Dermal exposure assessment in occupational medicine

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The importance of dermal exposure has increased during the last few years, mainly because of the reduction of respiratory exposure to toxicants. Pesticides, aromatic amines and polycyclic aromatic hydrocarbons are considered to be the chemicals at highest dermal risk. In the occupational exposure limit lists of the American Conference of Governmental Industrial Hygienists (ACGIH) and of many countries, compounds that can be absorbed through the skin are identified by a skin notation. However, a generally accepted criterion for assigning skin notation does not exist. The recent attempts to develop health-based dermal occupational exposure limits (DOELs) have not been accepted, thus in practice their use has remained limited. To predict the systemic risk associated with dermal exposure and to enable agencies to set safety standards, penetration data are needed. Moreover, there is a need for a practical risk assessment model, particularly for small and medium-sized enterprises.

Key words: Biological monitoring; dermal exposure; percutaneous penetration; skin notation.

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The three typical routes of chemical uptake for humans are inhalation, ingestion and percutaneous absorption. Oral and respiratory uptake of chemicals are well documented, while there is a lack of knowledge about dermal uptake. This is because dermal absorption is unlikely to be the predominant route of exposure in the workplace and in the general environment. Moreover, until the mid-1960s, skin was incorrectly considered as an almost impermeable barrier for chemicals.

In recent years, the general interest in percutaneous absorption of chemicals has increased. This is because [1]:

- as inhalational exposures to chemicals have decreased, as a result of both improved control technologies and the reduction of occupational exposure limits, the contribution of exposure through the skin to total exposure has increased;
- there are more data relating to dermal absorption of chemicals;
- there are more data relating to the protective capabilities of gloves and clothing that are used to limit skin absorption;
- there are regulatory requirements to assess dermal exposure for certain types of compound, such as pesticides;
- advances in biological monitoring have made total exposure or total internal dose more easily measured.

In the last three decades, percutaneous absorption has been demonstrated for a number of occupational toxicants and environmental contaminants. On the other hand, many chemicals in the workplace are primarily present as surface contaminants. In certain scenarios, dermal exposure may be greater than respiratory exposure, and several general intoxications due to skin exposure have been documented.

Assessing dermal exposure is becoming an important issue in regulatory toxicology because of the growing awareness of the extent of the problem. The European Commission (EC) has recognized the importance of risk assessment in relation to dermal exposure since 1996 [EC Dermal Exposure Network (DEN) 1997–1999], while the EU Directive 97/42/EC has established that, for some carcinogens, absorption via skin must be considered. In the field of dermal exposure risk assessment, the US Environmental Protection Agency (EPA) has developed a draft document aimed at water and soil exposures at hazardous waste sites (Risk Assessment Guidance for Superfund, Vol 1: Human Health Evaluation Manual—RAGS Part E). It proposes a consistent methodology for assessing the exposures from the dermal

In November 1997, the coordinators of the DEN organized a Delphic questionnaire intended to use the expertise within the network (composed of ~70 experts in the specific field from 14 European countries) to address a number of key issues, such as which substances and processes posed the greatest risk from dermal exposure. Pesticides, aromatic amines and polycyclic aromatic hydrocarbons were judged to be the substances at the greatest dermal risk, while agriculture, hairdressing, the rubber industry and the use and production of paints were identified as the processes with the greatest risks from dermal exposure.

In many countries, compounds considered a skin hazard are identified by skin notation (S) on the list of occupational exposure limits (OELs). In general, the S has the purpose of alerting attention to the fact that cutaneous exposure to these compounds can significantly contribute to total systemic exposure. Irritating and corrosive compounds do not have an S. However, a general agreement on S assignment criteria does not exist.

The Scientific Committee on Occupational Exposure Limits (SCOEL) of the EC was established to assign S when the contribution of dermal absorption to the body burden is relevant.

The compounds that can be absorbed through the skin and therefore cause health effects have an S in the Finnish list of OELs. More than 100 substances have an S, which accounts for ~20% of the listed compounds. Ss are officially used in the Swedish occupational safety and health legislation, and formally regulated by the Swedish Board of Occupational Safety and Health in Stockholm (the latest ordinance has the number 1996:2). The definition of the S is that ‘the substance can easily be absorbed percutaneously’, with a general remark on the skin effects of defatting agents and risks of skin exposure. About 70 chemicals out of a total of ~300 have an S.

The UK also uses an S that indicates in the Health & Safety Executive (HSE) OELs EH/40/99 (1999) substances that have the ability to penetrate intact skin and contribute to systemic toxicity. The HSE's Advisory Committee on Toxic Substances (ACTS) assigns an S in cases where the available data or experience (or predictions made in the absence of actual data) suggest that exposure via the dermal route may: (i) make a substantial contribution to the body burden (when compared with inhalation) and (ii) cause systemic effects, so that conclusions about exposure and health effects based solely on airborne concentration limits may be incomplete.

Germany has a technical rule—TRGS (Technischen Regeln für Gefahrstoffe)—for hazardous substances that are capable of penetrating the skin (TRGS 150). This rule is based on the governmental ‘hazardous substances order’ (Gefahrstoffverordnung) and regulates occupational contact with these substances [2]. Therefore, an S for a compound in the MAK (Maximum Arbeitsplatz Konzentration) list supports specific protective health and safety measures, such as arranging for biological monitoring. So, in this case, the S is more than just additional information and is based on scientific data. The DFG (Deutsche Forschungsgemeinschaft) commission for the investigation of the health hazards of chemical compounds in the work area assigns the S when the observance of the MAK value for the chemical is not sufficient to protect dermally exposed workers from adverse effects on their health. A substance is considered to be absorbed through the skin on the basis of: (1) surveys and field studies; (2) in vivo animal studies; (3) in vitro percutaneous penetration studies; and (4) theoretical models. Criteria 1–4 are arranged in order of decreasing significance, data obtained in the exposed population being considered the most important.

Ss are also assigned in Denmark, Ireland and Switzerland. In Italy and in France, there is no official system of S, and usually people involved in industrial hygiene use notations of the American Conference of Governmental Industrial Hygienists (ACGIH). In Italy, Rec. 46 12 June 1979 regulates dermal exposure in aromatic amine production.

Ss used by ACGIH in the threshold limit values (TLV) list have been criticized in the past for inconsistencies in the documentation [3–5]. The acute dermal toxicity (dermal LD_{50} < 1 g/kg) is the most frequently used criterion, although it is not uniformly used.

Assignment of S can be based on the comparison of dermal uptake with respiratory uptake at inhalation exposure levels equal to the TLV-TWA (time-weighted average). Following this approach, the Dutch Expert Committee on Occupational Standards (DECOS) established that an S has to be assigned when the amount absorbed by arms and forearms in 1 h is >10% of the amount absorbed by inhalation on exposure to the occupational exposure limit (OEL) for 8 h [6]. This approach is hampered by the fact that very little data are available in literature concerning skin absorption.

Fiserova-Bergerova et al. [3] used absorption rates obtained with the Berner and Cooper model to assign an S, and not experimental data. At the moment, the models used for skin notation assignment are based on non-validated data, thereby limiting the use of these models. Guy and Potts [7] have demonstrated that a quantitative structure–activity relationship (QSAR) model, based on physicochemical properties of compounds and derived from experimental data, gives better results. Even better results have been achieved using in vitro data obtained under the same experimental conditions [8]. However, at
the present time, the percutaneous absorption data available are derived from different experimental protocols and are too inconsistent to allow a general QSAR approach.

There are limitations in applying these predictive models for risk assessment [9]:

- compounds should be
  1. neutral (non-ionic),
  2. of low molecular weight (<750 Da),
  3. moderately hydrophobic;
- exposure period should correspond to pseudo-steady-state conditions.

Using validated percutaneous penetration data, QSARs could be used to predict absorption of closely related compounds under similar exposure conditions. This approach, which can reduce time and costs, is not possible at the moment.

The biggest limitation of the notation system is in pointing out the existence of a dermal risk without distinguishing the degree of hazard. Moreover, in many cases, if no $S$ is assigned it is not made clear whether the absence of an $S$ is because it is not considered necessary or because of insufficient data.

Where it is possible to make significant measurements of dermal exposure, it might be possible to develop dermal occupational exposure limits (DOELs) with which such measurements could be compared to enable an administrative approach to be taken to dermal exposure assessment. While there have been recent attempts to develop health-based DOELs [10,11], their use has been limited.

At the present time, DOELs are not set in any country, but many organizations/ agencies are interested in them. The Health Council of The Netherlands, by order of the Dutch Ministry of Social Affairs and Employment, is currently preparing advice about the necessity and possibilities of setting DOELs.

The major uncertainties that prevent the use of DOELs in quantitative risk assessment are considered to be:

- lack of validated and standardized techniques for dermal exposure measurements (there is no general agreement on how to measure skin contamination);
- difficulty in evaluating the extent of contaminated skin;
- regional variations in skin permeability;
- lack of percutaneous penetration data;
- influence of workers’ behaviour on skin contamination.

However, the estimate of dermal exposure cannot be exact because of the number of factors that can influence dermal penetration, such as different sites of application and concentrations of substances. Moreover, it is well known that diseased skin is more permeable. Nevertheless, damaged skin usually retains some barrier properties: permeability variation in these conditions is not easily predictable [12]. Thus, it is impossible to calculate dermal uptake without simplifications, but the same is true in calculating gastrointestinal and respiratory uptake.

For setting DOELs, a substantial amount of knowledge about the toxicology of the compound is required, including percutaneous penetration and kinetics data. Their use might be proposed for specific compounds in specific exposure scenarios, while a more generalized use of DOELs could be very difficult.

As an alternative to the quantitative approach for dermal risk assessment, a qualitative or categorical approach can be used. A recent HSE proposal uses a ‘banding’ approach of this type. The HSE commissioned a survey of COSHH (Control of Substances Hazardous to Health) regulations on how OELs are perceived and used by industry, particularly small and medium-sized enterprises. The results of this research [13] demonstrated that:

- OELs play a very minor part in risk assessment or risk management decisions in small and medium-sized enterprises;
- in deciding what steps to take, very heavy reliance is placed on information from suppliers, with the use of information from independent sources such as trade associations and the HSE being limited.

The HSE, with a working party of the Advisory Committee on Toxic Substances (ACTS), has developed a simple system of generic risk assessment based on readily available hazard information (e.g. risk phrases) and likely use scenarios. Information on hazard, exposure, area of body exposed and dermal uptake form bands, whose combination gives the degree of risk and the control strategies. In this risk banding scheme, it is not necessary to assess dermal absorption with precision, but to establish bands (such as 0–1%, 1–10%, etc.).

The ‘banding’ is not the only attempt at giving a practical dermal risk assessment model. The Risk Assessment Subgroup of DEN presented the research proposal ‘Risk assessment for occupational dermal exposure to chemicals’ (RISKOFDERM), which has been approved and financed by the EC Fifth Framework Programme—FP5 (Coordinator: J. J. Van Hemmen, TNO Nutrition and Food Research Institute, The Netherlands), whose aim consists in developing a validated predictive model for dermal exposure and a practical dermal exposure risk management toolkit for use in actual workplaces.

To achieve this aim, a research programme has been proposed that comprises four interrelated work parts:

- qualitative survey of processes, tasks, populations and determinants of dermal exposure throughout Europe;
- quantitative assessment of potential dermal exposure for selected tasks;
- development of a predictive dermal exposure model—
validity will be determined with biological monitoring and physiologically based pharmacokinetic (PBPK) models; 
- development of a practical risk management toolkit for workplaces—employers will be able to rank dermal exposure risks and choose control measures.

Biological monitoring is now widely accepted and a number of biological exposure indices (BEI) can be used for risk assessment. It can be used to quantify dermal exposure and skin absorption together, if it is undertaken in combination with effective respiratory protection. In a recent paper, Limasset et al. [14] compared the level of styrene absorbed percutaneously with that absorbed by inhalation in a real situation in the fibreglass-reinforced polyester industry. The study protocol consisted of comparisons of the patterns of urinary excretion of styrene metabolites by four groups of workers, all of whom performed the same task, at the same time and in the same workshop, but wore the following different protective equipment: total protection with an insulating suit and mask; respiratory equipment only; percutaneous protection only; and no protection. The urinary excretion level of the group with total protection did not differ significantly from that of the group with respiratory protection only, demonstrating that, in those working conditions, percutaneous absorption of styrene is not particularly important.

Protective gloves are used in many situations to protect skin against harmful chemicals and microorganisms. During the last few years, the occupational use of protective gloves has increased, as has interest in their protective capacity. This has brought the development of standard test methods. Another important issue concerns the side-effects (i.e. allergic reactions) that can occur in using protective gloves. In 1989, the EC adopted two council directives in the field of personal protective equipment (PPE) defining certification procedures (89/686/EEC) and the requirements for the use by workers of PPE in the workplace (89/656/EEC). The body responsible for establishing the new standards for Europe is the Committee for European Normalization (CEN). The Technical Committee CEN/TC 162 ‘Protective Clothing Including Hand and Arm Protection and Lifejackets’ started working in 1989 [15]. CEN collaborates with the International Standards Organization (ISO) and the American Society for Testing Materials (ASTM). Standardization is a continuous process. When European standards have been accepted by CEN, they exist in the draft form (prEN), losing the ‘pr’ prefix once they have been approved by all member countries. A number of ENs for protective gloves have been prepared by CEN/TC 162, regarding test methods of resistance to penetration/permeation by chemicals and other characteristics. However, some limitations of these protocols have been pointed out, because they may not necessarily represent in-use conditions.

In order to predict the systemic risk associated with dermally absorbed chemicals and to enable agencies to set safety standards, data are needed on the rates of percutaneous penetration of these chemicals. Therefore, although the potential of chemicals to cross the skin is an issue of increasing concern, very little is known about the contribution of dermal exposure in the overall risk to the general population or to occupationally exposed workers. There are very few chemicals where reliable quantitative and qualitative data on dermal exposure exist.

In the 1970s, a value of 10% was assumed by regulatory agencies to estimate the dermal absorption of chemicals when data were not available. In 1983, the Office of Pesticides Program’s Scientific Advisory Panel suggested that if no literature was available on a compound, a value of 100% (worst case scenario) as the percentage of absorption should be assumed to estimate the dermal absorption of chemicals for risk assessment [16]. This is a very conservative approach, which has been adopted to encourage the carrying out of studies on percutaneous penetration of compounds. Correction using percutaneous penetration data can have a major impact on regulatory toxicology, because the internal dose used in the risk calculation may be reduced significantly. Estimates of dermal absorption should be as close as possible to real exposure conditions, obtained by experiments conducted under finite dose conditions using doses and periods of exposure which reflect in-use conditions.

Ethical considerations limit studies in human volunteers. Where information on skin penetration exists, it is mainly from animal studies comparing toxicity and toxicokinetic data following administration of the chemical by oral and dermal routes. However, data from in vivo or in vitro studies of dermal absorption in animals cannot be directly extrapolated for prediction of absorption in humans. It is well established that animal skin overestimates human absorption, but that the ratio is both agent- and animal-specific, and therefore no simple correction factors can be used. Potentially, in vitro studies could provide such an alternative, with the added advantage of being more relevant to exposure in humans. However, different systems have been developed in individual laboratories and very few studies have been conducted to compare reproducibility, reliability and predictability. The specific need for a valid method of assessing human dermal absorption has led a number of organizations to produce draft guidelines for in vitro methods of assessing percutaneous penetration. These include the Organization for Economic Co-operation and Development (OECD), the European Cosmetics, Toiletries and Perfumes Association (COLIPA), the US Food and Drug Administration (FDA), the European Chemical Industry Council (CEFIC) and the European...
Centre for Validation of Alternative Methods (ECVAM), who have established a task force. These groups reviewed the scientific literature for in vivo predictions of penetration that related directly to in vivo studies in humans or animal models. They concluded that very few studies are available and that they could not be directly compared because of the lack of standardization of the experimental conditions. Therefore, overall, it was considered that the available data are insufficient to demonstrate the validity of the in vitro methodology. Standardization of in vitro tests and comparison of their results with the in vivo data could produce internationally accepted penetration rates and/or absorption percentages relevant for risk assessment and very useful for regulatory toxicology.

The Percutaneous Penetration Subgroup of DEN presented a research proposal ‘Evaluation of in vitro predictions of dermal absorption of toxic chemicals’ (EDETOX) approved and financed by EC FP5 (Coordinator: F. Williams, University of Newcastle upon Tyne, UK). The project involves 12 institutes and organizations from seven different European countries. The major objectives of the study are:

- to investigate the usefulness of in vitro models to deliver relevant data on percutaneous penetration of chemicals; the reliability and interlaboratory variation will be assessed in order to establish standards for acceptability;
- to demonstrate the relevance and predictability of these in vitro methods by conducting parallel in vivo measurements in human volunteers and comparing in vitro and in vivo data;
- to generate data that will improve knowledge of the dermal absorption process for a series of important environmental and occupational contaminants for which percutaneous penetration may play an important role in the total internal exposure;
- to use in vitro and in vivo experimental data generated in the project to evaluate and extend existing QSAR and PBPK (physiologically based pharmacokinetic) models so that they can be used for the prediction of the rates of absorption of dermal penetrants;
- to develop validated in vitro experimental strategies for the quantitative measurement of the dermal absorption of chemicals and corresponding predictive computational models;
- to provide relevant quantitative data which can be used directly in the risk assessment for dermal exposure, including information that will allow regulatory authorities to progress towards assignment of quantitative skin notations for potentially hazardous chemicals.

In addition to percutaneous absorption of chemicals after skin contamination and the linked risk of systemic illness, occupational dermatitis represents the most common illness resulting from chemical exposures. Dermal exposure assessment can be addressed to the potential irritative reactions and sensitization or systemic effects. Even if percutaneous penetration of chemicals is necessary for elicitation of the local effects (irritation and sensitization), in practice percutaneous absorption studies are only applied to the toxicological responses due to skin exposure. Potential cutaneous irritation and sensitization are studied in pharmacology and cosmetology by using bioassays that are not frequently used in the risk assessment process.

In conclusion, at the moment developing a dermal risk assessment strategy based on a sound scientific foundation is a major concern. Dermal risk assessment consists of comparing exposure levels with ‘no-observed-adverse-effect levels’ (NOAEL), which are commonly extrapolated from animal data. Nevertheless, a clear relationship between dermal exposure and systemic toxicity does not always exist. Very often, hazard identification of dermal exposure is carried out by route-to-route extrapolation. This hampers the development of quantitative DOELs, which is the aim of occupational hygienists in the specific field. At the moment, compounds considered as skin hazards are only identified by a qualitative skin notation (S) on the list of OELs. Moreover, S does not consider local effects, such as cutaneous carcinogenesis, skin irritation and hypersensitivity.

To predict the systemic risk associated with dermal exposure and to enable agencies to set safety standards, penetration data are needed. There is also a need for a practical risk assessment model, particularly for small and medium-sized enterprises.

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