the amount of chemical (mg) deposited on the worker, either on the (protective) clothing or the bare (uncovered) skin. Secondly, actual dermal exposure, which is the total amount of chemical actually coming into contact with the bare (uncovered) skin. Secondly, actual dermal exposure, which is defined as the amount of a chemical actually coming into contact with the bare (uncovered) skin, including the fraction transferring through (protective) clothing to the underlying skin, and which is, therefore, available for percutaneous absorption. Preferably, insight on actual exposure conditions (frequency and duration of exposure, skin surface area, and location) should be present for the derivation of an accurate DOEL. Otherwise, a DOEL may turn out to be too conservative because of several conservative assumptions that have to be made.

**Basic elements for a dermal occupational exposure limit**

**OUTLINE AND DEFINITIONS**

The OELs are assessed to control the internal exposure of the worker exposed to chemicals, to serve to keep the internal exposure below a concentration or dose at which no adverse health effects are expected, or below an accepted level. Similarly, a DOEL should represent the maximum amount of substance (mg) deposited on the skin surface within a given time (usually a workshift), without giving rise to adverse systemic health effects.

Fenske defined dermal exposure as the product of skin loading rate (mass per skin surface area per unit time) and area exposed (cm²). Dermal exposure is expressed in units of mass per unit time (µg/h). Cherrie and Robertson proposed an alternative definition which recognises the biological process involved in skin absorption—that is, the concentration of the substance at the skin surface.

Dermal exposure at the workplace is generally intermittent. Due to the reservoir function of the skin, internal exposure may continue even after the external exposure has ended. Occupational exposure may be due to contact with contaminated surfaces, gases, aerosols, liquids, and dusts. Two expressions of dermal exposure have been defined. Firstly, potential dermal exposure, which is defined as the amount of a chemical actually coming into contact with the bare (uncovered) skin. Secondly, actual dermal exposure, which is defined as the amount of a chemical actually coming into contact with the bare (uncovered) skin, including the fraction transferring through (protective) clothing to the underlying skin, and which is, therefore, available for percutaneous absorption. Preferably, insight on actual exposure conditions (frequency and duration of exposure, skin surface area, and location) should be present for the derivation of an accurate DOEL. Otherwise, a DOEL may turn out to be too conservative because of several conservative assumptions that have to be made.
been used to investigate crop harvesting activities where skin contact may occur with pesticide residues on the crop. In other occupational environments, it was thought that it would be more complex to set a DOEL at this level and to test it for compliance. Furthermore, regulating skin exposure at the third level is considered to be a derivation of the second level. Therefore, this report focuses on the second level, whether an applicable and useful external DOEL can be assessed for the amount of chemical deposited on the skin. It is hoped that the DOEL will be a useful tool in controlling the internal exposure as a result of skin uptake and should therefore be related to either the maximal internal dose that is expected not to affect the health of the worker, or to a generally accepted risk level.

**Basis for a Dermal Occupational Exposure Limit**

The maximal internal dose (based on the no adverse observed effect level (NOAEL)) can either be derived from human data (preferably) or from animal data. Such data should relate the external dermal dose directly to health effects, leading automatically to an acceptable value of a DOEL. Suitable human data are usually lacking, therefore, data for other exposure routes or animal data may be used to derive a DOEL. Acceptance of a pivotal role for the internal exposure (concentration of the toxicant in the central compartment) is then essential in the process of the extrapolations from animal to human and route to route.

If based on animal data, data from dermal toxicity experiments are preferred, provided that experimental exposure conditions resemble those at the workplace (exposed surface area, dose or concentration per surface area, exposure time, climatological conditions, etc.). The assessment of a DOEL from these experiments through direct extrapolation will generally include high to low dose extrapolation. It should then be taken into account that the absorption percentage may increase with a decreasing dermal area dose ($D_a$ mg/cm²). In the case of a high $D_a$ (infinite dose) a considerable amount of the substance may not be absorbed during the exposure period or workshift and may be finally left on the surface. Absorption percentage may increase with a decreasing dermal exposure until the exposure is ended and the skin is cleaned, and absorption percentage will then be much less than 100% of the applied dose. However, for a low $D_a$ the exposure period may be long enough for the deposited amount of substance to be absorbed. Thus an absorption percentage experimentally derived for a specific dermal area dose/unit area cannot be generally applied to other doses. Linear extrapolation of an estimated absorption percentage to lower dermal doses may, therefore, result in an underestimation of the amount absorbed. It was concluded by ECETOC that absorption data expressed as a percentage of applied dose absorbed per unit of time are relevant only to a particular dose and a particular time.

In the practice of setting standards, OELs for systemic effects have often to be based on oral or respiratory animal experiments, as suitable dermal toxicity studies are usually absent for most chemicals. In either case, route to route extrapolation has to be performed to derive an external DOEL. Based on these experiments an internal health based recommended OEL (HBR-OELint) for the worker will then be derived and will serve as a basis for a DOEL. (A basis for this derivation is given in a recent report.) The HBR-OELint is defined as the maximal internal dose (mg/day) not leading to adverse health effects for the worker. A NOAEL is translated into an HBR-OELint with toxicokinetic data (mainly bioavailability data) for the exposure route the NOAEL is based on. An external DOEL is derived from an HBR-OELint, with toxicokinetic data for dermal exposure—for example, dermal permeability constant, penetration flux, or absorption percentage. Because route to route extrapolation is the method extended farthest and most often applied in risk assessment processes, it is the estimation of the dermal uptake which may be based on estimated or measured absorption rate or absorption percentage.

**Proposal for a Standard: The Dermal Occupational Exposure Limit**

Crucial for the translation of an HBR-OELint into an external DOEL as defined in the previous section, is the estimation of the dermal uptake which may be based on estimated or measured absorption rate or absorption percentage.

**Assessment of a DOEL Based on Absorption Rate (Flux)**

If adequate data on absorption rate are available, a refined derivation of the DOEL is possible. For the undamaged skin, the variable for the steady state absorption rate is the flux $J$ (mg/(cm²·hour)), defined as $K \times A C$ (Fick’s first law of diffusion), where $K$ is the permeability constant, and $AC$ is the concentration gradient across the stratum corneum.

The absorption rate $J$ is dependent on $D_a$ (actually on the concentration in the vehiculum), and will increase with increasing $D_a$ until a steady state flux is reached. A further increase of $D_a$ will not result in a higher rate of uptake. For the purpose of the assessment of a DOEL, the maximal flux derived under exposure conditions relevant for the occupational situation ($J_{max;occ}$) should be the basis. The internal dose (mg) is then determined by the product $J_{max;occ} \times T \times A$, where $T$ is duration of exposure (hours/day)—that is, the time from the onset of dermal exposure until the exposure is ended and the skin is cleaned, and $A$ is the exposed skin surface area (cm²). The maximal internal dose is then equal to $J_{max;occ} \times T \times A$. Starting from a maximal accepted internal dose (HBR-OELint (mg/day)), it follows:

$J_{max;occ} \times T \times A \leq \text{HBR-OEL}_{\text{int}}$

or

$A \leq \text{HBR-OEL}_{\text{int}}/J_{max;occ} \times T$.

So, under the assumption of a specified exposure time (default: $T=8$ hours/day) the internal dose depends only on the exposed skin surface area $A$. This means that a maximal allowable exposed skin surface area ($A_{max}$) can
be defined (fig 2 in which the theoretical DOEL expressed as \( D \times A \) is graphically presented), so that if \( A \leq A_{\text{max}} \) no adverse health effects are to be expected because the HBR-OELint will then not be exceeded. If \( D > b \) (the dermal area dose at which \( J_{\text{max;occ}} \) is reached) a maximal penetration rate is reached, a further increase of \( D \) will not lead to a higher absorbed dose during a specified \( T \). The amount taken up is then independent of \( D \) and depends only on the exposed surface area \( A \). Thus as long as \( A < a \) (fig 2), the absorbed dose will not exceed the HBR-OELint; the DOEL can then simply be set as \( A_{\text{max}} = a \), calculated as HBR-OELint/\( J_{\text{max;occ}} \times T \). In case \( A > A_{\text{max}} \), the internal exposure can be reduced by either diminishing the exposure time \( T \) or reducing the flux \( J \). Then, as stated above, \( J \) is dependent on \( D \), and the flux can be reduced by decreasing \( D \).

This situation is similar to that described later with an absorption percentage as the starting point, the external DOEL can then be interpreted as the product \( D \times A \) (see later). As long as the value for \( D \times A \) assessed for an occupational situation lies in the shaded area of the curve (the AUC in fig 2), the HBR-OELint will not be exceeded.

**ASSESSMENT OF A DOEL BASED ON ABSORPTION PERCENTAGE**

If no adequate data are available to estimate an appropriate absorption rate a DOEL has to be based on absorption percentage. As already mentioned, an absorption percentage estimated for a specific \( D \) is not commonly applicable for other values of \( D \); the absorption percentage may increase with decreasing \( D \).

The percentage absorbed depends on the experimental conditions, including the exposure period and the concentration. Without further knowledge, the default value for maximal dermal absorption is set at 100\%, unless experimental data or physicochemical parameters may point to a lower maximal absorption percentage (see next section). The HBR-OELint (mg/day) may then be translated into an external DOEL by dividing the HBR-OELint through the absorbed fraction (\( F \)) of the substance: HBR-OELint/\( F \). This external DOEL can then be interpreted as the product of two variables, the dermal dose/unit area and the exposed skin surface area (\( A \times \) cm\(^2\)) for a given work shift—that is, \( D \times A \).

For testing whether exposure conditions comply with the external DOEL two approaches are now possible. Firstly, a single default value for \( A \) can be set for every occupational situation and \( D \) can then be determined at the workplace, or secondly, both parameters may be determined at the actual workplace and the product can be calculated. In the first situation, \( D \) is the single variable to be monitored for compliance. This is a rather conservative and rigid approach. In the second situation both variables are to be monitored and actual exposure conditions can be taken into account. A default value for \( A \) may be based on knowledge of the actual occupational exposure situation. Estimates for the surface area for different parts of the body have been presented.\(^{15}\)

For a given value of the DOEL (defined as \( D \times A \) (mg/day)) \( D \) is allowed to be higher for smaller values of \( A \). As already noted, if \( D \) increases, the absorption percentage will stay equal or will decrease when \( J_{\text{max;occ}} \) is reached. So, if for a given DOEL the actual \( A \) is much smaller than the default value on which the DOEL is based the amount of substance absorbed will be underestimated, the overestimation will increase as the actual \( A \) deviates more from the default value.

**SUMMARY**

The above considerations have been summarised in table 2. If \( J_{\text{max;occ}} \) can be estimated, a maximal skin surface area to be exposed can be calculated and the DOEL can be expressed as \( A_{\text{max}} \) (cm\(^2\)). As long as \( A < A_{\text{max}} \) no adverse health effects are to be expected. If \( A > A_{\text{max}} \), \( D \) (mg/cm\(^2\)) has to be estimated and the DOEL can be expressed as \( D \times A \) (mg).

If \( J_{\text{max;occ}} \) is unknown, the skin uptake has to be estimated with a relevant absorption percentage. The DOEL can then be interpreted as \( D \times A \). It is recommended that a DOEL should be derived relative to a standard exposed surface area. If the actual exposed skin surface area deviates from this standard area, the \( D \) can be adjusted accordingly. For instance, for a given maximal value for \( D \times A \) (the DOEL) \( D \) is allowed to be higher if \( A \) decreases. But then the absorption percentage may decrease, which means that if the appropriate data are available, a relatively high DOEL may be set for occupational settings where the actual exposed skin surface area is expected to be small, and a relatively low DOEL for a worst case default value for \( A \).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary of the possibilities for the setting of a dermal occupational exposure limit (DOEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting point</td>
<td>DOEL expressed as</td>
</tr>
<tr>
<td>Biological monitoring</td>
<td>( A \times ) exposed area; ( A_{\text{max}} ) = maximal surface area to be exposed; ( J_{\text{max;occ}} ) = maximal flux derived under exposure conditions relevant for the occupational situation; ( D \times A ) = dermal area dose.</td>
</tr>
</tbody>
</table>

Da > b (ID): \( A < a \)
Da < b (FD): \( Da A < DOEL \)
The estimation of dermal uptake with an absorption percentage will be more applicable with a finite dermal dose/unit area, whereas the approach with an absorption rate (flux) can be applied in situations where an infinite dermal dose/unit area is present. To illustrate this DOELs are calculated for MDA and cyclophosphamid in a later section.

**Estimation of dermal penetration**

**OCCUPATIONAL FACTORS AFFECTING DERMAL PENETRATION**

In the procedure for the assessment of a DOEL as proposed in the previous section, the estimation of dermal uptake, either expressed as a flux or as an absorption percentage, is of crucial importance. Comprehensive reviews on dermal penetration of chemical substances already exist. These reviews teach that factors affecting dermal penetration can be divided into three distinct categories: (a) substance related factors—for example, physicochemical properties such as molecular weight, octanol-water partition coefficient, volatility, and polarity (ionisability); (b) situation related factor—for example, environmental temperature, humidity, the presence or absence of occlusive material (clothing, gloves), the time frame of the exposure (duration and frequency)); (c) skin related factors—for example, anatomical site, physically damaged skin.

The compound will in practice be irregularly divided over the exposed skin area. However, the DOEL will usually relate to a continuous 8 hour shift exposure with a constant exposure level. Generally, it can be assumed that when the amount of substance is irregularly divided over the exposed skin surface area, the amount taken up will be equal or less than when the division is regular (under the assumption that the flux is roughly equal over the entire exposed surface area). As a worst case assumption, it is assumed that the total amount is present on the skin during the entire workshift.

In assessing a DOEL it is assumed that dermal penetration is measured for the pure substance. If a substance is part of a mixture, dermal penetration may vary greatly with the actual composition. Also, skin contact may affect the solubility of the compound in the vehicle, and, therefore, the absorption. It is important to note that not only the dermal dose/unit area, but the concentration in the vehicle at the skin surface is of importance. For equal absolute amounts of a substance applied per cm², different concentrations in any vehicle at the skin surface may lead to different absorption rates or percentages. This may at least partly explain the difference in absorption percentages for MDA found by two groups of investigators. In the present report, it is assumed that the concentration in the vehicle (solution) is more or less constant. The starting point is a pure substance or a constant concentration of the substance at the skin surface. Furthermore, it should be realised that occupational exposure may be due to contact with contaminated surfaces, gases, aerosols, liquids, and dusts, which will require different approaches in estimating both the actual dermal exposure and its uptake.

Basically, every departure of the skin condition from normal will alter the dermal penetration. Also, dermal penetration varies with anatomical site. Therefore, by choice, the DOEL relates to normal, healthy adult skin of the volar side of the arm. It is generally not necessary to differentiate DOELs according to race or sex. However, in vivo experiments indicated increasing lag times (the time before the onset of vasodilatation induced by application of methyl nicotinate) in skin from Asian, white, and black people, respectively, with the lag time in black people being twice as long as in Asian people.

**ESTIMATION OF DERMAL PENETRATION**

The estimation of dermal penetration is difficult due to the fact that absorption is influenced by several substance, situation, and skin dependent variables. Recently, US EPA and ECETOC have discussed several in vitro and in vivo techniques for the estimation of skin penetration in detail. The reliability of the estimated DOEL will increase if skin uptake can be estimated more precisely for the occupational exposure conditions.

The US EPA proposed several equations for the estimation of the dermally absorbed dose/day for aqueous solutions and vapours. The US EPA based the estimation of dermal penetration predominantly on the estimation of the permeability constant; equations for the estimation of this constant were presented for aqueous solutions and for vapours for steady state and non-steady state situations. The theoretical and experimental considerations for the estimation of an appropriate permeability constant in different exposure situations were reviewed in detail. The US EPA considered non-steady state conditions to characterise actual exposure more closely than do steady state conditions, especially for exposure periods which are relatively short compared with the lag time necessary to reach a steady state flux. It is recommended that the usefulness and applicability of these approaches for the occupational situation be studied.

Leung and Paustenbach reviewed some important principles involved in the assessment of percutaneous absorption and discussed some possibilities for a quantitative determination of chemical uptake through the skin. Although a mathematical model may provide a proper tool for estimating percutaneous absorption, the available models still need further validation (see previous section). The same authors proposed three indirect methods for the estimation of the dermal bioavailability of a substance: by comparison of the area under the plasma concentration-time curve after cutaneous and intravenous administration (preferably performed with labelled material), by estimating the total amount excreted relative to the administered dose, and by measurement of the amount of substance remaining on the skin at the end of exposure. The first method may be the most accurate;
however, these data are seldom available in risk assessment.

Recently, a tiered approach for the estimation of dermal absorption has been described.19 Briefly, this approach starts with a default value of 100% for dermal absorption when no data are available. In the next tier molecular weight or the log $P_{ow}$ were proposed to discriminate between poorly absorbed substances, and substances for which 100% absorption may be a reasonable estimate. It was stated that although no clear relation was presented, absorption would be considerably <100% if the molecular weight is greater than 500. For log $P_{ow}$, maximum absorption was associated with values between 1 and 2, whereas for log $P_{ow}$ values <-1 or >4 the dermal absorption was considered to be <10%.18 19

Formulas for the calculation of the flux or the permeation coefficient based on the log $P_{ow}$ and the molecular weight have been proposed.17 However, the US EPA warns that the log $P_{ow}$ will not be a valid parameter for the estimation of lipophilicity for certain classes of chemicals—for example, nitrophenols.15

Recently, the validity of five of these models has been evaluated by comparison with experimental in vitro permeation coefficients by Wilschut et al.37 They considered a revised version of an unpublished model by Robinson to be the most appropriate for the estimation of skin penetration from aqueous solutions. However, the usefulness of this model in actual occupational situations remains to be investigated.

The usefulness of in vitro and in vivo test systems has been reviewed recently.17 18 The results of in vitro studies for the determination of skin penetration are difficult to compare with those obtained in vivo. Standardised experimental conditions and the use of reference compounds for calibration should improve the comparability of the test systems. In general, animal skin seems to be more permeable than human skin.15 18 A single default correction factor cannot be derived, because the extent of overestimation seems to be specific to the agent and animal. We recommended that animal absorption data is considered as an overestimation of absorption in humans.15 18 19

Testing of the applicability of the concept
The applicability of the procedure described for setting a DOEL was tested by assessing a DOEL for two genotoxic carcinogens cyclophosphamide and MDA. The principle is similar for compounds for which a threshold value for the expression of toxic effects can be assessed. The assessments based on literature searches are briefly described, more details are reported separately (in Dutch).21 30 For both compounds, relevant dermal toxicity data were absent; an HBR-OEL$_{in}$ was derived as a starting point. These values were calculated according to the Dutch method for the calculation of health based calculated occupational cancer risk values (HBC-OCRV) for genotoxic carcinogens,30 as adopted by DELOS, a commission of the Health Council of the Netherlands.

DERIVATION OF A DOEL FOR CYCLOPHOSPHAMIDE
Risk evaluation
Key study for the risk evaluation of cyclophosphamide was the oral experiment with rats by Schmuhl and Habs.38 Under the assumption of 100% oral absorption and based on the previously mentioned method for derivation of an HBC-OCRV for genotoxic carcinogens41 an incidence of 0.97/mg cyclophosphamide absorbed/kg/day for malignant tumours was calculated for male rats. The incidence per mg absorbed cyclophosphamide per day for the worker (70 kg; 40 year exposure for five days/week) is then $5.3 \times 10^{-7}$. Reference values for a working life (40 years) additional mortality incidences of 4/1000 and 4/100 000 are requested by the Dutch Ministry of Social Affairs and Employment. The daily internal cyclophosphamide doses associated with these excess cancer levels are 0.75 mg and 7.5 µg, respectively.

Dermal absorption
Key studies for the estimation of dermal absorption were the volunteer studies of Hirst et al.,37 the studies with cancer patients by Mouridsen et al.,41 42 and the study with rats by Sessink et al.43 The animal study showed a urinary cyclophosphamide excretion of 5%–7% after dermal and intravenous administration, indicating 100% dermal absorption. The human studies indicated that after intravenous and dermal administration, about 10% and 1% of the administered dose, respectively, was excreted in the urine in 24 hours as cyclophosphamide. The human and rat data are difficult to compare, due to significant differences in exposure conditions. In the rat study cyclophosphamide was applied in a glycerol suspension which penetrates easily into the skin, and therefore may have enhanced the absorption. In the human volunteer study, cyclophosphamide was applied in methanol which evaporated within 30 seconds, the skin was covered and washed with water and soap after 6 hours. As the exposure conditions in the human volunteer study were considered to be more comparable with the occupational conditions (watery solutions; exposure for 6 hours before cleaning) this study was used as a starting point for the estimation of the absorption.

Based on these human studies the total urinary excretion of cyclophosphamide within 4 days after intravenous administration (0.02 mg/kg) was about 13%. A total of 2%–3% cyclophosphamide was estimated to be excreted in urine after dermal application of 1 mg (100 µg/cm$^2$; occlusion). So, urinary cyclophosphamide excretion after dermal application was maximally 25%–30% of that after a comparable intravenous dose.

Estimation of a DOEL for actual exposure
For preparation and application of cyclophosphamide as a drug it is expected that dermal exposure is limited to the hands and lower arms, an area of about 2000 cm$^2$. Starting from an absorption percentage of 30%, a daily internal dose of 0.75 mg equals a $D_{in}$ of $(750 \times 100/30)/2000 = 1$ µg/cm$^2$. However, the absorption
percentage of 30% was estimated based on a $D_1$ of 100 $\mu$g/cm$^2$. Considering the fact that absorption percentage may increase with decreasing $D_1$, an absorption percentage of 100% is assumed at a dermal dose/unit area of about 1 $\mu$g/cm$^2$. Therefore, the DOEL interpreted as $D_1 \times A$, was set at 0.75 mg/day. For an estimated maximum value for $A$ of 2000 cm$^2$ the $D_1$ will be 750/2000 = 0.4 $\mu$g/cm$^2$. Similarly, the cyclophosphamide dose of 7.5 $\mu$g associated with the lower reference value equals a $D_1$ of 4 ng/cm$^2$.

**DERIVATION OF A DOEL FOR 4,4'-METHYLENE DIAZINE**

**Risk evaluation**

The oral NTP study was the main source of data for the evaluation of the carcinogenic risk of MDA. Under the assumption of 100% oral absorption and based on the method for derivation of a HBC-OCRV for genotoxic carcinogens already mentioned an incidence was found of $4.67 \times 10^{-2}$ per mg MDA absorbed/kg day for neoplastic noduli for male rats. The incidence per mg absorbed MDA per day for a worker (70 kg; 40 year exposure for five days/week) is then $0.25 \times 10^{-3}$. The daily internal MDA doses associated with the reference values of 4/1000 and 4/100 000 are 16 mg and 0.16 mg, respectively.

**Dermal absorption**

The penetration of MDA in the skin is fast but not complete, even after application of low doses about 50% could be washed off. Generally, the absorption percentage decreased with increasing doses although the absolute amount taken up remained more or less the same. In vitro studies showed that about twice as much MDA penetrates human skin as rat skin. Occlusion increased the amounts taken up by twofold to 2.5-fold.

Absorption studies with volunteers have been carried out. Exposure conditions in most studies deviate from occupational conditions. In one experiment with exposure conditions resembling those at the workplace MDA (10% solution (w/v) in ethanol; $D_1$ = 0.6 mg/cm$^2$) was applied to the forearm of two volunteers, without occlusion. After three hours 41% and 47%, respectively, could be washed off. Based on these results an absorption percentage of 55% was derived for MDA.

**Estimation of a DOEL for actual exposure**

In general, occupational skin exposure is limited to hands and lower arms, an area of 2000 cm$^2$. Starting from an absorption percentage of 55%, a daily internal dose of 16 mg equals a $D_1$ of $(16 \times 100/55)/2000 = 15 \mu$g/cm$^2$. However, the absorption percentage of 55% was estimated based on a $D_1$ of 0.6 mg/cm$^2$. Considering the fact that the absorption percentage for MDA will increase with decreasing dermal dose/unit area, an absorption percentage of 100% is assumed at a dermal dose/unit area of about 15 $\mu$g/cm$^2$. Therefore, the DOEL interpreted as $D_1 \times A$ was set at 16 mg a day. For an estimated maximum value for $A$ of 2000 cm$^2$ the $D_1$ will be 16 000/2000 = 8 $\mu$g/cm$^2$. Similarly, the MDA dose of 0.16 mg associated with the lower reference value equals a dermal dose/unit area of 80 ng/cm$^2$.

**Discussion and conclusions**

The present report presents a first attempt to develop a procedure for the assessment of a relevant and useful quantitative parameter for controlling dermal exposure. It is meant as a starting point for further discussion to develop a practically suitable and applicable DOEL for occupational situations. The importance of the contribution of skin uptake to the total human exposure for many chemicals is widely recognised. Initiatives in the United States and the establishment of a European network on dermal exposure supported by the European Commission should provide important information in the near future for refinement of the proposed procedure. For some chemicals in the workplace and for certain workplaces skin uptake will be the predominant or only exposure route.

Dermal exposure is merely controlled by a qualitative parameter. One of the reasons for this is that the problems associated with quantitative standard setting for dermal exposure are thought to be complex. It is acknowledged that for the proposed procedure several assumptions and simplifications had to be made. However, many of the drawbacks and assumptions mentioned are not unique to dermal exposure and are basically not different from those associated with oral or respiratory exposure. For instance, in setting standards for occupational respiratory exposure, combined exposure is seldom dealt with, ventilation rate (and, therefore, uptake) may be concentration dependent, work load and working conditions may influence breathing rate and depth, and the ratio of mouth versus nose breathing may also be of importance. Furthermore, pharmacokinetic data for respiratory exposure are often lacking and default values for absorption have to be used. All these factors, which are seldom accounted for, will determine the pulmonary uptake of chemical substances, and therefore the internal dose.

Also, in respiratory exposure the amount actually absorbed is for some substances related to the proportions of differently sized particles, defining the inhalable and respirable fraction. Certain groups of substances—for example, fibres, dusts, and aerosols—require a specific approach. It may, therefore, be relevant to divide the respiratory uptake into three fractions: (i) animal fibres, (ii) dust and aerosols, and (iii) particulate matter. Absorption studies with volunteers have been carried out. Exposure conditions in most studies deviate from occupational conditions. In one experiment with exposure conditions resembling those at the workplace MDA (10% solution (w/v) in ethanol; $D_1$ = 0.6 mg/cm$^2$) was applied to the forearm of two volunteers, without occlusion. After three hours 41% and 47%, respectively, could be washed off. Based on these results an absorption percentage of 55% was derived for MDA.

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and the availability of an appropriate method for analysis. Often, a specific strategy for sampling biological fluids and analysis will be demanded, especially when both respiratory and dermal exposure are of importance. Both routes will probably result in different internal exposure patterns and, therefore, different urinary excretion patterns.

If an external DOEL is considered to be appropriate we recommend assessment of this DOEL relative to the surface area of exposed skin. Generally, the DOEL will be derived from an HBR-OEL\textsubscript{int} derived from animal toxicity data. Translation to an external DOEL is preferably performed with an appropriate estimation of the penetration rate of the substance under occupational conditions. If a \( J_{\text{max,occ}} \) can be estimated it may be possible to define a maximum skin surface area (\( A_{\text{max}} (\text{cm}^2) \)) to be exposed for a given \( T \). If the actual exposed surface area is \( \leq A_{\text{max}} \), no health risk is indicated for dermal exposure, independent of the dermal dose/unit area. If a \( J_{\text{max,occ}} \) cannot be derived or if \( A > A_{\text{max}} \) the approach will be the same as when an absorption percentage serves as a basis, the DOEL can then be interpreted as \( D_x \times A \). Compliance can then be tested by monitoring either both \( D_x \) and \( A \) or only \( D_x \) starting from a default value for \( A \). If for a given DOEL \( A \) decreases, \( D_x \) is allowed to increase. Hence, if the actual exposed surface area—for example, hand only exposure—is much smaller and the \( D_x \) is allowed to be, and the \( D_x \) is much higher than the initial values on which the DOEL is based, lower absorption percentages can be used in assessment of health risk. This means that for a relatively small area of exposed skin the DOEL expressed as \( D_x \times A \) may be set at a higher level. So, for a specific substance the DOEL may be set at different levels depending on the actual surface area of exposed skin.

A quantitative DOEL can be used to control dermal exposure, but also, in combination with dermal exposure data to rank substances for possible risks at the workplace. Also, it might be helpful to manufacturers of personal protective equipment for the development of appropriate products.

The present concept is mainly developed for substances that act systemically. In general, the occurrence of local effects will be predominantly dependent on \( D_x \), the actual concentration at the skin surface. Therefore, if a dose-effect relation for local effects is available, local effects may be regulated by assessing a maximum value for \( D_x \) as well as a maximal value for the DOEL expressed as \( D_x \times A \).

A quantitative DOEL will be a useful type of exposure limit complementary to respiratory OELs at the workplace. Together they may provide a more complete set of exposure limits which allow assessment of a worker’s health risk relative to chemical exposure at work. This is at least the case for those occupational situations where the uptake through respiratory exposure is far less than through dermal exposure. An integrated approach, summation of the internal exposures through both routes, is recommended for situations where both exposure routes contribute considerably to the internal exposure of the worker. In that case, a DOEL as well as a respiratory OEL may be set, taking into account that combined exposure through the dermal and respiratory route at the same time should not result in a health risk. Exposure to both routes should be controlled together. A concept for a procedure for this should be developed taking the route specific kinetics into account. It will, however, be difficult to assess whether the critical effect is related to dose or concentration. If related to dose, the absorbed doses may be summed, whereas, if related to concentration it should be realised that the internal exposure pattern (height, onset, and duration of measured concentrations of blood and tissue) may be completely different for both routes. In our institute this is currently under study.

A DOEL derived according to the proposed concept may already be useful as is illustrated by the evaluation of an external DOEL for MDA in the workplace investigated.\textsuperscript{12} In this study a significant correlation was found between cumulative MDA excretion in urine and the results of the dermal exposure measurements (assessed by hand washing). Testing for compliance was performed both by comparison between the MDA excreted in the urine and a BLV, and by comparison between the estimated external dermal exposure (hand wash method) and the external DOEL as derived in this report. Both comparisons were in close agreement, the exposure was estimated to be 20%–25% of the BLV and DOEL, respectively.\textsuperscript{12}

As stated before, one of the first steps now is to develop criteria to set a priority list of chemicals for which a DOEL is a useful and necessary tool in occupational health risk management. For this purpose the publications of ECETOC and US EPA and others may provide some basic elements, but these need further development and evaluation.\textsuperscript{15 31}

Of crucial importance for a proper assessment of a DOEL for systemic effects is the estimation of dermal uptake. If no relevant data on dermal absorption are available a default value of 100% may be used. If relevant physicochemical data are available a maximal expected absorption of \(<100\%\) may be calculated. Some proposals have been made for the estimation of dermal penetration.\textsuperscript{15 16 31 36} Further, recent comparison of a few models based on molecular weight and log \( P_w \) led to a proposal for an additional model for the estimation of skin penetration for aqeous solutions.\textsuperscript{77} A combined evaluation of the applicability of the proposed models and procedures for general and specific occupational environments may provide some useful tools for a protocol for the estimation of dermal penetration at the workplace and, therefore, of a more refined DOEL.

In summary, although several assumptions and simplifications have been made, the proposed concept is considered workable in an occupational environment. The extent and complexity of the problems associated with the assessment of a DOEL do not mean that applicable and relevant standards cannot be derived.
for skin exposure. Also during standard setting for respiratory and oral exposure, interpretation and applicability problems often have to be dealt with. Tentative DOELs were derived for two carcinogens, the procedure will be similar for non-neoplastic agents. Furthermore, the DOEL seemed to be relevant and applicable for MDA in an actual occupational setting. We recommend the testing of this approach for more substances in practice.

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