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

Risks of systemic effects after dermal exposure for workers

Part B: Inventory of substances of which systemic health effects can be expected due to dermal exposure of workers

RIVM letter report 320041002/2011
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This investigation has been performed by order and for the account of Ministry of Social Affairs and Employment, within the framework of chemical safety

Abstract

Risks of systemic effects after dermal exposure for workers – Part B: Inventory of substances of which systemic health effects can be expected due to dermal exposure of workers

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

Through literature research and consultation of experts several substances are identified. These substances can be readily absorbed through the skin and could cause adverse health effect in the body after absorption. For three substances the use, the hazard and the absorption through the skin are described.

Keywords:
chemicals, employee, risk assessment, dermal exposure

Rapport in het kort

Risico's op systemische effecten na huidblootstelling – Deel B: overzicht van stoffen die na dermale blootstelling bij werknemers systemische gezondheidseffecten kunnen veroorzaken.

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

Er is in de literatuur gezocht en verschillende experts zijn geraadpleegd om een selectie van chemische stoffen te maken. Voor deze stoffen geldt dat ze via de huid in het lichaam opgenomen kunnen worden en zo schadelijk voor de gezondheid kunnen zijn. Voor een drietal stoffen is in het kort het gebruik, de schadelijkheid en de opname via de huid beschreven.

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

Contents

1 Introduction

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

In contrast to the more acute local effects, such as irritation, it is unclear in what kind of branches systemic effects due to dermal exposure can be a serious health problem. The Labour Inspectorate has experience with the enforcement on adverse systemic health effects due to inhalation exposure, however only limited experience with dermal exposure. Therefore, it is desirable to gain more insight on the incidence and seriousness of systemic health effects by workers due to dermal exposure.

This report is part of an integral project on dermal exposure and systemic health effects in workers. This project consists of three parts; the first part (A) focuses on the development of a methodology for employers and/or employees to estimate the risk of systemic health effects after dermal exposure; the second part (B) is to identify two or three examples of working conditions of which systemic health effects could be expected after dermal exposure to substances; in the third and last part (C) the examples from part B will be tested in the developed methodology of part A.

1.1 Research question

The research question for this report was to identify two or three exemplary substances which through dermal exposure can lead to systemic health effects in the workplace in SME, in order to evaluate the developed method in part A (ter Burg et al. 2011). A literature search was performed and experts were consulted to identify those substances. The use, especially in the Netherlands, and the hazards are briefly described.

Exposure to pesticides and subsequent health effects was chosen by the Ministry of Social Affairs and Employment (SZW) to be beyond the scope of this investigation and therefore pesticides were excluded as potential candidates.

2 Method

Several approaches, including a literature search, desktop research and a questionnaire, were used to identify exemplary substances. Once two or three suitable examples were found, more in-depth research was used to gather relevant information to describe the use and possible effects of these substances.

Four stages of information gathering can be identified:

- Selection of candidate substances based on their toxicity profile and significant potential contribution of dermal exposure to the total internal dose.
- Removal of substances with only local effects
- Prioritisation of candidate substances and selection of the most relevant substances.
- Description of working conditions with and exposure to the most relevant substances.

2.1 Selection of candidate substances

A selection of candidate substances for prioritisation was made based on information found in a literature search and a search trough lists of substances with a skin notation from occupational exposure limits (OEL) in the Netherlands and the United States.

2.1.1 Lists of substances with a skin notation

Historic MAC-lists (Maximum Allowable Concentration) from the Social Economic Council (SER) of the Netherlands were used to identify substances with a skin-notation, implicating dermal exposure is of importance (SZW ; SER 2007). Further, a hierarchal hazard ranking scheme of 15 chemicals with a skin-notation published by the National Institute for Occupational Safety and Health (NIOSH) was used (NIOSH 2009). In this hazard ranking scheme, the 142 chemicals previously assigned the skin notation by NIOSH were systematically assigned a score from 0–7 to determine which substances posed the greatest potential occupational health hazard based on the following parameters:

- OEL potency
- Carcinogen
- Reproductive/developmental toxicant
- Irritant/corrosive
- Sensitizer
- High production volume chemical
- Exposure potential
- RTECS or risk phrases (R-phrases)

The substances with a skin-notation from the historic MAC-lists and the substances from the NIOSH hierarchal hazard ranking scheme were looked upon more closely. Information about their toxic effects was gathered from online documents available via the substance-specific sub page on the SER website (www.ser.nl/nl/taken/adviserende/grenswaarden.aspx). These documents were usually either reports from the Health Council of the Netherlands (Gezondheidsraad) or the European Scientific Committee on Occupational Exposure Limit Values (SCOEL).

2.1.2 Literature search

A literature search in Scopus using the following sets of keywords:
TITLE-ABS-KEY(dermal and occupational and (toxic or systemic) and (health or risk)) and DOCTYPE(re) and LANGUAGE(english or dutch)*

TITLE-ABS-KEY(dermal and occupational and (toxic or systemic) and (health or risk)) and LANGUAGE(english or dutch) and pubdate after 1990*

Some other possibly interesting substances, two articles (Rajan-Sithamparanadarajah et al. 2004; Bouwman et al. 2008) and a Dutch master thesis by Bos (*in prep*) were suggested to consider by RIVM colleagues and our TNO partner.

2.1.3 Removal of substances

Substances inducing only the following (local) health effects were excluded: irritation, corrosivity, sensibilisation and eczema. Although sensibilisation and eczema are not exclusively a true local effect, it is still excluded because the effect generally leads to local symptoms on the skin. If substances were the main ingredient of pesticides, no relevant information could be found or if the studied reports clearly indicated that exposure was none to limited (no wide spread use, phasing out of substance, closed system etc.) the substances were excluded as well. All remaining substances that did not meet the exclusion criteria were put on the shortlist.

2.2 Prioritisation of selected substances

Once a shortlist was compiled, a questionnaire (see appendix 1) was sent to occupational health experts from the industry (Shell), consultancy (Industox), a non-governmental organisation (Institute for Risk Assessment Studies (IRAS), University of Utrecht), a research organisation (TNO) and a governmental organisation (RIVM). In total seven experts were asked to fill out the questionnaire. This questionnaire contained a brief introduction to the project, the shortlist of substances with some relevant information and some questions aimed at prioritising the substances from the shortlist. Based on the comments and prioritisation received from the experts three substances were selected to serve as example substances relevant to the Netherlands and which may induce systemic health effects after dermal exposure under working conditions.

2.3 Description of the three selected example substances

Through desktop research more information was gathered on the three selected example substances. Information was sought trough *google* searches for existing risk or exposure evaluation reports for the selected substances. Data on the amount of the substance used in the Netherlands, working conditions and possible health effects are described briefly in chapter 4.

3 Results

3.1 Selection of candidate substances

3.1.1 List of substances with a skin notation

In the historic MAC-list from the SER a total of 36 substances were designated with a skin notation. On closer inspection, 29 substances could be removed based on the exclusion criteria described in chapter 2. The resulting remaining seven substances were put on the shortlist (see table 1).

The hierarchal hazard ranking scheme from the NIOSH contained 15 substances. On closer inspection, 12 substances could be removed based on the exclusion criteria described in chapter 2. The resulting remaining three substances were put on the shortlist (see table 1).

3.1.2 Literature search

Unfortunately, the search did not generate any satisfactory articles.

In the article by Bouwman, Cronin et al. 2008 the applicability of (Q)SARs for percutaneous penetration was described. They presented a table with a total of 62 substances that were selected based on their skin penetration *in vitro*. From this table, substances having both a high flux and k_p were selected because this may indicate a relatively high dermal absorption. Again, information about the toxicity profile of the selected substances was gathered from online documents available via the substance-specific sub page on the SER website. The same exclusion criteria were applied as described in the method section. The resulting remaining substances were added to the shortlist.

The article by (Rajan-Sithamparanadarajah et al. 2004) described some results from the RISKOFDERM European project on the collection of dermal exposure data in five European countries. Although the articles gives a good overview of the project no specific substances could be derived from it.

The master thesis of Bos (*in prep.)*, conducted in 2010 at TNO, described the physicochemical properties that may form the basis for waiving of dermal exposure within REACH. In this thesis seven volatile organic chemicals were used as screening chemicals to predict the ratio of dermal versus respiratory uptake during different exposure scenarios. From these seven chemicals none were selected for the shortlist mainly due to their low systemic toxicity or lack of information.

3.1.3 Shortlist

In table 1 the selected substances are described that fulfilled the inclusion criteria as described in chapter 2. For these substances dermal exposure can contribute substantially to the internal dose and adverse systemic health effects can occur as a result of that. It should be noted that this list is not exhaustive but merely serves as a starting point for the selection of example substances.

Table 1: Shortlist of substances identified after literature consultation and information provided by TNO and RIVM experts.

CAS number	Name	General information on usage	Systemic toxicity and classification	Limit values	Why skin notation?
74-90-8 151-50-8 143-33-9	**Cyanides (hydrogen, potassium and sodium)**	Decontamination or disinfectant agent; chemical synthesis, extraction and purification of gold and silver from ore; heat treatment of metals and galvanization.	Development of goitre R26; R50-53	1 ppm for concentration of the cyanide anion.	Very good skin penetration of HCN and cyanide anions in watery solutions.
54-11-5	**Nicotine**	Nicotine is a naturally occurring alkaloid and mainly isolated from the leaves of *Nicotiana tabacum* and *Nicotiana rustica* where it occurs at concentrations up to 8%.Nicotine and its salts are used in medicine for the therapy of ulcerative colitis, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, sleep apnoea, and attention deficit orders. Nicotine has therapeutic utility to aid smoking cessation.	The so called 'green-tobacco sickness' produces mild symptoms of intoxication, such as nausea, vomiting, weakness, and dizziness R25, R27, R51-53	No limit value	
98-95-3	**Nitrobenzene**	Used commercially for many years as a chemical intermediate in the production of aniline and dyes.	Nitrobenzene is possibly carcinogenic to humans (Group 2B IARC) R23-25, R40, R48/R23-24; R51-53, R62	1 ppm (no public derivation)	Not known
110-80-5	**2-ethoxyethanol**	Glycol ethers are/were primarily used as solvents in dyes, lacquer,	The critical effects of 2-ethoxyethanol and 2-	Cancelled as of 01-01-2007;	Dermal absorption can significantly contribute to the internal dose.

		stains, glues and sealants, and printing ink on a base of cellulose acetate and nitrocellulose. In addition, glycol ethers are being applied in the metal, electronics, and electro technical industry (for instance in photo lacquer) and as hydraulic brake fluid and as antifreeze in airplane fuels. The use of these substances in dyes, glues and ink is replaced by other solvents due to the teratogenic and volatile (vapor pressure> 10 Pa) properties. Nonetheless, the use of these substances still occurs, especially in the metal, electronics, and electro technical industry and in the dye industry.	ethoxyethyl acetate are on reproduction and the blood. R60-61; R20-22	The SCOEL states: 2 ppm	
109-86-4	**2-methoxyethanol**		The critical effects of 2ME and 2MEA are its toxic effects on reproduction and blood formation. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 1 ppm	Skin penetration can account for a large portion of the total uptake if the skin is exposed to liquids or even vapours containing 2ME or 2MEA
111-15-9	**2-ethoxyethylacetaat**		The critical effects of 2-ethoxyethanol and 2-ethoxyethyl acetate are on reproduction and the blood. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 2 ppm	Dermal absorption can significantly contribute to the internal dose.
110-49-6	**2-methoxyethylacetaat**		The critical effects of 2ME and 2MEA are its toxic effects on reproduction and blood formation. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 1 ppm	Skin penetration can account for a large portion of the total uptake if the skin is exposed to liquids or even vapours containing 2ME or 2MEA
68-12-2	**Dimethylformamide**	Dimethylformamide is predominately used as a solvent in the synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane	Dimethylformamide induces liver damage and alcohol intolerance reactions in humans.	Cancelled as of 01-01-2007; The SCOEL states: 5 ppm	Dermal uptake of dimethylformamide (liquid or gaseous) contributes significantly to systemic toxicity.

		coating and in the electronics industry. The remaining use is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners, and extractants.	Developmental effects are observed for maternal and developmental toxicity in rats R 20/21; R36 R61		
79-06-1	**Acrylamide**	Occupational exposure to acrylamide may occur during acrylamide production and use. The major use of acrylamide (more than 99%) is in the production of polyacrylamides. Acrylamide monomer is also used in the preparation of polyacrylamide electrophoresis gels in hospital, university and research labs	Acrylamide is genotoxic and rats exposed to acrylamide showed clear increases in tumours in several organs R45, R46, R20/21, R36/38, R43, R48/23-25, R62	0.16 mg/m^3 => 0.055 ppm	A skin notation was recommended as calculations of additional dermal uptake may considerately exceed the 10% of the maximum uptake by inhalation
	PAH's *in general*	Although information has focused primarily on exposure trough inhalation, the dermal route can be of significance as well. Exposure to bitumen could be of importance.	Carcinogenic	-	Dermal exposure increases the risk of skin cancer.
106-89-8	**Epichlorohydrin**	Epichloriohydrin is a major raw chemical for the production of epoxy and phenoxy resins. It is also used in the manufacture of glycerine, in curing propylene-based rubbers, as a solvent for cellulose esters and ethers, and in resins with high wet-strength for the paper industry.	Epichlorohydrin is a genotoxic carcinogen in animal studies R10; R45; R23-25; R34; R43	0.19 mg/m^3 => 0.05 ppm	Epichlorohydrin not only has local effects, but also shows systemic toxicity and is lethal after repeated epicutanueous application. However, here the corrosive effect may have destroyed the skin barrier. Absorption of diluted, no longer irritant solutions via intact skin cannot be ruled out.

50-18-0	**Cyclophosphamide**	The main use of cyclophosphamide, a cytostatica, is together with other chemotherapy agents in the treatment of lymphomas, some forms of leukemia and some solid tumors. It is a chemotherapy drug that works by slowing or stopping cell growth	In epidemiological studies exposure to antineoplastic drugs was associated with premature delivery (OR per unit increase in ln[exposure] = 1.08; CI = 1.00–1.17) and low birth weight (OR per unit increase in ln[exposure] = 1.11; 1.01–1.21 R25; R45; R46; R60; R61	No limit value available	Dermal exposure to cyclophosphamide is common among hospital personnel
101-77-9	**4,4-methylenediamine (MDA)**	More than 98% of the total production volume of 4,4-methylenediamine (MDA), i.e. the technical-grade MDA, is used as an intermediate for the production of 4,4'-methylenediphenyl isocyanate (MDI). MDI is further processed to make polyurethanes.	There is sufficient evidence of carcinogenic potential of MDA in rats and mice R39/R23-25; R43; R45; R48/R20-22; R68; R51-53	0.009 mg/m3 => 0.001 ppm	In view of the evidence for appreciable absorption of MDA through the skin, a "skin" notation is appropriate

3.2 Information received from questionnaires

Of the seven experts that were approached, four filled out the questionnaire.

3.2.1 Additional substances

The consulted experts indicated some additional substances that might be of concern (see table 2).

Table 2: Additional substances identified by consulted experts

CAS number	**Name**	**General information on usage**	**Systemic toxicity or classification**
-	Organic solvents (in general)	Organic solvents are widely used in industry for multiple applications. They can be used in paints, inks, dyes, glues etc.	Some organic solvents show toxicity to the nervous system, reproduction, liver and kidney damage and can be carcinogenic.
-	Asthmagens (in general)	Astmagens are a wide group of substances that can induce asthma. Well-known asthmagens in the workplace are isocyanates.	Possible development of airway hypersensitivity (asthma) (induction phase only)
872-50-4	*N*-methyl-2-pyrrolidone (NMP)	NMP is primary used as a solvent in a wide range of applications including paints, stripping and cleaning, for the removal of graffiti and a paint stripper.	R61; R36-38
78-93-3	Butanone	Butanone is mainly used as a solvent constituent in coatings, but also in extraction processes and as intermediate for the production of flavours and perfumes.	R36; R66; R67
108-95-2	Phenol	Phenol is used primarily in the production of phenolic resins, with lesser amounts used for manufacture of caprolactam, alkyl phenol and as a disinfectant and antiseptic.	R23-25; R34; R48/20-22; R68
71-43-2	Benzene	The main uses of benzene are as a constituent of petrol and as raw material in the chemical industry for the production of several chemical compounds.	R45; R46; R36-38; R48/23-25; R65
112-34-5	DEGBE	DEGBE and DEGME belong to the group of glycol ethers, which are mainly used as solvents. They have a wide range of uses as solvents in paints, dyes, inks, detergents and cleaners. Their major function is to dissolve various components of mixtures in both aqueous and non-aqueous systems.	R36
111-77-3	DEGME		R63
84-74-2	Dibutyl phthalate (DBP)	Phthalates are widely used as plasticizer in polymer products, mainly PVC. Flexible PVC is used in many different articles such as toys, flooring, cables, profiles, roofs, blood bags and dialysis equipment.	R50; R61; R62
28553-12-0	Diisononyl phthalate (DINP)		*Not classified*
117-81-7	Bis(2-ethylhexyl) phthalate (DEHP)		R60; R61

3.2.2 Prioritising of the substances

The consulted experts were asked to prioritize which substances (max 3) would pose the greatest risk for health effects for employers. In table 3 this prioritization is summarized

Table 3: Prioritization of selected substances by consulted experts.

Expert	Substances relevant for workers in the Netherlands		
1	PAH's	*N*-methylpyrrolidon	-
2	PAH's	Cytostatica	Organic solvents
3	PAH's	*N*-methylpyrrolidon	Butanone
4	DEGME	PAH's	Isocyanates

3.3 Conclusion and selection of example substances

Based on the prioritization given by the experts (table 3), the following substances could be selected to serve as example substances: PAH's; *N*-methylpyrrolidon and DEGME. The significance of PAH's is recognized but there are several practical limitations regarding the difficulties of identifying a single PAH with broad occupational use instead of mixtures. Also, single PAH's are not intentionally brought on the market, instead, they are constituents of mineral oil derivates.

N-methylpyrrolidon is chosen as it is mentioned several times by the experts and is known to have systemic effects. DEGME is chosen above butanone and cytostatica because DEGME is classified as possible reprotoxic and has a widespread use. Butanone is not classified for possible systemic effects and the use of cytostatica is very specific. For isocyanates the working mechanism on how these substances may induce airway hypersensitivity after dermal exposure is not yet apparent.

As third substance an organic solvent, methanol, is chosen because of its wide spread use; good skin permeability and systemic health effects. In table 4 some descriptive information is given on methanol

Table 4: General information on methanol

CAS number	**Name**	**General information on usage**	**Classification**
67-56-1	Methanol	Methanol is used in the industrial production of many important organic compounds. In addition, methanol is a constituent of a large number of commercially available solvents and consumer products including paints, varnishes, paint thinners, cleansing solutions, antifreeze solutions, automotive windshield washer fluids, denaturant for ethanol, and in hobby adhesives.	R23/24/25 R39/23/24/25

It must be stressed that this approach does not attempt to select the substances with the highest risk on adverse effects. It only serves as a screening method for the identification of example substances as input for the applicability assessment of the developed methodology for risk inventory and evaluation (part A of the project) and as examples for the Labour Inspectorate.

4 Description of example substances and working conditions

4.1 *N*-methylpyrrolidon

4.1.1 General usage

N-methylpyrrolidon (NMP) is primarily used as a solvent in a wide range of applications including the paints and petrochemical industries, for stripping and cleaning applications in the microelectronics industry, for the removal of graffiti, as a paint stripper and as a substitute for chlorinated solvents. It is also used as an intermediate in the pharmaceutical, polymer and other chemical industries, as a formulating agent for plant protection and biocidal actives, and as a solvent for pigments, dyes and inks. It is further used as a penetration enhancer for topically applied pharmaceuticals and as a vehicle in the cosmetics industry. It is increasingly used as a replacement for chlorinated solvents because of concern about the toxicological profile of some of the latter, e.g. it has been used to replace dichloromethane as a solvent in paint strippers (SCOEL 2007).

In Europe the production volume of MNP is estimated to be around 5.000 tonnes and 25.000 tonnes. Around the same amount is also imported into Europe as main ingredient and probably another several hundred tonnes are imported in the form of mixtures (European Chemicals Agency 2011).

In table 4 the approximate split between the different uses of NMP is put as a percentage of the total use of NMP.

Table 4: Uses according to NMP Producers reported in (OECD 2007) at a global level.

Industry	Application	% of total
Coatings	High temperature coating, urethane dispersions, acrylic and styrene latexes	20
Industrial and consumer cleaners	Paint removers, floor strippers, graffiti remover, industrial degreasing, injection head and cast-molding equipment cleaning	20
Agricultural chemicals	Solvent for herbicide, pesticide and fungicide formulations	15
Electronics	Cleaning, de-fluxing, edge bead removal, photo resist stripping	20
Petrochemical processing	Lube oil processing, natural and synthetic gas purification	10
Pharmaceuticals	Solvent	15

4.1.2 Hazard

Concerning systemic toxicity, developmental toxicity and some effects on fertility have been reported in reproductive toxicity studies in rats, rabbits and mice, following exposure to NMP by the inhalation or the oral route at maternally toxic doses (SCOEL 2007). Several effects in the fetuses were seen in different developmental studies including an increased pre-implantation loss, delayed ossification and an increased occurrence of supernumerary 13th ribs. In fertility studies in male rats a decreased testicular weight and histopathological changes were seen after high doses of NMP.

No human epidemiological data is available.

4.1.3 Dermal absorption

Human volunteer studies have shown that NMP is rapidly absorbed following exposure by the inhalation, dermal or oral route. Ligocka *et al.* demonstrated a mean 68% absorption of NMP through the skin in 12 human volunteers exposed to 300 mg NMP via a skin patch (Ligocka et al. 2003).

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

4.1.4 Usage in the Netherlands

In the Netherlands several MSDS's containing NMP for professional coatings, cleaning products and dyes are available indication the various use of NMP in the Netherlands. NMP is found to be used in the Netherlands as a component in paint or graffiti removers, construction glues, water resistant coatings and impregnating agent, floor lacquer and cleaning cloth.

No specific information is available on occupational dermal exposure levels in the Netherlands.

4.2 DEGME

4.2.1 General usage

Diethylene glycol monomethyl ether (DEGME) is a type of glycol ether, which are mainly used as co-solvent. There are a large number of industries in which DEGME is produced and/or used. The main use of DEGME is as an anti-icing agent in jet fuel. Furthermore, DEGME is also used as a chemical intermediate, a metal solvent for mineral oil-soap and mineral oil-sulfonated oil mixtures; a solvent for dyes, nitrocellulose, resins and lacquers; for setting the twist and conditioning of yarns and cloth; as a component of hydraulic fluids; as a solvent for solvent-based silk-screen printing inks, stamp pad inks, ballpoint and felt tip writing pen inks; in pastes used in printing cellulose acetate and polyester fabrics; and as a solvent and coupling agent for vat dyeing fabrics, rust removers, aluminium brighteners, and paint and varnish removers.

DEGME is used in water- and solvent-based paints and varnishes and as a component of floor cleaners, sealants, polishes, and in windshield washer fluid. It is also used as a coupling agent for making miscible organic-aqueous systems and as a raw material for plasticizers. Finally, DEGME is used as a deactivator and stabilizer for agricultural formulations used before crops emerge from the soil; and as a solvent for pharmaceutical manufacturing.

In the RAR report on DEGME from 1999 it was stated that one of the six production sites in Europe where DEGME is produced in quantities exceeding an annually production of 1.000 tones is in the Netherlands (European Union Risk Assessment Report 1999) In the RAR several exposure scenarios are described, most of the exposure is modeled as hardly any measured levels of occupational exposure to DEGME were found in a limited literature search or in occupational exposure databases. The outcome of the exposure scenarios for dermal exposure is summarized in table 5. Dermal exposure is assessed using the EASE model (inhalation and dermal exposure assessment).

Table 5: Modeled occupational dermal exposure to DEGME in different exposure scenarios (European Union Risk Assessment Report 1999).

Scenario	**Modeled (worst case)**	**Measured**
Production of DEGME	210 mg/day	NA
Production of products containing DEGME	420 mg/day	NA
Automated application of products containing DEGME	42 mg/day	NA
Manual application of products containing DEGME	1950 mg/day	NA

4.2.2 Hazard

Concerning systemic toxicity, developmental toxicity have been reported in reproductive toxicity studies in rats and mice following exposure to DEGME by the oral route with and without maternal toxicity (Gezondheidsraad 2003).

Yamano *et al*. observed decreased fetal body weight, decreased vialibility of the pups and affected thymus and ossification in rats after exposure to DEGME in the absence of maternal toxicity (Yamano et al. 1993). After comparable oral doses Hardin *et al*. found rib variations and dilated renal pelvis in rats in the absence of maternal toxicity (Hardin et al. 1986). Exposure to higher concentrations resulted in more pronounced developmental effects (decreased number of live pups and cardiovasular malformations), however maternal toxicity was observed as well.

In addition, Schuler *et al*. found a significant reduction of viable litters, number of live pups per litter, pup survival and a decreased fetal body weight in mice (Schuler et al. 1984). However, these effects were observed in the presence of severe maternal toxicity.

4.2.3 Dermal absorption

The absorption of DEGME through human skin was investigated *in vitro*. The absorption rate using isolated human abdominal epidermis was 0.21 mg/cm^2/hr for 98% pure DEGME (Dugard et al. 1984).

4.2.4 Usage in the Netherlands

In the Netherlands several MSDS's containing DEGME in products are available, mainly brake fluids but also in top coatings and graffiti removers, indicating the various use of DEGME in the Netherlands.

No specific information is available on occupational dermal exposure levels in the Netherlands.

4.3 Methanol

4.3.1 General usage

Methanol is used in the industrial production of many important organic compounds, such as methyl tertiary butyl ether (MTBE), formaldehyde, acetic acid, glycol methyl ethers, methylamine, methyl halides, and methyl methacrylate. In addition, methanol is a constituent of a large number of commercially available solvents and consumer products including paints, varnishes, paint thinners, cleansing solutions, antifreeze solutions, automotive windshield washer fluids, denaturant for ethanol, and in hobby adhesives. Potentially large use of methanol is directly in fuel, as a replacement for gasoline in gasoline and diesel blends. More recently developed industrial uses of methanol include its application as a denitrification agent in waste water treatment and as a reagent and solvent in biodiesel production facilities. New applications may be in fuel cells for vehicles and consumer electronic products (Gezondheidsraad 2010).

The Methanol Institute reported that the Caribbean, Persian Gulf, and Asia (China, Taiwan, Japan, South Korea) were the largest methanol-producing regions in 2006 with a production of each 7-8 million tonnes/year. Western-Europe produced about 3.3 million tonnes/year. Global production amounted to ca. 40 million tonnes/year, which is approximately 90% of the total capacity. For 2008, figures for production and capacity were ca. 48 and 61 million tonnes, respectively. In the Netherlands an innovative process to produce 'bio-methanol' from crude glycerine has been developed. Crude glycerine is a by-product formed during the manufacture of biodiesel. In 2009, a newly built unit in Delfzijl should have a capacity of 200,000 tonnes/year, which can be extended with another three such units, adding up eventually to a capacity of 800,000 tonnes/year' (Gezondheidsraad 2010).

In a report by the Finish Institute of Occupational Health the dermal exposure to methanol in six different REACH occupational exposure scenarios is modelled (Uuksulainen et al. 2008). The outcome of the modelled exposure is given in table 6.

Table 6: Modeled occupational dermal exposure to methanol in different exposure scenarios (Uuksulainen et al. 2008)

Scenario	**Modeled exposure**
Loading and unloading of methanol	3,0 mg/kg/d
Methanol as raw material in the manufacture of chemical products	6,86 mg/kg/day or 18,86 mg/kg/day *
Methanol as a carbon source in waste water treatment	6,86 mg/kg/day or 18,86 mg/kg/day *
Production of preparations containing methanol production of windshield washer fluids	6 mg/kg/day or 6,86 mg/kg/day *
Use of methanol as an industrial solvent in extraction processes	0.69 mg/kg/day or 18.6 mg/kg/day*
Use of methanol as a solvent in different fields of industry	0.69 mg/kg/day or 18.6 mg/kg/day*

* Depending on type of model used

4.3.2 Hazard

Methanol is a natural constituent of humans, animals and plants. Health effects of methanol are recently summarized by the Dutch Health Council (Gezondheidsraad 2010). In short, acute system effects after single high exposures in humans generally include central nervous system, depression, (followed by) metabolic acidosis, ocular toxicity, and death. There are no human studies which allow assessing health effects following chronic exposure to methanol. In animal studies in mice reproduction toxicity is indicated by methanol. Developmental effects, such as a decreased foetal weight and increased incidences of cervical ribs, were seen in absence of maternal toxicity.

4.3.3 Dermal absorption

Following dermal exposure to methanol in human volunteers, an average skin absorption rate of 0.19 mg/cm^2/min has been reported (Dutkiewicz et al. 1980). In an in vitro study, the penetration rate of pure methanol through the epidermis was 10.4 mg/cm^2/h (i.e., 0.18 mg/cm^2/min) (Scheuplein and Blank 1971).

4.3.4 Usage in the Netherlands

In the Netherlands several MSDS's containing methanol are available indicating the various use of NMP in the Netherlands. Products found containing methanol are: preservatives, glues, cleaning products, paint removers, silicon sealants, solvent, methylated spirits, disinfectant, thinner and more. No specific information was found on occupational dermal exposure levels in the Netherlands.

One case study was found (www.pleinplus.nl/nieuws/artikel/10229) on the internet that reported a case in which an electrician was occupationally exposed to methanol in cleaning products. The electrician developed serious neurological problems due to the methanol exposure. It was assumed that the dermal absorption contributed to the development of the systemic effects. The court ruled the employer liable for the health damage of the electrician.

5 Conclusion

This report is part of an integral project on dermal exposure and systemic health effects in workers. In this part B, the research question was to identify two or three exemplary substances, which through dermal exposure can lead to systemic health effects in the workplace in SME.

Through literature research, the use of the historic MAC-list from the SER, and consultation of experts via questionnaires, it was possible to select several substances. Further prioritization based on the use of these substances in the Netherlands and other practical limitations, such as… led to the selection of three substances: *N*-methylpyrrolidon, diethylene glycol monomethyl ether (DEGME) and methanol.

A brief description of the selected substances shows the use of these substances in the Netherlands, the potential for dermal absorption and the subsequent possible systemic health effects. The three substances will be used as case studies in part C of the integral project to evaluate the developed method set out in part A.

6 Acknowledgements

The authors highly acknowledge the valuable input of H. Marquart (TNO), P. Bos and N. Palmen (RIVM).

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8 Appendices

8.1 Appendix I Questionnaire

Introduction:
The Ministry of Social Affairs and Employment has asked the RIVM to initiate a project concerning dermal exposure and systemic health effects by employers. In this project, among others, a limited inventory of examples of working conditions where systemic health effects due to dermal exposure to chemicals are known or expected will be made.

Method
Several sources have been used for the first selection of substances. Former MAC-lists of the Social Economic Council have been used to identify substances with a skin notation. Furthermore, the NIOSH has recently prioritized fifteen substances and academic articles have been used. After further studying substances with only local (corrosive, irritating or sensitizing) effects have been removed from the selection.

In the end this has led to a shortlist of 13 substances of substance groups (see table 1). In the table short information is given about usage, toxicity, limit values and dermal exposure.

A number of experts in the field of occupational toxicology will be consulted via a questionnaire to provide additional information on other, not yet identified, substances that could lead to systemic health effects after dermal exposure (question 1), establish the relevance for The Netherlands (question 3 and 4) and to prioritize the selected substances (question 4).

Questions for the expert:

1. Do you know of any substances not yet mentioned in table 1 which could lead to systemic effects after dermal exposure?

2. Which of the substances in table 1 could be relevant for the working conditions in the SME in The Netherlands?

3. If you would prioritize the substances mentioned below, which substances (max 3) would pose the greatest risk for health effects for employers and why? (for instance wide spread use, potent substance, not possible in closed system etc.)

4. Other remarks that could be relevant for the identification of examples of substances and working conditions with systemic effects after dermal exposure.

Name	General information on usage	Systemic toxicity and classification	Limit values	Why skin notation?
Cyanides (hydrogen, potassium and sodium)	Decontamination or disinfectant agent; chemical synthesis, extraction and purification of gold and silver from ore; heat treatment of metals and galvanization.	Development of goitre R26-28; R32; R50-53	1 ppm for concentration of the cyanide anion.	Very good skin penetration of HCN and cyanide anions in watery solutions.
Nicotine	Nicotine is a naturally occurring alkaloid and mainly isolated from the leaves of *Nicotiana tabacum* and *Nicotiana rustica* where it occurs at concentrations up to 8%.Nicotine and its salts are used in medicine for the therapy of ulcerative colitis, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, sleep apnoea, and attention deficit orders. Nicotine has therapeutic utility to aid smoking cessation.	The so called 'green-tobacco sickness' produces mild symptoms of intoxication, such as nausea, vomiting, weakness, and dizziness R25, R27, R51-53	The Health Council of The Netherlands states in their adapted advice there is insufficient toxicological data for a well-founded limit value for employers.	
Nitrobenzene	Used commercially for many years as a chemical intermediate in the production of aniline and dyes.	Nitrobenzene is possibly carcinogenic to humans (Group 2B IARC) R23-25, R40, R48, R51-53, R62	1 ppm (no public derivation)	Not known
2-ethoxyethanol	Glycol ethers are/were primarily used as solvents in dyes, lacquer, stains, glues and sealants, and printing ink on a base of cellulose acetate and nitrocellulose.	The critical effects of 2-ethoxyethanol and 2-ethoxyethyl acetate are on reproduction and the blood.	Cancelled as of 01-01-2007; The SCOEL states: 2 ppm	Dermal absorption can significantly contribute to the internal dose.

	In addition, glycol ethers are being applied in the metal, electronics, and electro technical industry (for instance in photo lacquer) and as hydraulic brake fluid and as antifreeze in airplane fuels. The use of these substances in dyes, glues and ink is replaced by other solvents due to the teratogenic and volatile (vapor pressure> 10 Pa) properties. Nonetheless, the use of these substances still occurs, especially in the metal, electronics, and electro technical industry and in the dye industry.	R60-61; R20-22		
2-methoxyethanol		The critical effects of 2ME and 2MEA are its toxic effects on reproduction and blood formation. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 1 ppm	Skin penetration can account for a large portion of the total uptake if the skin is exposed to liquids or even vapours containing 2ME or 2MEA
2-ethoxyethylacetaat		The critical effects of 2-ethoxyethanol and 2-ethoxyethyl acetate are on reproduction and the blood. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 2 ppm	Dermal absorption can significantly contribute to the internal dose.
2-methoxyethylacetaat		The critical effects of 2ME and 2MEA are its toxic effects on reproduction and blood formation. R60-61; R20-22	Cancelled as of 01-01-2007; The SCOEL states: 1 ppm	Skin penetration can account for a large portion of the total uptake if the skin is exposed to liquids or even vapours containing 2ME or 2MEA
Dimethylformamide	Dimethylformamide is predominately used as a solvent in the synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining use is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners, and extractants.	Dimethylformamide induces liver damage and alcohol intolerance reactions in humans. Developmental effects are observed for maternal and developmental toxicity in rats R 20/21; R61	Cancelled as of 01-01-2007; The SCOEL states: 5 ppm	Dermal uptake of dimethylformamide (liquid or gaseous) contributes significantly to systemic toxicity.
Acrylamide	Occupational exposure to acrylamide	Acrylamide is genotoxic	0.16 mg/m3 => 0.055	A skin notation was

	may occur during acrylamide production and use. The major use of acrylamide (more than 99%) is in the production of polyacrylamides. Acrylamide monomer is also used in the preparation of polyacrylamide electrophoresis gels in hospital, university and research labs	and rats exposed to acrylamide showed clear increases in tumours in several organs R45, R46, R20/21, R36/38, R43, R48/23-25, R62	ppm	recommended as calculations of additional dermal uptake may considerately exceed the 10% of the maximum uptake by inhalation
PAH's *in general*	Although information has focused primarily on exposure trough inhalation, the dermal route is can be of significance as well. Exposure to bitumen could be of importance.	Carcinogenic	-	Dermal exposure increases the risk of skin cancer.
Epichlorohydrin	Epichloriohydrin is a major raw chemical for the production of epoxy and phenoxy resins. It is also used in the manufacture of glycerine, in curing propylene-based rubbers, as a solvent for cellulose esters and ethers, and in resins with high wet-strength for the paper industry.	Epichlorohydrin is a genotoxic carcinogen in animal studies R10; R45; R23-25; R34; R43	0.19 mg/m3 => 0.05 ppm	Epichlorohydrin not only has local effects, but also shows systemic toxicity and is lethal after repeated epicutanueous application. However, here the corrosive effect may have destroyed the skin barrier. Absorption of diluted, no longer irritant solutions via intact skin cannot be ruled out.
Cyclofosamide	The main use of cyclophosphamide is together with other chemotherapy agents in the treatment of lymphomas, some forms of leukemia and some solid tumors. It is a chemotherapy drug that works by slowing or stopping cell growth	In epidemiological studies exposure to antineoplastic drugs was associated with premature delivery (OR per unit increase in ln[exposure] = 1.08; CI = 1.00–1.17) and low birth	No limit value available	Dermal exposure to cyclophosphamide is common among hospital personnel

		weight (OR per unit increase in ln[exposure] = 1.11; 1.01–1.21 R25; R45; R46; R61		
4,4-methylenediamine (MDA)	More than 98% of the total production volume of 4,4-methylenediamine (MDA), i.e. the technical-grade MDA, is used as an intermediate for the production of 4,4'-methylenediphenyl isocyanate (MDI). MDI is further processed to make polyurethanes.	There is sufficient evidence of carcinogenic potential of MDA in rats and mice R45; R 48/20/21; R 43	0.009 mg/m3 => 0.001 ppm	In view of the evidence for appreciable absorption of MDA through the skin, a "skin" notation is appropriate

Sources:
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Published by:

National Institute for Public Health and the Environment
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