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The Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals

151. Occupational skin exposure to chemicals

With focus on skin exposure assessment, skin sensitisation and prevention by exposure reduction

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on *Occupational skin exposure to chemicals* were done by Dr Anneli Julander, Dr Anders Boman, Prof. Gunnar Johanson and Prof. Carola Lidén at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm.

The draft versions were discussed within NEG and the final version was adopted by the present NEG experts on 6 March 2017. Editorial work and technical editing were performed by the NEG secretariat. The following experts participated in the elaboration of the document:

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All criteria documents produced by the Nordic Expert Group may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

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Abbreviations and acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AES	atomic emission spectroscopy
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (Federal Institute for Occupational Safety and Health)
CLP	classification, labelling and packaging of substances and mixtures
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DMG	dimethylglyoxime
DNEL	derived no-effect level
EC3	estimated concentration to cause a 3-fold increase in draining lymph-node cell proliferative activity
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ED10	minimum elicitation dose giving a reaction in 10% of sensitised subjects
EU	European Union
GPMT	guinea pig maximisation test
HF	hydrofluoric acid
HRIPT	human repeated insult patch test
IARC	International Agency for Research on Cancer
ICP	inductively coupled plasma
IgE	immunoglobulin E
K_{ow}	octanol:water partition coefficient
K_p	permeability coefficient
LLNA	local lymph node assay
MS	mass spectrometry
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PBS	physiologically buffered saline
QSAR	quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROAT	repeated open application test
SAR	structure-activity relationship
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
TOCP	tri-*o*-cresyl phosphate
US	United States
UV	ultraviolet

Selected skin sensitisers mentioned in this document.

Abbreviation	Chemical name, INCI [a] name and/or common trade name	CAS no.
–	formaldehyde	50-00-0
–	isoeugenol	97-54-1
BIT	1,2-benzisothiazolin-3-one; benzisothiazolinone	2634-33-5
CMIT (or MCI)	5-chloro-2-methyl-4-isothiazolin-3-one; methylchloroisothiazolinone	26172-55-4
CMIT/MIT (or MCI/MI)	5-chloro-2-methyl-4-isothiazolin-3-one/ 2-methyl-4-isothiazolin-3-one (3:1); methylchloroisothiazolinone/methyl-isothiazolinone (3:1); Kathon™ CG	55965-84-9
DMFu	dimethylfumarate	624-49-7
HICC	4-(4-hydroxy-4-methylpentyl)cyclohex-3-enecarbaldehyde; hydroxyisohexyl 3-cyclohexene carboxaldehyde; Lyral™	31906-04-4
IPBC	3-iodo-2-propynyl butylcarbamate; iodopropynyl butylcarbamate	55406-53-6
MDBGN	2-bromo-2-(bromomethyl)pentanedinitrile; methyldibromo glutaronitrile	35691-65-7
MIT (or MI)	2-methyl-4-isothiazolin-3-one; methylisothiazolinone	2682-20-4
PPD	*p*-phenylenediamine	106-50-3

[a] INCI: international nomenclature of cosmetic ingredients.

1. Introduction

Occupational skin diseases represent up to 30% of the occupational diseases in Europe. The European Union Agency for Safety and Health at Work (EU-OSHA) has stated that skin disorders are the second most common occupational diseases in the EU, with chemicals being responsible for 80–90% of these (54). The most important exogenous risk factors for occupational skin diseases are exposure of skin to skin sensitising substances (contact allergens), skin irritants and wet work. Among the most frequently affected sectors and occupations are healthcare, hairdressing, cleaning, food processing, chemicals and metals industry, and construction work (39).

Contact dermatitis (including both allergic and irritant contact dermatitis) is the most frequent occupational skin disease and is most commonly localised to the hands. The one-year prevalence of hand eczema in the general population is 10%, and it affects women more frequently than men due to differences in exposure (208). Hand eczema causes job loss, unemployment, severe suffering and is often chronic. Occupational skin diseases in the EU cost in excess of 5 000 million euros/year in lost productivity, treatment and compensation (33, 109). Very few scientific reports on costs related to occupational skin diseases have been published, among them references (25, 38, 41, 168).

Contact dermatitis is also the most common skin disease caused by skin exposure to chemicals. Other skin diseases or effects on skin which can sometimes be chemically induced include contact urticaria, photo-contact dermatitis, burns, acne and lichenoid reactions.

Skin exposure to chemicals can also cause systemic effects and skin cancer (165). Arsenic, creosote and polycyclic aromatic hydrocarbons (PAHs) are known to cause skin cancer. Skin cancer will not be discussed further in this document.

EU legislation imposing restrictions and other regulatory measures on some skin sensitisers has been successful. The most prominent examples are chromium (VI) in cement, nickel in prolonged contact with the skin, some preservatives and the biocide dimethylfumarate (DMFu).

The present document on occupational skin exposure to chemicals is not a comprehensive review of the area, but rather an introduction to the field with emphasis on skin exposure assessment, skin sensitisation and prevention by exposure reduction. Information on contact allergy, contact dermatitis and prevention has been compiled from peer-reviewed original and review publications, and partly from text books.

2. The skin and its function

The skin is the demarcation between the body and the outside world and is essential for life in the relatively dry environment we exist in. The skin encloses and preserves vital substances and molecules in the body; most importantly, it

limits the loss of the water present in the body. It also protects against many external chemical and physical factors.

2.1 Skin barrier function in relation to water and chemicals

The skin consists of three layers: epidermis, dermis and subcutis (Figure 1). In the epidermis, which is composed of keratin cells (keratinocytes), it is possible to distinguish multiple layers where the horny layer (*stratum corneum*) is the outermost. The horny layer is 10–20 µm thick in most areas of the body and about 10 times thicker on the soles and palms. The *stratum corneum*, by its structure, constitutes the actual water barrier. It is composed of flattened converted keratin cells, so-called corneocytes, which are filled with structural protein. The intercellular space consists of a thin multilayer of lipids known as ceramides. Together with the corneocytes, these lipids form a virtually waterproof membrane around the body, often likened to a brick and mortar wall. Throughout the epidermis and *stratum corneum* there is, however, a slow diffusion of water acting as a plasticiser for the skin. This diffusion gives rise to a measurable evaporation of water from the skin surface, transepidermal water loss, which amounts to about 0.5 litres per day (13).

The human skin also serves as a relatively good barrier against exposure to chemicals in the environment. With the exception of a few toxins and contact allergens, chemicals found naturally in the environment rarely constitute a health hazard at dermal exposure. However, after the development of organic chemistry in the mid-1800s, many organic chemicals with dermal penetrating abilities and capacity to alter the properties of the skin barrier have been produced. A number of organic solvents are readily absorbed by the skin and

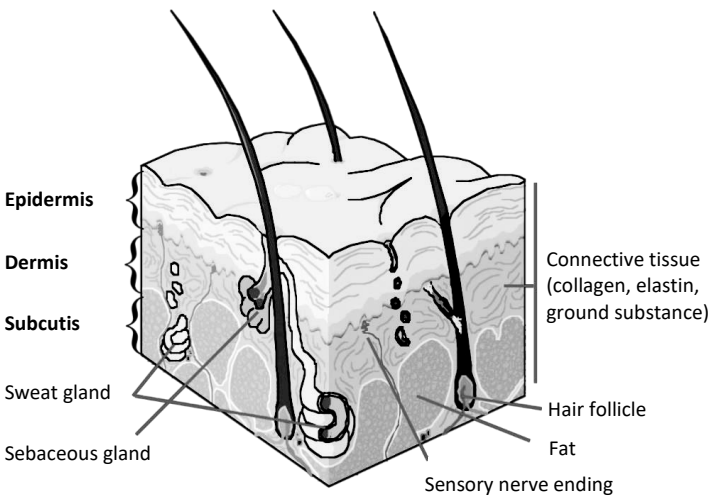

Figure 1. The skin with its three layers and different organs.

cause intoxication. Other substances that are highly toxic at skin exposure are organic phosphorus compounds used as insecticides. Many substances have an effect mainly on the skin lipids, altering the skin barrier properties and facilitating passage of other chemicals. This may result in systemic toxicity as well as local skin effects (13).

The driving force for diffusion across the skin barrier is the concentration gradient across the barrier. This means that higher concentrations of a harmful chemical result in higher flow rates across the skin barrier, causing more damage locally and systemically than more diluted chemicals. Nevertheless, one should not neglect exposures to products with low concentrations of chemicals such as mild irritants and contact allergens. Repeated or prolonged exposure may lead to the development of allergy (induction of skin sensitisation), allergic contact dermatitis (elicitation) or an irritant reaction. An injured skin is a poor barrier resulting in substances being absorbed to a greater extent. Exposure under occlusion, for example under a thick glove, can lead to increased uptake through increased hydration of the skin and reduced evaporation of the substance. The skin barrier itself is also impaired by occlusion.

The efficacy of the skin barrier does not vary with gender or colour of skin. However, the skin barrier function may decline with age due to a general thinning of the skin over time. Disease or injury to the skin may affect the barrier negatively and atopic skin usually has a higher permeability.

2.2 Additional skin functions

The skin is normally a good barrier against microorganisms. Its surface carries resident and transient microorganisms that usually do not pose any health threat. If the skin surface is damaged by external influences or eczema, microorganisms can pass the barrier and give rise to infections locally or systemically (13, 37).

The skin also provides a barrier against a variety of physical factors in the environment. One of the most obvious functions is to protect the body against external damage through the tensile strength of the cutis along with the padding (cushion) in the subcutaneous fat. The skin protects the body from ultraviolet (UV) and visible light by producing a dark pigment (melanin) in the melanocytes when exposed to UV light (13).

The skin also protects against heat and overheating. One of the most important functions is the regulation of body temperature. The body can be cooled down through dilation of the small surface vessels in the skin and by sweating. Thus heat is transported from the body's internal parts to the outer surface where it can dissipate. Conversely, skin blood flow is reduced at exposure to cold environments (13).

In addition to the barrier function, the skin has a metabolising function. Several of the xenobiotic metabolising enzymes in the liver are also found in the skin (223, 230). Metabolic activation of chemicals (prohaptens) in the skin can result in formation of new or more potent skin sensitisers. This has been shown for a

range of chemicals, including fragrance substances (116). The skin is also the major site for vitamin D formation (13).

Human skin has a signalling function, showing certain basic emotions through redness and paleness. It is also an important sensory organ. The dermis contains sensory cells that respond to physical stimuli such as pain, cold, heat, pressure, vibration and touch. This allows us to react and avoid hazards such as heat, pointed and sharp objects, and also to react positively to soft touches (13).

3. Sources of skin exposure

The skin is exposed to chemicals at contact with products, substances or materials. The contact can be intentional, as when washing the hands or using a cream, or unintentional usually from contaminated surfaces, accidental spills or splashes. The contact can also be due to processes that are less obvious, such as deposition of airborne compounds. There are many sources of skin exposure to chemicals. Typical examples are shown in Figure 2.

Airborne exposure of the skin to skin sensitisers, skin irritants and photoactive substances, may result in dermatitis on the air-exposed areas but not on covered body parts. Airborne exposure to some chemicals may also result in significant skin absorption and systemic effects (Chapter 4).

Contaminated surfaces in the workplace may be an important source of skin exposure, which is often overlooked. Surfaces may be contaminated by spillage, transferral by hands, tools or protective equipment, or from deposition of dust and the like.

Intentional exposure includes not only makeup, perfume and hair dyes but also soaps and creams [defined as cosmetic products in the European Cosmetic Products Enforcement Regulation (64)]. Cosmetic products are generally consciously applied onto the skin. The use of liquid soap in the workplace is often not considered when occupational exposure is discussed. This is important since such products generally contain sensitising preservatives and fragrance substances.

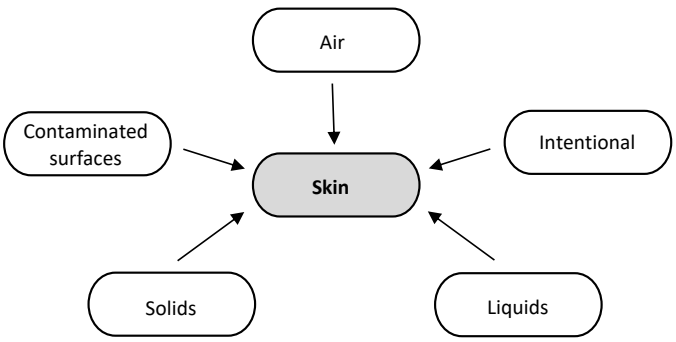

Figure 2. Examples of typical sources of skin exposure to chemicals.

Release of chemical substances from *solid items and materials* may be significant. Solids may release ions, compounds or particles by dissolution in sweat or other solvents or by friction against the skin. Both persistent contact and brief, repetitive contact may result in significant skin exposure. Typical examples are release of nickel ions from metal articles, chromium (VI) from leather articles, monomers from plastic, and rubber chemicals from rubber articles.

As regards *liquids*, leakage or permeation through insufficient protective equipment is often overlooked. Liquids may consist of solutions, dispersions and solvents. Liquid on the skin may be wiped or washed off, smeared out, dry on the skin or evaporate. The amount of harmful constituents deposited on the skin surface depends on several factors including duration and frequency of exposure, and affinity of the liquid or its constituents.

A model has been proposed by Schneider *et al.*, who attempted to compile all processes leading to dermal uptake (189). The model's primary objective was to allow assessment of all possible skin exposure routes to calculate the ultimate exposure metric, i.e. dermal uptake, for risk assessment. This might work for substances of concern for systemic uptake, but might not be the ideal solution for studying exposure leading to skin diseases. For this purpose, it would be more relevant to evaluate and standardise methods that measure the amount of a chemical or substance on the skin surface, since this is the most important metric for development of a skin disease (87).

4. Dermal absorption

In this document, dermal absorption (also called percutaneous or skin absorption) denotes the diffusion of a chemical from the outer surface of the skin through the skin and eventually into the systemic circulation. This contrasts dermal penetration which means diffusion across the outermost barrier, i.e. the *stratum corneum*, into the skin (160) and dermal permeation which denotes further diffusion into deeper skin layers. Many chemicals can more or less easily pass the skin barrier and thus raise concerns for systemic toxicity. Dermal absorption and penetration can be measured experimentally by various *in vivo* and *in vitro* methodologies.

4.1 In vivo methods

In vivo measurement of dermal absorption is advantageous, as the skin is intact, with retained metabolic capacity and blood supply to the dermis. The rat is the most commonly used species for *in vivo* testing. However, a wide variety of other species and strains have been used, including guinea pigs, mice, rats, dogs, minipigs, pigs, monkeys and humans, and some hairless strains.

In vivo studies in laboratory animals are preferably conducted as described by the Organisation for Economic Co-operation and Development (OECD) (160). In brief, the test sample is applied to a defined area (ideally about 10 cm^2) of the skin and allowed to remain for a specified period of time, relevant to human exposure.

Throughout the experiment, the animal is housed individually in a metabolism cage from which excreta (and breath if volatile metabolites are expected) are collected. At the end of the exposure period, excess sample is removed from the skin surface. The animals are then euthanised and the amount of parent chemical and metabolite(s) in skin, carcass and excreta is determined. These data allow for an estimate of the total recovery of the test substance.

Test chemical remaining in the skin after wash-off may disappear over time by diffusion to the environment, desquamation (shedding of the outer layers of the skin), ingestion during grooming, and by uptake to the systemic circulation. To avoid overestimation of the systemically absorbed dose, measures have to be taken to prevent the animal from grooming the site of application, and to prevent desquamated skin from falling into the urine and faecal collection systems.

The dermal absorption of a test substance can be expressed as the percentage of the dose that passes the skin per unit time or, preferably, as an average absorption rate per unit area of skin, e.g. $\mu g/cm^2/h$.

In vivo studies with human volunteers must use a different experimental protocol, as the total recovery cannot be directly determined. The dermally absorbed dose is then determined indirectly, by comparison to a known dose, for instance the net uptake by inhalation exposure. The dermal absorption, or rather, the systemic dose via the dermal route, is calculated for example by comparing the urinary recoveries of the chemical and/or its metabolite(s) after the two exposure routes. Alternatively, the areas under the concentration-time curves (AUCs) in plasma or blood are compared. For examples of this approach, see e.g. studies by Johanson and colleagues (100, 101, 103, 104).

A different approach to measure dermal absorption is microdialysis. A small probe equipped with a semipermeable hollow fibre is inserted superficially into the dermis, parallel to the skin surface. A physiological saline solution is slowly pumped through the fibre and allowed to equilibrate with the surrounding extracellular space. The solution is then retrieved and the concentration of the substance of interest can be measured. For overviews, see e.g. Anderson (7), Schnetz and Fartasch (190) and Stahl *et al*. (197).

Human pharmacokinetic microdialysis has only been carried out for a few decades and there are limited data, mainly on pharmaceutical drugs, on dermal absorption using this technique. There are several difficulties in obtaining quantitative measures of the dermal absorption by microdialysis. A major problem is that concentration and not flux is measured. The concentration will depend not only on influx via *stratum corneum* but also on efflux via the blood stream. Other difficulties stem from the positioning of the probe (as the concentration tends to decrease with the distance from the skin surface), and from defining the exposed skin area.

Tape stripping should also be mentioned here, as it is a convenient method to measure penetration into the skin. Tape stripping is further discussed in Section 7.1.1.1.

4.2 In vitro methods

In vitro, excised skin from experimental animals or humans is mounted in a so-called diffusion cell, where the test chemical is applied on the outer surface (apical side) of the skin. The inner (basal) side of the skin is held in close contact with a suitable receptor medium, usually physiologically buffered saline (PBS). Depending on the properties of the test substance, polyethylene glycol or other solubility enhancers may be added to the receptor medium. The diffusion cell may be static (Figure 3) or flow-through; the latter is more easily adapted for automation, i.e. online measurement or autosampling. An advantage of the *in vitro* methods is that toxic and skin damaging chemicals can be tested without risk of harming an animal or test person.

As with *in vivo* studies, the exposure duration should be relevant for human exposure situations. The receptor fluid is sampled at defined time points throughout the experiment and the concentration of the parent chemical as well as any significant metabolite(s) is determined by a suitable analytical method to determine the amount of test substance (including any significant metabolite) that has passed through the skin. At the end of exposure, excess sample is removed from the donor compartment by appropriate cleansing. The removed amount, the amount contained in the skin and the amount in the receptor fluid are determined to account for the mass balance.

To calculate the dermal absorption rate, the concentration in the receptor fluid is translated to absolute mass by multiplying by the receptor volume. The absolute mass rate, i.e. the increase in mass with time during steady-state condition, is obtained as the slope of the linear part of the mass versus time curve ("B" in Figure 4). Finally, the unit absorption rate or flux is obtained by dividing the mass rate by the exposed skin area. For more detailed descriptions, see e.g. the OECD guideline (161).

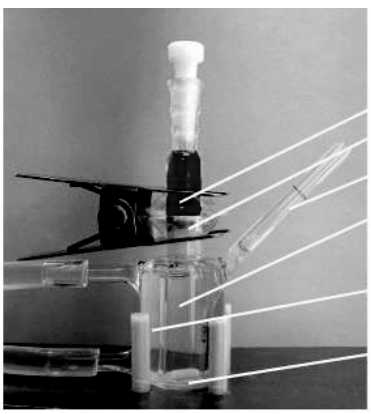

Figure 3. Static diffusion cell for dermal absorption studies *in vitro*. Reprinted from Johanson and Rauma (107). PBS: physiologically buffered saline.

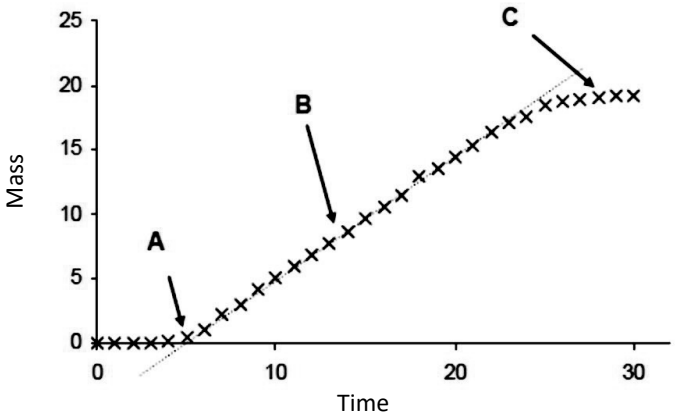

Figure 4. Mass of chemical versus time in the receptor medium static diffusion cell. A: Lag time of skin penetration, B: Steady-state, the slope (dotted line) equals absorption rate, C: Absorption rate decreases (curve levels off), either due to back diffusion (limited solubility in receptor medium) or depletion at donor site. Reprinted from Johanson and Rauma (107).

4.3 Structure-activity based methods

Several regression equations have been developed that relate permeability coefficients (K_p) to easily obtained chemical properties, such as the octanol:water partition coefficient (K_{ow}) and molecular weight (MW). The K_{ow} is thought to represent the solubility and MW the size and, hence, diffusivity of the molecule in the skin. The regression equations are often of the form (146):

$$\log K_p = a + b \times \log K_{ow} + c \times MW$$

The constants a, b and c are determined by fitting the equation to specific experimental data sets. One of the most commonly cited equations was developed by Potts and Guy (169):

$$\log K_p = -2.72 + 0.71 \times \log K_{ow} - 0.0061 \times MW$$

where K_p is expressed in cm/h. More complicated models have also been developed, e.g. the modified Guy (231), the Cleek and Bunge (32), the McKone and Howd (147), the modified Robinson (231) and the Frasch model (75). The United States National Institute for Occupational Safety and Health (US NIOSH) has developed an online skin permeation calculator that makes use of the Potts and Guy, the modified Robinson and the Frasch models (157).

These equations generally work well within homologous series and structurally related chemicals, but are often unreliable outside that range. The error may be up to one or two orders of magnitude, compared to experimental data (107).

4.4 Factors affecting dermal absorption

The dermal absorption rate (flux) is directly proportional to:

- the concentration (more correctly the chemical activity, partial pressure or fugacity) of the chemical at the skin surface (assuming that the inner concentration is negligible), and
- the permeability of the skin (expressed by K_p).

The total amount of absorbed chemical is proportional to (in addition to concentration and permeability):

- the exposed area (since K_p is expressed per area unit), and
- the duration of exposure.

Obviously, K_p depends on the properties of the chemical as well as those of the skin. Major properties of the skin that influence permeability are the thickness of the *stratum corneum*, and the temperature and degree of skin hydration. The thickness of the *stratum corneum* varies considerably between different species and locations on the body. In addition, the penetration tends to increase with temperature as molecules move faster, though this is only of minor importance as the skin temperature is fairly constant. However, increased body temperature, increased ambient air temperature and increased air humidity and skin occlusion all contribute to increased skin hydration and increased dermal blood flow, which in turn increases the penetration and absorption of chemical. Contact dermatitis and other adverse skin effects may also increase the systemic uptake (107).

4.5 Dermal absorption of selected chemicals

There are several reports on acute poisoning following skin contact with different types of chemicals such as hydrofluoric acid (HF) (24), 2,4-dinitrophenol (142), tetramethylammonium hydroxide (126, 164, 232), as well as paraquat (225, 235), pentachlorophenol (110) and other pesticides (see below).

HF is a highly corrosive acid widely used in various etching and cleaning processes. Skin contact with HF may, depending on concentration, area and duration, cause serious skin burns and life-threatening or lethal systemic toxicity (24, 204). Exposure of more than 1% of the body surface (i.e. approximately the palm of a hand) to concentrated HF may lead to systemic toxicity (86).

Clothing may reduce or prevent chemical exposures, but may also prolong the exposure, if the clothes are soaked with chemical or if the chemical is trapped inside the clothes. The occluding effect of the clothes (especially gloves) may further enhance the systemic exposure (Section 4.4).

Some important categories of chemicals for which significant dermal absorption has been shown are presented below.

4.5.1 Pesticides

Acute poisoning with pesticides is a global public health problem especially in developing countries, and has been estimated to account for 300 000 deaths per year worldwide. Most deaths are caused by organophosphates, organochlorines and aluminium phosphide (82).

Wester *et al.* studied the dermal absorption of paraquat in 6 volunteers. Between 0.2% (hand) and 0.3% (leg, forearm) of the applied dose (9 µg/cm^2) was absorbed in 24 hours, corresponding to a relatively low uptake rate of 30 ng per cm^2 and 24 hours (226). Yet, the dermal route has been implicated in serious paraquat poisonings (225, 235). Two female workers with massive skin exposure (2–3% of the body surface) to paraquat after spraying developed skin erythema, blistering and bleeding and later on systemic symptoms like dyspnoea (235). Wesseling *et al.* investigated 15 fatalities (all males) caused by paraquat. In 10 of the cases exposure had occurred via ingestion, whereas no apparent oral intake could be identified in the remaining 5. For 3 of the latter, the route was clearly dermal (225).

Pentachlorophenol and other chlorophenols have a long history of use as pesticides and disinfectants. Pentachlorophenol was banned in Sweden in 1978 (141), by the EU in 1991 (55) and by the Stockholm Convention in 2015 (200). It was widely used as a wood preservative and is still used in large quantities worldwide, the estimated annual production being 15 400 tonnes (98). Acute poisonings have occurred repeatedly e.g. in workers after dipping wood in pentachlorophenol liquid formulations, and in hobbyists after brushing pentachlorophenol onto logs (110). Riviere *et al*. measured the dermal absorption of dissolved pentachlorophenol *ex vivo* in pig skin flaps. Depending on formulation, between 8% (ethanol) and 27% (water, ethanol, sodium lauryl sulphate (detergent) and methyl nicotinate (vasodilator)) of the applied pentachlorophenol (40 µg/cm^2) passed the skin in 8 hours (174).

Aggarwal *et al*. (3) compiled dermal absorption data for pesticides (295 studies in total, covering 152 active substances, 19 formulation types and representative ranges of spray concentrations) obtained with human skin *in vitro* according to the OECD guideline (161) and using the European Food Safety Authority (EFSA) guidance worst-case assumption that all chemicals not remaining in the skin and the first two tape strips were absorbed (51). The compilations showed that the median percent absorbed active substance was 0.6% (95th percentile 5.2%, n=250) for liquid concentrates, 0.3% (95th percentile 1.6%, n=53) for solid concentrates, and 6.7% (95th percentile 32%, n=446) for diluted formulations. No clear relation between percent absorbed and molecular weight or log octanol:water partition coefficients (log K_{ow}) was seen (3).

4.5.2 Phosphate triesters

Several phosphate triesters are frequently utilised as flame retardants, plasticisers, stabilisers and additives in products such as floor polishes, lubricants and hydraulic fluids (195). In cats dermally exposed to tri-*o*-cresyl phosphate (TOCP), 48% of

the applied dose was recovered in urine and faeces within 10 days post-exposure (158). Neurological effects in dermally exposed European ferrets also indicated a high dermal absorption (201). Marzulli *et al.* reported a dermal absorption rate for TOCP of 0.18 μg/cm^2/h (145). Applying the ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) criteria (43) (Section 9.1) this would correspond to a systemic dose via skin of 72% of that inhaled at an occupational exposure limit (OEL) of 0.1 mg/m^3.

Tri-*n*-butyl phosphate (TBP) showed a high penetrating capacity in isolated human skin *in vitro*. The average steady-state absorption rate was 10.8 μg/cm^2/h (145). Applying the ECETOC criteria, the dermal systemic uptake would be nearly 200% of that inhaled at an OEL of 2.2 mg/m^3.

In vitro, tris(1,3-dichloro-2-propyl) phosphate (TDCPP) was readily absorbed through skin from hairless mice and 39–57% of the applied dose was detected in the receptor fluid by 24 hours (94).

Taken together, although few human skin exposure studies *in vivo* have been conducted (195), the above examples show that exposure to phosphate triesters via skin will result in significant systemic exposure.

4.5.3 Organic solvents

All organic solvents can more or less easily pass the skin. Several organic solvents may even cause acute toxic effects, including mortality, following skin exposure, as shown in animal experiments (222), and human deaths have been reported after accidental skin exposure, e.g. to 2-chloroethanol (83) [cited by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) (159)].

The skin absorption is dependent on the physicochemical properties of the solvents; low molecular weight and high lipophilicity result in high solubility and mobility in the lipid phase of the *stratum corneum*. Chemicals with the highest dermal absorption rate are generally found in the group of amphiphilic organic solvents, e.g. glycol ethers. The combination of high lipid solubility and high water solubility means that there are no solubility barriers – neither in the intracellular lipid phase of the *stratum corneum*, nor in the hydrophilic epidermis or the transfer into circulating blood.

Johanson and Rauma reviewed experimental data on dermal absorption of 165 substances, many of which are organic solvents. The review showed that quantitative information on dermal absorption was lacking for about one third of the substances. For those with quantitative data, a variety of species and experimental techniques had been used. There was a trillion-fold (10^{12}) span in permeability coefficients (K_p) between all substances and a hundred thousand-fold (10^5) span between organic solvents. Moreover, for many chemicals with several experimental data sets on permeability, there was a huge intrachemical span, sometimes several orders of magnitude (107).

Rauma *et al.* reviewed and analysed the dermal absorption of chemical vapours (mainly organic solvents) using experimental data and regression and pharmaco-

kinetic models. Dermal contribution ratios, i.e. the amount absorbed through skin relative to the total uptake (skin plus inhalation), were calculated for 33 chemical vapours. The ratios varied from approximately 0.0002 (i.e. 0.02% via skin) for vinyl chloride to 0.8 (80% via skin) for 2-butoxyethanol, with hydrophilic chemicals having a higher ratio than lipophilic ones. Multiple regression analysis of the data suggested that the ratio is largely explained by the octanol: water partition coefficient (K_{ow}), vapour pressure and molecular weight. The authors concluded that dermal absorption of chemical vapours needs more attention, as such exposures are common, data are scarce and few predictive models exist (173).

Some organic solvents may act as dermal penetration enhancers, i.e. they increase the penetration (and absorption) of other chemicals. Thus, several aprotic organic solvents, such as dimethyl sulphoxide, dimethyl formamide, dimethyl acetamide as well as several terpenes and glycol ethers, are used as penetration enhancers in various situations (85, 187). Even water may act as a penetration enhancer of organic solvents (104).

4.5.4 Metals

Systemic uptake of metals via skin has previously not been considered to be of major concern. However, absorption of metal ions was shown already in the 1960s in experimental animals.

Skog and Wahlberg studied the dermal absorption of several metal ions in guinea pigs using radioactive isotopes and scintillation counting. For mercury (Hg^{2+}), the amount absorbed in 5 hours, calculated from the reduced radioactivity at the exposure site, varied between 1.7% and 4.5% (depending on pH and concentration) of the applied amount. The 5-hour absorption of cobalt, zinc and silver ions was lower and generally below 1%. Absorption through skin was confirmed by elevated radioactivity in various organs of the test animals (196). The same group also studied the absorption of these metal ions through guinea pig and human abdominal skin *in vitro*. The absorption rate through human abdominal skin (autopsy material, washed with soap and water and frozen before use) during the first 4 hours of exposure to 0.085 M cobalt chloride was 38 nmol/cm^2/h (2.2 μg Co/cm^2/h). The *in vivo* dermal absorption rate in guinea pigs was in the same range as the *in vitro* dermal absorption rate reported for humans (221).

Skin absorption following exposure to elemental metals has also been demonstrated. Thus, Scansetti and co-workers showed that experimental exposure of hands only to hard metal powder (tungsten carbide with 5–15% cobalt) caused elevated levels of cobalt in the urine of the test persons (181). Using the Scansetti data (181), Palmen calculated the 24-hour cumulative uptake (one hand exposed) to 21 μg Co and the dermal absorption rate to 33 ng Co/cm^2/h (163). Applying the ECETOC criteria (44) the calculated uptake was 66 μg, or 18% of the amount absorbed during 8-hour inhalation exposure to 50 μg Co/m^3.

Cobalt absorption through the skin was studied in volunteers immersing both hands in a used coolant solution (containing 1 600 mg Co/l) for 1 hour. The total

24-hour excretion was calculated from analysis of cobalt in urine (140). From the results, a dermal absorption rate of 1.4 ng Co/cm^2/h was calculated (163).

Larese *et al.* applied powders of nickel, cobalt and chromium (5 g/100 ml) in synthetic sweat (pH 6.5) on human skin mounted in Franz diffusion cells. Analysis by several methods [electrothermal atomic absorption spectroscopy, differential pulse polarography, differential pulse voltammetry, inductively coupled plasma atomic emission spectroscopy (ICP-AES)] confirmed the presence of ionic nickel and cobalt, but not chromium (< 0.1 mg/l) in both donor and receptor medium after 24 hours. The permeation fluxes were determined to 12 ng/cm^2/h (nickel) and 17 ng/cm^2/h (cobalt). These experiments thus showed that metallic nickel and cobalt can be oxidised when suspended in synthetic sweat and that measurable amounts of the ions can pass through human skin. According to the authors, chromium would probably need stronger oxidising conditions (122).

4.5.5 Nanomaterials

Numerous studies have examined the dermal penetration of various types of nanomaterials, mostly by different microscopic imaging techniques. The studies consistently show that an overwhelming proportion of the topically applied nanomaterial remains on the surface or in the outermost layers of *stratum corneum*. Furthermore, nearly all studies have failed to demonstrate penetration beyond the epidermis. A limitation with these studies is that they are qualitative rather than quantitative in nature, and detection limits are not available (102).

A few studies have used sensitive analytical methods to measure absorption through skin *in vitro* with diffusion cells, mainly by using metal-containing nanoparticles and analysis by inductively coupled plasma-mass spectrometry (ICP-MS). These studies are summarised in Table 1. The amount that passes through human skin *in vitro* ranges from 0.0007% (silver) to 0.5% (gold) per 24 hours of the dermally applied dose. Many factors besides composition, size, shape and surface charge (zeta potential) may influence the results, including coating, agglomeration, concentration of nanomaterial in donor medium, composition of donor and receptor medium, pH and design of diffusion cell. Two major factors may

Table 1. Estimates of absorption of nanoparticles through intact skin *in vitro*.

Main constituent	Size (nm)	Zeta potential	Species	Applied dose	Recovery in receptor medium after 24 hours	Fraction absorbed after 24 hours (%)	Ref.
Gold	13	ns	Human	45 µg/cm^2	214 ng/cm^2	0.5	(71)
Gold	18 × 40	+	Mouse	50 µg [a]	60 ng [b]	0.1 [a]	(127)
Gold	18 × 40	-	Mouse	50 µg [a]	360 ng [b]	0.7 [a]	(127)
Silver	25	ns	Human	70 µg/cm^2	0.46 ng/cm^2	0.0007	(123)
Titanium dioxide	20–70	ns	Human	60 µg/cm^2	< 42 ng/cm^2	< 0.07	(42)
Zinc oxide	200	ns	Human	20 µg/cm^2	< 32 ng/cm^2	< 0.16	(42)

[a] Unknown area.
[b] After 48 hours.
ns: not stated.

contribute to falsely high values: disruption of the barrier during preparation and, perhaps more importantly, dissolution of metal from the nanomaterial prior to absorption.

Larese Filon and colleagues recently performed a thorough review of the dermal penetration and permeation (i.e. the movement to deeper skin layers) of nanoparticles (124). In contrast to the above reasoning on diffusion, they concluded that experimental data allows for a differentiation by size in that nanomaterial:

≤ 4 nm can penetrate and permeate intact skin,
4–20 nm can potentially permeate intact and damaged skin,
21–45 nm can penetrate and permeate damaged skin only,
> 45 nm can neither penetrate nor permeate the skin.

The studies presented in Table 1 and the above size categories suggested by Larese Filon *et al.* (124) are at odds with theoretical calculations made by Watkinson *et al.* (224). Thus, based on the Potts and Guy equation, Watkinson *et al.* calculated permeability coefficients (K_p) for the diffusion through intact skin of nanoparticles, assuming spherical shape, a density of 1 g/cm^3 and a log octanol: water partition coefficient (log K_{ow}) of 2. The predicted K_p values were 6×10^{-4}, 2×10^{-17} and 0 cm/h for 1, 2 and 5 nm nanoparticles, respectively. For comparison, the K_p values for neat chemicals with a skin notation (Section 9.1) are typically between 0.1 and 10^{-4} cm/h (107). Using the equation of Magnusson *et al*. (144) [= eq. 2 in Watkinson *et al.* (224)], the predicted maximum flux values were calculated to 0.34, 2×10^{-28} and 0 µg/cm^2/h, compared to typically 0.1–10^4 µg/cm^2/h for chemicals with a skin notation. These calculations suggest that nanoparticles, except the very smallest ones of 1 nm, are too large to permeate intact skin by diffusion.

The nanoparticle surface charge (zeta potential) may also influence dermal penetration and permeation; however, seemingly opposite results have been reported. For example, Ryman-Rasmussen *et al*. reported deeper penetration into the *stratum corneum* of positive compared to negative quantum dots (QDs) (178), whereas Lee *et al.* measured up to 6-fold lower percutaneous absorption of positive compared to negative gold nanorods (127). Kim and co-workers, using cultured human colon carcinoma cells and mathematical modelling, showed that positively charged drug-carrying gold nanorods had higher uptake and dissociation by viable cells, whereas negative nanorods diffused faster (118). Rancan *et al.* similarly found that despite partial particle aggregation, silica particles were taken up by skin cells in a size-dependent manner and that positive particles had a higher cellular uptake rate. On the other hand, the positive particles tended to aggregate, lowering the uptake rate (171). Overall, there appears to be a complex relation between size, surface charge, pH, aggregation and dermal penetration and permeation.

For pharmaceutical drugs and other chemicals, the follicular route has previously been considered to be of minor importance. However, it has been shown that the skin penetration rate of various drugs is significantly lower in hairless than in hairy rodents, that the rate correlates with the follicle density and that it

can be lowered by blocking the follicular openings [for references see e.g. Rancan and Vogt (172)]. There are several reasons for a potential importance of this route also for nanomaterials: large contact area and large storage volume of the follicles, well developed capillary network, and less developed *stratum corneum* (compared to the skin surface). Thus, once accumulated in the follicular canal, nanoparticles might more easily translocate across the *stratum corneum* and reach the lymph and blood circulation. Skin penetration of nanomaterial via the hair follicles has therefore received considerable attention.

The size categories suggested by Larese Filon *et al.* (124) (see above) still need to be confirmed. In any case, smaller nanoparticles are expected to have a greater ability to penetrate through the skin than bigger ones. In real-life conditions, the dermal absorption through intact skin of larger nanoparticles (at the 100-nm end) is likely zero or insignificant. The absorption of small-scale nanoparticles (at the 1-nm end) may be a concern. Still it is likely very low compared to, e.g., organic solvents.

A remaining concern, especially for metal nanoparticles, is that of dissolution, e.g. in sweat, and subsequent skin penetration of the dissolved molecules/ions. It is well known that metal and metal oxide powders, once placed in biologic media, can release metal ions (149-151). Experiments by Larese Filon *et al.* have demonstrated that metallic nickel and cobalt can be oxidised when suspended in synthetic sweat (122). Release of metal ions may not only enhance the penetration and permeation of the metal but also result in a changed tendency to form aggregates and an increased sensitising potential (124).

5. Skin sensitisers

Contact allergy is mediated by antigen-presenting cells in the epidermis (Langerhans cells), by antigen-specific T-cells, and cytokines. Contact allergy (also called Type-IV reaction or delayed hypersensitivity) is a type of allergy distinct from immunoglobulin E (IgE)-mediated allergy in asthma and rhinitis. Skin exposure to contact allergens may cause *induction* of contact allergy, and re-exposure of a sensitised individual or animal to the substance may result in *elicitation* of allergic contact dermatitis or a positive test reaction (Figure 5). *Allergic contact dermatitis* is the clinical disease caused by skin exposure to skin sensitising substances (contact allergens). The dose sufficient for induction of contact allergy is generally larger than the dose sufficient for elicitation. A sensitised individual has to avoid further exposure to the substance to avoid allergic contact dermatitis. Contact allergy is life-long, whereas allergic contact dermatitis may clear up if skin exposure to the substance is avoided (177).

Figures on the prevalence of contact allergy are generally based on results from diagnostic patch testing of patients with dermatitis, done in dermatology clinics (167, 218). The prevalence of contact allergy is generally significantly

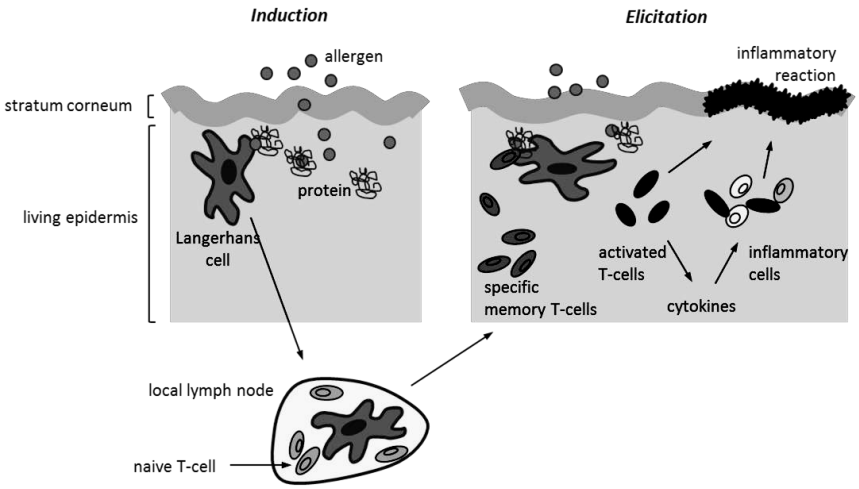

Figure 5. The two phases of skin sensitisation: induction of contact allergy, and, upon re-exposure, elicitation resulting in allergic contact dermatitis (Midander K and Yazar K).

higher among dermatitis patients than in the general population (Table 2). Only a few large studies of contact allergy in the general population have been performed, see e.g. references (40, 121, 209). Contact allergy is estimated to occur in approximately 20% of the adult general population in Europe (40, 209). Children are also affected by contact allergy, but less frequently (121). The prevalence figures differ between studies, possibly depending on population selection, exposure and patch test technique.

There are large differences between women and men for some allergens, and between certain occupational groups. There are also regional differences in prevalence of contact allergy. These differences are related to differences in exposure, particularly owing to occupational exposure and use of consumer products.

More than 4 000 chemical substances have until now been identified as skin sensitisers. These are organic and inorganic substances with a molecular weight below 1 000 Da, often below 500 Da (74).

The most frequent causes of contact allergy and allergic contact dermatitis are metals, preservatives, fragrance substances (perfumes), chemicals in plastic and rubber, and hair dyes. Some potent skin sensitisers may induce sensitisation by contact on single occasions, such as epoxy resins, some preservatives, some hair dye substances, and experimental allergens e.g. dinitrofluorobenzene (DNFB) and dinitrochlorobenzene (DNCB). Also less potent sensitisers such as nickel and many fragrance substances frequently cause contact allergy and dermatitis because exposure is difficult to avoid. Repeated exposure to the sensitiser, impaired skin barrier like in dermatitis, and occlusion of the skin are other factors that increase the risk of sensitisation and dermatitis (170, 177).

Guidance on how to evaluate human and animal data on skin sensitisation and set specific concentrations limits according to the CLP Regulation (EU regulation on *classification*, *labelling* and *packaging* of substances and mixtures) is available (50).

Table 2. Prevalence of contact allergy and risk occupations. Examples of some of the most frequent skin sensitisers included in the European or Swedish baseline series for patch testing.

Substance	Property, presence or use, examples	Prevalence (%) [a]		Occupational groups frequently affected by contact allergy, non-exhaustive list (39)
		General population in 5 EU countries 2008–2011 (40)	Dermatitis patients in Sweden 2009 (66)	
Nickel	Metal	14.5 m: 5.2; f: 22.2	19.6 m: 7.0; f: 26.7	Cleaners, electronics workers, hairdressers, mechanics, metal workers
Cobalt	Metal	2.2 m: 1.1; f: 3.0	5.8 m: 3.0; f: 7.3	Construction workers, dental technicians, hard metal workers
Fragrance mix I [b]	Perfumes, in cosmetics, chemical products	0.9 m: 0.5; f: 1.3	5.6	Beauticians, hairdressers
Chromium	Metal, in cement, leather	0.8	5.1	Construction workers, leather workers, tile setters
Colophony	Rosin, adhesive, soldering flux	0.9 m: 0.4; f: 1.4	3.0	Electronic workers, metal workers, musicians
Form-aldehyde	Synthesis, preservative	0.4	2.7 m: 1.9; f: 3.2	Beauticians, cleaners, healthcare workers, metal workers
Fragrance mix II [c]	Perfumes, in cosmetics, chemical products	1.9	2.3	Beauticians, hairdressers
p-Phenylene-diamine	Dye, hair dye substance	1.0	2.3 m: 1.0; f: 3.0	Hairdressers
CMIT/MIT	Preservative, biocide	0.5	2.1	Hairdressers, metal workers, painters
Thiuram mix	In rubber products, biocide	0.5	1.7	Cleaners, construction workers, health care workers, rubber industry workers
Epoxy resin	Plastic chemical	0.9	1.1 m: 1.8; f: 0.7	Construction workers, tile setters

[a] Presented by gender if significant difference; m: male, f: female.
[b] Mixture consisting of 8 fragrance substances.
[c] Mixture consisting of 6 fragrance substances.
CMIT/MIT: methylchloroisothiazolinone/methylisothiazolinone (3:1), EU: European Union.

5.1 Metals

5.1.1 Nickel

Nickel (Ni) is used in numerous alloys and coatings, and in chemical compounds. It is used in articles for occupational and private use, many of which may come into contact with the skin. Two thirds of the nickel produced is used in stainless steels. Stainless steels contain iron, chromium and nickel and are produced in many qualities for different applications. Stainless steels are relatively resistant to corrosion, due to the formation of a thin inert film of chromium oxide on the surface. Nickel release from stainless steel at contact with skin is generally low, and most stainless steels are unlikely to cause nickel allergy (131, 133).

Nickel is the most frequent cause of contact allergy (Table 2). Based on a recent study in 5 EU countries, it is estimated that approximately 14% of the adult general population (5% men, 22% women) is allergic to nickel (40). In a study in Sweden, 20% of the dermatitis patients (7% men, 27% women) were allergic to nickel (66). The lower prevalence in men is due to differences in exposure. The prevalence figures vary considerably between countries and over time, depending on differences in exposure, selection and other factors (78). About 30–40% of nickel-allergic individuals develop hand eczema which may become chronic (133). Occupational nickel dermatitis occurs in electronics industry workers, metal workers, hairdressers, car mechanics, construction workers, cleaners, hospital workers, cashiers and many other occupations (131).

Nickel allergy is often associated with jewellery and other items in prolonged contact with the skin. The former EU Nickel Directive which now is part of the REACH legislation (EU regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals), entered into force in the year 2000 (60). It restricted nickel release from certain consumer items intended for direct and prolonged contact with the skin (Section 9.3.1). Subsequently, nickel allergy has started to decline in European countries where there has been compliance with the regulation (78, 214). Despite the regulation, nickel is still the most frequent cause of contact allergy in Europe. One important reason is that also contact of relatively short duration with items such as handles, keys, coins, and tools cause nickel exposure, allergy and dermatitis.

Methods to quantify skin exposure to nickel have been developed (Section 7.1). Knowledge on levels of skin exposure in different occupations will contribute to improved risk assessment and prevention. The dimethylglyoxime (DMG) test (Section 7.1.1.4) for nickel ions is a useful spot test for detecting nickel exposure and initiating exposure reduction measures at the workplace (114, 117, 212).

5.1.2 Chromium

Chromium (Cr) exists mainly in oxidation states 0, II, III and VI. Chromium has been used since the 19th century in leather tanning, alloys and platings. Chromium in different oxidation states and compounds is also used in anticorrosive paints, lacquers, wood preservatives and stainless steel, and has numerous other applications. Metallic chromium (Cr 0) is generally not considered sensitising, due to the

formation of a thin layer of chromium oxide on the surface. Cr VI is the most potent sensitiser, and chromium compounds – especially Cr VI compounds – have the capacity to induce sensitisation and elicit contact allergy. Cr III is used for leather tanning, but may be oxidised to Cr VI in the products. Cr VI was first detected in cement in 1950 (29, 133, 194).

In Europe, 1–2% of the general adult population, and approximately 6% of dermatitis patients are allergic to chromium. Allergy to chromium was previously more frequent among men, but the gender difference has diminished during the last decade. The prevalence has decreased in men as a result of the restriction of chromium in cement in Nordic countries in the beginning of the 1980s and since 2005 in the EU (61) (Section 9.3.1). There are strong indications that chromium allergy has increased in women during recent years due to exposure to chromium in leather (Cr VI and possibly Cr III) (29, 213). This has resulted in a restriction of Cr VI in leather in the EU, which entered into force in 2015 (58) (Section 9.3.1).

5.1.3 Cobalt

Cobalt (Co) is used in rechargeable batteries, hard metals, pigments, glass and glaze, paint and putty, magnetic materials, catalysts, dental alloys and orthopaedic implants, and cosmetics. Cobalt is a frequent cause of contact allergy. In Europe, 1–2% of the general adult population and approximately 6% of the dermatitis patients are allergic to cobalt. Workers in the hard metals industry, electronics industry, construction workers and dental technicians handle cobalt. Workplace studies and studies based on patient materials have shown higher prevalence of cobalt allergy among these workers than among people with other occupations, the general population or dermatitis patients (111, 134).

Allergy to cobalt is often seen together with allergy to nickel or chromium, but in half of the cases, allergy to cobalt is solitary (132). Concomitant exposure to cobalt and nickel is often assumed to occur, but is less likely today due to efficient refining. Little is known about sources of skin exposure to cobalt, and what causes cobalt allergy, except in the occupations with obvious exposures. A spot test for cobalt has recently been introduced for application in dermatology, and it will hopefully be useful in the search for sources of exposure (117, 210).

5.2 Preservatives and biocides

Preservatives are used to prevent products from being destroyed by micro-organisms. The use of preservatives is increasing and new preservatives and areas for application are introduced. All preservatives in use have the ability to cause skin sensitisation; some of them are categorised as extremely potent skin sensitisers (128). Preservatives in cosmetics (including liquid soaps and creams for occupational use), paints and metalworking fluids come into contact with the skin and cause allergy and contact dermatitis (80, 130, 227).

Contact allergy to preservatives as a group is seen in 12% of dermatitis patients in Denmark (192) (Figure 6). Methylchloroisothiazolinone/methylisothiazolinone (3:1) (CMIT/MIT, also known as MCI/MI, Kathon CG®), methyldibromo glutaro-

nitrile (MDBGN), and several formaldehyde releasers are substances which have caused a rapid and alarming increase in contact allergy and dermatitis in recent decades. MIT on its own was introduced in chemical products around 2000 and in cosmetics in 2005; this has resulted in an ongoing epidemic of contact allergy to MIT. Benzisothiazolinone (BIT) and other sensitising isothiazolinones are also used in chemical products. MIT and BIT are both now used in almost all indoor paints (191). Parabens do not frequently cause contact allergy. Some preservatives have been restricted or banned in cosmetics to reduce the risk of skin sensitisation, while there are no restrictions on preservatives in paints, metalworking fluids or detergents (Section 9.3.1).

Biocides are used to prevent harm to human health or property caused by animals, plants or micro-organisms, including viruses. The main groups of biocidal products are disinfectants, preservatives, pest control, and other products. CMIT/MIT, MIT, BIT and other frequently used preservatives are used also as biocides. Chlorothalonil is a highly toxic, broad spectrum fungicide used in wood protection, agriculture, paints, etc. It is an extremely potent skin sensitiser (27).

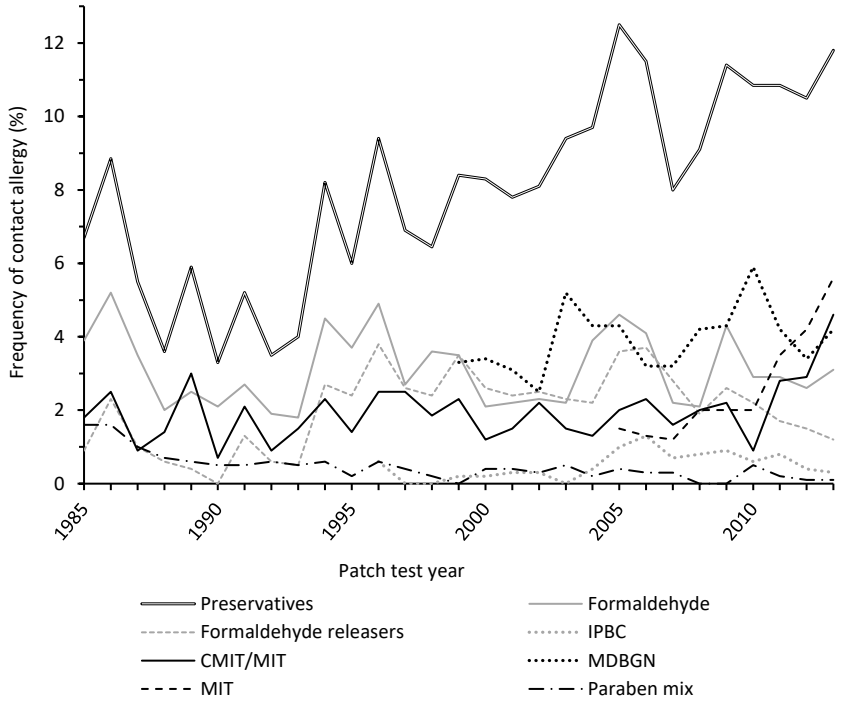

Figure 6. Frequency of contact allergy to preservatives in patch-tested dermatitis patients (n = 23 138) in Denmark 1985–2013. "Preservatives": contact allergy to at least one preservative. Based on Schwensen *et al*. 2015 (192).
CMIT/MIT: methylchloroisothiazolinone/methylisothiazolinone (3:1),
IPBC: iodopropynyl butylcarbamate, MDBGN: methyldibromo glutaronitrile.

5.3 Plastic and rubber chemicals

Epoxy resins are well known to cause severe occupational contact allergy. The monomer is the main allergen in epoxy of the bisphenol-A type (bisphenol A diglycidyl ether also known as DGEBA or BADGE) (1). Besides epoxy resins, phenol formaldehyde resins, acrylates and some diisocyanates [e.g. methylene-bis(phenyl isocyanate) (MDI), hexamethylene diisocyanate (HDI), toluene di-isocyanate (TDI)] are common contact allergens in thermosetting plastics, several of which are potent skin sensitisers (76, 206). Thermosetting plastics are used in many areas in workplaces, but also in consumer products. Large volumes are used in the construction industry, the furniture industry and in printing. Composite materials, paints and coatings are large-volume products. Small volumes of acrylates are used in dentistry, in orthopaedic surgery as bone cement, for wound sealing, and by beauticians for artificial nails and lengthened eyelashes (52, 176).

Work with thermosetting plastics still causes contact allergy, but the problem is not as prevalent as in the 1970s. Work environment regulations (Chapter 9), new knowledge about the substances' skin sensitising potential and ability to permeate through glove materials contributed to the improvement. It is generally considered that workers in industrial settings are better protected than other workers. New applications and lack of knowledge about risks and regulations have caused outbreaks of allergy to epoxy in workers involved in pipe relining, and to acrylates in "nail artists" and previously in dental workers (10, 52, 70).

Contact with rubber products may cause two types of allergy: contact allergy and IgE-mediated allergy from natural rubber latex (also called latex allergy).

Hundreds of chemicals are used to manufacture rubber products. Thiurams, mercapto substances, derivatives of *p*-phenylenediamine (PPD), and carbamates are known skin sensitisers with different functions in rubber (20, 81). Several chemicals used in the rubber industry are also used for other applications, e.g. as biocides in paints, glues and metalworking fluids. Rubber gloves are a frequent cause of contact allergy to rubber chemicals. Boots, other protective equipment, hoses, gaskets, tires, etc. are sources of rubber allergy. It is often difficult to know which rubber chemicals are present in products, since ingredient labels are lacking. It may likewise be difficult to tell whether products are made of rubber or plastic.

Latex allergy mainly affected health care personnel in the 1980s and 1990s. Initial symptoms were contact urticaria of the hands, sometimes also rhinitis and asthma, with a risk of developing anaphylactic shock (5). Latex allergy is less frequent now that the use of powdered latex gloves has decreased. Latex allergy will not be further discussed.

5.4 Fragrance substances

Contact allergy to fragrance substances in cosmetics and chemical products is common, affecting at least 16% of dermatitis patients in Europe, as shown by diagnostic patch testing with the very limited number of fragrance patch test substances used (currently 15 fragrance substances in the European baseline

series) (220). Sensitisation to fragrance substances is considered most often to be caused by cosmetic products such as perfumes and deodorants. Exposure to the same substances in soaps, creams, detergents and other products in the workplace and in consumer products causes dermatitis in sensitised individuals. Examples of occupational groups with work-related allergy to fragrance substances are beauticians, cleaners, hairdressers and metalworkers (35).

More than 2 500 substances are used as fragrance ingredient in cosmetics. A recent risk assessment of fragrance allergens by the EU Scientific Committee on Consumer Safety (SCCS) (184) concluded that more than 100 substances had such skin-sensitising properties that they should be identified by name on the label. This number far exceeds the current 26 substances that must be named on cosmetics packaging (220). In addition, SCCS listed 11 substances of special concern, for which maximum concentrations should be set. The substances were categorised as established contact allergens in humans based on patch test data (n = 82), established contact allergens in animals (n = 19) or likely contact allergens based on structure-activity relationships (SARs) and limited human data (n = 26). Special concern was assigned to substances with a high number of reported cases (n > 100). The SCCS also concluded that three substances, hydroxy-isohexyl 3-cyclohexene carboxaldehyde (HICC), atranol and chloroatranol, should not be present in cosmetic products (184, 220). The European Commission has decided to ban HICC, atranol and chloroatranol in cosmetic products and has proposed restrictions and labelling requirements in line with the SCCS opinion (59, 128).

5.5 Hair dyes

p-Phenylenediamine (PPD) is the most well-known hair dye and has been used for more than a century. It is an extremely potent skin sensitiser. Many other potent sensitisers have been introduced in hair dyeing. Oxidative (also called permanent, semi-permanent, etc.) hair dye products generally contain several potent skin sensitisers. Resorcinol, toluene-2,5-diamine and *m*-aminophenol are the most frequently used sensitisers in hair dyes in Sweden, Denmark and Germany, while the use of PPD is more frequent in Spain and the US (34, 88, 120, 233).

Up to 5% of dermatitis patients and 30% of hairdressers with dermatitis in Europe are allergic to PPD. Hair dyeing is increasingly popular and contact allergy to hair dyes is increasing. The allergy results in acute dermatitis on the face, scalp, and neck among consumers, and hand eczema among hairdressers. PPD is the only hair dye substance regularly used in diagnostic patch testing. The prevalence of contact allergy to other hair dye substances is thus largely unknown (219).

The SCCS and its predecessors have performed risk assessments of more than 100 hair dye substances, as part of the European Commission hair dye strategy for assessment of potential genotoxicity or mutagenicity (182). A large number of substances have been allowed, restricted or banned. The SCCS also assessed the skin sensitising potency, based on animal data, and concluded that 56 of 114 hair

dye substances are skin sensitising, and 36 of them are potent sensitisers (128, 185).

Some hair dye substances are absorbed through the skin and may increase the risk of cancer. Occupational exposure as a hairdresser or barber is classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (Group 2A) (95) and *o*-toluidine as carcinogenic to humans (Group 1) due to its association with cancer of the urinary bladder (96). In Europe, *o*-toluidine and several other aromatic amines are banned as ingredients in cosmetics (64). However, recent studies have detected *o*-toluidine in hair dye products, and haemoglobin adducts of *o*-toluidine in blood from hairdressers (4, 108). Some of the most well-known hair dye substances (PPD, resorcinol, and toluene-2,5-diamine) are classified by IARC as Group 3 (not classifiable as to its carcinogenicity to humans) (97).

5.6 Other

Several contact allergens can be found in natural products. The most commonly identified is pine resin or rosin derived from coniferous trees. Other natural sources of contact allergens are chemicals in various plants among which some are known to be very potent skin sensitisers. Some organic solvents of natural origin have sensitising properties, such as turpentine, limonene and other terpenes. It is not the solvent itself that is considered allergenic but oxidation products formed upon storage with access to oxygen or air (35, 89, 115).

Several pharmaceutical drugs are potent skin sensitisers. They are usually not a problem when used for peroral treatment but may be an occupational hazard during manufacturing, handling and dispensing, by direct skin contact, airborne exposure of the skin or by inhalation. Examples of skin sensitisers are nitroglycerine used for angina pectoris, omeprazol for gastric ulcer, clonidine for hypertension, neomycin and several other antimicrobial drugs for topical antimicrobial treatment (23).

Spices as well as many other plants contain contact allergens and cause contact allergy in many occupations including chefs, bakers, food industry workers and food handlers (166). It has been suggested that enzymes in laundry detergents may cause dermatitis (either by irritancy or contact allergy), though this outcome is probably rare, and the mechanism has not been confirmed (16, 21).

6. Skin irritants and corrosives

According to the international chemicals regulations [GHS (Globally Harmonized System of Classification and Labelling of Chemicals) and CLP], *skin irritation* means the production of *reversible* damage to the skin following the application of a test substance for up to 4 hours, and *skin corrosion* means the production of a corresponding *irreversible* damage to the skin. Substances and mixtures are classified and subcategorised as skin irritants and corrosives based on data from

humans and non-human species (63, 215). Guidance on how to evaluate data and set specific concentrations limits according to the CLP Regulation is available (50).

6.1 Wet work

Wet work is an important and very common risk factor for hand eczema due to skin irritation (irritant contact dermatitis), particularly in subjects with previous or present atopic dermatitis. Prolonged or repeated contact with water, detergents, fresh food, organic solvents and other chemicals in liquid form is considered as wet work. Gloves can offer protection, but may also cause skin irritation (8, 9, 148).

According to the Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA) in Germany, "Activities during which workers spend a considerable portion of their working time in a wet environment or wear liquid-proof gloves or wash their hands frequently or intensively count as wet work". Exposure factors considered are thus duration, frequency and intensity. The use of protective gloves for more than 2 hours is also considered as wet work (19).

6.2 Organic solvents

Organic solvents have a range of local dermal effects (187). One very conspicuous but non-irritant reaction is a whitening effect on the skin, which may occur after a single exposure. The whitening is attributed to conformal changes in the lipids on the skin.

Repeated skin exposure to organic solvents often leads to irritant contact dermatitis. The solubility of lipids in organic solvents means that both lipids on the skin surface and intercellular lipids are extracted from exposed skin. An increase in transepidermal water loss generates a subsequent inflammatory response in the skin, leading to eczema. Structural changes in the cells in the skin have also been demonstrated already after a few minutes of solvent exposure (28).

6.3 Corrosives

Chemical burns are caused by a number of exposures: extreme pH (acids and bases), reactive chemicals e.g. oxidising or reducing, phenols, some organic solvents, and some concentrated preservatives.

The destruction of tissue leading to chemical burn can likely be attributed to the various chemical reactions caused by the irritants. Chemical burn related to pH is either from low acidic pH (< 4) or from high alkaline pH (> 10). Skin exposure to extreme pH usually disrupts the natural buffer balance in the tissue. Acids denature protein and thus affect its absorption and lead to formation of blisters and dermal necrosis. High pH is associated with saponification of triglycerides and dissolution of proteins in the skin. This is seldom associated with acute pain and the acute

exposure may therefore be overlooked, resulting in prolonged exposure and severe reactions in the skin. It is not just the obvious exposures to strong alkali that can give chemical burns but also several alkaline compounds such as amines (31).

Hydrofluoric acid (HF), apart from being strongly corrosive, is also a strong binder of Ca^{2+} ions. Exposure to HF leads to acidic destruction of the skin and may also have systemic effects by generating hypocalcaemia. Reactive chemicals oxidise or reduce the tissues in the skin and give rise to chemical burn. One example of a strong oxidising agent is hypochlorite that is present in chlorine bleaches. Phenols are easily absorbed through the skin and give rise to local effects on the nerves and blood vessels leading to necrosis and chemical burn. Sulphuric acid causes chemical burn and may also cause thermal burn, as heat is generated when strong sulphuric acid is exposed to water. The risk of acquiring a chemical burn is usually diminished at lower concentration (31).

7. Methods to assess skin exposure and skin effects

7.1 Skin exposure assessment

Traditionally, occupational hygiene has focused on assessment of airborne exposure, but during the last decade several methods to measure skin exposure have been developed and to some extent standardised. Methods for sampling from the skin surface are most common since they are less invasive, but methods for sampling the skin, assessing uptake into and through skin and for biomonitoring also exist.

7.1.1 Estimation of skin surface dose

Estimating the dose of a chemical on the skin surface ($\mu g/cm^2$) is of importance when discussing contact allergy, since the dose is the determinant of development or onset of the allergy. Several methods exist to measure the presence and the dose of a chemical on skin. Three major measurement strategies have been identified (67):

- Removal techniques
- Surrogate skin techniques (interception techniques)
- Fluorescent tracer techniques

These three main techniques have been used frequently to monitor both occupational and consumer skin contamination by different groups of chemicals and contact allergens.

7.1.1.1 Removal techniques

All removal techniques actually remove substances from the skin. The most commonly used technique involves moistened wipes. Wipe sampling of elements from surfaces has been described by US NIOSH (155). In this method, pre-packaged moist disposable wipes are rubbed on each surface in an overlapping

S-pattern. The wipes are then digested using concentrated nitric acid (HNO_3) and perchloric acid ($HClO_4$), before dilution and analysis of metals using ICP-AES. A drawback with the method is that the wipe-moisturising solvent is undefined.

Later, a standardised technique called acid wipe sampling (135) was developed to analyse the dose of nickel, cobalt and chromium on the skin. In short, a cellulose wipe moistened with 0.5 ml of 1% HNO_3 is used to wipe the skin. Three consecutive wipes are used to sample from one area. The wipes are pooled and extracted in 1% HNO_3 for 30 minutes. The extract is then analysed chemically using graphite furnace-atomic absorption spectrometry (GF-AAS) or ICP-MS. The recovery is > 90% and most of the metals are removed with the first wipe. The major difference between the two methods is that the solvent for wiping is clearly defined in acid wipe sampling. This reduces the variability in sampling efficiency and the risk of exposing the skin to harmful substances (such as preservatives and fragrance substances) during sampling. Acid wipe sampling has been used to measure metal content on the skin in several occupations (113, 136), and in manipulation experiments with tools (114) and coins (112, 137) in the laboratory.

Another strategy to measure metals on skin is the finger immersion method (198), in which fingers are immersed in tubes containing Milli-Q water for 2 minutes with gentle agitation. After removing the finger from the tube, the solution is acidified using HNO_3. The technique requires a sensitive chemical analysis such as ICP-MS to determine the metal content in the water. A drawback is the difficulty of calculating the exact dose per skin surface area, since the entire finger is dipped into the water. The method has been used to evaluate exposure to nickel in different occupations (79).

Hand washing and hand rinsing techniques have also been developed. A washing technique involves mechanical agitation like rubbing the hands together, whereas rinsing mainly involves a wet chemical dissolution (30). Both methods have been used extensively to monitor occupational exposure to pesticides and are standard procedures in the US for sampling of several pesticides (216). Usually one hand is washed or rinsed with a solvent like isopropanol or water (68, 91) and the liquid is then analysed chemically using high performance-liquid chromatography (HPLC) often in combination with MS. Hand wash sampling with bag rinsing was also used in a study of permanent hair dyes (139). The solvent in this case was a buffer solution in combination with ethanol. The sampling efficiency (i.e. recovery) was between 70 and 90% for the different compounds studied.

One major issue to consider when designing a study using washing, rinsing or wiping techniques is which material to use. The type of wipe, solvent, soap or bag may influence both the absorption of sample from skin and the chemical analysis. An ideal sampling technique should not be harmful to the skin (not containing allergens or irritants) and should have a high sampling efficiency.

Figure 7. Tape stripping of skin (photo by Julander A).

To collect particles from the skin, a method using a small vacuuming sampler was developed (143). Using a standard air pump connected by tubing to a filter cassette, particles deposited on the skin can be removed by suction and collected on the filter. The filter can then be analysed chemically or put into a microscope for visual identification of particle morphology or composition. Such a suction sampler is ideal for sampling of large skin areas.

Another method to remove particles from the skin is tape stripping (92). An area of the skin can repeatedly be stripped off using a piece of tape (Figure 7). The number of times that the area is stripped depends on the purpose of the study. To collect particles from the skin surface, no more than 3 strips are required and it can be done to monitor exposure at workplaces. The tape strips are treated in the same way as the filter mentioned above, i.e. chemical dissolution and analysis or using a microscopic technique to visualise the particles.

7.1.1.2 Surrogate skin

When the skin surface itself cannot be sampled, patches, whole-body coveralls or gloves may be used (91). Patches can be put onto the clothes, under protective clothes or onto the naked skin to assess potential or actual skin exposure. The method is commonly used, especially for occupational studies investigating pesticide exposure of agricultural workers (69), but it has also been used for analysing metalworking fluids and electroplating fluids (175). The material used for patches may be cotton or other types of fabrics, filter paper or other materials. The patches are applied before the work starts and removed at end of shift, the substance is extracted and chemically analysed. Using this technique, large areas of the body can be scanned for contamination; however, the measure is always only an estimate of the true skin dose.

7.1.1.3 Fluorescence technique

If determining the skin exposure dose is not the objective of the study, but rather to find out which areas of the skin or the work environment that are contaminated, a fluorescent tracer can be used for qualitative or semi-quantitative assessment. Commonly used tracers are laundry whiteners that do not harm the skin. In brief,

the fluorescent tracer is mixed with the formulation of interest prior to use. After performing the work under assessment, exposure can be visualised from the fluorescence by using UV-light in a semi-dark room. The technique has been used to determine exposure to pesticides (11) and dental acrylates (179).

7.1.1.4 Dimethylglyoxime test

Apart from the three major techniques discussed thus far, the dimethylglyoxime (DMG) test (Section 5.1.1) is applicable to screen for the presence of nickel on the skin surface. In the DMG test (also called the nickel test), a cotton-wool stick with a drop of test solution on the tip is rubbed against the skin or an item for 30 seconds, and will yield a pink colour if nickel ions are present on the surface (114). The test can be used in a semi-quantitative manner to perform a quick scan of working environments. It is important not to use the test on damaged skin, or skin with eczema or fissures.

7.1.2 Biomonitoring of exposure

Classical biomonitoring of exposure uses blood or urine samples (sometimes even hair and nail clippings) to determine uptake of a substance which is of importance for chemicals that pass the skin and thereby cause systemic effects (Chapters 4 and 9). However, these techniques are not suitable for monitoring of local effects in the skin.

To measure the amount of a chemical present *in the skin*, two standard dermatological methods are available: tape stripping and skin punch biopsies. Both techniques are also used by clinicians when investigating patients for purposes other than measuring uptake into the skin, e.g. to diagnose skin disorders. The tape stripping method, described in the previous section, can be expanded by taking more strips from the same area. If uptake in skin is to be evaluated, at least 10 tapes are needed from the same area. The method has been used to evaluate penetration of nickel salts and copper into the skin (92, 93). To trace the contaminants down through the skin layers, 20 tape strips were taken from the same area, until the glistening epidermal layer was exposed. The technique is reliable but rather invasive and will give rise to a wound in the skin. Therefore, it should be used with caution and not as a tool for assessing exposure in the workplace. For workplace assessments, no more than 3–5 tapes should be used to prevent damage to the skin and allow the worker to continue work after sampling.

Taking skin punch biopsies is also invasive and requires local anaesthesia. Using biopsies, different layers of the skin can be evaluated for chemical penetration and transport in the skin. One example of using biopsies is tracing of nanoparticles in the skin after application of sun screens (153). The biopsy can be evaluated using various microscopic techniques, either in its entirety or after slicing into thin section.

7.1.3 Examples of occupational skin exposure data

Table 3 displays a non-exhaustive list of data concerning exposure of skin on hands, obtained by different methods.

Table 3. Examples of skin exposure of hands in different occupations. Sampling by different techniques (rounded values).

Occupation (n=x)	Sampling method	Substance	Skin surface dose (µg/cm²/h), arithmetic mean if not stated otherwise [a]	Reference
Locksmiths (n=3)	Acid wipe	Ni Co Cr	0.36 0.002 0.045	(136)
Cashiers (n=7)	Acid wipe	Ni Co Cr	0.20 0.002 0.003	(136)
Office staff (n=4)	Acid wipe	Ni Co Cr	0.018 0.001 0.002	(136)
Carpenters (n=4)	Acid wipe	Ni Co Cr	0.077 0.002 0.007	(136)
Metal workers (tool sharpening) (n=8)	Acid wipe	Ni Co Cr	0.068 0.36 0.011	(113)
Metal workers (components) (n=8)	Acid wipe	Ni Co Cr	0.52 0.050 0.056	(113)
Metal workers (thermal applications) (n=8)	Acid wipe	Ni Co Cr	0.41 0.14 0.014	(113)
Electroplaters (n=5)	Finger immersion (water)	Ni	1.8 [b]	(79)
Cashiers (n=7)	Finger immersion (water)	Ni	0.15 [b]	(79)
Sales assistants (n=5)	Finger immersion (water)	Ni	0.10 [b]	(79)
Office staff (n=5)	Finger immersion (water)	Ni	0.062 [b]	(79)
Furniture industry workers (n=36)	Tape stripping	TPGDA	0.38 30 µg/10 cm²/work shift [c]	(202)
Hairdressers (n=33)	Hand rinsing (plastic bag, buffer solution)	PPD	22–940 nmol/hand [d]	(138)
Metal workers (n=37)	Hand rinsing (plastic bag, isopropanol)	EA DEA EA+TEA	10 [e] 19 [e] 1.9+3.4 [e]	(90)

[a] Sampling areas differed between studies, see original publications for details.
[b] Sampling after at least 1 hour of normal work; correction factor for surface area applied.
[c] 8-hour work shift according to Jouni Surakka (personal communication).
[d] Sampling after hair dye application, cutting newly-dyed hair (min-max).
[e] Sampling after 2 hours work with metalwork fluids, median value mg/dominant hand.
DEA: diethanolamine, EA: monoethanolamine, PPD: *p*-phenylenediamine, TEA: triethanolamine, TPGDA: tripropylene glycol diacrylate.

7.2 Methods to assess skin sensitising potential and potency

7.2.1 Experimental sensitisation in humans

Experimental testing of a chemical's inherent ability to sensitise may be performed according to a variety of methods. Predictive tests such as the human repeated insult patch test (HRIPT) and human maximisation test (HMT) are performed in healthy volunteers to study induction of sensitisation. Such studies may be of historical relevance but new studies are prohibited by EU regulations (50, 63, 186). This type of testing is now considered unethical, as participants may develop lifelong contact allergy by the experiment. HRIPT studies are still performed on behalf of industry, often outside Europe (183).

7.2.2 Experimental sensitisation in animals

Another approach, which is fairly relevant to skin sensitisation in humans, is to perform sensitisation/elicitation studies on experimental animals. The animal of choice is often the guinea pig, e.g. in the guinea pig maximisation test (GPMT) and Buehler test.

Since the mid-1980s, an alternative method to study the induction phase in mice has been developed: the local lymph node assay (LLNA). This method is relatively fast and cheap (14). The LLNA has an inherent dose-response design and can be used to assess sensitising potency, which is useful for classification and subcategorisation of skin sensitisers (Table 4) (15). This can also be done with the GPMT, by a method alteration. The LLNA has a few drawbacks, such as studying only the induction phase and not elicitation, not being able to detect cross-reactivity to chemicals, and being sensitive to irritants that may give false positives. The results from LLNA are also dependent on the vehicle used. LLNA is better at inducing sensitisation to organic chemicals than to metals. It is difficult to sensitise mice to nickel, as the receptor responsible for binding metals and starting the immunological response is different from that in humans (188).

The above methods shall be used, and the LLNA is currently the first choice method, for regulatory purposes for hazard identification by assessing sensitising potential and potency (63, 65). The OECD has developed guidelines for the methods (see Appendix 1). A compilation of LLNA results and EC3 values[1] for 204 substances (fragrance substances, preservatives and hair dye substances), conditions for their use according to the Cosmetics Regulation (64) and harmonised classification as skin sensitiser (H317)[2] according to the CLP Regulation (63) has been published (128).

The European Chemicals Agency (ECHA) has published guidelines for the requirements for risk characterisation and derivation of derived no-effect levels (DNELs) for skin sensitisation, and for classification and labelling based on animal data (Table 4) (49, 50) (Section 7.2.3).

[1] Estimated concentration to cause a 3-fold increase in draining lymph-node cell proliferative activity.

[2] May cause an allergic skin reaction.

Table 4. Skin sensitising potency based on LLNA EC3 values. Classification as skin sensitiser (H317) subcategories and recommended concentration limits for classification of mixtures according to the CLP Guidance 2017 (50).

EC3 value	Potency	H317 subcategory	Concentration limit for classification of mixtures
≤ 0.2%	Extreme	1A	0.001%
> 0.2% to ≤ 2%	Strong	1A	0.1%
> 2%	Moderate	1B	1%

CLP: classification, labelling and packaging of substances and mixtures, EC3: estimated concentration to cause a 3-fold increase in draining lymph-node cell proliferative activity, H317: may cause an allergic skin reaction, LLNA: local lymph node assay.

7.2.3 Non-animal based models

Current assessment of skin sensitisation relies mainly on animal tests; however, a ban on animal testing of chemicals to be used in cosmetic products was introduced in the European Cosmetic Products Enforcement Regulations 2013 (64). This, and also the REACH legislation, have stressed the urgent need for *in vitro* and *in silico* methods for the prediction of the sensitising potential and sensitising potency of chemicals. The REACH Guidance on information requirements in Annex VII in relation to skin sensitisation has been updated, taking into account how to predict the sensitising potential based on non-animal methods (49). Two *in vitro* methods for prediction of skin sensitising potential and one *in chemico* test have until now been validated and accepted as OECD test guidelines (Appendix 1).

In silico methods in the field of skin sensitisation are mainly based on models of (quantitative) structure-activity relationships or (Q)SARs and expert systems with knowledge-based information on relevant toxicological endpoints. *In vitro* methods include *in chemico* tests that investigate the ability of a specific chemical to react with selected peptides, so as to predict the sensitisation potential, and cellular tests. Currently available *in silico* and *in vitro* methods to predict sensitisation in humans, and methods under development, were discussed and summarised in a recent review (207). The review concluded that a number of *in silico* and *in vitro* methods may potentially become useful for the prediction of the sensitising potential of chemicals in a regulatory context.

Current general drawbacks are that the methods cannot yet predict sensitising potency [required in the CLP Regulation and for subcategorisation into 1A (strong or extreme) and 1B (moderate)], and are poor at predicting which chemicals are non-sensitisers, pre-haptens (sensitisers formed by oxidation), prohaptens (sensitisers formed by metabolic activation) or cause cross reactivity.

7.2.4 Diagnostic patch testing and use tests in humans

Diagnostic patch testing is the procedure used to diagnose contact allergy (99). Patch testing is performed in patients with dermatitis and in experimental and epidemiological studies. The test procedure is standardised. The European baseline series for routine patch testing consists of 30 compounds (in total 59 different substances) in validated concentrations and vehicles. Patch testing

is performed also with additional substances, test series, mixtures and solid materials in specialised clinics. The test material is applied to the upper back and removed after 2 days. Reading on two occasions is recommended; general practice in Sweden is to read 3 days and 5–7 days after application. Evaluation of test reactions is performed according to internationally agreed criteria (99).

Other clinical test methods simulating normal exposure are sometimes used for elicitation in individuals with contact allergy. Examples are the repeated open application test (ROAT), shampoo use test, axillary test and finger immersion test. These methods use commercial products (mixtures) and substances at use concentrations or other defined concentrations. They may be performed in the clinic to verify a patient's allergy to products and in dose-response studies for research and risk assessment (73, 99, 234).

7.2.5 Dose-response studies in humans

Both induction and elicitation of contact allergy display dose-response relationships and have thresholds. The threshold for induction can be defined as the highest level of exposure that fails to induce sensitisation. The threshold for elicitation can be defined as the highest level of exposure that fails to elicit a reaction in a previously sensitised subject. Thresholds for induction in humans are difficult to set while thresholds for elicitation can be set by dose-response testing in previously sensitised individuals, often dermatitis patients (15, 46).

The minimum elicitation dose that gives a reaction in 10% of sensitised subjects (ED10) has been set for some skin sensitising metals, fragrance substances and preservatives, and is useful in risk assessment. Examples are displayed in Figure 8 and Table 5. The results in Table 5 show that the EC3 values (induction by LLNA in mice) (Section 7.2.2) and ED10 values (elicitation by patch test in sensitised individuals) for the same substance may differ by several orders of magnitude, illustrated by the broad span in the quotient between EC3 and ED10 values. This is important to consider, since it has sometimes been suggested that regulatory measures such as specific concentration limits for classification, information or restrictions could be based on EC3 values. It has also been shown that there is good correspondence between dose-response testing by patch test and by ROAT (72, 73).

It was concluded in the SCCS opinion on fragrance allergens that elicitation data in humans can provide thresholds indicative for safe use of substances which have already caused significant clinical problems. In the absence of adequate substance-specific data, however, it is possible to use a general threshold. A threshold of 0.8 μg/cm^2, corresponding to 0.01% in cosmetic products, was suggested based on statistical analysis of the available data (184).

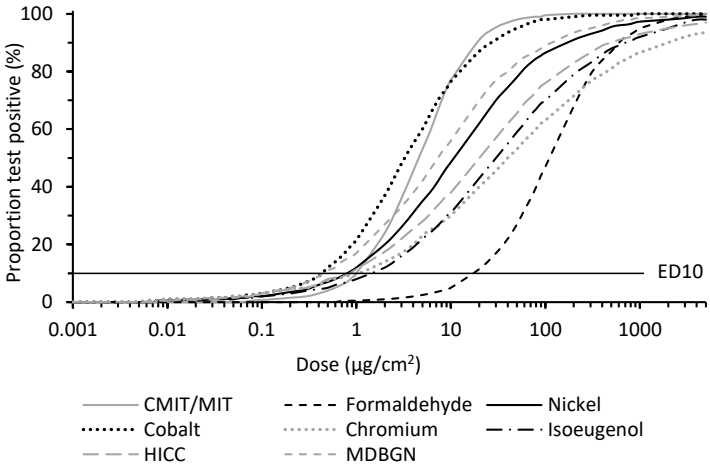

Figure 8. Dose-response curves for 8 skin sensitisers (fragrance substances, metals and preservatives) determined by patch testing of allergic individuals. The intersection between the horizontal line and a dose-response curve indicates the ED10 value (i.e. the minimum dose that will elicit a positive response in 10% of sensitised individuals). Based on data from Fischer *et al.* 2011 (72).

Table 5. EC3 values in the LLNA compared with doses that elicit positive response by patch test in 10% of allergic individuals (ED10) with the same substances. Based on data from 16 studies reviewed by Fischer *et al.* 2011 (72).

Substance	EC3 (µg/cm²) [a]	ED10 (µg/cm²) [b]	EC3/ED10 [c]
CMIT/MIT	1.225	*1.05*	1.2
Formaldehyde	135	*20.1*	6.7
Nickel	140	1.58; 0.82; 7.49; 0.74; *0.82*	141.4 [d]
Cobalt	297	*0.44*	675
Chromium	10	*1.04*	9.6
Isoeugenol	550	*1.48*; 0.23	640
HICC	4 275	*0.85*; 1.17; 0.66	4 803
MDBGN	325	0.025; *0.5*	1 250

[a] EC3 values are normally given as %, however here as µg/cm² for comparison with ED10.
[b] The ED10 values in italic are from the 8 studies shown in Figure 8.
[c] The mean ED10 value was used when more than one ED10 value was available.
[d] Outlier excluded.

CMIT/MIT: methylchloroisothiazolinone/methylisothiazolinone (3:1), EC3: estimated concentration to cause a 3-fold increase in draining lymph-node cell proliferative activity, ED10: minimum elicitation dose giving a reaction in 10% of sensitised subjects, HICC: hydroxyisohexyl 3-cyclohexene carboxaldehyde, LLNA: local lymph node assay, MDBGN: methyldibromo glutaronitrile.

7.2.6 Dose-response studies in animals

Dose-response relationships for chemicals with inherent ability to induce contact allergy can fairly easily be studied in predictive testing. The GPMT can be modified to study dose-response both in sensitisation and elicitation (6). The LLNA has in itself a dose-response design at induction, but does not study the eliciting phase (119). A modified LLNA employing both induction and elicitation has been introduced; a method useful for dose-response and cross-reactivity studies (125). Different vehicles may influence the result significantly, as shown in Figure 9, which may result in different classification and subcategorisation (1A or 1B) as skin sensitiser (Table 4).

7.3 Methods for evaluation of skin irritation and corrosion

Several methods are described in OECD standards for testing skin irritation and skin corrosion. Some methods use rabbits or rats as test animals, others use human or reconstructed human skin. For a full reference of guidelines and test methods (both *in vivo* and *in vitro*), see Appendix 1.

There is no clinical test method to prove that contact dermatitis is caused by skin irritancy (77). The diagnosis of irritant contact dermatitis is based on the result of exposure assessment and the exclusion of contact allergy by patch testing.

8. Previous evaluations by national and international bodies

The *World Health Organization* (WHO) published an Environmental Health Criteria (EHC) monograph on dermal exposure in 2014 (228), which concluded that dermal exposure to chemicals and products is an important exposure route and that resulting diseases may have significant impact on human health. The monograph also concluded that the best risk management approach is to identify hazards, sources and pathways for risk assessment, and to eliminate or reduce and control the exposure.

EU-OSHA published a report from the European Risk Observatory on occupational skin diseases and dermal exposure in 2008 (53) and another on priorities for occupational safety and health research in 2013 (54). It was concluded that skin diseases are the second most common work-related health problem in Europe and one of the most important emerging risks related to chemical risk factors. The importance of recognising risk factors and developing methods for assessing and controlling the exposure was emphasised.

In 2010, *US OSHA* likewise stressed that skin exposure to chemicals in the workplace is a significant problem and stated that recordable skin disease in the US exceeds recordable respiratory illnesses. It is concluded that most chemicals are readily absorbed through the skin, which in many cases is a more significant route of exposure than inhalation (217). According to the US Bureau of Labor Statistics report from 2015, the number of occupational illnesses caused by skin absorption of chemicals in the US is unknown (26).

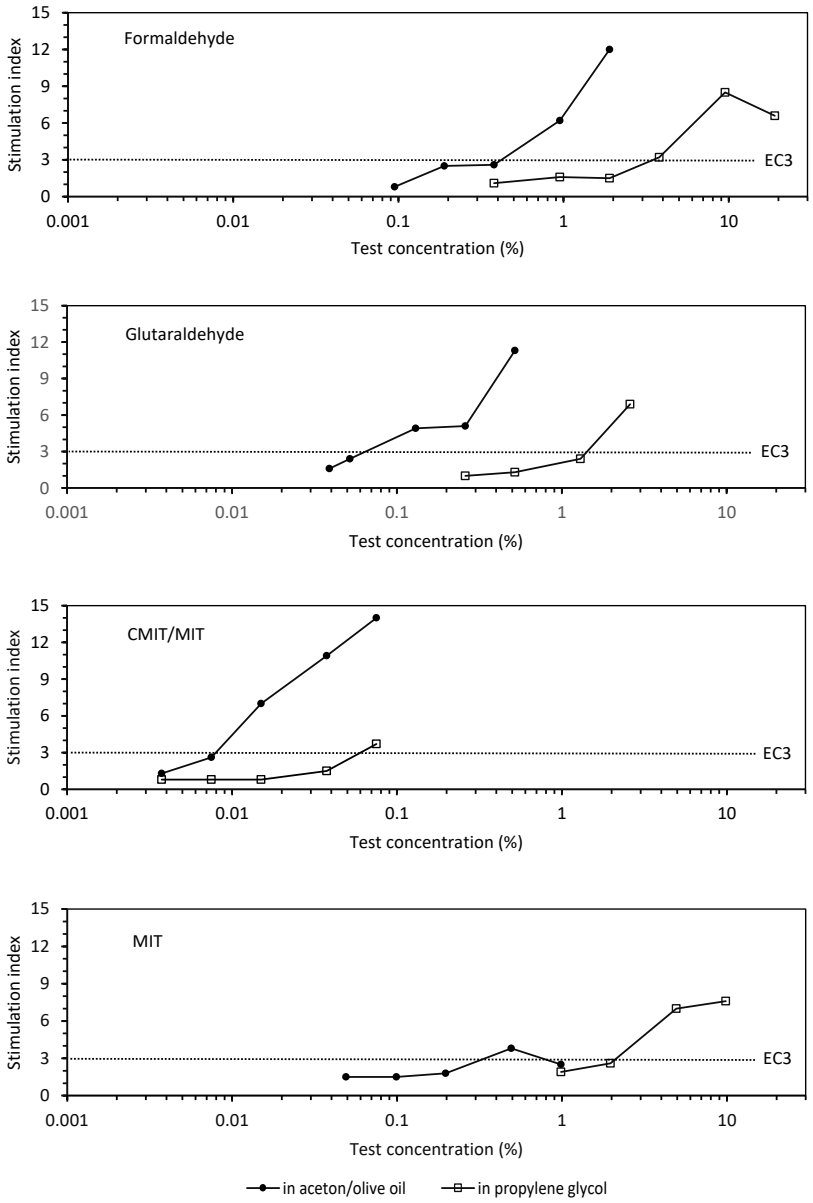

Figure 9. Preservatives tested by the LLNA in mice in the same experiment. Two vehicles (acetone/olive oil; propylene glycol) were used for comparison of induction potency. If the EC3 is reached, the substance fulfils the criteria for classification as skin sensitiser. Based on data from Basketter *et al.* 2003 (17).
CMIT/MIT: methyl-chloroisothiazolinone/methylisothiazolinone (3:1),
EC3: estimated concentration to cause a 3-fold increase in draining lymph-node cell proliferative activity, LLNA: local lymph node assay.

9. Current regulations, standards and guidelines

9.1 Skin notations for the work environment

The “skin notation” is a warning that a substance may easily be absorbed via the skin. It is usually communicated as “S”, “Sk” or “Skin” (in English) in conjunction with the OEL value for the substance. Skin notations are used by many organisations and in many countries. The criteria for assigning a skin notation vary widely but most are qualitative rather than quantitative in nature (Table 6). During the last decades, focus has shifted towards more quantitative assessments, basically moving from level 1 to 3 in the following scheme (107):

Skin notation assigned based on:

1. the intrinsic properties of the chemical in numerical terms, such as dermal absorption rate in defined conditions.
2. the dermally absorbed dose, i.e. a combination of intrinsic properties and defined exposure conditions (exposed skin area, exposure duration, etc.).
3. the dermally absorbed dose relative to the inhaled dose in defined conditions.

Gorman *et al*. (84) recently presented a tool (UPERCUT) for assigning skin notation corresponding to the third level in the scheme above. The tool uses quantitative dermal absorption data and QSAR estimates to calculate the systemic dose via skin and OEL values (or toxicological data in the absence of an OEL) to calculate the acceptable dose.

For substances with significant dermal absorption, biological exposure monitoring may be preferable to air monitoring, as the former captures all routes of exposure including skin. The EU Scientific Committee on Occupational Exposure Limits (SCOEL) has decided to recommend biological limit values (in addition to OELs) (Section 10.1) for compounds with a skin notation as a priority (193).

The skin notation has several shortcomings. The first major problem is that common criteria do not exist and that the variable criteria (Table 6) and missing, unreliable or contradictory dermal absorption data (43, 107) (see Chapter 4 for more details) result in divergent classifications by different countries and organisations (107, 154, 180, 205). Second, skin notations are assigned rather generously. Thus, approximately one third of the chemicals with an OEL have a skin notation (107, 154). This may undermine the warning effect of the notation. Third, the categorical (yes/no) nature of the skin notation may mask the enormous differences in skin permeability between substances (107). Fourth, none of the criteria explicitly account for the huge differences in evaporation of chemical from the skin. This is an important aspect, as evaporation reduces the amount of chemical available for dermal absorption. The evaporation rate differs by several orders of magnitude between chemicals with a skin notation (105, 106).

Johanson *et al.* compared evaporation and dermal absorption rates by combining experimental data and theoretical calculations for 54 chemicals with a skin

notation. Under the assumption of identical exposure conditions (exposed skin area, film thickness, wind speed), the investigated chemicals varied by 8 orders of magnitude in evaporation rate, by 5 orders of magnitude in absorption rate, from 2% to 100% in dermally absorbed dose, and by 6 orders of magnitude in time required to reach a toxic systemic dose. The investigators concluded that evaporation needs to be taken into account when setting skin notations (105). The issue of occluded exposure, e.g. inside clothing or protective gloves, was not addressed at this point.

It was further noted that more than one third of the chemicals that fulfilled the ECETOC criteria (Table 6) for a skin notation lacked such a notation in the Swedish OEL regulation (12). The authors therefore suggested that all substances in the Swedish OEL list should be revised with respect to skin notations.

9.2 Notations for sensitisers

Many OEL setters (e.g. US NIOSH, see Table 6) use a single notation to warn for sensitising substances and thus do not differentiate between respiratory and skin sensitisers. The EU SCOEL acknowledges that although some sensitisers may affect both the respiratory system and the skin, different mechanisms are involved and the majority of skin sensitisers do not affect the respiratory system. SCOEL uses notations for respiratory (193) and dermal sensitisers (Table 6). Also some other organisations, e.g. the American Conference of Governmental Industrial Hygienists (ACGIH) and Deutsche Forschungsgemeinschaft (DFG) differentiate between respiratory and skin sensitisers in their notations (Table 6).

9.3 Restrictions for prevention of skin sensitisation

Skin sensitisation (contact allergy and allergic contact dermatitis) is addressed in the EU legislations on chemicals and cosmetics. Measures intended to prevent skin sensitisation – induction as well as elicitation – have been applied. They include classification and warning labelling, ingredient labelling, and restriction of use. All chemicals regulations state that available human data showing skin sensitisation shall be used, and give reference to the CLP Regulation (63) concerning how classification shall be done. A brief overview is given in Table 7.

Table 6. Criteria for notations of skin absorption, skin and respiratory sensitisation, and skin irritancy by some countries and organisations.

Organisation, Country	Designation	Criteria	Reference
ACGIH, US	Skin	A potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. Alerts that overexposure may occur following dermal contact with liquid and aerosols, even when airborne exposures are at or below the threshold limit value (TLV®). Irritation, corrosion, dermatitis and sensitisation in the absence of systemic toxicity are not considered relevant.	(2)
	SEN	Potential for an agent to produce sensitisation, as confirmed by human or animal data; may refer to dermal and/or inhalation sensitisation.	
	RSEN or DSEN	Respiratory or dermal sensitisation notation – used in place of SEN when there is specific evidence of sensitisation by the respiratory or dermal route, respectively. DSEN and RSEN notations do not imply that sensitisation is the critical effect, nor that sensitisation is the sole basis for the TLV®. TLV®s based on sensitisation are meant to protect workers from induction of this effect but are not intended to protect those already sensitised.	
DFG, Germany	H	Danger of percutaneous absorption. A designation with an "H" can be based on workplace studies, animal studies, *in vitro* studies or theoretical models. "H" does not indicate that the substance can cause skin irritation.	(36)
	S	Designation of a substance as an allergen is based on the available evidence of allergenic effects (in man, in animals, structure-activity relations or *in vitro*) and, when, possible also on the basis of the expected levels of exposure.	
	Sa/Sh/Sah	Danger of sensitisation of the airways/the skin/the airways and the skin.	
ECETOC	–	When the amount of chemical absorbed upon exposure of both hands and forearms (2 000 cm^2) for 1 h is expected to contribute more than 10% to the systemic dose, compared to the amount absorbed via inhalation exposure at the OEL during a full work day, assuming that 10 m^3 air is inhaled during an 8-h workday and that 50% is absorbed. Or, in the absence of dermal absorption data, if the dermal LD_{50} is less than 10 times the intraperitoneal or calculated inhalational LD_{50}. These criteria apply only for chemicals for which the OEL is based on systemic toxicity.	(43)

Table 6. Criteria for notations of skin absorption, skin and respiratory sensitisation, and skin irritancy by some countries and organisations.

Organisation, Country	Designation	Criteria	Reference
SCOEL, EU	Skin	Warns of a possible significant contribution of dermal absorption to the total body burden: the meaning of significant is established on a case-by-case basis, but may in general be in the order of 10% or more of the respiratory uptake during exposure at the OEL (8-h TWA). The skin notation does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation.	(193)
	Sensitisation (respiratory/dermal [a])	The substance is a respiratory/dermal sensitiser.	
STM, Finland	Iho/Hud	A warning sign that the total body burden cannot be estimated only by measuring air concentrations. Chemicals causing irritation or corrosion should not be designated with a skin notation.	(199)
SWEA, Sweden	H	The substance can easily be absorbed through the skin. The prescribed limit value is deemed to provide sufficient protection only on the condition that the skin is protected against exposure to the substance in question.	(12)
	S	The substance is sensitising. Sensitising substances can lead to allergies or other hypersensitivity. Hypersensitivity problems mainly affect the skin or respiratory organs.	
NIOSH, US	SK: SYS	Potential to contribute substantially to systemic toxicity through dermal absorption.	(156)
	SK: SYS(FATAL)	Highly or extremely toxic and potentially lethal or life-threatening following acute contact with the skin.	
	SK: DIR	Indicates non-immune mediated direct effect(s) of a chemical on the skin at or near the point of contact, including corrosion, primary irritation, bleaching (blanching), staining, and reduction/disruption of the skin barrier integrity.	
	SK: DIR(IRR)	A subnotation of DIR, indicates that a chemical is a skin irritant.	
	SK: DIR(COR)	A subnotation of DIR, indicates that a chemical is a corrosive.	
	SK: SEN	Indicates that skin exposure to a chemical may cause or contribute to the onset of allergic contact dermatitis or other immune-mediated responses, such as airway hyperreactivity (asthma).	

[a] SCOEL has recently introduced a notation for dermal sensitisation and is currently updating their methodology document (193).

ACGIH: American Conference of Governmental Industrial Hygienists, DFG: Deutsche Forschungsgemeinschaft (German Research Foundation), ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals, EU: European Union, NIOSH: National Institute for Occupational Safety and Health, OEL: occupational exposure limit, SCOEL: Scientific Committee on Occupational Exposure Limits, STM: Ministry of Social Affairs and Health, SWEA: Swedish Work Environment Authority, TWA: time-weighted average, US: United States.

Table 7. Examples of EU regulations with measures aiming at the prevention of skin sensitisation.

Regulation (reference)	Measure	Substance, limit value or application	Shortcomings in relation to prevention. Aspects discussed in references (72, 191, 192, 214, 220)
CLP (50, 63)	Classification as skin sensitiser (H317) by harmonised classification (legally binding) or notified (by industry). Generates warning labelling and information on packages above certain concentrations in products.	Generic concentration limits for classification of mixtures are 1% for category 1 and subcategory 1B (moderate sensitisers), and 0.1% for subcategory 1A (strong) and recommended 0.001% for subcategory 1A (extreme). Specific concentration limits can be set for the most potent sensitisers. Information on package about content of classified sensitiser above certain concentrations, intended to protect already sensitised: Chromium (VI) (EUH203), isocyanates (EUH204); and epoxy (EUH205) regardless of concentrations; and of all classified skin sensitisers (EUH208) in mixtures: 'Contains (the name). May produce an allergic reaction.'	The concentration limits for classification are generally far too high for prevention of induction and elicitation. Need for ingredient labelling regardless of concentration. No use limit. The lower limit for EUH208 is 1/10 of the classification limit. This is far too high since sensitised individuals may react to very low concentrations.
REACH/ restrictions and SDS (49, 65)	Restriction of use for some skin sensitisers. SDSs for chemical products (mixtures).	Nickel in articles intended for prolonged skin contact (release 0.5 μg/cm^2/week) [a] Chromium (VI) in cement (2 ppm) [a] Chromium (VI) in leather (3 ppm) Dimethylfumarate (DMFu) in articles (0.1 mg/kg). Generic concentration limit for information in SDS on classified skin sensitisers category 1 and subcategory 1B in mixtures is 0.1% (w/w); see further CLP above concerning subcategory 1A, specific concentration limits and EUH.	The nickel restriction has not been sufficiently protective. A definition of "prolonged" has been published by ECHA, and will hopefully support prevention. Too few skin sensitisers are restricted. SDS information on skin sensitisers is often insufficient for protection due to too high generic and specific concentration limits for classification, and the lack of information on non-classified sensitising substances and mixtures. SDS are targeted at the employer and not intended for workers or consumers.

Table 7. Examples of EU regulations with measures aiming at the prevention of skin sensitisation.

Regulation (reference)	Measure	Substance, limit value or application	Shortcomings in relation to prevention. Aspects discussed in references (72, 191, 192, 214, 220)
Detergents (62)	Information	All preservatives shall be identified on the label regardless of concentration. Fragrance allergens shall be identified on the label according to the Cosmetics Regulation.	No use limit.
Cosmetics (64)	Restriction, ban, ingredient labelling	Some substances are banned or severely restricted due to the risk of sensitisation. Examples are some preservatives, hair dye and fragrance substances, and nickel. The names of all ingredients, except fragrance substances, shall be given on the label, regardless of concentration.	The use concentration of many sensitisers is often too high for prevention of induction and elicitation. Preservatives, fragrance substances and hair dyes are the most prominent sensitisers. Only 26 of 100 known fragrance sensitisers are currently required to be stated on the label. The time from risk assessment to decision on risk management is often long. Animal experiments for the Cosmetics Regulation have been prohibited since 2013, limiting the possibility to identify new skin sensitisers. (Ingredients tested in animals for other purposes may however still be used in cosmetics).

[a] Preceded by other EU or national legislation.

CLP: classification, labelling and packaging of substances and mixtures, ECHA: European Chemicals Agency, EU: European Union, EUH: EU hazard statement, REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals, SDS: safety data sheets.

9.3.1 Examples of successful restrictions in the EU

Restrictions on some skin sensitisers by REACH and the Cosmetics Regulation have been successful. The most prominent examples are chromium (VI) in cement, nickel in products that come in prolonged contact with the skin, some preservatives and the biocide DMFu.

Chromium (VI) in cement is a well-known cause of allergic contact dermatitis in construction workers. Chromium (VI) in cement was restricted in Sweden, Finland and Denmark in the early 1980s, and the reduction was achieved by adding iron sulphate to the cement. The restriction was introduced in the EU in 2005 (61) and contact allergy to chromium has since decreased in construction workers (29). However, over the past decade, chromium allergy has increased markedly in women, which has been attributed to chromium (VI) in leather products (29). Restrictions on chromium (VI) in leather products entered into force in 2015 (29, 58).

Nickel is the most common cause of contact allergy. A restriction on nickel release from items in prolonged contact with the skin was introduced in Denmark in 1990, adopted by the EU in 1994, and entered into force in 2000 (Figure 10) (60, 133, 211). The prevalence of nickel allergy has begun to decrease in countries where there is compliance with the restriction, e.g. Denmark, Germany and Sweden (22, 66, 78, 211, 214). A decrease in nickel allergy is being observed in young female dermatitis patients (Figure 10). The term "prolonged contact" was given a strict definition by ECHA in 2014, for more efficient prevention (47).

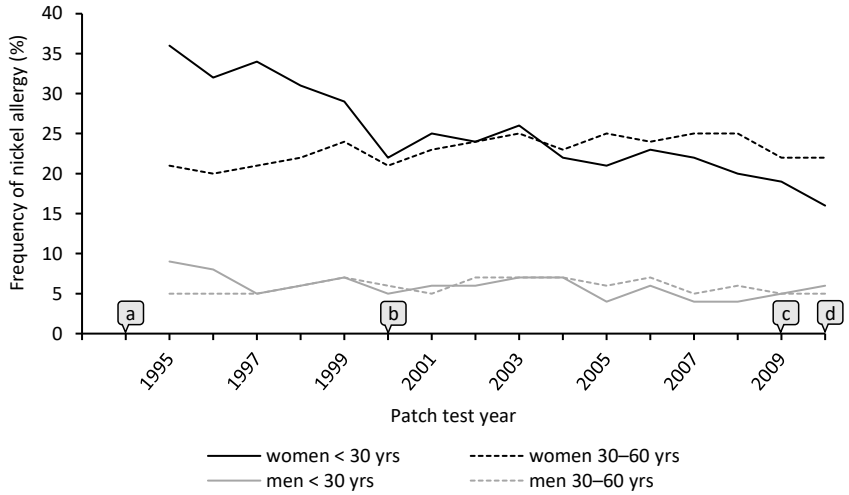

Figure 10. Frequency of contact allergy to nickel in patch tested dermatitis patients in Germany 1994–2010. Based on data from Garg *et al.* 2013 (78). Important dates in the EU restriction of nickel by legislation for prevention of nickel allergy are indicated on the x-axis: a) Nickel Directive adopted; b) Nickel Directive entered into force; c) nickel restriction part of REACH; d) definition of "prolonged contact" discussed by Member States Competent Authorities for REACH and CLP (CARACAL). A definition agreed upon in 2014.

The preservative CMIT/MIT was introduced in chemical products (mixtures) and cosmetics in the 1980s. A rapid increase in contact allergy was noted. CMIT/MIT received a low concentration limit for use in cosmetic products in 1990 (59). Not until 2001 was CMIT/MIT classified as skin sensitiser with a low specific concentration limit for classification according to the Dangerous Substances Directive preceding the CLP Regulation (56, 129). Together, these actions resulted in a marked decrease in sensitisation rate among dermatitis patients in Europe (203). The occurrence of allergy to CMIT/MIT has, however, increased following the introduction of MIT at much higher concentrations in chemical products and cosmetics. Further restrictions of CMIT/MIT and MIT in cosmetic products have recently been decided (59) (Figure 11, Table 8).

The use of MDBGN in cosmetics and chemical products increased during the 1990s, which resulted in an alarming increase in contact allergy (Figure 11). In the EU, its use was banned in leave-on cosmetic products in 2005, and in all cosmetic products in 2008 (59) (Table 8). The use in chemical products has also decreased markedly. The occurrence of allergy to MDBGN among dermatitis patients has decreased significantly in the EU following the ban (192, 203).

An alarming outbreak of contact allergy to the fungicide DMFu caused by footgear, clothing and furniture was first noted in some EU countries around 2007. DMFu was used as fungicide in articles imported from Asia. A restriction was rapidly introduced in the EU (57) and the problem has declined (18, 152).

9.4 Measures to reduce exposure to skin irritants

The only approach including notations for irritants and corrosives is published by the US NIOSH (156) (Table 6).

The definition of wet work by the German Federal Institute for Occupational Safety and Health (BAuA), and the measures employers need to take (technical, hygiene, organisational, etc.) to reduce wet work for prevention of hand eczema is another approach to reduce exposure to skin irritants (Section 6.1) (19).

9.5 Guidelines for toxicology testing

The OECD as well as industry (ECETOC) have developed several guidelines for testing skin absorption, irritation, corrosion and sensitisation. The relevant guidelines are summarised in Appendix 1.

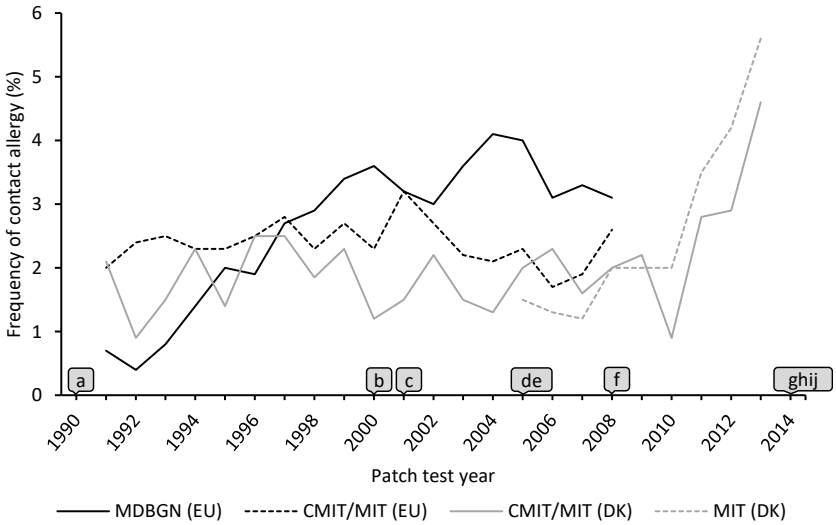

Figure 11. Frequency of contact allergy to some preservatives in patch tested dermatitis patients at 15–16 European patch test centres (EU) and in Denmark (DK). Based on data from Wilkinson *et al.* 2002 (229), Svedman *et al.* 2012 (203) and Schwensen *et al.* 2015 (192). Important dates concerning use, restriction and classification by legislation for prevention of contact allergy are indicated on the x-axis: a–j explained in Table 8.

Table 8. Important dates concerning use, restriction and classification of some skin sensitising preservatives, and legislation to prevent contact allergy (Figure 11).

Note Fig.11	Substance	Use, restriction or classification	Year	EU legislation	Ref.
a	CMIT/MIT	Max allowed conc. 0.0015% in cosmetic products.	1990	CD	(59)
b	MIT	Introduced in chemical products.	2000	–	(129)
c	CMIT/MIT	Skin sens. R43, specific conc. limit 0.0015%.	2001	DSD	(56)
d	MDBGN	Banned in leave-on cosmetic products.	2005	CD	(59)
e	MIT	Allowed up to 0.01% in cosmetic products.	2005	CD	(59)
f	MDBGN	Banned in all cosmetic products.	2008	CD	(59)
g	CMIT/MIT	Banned in leave-on cosmetic products.	2014	CR	(59)
h	MIT	Banned in leave-on cosmetic products.	2016	CR	(59)
i	MIT	RAC opinion: H317 Skin Sens. 1A, specific conc. limit 0.0015%.	2016	CLP	(48)
j	MIT	Allowed up to 0.0015% in rinse-off cosmetic products.	2017	CR	(59)

CD: Cosmetics Directive, CLP: classification, labelling and packaging of substances and mixtures, CMIT/MIT: methylchloroisothiazolinone/methylisothiazolinone (3:1), CR: Cosmetics Regulation, DSD: Dangerous Substances Directive, EU: European Union, MDBGN: methyldibromo glutaronitrile, RAC: Risk Assessment Committee, H317: May cause an allergic skin reaction, R43: May cause sensitisation by skin contact, Skin Sens. 1A: Category strong or extreme skin sensitiser.

10. Possibilities for regulation

Airborne exposure of the skin to chemicals may to some extent result in skin effects as well as systemic effects. However, skin exposure and resulting effects are mainly a result of direct skin contact with solids, liquids and contaminated surfaces. Therefore, the level of chemical in air does not reflect the skin exposure. Hence, traditional OELs (i.e. limit concentrations in air), are insufficient for protection against adverse health effects by skin exposure, be it skin sensitisation, skin irritation, corrosion or systemic effects. Moreover, few skin sensitisers have an OEL.

On the other hand, there are several possibilities for regulation in order to reduce dermal exposure to hazardous chemicals at the workplace. These possibilities (discussed in the following) include: biological limit values, warnings (notations) for skin absorption and sensitisation, and restrictions on occupational use.

10.1 Biological limit values

Biological exposure monitoring (e.g. measurement of the chemical or its metabolite in urine or blood) captures all routes of exposure including skin. Therefore, dermal absorption of chemicals resulting in systemic effects may to some extent be regulated by biological limits. The EU SCOEL has decided to recommend biological limit values (in addition to OELs) for compounds with a skin notation (193). However, biological limits and biomonitoring of exposure are not suitable to control for local effects in the skin.

10.2 Skin notations

10.2.1 Dermal absorption

The criteria for skin notation for dermal absorption vary between countries and organisations, resulting in divergent classifications. The criteria need to be harmonised and should be quantitative (as e.g. the ECETOC criteria, Table 6) rather than qualitative in nature.

A drawback with the yes/no (notation/no notation) nature of skin notation is that it does not reflect the huge difference in dermal absorption between substances. A future development would be to introduce dermal indices (the ratio between the skin uptake and the inhalation uptake at the OEL at defined conditions or the skin area that results in the same systemic dose as inhalation at the OEL at defined conditions).

According to the ECHA Guidance on REACH, DNELs should be established for likely exposure routes, including dermal DNELs for systemic effects. The unit should be expressed as mg/kg/day (46). Dermal DNELs for systemic effects are not intended for regulatory purposes *per se*, only for comparison against plausible exposure scenarios. Furthermore, as the unit implies, prior to any regulatory use

one would still need to incorporate data or assumptions on exposed skin area, exposure duration and dermal absorption rate.

10.2.2 Skin sensitisers

The criteria for notation of sensitising substances are, as with the skin notation for dermal absorption, variable and, in many instances, inadequate. The criteria for sensitisation notation need to be harmonised. In particular, skin and respiratory sensitisers should have separate notations (as introduced by the ACGIH, DFG and SCOEL, see Table 6), as in the CLP Regulation and its predecessor, the Dangerous Substances Directive.

10.3 Classification, labelling and restrictions

Substances fulfilling the CLP criteria for classification as skin sensitiser (H317, may cause an allergic reaction) shall be classified based on human, animal and/or other data and be subcategorised (1A and 1B) according to potency, to strengthen protection (Tables 4 and 7). However, only a minor part of the most important skin sensitisers have a harmonised (legally binding) classification. For classification of mixtures, the generic concentration limit is 1% for category 1 and subcategory 1B, which generally is too high for prevention of skin sensitisation. The generic concentration limit for subcategory 1A is 0.1%, and lower specific concentration limits may be set for the most potent sensitisers, which is beneficial for protection. The use concentration of many skin sensitisers is, however, often so low that no information on their presence is given in safety data sheets or on labels, even if they are known to elicit allergic contact dermatitis. Mandatory ingredient information regardless of concentration (as for cosmetics and preservatives in detergents) would support secondary prevention.

Restrictions by REACH of some skin sensitisers have proven efficient for prevention of skin sensitisation to chromium in cement, and partly efficient to prevent allergy from nickel. Restrictions of additional frequent skin sensitisers by REACH would promote prevention.

Many skin sensitisers (mainly preservatives and hair dye substances) are restricted and some are banned in cosmetic products by the Cosmetics Regulation for protection of consumers and occupationally exposed. This approach has been efficient particularly concerning contact allergy to some preservatives. The full ingredient labelling of cosmetic products supports secondary prevention by enabling exposure reduction in those who know they are sensitised.

10.4 Restrictions on occupational use and skin exposure

Several EU regulations on chemicals, e.g. REACH and the Cosmetics Regulation, address hazards and risks from skin exposure to substances by imposing restrictions on use or providing information about content or hazards (Table 7). Such restrictions can be applied also for the work environment.

Methods are available for quantitative or semi-quantitative assessment of skin exposure to metals and some hair dyes, acrylates, epoxy resin and pesticides. The amount of published data on skin doses of metals, hair dyes and some other chemicals in workplaces is increasing. The link between skin dose and elicitation dose in contact allergy is being established for the important skin-sensitising metals, some preservatives and fragrance substances. Such data on minimum elicitation dose (ED10) together with skin exposure doses in various occupational settings will support development of limits for workplace exposure.

Restrictions on occupational use of products containing sensitising chemicals could be based on skin exposure limits retrieved from ED10 values ($\mu g/cm^2$) for important skin sensitisers, and on restrictions of skin sensitising substances in REACH and the Cosmetics Regulation.

Control of compliance in the workplace could be based on various measures, including skin exposure assessments (quantitative, semi-quantitative and qualitative test methods), assessment of metal release from surfaces and of content in products in contact with the skin (including personal protective equipment, soaps and creams).

11. Research needs

Several aspects of skin exposure, exposure assessment and health effects require additional research.

Methods for assessment of skin exposure to hazardous chemicals other than those mentioned in Section 10.4 need to be developed, standardised and validated.

The relative importance of dose, duration and frequency of exposure to skin sensitisers, irritants and other hazardous chemicals is largely unknown. These factors need to be clarified since such knowledge is vital for health risk assessment, prevention and prioritisation of measures. Dose-response studies of elicitation of contact allergy can be used for risk assessment, risk management, and setting no-effect limits for skin sensitisers. Dose-response studies to determine elicitation thresholds (ED10) of important skin sensitisers in already sensitised individuals are needed. Such knowledge will contribute significantly to setting relevant and protective limits for occupational skin exposure.

Use of and exposure to nanomaterials is constantly expanding. It is well known that small metal particles release more metal than larger ones. How this affects skin doses and health effects, including sensitisation, is unknown. Knowledge about how risks are related to particle size and other properties is thus needed.

Current alternative methods for determination of skin sensitisation potential (*in silico* and *in vitro* methods) are only indicative. They cannot yet predict sensitising potency, and prediction of non-sensitisers, pre- and pro-haptens and cross-reactivity is poor. This is a complex area that still relies mainly on animal tests. It is urgent to develop and validate methods to test for skin sensitisation that can fill these gaps.

12. Summary

Julander A, Boman A, Johanson G, Lidén C. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 151. Occupational skin exposure to chemicals. With focus on skin exposure assessment, skin sensitisation and prevention by exposure reduction. Arbete och Hälsa 2018;52(3):1–69.

Skin exposure can be due to airborne deposition, contact with solid materials, liquids, contaminated surfaces or intentional application. Skin exposure, especially if repeated or prolonged, may result in dermal penetration and absorption, skin sensitisation and irritant reactions. Occupational skin diseases represent up to 30% of the occupational diseases in Europe. The most important exogenous risk factors are exposure to skin sensitising substances (contact allergens), skin irritants and wet work. Skin exposure to chemicals can also cause systemic effects and skin cancer.

Skin exposure to contact allergens may cause induction of contact allergy, and re-exposure of a sensitised individual to the substance may result in elicitation of allergic contact dermatitis, the clinical disease. Contact allergy is distinct from IgE-mediated allergy in asthma and rhinitis. The most common skin sensitisers are metals, preservatives, plastic and rubber chemicals, fragrance substances and hair dyes.

Occupational exposure limit values for airborne exposure are irrelevant and insufficient for protection against adverse health effects from skin exposure. Meanwhile, there are several possibilities for regulation in order to reduce dermal exposure to hazardous chemicals at the workplace, including: biological limit values, skin notations as warnings for skin absorption and sensitisation, and restrictions on occupational use.

Methods are now available for quantitative or semi-quantitative assessment of skin exposure to metals and some hair dyes, acrylates, epoxy resins and pesticides. The link between skin dose and elicitation dose in contact allergy is being established for skin sensitising metals, some preservatives and fragrances. Such data can support the development of limits for skin exposure in the workplace. Control of compliance in the workplace could be based on various measures, including assessment of skin exposure, of metal release from surfaces, and concentration in products in contact with the skin.

Keywords: contact allergy, dermal absorption, dermatitis, skin irritant, skin exposure, skin notation, skin sensitiser.

13. Summary in Swedish

Julander A, Boman A, Johanson G, Lidén C. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 151. Occupational skin exposure to chemicals. With focus on skin exposure assessment, skin sensitisation and prevention by exposure reduction. Arbete och Hälsa 2018;52(3):1–69.

Hudexponering för kemikalier kan ske genom kontakt med luft, fasta material, vätskor, kontaminerade ytor eller genom avsiktlig applicering. Hudexponering kan orsaka upptag genom huden, hudsensibilisering och hudirritation, i synnerhet vid upprepad eller långvarig exponering. Upp till 30% av yrkessjukdomarna i Europa utgörs av hudsjukdomar. De viktigaste yttre riskfaktorerna är exponering för hudsensibiliserande ämnen (kontaktallergen), hudirriterande ämnen och våtarbete. Hudexponering för kemikalier kan också orsaka systemeffekter och hudcancer.

Hudexponering för hudsensibiliserande ämnen kan inducera kontaktallergi och upprepad exponering kan hos en redan sensibiliserad person orsaka allergiskt kontakteksem, den kliniska sjukdomen. Kontaktallergi är en annan form av allergi än den vid IgE-medierad astma och rinit. De ämnen som oftast orsakar kontaktallergi är metaller, konserveringsmedel, plast- och gummikemikalier, parfymämnen och hårfärgämnen.

Gränsvärden för luftburen exponering i arbetsmiljön är inte relevanta eller tillräckliga för att skydda mot negativa hälsoeffekter av hudexponering. Det finns flera möjligheter att genom lagstiftning begränsa hudexponeringen för farliga ämnen i arbetsmiljön, till exempel biologiska gränsvärden, varning/notering för hudupptag och sensibilisering, och begränsningar av yrkesmässig användning av kemikalier.

Det finns nu kvantitativa och semikvantitativa metoder för att mäta hudexponeringen för metaller och vissa hårfärgämnen, akrylater, epoxiharts och bekämpningsmedel. Sambandet mellan huddos och den dos som orsakar eksem vid kontaktallergi har fastställts för ett antal metaller, konserveringsmedel och parfymämnen. Sådan kunskap kan stödja arbetet med att ta fram gränsvärden för hudexponering i arbetsmiljön. Kontroll och tillsyn på arbetsplatser skulle kunna baseras på olika mått, bland annat genom att mäta hudexponering, frisättning av metaller från ytor och koncentrationen i produkter som kommer i kontakt med huden.

Nyckelord: eksem, hudexponering, hudirritation, hudmärkning, hudsensibilisering, hudupptag, kontaktallergen, kontaktallergi.

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Appendix 1. Guidelines for skin toxicology by OECD and ECETOC

Table A. OECD guidelines for testing of chemicals (162).

No.	Title	Endpoint	Year
402	Acute dermal toxicity	Systemic toxicity after single skin exposure to test chemical.	2017
404	Acute dermal irritation/corrosion	The degree of irritancy as seen on rabbit skin after exposure to test chemical.	2015
406	Skin sensitisation	Rate, extent and degree of skin reaction in guinea pigs after induction and challenge exposure to test chemical.	1992
410	Repeated dose dermal toxicity: 21/28-day study	Systemic toxicity after repeated skin exposure to test chemical.	1981
411	Subchronic dermal toxicity: 90-day study	Systemic toxicity after repeated skin exposure to test chemical.	1981
427	Skin absorption: *in vitro* method	Rate or amount of test chemical absorbed into the skin.	2004
428	Skin absorption: *in vitro* method	Amount of test chemical absorbed into and through the skin.	2004
429	Skin sensitisation: local lymph node assay	Relationship of incorporation of ^{3}H-thymidin in cells in draining auricular lymph nodes between mice exposed to test chemical and mice exposed to vehicle only.	2010
430	*In vitro* skin corrosion: transcutaneous electrical resistance test method (TER)	Reduction of resistance in rat skin after exposure to test chemical.	2015
431	*In vitro* skin corrosion: reconstructed human epidermis (RHE) test method	Time to viability loss of cells in reconstructed human epidermis by enzymatic conversion of MTT after exposure to test chemical.	2016
432	*In vitro* 3T3 NRU phototoxicity test	Skin phototoxicity.	2004
435	*In vitro* membrane barrier test method for skin corrosion	Time to colour change in a detection fluid after absorption of test chemical through a collagen matrix.	2015
439	*In vitro* skin irritation: reconstructed human epidermis test method	Time to viability loss of cells in reconstructed human epidermis by enzymatic conversion of MTT after exposure to test chemical.	2015
442A	Skin sensitization: local lymph node assay: DA	Relationship of ATP in draining auricular lymph nodes between mice exposed to test chemical and mice exposed to vehicle only.	2010
442B	Skin sensitization: local lymph node assay: BrdU-ELISA	Relationship of incorporation of BrdU in cells in draining auricular lymph nodes between mice exposed to test chemical and mice exposed to vehicle only.	2010

Table A. OECD guidelines for testing of chemicals (162).

No.	Title	Endpoint	Year
442C	*In chemico* skin sensitisation direct peptide reactivity assay (DPRA)	Addressing the molecular initiating event leading to skin sensitisation. Supporting the discrimination between skin sensitisers and non-sensitisers.	2015
442D	*In vitro* skin sensitisation ARE-Nrf2 luciferase test method (also known as KeratinoSens™)	Addressing the second key event of the skin sensitisation AOP. Supporting the discrimination between skin sensitisers and non-sensitisers.	2015
442E	*In vitro* skin sensitisation: human cell line activation test (h-CLAT)	Addressing the third key event of the skin sensitisation AOP. Supporting the discrimination between skin sensitisers and non-sensitisers.	2016

AOP: adverse outcome pathway, ATP: adenosine triphosphate, BrdU: 5-bromo-2-deoxyuridine, ELISA: enzyme-linked immunosorbent assay, MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide, NRU: neutral red uptake, OECD: Organisation for Economic Co-operation and Development.

Table B. ECETOC monographs (45).

No.	Title	Year
14	Skin sensitisation testing	1990
15	Skin irritation	1990
20	Percutaneous absorption	1993
29	Skin sensitisation testing for the purpose of hazard identification and risk assessment	2000
32	Use of human data in hazard classification for irritation and sensitisation	2002

ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals.

Appendix 2. Previous NEG criteria documents

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D
Diesel exhaust	1993:34, 1993:35*

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Substance/Agent	Arbete och Hälsa issue
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*

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Substance/Agent	Arbete och Hälsa issue
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*

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Substance/Agent	Arbete och Hälsa issue
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Silicon carbide	2018;52(1)*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

*: in English, remaining documents are in a Scandinavian language.
D: collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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