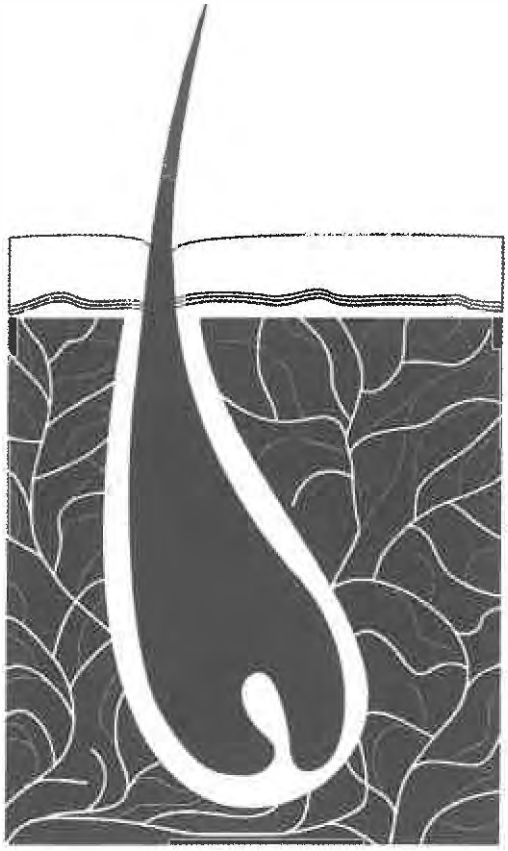
International Conference on Occupational and Environmental Exposures of Skin to Chemicals: Science and Policy

Conference Chair: Sidney Soderholm, PhD



September 8-11, 2002
Hilton Crystal City

Final Program
Plenary Presentation Abstracts
Poster Abstracts

International Conference on Occupational and Environmental Exposures of Skin to Chemicals: Science and Policy

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Final Program

Sunday, September 8, 2002

1:30 pm **Opening Session**
Sidney Soderholm, PhD

1:45 pm **Welcome**
Kathleen M. Rest, PhD, MPA

Session 1: Defining the Problem

Session Chair: Päivikki Susitaival

2:00 pm **The Role of Exposure in the Chain of Events from Sources to Health Outcomes: Dermal And Aggregate Exposures**
Matti Jantunen, PhD, KTL

2:30 pm **Systemic Toxicity from Skin Exposures**
James McDougal, PhD

3:00 pm **Allergic and Irritant Reactions in Skin – Pathophysiology**
David Basketter, DSc, MRCPath, FIBiol

3:30 pm Break

4:00 pm **Risk of Work-Related Dermatitis: Agents, Occupations and Hospital Factors**
Päivikki Susitaival, MD, PhD

4:30 pm **Diagnosis and Management of Occupational Skin Disease**
James S. Taylor, MD

5:00 pm Introduction of Posters

Monday, September 9, 2002

Session 2: Health Effects and Hazard Identification

Session Chairs: Pietro Sartorelli and Frank Gerberick

8:30 am **Percutaneous Penetration Studies for Risk Assessment**
Faith Williams, PhD

9:00 am **Factors Influencing Percutaneous Penetration in the Workplace and General Environment**
Howard Maibach, MD

9:30 am **Theoretical Models of Percutaneous Absorption**
John Corish, PhD and Dara Fitzpatrick, PhD

10:00 am Break

10:30 am **The Importance of Exposure and Potency in the Assessment of Skin Sensitization Risk**
Frank Gerberick, PhD

11:00 am **Criteria for Skin Notation in an International Perspective**
Jesper Bo Nielsen, PhD and Philippe Grandjean, MD

11:30 am Introduction of Posters

Session 3: Measuring and Predicting Exposures

Session Chair: Leena Nylander-French

2:00 pm **Dermal Exposure Processes and Mechanisms: Implications for Exposure Sampling Methodology and Strategy**
Derk Brouwer, PhD

2:35 pm **Issues in Understanding Dermal Exposures Resulting from Contact with Contaminated Surfaces, Measuring Surface Contamination, and Characterizing Transfers**
Elaine A. Cohen-Hubal, PhD

3:10 pm Introduction of Posters

3:30 pm Break

4:00 pm **Measuring Dermal Exposure: Practical and Scientific Considerations**
Alastair Robertson, PhD

4:35 pm **Predictive Models of Dermal Exposure**
John Kissel, PhD, PE

5:10 pm Introduction of Posters

8:00 pm Planning for the Next Conference – Open Meeting

Tuesday, September 10, 2002

Session 4: Controlling Exposures and Prevention

Session Chair: Hans Marquart

8:30 am **Intervention Research**
Linda Goldenhar, MS, PhD

9:05 am **Work Practices and Behavioral Modifications – Evidence-Based Prevention Programs and Implementation at Workplaces**
Mari-Ann Flyvholm, MSc, PhD, Lone Borg, MSc, PhD and Karen Mygind, MSc Pharm

9:40 am Introduction of Posters

10:00 am Break

10:30 am **Practical and Cost-Effective Methods for Dermal Exposure Risk Management**
Chris Packham

11:05 am **Selection, Testing and Effectiveness in the Field of PPE and Gloves**
Reinhard Oppl, MSc

11:40 am Introduction of Posters

Session 5: Developing Policy and Communicating Effectively

Session Chair: Michael Dellarco

2:00 pm **US EPA's Recently Released Superfund Dermal Risk Assessment Guidance: Application and Policy**
Daniel Stralka, PhD

2:30 pm	**Protecting Workers from Dermal Exposure – the German Experience** *Eva Lechtenberg-Auffarth, PhD and Bruno Orthen, PhD*
3:00 pm	**Protecting Workers from Dermal Exposure – the American Experience** *Lyn Penniman, MPH*
3:30 pm	Break
4:00 pm	**How the Food Quality Protection Act Affects EPA Regulation of Pesticides via the Dermal Route of Exposure** *Elizabeth Doyle, PhD*
4:30 pm	**Prevention of Contact Dermatitis by European Legislation** *Carola Lidén, MD, PhD*
5:00 pm	**Perspectives on Industry Reactions to US Government Policies** *Christine Chiasson, PhD*

Wednesday, September 11, 2002

Concurrent Workshops

8:30 am	**Concurrent Workshops** *1. Defining the Problem* *2. Health Effects and Hazard Identification* *3. Measuring and Predicting Exposures* *4. Controlling Exposures and Prevention* *5. Developing Policy and Communicating Effectively*
10:00 am	Break
10:30 am	**Concurrent Workshops Continue**
12:00 pm	Lunch (on your own)
1:30 pm	**Concurrent Workshops Continue**
3:00 pm	Break
3:30 pm	**Workshop Closing Session** *Sidney Soderholm, PhD*
4:30 pm	Adjourn

Plenary Session 1: "Defining the Problem"

Session Chair: Päivikki Susitaival

1.1 **The Role of Exposure in the Chain of Events from Sources to Health Outcomes: Dermal and Aggregate Exposures,** Matti Jantunen, PhD, KTL (National Public Health Institute), Kuopio, Finland

1.2 **Systemic Toxicity from Skin Exposures**, James McDougal, PhD, Wright State University School of Medicine, Dayton, Ohio, USA

1.3 **Allergic and Irritant Reactions in Skin – Pathophysiology**, David Basketter, DSc, MRCPath, FIBiol, Unilever Colworth Laboratory, Bedford, UK

1.4 **Risk of Work-Related Dermatitis: Agents, Occupations and Host Factors**, Päivikki Susitaival, MD, PhD, North Karelia Central Hospital Dermatology Department, Joensuu, Finland

1.5 **Diagnosis and Management of Occupational Skin Disease**, James S. Taylor, MD, Cleveland Clinic, Cleveland, Ohio, USA

Session Planning Committee:
Päivikki Susitaival, Coordinator
Elaine Cohen-Hubal
Boris Lushniak
James Taylor

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Abstract from the International Conference on Occupational and Environmental Exposures of Skin to Chemicals: Science and Policy, Washington, DC, September 8-11, 2002

The Role of Exposure in the Chain of Events from Sources to Health Outcomes: Dermal and Aggregate Exposures

Matti Jantunen, PhD, KTL (National Public Health Institute), Kuopio, Finland

The term exposure has many quite different meanings, which sometimes result in confusion when people representing different curricula communicate. The situation is not different from many other scientific terms and their usage.

Outside of science exposure as a term is not commonly, except as a picture image on a film, or the visibility that this picture can give to a politician when it appears in print.

In epidemiology exposure has, rather than many meanings, an extremely broad meaning. It is used to name practically anything that a disease or symptom could be associated with. The term might mean e.g. "being born in a dairy farm", "working in rubber industry" or, more specifically "7 years of skin exposure through diazinon spraying in an apple farm". These are all useful definitions - depending on the study design. But they are also quite different from each other, on one extreme qualitative classifications relating to no specific route of entry and no specific agent and on the other quantitative measures of air concentrations.

In toxicological studies exposure can mean, e.g., the concentration in the blood or fluid surrounding a specific tissue and exposure time can mean the time between injection of an agent and sacrifice of the animal for pathologist's investigation.

In occupational hygiene exposure often refers to an 8 hour TWA concentration in the working zone, in radiation hygiene the term refers to ionisation of air by radiation (in contrast to dose, which in radiation refers to energy absorbed from radiation to tissue).

On one hand it is clear that the mentioned uses of the term, exposure, are legitimate in their own contexts, on the other hand it should be equally clear that no scientific curriculum for Exposure Analysis can be built around a concept, which can have a practically unlimited number of little related quantitative and qualitative meanings and dimensions. Therefore exposure analysis has to produce its own definition(s) for exposure.

Within the science of exposure analysis the most widely accepted definition for exposure is that of Wayne Ott: "the existence of a person and an agent (contaminant) in the same microenvironment at the same time (in potential contact with each other)". This definition is still rather broad. It does not distinguish between exposure integrated over time, or exposure as an average concentration in the microenvironment (over some time).

Other definitions of exposure within Exposure Analysis locate the role of exposure in the chain of events - or flow of molecules - from source via environmental concentration, exposure and absorbed dose to dose in the target organ (Lioy, and Georgopoulos Lioy).

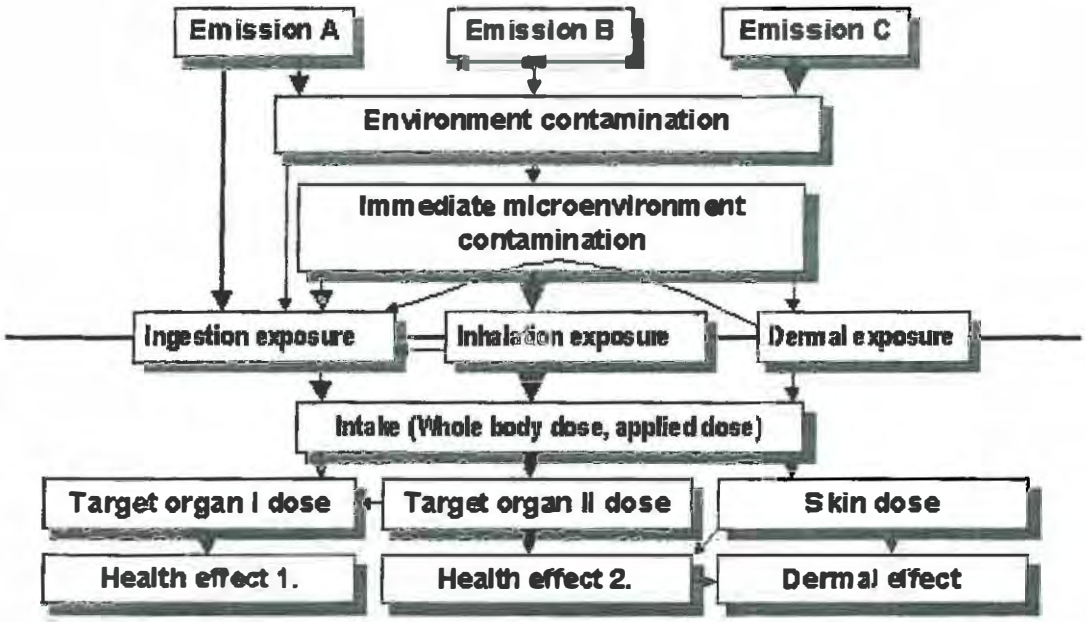
In a comprehensive synthesis exposure has been given a strict mathematical definition beginning with "instantaneous concentration at a point of contact" (Zartarian and Ott), and then integrating, as necessary, from an instant and a dimensionless point over time, (skin) area and volume. This definition has, however, been criticised for adding theoretical complexity with little practical benefit (Mage and others).

In my own mind the term exposure should be allowed certain flexibility to maximise its practicability. To keep it within a single concept, however, this flexibility should not extend outside of the original definitions of Ott and Lioy. I.e. exposure requires a contact between man and the contaminant, and the dimension of time must always, implicitly or explicitly, be there. The shortest definition of exposure, in accordance with Ott's and Lioy's definitions, is the interface between man and the environment. Quite suitable for skin, isn't it?

Still one new concept is useful, the microenvironment. Also this definition allows flexibility. The contaminant concentrations measured in a microenvironment are considered as representative for the exposure of an individual or group of interest. For dermal exposure the microenvironment, depending on the study design, can be the contact surfaces of one's home or workplace, or it could be the boundary layer immediately above the skin (e.g. between cloths and skin).

Natural exposure model

The natural exposure (and risk) model literally follows the molecules of interest from their sources to the affected organs. These tracks are called exposure pathways. The routes of entry from the environment into a human body are ingestion, inhalation and through the skin.



As the figure shows, skin can act as the route of exposure (e.g. for dioxins and solvents), as the target organ of interest (e.g. UV-sensitivity from Tetracyclin treatment), or in both roles at the same time (e.g. skin contact allergens, nickel, latex).

There are some interesting complications, though. A part of the dermal exposure may also end up as non-dietary ingestion exposure (this is why our mothers told us to wash our hands before dinner). For small children, who put their hands on the ground, handle toys and then put their hands into mouth, this is a major source of exposure to pesticides, lead etc. In this case skin acts as a reservoir (immediate microenvironment contamination) for ingestion exposure.

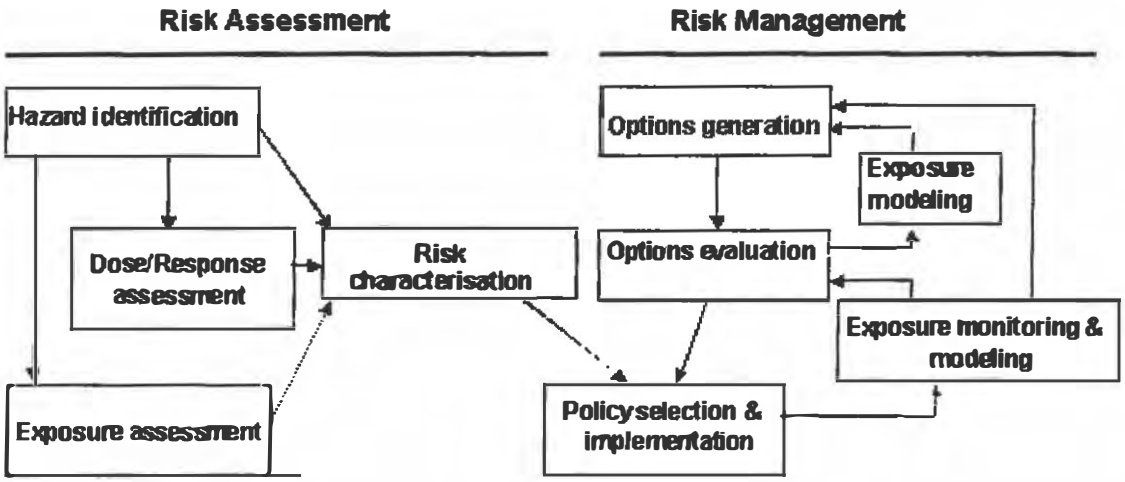
Dermal exposure can form a variable part of aggregate exposure, which refers to the sum effect of exposures via all routes of entry to a single chemical (agent). An example is the use of solvents or volatile pesticides where exposure occurs via inhalation and dermal absorption. Inhalation exposure depends on the volatility of the solvent, temperature, ventilation rate and proximity. Dermal exposure depends on the exposed skin area, frequency of contact, and the molecular weight, volatility and lipophilic characteristics of the chemical. As these characteristics are mostly independent of each other, neither route can be automatically excluded until both have been assessed. Aggregate exposures can only be assessed and different routes of entry ranked at the whole body dose or target organ dose level.

Finally, dermal exposure route can also be a significant part of cumulative exposure, which refers to all agents and all routes of entry having a common effect in the same target organ. The significance of each agent and route of entry for cumulative risk can only be compared and summed up via the target organ effect/risk.

For both aggregate and cumulative exposure and risk assessment skin is more likely to play the role of the route of entry into the body, than the actual target organ of concern.

Administrative exposure model

The administrative risk assessment and management model differs from the natural, because it follows, not the logic of molecules, but the logic of decision making. Exposure assessment has two distinctly different roles in this process. As there is no risk without exposure, measured exposure data is a crucial element of risk assessment. On the other hand, because risk management options can rarely influence dose/response, the only way to compare policy options is comparing their impacts on exposure - which can only be done by exposure modeling.



Administrative Risk Assessment & Management Model of U.S.EPA (NAS/NRC 1983) and EU (Commission directive 93/67/EEC)

Something that seems often to be too obvious to be remembered is that environmental health regulations can in long term only be justified by their public health benefits - although sometimes, in short term, public trust on decision makers and the regulatory agencies is the legitimate driving concern. Public health benefits can only be achieved, if the original risk characterization is sufficiently correct to lead the policy makers towards the right direction. Options evaluation and policy selection - to maximize the benefits and minimize the costs and opportunity losses due to general regulation and focussed intervention - must be based on qualitatively (the agent of concern is the true causal agent) and quantitatively (the predicted exposure reductions are of correct magnitude and those of the evaluated options correctly ranked). Finally, policy selection should be based on defined public health or public health proxy (exposure) objectives, and implementation should be accompanied with follow up and feedback loops, which ensure early detection of failure and correction of the course, if needed. Needless to say, if these conditions are not met, public health benefits of invasive and expensive programs may never materialize, may never be verified, and may even be negative.

Dermal Exposure and Dose models
Dermal exposure (to a contaminant in soil) is

$$EDA = Csoil \times SA \times SL \times t \quad \text{unit} = (\text{mass} \times \text{time})$$

Csoil = concentration of agent in soil
SA = surface area of exposed skin
SL = soil loading on skin
t = time from skin contamination to cleaning

Calculation of the dose from dermal exposure depends on whether the ultimate concern is whole body (systemic effects) dose through skin, dose of the skin and subcutaneous tissue (skin effects), or transfer from skin to mouth. Other presentations in this Conference will go deeper into these issues.

Conclusions

Exposure is the interface between man and the environment. Exposure analysis studies the phenomena affecting this interface.

Exposure assessment is a key element in all environmental health risk assessment. Exposure analysis, however, is also necessary for risk management. Exposure modeling is the only way of comparing the risk reductions achievable by alternative risk management options. Accordingly policy selections should be based on public health gain targets, which can rarely be measured directly. Exposure provides the most relevant indirect information. Carefully focussed exposure monitoring and modeling campaigns should therefore also accompany all environmental health policy implementations in order to provide early feedback for policy review when needed.

Skin is one of the 3 major exposure routes, often acting in combination with the other two, inhalation and ingestion. In exposure and risk analysis skin can independently act as a contaminated microenvironment, route of exposure and target organ.

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Systemic Toxicity from Skin Exposures

James N. McDougal, PhD, Fellow ATS, Department of Pharmacology Toxicology, Wright State University School of Medicine, Dayton, OH, USA

Although exposures to many chemicals may result in local toxic effects to the skin, systemic toxicity is a major regulatory concern with skin exposures. Systemic toxicity is normally estimated from experimental studies in laboratory animals or human epidemiology studies. Good experimental toxicology studies from skin exposures are frequently not available. Often, with epidemiology studies, skin is not the only route of exposure and the exposure level is uncertain. As a result, we frequently assess potential toxicity from dermal exposures by making estimates of chemical penetration through the skin (route-to-route extrapolations). The purpose of this presentation is to provide an overview of the techniques used to assess systemic toxicity from skin exposures and to attempt to put systemic toxicity in perspective by reviewing historical incidents of systemic toxicity from skin exposures

Allergic and Irritant Reactions in Skin – Pathophysiology

David Basketter, DSc, MRCPath, FIBiol, Unilever Colworth Laboratory, Bedford, UK

The skin provides a superb, self-repairing barrier between the outside world and the internal milieu. However, disturbances to this barrier can result in a wide range of effects and amongst these, allergic and irritant skin reactions represent probably the most commonly occurring. A very wide range of chemicals is capable of causing direct disturbance to skin homeostatis/integrity, the response to which is seen as irritation (the most extreme expression of which is corrosion, involving permanent damage). Typically, skin irritation is seen as erythema, dryness and roughness; the underlying picture is one of an inflammatory infiltrate involving particularly neutrophils. However, this infiltrate represents late events – the triggering events which caused the infiltration are much less well characterised. These include the disruption of the primary stratum corneum barrier, disturbance to membranes of cells in the viable epidermis and the release of inflammatory mediators, such as cytokines. The contrast with allergic skin reactions, typically delayed hypersensitivity mediated by T lymphocytes, is far from clear. The gross appearance of the allergic skin reaction is broadly indistinguishable from irritant dermatitis and at the microscopic level, the same is true of the inflammatory cell infiltrate. In consequence, it is unsurprising that the chemical mediators of inflammation are often discovered to be very similar. Even the antigen presenting cell of the epidermis, the Langerhans cell, responds by activation and migration equally in response to irritants and allergens. Nevertheless, there are important distinguishing characteristics, including the chemistry of allergens/irritants, dose response patterns, and subtleties of Langerhans cell responses – and it is these elements that will form an important part of the presentation.

Risk of Work-Related Dermatitis: Agents, Occupations and Host Factors

Päivikki Susitaival, MD, PhD, North Karelia Central Hospital Dermatology Department, Joensuu, Finland

Good occupational disease statistics exist in few countries. The coverage differs greatly depending on the notification system, legal concept of occupational disease, and workers' compensation coverage of different occupational groups. For example, farmers and other independent entrepreneurs are often missing from the statistics because they are not covered by compensation systems. Some statistics include only those that have lost work days for the skin disease. All statistics underestimate the true incidence of occupational skin diseases.

In epidemiological studies, the reported point prevalence of occupational hand dermatitis has been at least 10 % of workers in occupations with skin contact with allergens or irritants. This figure is much higher in risk occupations (examples: hairdressers, dental health workers, other health care workers, veterinarians). The majority of occupational skin diseases are contact dermatitis, either allergic or irritant, affecting mainly hands or forearms but also other (open) skin areas, mainly face. New sources of allergic contact or protein contact dermatitis are constantly found. Detection of the cause is crucial and the only way to attempt to cure occupational contact dermatitis.

According to the US Bureau of Labour Statistics, the incidence of occupational skin disease has decreased since 1994, and the same tendency can also bee seen in other countries (e.g. Finland). In the same statistics, the highest annual incidence of occupational skin disease has been in agriculture, forestry and fishing (in 1999 15,5/10 000) followed by manufacturing (11/10 000). Finnish Register of Occupational Diseases (FROD) has collected information on diagnosed cases of work-related diseases since 1964. Information is not based on compensation only but on notification by the physician diagnosing the disease. As of now, FROD has collected information on over 30,000 cases of occupational skin diseases. The register includes, on top of the diagnosis, causative agent(s), occupation, industry, age, and sex of the patient. Skin diseases are categorized into five diagnostic groups – allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), contact urticaria or protein contact dermatitis (PCU), skin infections, and other. About 30-35% of occupational dermatoses have been ACD, about the same amount ICD, 15-20% PCU and 10-15% other skin diseases. The annual incidence has been about 4 cases/10 000 workers on average, 20/10 000 in food industry, 15/10 000 in farming and 12/10 000 in manufacturing. In the UK statistics which cover only a region of the country and dermatological patients that have been disabled for two weeks for skin disease, the top occupational groups are manufacturing/mining, social/personal services, health and education, agriculture, and construction.

There are many limitations to getting information on exposure to specific chemicals: product labeling as well as material safety data sheets (MSDS) are often limited (only substances exceeding a certain concentration, no byproducts, metabolites, or contaminants) and the information may be lacking or false. Especially (meth)acrylate

containing products regularly contain undeclared (meth)acrylate compounds. Inquiries to manufacturers may take time and lack (specific) information. Product data bases can be simple and quick, but information is often limited to the needs of the provider, and updating is often a problem. Therefore, chemical analyses are sometimes needed to analyze products for potential allergens.

Risk occupations for irritant dermatitis include those with moisture, detergents, dirt, and chemical exposure. The most important causes for ACD in Finland have been rubber chemicals, synthetic resins and plastics (epoxy resin systems, (meth)acrylates, phenolformaldehyde resins), metals, plants, and biocides. Protein contact dermatitis (PCD), often clinically indistinguishable from ACD, and contact urticaria (CU), both representing immediate allergy, are caused mostly by proteinaceous substances in nature, including latex, food stuffs, animal proteins and plant proteins. Diagnosis of occupational allergy requires usually skin testing not only with standard series but with specific series and patient (workplace) supplied materials. Depending on the industry, about one third of occupational skin allergy can be immediate (PCD, CU), and therefore, in addition to patch tests, skin prick tests and/or specific IgE-antibody determinations (e.g., RAST) are needed for diagnosing these conditions.

History of atopy (childhood eczema, flexural eczema, allergic respiratory symptoms) or other constitutional risk factors increase the risk for occupational hand eczema. History of metal dermatitis (nickel allergy), wool intolerance, itch when sweating, or generally dry and itchy skin, all are markers of sensitive skin and predispose to irritant (and allergic) hand eczema. Pollen allergies often coexist with allergies to raw vegetables, fruits, and spices causing hand eczema (protein contact dermatitis) in, e.g., food handling. Atopic allergies seem to be major contributors to skin reactions in livestock farmers, veterinarians, and laboratory animal workers. Household work, renovation and maintenance of buildings, car maintenance, and some hobbies (exposure to paints, glues, garden, etc.) may also be major contributors to dermatitis.

Studies have shown that the prognosis of allergic dermatitis can be good once the allergen is detected and avoidance or protective measures started. Total removal from exposure often brings about rapid resolution, but it may take months if exposure and/or the reaction has been severe. In an uncomplicated case, the rash may resolve in 3-7 days but the skin will remain in a vulnerable state for at least 3 weeks. The prognosis is much worse if hidden exposure sources or other concomitant allergies (e.g., to corticosteroids), either at work or home, have not been detected and eliminated.

Diagnosis and Management of Occupational Skin Disease

James S. Taylor, MD, Section of Industrial Dermatology, The Cleveland Clinic Foundation, Cleveland, OH, USA

The spectrum of occupational skin diseases will be illustrated. Ninety five percent of cases are contact dermatitis, of which up to 80% is irritant contact dermatitis (ICD). Cumulative ICD, in contrast to acute ICD and chemical burns, is the most common type and develops slowly after additive, sub threshold exposures to mild irritants (e.g. soap, water, detergents, industrial cleansers, and solvents) under a variety of conditions. Allergic contact dermatitis (ACD) is the next most frequent disorder accounting for about 20% of contact dermatitis cases. Major occupational contact allergens include biocides (e.g. isothiazolones and formaldehyde releasing chemicals), chromate, cobalt, colophony, dyes, epoxy resins, formaldehyde and formaldehyde resins, fragrances and essences, nickel, plants and woods, and rubber processing chemicals. Other disorders include contact urticaria, photosensitivity, acne and folliculitis, increased and decreased pigmentation, ulcerations, granulomas, and neoplasms.

Essential to evaluating and managing occupational skin diseases are:
1) Accurate diagnosis, including underutilized procedures to identify allergy (patch and photo patch testing, and serologic and cutaneous tests for contact urticaria);
2) Determining causation or work relatedness of disease;
3) Recommendations for a) medical therapy, b) prevention {environmental (hazard identification, substitution, and other industrial hygiene and environmental engineering methods), personal (chemical protective clothing, cleansers and barrier agents), and medical (initial and periodic examination, workplace accommodation, etc)}, c) job placement, d) impairment and disability evaluation, and e) rehabilitation.

Key to management of occupational skin disease is health risk assessment:
1) Hazard identification,
2) Dermal exposure assessment,
3) Dose response assessment, and
4) Risk characterization.

Plenary Session 2: "Health Effects and Hazard Identification"

Session Chairs: Pietro Sartorelli and Frank Gerberick

2.1 **Percutaneous Penetration Studies for Risk Assessment,** Faith Williams, PhD, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

2.2 **Factors Influencing Percutaneous Penetration in the Workplace and General Environment**, Howard Maibach, MD, Prof, Derm, University of California at San Francisco, San Francisco, California, USA

2.3 **Theoretical Models of Percutaneous Absorption**, John Corish, BSc, MA, PhD and Dara Fitzpatrick, BSc, PhD, University of Dublin, Dublin, Ireland

2.4 **The Importance of Exposure and Potency in the Assessment of Skin Sensitization Risk,** Frank Gerberick, PhD, Procter and Gamble Co., Cincinnati, Ohio, USA

2.5 **Criteria for Skin Notation in an International Perspective,** Jesper Bo Nielsen, PhD and Philippe Grandjean, MD, Institute of Public Health, University of Southern Denmark, Odense, Denmark

Session Planning Committee:
Pietro Sartorelli, Coordinator
Heinz Ahlers
Peter Elsner
Pat Engasser
Frank Gerberick
Gerald Kennedy

Percutaneous Penetration Studies for Risk Assessment

Faith Williams, PhD, Skin Toxicology unit, Department of Environmental and Occupational Medicine, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

The dermal route is an important component of exposure to occupational and environmental chemicals. Skin (stratum corneum) acts as a barrier to the passage of chemicals into the body and to predict systemic risk and set safety standards reliable measures of rates of percutaneous penetration are required. Useful data can be obtained from in vivo human volunteer and animal studies, dermal occupational biomonitoring, predictions from structure activity relationships and PBPK models and increasingly percutaneous penetration measurements with isolated human or animal skin maintained in an in vitro diffusion system. Studies with animals can be related to available toxicology data whereas human skin is most relevant for human risk assessment. It is important to standardise in vitro penetration studies and to validate, with parallel in vivo studies. Many different in vitro systems are in use and a number of organisations have produced guidelines. A standardisation study with 10 European laboratories has recently been conducted as part of an EI funded research project. Studies with a flow through diffusion cell with rat skin and various receptor fluids have been directly compared to in vivo studies in the rat using the same dose, vehicle and application time for a range of chemicals of differing physicochemical properties and lipophilicities. In vitro studies with human skin have been related to human volunteer studies. In vitro experiments can also be designed to reproduce work place scenarios and confounders such as multiple doses, mixed exposures, vehicles, exposure patterns, local skin damage, local metabolism investigated and occupationally relevant finite doses compared to infinite doses. In conclusion, results indicate that the in vitro penetration rate and distribution is influenced by the source of human skin but as with the rat generally reflects passage through the stratum corneum and subsequent distribution in vivo.

Factors Influencing Percutaneous Penetration in the Workplace and General Environment

Howard Maibach, MD, Prof, Derm, Department of Dermatology, University of California at San Francisco, San Francisco, CA, USA

This presentation will provide the limited in vivo human and rhesus monkey flux data that permit realistic assessment of systemic dosing in man.

Factors for which data exist include: regional variation (~ 50 x factor from least to most permeable areas), effect of clothing, washing, soil, mass / unit area, and "delivery" vehicle (matrix).

Areas requiring further definition will be summarized.

Theoretical Models of Percutaneous Absorption

John Corish, BSc, MA, PhD, Department of Chemistry, Trinity College, University of Dublin, Dublin, Ireland (Speaker)
Dara Fitzpatrick, BSc, PhD, Department of Chemistry, Trinity College, University of Dublin, Dublin, Ireland

The great value of being able to accurately predict the extent to which a molecule will be percutaneously absorbed, without the need to make experimental measurements, has long been realised. Truly dramatic progress has been made in recent years in the application of atomistic simulation methods to quantitatively study diffusion processes through both inorganic and organic media. However, these techniques cannot, as yet, be used to study matter transport through complex biological systems such as human stratum corneum. Current predictive models of percutaneous penetration are therefore confined to a range of different algorithms that relate the permeability of the substance to some of its physicochemical properties, typically the octanol-water partition coefficient and molecular weight. The predictive capacity and scope of these models therefore depend on the availability of reliable data determined under controlled conditions and for as representative a range of compounds as is possible. This paper will review the models now in use, which are based on membrane, compartmental and fuzzy logic approaches. It will consider both steady state and non-steady state regimes, examine the limitations of the models and identify the additional measurements that would be necessary to extend their scope and reliability. For occupational and environmental exposures special emphasis is required on contact with liquid substances and, in general, it will be important for the future to extend the models so that they can treat a wider range of exposure conditions.

The Importance of Exposure and Potency in the Assessment of Skin Sensitization Risk

Frank Gerberick, PhD, Procter and Gamble Co., Cincinnati, OH, USA

For new chemicals introduced into the workplace or marketplace, and which come into contact with the skin, it is necessary, to conduct a thorough skin safety testing and risk assessment program to be certain that the exposures will be well tolerated. One vital risk assessment process involves the determination of allergic skin reactions, referred to as skin sensitization, the clinical manifestation of which is allergic contact dermatitis (ACD). Essential elements for conducting a sound risk assessment involve the development of an understanding of the sensitization potential of the contact allergen and the likely dose, nature, extent and duration of exposure. The critical exposure determinant for evaluating skin sensitization risk is dose per unit area of skin exposed. One area of difficulty in the development of a quantitative risk assessment for a contact allergen is objective information regarding its relative potency compared with other skin sensitizers.

It has been well known for years that chemical allergens display dose-response characteristics regardless of whether the sensitization is induced in an experimental system or in humans. The development of a novel predictive assay in the mouse, the Local Lymph Node Assay (LLNA), provides new opportunities for the objective and quantitative estimation of skin sensitization potency. For the purposes of hazard identification, the LLNA measures sensitization potential as a function of lymphocyte proliferative responses induced in draining lymph nodes by test chemicals; those chemicals that at one or more test concentration provoke a 3-fold or greater increase in LNC proliferation compared with vehicle controls are classified as potential contact allergens. This method has been applied more recently to determination of relative potency, with comparisons between chemicals based on the mathematical derivation of an EC3 value, this being the estimated concentration of chemical necessary to cause a 3-fold increase in lymph node cell proliferative activity. Experience to date with this approach has been very encouraging; clear differences between skin sensitizing chemicals can be discerned and such differences appear to correlate with the ability to induce contact allergy in experimental models and with what is known of their sensitizing activity among humans. It is this latter correlation that is of greatest significance in evaluating the accuracy of relative potency determinations made using the LLNA and the utility of these in the risk assessment process.

We have shown that derivation of the EC3 for a chemical provides an objective and quantitative measure of potency when compared with chemicals that had been assigned to classes based on their human sensitizing potency. In one study, 20 chemicals were assigned to 1 of 5 human potency classes (strong, moderate, weak, extremely weak and non-sensitizing) based solely on the expert clinical judgment of the authors. These classifications correlated well with the calculated EC3 values from LLNA studies. In a second study, we have determined the potency rankings for 21 chemicals based upon quantitative data from human repeat patch test studies reported in the literature, together with our clinical experience, and compared these with the rankings derived from LLNA

EC3 values. The results show clearly that LLNA EC3 values are very comparable with the NOELs calculated from the literature. Moreover, the potency rankings based upon LLNA EC3 data support their human classification.

In summary, it is clear that the LLNA can be used to provide quantitative estimates of relative skin sensitizing potency (EC3 values) that correlate closely with what is known of the ability of chemicals to cause skin sensitization in humans. Such information, in combination with an understanding of the exposure, will be of considerable utility in the development of sound risk assessments for skin sensitizing chemicals.

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Criteria for Skin Notation in an International Perspective

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Many industrialised countries have decreased their occupational exposure limits for a substantial number of chemicals. However, these limits relate to pulmonary exposures only, and decreased concentrations in the inhaled air will not necessarily reduce dermal absorption. In contrast, at a decreased respiratory uptake, the dermal exposure route may gain increased importance.

Skin notations were originally introduced as qualitative indicators of hazards related to dermal absorption. Thus, skin notations were to be used as warning signs only. They therefore need to be supplemented by some kind of quantitative measure to be useful in most practical settings. Further, as a qualitative hazard warning, the skin notation does not allow differentiation between chemicals depending on their toxicity or percutaneous penetration rates. As an indication that skin notations have not been applied as intended, only few new skin notations have been added even when respiratory exposure limit were substantially lowered.

As the understanding of percutaneous absorption processes improved, some countries/organizations developed alternative and more sophisticated guidelines for assigning skin notations to chemicals. These guidelines also aim at taking into account the relative importance of the dermal absorption compared to inhalation at an exposure level equal to the exposure limit. Thus, a skin notation is assigned if dermal absorption is expected to potentially cause a significantly increased total systemic exposure when pulmonary exposure equals the current exposure level. Several issues must be considered. First, how much is a 'significantly' increased absorption? Second, should this assessment take into regard that percutaneous absorption may be considerably increased in certain dermatological diseases and after defattening of the skin? Third, many skin exposures involve chemical mixtures where one agent may enhance or attenuate the penetration of another. Should skin notation include substances that enhance the penetration of other, more toxic, chemicals? These issues have not yet been resolved appropriately and may be difficult to address with a simple administrative instrument as a notation in official lists of exposure limits. However, the goal of skin notation remains to serve at least as a warning signal that can lead to appropriate prevention locally.

The different guidelines used for assigning skin notations and the fact that some countries also include skin irritation as a reason for assigning skin notations on chemicals, has lead to a very uneven distribution of skin notations between countries that normally have very comparable exposure limits. A continuing reason for uncertainty is that proper data on dermal penetration of chemicals are very often missing, of questionable quality or only exists for the pure chemical but not for the mixture present in the commercial product. This lack of relevant information on penetration characteristics for sales products has

most recently caused authorities to strengthen their requirements for approval of new products. Still, despite the lack of attention to percutaneous absorption in the workplace, the need for skin notation and preventive measures in this regard have only expanded during recent years.

The latest thorough comparison on the use of skin notations on occupational relevant chemicals in different countries dates back some ten years (Grandjean, 1991). We have now attempted to update this information for the purpose of this meeting. The conclusion remains unchanged, that skin notation varies substantially from country to country. Some decisions whether or not to include such notation appear contrary to the evidence. In our view, an improved notation should include a (semi)quantitative measure for assigning skin notations to occupationally relevant chemicals. We propose that the issue of skin notation be taken up by international organizations with the purpose of obtaining an improved tool for preventing hazardous percutaneous uptake of toxic chemicals in the workplace.

Plenary Session 3: "Measuring and Predicting Exposures"

Session Chair: Leena Nylander-French

3.1 **Dermal Exposure Processes and Mechanisms: Implications for Exposure Sampling Methodology and Strategy,** Derk Brouwer, PhD, TNO Chemistry, Zeist, The Netherlands

3.2 **Issues in Understanding Dermal Exposures Resulting from Contact with Contaminated Surfaces, Measuring Surface Contamination, and Characterizing Transfers,** Elaine A. Cohen-Hubal, PhD, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA

3.3 **Measuring Dermal Exposure: Practical and Scientific Considerations,** Alastair Robertson, BSc (Hons), PhD, Institute of Occupational Medicine, Edinburgh, UK

3.4 **Predictive Models of Dermal Exposure,** John Kissel, PhD, PE, University of Washington, Seattle, Washington, USA

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Dermal Exposure Processes And Mechanisms: Implications For Exposure Sampling Methodology And Strategy

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Dermal exposure is considered to be the result of possibly different mass transport processes, either directly or indirectly from a source to the skin. Basically, this has been distinguished in processes towards the skin (compartment) and from the skin, whereas overall pathways have been identified as direct contact, surface contact transfer and deposition of aerosols. These processes and pathways have been conceptually described (Schneider et al., 1999,however, neither all process parameters or determinants have been identified nor their influences have been quantified. Currently, research projects, e.g. RISKOFDERM, are carried out to develop predictive exposure models that are based on the concepts of dermal exposure processes. Many process parameters and exposure determinants are being and will be evaluated for their influence on the processes.

If dermal exposure needs to be quantified, a sampling strategy should be designed. The objective(s) of the sampling will affect the design of the sampling strategy very much. Basic questions as sampling location, timing, duration and frequency should be answered in view of both knowledge of the exposure processes and pathways, and the objectives of sampling. Timing of the sampling, and sampling duration may largely determine the impact on sampling results in cases where the mass transport rates away from the skin, e.g. by resuspension, evaporation or permeation, are high. Sampling for risk assessment may result in other choices of duration and frequency compared to those made in view of sampling for an intervention study. For an exposure pathway by surface-contact transfer the selection of sampling locations may differ from those for a deposition pathway.

The selection of sampling methods is also an integral part of sampling strategy. Again, exposure processes and pathways, and the objectives of sampling will affect the selection of the sampling method very much. In addition to customary criteria for evaluation of the performance of sampling methods, e.g. accuracy, precision, repeatability, resolution, robustness etc., the conceptual model of dermal exposure has been useful to evaluate current sampling methods, e.g. surrogate skin, removal, and in situ detection methods, in view of what processes are reflected by the results, and the suitability of the results for the objective(s) of sampling. For example, for risk assessment it is considered relevant to estimate uptake, i.e. biologically relevant (dermal) exposure. Cherrie and Robertson (1995)defined an exposure metric (Esk) as the integral of the concentration of the contaminant substance in the skin contaminant layer (Csk) over the whole surface of the skin and over the whole period of exposure. For a concentration Esk= Csk.s.t, where s is the area exposure and t is the duration of exposure, exposure metrics would be mg.kg-1.cm2.s, which shows that both determination of mass and area of exposure are relevant for the specific sampling objective.

Future research should be focussed on issues related to validation of presently available exposure sampling methods, e.g. by 'benchmarking' methods to compare sampling

performance. The need for harmonisation and standardisation has already been recognised by starting new working group within the European standardisation commission (CEN) dedicated to dermal exposure methods and strategies.

It is assumed that attention will be paid to develop new methods, since no sampling method is available that assesses dermal uptake, relevant for risk assessment, adequately. The knowledge on dermal exposure processes and exposure sampling methods also provides guidelines for the design of appropriate sampling strategies. The strengths of different methods may be combined to improve risk assessment.

Issues in Understanding Dermal Exposures Resulting from Contact with Contaminated Surfaces, Measuring Surface Contamination, and Characterizing Transfers

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Although monitoring for surface contamination in work with radioactive materials and dermal monitoring of pesticide exposure to agricultural workers have been standard practice for 50 years, regular surface sampling and dermal monitoring methods have only been applied to industrial and residential contamination since the 1980s. In recent years, there have been significant advances in the tools available to measure and assess dermal exposures resulting from contacts with contaminated surfaces. However, there are still important gaps in our understanding of the determinants of this type of dermal exposure and how best to measure and assess the exposure.

To identify the major uncertainties associated with quantifying dermal exposures resulting from contact with contaminated surfaces it is useful to consider the pathways and mechanisms for these exposures. Transfer of contaminants from a contaminated surface to the skin is a function of:
(1) the form of the contamination (residue, particle, formulation, age, physicochemical properties);
(2) characteristics of the surface (hard, plush, porous, surface loading, previous transfer);
(3) characteristics of the skin (moisture, age, loading, previous transfer);
(4) contact mechanics (pressure, duration, smudge, repetition); and
(5) environmental conditions (temperature, relative humidity, air exchange).
In addition, human behaviors in both occupational and non-occupational settings represent an important determinant of exposure that adds significant variability to estimates of dermal exposure.

In this presentation, important data gaps associated with the mechanisms of transfer from contaminated surfaces will be identified. In addition, our current approaches for characterizing and assessing dermal exposure resulting from contact with contaminated surfaces in both residential and occupational environments, as well as the research needed to move the state-of-the-science forward, will be considered.

Disclaimer
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Measuring Dermal Exposure: Practical and Scientific Considerations

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Occupational dermal exposure to chemicals is known to cause a variety of skin diseases and, in the UK, the Health and Safety Executive has estimated that there are 85,000 cases of work-related skin disease at any one time. In addition, many hazardous chemicals can pass through the skin and add to inhalation exposure.

Against this background there has been considerable effort to develop quantitative methods of assessing exposure. Fenske conveniently grouped the various sampling techniques into three categories: surrogate skin techniques which rely on a collection medium placed against the subject's skin; removal techniques where substances deposited on the skin are removed, generally by washing or wiping; and fluorescent tracer techniques that rely on the measurement of UV fluorescence from materials deposited and retained on the skin. Each of these categories of methods measures slightly different aspects of dermal exposure and has its own strengths and weaknesses. All these procedures measure mass of material on the skin surface.

However, to date, there has been little work on the biological relevance of dermal exposure sampling techniques. For example, uptake through the skin is driven by diffusion, which, in turn, is driven by the concentration of the material on the skin. In many instances, the concentration on the skin is also a better indicator of the potential of a chemical to cause direct damage to the skin. Mass may therefore not be the most appropriate measure of dermal exposure. In addition, surrogate skin samplers almost invariably retain a much higher proportion of any chemical contact than the skin. While removal techniques and fluorescent tracers tend to look at what is left on the skin rather than what can damage or penetrate the skin.

This paper will discuss the rationale for radical changes in the design of 'surrogate skin' dermal exposure samplers to chemicals. In addition it will describe the development and preliminary laboratory testing (funded by the Health and Safety Executive) of a prototype 'surrogate skin' dermal exposure patch sampler. This has been designed to measure the concentration of liquids on skin surfaces and incorporates a diffusion barrier. The diffusion barrier allows the sampler to measure concentration of contact rather than simply mass and liquid retention properties closer to those of human skin than standard patch surfaces.

Predictive Models Of Dermal Exposure

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Early efforts to use mathematical models to predict dermal exposures to chemical substances can be traced to persons evaluating occupational exposures in agriculture. Relatively low vapor pressure and moderate to high lipid solubility are useful characteristics for pesticides. They are also characteristics that are likely to elevate the importance of dermal exposures relative to inhalation exposures. Hence mathematical prediction of dermal exposure was attempted earlier in agriculture than in many other industries. Initial models were relatively simple and heavily dependent upon empirical measurements. Multiple factors, including increased awareness of the transport of synthetic chemicals in the environment, changing definitions of acceptable risk, and mitigation of respiratory exposures in the occupational sector, have lead to consideration of a broader range of possible dermal exposure scenarios. In the United States, the Food Quality Protection Act (FQPA), which requires assessment of aggregate pesticide exposure, is an important driver of dermal exposure research. FQPA inspired residential exposure models feature relatively elaborate descriptions of human behavior linked to fairly simple models of surface-to-skin transfer and subsequent absorption. Not surprisingly, the latter components of these models draw upon prior experience in occupational agricultural exposure assessment. Also in the U.S. the necessity of setting soil cleanup standards at hazardous waste sites has fostered the modeling of dermal exposure to soils and concern over exposure to by-products of chlorine disinfection in drinking water and to groundwater contaminants has fostered modeling of dermal absorption of water-borne chemicals. Similar pressures are at work in Europe and reflected in significant initiatives and a rapidly expanding dermal exposure literature.

Dermal chemical exposures may lead to direct dermatological effects or to systemic absorption of those chemicals. Most dermal exposure modeling to date has focused on the latter question. In that context, its purpose is to facilitate the further step of predicting absorbed dose. To be useful, dermal exposure models should at least address the following three basic questions. 1) How much of the medium containing the chemical of interest or of the neat compound is transferred to the skin and how is it distributed? Characterization of distribution must include areal extent and should include evaluation of completeness of coverage and potential layering effects. Immersion in an effectively infinite source is an exception. In that case, exposure modeling is trivial and the problem is reduced to absorption modeling. 2) What is the thermodynamic activity of the compound on the skin surface? If the target compound is not present in neat (or unbound) form, the matrix in which it is found on the skin and the affinity of that matrix for the compound are critical determinants of absorption behavior. 3) How long does the compound of interest reside on the skin? Dermal absorption is time-dependent. Loss mechanisms that compete with absorption such as volatilization or removal by washing should be considered.

Mathematical treatment of each of these questions can range from relatively simple to very complex. Regulatory deadlines and data gaps impose constraints on modelers. An increase in modeling sophistication that is currently within reach involves treatment of inputs as stochastic variables. Historically deterministic models have been used in regulation. Disputes over the extent to which model predictions are or are not conservative have fostered increasing use of stochastic models. An additional question can be posed. 4) How temporally and demographically variable are the exposures and how uncertain are the measurements and sub-models used to characterize them? Characterization of the uncertainty of predicted exposures is necessary if models are to be tested against observations (which is essential) and if regulatory decisions based on those predictions arc to be well founded.

Plenary Session 4: "Controlling Exposures and Prevention"

Session Chair: Hans Marquart

4.1 **Intervention Research**, Linda Goldenhar, MS, PhD, University of Cincinnati, Cincinnati, Ohio, USA

4.2 **Work Practices and Behavioral Modifications - Evidence-Based Prevention Programs and Implementation at Workplaces**, Mari-Ann Flyvholm, MSc, PhD, Lone Borg, MSc, PhD and Karen Mygind, MSc Pharm, National Institute of Occupational Health, Copenhagen, Denmark

4.3 **Practical and Cost-Effective Methods for Dermal Exposure Risk Management**, Chris Packham, Enviroderm Services, Evesham, UK

4.4 **Selection, Testing, and Effectiveness in the Field of PPE and Gloves**, Reinhard Oppl, MSc, Eurofins GfA (formerly MILJO-CHEMIE), Hamburg, Germany

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Intervention Research

Linda Goldenhar, MS, PhD, University of Cincinnati, Cincinnati, OH, USA

The overarching goal of intervention effectiveness research is to demonstrate the impact of interventions to prevent work-related injury and illness. To develop optimal strategies for improving occupational safety and health intervention effectiveness research however, effectiveness studies must be considered within the context of the broader intervention research field as a whole. Research studies that inform intervention development as well as studies that evaluate the implementation of interventions are essential complements to effectiveness studies. The relationships between the proposed intervention research phases of development, implementation, and evaluation will be presented as the core of the Intervention Effectiveness Research team's framework for outlining the intervention research process. Other important aspects of intervention effectiveness research areas will also be discussed including conducting diffusion research on OSH interventions, evaluating on-going interventions, implementing and evaluating policy interventions.

Work Practices and Behavioral Modifications - Evidence-Based Prevention Programs and Implementation at Workplaces

Mari-Ann Flyvholm, MSc, PhD, National Institute of Occupational Health, Copenhagen, Denmark (Speaker)
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Karen Mygind, MSc Pharm, National Institute of Occupational Health, Copenhagen, Denmark

Occupational skin diseases are among the most frequent occupational diseases in many countries. More than 90% of the occupational skin diseases are hand dermatitis and the majority of these are contact dermatitis. Occupational skin diseases are often recurrent with a long-standing course. Wet work occupations such as the health care sector and the food processing industry have a high risk of occupational skin diseases.

Prevention of occupational skin diseases in the food processing industry is particular challenging. Skin exposures to occupational factors causing dermatitis range from, e.g. soaps, hand disinfectants and skin care products over water to foodstuffs. Work procedures and methods are usually manual and automation is often not possible due to a necessity of individual handling of the foodstuffs. Thus, measures to prevent contact dermatitis in the food processing industry cannot solely be based on controlling the work process or changing products or raw materials used. Even though, much can be done by choosing less skin damaging products, the prevention of skin diseases in wet work occupations should also take into account changing the workplace routines and habits of the employees and developing the overall safety climate throughout the organization.

Occupational and environmental risk factors of importance for occupational skin diseases should be thoroughly documented, i.e. based on scientific evidence, in order to explain the reasons for changing workplace routines, work procedures, methods or equipment. This scientific documentation has to be transferred to logic and understandable recommendations on how to reduce exposures to skin damaging factors. An evidence-based prevention program for occupational skin diseases including evidence-based recommendations derived from scientific documented risk factors is a necessary but not sufficient prerequisite for workplace prevention of occupational skin diseases.

Another prerequisite for a successful prevention of occupational skin diseases (i.e. an intervention) is the implementation of the prevention program at the workplace.

One way of achieving changes in workplace routines, safety climate and attitude to occupational skin diseases is to establish and maintain an occupational health and safety management system in regard to eliminate or minimize skin risk associated with the production activities.

A local project group should establish the occupational health and safety management system. This group must include representatives from all organizational levels, i.e. members of the safety board and the top management. The project group go through an

educational program covering the necessary theoretical and practical background for understanding the prevention program and subsequently establish the occupational health and safety management system. This involves developing a skin prevention policy, and in addition, to draw up written instructions referring to the prevention program and adapted to the workplace and the work. Furthermore, the tasks for the project group include introduction of the prevention program and supervision during the daily work to colleagues in order to reduce the risk of occupational skin diseases.

This strategy for prevention of work-related skin diseases including a combination of an evidence-based prevention program and an evidence-based implementation is used in an ongoing intervention study among Danish gut cleaners. The evidence-based prevention program will be implemented by a number of activities at the intervention workplaces. The effect of the intervention will be evaluated by questionnaire surveys using Nordic Occupational Skin Questionnaire (NOSQ-2002) supplemented by questions on work routines etc. These surveys are be made before and after the intervention activities both at intervention workplaces and comparison workplaces.

Practical and Cost-Effective Methods for Dermal Exposure Risk Management

Chris Packham, Enviroderm Services, Evesham, UK

Once dermal exposure risk assessment has been completed, then the process of managing any risks that have been identified must commence. The aim must be to reduce any risks of damage to health due to dermal exposure to a level that is considered acceptable. In doing so there are several important considerations:

- We should concentrate upon controlling the process rather than the person,
- The controls introduced should be simple and, ideally, have only a beneficial effect upon productivity,
- The cost of introducing the control techniques should be kept as low as possible,
- The techniques should be acceptable to the worker and be ones that he or she cannot easily circumvent.

There are several valid reasons why we should concentrate upon controlling the process rather than relying upon controlling the person, the latter also including the use of personal protective equipment such as gloves. In essence, what we must seek to achieve is to structure the workplace, the equipment used and the way in which the process is conducted so that the workplace is intrinsically safe and does not rely upon the actions of the worker to ensure his or her safety. In achieving this, however, we must take account of cost of control measures and the need not to introduce measures that have an adverse effect upon productivity or operating costs.

In practice, there are many simple methods that can be used to achieve our aims. What is required is firstly an understanding of the actual process and then a knowledge of what equipment or techniques are available to us. Lateral thinking can often suggest original methods for controlling exposure independent of the worker.

Several case studies from different industries will demonstrate how simple changes to the process or the equipment can have significant benefits in eliminating or reducing exposure to an acceptable level. In many cases the cost of introducing such controls had no adverse effect on either productivity nor operating costs. Indeed, the result of introducing these changes can be shown to have the opposite effect, that of increasing productivity and/or reducing operating costs.

Guidelines will be proposed to assist in developing a pragmatic and effective approach to dermal exposure risk management.

Selection, Testing, and Effectiveness in the Field of PPE and Gloves

Reinhard Oppl, MSc, Eurofins GfA (formerly MILJO-CHEMIE), Hamburg, Germany

1. General

Avoiding skin exposure to chemicals is the best way to control dermal exposure and to prevent occupational skin disease. Protective clothing and gloves can reduce the residual risk. The safe protection time is determined by three processes:

- Penetration of a liquid through the material,
- Degradation of the material by chemical reaction,
- Permeation of molecules through the liquid-tight membrane.

While there are adequate performance standards and testing standards for penetration of chemicals through skin protective material, and for degradation of elastomeric membranes, it has to be stated that permeation is not always handled and tested in an appropriate manner. Based on a research project for the German Work Insurance, and on several projects for industry and for authorities, the following points have been worked out.

2. How permeation works

After the chemical landed on the skin it may be solved in the outer surface of the membrane, then diffuse through the layers that form the barrier, and finally be set free from the inner side of the membrane. There it can meet the skin - or the permeation test sampling medium.

2.1 How permeation is determined

A cut-out piece is placed into a test apparatus. The chemical is placed onto that piece and a collection medium is passed by or pressed against the inner surface of the test medium. If any breakthrough occurred then the amount of the permeated chemical is determined by chemical detection. Adequate detection is easy for volatile solvents (FID or PID may be used) and for inorganic acids or alkaline solutions (a pH electrode is appropriate). Detection is tricky for chemicals that are not volatile and not soluble in water (e.g. PAH), or that are reactive (e.g. isocyanates, or some aldehydes). In these cases a solid medium may be pressed against the inner surface and replaced and analyzed in regular intervals. This may be a solid medium that was impregnated for giving stable derivatives of the chemical in test. Wetting the sampling medium will improve the adhesion and increase the transfer of any contaminant from the inner side of the membrane to the sampling disc. There is the hypothesis that solutions of these non-volatile and non-water-soluble, or reactive, chemicals are easier to monitor just by measuring the permeation of the solvent. This was confirmed by a number of comparative studies, especially on active ingredients of pesticides. There is another hypothesis that large molecules will not pass through protective barriers made of elastomers. But when applying the solid sampling technique for the permeation test, this assumption showed to be wrong for Polycyclic Aromatic Hydrocarbons (PAH). Permeation can be described as the permeation rate PR (the flow through the barrier) and as the normalized breakthrough time BTT. In European

standards, BTT is the only criterion that is accepted for assigning protection factors to PPE and gloves. Normalized BTT is the time that goes between the start of the test and the point of time when permeation exceeds the threshold of 0.1 or 1 mg/(cm² x min) (see ASTM 739 resp. EN 374-3)

2.2 Conditions in test and conditions in service
Several parameters of the standard permeation tests as described in the testing standards ASTM 739, ISO 6529 and EN 374-3, differ from the conditions that are likely to be found in service.

2.2.1 Duration of exposure
Testing is done as continuous contact over 8 hours. In reality, most dermal exposures are intermittent or occasional. On the other hand, many gloves are re-used over several days and weeks. If no permeation occurs after 8 hours, nobody knows what will happen after (e.g.) 3 days. On the other hand, in the case of intermittent exposures to volatile chemicals a barrier may serve much longer than a standard eight hour test will predict - especially if evaporation is faster than permeation.

2.2.2 Temperature
Testing is done at 23 °C. In reality, the PPE or the glove will reach a higher temperature at the inner side due to body heat. This may shorten the breakthrough time and increase the permeation rate dramatically, giving worse protection and a shorter safe protection time than the standard test will predict.

2.2.3 Stretching
Testing is done without any mechanical challenge. In reality, the PPE or the glove will be stretched by movements. For gloves, closing the hand may lead to 20 % stretching or even more, resulting in a thinner membrane, at the knuckles. This was shown to lead to a shorter breakthrough time, but the impact of stretching is less dramatic than that of the elevated temperature.

2.3 A new approach
In Germany, a test procedure was designed that uses the standard test cell but with a simulation of in-use conditions (35 °C inside glove temperature and 20 % length stretching), as well as of short-term exposure and re-use if relevant. The new testing protocol was applied to 5 chemical products containing volatile organic solvents. A total of 19 protective gloves were tested and under these conditions the breakthrough time was ½ or even 1/3 when compared to the respective standard test results. This proved that the official testing standards are reflecting insufficiently the in-use conditions. Elevated temperature inside the PPE or glove due to body heat was the most important factor. Short-term or occasional exposure was also important for some (but nor for all) of the solvents that were monitored. Mechanical stretching (e.g. due to hand moving) showed to be of minor importance. In a number of projects the solid sampling permeation test method proved to give reliable results for PAH, isocyanates, acrylates, and for compounds of epoxy resins. Had these been tested with the standard testing technique only, then permeation would not have been detected just and only for analytical reasons.

3. How significant are test results?
Not only the testing protocol may lead to a limited significance of the testing results, also the barrier material itself shows variations of the barrier effect.

3.1 Membrane properties and barrier effect
Elastomers may show a barrier effect towards chemicals. The barrier is weak if the challenge chemical is soluble in the membrane or if it may move through the membrane by diffusion - and vice versa. A number of physico-chemical parameters influence these processes such as molecular size, hydrophobic/hydrophilic nature, bonding polarities, hydrogen bondings, Van der Waals forces and more. Many barrier membranes are built from different layers - this complicates a quantitative description and prediction of the permeation process enormously. Thickness of the membrane is another but well known important determinant of the barrier effectiveness.

3.1.1 Nitrile does not equal Nitrile, Latex does not equal Latex
Different brands and qualities of elastomers may have different ingredients and different degrees of cross-bonding. Therefore two membranes made of two elastomer brands, although being of the same type of elastomer, may show very different barrier properties.

3.1.2 Batch to batch variation
Even different batches of the same membrane may show different barrier properties because of variations of the manufacturing process and of the ingredients.

3.2 Analogies between chemical mixtures
Two mixtures containing the same or very similar chemicals may behave in a similar manner in many cases but there are some reports on unexpected observations. Small amounts of chemicals may change the physico-chemical properties of the total product dramatically in some cases. It will need chemical expertise to decide whether a selection of a barrier material by analogy should be verified by a new test or not. In case of doubt it is essential to carry out a permeation test not with the main ingredients only, but with the chemical product as it is.

3.3 A new approach
PPE and glove selection based on the polymer type (e.g. "Nitrile" rubber) can be misleading if the selected membrane shows a different barrier effect than the tested one. This is still more true if a "Nitrile" material is made from both Nitrile and Latex layers. The same showed to be true for Chloropren and for Latex materials. Butyl rubber qualities were reported to be better comparable between each other. Therefore test data should only be used for the PPE that was tested, and for PPE that was made from the same membrane brand and with a similar thickness.

4. Conclusions
Today, selection of PPE or gloves based on published data alone is a guess rather than a sound procedure. Earlier test data are only relevant for the selection of PPE or gloves if the test results refer to the barrier material in question, and if the tests were carried out with a chemical or a mixture that is similar to the challenge chemical. The standard

permeation test method needs an update for inclusion of the influence of temperature, stretching, and exposure time patterns, and for testing chemicals that are neither volatile nor water soluble, or that are unstable under the testing conditions.

For more information on the newly developed permeation testing methods please contact the author.

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Plenary Session 5: "Developing Policy and Communicating Effectively"

Session Chair: Michael Dellarco

5.1 **US EPA's Recently Released Superfund Dermal Risk Assessment Guidance: Application and Policy**, Daniel Stralka, PhD, US Environmental Protection Agency, San Francisco, CA, USA

5.2 **Protecting Workers from Dermal Exposure - the German Experience**, Eva Lechtenberg-Auffarth, PhD and Bruno Orthen, PhD, Federal Institute for Occupational Safety and Health (BAuA), Dortmund, Germany

5.3 **Protecting Workers from Dermal Exposure - The American Experience**, Lyn Penniman, MPH, US Occupational Safety and Health Administration, Washington, DC, USA

5.4 **How the Food Quality Protection Act Affects EPA Regulation of Pesticides via the Dermal Route of Exposure**, Elizabeth Doyle, PhD, US Environmental Protection Agency, Washington, DC, USA

5.5 **Prevention of Contact Dermatitis by European Legislation**, Carola Lidén, MD, PhD, Dept Occupational and Environmental Dermatology, Stockholm County Council; Karolinska Institutet, Stockholm, Sweden

5.6 **Perspectives on Industry Reactions to US Government Policies**, Christine Chaisson, PhD, Chaisson Scientific Advisors, Annandale, Virginia, USA

Session Planning Committee:
Mike Dellarco, Coordinator
Heinz Ahlers
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Howard Maibach
John McAlinden
Lyn Penniman

US EPA's Recently Released Superfund Dermal Risk Assessment Guidance: Application and Policy

Daniel Stralka, PhD, US Environmental Protection Agency, San Francisco, CA, USA

The Superfund Dermal Risk Assessment Guidance was published in the Federal Registrar in December 2001 and solicited public comment and additional data. The guidance was a refinement and application of the US Environmental Protection Agency's Office of Research and Development 1992 Dermal Exposure Assessment: Principle and Applications report. The intent of this guidance was to present a concise description of the dermal pathway for exposures to soil and water with an evaluation of the exposure parameters such that in the Superfund program there could be a more consistent evaluation of this pathway. The dermal pathway is a routinely questioned exposure route by community members around Superfund sites and is often only qualitatively evaluated.

The release of this guidance was after several rounds of internal peer review, external peer review and a peer workshop where several policy questions were discussed. Questions on the strength of the science, correct application of the principles and the ability to extrapolate the principles outside of experimental data were addressed. In this presentation, some of these policy issues will be presented along with the practical implications for routine evaluation of this pathway in Superfund risk assessments.

Protecting Workers from Dermal Exposure - The German Experience

Eva Lechtenberg-Auffarth, PhD, Federal Institute for Occupational Safety and Health (BAuA), Dortmund, Germany
Bruno Orthen, PhD, Federal Institute for Occupational Safety and Health (BAuA), Dortmund, Germany (Speaker)

Skin diseases are the most frequent occupational diseases in Germany. About 19000 suspected occupational skin diseases were communicated to the statutory accident insurances in 2000. Each suspected case is estimated to produce costs mounting to 14000 €. If skin diseases are confirmed to have an occupational origin (ca. 8000 in 2000) or if workers have to give up their occupation (ca. 450 in 2000) allowances are significantly higher. These figures only reflect cases of irritative and allergic contact dermatitis, systemic effects via the dermal route are not included.

A broad legal framework for risk characterisation and protective measures against (dermal) risks of chemical agents exists which is in close relation to the EU legislation

German legislation	EU legislation
Arbeitsschutzgesetz (Act on Workers´Health Protection) from 7.8.1996	Council Directive 89/391/EEC on the introduction of measures to encourage improvements in the safety and health of workers at work
Gefahrstoffverordnung (Hazardous Substances Ordinance) from 7.8.2000	Council Directive 98/24/EEC on the protection of the health and safety of workers from the risks related to chemical agents at work
PSA-Benutzungsverordnung (Ordinance on Use of PPE) from 4.12.1996	Council Directive 89/656/EEC on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace
Gefahrstoffverordnung (Hazardous Substances Ordinance) from 7.8.2000	Commission Directive 2001/58/EEC "Safety Data Sheets"
Chemikaliengesetz (Chemicals Act)amended 14.5.1998	Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to classification packaging and labelling of dangerous substances

Fundamental demands for workers´ protection are outlined in the Act on Workers´ Health Protection (corresponding to Directive 89/391/EEC) and Hazardous Substances Ordinance (corresponding to Directive 98/24/EEC):
- Risks resulting from work must be minimised
- Risks must be assessed and protective measures must be implemented
- Risk assessment and measures have to be document

A general ranking for protective measures against chemical agents is also formulated:
- General and technical prevention is to be applied first
- Hazards are to be prevented at the source
- Personal protective measures are last choice

In Hazardous Substances Ordinance, which addresses dermal hazards explicitly, the hierarchy of measures is supplemented:
- substitution
- technical measures
- measures via changes in organisation
- personal protective equipment as last choice

Directive 98/24EEC addresses risk assessment and precautionary measures for handling chemical substances. Though the words "skin" or "dermal" do not occur in the directive, it is important for dermal risk management, because it gives a definition of "hazardous substance" that includes more substances than those that arc formally classified. It creates a legal basis for protective measures for any chemical substance causing a risk in specific workplace scenarios (e.g. degreasing of skin, mechanical stress).

Personal protective equipment, though ranking last in hierarchy, is important and frequently applied at workplaces. In the Ordinance on Use of PPE it is stated:
- The employer is legally responsible for selecting and providing PPE
- PPE must meet European standards
- PPE must be adequate and ergonomically acceptable
- Use of PPE must not cause a significant hazard
- Workers have to be instructed and trained on the use of PPE
- Barrier and other creams are regarded as PPE

Substance specific information is in principle available via Directive 67/548/EEC. It contains criteria for assigning dermal risk phrases to substances, describing skin damaging properties or a systemic hazard following dermal exposure. All substances must be classified. If a substance is not included in the official list of Annex I of this directive producers are obliged to classify on their own responsibility. Labelling and Safety Data Sheets (SDS) are established means to inform employer and represent a central instrument of communication. The new Directive 2001/58/EEC on SDS is far-reaching, since it allows to identify nearly a large number of hazardous ingredients in nearly all chemical products.

Technical rules (TRGS) have been developed on the basis of the Hazardous Substances Ordinance; they specify the requirements and support enforcement of the regulation. Some of these TRGS address dermal exposure explicitly:

TRGS 150	Direct dermal exposure to substances that may be absorbed through the skin (first ed.1989)
TRGS 530	Hairdressers (first ed. 1992)
TRGS 531	Dermal risks caused by working in wet milieu (first ed. 1996)
TRGS 540	Sensitising substances (first ed. 1996)
TRGS 907	Inventory of sensitising substances (first ed. 1997)
TRGS 900	Skin notations in the list of Occupational Exposure Limits (first ed. 1992)

Especially TRGS 531 "Working in wet milieu" should be regarded as innovative approach for skin protection. It is of considerable practical relevance, since many skin problems are caused by frequent exposure to water or prolonged work with protective gloves leading to a wet milieu within gloves.

The statutory accident insurances have their own responsibility for reducing risks at workplaces. In parallel to the 16 federal states that enforce national legislation there are 36 branch-specific and regionally based statutory accident insurances which are commissioned to prevent and compensate occupational injuries and diseases. In accordance with the federal legal framework they have their own set of rules and guidance, which may be very effective, because it is tailored to the specific needs of a certain branch. Examples for such rules are:

BGR 196	Chemical protective gloves
BGR 197	Use of skin care products
BGI 584	Skin cleaning, care and disinfection

Replacement of a skin damaging substance is the first choice of available measures. In Germany the process of substitution has been started and maintained several times by discussions on new technical rules (TRGS) in the Hazardous Substances Committee with all affected parties. Discussions were often complemented by activities of the statutory accident insurances. Some campaigns have been successful in recent years:

Latex allergies developed into a significant problem, since the use of gloves became routine in the health care services. As most problems were associated with powdered gloves these were restricted by the TRGS 540 in 1997. At the same time the responsible statutory accident insurance ran a broad information campaign. As a result, in 2001 there were about 75% less suspected latex allergies compared to 1998.

Hairdressers have combined exposures to sensitising and irritating substances in a wet surrounding. A bundle of precautionary measures including not only the elimination of known sensitising substances (esters of thioglycolic acid, nickel, latex, introducing products with reduced emission potential) but including also measures concerning the organisation (e. g. to reduce prolonged contact with water) and personal protection (use of gloves for certain work, skin care measures) were formulated in the TRGS 530 and mainly enforced by extensive campaigns of the responsible statutory accident insurance. As a result the communications of suspected occupational skin diseases decreased from 4500 in 1991 to 1500 in 2001.

In Germany about 400 cases of sensitisation to chromate (in cement) are confirmed every year in construction industries. Starting from a TRGS on the substitution of cements containing chromate the German cement producing industry made a voluntary commitment to reduce chromate in cement mid of the nineties. This approach has not been sufficiently effective. Therefore Germany proposed on EU-level to classify cements containing more than 0,2 ppm chromate as sensitising. This has been agreed and as a next step a proposal is under way to ban marketing and use of such cements at least for manual activities.

Hairdressers are also an encouraging example, that it may be possible to restore health of persons with dermal diseases. By an integrated approach (secondary individual prevention) of seminars, training and risk assessment at workplace the incidence of severe skin problems could be reduced by one third.

Despite the existing legal framework, specific rules and campaigns dermal diseases remained a main problem of workers´ health protection. In addition uncertainties about systemic effects after dermal exposure represent an important field of concern. The following items reflect actual discussions:

- Only existing toxicological information has to be used for classification and labelling, but many substances have not been tested sufficiently and exhibit data gaps.

- A quantitative risk characterisation is often connected with considerable uncertainties, because dermal exposure is difficult to assess in a quantitative sense. Actually we are awaiting the results of a European project (RISKOFDERM) and have started national discussions on a respective Technical Rule

- Skin permeation is a prerequesite of systemic effects after dermal contact. The scientific database to estimate the permeation rate is in many cases weak. Worst case assumptions are often used, which can weaken the reliability of a risk characterisation. Research

projects are intended to be initiated and coordinated.

- Technical measures need to be systematically developed and endorsed. There are some strategies and examples of "good practice", but there is no systematic technical guidance up to now. Research projects are intended to be initiated and coordinated.

- The use of gloves seemed a safe resort for risk management for a long time. However, many presumptions have been questioned during the last years.

- A list of sensitising substances in gloves has been established for the German market.

- It has also been questioned, whether the European Standards for glove testing are adequate (testing temperature, stretching of material) and whether permeation resistance can be sufficiently predicted from data bases that only contain rough information on the glove material. Several producers of chemical substances have begun to indicate in their SDS gloves, that have been tested especially for the specific product.

- There are current discussions whether it is possible to characterise workplace situations, in which contact with chemicals is a minor risk than prolonged wearing of protective gloves.

- It has become open to discussion how often protective creams keep their promises or whether they might even enhance the risks in certain cases.

Protecting Workers from Dermal Exposure – the American Experience

Lyn Penniman, MPH, Occupational Safety and Health Administration, Washington, DC, USA

In the US, exposure to hazards encountered in the workplace is regulated by the Occupational Safety and Health Administration (OSHA). Exposure to some specific high use/high hazard substances (e.g., benzene and 1,3-butadiene) is addressed in comprehensive standards, which specify control measures for reducing total exposure, including skin exposure. OSHA's Z-1 Table includes a "skin designation" column for those substances thought to be absorbed into the skin and contribute to total body burden. OSHA's primary mechanism for communicating risk to workers potentially exposed is its Hazard Communication standard. This presentation will highlight these and other regulatory and non-regulatory approaches to reducing skin exposure in workers. Future challenges to the agency will also be discussed.

How the Food Quality Protection Act Affects EPA Regulation of Pesticides via the Dermal Route of Exposure

Elizabeth Doyle, PhD, US Environmental Protection Agency, Washington, DC, USA

The passage of the Food Quality Protection Act (FQPA) imposed a new standard on human health risk assessments performed for pesticides. Under FQPA, EPA was required to demonstrate that there was a "reasonable certainty of no harm" from the use of pesticides on foods and from other non-occupational exposures. The Office of Pesticide Programs (OPP) has historically emphasized exposure to pesticides in foods in its risk assessments. FQPA increased the focus on exposure to the public from residential uses of pesticides. The most significant route of exposure by this pathway is dermal.

OPP has expanded its risk assessment process to evaluate dermal exposure over three time frames: short term (<30 days), intermediate term (1 to 6 months), and chronic (>6 months). These windows of time are used to establish endpoints for use in risk assessment. OPP's toxicity testing paradigm continues to focus on oral exposure. However, staff risk assessors have responded to the greater emphasis on dermal by attempting to creatively use existing data. In the meantime, OPP is considering approaches to modifying existing toxicity testing requirements to better address this issue.

Prevention Of Contact Dermatitis By European Legislation

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Legislation is an important tool in primary and secondary prevention of contact dermatitis. There are similarities and differences between the European and North American legislations. A brief description will be given of the European system and some examples of how exposure to major contact allergens has been limited.

Classification of dangerous substances and preparations
The EU Directives on classification, packaging and labelling of dangerous substances (Directive 67/548/EEC and amendments) and preparations (Directive 88/379/EEC and amendments; from July 2002 substituted by Directive 1999/45/EC) covers chemicals intended for both consumer and workplace use. Today, approximately 500 substances are classified as skin sensiter. Classified substances are listed in Annex I of Directive 67/548/EEC. The general concentration limit for classification of preparations/products as skin sensitiser is 1% (corresponding to "percentage cut-off"). Specific and lower limits are increasingly used, and specific concentration limits have been set for more than 30 substances. The lowest being 15 ppm for the preservative MCI/MI. Preparations have to be labelled with the name of the sensitiser and a risk phrase (R 43 "May cause sensitisation by skin contact"). The new Dangerous Preparations Directive (1999/45/EC) requires also that the packaging of products containing 0.1% or more of a skin sensitiser must bear the inscription "Contains 'the name of sensitiser'. Many produce an allergic reaction."

In the EU, consumer products are subject to the same classification and labelling procedure as for workplace preparations. Safety Data Sheets have to be provided for professional users.

Nickel
The EU Nickel Directive (Directive 94/27/EEC) entered into full force in July 2001. Nickel is limited (1) in posts used during epithelization after piercing (nickel content below 0.05%); (2) in objects intended for direct and prolonged contact with the skin, such as jewellery, watches, buttons, zippers etc. (nickel release below 0.5 microgram/cm2/week); and (3) coated items under (2) must fulfil the criteria after "two years of normal use". The Nickel Directive is based on three reference test methods, CEN standards, for control of compliance with the requirements of the directive. There are strong indications that nickel allergy is decreasing in Denmark, where nickel has been limited for more than 10 years. The market in Sweden had, already before the entry into force, started to adapt to the requirements.

Cosmetics
The EU Cosmetics Directive (Directive 76/768/EEC, and amendments) covers cosmetics and hygiene products and ingredients. The Directive requires full ingredient identification by INCI names, with the exception that perfumes are not fully identified. Negative,

restrictive, and positive lists control cosmetic ingredients. Several skin sensitisers are restricted and some are prohibited by the directive.

Chrome(VI) in cement

National regulation in Nordic countries limits chrome(VI) in cement (below 2 mg/kg, by the addition of iron sulfate). A similar approach has been proposed also on the European level. Cement, containing more than 2 mg/kg chrome(VI), requires labelling in Europe from July 2002 (1999/45/EC, first amendment) with the phrase "Contains chromium(VI). May produce an allergic reaction".

Standardisation

European standardisation (CEN) may support European and national legislation aiming at the prevention of contact dermatitis, such as the Nickel Directive. A standardisation project (CEN BT/WG 132 "Methods for analysis of allergens") is currently trying to identify also other areas where the development of standardised analytical methods for specific allergens could support existing or planned European legislation.

Active participation of experts on contact dermatitis, including dermatologists, chemists, hygienists and toxicologists is essential for the development of clinically relevant regulations. Scientific studies should be performed to evaluate the effects of legislation aiming at prevention of contact dermatitis.

Perspectives on Industry Reactions to US Government Policies

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Regulatory government agencies execute their legislative mandates through a series of "traditional practices", formal policy, and structured processes. Collectively, these largely define how an Agency really operates, and are important points to which all stakeholders react. Examples of such include: data requirements and data review processes; "bright-line" for risk determinations, and the methods for calculating risk; process and policies for inspections, reporting requirements, public access to violation records; function of multi-stakeholder committees in process and policy.

This presentation will be a reflection of how industry has responded to these elements, as observed by industry, regulatory officials, and advocate representatives in the US, noting that this perspective is quite different in other countries.

Poster Session 1: "Defining the Problem"

1.1 **Dermal Hazards in the Workplace: A Survey Assessment of Protection and Exposure**, Timothy J. Buckley, PhD, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD and Daniel Anna, PhD, Millersville University, Department of Industry Technology, Millersville, PA, USA

1.2 **Occupational Environment and Skin Diseases in Pesticide Exposed Subjects in Some Tea Farms in Vietnam**, K Xuyen, PC Hoi* and PQ Trung*, National Institute of Occupational and Environmental Health and *Ministry of Agricultural and Rural Development, Hanoi, Vietnam

Dermal Hazards in the Workplace: A Survey Assessment of Protection and Exposure

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Daniel Anna, PhD, Millersville University, Department of Industry Technology, Millersville, PA, USA

Despite growing evidence that dermal exposure is substantially contributing to significant occupational illness, dermal hazards in the workplace are largely unrecognized due to both the absence of health standards or guidelines and the rudimentary methods of assessment. To substantiate this assertion, we developed and are administering a dermal exposure survey to 20 industries in the Baltimore, Maryland and southern Pennsylvania regions. One half of the industries surveyed will have fewer than 40 employees. The survey includes a plant walk-through and questionnaires administered to workers and the health and safety officer.

Details about chemicals, job tasks, activities, use of PPE, training, supervision, and available controls will be collected. We will present the study design, dermal questionnaire, and preliminary results from industries sampled during the summer of 2002. Through this research we will identify the extent of dermal exposure and the need for better recognition, evaluation and control of dermal hazards. We expect the preliminary results to show unrecognized dermal hazards across various industries and the ineffective use of control strategies including improper use of PPE. This study is intended to provide access and lay the groundwork for future investigations that will include quantitative exposure assessment, an evaluation of the effectiveness of controls, and ultimately, an intervention study to test strategies for minimizing workplace dermal exposure.

Occupational Environment and Skin Diseases in Pesticide Exposed Subjects in Some Tea Farms in Vietnam

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Aims
The study was carried out to evaluate the relationship between working environment and farmers' health, especially the occupational skin diseases of pesticide exposed subjects.

Method
The research work was based on questionnaires, organophosphate sampling in the air, clinical examination and paraclinic test. It was carried out in 369 subjects directly and 150 subjects indirectly exposed to pesticides by applying a cross-sectional study method.

Results
The obtained results showed that the most frequently used pesticides were organophosphates and carbamates (85-96.8%), the concentration of wofatox was 6-10 times higher than MAC. Spraymen had such symptoms as prurigo (58.26%), dizziness (24.39%), headache (44.44%), fatigue (36.58%), nausea (15.17%). The work-related disease such as melanosis was 8.94% and allergic contact dermatitis of direct group and the difference between rates of diseases was statistically significant ($p<0.001$) OR= 16.06, 95% CI=8.32-31.64).

Conclusions
The authors underlined that the organo-phosphorous pesticides and carbamates induced work-related diseases (irritant contact dermatitis, allergic contact dermatitis and occupational melanosis...). On that basis, education and training on the safe use of pesticides should be recommended.

Poster Session 2: "Health Effects and Hazard Identification"

2.1 **Dermal Exposure to Powdered Solids and Aqueous Solutions: Are the Risks Different?**, Annette L. Bunge and Eugene E. Ley, Colorado School of Mines, Golden, CO, USA

2.2 **A Mathematical Approach for Evaluating Dermal Exposure and Facilitating Assignment of Skin Notations**, Chen-Peng Chen, Mark F. Boeniger and Heinz W. Ahlers, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

2.3 **Use of Real-Time Breath Analysis and PBPK Modeling to Evaluate Dermal Absorption of Aqueous Toluene in Human Volunteers**, Karla D. Thrall, Karl K. Weitz and Angela D. Woodstock, Battelle Pacific Northwest Division, Richland, WA, USA

2.4 **Molecular Changes in Skin Following Acute Dermal Exposures to Irritating Chemicals**, James N. McDougal, Wright State University School of Medicine, Dayton, OH, USA (Corresponding Author)
Carol M. Garrett, Operational Toxicology (AFRL/HEST), Air Force Research Laboratory, Wright Patterson AFB, OH, USA
James V. Rogers, Operational Toxicology (AFRL/HEST), Air Force Research Laboratory, Wright Patterson AFB, OH, USA

2.5 **Dermal Absorption of Vapours: Comparison of In Vivo and In Vitro Data**,Kate Jones, Ian Dick, John Cocker and Martin Roff, Health Safety Laboratory, Sheffield, UK

2.6 **Factors Affecting Dermal Absorption of Vapours**, Kate Jones, John Cocker,Lisa Dodd, Isla Fraser* and Martin Roff, Health Safety Laboratory, Sheffield and *Health and Safety Executive, Liverpool, UK

2.7 **Active Ingredients in Sunscreens Act as Topical Penetration Enhancers for the Herbicide 2,4D**, Adam R. Pont, University of Nebraska, Lincoln, NE and Anna R. Charron and Rhonda M. Brand, Evanston Northwestern Hospital, Evanston, IL, USA

2.8 **Dry Trimellitic Anhydride (TMA) Powder Dermal Sensitization Induces Specific IgE and Airway Responses Following Challenge in Brown Norway Rats**, Xing-Dong Zhang, Jeff S. Fedan, Daniel M. Lewis and Paul D. Siegel, National Institute For Occupational Safety and Health, Morgantown, WV, USA

2.9 **Biologically-Based Environmental Exposure Levels (BEELs): The Case for 4,4'-Methylene Dianiline (MDA)**, Shane S. Que Hee, Department of Environmental Health Sciences and the UCLA Center for Occupational and Environmental Health, University of California at Los Angeles, Los Angeles, CA, USA

2.10 **One NIOSH Approach to Estimating Dermal Absorption**, H. Fred Frasch, PhD and Ana M. Barbero, National Institute for Occupational Safety and Health, Morgantown, WV, USA

2.11 **Development of New QSAR Approaches in Occupational Contact Dermatitis**, Adam Fedorowicz(1), Hamed Afshari(1,2), Lingyi Zheng(2), Harshinder Singh(1,2) and Eugene Demchuk(1,2), (1)National Institute for Occupational Safety and Health and (2)West Virginia University, Morgantown, WV, USA

2.12 **Determination of Caffeine and Its Metabolites in Human Skin Homogenate by High-Performance Liquid Chromatography**, Lun-Yi Zang, Jean I. DeHaven and Sidney C. Soderholm, National Institute for Occupational Safety and Health, Morgantown, WV, USA

2.13 **Percutaneous Absorption of Neat and Water Solutions of 2-Butoxyethanol in Man**, S.Kezic, N. Mohammadi, I. Jakasa, J. Kruse, A.C. Monster and M. Verberk, Coronel Institute of Occupational and Environmental Health, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Dermal Exposure To Powdered Solids And Aqueous Solutions: Are The Risks Different?

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Although many occupational dermal exposures are to powered solids, almost nothing is known about dermal absorption from these materials. In this study, we investigated absorption of pure powered chemicals (sieved to 38-65 um) into polydimethyl-siloxane (silicone rubber) membranes (200 - 350 um thick) meant to simulate human stratum corneum and compared these results to absorption from saturated aqueous solutions. Silicone rubber (SR) is essentially impermeable to water and has the advantage that surface oils or moisture are not present. Penetration of 4-cyanophenol (CP, Tm = 112C, MW = 119, logKow = 1.60) and methyl paraben (MP, Tm = 128oC, MW = 152, logKow = 1.96) through SR membranes was measured. Solutions and powders completely covered the membrane surface and the concentration in the receptor fluid was determined by HPLC. Penetration rates from the powders were almost the same as from the aqueous solutions. This is persuasive evidence that solid chemicals can dissolve into synthetic membranes and perhaps skin without the assistance of liquids. Studies of powdered MP and CP absorption into human skin are currently in progress and will be discussed. Significantly, chemical absorption from powders into protective clothing such as gloves may be the same as from liquid solutions of the same compound.

A Mathematical Approach for Evaluating Dermal Exposure and Facilitating Assignment of Skin Notations

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Dermal exposure to hazardous substances is of increasing concern for workers in various occupational environments. The National Institute for Occupational Safety and Health (NIOSH) currently has skin notations (SNs) as a part of the Recommended Exposure Limits (RELs) for 142 compounds and chemical groupings, serving as a mechanism to inform the workers of health risks from dermal exposure to these substances. In the present form the SNs only provide a qualitative indication of skin hazards. An explicit approach is needed that quantitatively characterizes dermal absorption potential of chemical and facilitates systematic assignment of the SN.

Here we present an evaluation scheme that can be used as a tool to assess the contribution of hazards to systemic toxicity via skin absorption when the empirical data are not readily available or are of questionable quality. In this scheme, a mathematical model is used to predict the skin permeation coefficient (Kp) of a chemical based on its octanol-water partitioning coefficient and molecular weight. The Kp is used to determine the dermal uptake of chemical from saturated aqueous solution (dermal dose) following a conservative default scenario in which the unprotected palmer skin on both hands (a surfacc area of 360 cm2) of a worker is continuously exposed for 8 hours. The dermal dose is compared to the dose absorbed and accumulated in the body via inhalation in 8 hours (inhalation dose), as estimated by multiplying the chemical's REL with an inhalation volume of 10 m3 and a default retention factor of 75%. A chemical is considered a dermal absorption hazard if the ratio of skin dose to inhalation dose (S-I ratio) is equal to or larger than one. The evaluation was performed for 137 REL compounds with SNs for which the parameters required for model input were properly identified.

The preliminary results show that 70 of the 137 evaluated compounds were considered by the scheme as a possible absorption hazard (a positive compound). The S-I ratio for 53 positive compounds (76%) was exceeded in 2 hours after the onset of exposure, indicating that the dermal uptake needed to reach the toxic levels of these compounds proceeded at a rate higher than that for the uptake by inhalation. To examine the applicability of the scheme and of underlying assumptions to chemicals of different toxicological and chemical properties, the negative compounds were reviewed for toxic effects reported for dermal exposure and analyzed for structural composition. The reviews established that for 28 negative compounds the skin absorption of chemical resulted in acute and chronic toxicity (including tumorigenic and reproductive effects), and for 9 compounds the absorption might result in marginal or less-than-marginal

toxicity. The primary adverse effects from dermal exposure to 20 compounds were combinations of skin irritation, sensitization and/or physical damage. The structural analysis shows that 48 negative compounds (approximately 72%) have aromatic or cyclic rings in the chemical structure. Those with bicyclic heptane derivatives, heterocyclc rings with nitrogen, oxygen and/or sulfur, and organophosphates were among the substances for which the scientific information and modeling results disagreed on the significance of dermal absorption to systemic toxicity. The same informational review and structural analysis are currently underway for the compounds considered as positive absorption hazards. Limitations, alternative scenarios, and potential application in SN evaluation of the current approach will be discussed.

Use of Real-Time Breath Analysis and PBPK Modeling to Evaluate Dermal Absorption of Aqueous Toluene in Human Volunteers

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Toluene is a ubiquitous chemical that is commonly used for its solvent properties in industry and manufacturing, and is a component of many paint products. Although human exposure to toluene is most likely to be through inhalation, toluene is also found in well and surface water. Therefore, an assessment of the dermal contribution to total toluene uptake is useful for understanding human exposures. To evaluate the significance of these exposures, the dermal absorption of toluene was assessed in human volunteers using a combination of real-time exhaled breath analysis and physiologically based pharmacokinetic (PBPK) modeling. Human volunteers wearing swimsuits were submerged in warm tap water to neck level in a stainless steel hydrotherapy tub containing an initial concentration of approximately 500 μg/L toluene. Volunteers were provided purified breathing air to eliminate inhalation exposures, and exhaled breath was continually analyzed before, during, and post exposure to track the absorption and subsequent elimination of the compound in real time. A PBPK model was used to estimate the dermal permeability coefficient (Kp) to describe each set of exhaled breath data from n=6 human volunteers. An average Kp value of 0.012 + 0.007 cm/hr was found to provide a good fit to all data sets. Volunteers also participated in a second study phase, in which the subject was allowed to breathe the room air during immersion, thus both dermal and inhalation exposures to toluene occurred. Exhaled breath analyses revealed that concurrent inhalation of volatilized toluene resulted in a transient increase in the peak exhaled breath level by 100 ppb, or an approximate 50% increase over breath levels observed in dermal only studies. For perspective, the total intake of toluene associated with oral consumption of 2 liters of water containing toluene at bath water concentrations were estimated to be more than 30 times greater than the dermal contribution due to bathing.

Molecular Changes in Skin Following Acute Dermal Exposures to Irritating Chemicals

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Many products and chemicals cause irritation when they contact the skin. Whole animal primary irritation testing (Draize test) has been around since 1944 with many modifications and variations. Because chemicals diffuse through the skin at different rates and have different irritant potencies, there is an exposure duration for most substances that would not cause irritation. Only minutes of contact could be safe for some substances but it might take hours or days for other substances to cause irritation. The general purpose of these studies is to characterize the biological cascade in the skin that results from acute chemical exposure. Ultimately our goal is to develop a biologically based model of irritation that can be used to predict safe exposure durations for a wide variety of compounds. We exposed rats, in vivo, to irritating chemicals for one hour and investigated the temporal changes in gene expression and protein levels. Traditional histopathology and immunohistochemistry were also used to compare response of the skin to the fuel and solvents. We found that the parameters in the irritant cascade that we investigated responded differently depending on the degree of irritancy of each chemical. Measurements of protein levels will refine our preliminary understanding of this acute irritant cascade.

Dermal Absorption of Vapours: Comparison of In Vivo and In Vitro Data

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Introduction

Although skin absorption of organic solvents in the liquid phase is well recognised there has been less data on absorption of solvent vapours through the skin. There have been some studies looking at dermal absorption of some solvents (either liquid or as vapours) in human volunteers (Brooke et al, 1998; Johanson and Boman, 1991; Corley et al, 1997, Kezic et al, 1997, Mraz and Nohova, 1992). However, in the UK at least, human volunteer studies are restricted to substances with health-based Occupational Exposure Limits. In addition, human volunteer studies require ethics approval for each study, are expensive and can only use a small number of volunteers.

The rise of in-vitro techniques for studying percutaneous penetration allows the study of chemicals that would be unethical to study in volunteers and offers the potential to use more 'individuals' (donors) allowing a better understanding of inter-individual variation. However, there are differences in response between in vivo and in vitro systems and these need to be studied before using in vitro techniques as a replacement for human volunteer studies. Although in vitro systems will never replicate the entire in vivo system, they do provide an opportunity to study specific skin related issues.

We have conducted a number of human volunteer studies looking at the dermal absorption of solvent vapours and have replicated these investigations using an in vitro percutaneous absorption cell (IVPAC).

Methods

The solvent vapours under study were 1-methoxy-2-propanol, 2-butoxyethanol, 2-butanone (MEK), and xylene.

In vivo studies

Exposures were performed at the Health and Safety Laboratory Controlled Atmosphere Facility, a purpose built room of approximately 8 m3 volume, as previously described (Brooke et al, 1998). Volunteers were exposed on 2 occasions – once as a 'whole body' exposure and once as a 'skin only' exposure. For the "skin only" exposure, the volunteers wore air-fed half-masks so that the inhalation route was excluded as a source of uptake. The body burden of each exposure was determined by biological monitoring and the body burden of the 'skin only' exposure was then expressed as a percentage of that of the 'whole body' exposure in order to determine the extent of dermal absorption. Volunteers acted as their own control.

Absorption of 1-methoxy-2-propanol, 2-butoxyethanol, 2-butanone and xylene was determined by post-exposure blood sampling, measuring 1-methoxy-2-propanol, 2-

butoxyacetic acid, 2-butanone and xylene respectively. Butoxyethanol was not measured as a marker itself as there has been some controversy over blood butoxyethanol measurements (Johanson and Boman, 1991; Corley et al, 1997).

In vitro studies

Dermatomed human skin samples (approx 700 micrometers thick) were mounted in IVPAC diffusion cells (Griffin et al, 2000) and maintained at 32 C in a heated manifold. The skin surface (donor chamber) was exposed to a constant flow of the vapour (20 L/min) in each diffusion cell, and the undersurface of the skin (receptor chamber) was exposed to a constant flow of a blood surrogate, the receptor fluid (10% w/v bovine serum albumin, 1.5 ml/hr). The receptor chamber contents were magnetically stirred. Vapour penetrating the skin was absorbed into the receptor fluid and eluted into cooled vials (on cardice) held in a fraction collector. Receptor fluid samples were collected at 30 minute intervals and analysed by GC-MS.

Results

Table 1 summarises the exposure conditions for all the studies.

Table 1. Concentration (ppm) and length (hours) of exposure in the various studies.

Solvent	In vivo	In vitro	In vitro/in vivo ratio
1-Methoxy-2-propanol			
100 ppm (4 h)	700 ppm (4h)	7	
2-Butanone	200 ppm (4h)	790 ppm (4h)	3.95
2-Butoxyethanol	50 ppm (2h)	500 ppm (4h)	20
m-Xylene	50 ppm (4h)	540 ppm (4h)	10.8

Table 2. Comparison of results from in vivo and in vitro studies.

Solvent	In vivo dermal contribution to body burden (%)	In vitro absorption rate (micrograms/cm²/hr)	In vitro permeability coefficient (cm/hr)
1-Methoxy-2-propanol	8.1	1.90	1.51
2-Butanone	3.7	0.66	0.58
2-Butoxyethanol	11.9	2.41	1.95
m-Xylene	1.7	0.13	0.11

Figure 1 compares in vivo and in vitro data. When the scales are adjusted to allow overlay, it can be seen that the in vivo and in vitro data are in broad agreement as to the extent of absorption of solvent vapours. As expected 2-butoxyethanol and methoxy-2-propanol are most readily absorbed through the skin although there is not the large discrepancy in absorption that might be expected from the predicted permeation coefficients (Kp) which range from 0.7 cm/hr (xylene) to 27.3 cm/hr for butoxyethanol.

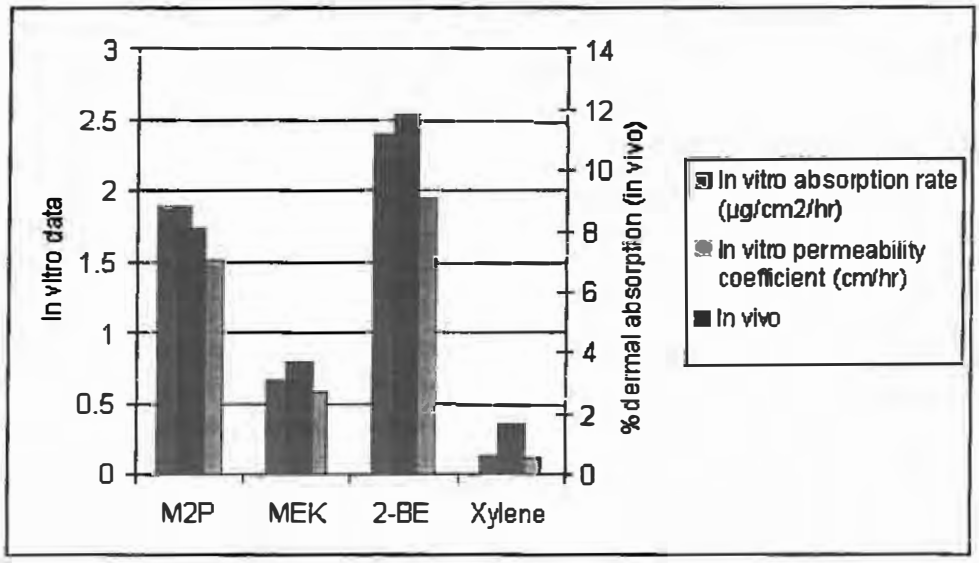

Figure 1. Comparison of in vivo and in vitro data.

Conclusions

The in vitro data compare well with the in vivo data in ranking the extent of dermal absorption of solvent vapours and to some extent in the relative magnitude of the absorption. The glycol ethers (methoxy-2-propanol and butoxyethanol) are, as expected, most readily absorbed both in vivo and in vitro although both predict butoxyethanol to have the greatest dermal absorption potential. This is in contrast to Dugard et al (1984) who reported that the in vitro absorption rate of methoxy-2-propanol was nearly 6x that of butoxyethanol (1.17 mg.cm-2.h-1 compared to 0.198 mg.cm-2.h-1) for absorption of the neat liquid solvents, although there was considerable variation in their results. This contradiction may indicate a difference in behaviour of solvents in the liquid and vapour phase.

Our studies have shown that in vitro absorption data may be useful in ranking solvents as to their dermal absorption potential and may allow estimates of potential skin absorption of chemicals that cannot ethically be studied in vivo, such as carcinogens and sensitisers. Further work is needed on developing relationships between an in vitro dermal absorption rate and an in vivo body burden.

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Factors Affecting Dermal Absorption of Vapours

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Introduction

We have previously reported (Brooke et al, 1998) that solvent vapours can be absorbed through the skin and that the extent varies markedly and depends on the chemical. For some chemicals, the extent of absorption is significant e.g. for 1-methoxy-2-propanol dermal absorption accounts for up to 14% of the total absorbed dose after 8h exposure at the Occupational Exposure Standard. Other studies have shown that increased temperature (Vanakoski et al, 1996) and increased humidity (Meuling et al, 1997) can increase dermal absorption and that these conditions can cause physiological changes in the skin barrier function (Schafer et al, 2002).

We have conducted a second study using 2-butoxyethanol to investigate the influence of temperature, humidity and clothing on the dermal absorption of vapours. As for the first study, the extent of dermal absorption was determined by biological monitoring to measure the resultant body burden of the chemical.

Methods

Four volunteers were exposed on nine occasions. For eight of these exposures they wore air-fed half-masks to supply clean air for the inhalation route. The 'baseline' conditions (one 'whole body' and one 'skin only' exposure) were 25oC, 40% relative humidity with volunteers wearing shorts and T-shirt. For each subsequent exposure, a single parameter was changed: humidity (60%, 65%), temperature (20oC, 30oC) or clothing (minimal, Tyvek overalls). Finally, a 'industrial scenario' was conducted where volunteers wore overalls over their shorts and T-shirts and environmental conditions reflected high temperature and high humidity (30oC, 60%), such as might be encountered in a tank-cleaning operation or similar.

Body burden in each of the exposures was determined by the measurement of butoxyacetic acid excreted in urine after exposure. 'Total' butoxyacetic acid was measured after acid hydrolysis of any conjugated butoxyacetic acid, followed by derivatisation (using pentafluorobenzyl bromide) and analysis by GC-MS.

Results

Results show that 'baseline' dermal absorption of 2-butoxyethanol vapour was, on average, 11% of the total absorbed dose. Higher temperature (30oC, mean 14%, $p=0.03$) and greater humidity (65% RH, mean 13%, $p=0.1$) increased dermal absorption. The wearing of whole-body overalls did not attenuate absorption (mean 10%). By combining several factors together in the 'industrial scenario', dermal absorption of vapours was significantly increased ($p<0.005$) with a mean of 39% of the total absorbed dose.

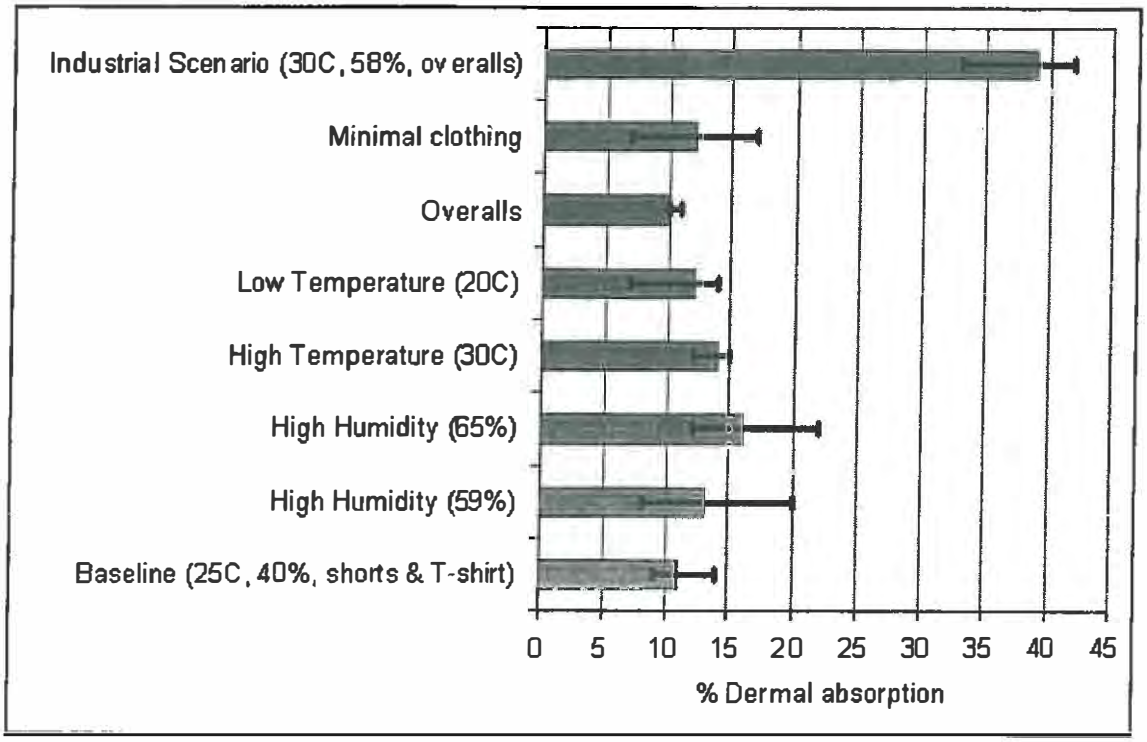

Figure 1. Mean and ranges (N=4) for the % body burden attritubable to dermal absorption.

Conclusions

The work has shown that dermal absorption of vapours can be significant and that environmental conditions can affect the absorption. This is likely to be due to increased surface blood flow (as purported by Vanakoski et al, 1996), increased skn hydration (as observed by Schafer et al, 2002) and perspiration (aiding dissolution of 2-butoxyethanol, forming a solution on the surface of the skin) and opening of skin pores under conditions of increased temperature and/or humidity.

Some types of protective clothing may not be suitable to reduce absorption and may encourage a high humidity microclimate between the skin and the overall exacerbating dermal absorption. The possibility of significant absorption of vapours through the skin should be considered, particularly for workers in high vapour concentration conditions where control of exposure relies on respiratory protection.

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Active Ingredients in Sunscreens Act as Topical Penetration Enhancers for the Herbicide 2,4D

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Agricultural workers are encouraged to use sunscreen to decrease the risk of UV related skin cancer. Our previous studies have shown certain commercial sunscreens to be penetration enhancers. The focus of this project is to determine whether active ingredients in sunscreen formulations (i.e. the UV absorbing components and/or insecticides for the sunscreen/bug repellant combinations) also act as dermal penetration enhancers for herbicides.

Freshly excised female hairless mouse skin was placed in an in vitro Bronaugh style flow through diffusion chamber with Hank's Balanced Saline Solution, supplemented with 4 % bovine serum albumin, used as the receptor fluid. The epidermal side of the skin was pretreated for 30 minutes with one of 7 active sunscreen ingredients (octyl methoxycinnimate, octocrylene, oxybenzone, homosalate, octyl salicylate, padimate, or DEET). A 100-microliter aliquot of 2,4-D amine spiked with radiolabeled 2,4-D was then placed on the epidermal side of each skin for 24 hours. As the 2,4-D diffused through the skin into the receptor compartment, fractions were collected at 90-minute intervals and later counted via liquid scintillation. The flux of 2,4-D through the skin for each treatment was calculated to determine the cumulative percent of 2,4-D across the skin, and these values compared by ANOVA followed by a Dunnett's Multiple Comparison Test. Values are reported as mean ± s.e.m.

The total percentage of 2,4-D penetrating through the skin in 24 hours ranged from 54.4 + 5.2 for no sunscreen control to 83.3 + 2.4 for DEET. Of the 7 active ingredients, all but octocrylene led to a significant increase in total 2,4-D penetration as compared to the control ($p < .05$). Thus, the active ingredients of sunscreen formulations enhance dermal penetration of the moderately lipophilic herbicide 2,4-D.

Further studies are currently investigating whether combinations of active ingredients present in commercial sunscreen formulations exhibit synergistic or antagonistic penetration effects, with an ultimate goal being to find a combination that minimizes dermal penetration of agrochemicals.

Dry Trimellitic Anhydride (TMA) Powder Dermal Sensitization Induces Specific IgE and Airway Responses Following Challenge in Brown Norway Rats

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TMA is a low-molecular-weight chemical that can induce production of specific IgE and occupational asthma in sensitized individuals. The respiratory tract is considered to be the major exposure route leading to immunological sensitization, but dermal exposure also has the potential to induce TMA-sensitization. Our previous work demonstrated a dose-dependent production of specific IgE and airway response after TMA aerosol challenge in Brown Norway (BN) rats sensitized by overnight TMA (occluded) dermal exposure.

IgE production and airway responses to inhaled TMA after repeated, short-term (5 hr) dermal exposures to dry TMA powder without occlusion were investigated in two groups of rats (n=8/group, dose: 40 mg or 4 mg) in the present study. Dermal exposures were performed on days 0, 7, 14 and 21. Sera were collected on days 0, 7, 14, 21, 28, 35 and positive IgE was found after 14 days. Rats were challenged by a 10 min, 40 mg/m3 TMA (nose-only) aerosol and respiratory physiology monitored on day 35 immediately following exposure in unrestrained rats using a whole body plethysmography system.

Compared to non-sensitized rats, the two groups of sensitized BN rats displayed distinct early (EAR) and late airway responses (LAR), as noted by an increase in enhanced pause (Penh, an index of airway resistance). The EAR was noted immediately following the challenge and lasted approximately 0.5 to 1 hour. The LAR began 3 to 4 hours post-challenge durations ranging from 4 to 8 hours.

This work demonstrates that dermal exposure to TMA powder can lead to immunological sensitization and obstructive airway responses on subsequent exposure to TMA aerosol.

Biologically-Based Environmental Exposure Levels (BEELs): The Case for 4,4'-Methylene Dianiline (MDA)

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The lack of a scientific body to put forth recommendations for chemicals whose major route of exposure was not by inhalation led to the formation in 2000 of the BEEL Committee, comprised of members of the Biological Monitoring and WEELs Committees of the American Industrial Hygiene Association. The first chemical chosen for study was MDA. It is a liver/thyroid carcinogen in rats and mice, and also causes liver tumors in mice through the skin. Epidemiology and exposure assessment studies have shown that workplace exposure to MDA is predominantly though the skin except for unprotected workers close to hot processes, and that biological monitoring must be done to demonstrate the real extent of exposure from all routes. Exposed workers and the public exposed by accident are known to experience jaundice and liver damage. Based on a liver/thyroid cancer risk of 4 x 10-4 that was shown to be equivalent to the current OSHA air PEL of 0.08 mg/m3, the calculated post-shift critical 24-h urine concentration was 72 microgram/L or 72 microgram/g creatinine. The equivalent risk for the hands and lower forearms led to 0.45 microgram cm-2 as the allowed glove permeation or skin coverage. The ingested dose equivalent was 13 microgram/kg. The ATSDR Intermediate Oral Minimal Risk Level (MRL)for liver damage was shown to be maximally equivalent to a cancer risk of 4 x 10-3 over 12 weeks of exposure, equivalent to the current air TLV-TWA of 0.8 mg m-3. The ATSDR Acute Oral MRL (liver damage)was maximally equivalent to a cancer risk of 6 x 10-3. The poster will show the details of the modus vivendi of the BEEL Committee, and the calculations and assumptions used to derive these guidelines for MDA.

One NIOSH Approach to Estimating Dermal Absorption

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Skin diseases are recognized as the second leading occupational disease in the US. These diseases are local effects due to dermal exposures to chemicals, and there is an uncounted toll of systemic effects as well. In considering ways in which to improve the NIOSH recommendations for identifying and controlling diseases due to dermal exposures, NIOSH researchers have focused on the utility of predictive equations for percutaneous absorption to help identify hazards resulting in systemic effects. Currently, the Robinson Equation is widely used for this purpose, but it has many short-comings, including its basis in uncertain data and its inability to predict important time-dependent variations in absorption.

In our approach, the experimental skin permeation data available in the literature were critically reviewed and some important flaws were reported. The main focus of the work is the development of a computer-based model of time-dependent skin absorption using realistic depictions of stratum corneum morphology tied to a series of experimental studies to obtain detailed information on the pathways chemicals take through the stratum corneum and to check the model's predictions. This project is part of the interdivisional NORA Dermal Exposure Research Program.

A recent publication has identified flaws in permeability data reported in the literature (Frasch and Landsittel, 2002). A second publication (Frasch, 2002) describes the modeling approach and demonstrates its advantages over other current approaches. As this work is refined and validated, it is anticipated that this model will replace the Robinson equation in the NIOSH approach to identifying chemicals that are hazardous by the dermal route, and they will allow extension to a variety of situations in which the non-time dependent equations will give misleading information.

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Development of New QSAR Approaches in Occupational Contact Dermatitis

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The Bureau of Labor Statistics estimates that occupational skin diseases constitute the second largest group of occupational injuries in the U.S. [1]. Among them, occupational contact dermatitis (OCD) is the most common cause of work-related skin illness comprising up to 95% of registered cases. Allergic contact dermatitis (ACD) may lead to severe recurrent forms of OCD because of long-lasting memory of the immune system. ACD usually develops as a result of repetitive skin exposures to a sensitizing chemical agent. Usually at least a single excessive exposure is essential in the development of the immune response.

A variety of experimental tests have been suggested to assess the skin sensitization potential of a chemical [2]. Providing information that leads to the development of recommended skin exposure limits that would prevent workers from sensitizing overexposures may be an important factor in predictive testing. Unfortunately, many experimental protocols result in a dichotomous conclusion, more appropriate for denial/acceptance decision-making in chemical manufacturing rather than for protection of workers occupationally involved with sensitizing chemical agents. Essentially only one of them, the murine Local Lymph Node Assay (LLNA), has the capacity to provide a reliable continuous scale in the quantitative assessment of skin sensitization.

A combination of methods in statistics and computational chemistry, commonly referred to as Quantitative Structure-Activity Relationship (QSAR) modeling, complements the experimental approach. A method of QSAR is based on the examination of measured and calculated physical-chemical properties, called molecular descriptors, of many chemical compounds with known biological activity, in this work the sensitization potential, and then relating a few of the informative descriptors to the target bioactivity. The structure-activity relationships constructed this way provide a means of investigating and predicting the toxicological effect of a chemical with yet unknown sensitization potential.

We rely on LLNA data to quantify the skin sensitization potential [3]. At present the LLNA data are (1) outnumbered by the long history of guinea pig assays, and (2) often reported as a dichotomous scale congruous to the guinea pig data. Therefore, the work has been started using the dichotomous LLNA data to identify molecular descriptors that may be effective in the continuous-scale LLNA QSAR. The work began from building a

database of chemical names, structures, properties and bioactivities, along with design of appropriate software. Our immediate goal is to identify a pool of potentially informative molecular descriptors and chemical classes that are most appropriate for QSAR modeling to predict LLNA results.

In the present work a QSAR based on a generalized linear model of logistic regression is proposed. The logistic regression permits construction of standard QSAR equations, in which the activity data are represented only in terms of activity (1) or non-activity (0) values. In order to evaluate molecular properties, which are significantly associated with LLNA data on skin sensitization, 1203 molecular descriptors were calculated and tested for their significance in predicting the skin sensitization potential. Only a small number of molecular descriptors were found to be statistically significantly associated with skin sensitization.

At this stage we were able to define a statistically significant QSAR on 54 selected compounds, which includes three molecular descriptors. These specialized descriptors from computational chemistry are (1) the number of double bonds, nDB, (2) mass-weighted Geary graph autocorrelation coefficient of the sixth lag, GATS6m, and (3) the spatial first component accessibility directional unweighted holistic invariant molecular descriptor index, E1u [4]. A QSAR model built on only these three descriptors using logistic regression is successful as shown by the chi-square goodness of fit test, indicating the suitability of these descriptors to predict the sensitization potential. We are in the process of refining these results by: (1) the investigation of the probability of correct classification of a compound using the fitted logistic regression based on these three descriptors and (2) the study of interrelationships between various descriptors and their effect on the fitting of the logistic regression.

These results suggest that a comprehensive QSAR model of ACD may be built by using only few appropriate parameters, although the relevance of identified descriptors to the continuous-scale ACD QSAR has yet to be shown. Further work will be focused on populating the QSAR database with continuous-scale ACD data and molecular descriptors that are obtained in the present study. New predictive QSARs are expected to be useful in screening large sets of compounds for their potential impact on skin sensitization, and thus may suggest a useful order of priorities in experimental testing.

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Determination of Caffeine and Its Metabolites in Human Skin Homogenate by High-Performance Liquid Chromatography

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A method has been developed for the separation and quantification of caffeine and its metabolites in human skin homogenate. The method development was based on high-performance liquid chromatography (HPLC) equipped with UV-visible diode array detector and a Symmetry Shield RP8 column (3 mm, 2.1 mm x 150 mm). Beta-hydroxyethltheophylline (ISTD) was used as the internal standard for quantitation. The analytes in human skin homogenate were extracted with a Waters Oasis HLB solid phase extraction plate or by liquid-liquid extraction using methanol-methylene chloride (1:2, v/v). The mobile phase consisted of 20 mM ammonium acetate and acetonitrile at the gradient ratios from 100:0 for 5.5 min to 90:10 for 10 min at a constant flow rate of 0.3 mL/min. The compounds were monitored at 275 nm and a reference wavelength 360 nm with 100 nm widths. The elution order of these species was found to be 3-methyluric acid, 7-methyluric acid, 1-methyluric acid, 37-methyluric acid, 17-dimethyluric acid, 13-dimethyluric acid, 7-methylxanthine, 3-methylxanthine, 1-methylxanthine, 37-dimethylxanthine, 17-dimethylxanthine, 13-dimethylxanthine, ISTD, and 137-methylxanthine. The limits of quantification (LOQ) for these compounds were 1.0 - 2.5 ng per total injection. Reproducibility of the sample handling and HPLC assay had a relative standard deviation of ±10%. The average recoveries were better than 90% for liquid-liquid extraction and 82% for solid phase extraction.

Percutaneous Absorption of Neat and Water Solutions of 2-Butoxyethanol in Man

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Aims
To determine percutaneous absorption of 2-butoxyethanol (BE) dermally applied as a neat liquid and in 50 and 90 % solutions.

Methods
Six male volunteers were dermally exposed for 4 hr on the volar forearm over an area of 40 cm^2. An inhalation exposure with a known input rate served as a reference. Dermal absorption was assessed for each individual from the concentration courses of BE in blood and butoxyacetic acid in urine, measured after both inhalation and dermal exposure. The Medical Ethics Committee of the Academic Medical Centre, University of Amsterdam approved the experimental protocol. Each subject signed an informed consent form.

Results
The amount of BE that was absorbed after skin exposure to 50 and 90 % BE was one order of magnitude higher than that of neat BE. The average absorption rate of 50 % BE amounted to 0.8 $mg/cm^2/hr$.
Inter-individual differences in dermal absorption rates of 50 % BE were moderate, the coefficient of variation (CV) amounted to 30 %. This was significantly lower than the variation previously reported for neat BE (Johanson et al 1988).

Conclusions
Dermal uptake of BE increases in the presence of water. This has already been reported in vivo in guinea pigs (Johanson et al 1988) and in vitro studies with human skin, however this is the first time that it has been shown also in humans in vivo. These findings should therefore be considered in the health risk assessment of occupational dermal exposure to BE where water-based products containing glycol ethers are used. Comparing the dermal uptake with the respiratory uptake at the occupational exposure limit (OEL, currently 100 mg/m^3), BE showed substantial skin absorption. Assuming 60 min skin contact of both hands (skin area of about 1000 cm^2) with 50 % BE, dermal

uptake would equal the pulmonary uptake of the 8-hr occupational exposure. Therefore, in monitoring exposure at the work place, biological monitoring (BM) is to be preferred over environmental monitoring. For the purpose of BM, both BE in blood or BAA in urine can be used.

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Poster Session 3: "Measuring and Predicting Exposures"

3.1 **Electrospray Ionization Tandem Mass Spectrometry (ESI-MS/MS) Analysis of 1-Bromopropane Mercapturic Acid Metabolites in Urine**, Kenneth L. Cheever, Kate L. Marlow, Derek Stinson, Alex W. Teass and D. Gayle DeBord, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

3.2 **Development of a Procedure for the Quantification of the Biomarker (2-Methoxyethoxy)Acetic Acid in Human Urine**, Clayton B'Hymer, Mary Ann Butler and Kenneth L. Cheever, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

3.3 **Worker Exposure Scenarios and Modelling for Biocidal Products**, Joop J. van Hemmen, TNO Chemistry, Delft, The Netherlands

3.4 **Risk Assessment of Dermal Exposure to Industrial Chemicals**, Joop J. van Hemmen, TNO Chemistry, Delft, The Netherlands

3.5 **Improved Method to Measure Alkoxyacetic Acid in Urine: A Solid Phase Extraction -Gas Chromatography - Mass Spectrometry Method for 2-Butoxyacetic Acid**, Kenneth K. Brown, Kenneth L. Cheever, Mary Ann Butler, Peter B. Shaw and Jeffery L. McLaurin, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

3.6 **Measurement of Dermal Exposure to Epoxy Components**, Roger Lindahl, Anders Östin, Leif Wiklund, Kåre Eriksson* and Jan-Olof Levin, National Institute for Working Life, SE-907 13 Umeå, Sweden and *University Hospital of Northern Sweden, Umeå, Sweden

3.7 **Assessment of Skin Exposure to Permanent Hair Dyes**, Marie-Louise Lind, Birgitta Meding, Jan Sollenberg, Jouni Surakka and Anders Boman*, Occupational Dermatology, National Institute for Working Life, Stockholm, Sweden and *Occupational and Environmental Dermatology, Department of Medicine, Karolinska Institutet and Stockholm County Council, Stockholm, Sweden

3.8 **Sampling Efficiency of Cotton Gloves When Used for Dermal Exposure Measurements**, Martin Roff and Lisa Griffiths, Health and Safety Laboratory, Sheffield, UK

3.9 **Mathematical Model for the Disposition of Volatile Compounds on Skin Following Topical Application**, Penpan Saiyasombati and Gerald B. Kasting, University of Cincinnati, Cincinnati, OH, USA

3.10 **Qualitative and Quantitative Assessment of Isocyanate Contamination of Workplace Surfaces**, Roy J. Rando, ScD, Rachele A. Gibson, MSPH, Zachariah Fridge, Cheol Kwon and Jody Kliebert, Tulane University School of Public Health, New Orleans, LA, USA

3.11 **Determination of Keratin Protein in a Tape-Stripped Skin Sample from Jet Fuel Exposed Skin: Standardization of the Tape-Stripping Method**, Yi-Chun Evelyn Chao and Leena A. Nylander-French, University of North Carolina, Department of Environmental Sciences and Engineering, School of Public Health, Chapel Hill, NC, USA

3.12 **Dermal Exposure Model for Jet Fuel Exposure Using Tape-Stripping Method**, Yi-Chun Evelyn Chao and Leena A. Nylander-French, University of North Carolina, Department of Environmental Sciences and Engineering, School of Public Health, Chapel Hill, NC, USA

3.13 **Estimating Dermal Exposure to Hazardous Chemicals in Water and Soil**, Michael Dellarco, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA

3.14 **Dermal Exposures to Particles from Smooth and Carpeted Surfaces**,Charles Rodes, Jonathan Thornburg and Peter Ashley* , Research Triangle Institute, Research Triangle Park, NC and *US Department of Housing and Urban Development (HUD), Washington, DC, USA

3.15 **Development of an Analytical Method to Quantify Dermal Exposure to Hexamethylene Diisocyanate**, Chris B. Trent, Leena A. Nylander-French, Louise M. Ball, Avram Gold and Hasan Koc, The University of North Carolina at Chapel Hill, Department of Environmental Sciences and Engineering, Chapel Hill, NC, USA

3.16 **Wipe Sampling to Assess Pesticide Exposures on Skin: Preliminary Method Evaluation**, Mark F. Boeniger, Marcia Nishioka*, Tania Carreon and Wayne Sanderson, National Institute for Occupational Safety and Health, Cincinnati, OH and *Battelle, Columbus, OH. USA

3.17 **Comparison of Three Methods for Determining Removal of Stratum Corneum Using Adhesive Tape Strips**, Mark F. Boeniger, National Institute for Occupational Safety and Health, Cincinnati, OH and Leena Nylander-French, University of North Carolina, Department of Environmental Health Sciences and Engineering, School of Public Health, Chapel Hill, NC, USA

Electrospray Ionization Tandem Mass Spectrometry (ESI-MS/MS) Analysis Of 1-Bromopropane Mercapturic Acid Metabolites In Urine

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1-Bromopropane (1-BP, CAS 106-95-5), used as an alternative solvent to chlorofluorocarbons and 1,1,1-trichloroethane, has been reported to cause reproductive and neurotoxicity in male rats. The related 2-bromopropane has been shown to cause similar toxicity in rats as well as amenorrhea, oligozoospermia, and anemia induction in workers. Although the mechanism of action of 1-BP has yet to be explained, it is thought that metabolic activation to reactive intermediates may be important. Metabolism of 1-BP is complex and is reported to occur by pathways which include debromination, oxidation by CYP2E1 and glutathione S-conjugation. 3-Bromopropionic acid and n-propanol are reported urinary metabolites of 1-BP whereas the glutathione conjugate, S-n-propyl-glutathione is further cleaved to S-n-propyl-L-cysteine and further to mercapturic acids N-acetyl-S-(n-propyl)-L-cysteine (M1), N-acetyl-S-(n-propyl)-L-cysteine-S-oxide (M2), N-acetyl-S-(2-carboxyethyl)-L-cysteine (M3), and N-acetyl-S-(3-hydroxy-n-propyl)-L-cysteine (M4). A potential biomonitoring method was developed to measure urinary levels of (M1), (M2), (M3) and (M4). The mercapturic acid standards as well as the stable isotope-labeled analog of (M1) internal standard were synthesized using the general procedure of van Bladern et al. (1980). A BenchMate® II robotic workstation was used to automate sample preparation. Bond Elute® 500 mg C18 SPE columns were conditioned with acetone, MeOH (5% HCl) and 5% MeOH in H2O pH 3. Samples were mixed with internal standard and loaded onto columns. A fraction containing >90% of 1-BP metabolites was collected in 3-mL acetone, reduced to dryness under N2 and dissolved in 1 mL MeOH for HPLC-MS/MS (ThermoQuest Finnegan LCQ tandem mass spectrometer) analysis on a 150 X 2 mm Phenomenex Aqua 3ìm C18 300A column. Chromatographic standards were chromatographed using a 10-min linear gradient H2O 1% acetic acid to MeOH 1% acetic acid at 300 microliters/min to elute the compounds of interest within 10 min. During the chromatographic run the mass spectrometer was operated in multiple segments using ESI-MS/MS, in the positive ion mode for detection of protonated (M1), (M2), (M3) and (M4) and Selected Reaction Monitoring of major transition products. Urine samples fortified with a mixture of standards were mixed with 10 micrograms/mL of internal standard and processed for evaluation of recovery, limits of detection (LOD) and limits of quantitation (LOQ). Calibration of (M1), (M2), (M3) and (M4) was linear from 30 - 10000 ng/mL (r2>0.99). The sample preparation and analysis appears to offer significant advantages over typical preconcentration and

derivatization procedures that would be required for GC-MS analysis of these compounds. Thus, 1-BP internal exposure levels for various exposure situations can be rapidly determined by analysis of these metabolites in a single assay using a selective automated sample preparation system.

Development Of A Procedure For The Quantification Of The Biomarker (2-Methoxyethoxy)Acetic Acid In Human Urine

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A simple and effective procedure was developed for the detection and quantification of (2-methoxyethoxy)acetic acid (MEAA), which is a metabolite and biomarker for exposure to 2-(2-methoxyethoxy)ethanol. Human dermal exposure to 2-(2-methoxyethoxy)ethanol is of concern because of the general toxicity of glycol ethers and this compound, specifically, is used as an anti-icing additive to the military jet fuel, JP-8. Possible dermal absorption by aircraft fuel cell maintenance personnel is of concern; therefore, a test procedure for MEAA in urine samples was devised. The urine sample preparation consisted of ethyl acetate extraction, followed by esterification of the MEAA to produce the ethyl ester. Extraction of the ethyl ester with methylene chloride and concentration of sample solution to a one milliliter volume was done to produce the final solution for analysis. Measurement was by a gas chromatograph equipped with a mass selective detector (MSD) using a 50-m X 0.20-mm (id) HP-1 capillary column and a temperature program of 50° to 230° C. Deuterated (2-butoxy)acetic acid was used as a procedural internal standard for this analysis procedure. Ion m/z 59 was monitored for the ester of MEAA and ion m/z 66 was monitored for the internal standard. A recovery study of spiked urine demonstrated good accuracy and precision; recovery varied between 95-103% for 2 to 20 micrograms/ml MEAA spiked urine samples. The limit of detection (LOD) was determined to be approximately 0.1 micrograms/ml for this procedure.

Worker Exposure Scenarios and Modelling for Biocidal Products

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Under current European and national legislation in Europe, biocidal products must be registered based on a risk assessment for humans, animals and the environment. Especially human exposure assessment shows many knowledge gaps, which make it hard to properly assess health risks for many biocidal application scenarios. An EU-funded project is currently tackling this issue and guidance is developed to deal with the problem in an appropriate fashion.

Introduction

The Biocidal Product Directive 98/8/EC requires registration of biocidal products on the basis of a risk assessment for their uses. The Directive is currently being implemented in member state law, and initial studies have been carried out to investigate the approaches as laid down in the various regulations. There are 23 different biocidal product types, in four major groups:

- disinfectants and general biocidal products;
- preservatives;
- pest control products;
- other biocidal products.

A major shortcoming in our present knowledge is the assessment of human exposure for biocides. This was also shown in the pilot programme, indicated above. To fill this knowledge gap, a project proposal by Institutes/organisations from 6 European member states, together with representatives from CEFIC, the producing and formulating industry in Europe, was accepted by DG Environment (B4-3040/2000/291079/MAR/E2). The project is to deliver its final report mid 2002.

The aims of this project are:

- to develop relevant exposure scenarios of humans to biocidal products;
- to develop operational predictive model(s) and guidance on how to use these for the purpose of registration of the various biocidal active substances in the many different use and exposure scenarios identified.

Results

The project focuses on exposures to workers and consumers. In this presentation only results with respect to worker exposure will be discussed. To assess exposure to biocidal products for risk assessment purposes, one needs to know the use pattern of the product:

- the product (physical state, package form, etc.) and its purpose;
- where, how and by whom it is used;
- expected control measures;
- tasks, frequencies and durations
- for mixing/loading
- for application

- for post-application activities (secondary exposure);
- who else may be exposed (bystanders).

Occupational exposure data have been requested from industry (sectors), governmental agencies, and academia from North America and Europe. All these publications have been quality-assessed based on pre-developed criteria, regarding aims, documentation and analytical-chemical quality aspects. From the study reports that were considered adequate, data were extracted and compiled in a series of databases.

For use of the databases two different approaches are taken. These are both based on the assumption that for most biocidal uses (applications), the exposure is task-based and not dependent on specific chemical properties of the biocide. This means that extrapolation from one study to another is possible when the exposure data have a suitable format and the exposure scenario (series of tasks, preferably one task) is similar.

First approach
For some tasks the database provides an adequate series of study results, meaning that for that task a predictive exposure model is developed.
A matrix was developed with two axes: one for width of distribution and one for central tendency of distribution.

All available study results were entered in the matrix at the right cell(s). Currently these cells are being filled with additional (new) exposure data.

The matrix has four typical central tendency values (GM), varying from 4 mg/min (low), 20 mg/min (medium), to 100 mg/min (high) and 500 mg/min (top). The other axis involves the width of the distribution and its GSD varies from 2.45 (narrow), via 3.36 (intermediate) to 6.04 (wide), as shown in the table. From this description it is clear that log-normal distributions have been assumed for these exposures, and the typical cell values have been chosen to accommodate the current experimental study results.

The databases are described with respect to the involved tasks and have been evaluated for relevant levels of exposure using 75-percentile values for typical exposure levels and 95-percentiles for 'reasonable worst case exposures'. These values are used for chronic health effects, whereas the 95-percentiles are proposed for use in case of acute health effects. 95-Percentiles may be used to ascertain possible levels of exposure in case of foreseeable misuse.

If the task under consideration is not available in the matrix then the exposure assessor should present arguments for specific choices for an exposure cell in the matrix. If there is some doubt, a higher width and higher typical value should be chosen. If no arguments at all can be presented for specific choices, the assessor is to choose for the cell with the largest width and highest typical value. This forces industry (registrants) to produce data for that specific task or set of tasks (use scenario).

Second approach
Bayesian statistics are used to develop an exposure assessment for tasks that have no specific exposure model, but do have assessable (dis)similarities with all the other sets of data in the matrix. In this approach, called BEAT (Bayesian Exposure Assessment Toolkit), all databases (for the time being only for body exposure) have been computerised and are transformed into distributions with discrete GMs and GSDs.

For a new task (or scenario) that can be described in terms of similarity or dissimilarity a set of questions must be answered and entered into the model. Using Baye's theorem, the (dis)similarities are calculated for all the databases in the model, leading to a new distribution which is then fitted to the cells of the above-mentioned matrix, since this is used to model the output in terms of maximum likelihood that the distribution fits into the various cells.

The so-called rule base for assessing the degree of similarity between tasks (scenarios) determines of course the output from the model. The rule base is determined on the basis of expert knowledge from field experience. Its validity is checked internally, by taking a study out and entering it again using the rule base. External validity can be determined using a new task (scenario) and assessing it on the basis of the rule base and concomitant comparison with actual field data to be collected.

In principle there is no problem to add a rule base for inhalation exposure data and hand exposure data. The databases for these exposures are already in the computerised approach.

There are currently hardly any data for post-application exposure. Some 'reference scenarios' have been developed that might help in estimating the most relevant exposures. These scenarios can only be handled for the exposure viewpoint with conservative assumptions and will thus require further exposure studies which will then help to obtain more realistic assumptions and possibly suitable databases.

Discussion and conclusion
The Bayesian approach for modelling, which combines objective and subjective data, is being considered and will be subject of validation exercises.

Exposure scenarios ("patterns of use") are described for all 23 biocidal product types.

Guidance is written -with many worked out examples- to enable authorities and registrants to do exposure assessments in a harmonised way, throughout European member states, with quite a bit of specific expertise still required for use.

A draft report is prepared and discussed at EU level (Biocide Technical Meeting in May 2002). Based on these discussions, the document will be finished mid 2002. Development of the BEAT model will continue for quite some time afterwards. The current idea is to also include the exposure data from other European exposure databases under development, such as RISKOFDERM and EUROPOEM.

The project report is considered a 'living document' by the project team, underlining the need to update it and adapt it in view of further developments in experimental studies and scientific approaches for exposure modelling.

Partners in the project
1. TNO Chemistry, Zeist, the Netherlands (project co-ordination)
2. Finnish Institute of Occupational Health, KRIOH, Kuopio, Finland
3. Health and Safety Executive / Laboratories, Bootle/Sheffield, UK
4. Institute of Occupational Medicine, Edinburgh, UK
5. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany
6. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven, the Netherlands
7. CEFIC representatives from BAYER, Germany and Rohm & Haas, France

Risk Assessment of Dermal Exposure to Industrial Chemicals

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Dermal exposure to industrial chemicals during work is of major concern in the risk assessment of chemicals. In the current procedures for European legislation, an approach is taken for which experimental data on dermal exposure in workplaces are lacking.

A large project, with four interrelated work parts, was granted by the European Commission (DG Research) in order to overcome large parts of these problems. The four-year project is now half-way and preliminary results are described.

Introduction

In a project funded by the European Commission (RISKOFDERM, QLKA4-CT-1999-01107), scientists from 15 Institutes from 10 European countries work together with the following major aims:
- Develop a validated predictive model for estimating dermal exposure for use in generic risk assessment for single chemicals.
- Develop a practical dermal exposure risk assessment and management toolkit for use by small and medium-sized enterprises (SMEs) and others, in actual workplace situations.

Research goals

To achieve the above-mentioned aims, a research programme comprising four interrelated work parts was formulated:
1) Qualitative survey in European workplaces to obtain an overview of tasks, processes and determinants relevant for dermal exposure.
2) Quantitative survey to obtain detailed data on dermal exposure and determinants in the most relevant tasks and processes.
3) Predictive dermal exposure model (set) using all relevant variables.
4) Risk assessment and management toolkit (on CD-ROM) from data on hazard, dermal absorption, dermal exposure and effectiveness of control measures for use in workplaces.

Results and discussion

For work part 1, it is assumed that dermal exposure, in the right format dimensions, can be extrapolated from one compound to another when it is task-based. This may not hold for every task, so expert knowledge is required to check the assumption for the task under consideration. To obtain these 'tasks', Dermal Exposure Operation (DEO) units were defined, with different scenarios per DEO unit. The scenarios that must be defined should be measurable, observable, relevant for exposure modelling, and universal.

Since hygienists in different countries are making observations with respect to dermal exposure and exposure determinants, it was essential to develop an extensive "Questionnaire for on-site surveys", as well as a detailed "Instruction manual". Furthermore, the observers needed to be trained in order to get comparable results. Observations are made for ten different scenarios taken in such a way that all DEO units are covered. Pilot studies have been carried out and were reported and

discussed/evaluated in order to make appropriate changes for the main studies. On the basis of the evaluation, the questionnaire was adapted to some extent for work part 1, but extensively for use to collect data for work part 2. The questionnaire contains many questions which cover possible exposures as relevant for work part 3 (see later).The main studies have been carried out. The results have to be reported mid 2002.

In work part 2, the state-of-the-art methodology for measuring external dermal exposure has been discussed and choices have been made for the selected scenarios. Each Institute has selected three scenarios in such a way that all DEO units are covered. The methodology varies with the studied scenario. Also in this work part, pilot studies have been carried out, reported and discussed/evaluated with respect to required changes for the main studies. Currently, the main studies are being carried out or are already finished; the results have to be reported late 2002.

Table: DEO units and Scenarios (with compound) that are being studied in work part 2
1 Handling of objects
- Filling (DEGBE)
- Collecting (colophony)
- Maintenance (cyclophosphamide)
- Loading (DEGBE)
- Filling (metal paint)
- Mixing/diluting (cyclophosphamide/metal)
2 Manual dispersion of substance
- Wiping (metal)
3 Dispersion of substance with hand-held tool
- Pouring (cyclophosphamide)
- Spreading with comb (1methoxy-propanol)
- Rolling (styrene)
- Brushing (DEGBE)
4 Spray dispersion of substance
- Spraying (TGIC powder/metal/organometal)
5 Immersion
- Immersing (chromium/organometal)
6 Mechanical treatment (of solid ob-jects)
- Machining (nickel)
- Grinding (chromium)
- Sawing (colophony)

In work part 3, the exposure is considered to occur through three different routes: direct contact, surface contamination, and deposition and impaction. On the basis of a thorough evaluation of the literature on dermal exposure (assessment), some dermal exposure levels were obtained, as well as determinants of exposure, and available approaches for modelling. On basis of this, a framework of theoretical approaches was developed, including 1) processes and tasks, 2) substance and product characteristics and 3) situations and conditions. This information (a list of possibly relevant variables) is essential for the experimental work to be done in the other three work parts. The

variableas are divided along the three routes of exposure: 1) Direct contact, 2)Surface contact, and 3) Deposition and impaction.

Model(s) to be developed on basis of the results of work parts 1 and 2 will be validated/benchmarked with experiments in which model results will also be measured, both externally and internally (by biological monitoring) in actual practice for scenarios with a well-chosen, with respect to knowledge on (human) PBPK-modelling and absorption data, solid and liquid compound. Definitive choices for these compounds have not yet been made. Currently, the general model structure has been developed.

In work part 4, the available literature has been analysed for approaches of risk assessment that could be of use for the toolkit development. For this toolkit approaches are developed for hazard, exposure and risk assessment of dermal exposure on basis of label information and MSDSs for the hazard assessment, and on basis of the approach taken in work part 3 for exposure assessment. The risk assessment is carried out for systemically and locally acting chemicals. The risk management (control) section is based on literature information.

For the exposure assessment method an approach is taken that uses all available dermal exposure studies. From this information typical default values for defined scenarios are derived that can be used to assess dermal exposures, which are then corrected using a graded system for the effect of most of the variables indicated by work part 3.

Table: Essentials of the toolkit concept
The toolkit is transparent and easy-to-handle, and should be able to:
- Activate awareness
- Estimate exposure
- Lead to control actions
- Recognise damaging and/or penetrating potential
- Evaluate risks
- Use STOP principle

The draft toolkit will be considered by teams of occupational hygienists and adapted on the basis of the results obtained form an evaluation in practice.

The final outcome will be a toolkit on paper, but also on CD-ROM. The user, who is supposed to be a non-expert, must answer relatively simple questions and will be guided for that, to obtain qualitative scales for the dermal exposure, the concomitant risk and suggestions for possible control measures to deal with the risk. There will be many text blocks with relevant information on the various issues related to skin exposure, dermal penetration and risk of locally acting and systemically acting compounds.

Conclusion
About half way in a complex four year project, the results cannot yet be discussed in appreciable detail in the light of the project aims. At this point in time, it is clear that the

numerous partners from distinct parts of Europe are well-committed and that the project is a bit behind schedule.

Partners in the project

1. TNO Chemistry, Zeist, the Netherlands (project co-ordination and lead Institute for WP 3)
2. Finnish Institute of Occupational Health, KRIOH, Kuopio, Finland
3. Health and Safety Executive / Laboratories, Bootle/Sheffield, UK (lead Institute for WP 2)
4. Institute of Occupational Medicine, Edinburgh, UK
5. Institute of Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
6. National Institute of Working Life, Umea, Sweden
7. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany (lead Institute for WP 1)
9. Institut National de Recherche et de Sécurité, Nancy, France
9. Instituto Nacional de Saude Dr. Ricardo Jorge, Lisbon, Portugal
10. Occupational Medicine, Turin University, Turin, Italy
11. Miljø-Chemie, Hamburg, Germany (lead Institute for WP 4)
12. FoBiG, Freiburg, Germany
13. Allgemeine Unfallsversicherungsanstalt, Vienna, Austria
14. Bau-Berufsgenossenschaft, Frankfurt, Germany
15. Instituto Nacional de Seguridad e Hygiene en el Trabajo, Seville, Spain

Improved Method to Measure Alkoxyacetic Acid in Urine: A Solid Phase Extraction -Gas Chromatography - Mass Spectrometry Method for 2-Butoxyacetic Acid

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The study of dermal exposures of workers to toxic chemicals is an important part of the National Occupational Research Agenda developed at NIOSH. A critical area for research on dermal exposure involves the development of biomonitoring methods for the analysis of those chemicals that penetrate the dermal barrier. For the current project, Biomonitoring Analysis for Studies of Dermal Exposures, 2-butoxyethanol was selected as a model because of its dermal adsorption characteristics. A recent article on the prioritization of chemicals for research affirmed the importance of 2-butoxyethanol as a potential workplace hazard (Moorman, et al., 2000. Repro. Toxicol. 14, 293-301). Glycol ethers are metabolized in vivo via alcohol dehydrogenase to yield alkoxyacetic acid metabolites and conjugates, which are excreted in urine.

Historically, the analysis of these polar organic acid metabolites has been problematic, involving laborious extraction and derivatization (i.e., Smallwood et al., 1988, Appl. Ind. Hyg. 3(2), 47-50). Thus, a method was developed for biomonitoring alkoxyacetic acids based on a published method for butoxyacetic acid (Shih et al., 1999. J. Occup. Environ. Med. 56(7), 460-467). Using GC/MS with a FFAP capillary column, Shih et al. eliminated the derivatization step but still obtained selective and sensitive SIM-MS quantitation of butoxyacetic acid. Our current method also eliminates the need for liquid extraction by incorporation of a solid phase extraction (SPE) using a pH-resilient anion exchange resin in 96-well formats. The method was optimized using butoxyacetic acid (BAA), deuterated butoxyacetic acid (dBAA) as an isotopically diluted internal standard, and 2-methylbutoxyacetic acid (MBAA) as a recovery/instrumental performance standard. The method's characterization will be presented.

Measurement of Dermal Exposure to Epoxy Components

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Epoxy resins are important industrial polymers mainly used in protective coatings and in electrical applications. A majority of epoxies are based on diglycidyl ether of bisphenol A (DGEBA). The most widely used curing agent for epoxy coatings are different polyamines but carboxylic acids, anhydrides etc. have also been used. Epoxy compounds and amines may cause skin irritations and contact dermatitis. The allergic effect of DGEBA is decreasing with increasing molecular weight and the smallest DGEBA with a molecular weight of 370 is considered as the most potent.

We have tested a chromatographic method for determination of epoxies and polyamines without derivatisation. Dimethyl formamide (DMF) stops the curing reaction and allows the free epoxy groups to be preserved. With the use of LC-MS with electrospray ionisation in positive mode, a simultaneous qualitative determination of epoxies and polyamines was achieved. Separation of the analytes and DMF was performed with reversed phase chromatography on an ODS column. The spectras showed the protonated molecule and some diagnostic fragments for polyamines and the epoxy, respectively. This analytical procedure is to be used for product analysis and together with sampling methods for air concentration measurements and skin exposure determinations.

For the assessment of dermal exposure to DGEBA, field sampling was performed on persons working with application of seamless floors. The product used was a two-component system with 7% DGEBA. The sampling was performed either with patches attached to the skin during a work shift or as tape stripping after a work shift. For the method comparison the two methods were used side by side. For both methods Fixomull® (Beiersdorf AG, Germany), 3 x 3 cm was used. The Fixomull® is a self-adhesive gauze with woven polyester backing and a polyacrylate adhesive. The workers used ordinary leather gloves and sampling was performed on the right and left hand inside the glove and on the skin just above the glove. Sampling was performed on two persons during five work shifts. Method comparison measurements were performed during three of the work shifts.

The tapes were transferred to glass vials with 1 ml of DMF, extracted during ultrasonification and stored in freezer prior to analysis. A detection limit of about 0.045 μg DGEBA (Mv 370)/sample was achieved. No negative effects or increased blank values due to the tape could be seen.

DGEBA was detected in all sampling locations with both sampling methods. The amount found with the stripping method was about 60% of the amount found with the patch

method with a variation from 2 to 400%. The mean concentration found with the patch method was 0.08 µg cm-2 h-1 with a maximum value of 0.41 µg cm-2 h-1. For the stripping method, a mean value of 0.03 µg cm-2 h-1 and a maximum value of 0.24 µg cm-2 h-1 were found. The use of leather gloves does not protect against DGEBA skin exposure.

These sampling methods are to be more thoroughly studied at the laboratory and during field sampling in different occupational environments. The measurements give information on current exposure levels but are also intended to be a basis for recommendations on sampling strategy in different workplaces.

Assessment of Skin Exposure to Permanent Hair Dyes

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Background
Hairdressers are a high-risk group for developing hand eczema. Permanent hair dye products contain contact allergens such as p-phenylenediamine and similar aromatic amines. Assessment of dermal exposure of the hands may be a useful tool for prevention of occupational skin disease in hairdressers.

Aim
To develop a method for assessment of occupational skin exposure to permanent hair dyes.

Method
Human volunteers were exposed to known amounts of hair dye products on the hands. Skin sampling was performed by hand washing with a borate buffer using a bag rinsing technique. The wash fluids were collected and analysed by HPLC. The sampling efficiency, the effect of residence time and sample load were studied for two hair dye products and a solution of 5 reference compounds that were stabilized with ascorbic acid. The 5 reference compounds were selected after an inventory of existing compounds in common permanent hair dye products in Sweden.

Results and conclusion
Preliminary results indicate that the sampling efficiency decreases with increasing residence time for the compounds in the hair dye products while the sampling efficiency for the compounds in the reference solution is not affected to the same extent. The sampling efficiency is sufficient for assessment of dermal exposure in the laboratory and in a pilot study performed in a hairdressing salon.

Sampling Efficiency of Cotton Gloves When Used for Dermal Exposure Measurements

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Introduction

For forty years, Occupational Hygienists have used a variety of brands of cotton gloves as sampling gloves to estimate dermal exposure to the hands. Many brands of sampling gloves have been reported, but the selection criteria are rarely detailed. The sampling gloves are mainly selected for low analytical background, but local availability appears to be a major consideration. The gloves are made for purposes other than sampling, e.g. pall-bearers gloves, photographer's gloves, disposable work gloves, lining gloves. Some gloves are bleached to improve appearance, but cheaper ones are unbleached. Most contain some residues of fabric treatment such as oil to assist weaving or knitting.

When used as sampling gloves, they can used in three ways: a) outside the protective glove to measure potential dermal exposure; the amount retained on the sampling glove is assumed to represent the challenge to the protective glove.
b) directly on the hand when no protective glove is worn; the amount retained on the sampling glove is assumed to represent the amount falling onto the skin.
c) inside the protective glove (directly on the hand) to measure actual dermal exposure; the amount retained on the sampling glove is assumed to represent the amount falling onto the skin due to the limitations of the protective glove. It is often compared with a) to calculate the protection offered by a glove.

Contamination can collect on the sampling glove through several mechanisms:
d) direct contact with a contaminated surface; the removal efficiency from the surface may be very different to the skin or a protective glove.
e) direct deposition from the air; spray or dust settles onto the exposed sampler but the fibres may retain more than relatively smooth skin.
f) immersion into a contaminant; the large quantities retained in the fibres may bear little relation to that retained on skin.

Guidance, provided for example by WHO and OECD, specifies that samplers be changed for fresh ones as soon as they are saturated, although this bears no relation to the sampling properties of the skin, and it is almost impossible to determine whether a sampler is saturated or not. Certain parts of the glove will always saturate first, usually the fingertips.

There is little information to relate the amounts found on the sampling gloves to the amounts that would have been retained on the skin of the hands in their absence. Limited studies have been conducted to compare hands and sampling gloves, but the issue has been raised as an aside to field survey work. It is generally accepted that oversampling must occur, but for occupational hygiene surveys and subsequent modelling, sampling efficiency is assumed to be the same as the skin for lack of any comparison data. It is not

generally appreciated that the results might have been quite different had a different brand of sampling glove been selected. It is an issue that is often ignored.

Most of these cotton gloves are of low manufacturing quality. For the purpose of dermal sampling, there are no quoted standards for quality control that they are required to meet, either for the raw materials or the construction. Lack of quality control of materials could result in batch-to-batch variability, and could affect the consistency of the sampling rate. Pre-treatment of the gloves, such as washing to remove interfering background levels or to increase absorbency, could also affect their sampling properties and possibly increase variation.

Aims of this work

- To obtain a selection of types of sampling gloves used by occupational hygienists throughout the world.
- To measure their sampling efficiency relative to the skin.
- To enable occupational hygienists to relate their past results obtained using gloves, to the sampling properties of the skin.
- To develop a specification for a material that could be widely used as a sampling glove, that would replicate the transfer and retention properties of the skin.

Methods

1. Identification of gloves

Ten brands of glove were obtained that represented reported use worldwide by searching literature of occupational hygiene studies and following through to a supplier. Batches of the gloves were washed in non-biological washing powder in an automatic washing machine because several of the studies reported that this was done to reduce background levels. Tests were carried out on washed and unwashed gloves.

2. Liquid retention Saturation tests were performed by dipping gloves (unworn) and ungloved hands into a beaker of water. The hands were removed after a few seconds, but the gloves were tamped for one minute with a glass rod to allow the fibres to take up the liquid before removal and one minute's drain back into the beaker. The weight loss of water from the beaker indicated the amount retained on the hand or glove.

Lower challenge levels were achieved with a spray mist inside a chamber. Volunteers wore one glove and performed a series of hand movements in the chamber through ports. Retention of spray was measured by rinsing bare hands and gloves separately in pure water, followed by assay for a soluble strontium salt tracer in the spray. Recovery efficiencies from spiked hands was 90-100%, and from gloves was 100% after pre-treatment and acid leach.

3. Dust retention

Four of the ten brands of gloves were tested against chalk dust (calcium carbonate) which according to manufacturer's data was 99.8% pure, and of 28μm median diameter (by seiving). Saturation tests were performed by dipping a gloved or ungloved hand into a large beaker of dust and performing a short series of hand movements to coat the hand or

gloved hand thoroughly. The hand or gloved hand was removed, and a further short series of hand movements performed to dislodge loosely-bound dust. The dust was recovered from the hand by bag-washing in water. The glove was carefully removed and bagged over a paper surface, and all the dislodged dust recovered from the paper. The calcium carbonate was dissolved with sufficient nitric acid to clarify the solution, and analysed by assay for calcium. Second bag-washes of the hand showed that no further calcium was removed, so 100% recovery efficiency was assumed from the hands. Spiked amounts of dust on the gloves showed that 100% recovery was achieved. Lower challenge levels have not been started yet, but will be achieved with a dust generator inside the chamber as above.

Results

1. Glove materials

The glove materials were usually reported as 100% cotton, but mixtures were frequently encountered. Cuffs of different materials to the gloves were also found. The materials varied in their size, thickness and weight. Total glove weights were in the range 5-29g, equivalent to area weights of 0.01-0.07 g.cm-2 of material. Differences were also observed in the weave, texture, absorbency and elasticity.

2. Liquid retention

Retention after saturation ranged from 6.4-62g per glove, a factor of 3-39 times greater than the hand retention of 1.6-2.3g per hand. Retention of spray mist was surprisingly constant for the different types of gloves, being approximately twice that of the hands.

3. Dust retention

Retention after saturation ranged from 12-22g per glove, a factor of 12-40 times greater than the hand retention of 0.5-1.0g per hand. Lower challenge levels are planned but have not yet been carried out at the time of writing.

Conclusions

Cotton gloves were shown to oversample. At lower challenge levels, sampling efficiency is brand-independent. The higher retention of the glove may be caused by a higher evaporation rate from the fabric than the bare hand. Future tests with dry dusts at low challenge levels can test this theory later. However at saturation, sampling efficiency rises many-fold to a brand-dependent level. The response of the sampling glove depends on the mechanism by which the glove became contaminated - either by deposition directly from the air, or by total saturation from immersion or from partial saturation from contact with contaminated objects.

In field use, there will be parts of the glove that are saturated, for example the fingertips, and parts that are not saturated such as the back of the hand. Past field studies have consisted of an unknown mixture of these brand-dependent and brand-independent sampling efficiencies, and the results have unwittingly depended on the type of sampling glove selected.

It will not be possible to re-assess previous studies in the light of this knowledge unless the deposition mechanism was well-defined. Comparison and collation of different studies that have used different sampling materials must be carried out with a great deal of circumspection.

It is possible to define a specification for a new glove material that mimics the sampling properties of the skin: 410 cm^2 of it should retain 1.8-2.3 g of water and 0.5-1.0g of dust when saturated, but the material should sample at the same rate as the hand in a controlled deposition study.

General Discussion

This paper deals with gloves, but our lack of knowledge is not confined just to gloves. Looking at the wider issue, surrogate sampling materials used in patch measurements and whole-body measurements are selected mainly to increase sampling efficiency.

Some occupational hygienists take the line that "more is better", preferring to oversample rather than risk undersampling. Dusts are sampled using gauze to trap more particles than would adhere to the skin. Vapours and volatile chemicals are sampled with cotton-carbon cloths that absorb vapours from the air and reduce evaporative losses from splashes, whereas the skin may absorb from the air quite differently and retain only a fraction of the splash.

In a similar fashion, transfer of residues from surfaces to skin are measured using surrogate techniques involving cotton pads or denim cloth. Even those samplers that claim to dislodge similar quantities as the skin have had very limited testing against a limited subset of surfaces.

Before undertaking dermal exposure measurements, researchers should always consider carefully what their measurements are trying to represent.

Mathematical Model for the Disposition of Volatile Compounds on Skin Following Topical Application

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Purpose

To develop a mathematical model for predicting the absorption and evaporation of volatile materials from skin, for use in dermal exposure assessment and improved understanding of dose-related contact allergy.

Background

Allergy to perfume is known to be among the most common causes of cosmetic contact dermatitis. Currently, 100% absorption (an overestimate for volatile ingredients) is assumed for dermal exposure assessments. To improve the current dermal risk assessment process for volatile materials, a mathematical model for accurately estimating the actual fraction that will be dermally absorbed is desired.

Methods

As a first step in this undertaking, we considered a first-order kinetic approach, which is expected to be applicable for small doses applied to skin. Skin penetration rate was calculated as a fraction of the maximum flux estimated from the compound's lipid solubility, Slip = KoctSw, and molecular weight, MW [Koct = octanol/water partition coefficient, Sw = water solubility]. Evaporation rates were estimated from a modified Henry's Law approach with a stagnant boundary layer whose thickness is a function of surface airflow, v. At a given value of v, evaporation rate is proportional to Pvp/Slip, where Pvp is the vapor pressure of the ingredient at skin temperature. Values of Pvp were estimated from structure and normal boiling points using a commercially available program.

Results

The model predicts a relationship for total evaporation from skin of the form %evap = 100x/(k + x) where x = PvpMW2.7/(KoctSw) and k is a parameter that varies inversely with v. Comparison with published data on perfume evaporation from human skin in vivo (Vuilleumier et al., Int. J. Cosmet. Sci., 1995) showed good agreement between theory and experiment for two closely related perfume mixtures (r^2 = 0.52-0.74, s = 12-14%, n = 10).

Conclusions

The proposed model has a good prospect of providing skin absorption estimates suitable for use in exposure assessment.

Next Steps

The current model assumes no ingredient interactions. Better predictions may be attained by incorporating composition-dependent activity coefficients, calculated according to the

UNIFAC method, into the model. Results of initial calculations of this nature will be reported.

Qualitative and Quantitative Assessment of Isocyanate Contamination of Workplace Surfaces

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Isocyanates are major chemical commodities used in various applications including polyurethane paints and polyurethane foam structural components. Recently, there has been increasing interest in the contribution of dermal exposure to isocyanate-induced occupational disease. The isocyanates are among the most potent sensitizing agents found in the workplace environment and are known to cause contact dermatitis through both immunologic and irritant mechanisms, as well as occupational respiratory diseases, especially asthma and to a lesser extent, hypersensitivity pneumonitis. Furthermore, while it has long been assumed that isocyanate-induced respiratory disease is elicited by inhalation exposure, there is some concern that dermal exposure may play a role in the induction of respiratory sensitivity. This concern originated from the results of various animal experiments in which the epicutaneous application of isocyanate has resulted in the induction of respiratory sensitivity to isocyanate. Yet there is little information available on the extent, nature, and significance of workplace surface contamination by isocyanate and resulting dermal exposure of workers.

In this work, a new method for quantitative assessment of surface contamination by total reactive isocyanate group (TRIG) is being developed and an existing, commercially available qualitative colorimetric surface test kit for isocyanates (SWYPE[TM]) is being evaluated. The quantitative surface sampling method is based on an existing air sampling method for TRIG that uses MAMA reagent with HPLC analysis (Rando, et al, J. Liquid Chrom., 18:2743, 1995) and utilizes Pallflex filters for wipe collection of surface isocyanate contamination. Preliminary testing of the method in the laboratory has been done for TDI, HDI, and MDI on various surfaces at loadings ranging from 0.1 to 10 μg/cm2. Recovery of isocyanate in these tests has ranged from none detected to approximately 70%, with efficiency improving with higher loading and smoother surfaces.

Detailed characterization of the performance of the method will be completed in the laboratory and followed by field evaluation of the technique. Demonstration of the method as an assessment tool and as an aid in training of workers is planned in pilot studies at an aerospace facility using polyurethane foam insulation materials and in autobody repair shops that use polyurethane paints. Preliminary qualitative examination of surface contamination at these sites with the SWYPE[TM]samplers has indicated no detectable surface contamination in the aerospace facility, whereas in the autobody shops,

approximately 36% of samples have been positive, with contamination commonly found on spraybooth door handles and paint mixing benchtops.

Determination of Keratin Protein in a Tape-Stripped Skin Sample from Jet Fuel Exposed Skin: Standardization of the Tape-Stripping Method

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Dermally-deposited contaminants may bind to and react with keratin proteins in the stratum corneum. We have developed and evaluated a non-invasive tape-stripping method for the removal of keratin proteins from the stratum corneum for normalization of extract concentrations from 20 human volunteers before and after exposure to 25 μl of jet fuel (JP-8). Due to the potential for variable amounts of squame tissue recovered in each tape-stripped sample, we investigated the need to normalize recovered or extracted chemical to the amount of tissue stripped. Keratin proteins were extracted in a buffer and quantified using a modified Bradford Method (AmrescoTM). Confirmation of the extraction of keratin proteins was verified by western blotting using a monoclonal mouse anti-human cytokeratin antibody (DakoTM Corporation). This tape-stripping method removed a constant amount of keratin proteins, which decreased with sequential tape strippings. The mean mass of keratin proteins for sequential tape strips varied from 154 ± 75.3 μg for the first tape strip to 52.8 ± 17.3 μg for the fifth tape strip for the unexposed sites and from 128 ± 63.8 μg for the first tape strip to 58.4 ± 21.6 μg for the fifth tape strip for the exposed sites. Thus, duration of jet fuel exposure did not affect the amount of keratin protein recovered from the tape strips. There was no difference in the removal of keratin proteins per tape strip from unexposed and exposed sites between sex, age, ethnicity, or skin pigmentation at the significance level of 0.05. Normalization against the amount of keratin in each tape-strip sample did not improve quantification of dermal exposure to naphthalene. Thus, we concluded that normalization of the tape-strip samples for keratin content is not required when determining dermal exposure to jet fuel. The technique developed may have a wide range of applications from determining the actual amount of compound absorbed by the skin, assessing exposure in field studies, development of better models for the prediction of exposure, and determining risk.

Dermal Exposure Model for Jet Fuel Exposure Using Tape-Stripping Method

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A model to predict dermal exposure to jet fuel was developed using a noninvasive tape-stripping method and naphthalene as a marker for jet fuel exposure. Twelve human volunteers, including 7 females and 5 males, were exposed to jet fuel on two sites on both lower volar arms (four sites total) inside an exposure chamber. Jet fuel was applied within an aluminum application chamber to avoid fuel spread. One additional site on the right arm was selected as an unexposed control area. Tape-strip samples were collected at 10, 15, 20, or 25 minutes after 25 μl of fuel application on each site. Cover-Roll adhesive tape (Beiersdorf AG, Germany), precut in size to 2.5 cm x 4 cm, was applied to the exposed or unexposed site after exposure. Each site was tape stripped five consecutive times.

The tape-stripping samples were extracted with 5 ml acetone and analyzed by gas chromatography/mass spectrometry (GC/MS). Evaporation of naphthalene was measured during the experiment using Tenax tubes and analyzed by gas chromatography. Residual jet fuel remaining on the application chamber was collected and analyzed by GC/MS. By fitting a mixed-effect linear regression model to the data, we were able to estimate the amount of JP-8 initially applied when taking into account jet fuel evaporation and loss due to residual agent remaining on the application chamber walls. Covariates including race, gender, age, and skin type did not significantly affect the jet fuel penetration into the skin. With sufficient field evaluation, this model may be used to predict dermal exposure to jet fuel in occupational field settings as well as to understand the capacity of this technique to assess dermal exposures. Furthermore, this method could be valuable when considering the role of dermal exposure in the assessment of total body burden.

Estimating Dermal Exposure to Hazardous Chemicals in Water and Soil

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Dermal contact with chemically contaminated water and soil may be an important route of exposure. Water and soil can be contaminated directly as a result of chemical application and spills or indirectly as a result of contaminated surface water runoff or erosion. Individuals may be exposed by playing or working in contaminated water or soil. Estimating dermal exposure entails obtaining information about the amount of skin surface exposed to the contaminated media, the duration of exposure, physical/chemical factors that influence the amount of media contact with skin, and the likelihood that the chemical contaminant can penetrate the skin. EPA sponsored studies in the 1990's demonstrated approaches to obtain this kind of information. Studies were conducted: to characterize and categorize activities that involve soil contact and to identify physical and chemical factors that enhance chemical penetration through skin under a variety of conditions. Results from these studies have been incorporated into Agency regulatory guidance documents for dermal exposure.(1,2)

Notwithstanding the success of these investigations, many issues remain. Currently, information about dermal contact with highly lipophilic chemicals in contaminated water and soil are limited; making it difficult to accurately estimate dermal exposure to these compounds. Likewise, models that attempt to predict dermal contact and penetration are based on limited data and have not been validated which limits their usefulness. Collectively, this has often resulted in debate about the magnitude of public health risks posed by hazardous wastes at Superfund sites.

To improve dermal exposure assessments and to foster development of improved dermal absorption models, we have embarked on investigations of the dermal absorption potential of highly lipophilic chemicals in soil or water, the influence of soil characteristics and loading procedures, chemical and physical properties of soil that affect chemical movement from soil to skin, and development of rapid reliable dermal absorption test methods. Additional work is being conducted to standardize dermal absorption test procedures and to validate them for chemicals of interest. We believe this approach will yield results that will improve the ability of Agency risk assessors to identify population segments potentially at risk and to estimate their exposure to chemical contaminates of concern more accurately.

The opinions expressed in this manuscript are those of the author and do not reflect opinions or policy of the Environmental Protection Agency. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

References

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Dermal Exposures to Particles from Smooth and Carpeted Surfaces

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Although many contaminants are applied as liquids and produce dermal exposures as dried residues, some chemicals are applied in the particle phase or move in that direction through absorption/adsorption onto the surfaces of dust particles. The particle phase injects additional physical mechanisms into the dermal exposure process that can substantially alter mass transfer factors and important source/sink relationships. Residues deposited on particle surfaces can facilitate movement within a microenvironment, as well as foster a large sink capacity within the dust pore structure long after the surface residues have evaporated. Particle-phase contaminant movement between surfaces and within microenvironments are strongly particle size dependent, and influenced by factors that are not necessarily relevant to residues. One of the most important factors is contact surface charge which can provide bonding forces that limit the release of the smallest particle sizes to the skin during dermal contact, to vacuum cleaner collection, or to resuspension while walking. Combining this bonding force with the very limited fiber surface that actually contacts the skin, substantially reduces mass transfer factors as compared to smooth surfaces - often 1000x less or smaller. It is currently not clear whether wetted dermal surface sufficiently drain away residual surface charges, facilitating enhanced transfer.

Smooth surfaces can be important sources for dermal exposures, with relatively large mass transfer factors that leave little residual material available for transfer in subsequent-contact events. Surface roughness reduces the actual contacted surface area, and adds reservoirs that can serve as contaminant sinks. While carpeting is often characterized as an areal source, it is actually the ultimate "depth" source - exhibiting a huge internal surface area (and volume, depending on the pile height). Much of the fiber surface area and backing are essentially unavailable for dermal contact, and serve as an enormous sink for dusts and particle-phase contaminants. Apparently, only the upper fiber surfaces actually take part in dermal press or smudge contact events, thus providing a limit to the mass of material actually available for transfer during repeated dermal contact events.

Research studies conducted at the Research Triangle Institute, and supported by both HUD and EPA during the past 3 years have added greatly to our understanding of particle phase dermal transfers from both smooth and carpeted surfaces. Because of its prevalence in both residential and commercial buildings, carpeted surfaces can play important intermediary roles in multi-pathway risk analyses (especially for children) and can serve as both a sink and a source. The transferability of particles from smooth and carpeted surfaces are beginning to be characterized during controlled studies to allow the application of microactivity dermal exposure models. The use of Pb-dust contaminated

carpet samples for testing provided a tracer species (lead) that was easily detectable at low concentrations (by ICP-AES) and very stable (no vapor pressure issues).

Key findings will be summarized, supporting data summarized, and the implications discussed, including that:
(1) the mass of Pb particle contaminants found in the backing and the base of fibers are essentially unavailable for exposure (but may become available through a high energy event),
(2) contact mass transfer rates of particles to both dermal and wipe surfaces are almost solely associated with carpet fiber loadings,
(3) areal mass transfer factors are much less than 1% of the contaminant loading found on the fibers,
(4) contaminant particle sizes smaller than about 1 micrometer (e.g. very prevalent for Pb-contaminated carpeting) are held tightly to fibers by surface charges and are minimally available for air resuspension or transfer to either skin or wipes,
(5) particle-phase contaminant degradation indoors may include eventual oxidation to submicron sizes,
(6) repeated contacts of the same contaminated carpet surface can rapidly remove the easily dislodged particles, substantially reducing the mass available for transfer relatively quickly,
(7) the areal particle loading capacity of the skin is finite, such that successive contacts exhibit exponentially smaller mass transfer rates, and
(8) carpet fibers represent a very finite source for particles (and probably residues) such that the source may become depleted within only a few dermal contacts (e.g. total fiber loadings cannot be used to estimate dermal exposures without applying a depletion factor).

Current research uncertainties include the amount of energy that must be imparted to the carpeting (e.g. vacuuming, walking) to replenish fiber loadings from the carpet backing reservoir, after contact or cleaning events, and the role of wet contact surface films (e.g. hands, wipes) in altering the transfer of surface charges that are so dominant in bonding particles to the surfaces.

Development of an Analytical Method to Quantify Dermal Exposure to Hexamethylene Diisocyanate

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Occupational exposure to diisocyanates is well documented as a cause of respiratory sensitization and occupational asthma. Hexamethylene diisocyanate (HDI) is a commonly used diisocyanate in the surface coating industry. The focus of research in the past has been on the inhalation hazards associated with the use of HDI. However, inhalation exposure may account for only part of the total body dose resulting from exposure in occupational settings. Recent animal studies have suggested a link between dermal exposure to diisocyanates and respiratory sensitization, but dermal exposure assessment methods and techniques for these compounds have been slow to emerge.

An analytical method using liquid chromatography-mass spectrometry (LC-MS) was developed to detect and quantify dermal exposure to HDI. NIOSH Method 5521: "Isocyanates, Monomeric", originally developed for air samples, was modified for use with our non-invasive dermal tape-stripping technique. HDI was detected as the urea derivative by monitoring its protonated molecular ion at m/z 553.7. An octamethylene diisocyanate (ODI) urea derivative (1000 pmol spike) was used as an internal standard for all samples, and was detected using the protonated molecular ion at m/z 581.7. A standard curve developed with pure HDI urea derivative and spiked with 1000 pmol of the internal standard was used to evaluate sample results. Evaluation of the method included storage stability and extraction efficiency tests.

To evaluate sample stability during storage, tape strips (in triplicate) were spiked with a known amount of HDI-containing paint and held in a toluene/1-(2-methoxyphenyl)-piperazine solution at 4°C for a period of time ranging from 1 to 13 days. Samples were acetylated, evaporated, and redissolved in methanol before analysis by LC-MS. Results were evaluated using a standard curve prepared on each day of analysis.

Extraction efficiency of the method was also investigated. Tape strips (in triplicate) were spiked with known amounts of base paint and pure liquid HDI, and held overnight in a toluene/1-(2-methoxyphenyl)-piperazine solution at 4°C. The extraction efficiency was evaluated for eight different amounts of pure HDI, ranging from <10 pmol to 1000 pmol. Samples were analyzed by LC-MS on the next day and the results evaluated using a standard curve.

The method will be evaluated in upcoming field studies of industrial spray-painting operations.

Wipe Sampling to Assess Pesticide Exposures on Skin: Preliminary Method Evaluation

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Background
Skin exposures to pesticides in agriculture are considered to be the primary route of worker exposure. However, there remains a paucity of data for quantifying such exposures. In addition, the methods used to measure exposures vary and the efficiency of each method of sampling may differ, adding to the difficulties in interpreting results. A preliminary range finding and method evaluation survey was recently performed in California in preparation for a larger study to determine exposure reduction intervention effectiveness.

Methods
Hand wipes (using the NHEXAS isopropanol moistened J&J Sof-Wick gauze wipe method consisting of 2 consecutive wipes) were obtained during harvesting of a strawberry field that had been previously sprayed with malathion. To evaluate the performance of the hand wipe method, samples were collected from whole hands and individual digits (thumb and forefinger) both before and after cleaning up with soap & water. In addition, triplicate consecutive samples were analyzed separately to assess completeness of malathion removal. Additional types of samples were collected, included end-of-shift urine for mono- and diacetyl metabolites, and foliar residue samples (using a new method involving solid sorbent field extraction).

Results
Mean whole hand pre-wash and post wash malathion loading (n=5) was 8582 ng and 3493 ng while mean digit pre-wash and post wash malathion loading (n=6) was 1457 ng and 965 ng, respectively. Furthermore, mean consecutive removal of pre-washed digits (n=3 pair) were 1154, 558, and 436 ng, while for whole hand (n=1 pair) 5550, 1340, and 1490 ng. After washing, mean consecutive removal for digits was 557, 315, and 217 ng, respectively, while for whole hand it was 1420, 1560, and 1130 ng. Wearing new latex gloves during harvesting appeared to dramatically reduce skin loading, while wearing old latex gloves did not.

Conclusions
The EPA hand wiping method apparently did not efficiently remove the amount of malathion loading present either before or after washing, although when loading was low (as when wearing gloves) removal appeared complete. Perhaps alternative sampling methods are more efficient, but this would need to be similarly evaluated. Efficiency of

skin sampling methods and comparison to other methods continues to be a significant need for accurate exposure assessment characterization.

Comparison of Three Methods for Determining Removal of Stratum Corneum Using Adhesive Tape Strips

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Adhesive tape stripping (ATS) has been used to remove layers of the outermost stratum corneum from skin. These tapes can be used to measure the physical condition of the skin or for quantifying exogenous or endogenous compounds present within the skin. There is also the need for a non-destructive approach to measure the mass of stratum corneum adhering to the tape so that samples taken for chemical analysis can be normalized per the amount of stratum corneum present. Although used for years, there is still not a uniform approach for performing ATS sampling and several potentially influential variables have not been carefully evaluated. Our goal here is to evaluate a new instrumental procedure that might provide us the means of performing both of the above measurements of ATS on samples collected from workers in various occupations. We report our analysis of ATS samples using three types of analysis: (1) protein assay of keratin mass, (2) desquamation index (CuDerm, Inc, Dallas TX), and (3) an instrumental light reflective device for direct measurement of adhering skin (Visioscan VC 98, Courage & Khazaka, Köln, Germany). Only the latter method has the ability to both assess skin condition and possibly mass of stratum corneum on the ATS samples. Measurement analysis using the above approaches was performed on 90 skin samples and 10 blank samples.

Poster Session 4: "Controlling Exposures and Prevention"

4.1 **Problems and Solutions in Practical Dermal Exposure Risk Assessment**, Christopher L. Packham, Enviroderm Services, Evesham, UK

4.2 **Investigating a Suspected Case of Occupational Skin Disease**, Christopher L. Packham, Enviroderm Services, Evesham, UK

4.3 **Measurement of Dermal Exposure - So What?**, Christopher L. Packham, Enviroderm Services, Evesham, UK

4.4 **Use of Bioengineering Techniques for Skin Health Surveillance**, Helen E. Packham, Enviroderm Services, Evesham, UK

4.5 **Development of Colorimetric Indicators: A New Technique to Determine Glutaraldehyde and Alkaline Glutaraidehyde Contamination**, Evanly Vo, National Personal Protective Technology Laboratory, National Institute for Occupational Safety and Health, Morgantown, WV, USA

4.6 **Development and Validation of Solvent End of Service Life Indicators for Chemical Permeation of Gloves**, Thomas D. Klingner, Colormetric Laboratories, Inc., Des Plaincs, IL, USA

4.7 **D-Tam Glove Permeation Study**, Thomas D. Klingner, Colormetric Laboratories, Inc., Des Plaines, IL, USA

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4.9 **The Routes and Consequences of Internal Contamination of Gloves**, Beth Rawson, James Wheeler*, Martin Roff and John Cocker, Health and Safety Laboratory, Sheffield and *Health and Safety Executive, Bootle, Liverpool, UK

4.10 **A Comprehensive Approach of a Hand Regimen System in Oil Production and Refinery Facilities**, Brian Hammond, José Henriques da Silva Tavares*, Elenor Fendler and Alberto de Abreu Sodré, GOJO Industries, Akron, OH, USA and *Petrobras, Macaé, Brazil

4.11 **The Impact of a Skin Care Program in a Fiberglass Facility Utilizing Bioengineering Techniques**, Brian Hammond, and Eleanor Fendler, PhD., GOJO Industries, Akron, OH, USA

4.12 **Thermal Desorption of Solvents Using a Passive Dermal Dosimeter**, Linda S. Coyne, SKC Inc., Eighty Four, PA and Tom Klingner, CLI Laboratories, Des Plaines, IL, USA

4.13 **Effect of Cycles of Contamination and Decontamination on Chemical Glove Performance**, Nadia S. El-Ayouby, MS, Pengfei Gao, PhD, James T. Wassell, PhD* and Rotha C. Hall*, National Personal Protective Technology Laboratory and *Division of Safety Research, National Institute for Occupational Safety and Health, Morgantown, WV, USA

4.14 **An Evaluation of Dermal Exposures from an Engineering Perspective**, Duane Hammond and R. Leroy Mickelsen, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

4.15 **Investigation of the Compatibility of a Skin Protection Gel and Natural Rubber Gloves**, Annette zur Muehlen, Andreas Klotz and Brigitte Thoerner, Stockhausen, Krefeld, Germany

4.16 **Diphoterine(R) and Hexafluorine(R): New Active Skin/Eye Decontamination Compounds**, Alan H. Hall, TTUHSC-El Paso and Toxicology Consulting and Medical Translating Services, Inc., El Paso, TX, USA and Joel Blomet and Laurence Mathieu, Laboratoire Prevor, Valmondois, France

4.17 **Development of a Glove End of Service Life Indicator (ESLI) for Weak Organic and Inorganic Acids**, Evanly Vo, Tom Klingner*, Zhenzhen Zhuang, National Personal Protetive Technology Laboratory, National Institute for Occupational Safety and Health, Pittsburgh, PA and *Colormetric Laboratories, Inc., Des Plaines, IL, USA

Problems And Solutions In Practical Dermal Exposure Risk Assessment

Christopher L. Packham, EnviroDerm Services, Evesham, UK (Corresponding Author)

Risk assessment for dermal workplace exposure is an essential element of any effective health and safety system. Yet all too often it is either ignored, or performed superficially. This may help to explain why occupational skin disease remains a major cause of occupationally caused ill health. The complexity and problems associated with dermal exposure risk assessment are often not appreciated. The result can be:

- The hazard to health arising out of contact with the chemical or product is not properly characterised,

- The exposure, either actual or potential is not identified, or

- Its significance is either over or under-estimated, leading to inadequate or excessive control measures. Both can result in occupationally induced skin problems.

It is often not appreciated, even by those with a professional qualification in health, safety or hygiene, just how complex this aspect of occupational health and safety is and how easy it is to take what appears to be a logical course of action that, in reality, increases the probability of occupational skin disease or other damage to health from dermal exposure. The problems with dermal exposure risk assessment arise out of its complexity and our lack of knowledge about how the skin interacts with the working environment. There are many uncertainties we have to take account of when conducting a dermal exposure risk assessment. These include:

- The hazard data for the chemical may be inadequate. In many cases there will be no data on chronic effects.

- We currently have no validated, practical methods for measuring workplace dermal exposure, particularly for the small and medium sized enterprise.

- Biodiversity among individuals can introduce a large uncertainty element in our assessment.

- Concomitant factors can play a major role in modifying the effect of exposure. These include skin condition and location of exposure, synergistic effects of mixtures, ambient conditions, and personal behaviour.

Given these factors, dermal exposure risk assessment is, perforce, highly subjective. What is important, therefore, is that we adopt a strategy and technique that:

- Helps us identify all hazards and characterise these adequately for dermal exposure effect.

- Ensures that we are aware of the less obvious routes for dermal exposure.

- Can be used by those with limited training in industrial hygiene or scientific investigation techniques.

- Provides a structured method of assessing risks so that a high level of consistency is ensured.

Such a system has been developed and tested. Information on this will be available in the form of a Technical Bulletin.

Investigating A Suspected Case Of Occupational Skin Disease

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Experience suggests that many cases of skin disease are diagnosed as occupational when, in reality, they are either completely non-occupational in origin or at least have a significant non-occupational element among the causative factors. Not infrequently action is taken that is counter productive. Inappropriate treatment may actually increase the skin problem. Redeployment or even dismissal may have serious consequences for the employee, be unnecessary and, in many countries, result in significant costs for compensation. At the least there will be retraining costs, either for the affected employee or for his or her replacement.

One of the main reasons for this is that the investigation of the skin problem and the clinical diagnosis often do not take all relevant factors into account. Assumptions are made that may not contribute to the correct assessment of the problem. Even dermatologists are not immune from producing diagnoses that are, at best, not relevant and that sometimes may be misleading.

What is required is a structured approach that attempts to identify all the potentially relevant factors and evaluate their significance. Where clinical diagnosis is sought it must be on the basis of a knowledge by the medical practitioner, preferably a dermatologist, of these factors and an appreciation of their import. Once the diagnosis has been made its relevance to the actual problem cannot be taken for granted, but must be carefully established. Only then can action be considered that hopefully will keep the worker in his or her job but without a reoccurrence of the skin problem. Our experience is that if such a structured approach is adopted much time and cost can be saved and the worker's career kept intact.

We will propose such a structured approach that attempts to meet the criteria outlined and, through case studies, demonstrate how this can avoid costly mistakes, save the employer time, money and much aggravation and maintain the worker's quality of work life.

Measurement Of Dermal Exposure - So What?

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Much emphasis is currently being given to developing techniques for the measurement of dermal exposure, development of dermal occupational exposure limits and modelling of dermal exposure levels. Could all of this be a waste of time and money?

Whilst obviously there is a need to know more and to develop standards, we question whether the emphasis on these aspects is really what is currently needed. Perhaps we would achieve greater benefits for our investment if we were to concentrate upon other aspects of the prevention of damage to health from dermal workplace exposure.

In defence of measurement of dermal exposure it does give us quantitative data on the actual exposure occurring. However, all measurement techniques are complex, time consuming and frequently introduce artefacts that mean that the results may not reflect what is truly happening on a day to day basis. Interpretation of the data is also difficult and fraught with uncertainty. Certainly, dermal exposure measurement is hardly likely to be a practical proposition for most small and medium sized employers and probably also for many larger employers too.

Biodiversity among humans is enormous. The way in which each of us reacts to many chemicals is highly variable. This makes the creation of dermal occupational exposure limits extremely difficult. If we are to set these at a level that applies to everyone, then in many cases for the vast majority of the population these levels will be far too low. The increased costs to industry in achieving such levels could put the organisation's very existence at risk, particularly in these days of the global market. On the other hand, if we put the limit at a level that is applicable to the majority we will be accepting that certain people will be harmed. The legal implications of this are fascinating. In any event, limits and regulations encourage a minimalist approach, i.e. do just enough that we are not in contravention of the law! What is needed is a much more positive attitude.

Measuring dermal exposure only indicates the level of the problem. It does not indicate what we should be doing to control the exposure such that workers do not have their health damaged. We would argue that what we should be concentrating upon is risk management, that is the control of dermal exposure to a level where practical experience indicates that damage to health is either eliminated or the risk reduced to what society considers an acceptable level.

One of the major factors in the high incidence and prevalence of occupational skin disease is the lack of knowledge of many of those concerned with worker health and safety. Skin management is rarely dealt with adequately in most health and safety training. In many cases, its complexity is simply not recognised. It is often assumed that dermal exposure management is simple. Action is taken that may appear logical but that in reality increases the probability of damage to health from dermal exposure. Thus more

emphasis on education and training would probably be more effective in reducing the incidence of occupational skin damage.

A considerable amount of data exists on how people's skin is affected by the working environment. Unfortunately, this is not in a form that is easily accessible to those concerned with the health of their workers. There is a case for some central organisation that could collect, evaluate and coordinate these data. Not only would this provide a useful resource to ensure that we direct our efforts in research to the areas where the greatest harm is being done but it would assist in providing guidance on how we should be developing our dermal exposure risk assessment and risk management techniques.

Use Of Bioengineering Techniques For Skin Health Surveillance

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Occupational ill health due to skin disease is a significant problem in most countries. Skin health surveillance, as part of a comprehensive skin management system, can help in the prevention of occupational skin disease.

It has been shown to be important that when assessing skin condition we obtain data on conditions within the skin as well those of the skin's immediate surface. Thus traditional methods, such as visual and tactile skin condition assessment should be augmented by the use of skin bioengineering techniques. Simplified equipment, suitable for use in an occupational health environment, is now available.

Several different skin condition parameters can now be measured easily and quickly using non-invasive techniques. These are based on methods well established in dermatological research and skin care product development, but not yet common in occupational health.

These techniques provide quantitative data and, in some cases, may enable the detection of skin damage whilst this is still at the sub-clinical stage. The data provided can be useful in the development of more effective skin management strategies. The data can also be useful in identifying the cause of an occupational contact dermatitis. It can also help in determining the relative irritancy potential of different chemicals, thus enabling the least irritant chemical to be identified.

Case studies will indicate how these techniques can help to create a more effective skin management system. In addition, the use of these techniques has been shown to raise management and workforce awareness, thus encouraging better skin management and skin care standards.

It would be of considerable benefit to those concerned with the prevention of occupational skin disease if such measurement data could be collected together with information about the conditions under which the people being measured were working. This would provide us with much useful information about the effect of the working environment on the skin and the benefits of intervention in the form of skin management systems.

Development of Colorimetric Indicators: A New Technique to Determine Glutaraldehyde and Alkaline Glutaraldehyde Contamination

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The aim of the study was to develop a new indicator sensor pad for detection of glutaraldehyde permeation of chemical protective gloves. The pad carries a reagent which responds to glutaraldehyde contaminant by producing a color change. Some commonly used glutaraldehyde and alkaline glutaraldehyde solutions, Metricide®, Cetylcide-G®, and 50% glutaraldehyde solution, were analyzed by solvent desorption and gas chromatography. All glutaraldehyde solutions exhibited >98% adsorption on the pads over the spiking range 0.05-5.0 μL. Recovery for each glutaraldehyde solution was calculated, ranging from 58-92% (RSD=4.0%) for all glutaraldehyde solutions. Breakthrough times for two protective glove materials (PVC and polymerized alkene) were determined using the Thermo-Hand Method, and found to range from 76 to 150 min for Metricide®, from 170 to 230 min for Cetylcide-G®, and from 232 to 300 min for 50% glutaraldehyde. The quantitative mass of the glutaraldehyde solutions on the pads at the time of breakthrough detection ranged from 35-37, 37-39, and 38-40 μg/cm2 for Metricide®, Cetylcide-G®, and 50% glutaraldehydc, respectively. The new aldehyde indicator pad should find utility in detecting, collecting, and quantitative analyzing glutaraldehyde and alkaline glutaraldehyde permeation samples in the workplace.

Development and Validation of Solvent End of Service Life Indicators for Chemical Permeation of Gloves

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The selection of gloves and chemical protective clothing (CPC) is most often based on laboratory generated permeation data. However, as discussed in a recent paper (Klingner and Boeniger, 2002) it is necessary to test the performance of gloves under actual use conditions to ensure worker safety.

The development of color indicating chemical permeation detectors that can be worn under gloves or CPC during actual use is a simple method to assure protection performance. However, most gloves are worn to protect against exposure to organic solvents or solvent mixtures. A visual indicator for solvent detection has been developed to detect permeation of polar solvents. The detection is based on microencapulation of a colored dye. The capsule is sensitive to dissolution when exposed to solvents.

It is important that an indicator of glove failure be correlated to the toxicological risk associated with the dermal exposure. In a second paper (Boeniger and Klingner, 2002) a target level of toxicological risk was proposed based on a percentage of the 8 hour OEL inhalation dose. The objective of this study was to compare the response of the solvent indicator to the target risk level for selected solvents.

Methods

An ASTM glove permeation test cell procedure was used to quantitate the permeation dose of solvent/glove polymer combinations. The time to respond for the indicator was then compared to the target risk level to determine the indicator's ability to serve as a useful warning of exposure.

Results

The response of the color indicator was well correlated to the risk level for a number of polar solvents tested. The response of the indicator to non-polar solvents was poorly correlated to exposure risk.

Conclusion

The ability to assess the degree of worker protection afforded by gloves and CPC is an increasingly important issue. The simplicity and low cost associated with direct reading colorimetric indicators versus laboratory analysis of exposure enables a broader range of small industry access to this important aspect of worker safety. The poor response of the indicator to non-polar solvents is an area for future development.

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D-Tam Glove Permeation Study

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It is well established that the use of common solvents will enhance the permeation of chemical contamination through skin and chemical protective clothing and gloves. This vehicle effect of solvents is due to their own rapid permeation characteristics. Thus, the use of solvents to clean the skin or CPC of chemical contamination will potentially enhance exposure.

D-TAM Skin Cleansers are high molecular weight (HWM) formulations that have limited theoretical skin permeability. The use of HMW solvents has been demonstrated to be superior to soap and water for skin decontamination of isocyanate exposure. (Wester et al, Toxicol Sci 48:1-4, 1999.)

Likewise, it is theorized due to steric hinderance, HWM solvents will permeate CPC at a slower rate than low molecular weight solvents. Whereas the use of solvents to clean skin has long been discouraged, it remains common practice in industry to use solvents for cleaning chemical contamination from gloves and CPC. This study is designed to determine if the use of HMW solvents to clean gloves will reduce the permeation of chemicals through CPC.

Study Design
The combination of aniline and 18 ml industrial latex gloves was chosen as a challenge test because of the relatively rapid breakthrough time data already published. CLI's colorimetric Permea-Tec Sensor detection system for aromatic amines was used to determine breakthrough time and relative permeation rates. A modified ASTM procedure was used for the glove challenge testing.

A 10% solution of aniline in four different decontamination solutions was used for the glove challenge with 100% aniline as a control.

Decontamination solutions:

- 10% Ivory soap and water (S/W)
- D-TAM polyglycol cleanser (D-PG)
- D-TAM oil based cleanser (D-OIL)
- Fast Orange natural citrus hand cleaner (CIT)

Observations
The octanol water partion coefficient Ko/w of aniline is 0.9, and that will theoretically demonstrate maximum solubility in the D-PG. Aniline has a 4% saturation solubility in water and at the 10% concentration was immiscible with the S/W. 10% aniline was observed to be soluble in the D-OIL and CIT solutions.

The colorimetric indicators were used to detect breakthrough at 30 minutes and every 15 minutes thereafter.

Results

Breakthrough of aniline was detected after 30 minutes for all challenge solutions except D-PG. The colorimetric indicator's detection limit is 5-10 ug aniline. Permeation dose was qualitatively determined by observing the color intensity on the indicator.

Permeation dose at 30 minutes: CIT > neat aniline > D-OIL > S/W.

Breakthrough was detected at 90 minutes for the D-PG at a level similar to the other challenge solutions.

Discussion/Conclusions

The theory that the high solubility of aniline in the D-PG and the apparent low permeability of this HMW formulation resulted in a three-fold increase in the protection factor for this latex glove compared to aniline or aniline solutions. The use of compatible HMW solvents to decontaminate gloves and CPC offers a safer approach than the use of common solvents and has the potential to significantly extend the useful life of CPC in industry at a minimal cost.

Hand Contamination and Protection During Dental Work

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Background
Several of the components in the modern acrylate based dental materials are known to be skin irritants and contact sensitizers. To avoid dermatitis it is important to reduce skin exposure to these chemicals. One first step to this is to identify where and during which moments of work the exposure takes place. Secondly it is important to have knowledge about the protective effect of gloves available on the market.

Aim
The aims of the study were
1) to identify where and when skin contamination with dental material takes place during work and
2) to find out to what extent acrylates permeate gloves.

Methods
The first part was studied by mixing a fluorochrome in commercially available dental bonding materials. Ordinary dental work of treating two cavities with bonding was simulated on training dolls. The work was filmed on video. The contamination was visualized by exposing the hands, arms, face and equipment to UV-light and fluorescence was documented with photography before and after work.

The second part was studied by testing permeation through glove materials according to a standardized method. Gloves tested were made of natural rubber latex (NRL), nitril rubber (NR), polyethylene-copolymer (PEC) and polyvinyl chloride (PVC).

A glove membrane was mounted in a two compartment permeation cell and exposed to water ethanol and acetone solutions of methyl methacrylate (MMA), hydroxyethyl methacrylate (HEMA) and tetraetyleneglycol dimethacrylate (TEGDMA). Analysis of permeated acrylates was done using a gas chromatograph with an in-line gas-sampling valve or by manual sampling.

Results
Fluorescence could be found on 25 of 34 exposed persons. The heaviest contamination

was found on the fingers and on the bottles with dental material on unassisted dentists and assisting dental nurses. Some contamination was located to the hands and, in a few cases, the arms were contaminated. Some spread to working tools could be seen. Work technique strongly influenced the contamination pattern. Using a dappen dish instead of dripping direct on Quick sticks gave more extended contamination.

The glove materials studied were all permeable to acrylate monomers. The highest permeation rates were found for MMA. Of the gloves tested, a methylethylacrylate co-polymer and a thick natural rubber latex glove showed the best protective effect. There was a higher penetration rate from an acetone solution compared to an ethanol or water solution of the same concentration.

Conclusion

Using a cautious working technique, long sleeve shirt and proper protective gloves reduces the risk of skin contamination with allergenic and irritant dental materials. Video documentation of the work process was a very helpful tool in the analysis of the results. The different solvents the acrylates were dissolved in influenced the penetration rate through the protective gloves.

The Routes and Consequences of Internal Contamination of Gloves

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Introduction

Gloves are one of the most widely used types of Personal Protective Equipment (PPE). However, their effectiveness in reducing the risk of contamination can be very poor due to inappropriate choice or incorrect use. The mechanisms of skin contamination inside gloves are not well understood, nor are the health consequences of wearing them. Substances can permeate the glove material, but the quoted breakthrough times can be misleading. Permeation could increase with temperature and flexing of the glove during use. Ingress could be around the edges of the gloves, through the seams or through imperfections in the material. Contamination could be transferred from the gloves to the hands through handling. Knowledge of the routes of contamination is required if PPE is to be made more effective and control procedures improved.

Objectives

The main objective of this study is to determine quantitatively the routes and sites of internal contamination of gloves by carrying out a volunteer study.

Methods

The experimental plan comprised three sets of tests carried out in turn on each subject: a) no instruction (medium gloves), b) after instruction (medium gloves), c) after instruction (short gloves). In a), volunteers were asked to wear and remove a pair of medium length gloves and perform a simple task of washing the inside of a fume cupboard. Three repeats were carried out. They were observed to find out where contamination was occurring. Tracer techniques based on non-toxic fluorescent dye and strontium chloride were used to identify and quantify routes of entry. Transepidermal water loss (TEWL) and Corneometry monitored the skin condition of the volunteers before and after the tasks to show the effect on the skin of wearing the gloves. The study was repeated in b) as a second set of trials after showing the volunteers how to remove and use gloves correctly. A third set of trials c) were carried out using short disposable gloves.

Results

The results from the first set of tests (volunteers given no instruction or training) showed high levels of contamination on eight out of ten of the volunteers (equivalent to over 30 microliters of washing solution). The fluorescent dye was mainly on the fingertips that had removed the gloves. After instruction and training on how to use the gloves properly the levels of contamination were considerably reduced to one in ten (up to 3 microliters of solution), and little or no fluorescent dye was found on the volunteers' hands. However, contamination was found on the arms and around the cuff of the gloves of some volunteers even after instruction on how to use gloves. Hand contamination was

much greater after using disposable gloves, appearing on three out of ten after training, but this was exacerbated by two faulty glove fingertips that allowed water through.

Discussion

The contamination of the hands can be greatly reduced with proper instruction and training on how to put on and remove gloves. However, even with instruction and training some volunteers still managed to transfer dye onto their arms. The occurrence of two faulty gloves out of thirty pairs is far above what would be expected from Quality Assurance standards.

Further data will be collected on the consequences of these findings by applying the same quantities of contamination to the hands with and without wearing gloves. This time, the contamination will contain n-methyl-pyrrolidone, which quickly penetrates the skin and can be detected by biological monitoring of urine. This experiment will show whether the increased temperature and humidity inside a glove enhances permeation through the skin.

A Comprehensive Approach of a Hand Regimen System in Oil Production and Refinery Facilities

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Background
A study was conducted at three oil production and refinery facilities to better understand the effects of a skin care regimen. A comprehensive analysis of the skin care program was conducted that evaluated costs, skin condition, washing practices, and waste management.

Methods
To evaluate skin condition, a technical approach, which included skin bioengineering techniques and expert dermal evaluation, was employed to characterize skin condition and the effectiveness of the skin care program. Skin bioengineering measurements were analyzed in conjunction with self-assessment questionnaires completed by the panelists. Costs and waste management were analyzed by the company's current expenditures. Washing practices were evaluated by on-site inspections and observations of how workers cleaned their hands.

Results
With the implementation of the hand regimen system, significant cost reduction was evaluated. The washing practices of the workers demonstrated a reduction in cleaning time and the use of an appropriate cleaner instead of harmful chemicals and solvents to clean their hands. Comparison of the change in the skin condition of workers using the skin care program (product group) with those not using it (control group) demonstrated significant ($p<0.05$) improvements in skin condition. The quantitative improvement in skin condition was demonstrated in the skin hydration, skin moisture capacity, and expert dermal evaluation data. The qualitative improvement in skin condition was evident in the perception of skin condition improvement observed in the analysis of the self-assessment questionnaires.

Conclusion
These studies indicate clearly the benefits in cost reduction, lost work hours, waste management, and overall skin condition of the workers by implementing a skin care program.

The Impact of a Skin Care Program in a Fiberglass Facility Utilizing Bioengineering Techniques

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Background
A study was conducted at a fiberglass manufacturing facility to better understand the effects of a skin care regimen. A comprehensive skin care program was implemented that included site surveys and analyses, a training program, and the use of GOJO products such as Multi Green (a medium duty industrial hand cleanser) and GOJO Hand Medic (a professional skin conditioner).

Methods
A technical approach, which included various skin bioengineering techniques, was employed to characterize skin condition and the effectiveness of the skin care program. Skin bioengineering measurements were analyzed in conjunction with self-assessment questionnaires completed by the panelists. The objective of this study was to assess the effectiveness of using a comprehensive skin care program in the fiberglass-manufacturing environment.

Results
Comparison of the change in the skin condition of workers using the skin care program (product group) with those using not using it (control group) demonstrated significant ($p<0.05$) improvements in skin condition. The quantitative improvement in skin condition was demonstrated in skin hydration, skin moisture capacity, transepidermal water loss, and three-dimensional color scans of the hand. The qualitative improvement in skin condition was evident in the perception of the improvement in skin condition found in the analysis of the self-assessment questionnaires.

Conclusion
This study indicates clearly the benefits in terms of improved skin condition that result from the regular use of a skin treatment product as part of an industrial skin care regimen.

Thermal Desorption of Solvents Using a Passive Dermal Dosimeter

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The American Conference of Governmental Industrial Hygienists lists more than 170 chemicals with a skin hazard designation that supplements the Threshold Limit Values for inhalation concentration. Because about 13 million workers in the United States are potentially exposed to these chemicals, efforts are required to prevent dermal exposure that may contribute to systemic toxicity. In addition, dermatitis which is the primary cause of occupational disease is not generally covered by a skin notation. Protective clothing and gloves can reduce the risk but before a glove can be used, it needs to be tested. The ASTM has developed procedures which test the gloves for breakthrough time and permeation rate; but these tests are conducted in a laboratory and do not always represent field use conditions.

Passive dermal dosimeters allow personal protective equipment (PPE) to be evaluated for effectiveness under actual field use conditions. These sensors include both colorimetric detectors and charcoal pad systems. These methods greatly improve PPE selection for specific applications.

This paper will describe a Permea-Tec Sensor which utilize a charcoal pad for organic solvents. This pad will respond colorimetrically to polar organic compounds but can also be extracted by solvent or thermal desorption and analyzed by GC/FID for those compounds that are not sensitive to the color chemistry. Several compounds were spiked onto the sensors to compare desorption efficiency and also to test for storage of the chemicals on the pad. Both solvent extraction and thermal desorption were evaluated for their effectiveness in removing contaminants. Pads can be sent to the lab for analysis or desorbed in the field with a portable gas chromatograph.

The objective of the study is to evaluate both thermal desorption and solvent extraction in removing contaminants from this pad. By using thermal desorption, the industrial hygienist will be able to evaluate the effectiveness of a glove in the field.

Effect of Cycles of Contamination and Decontamination on Chemical Glove Performance

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Chemicals that saturate protective gloves cause matrix contamination to the glove materials. Following exposure, the contamination may then diffuse from the matrix to both sides of the gloves. As a result, subsequent wearing of the gloves without decontamination may expose the wearer's skin to the diffused chemicals. An adverse skin reaction may result, such as allergic contact dermatitis, which requires only a very minute concentration to trigger an allergic response.

In this study a method was developed for matrix decontamination based upon the permeation theory and glove resistance. The ASTM F739 method of permeation was used to measure the breakthrough (BT) and steady state permeation rate (SSPR) of toluene, which was used as the contaminant of three glove materials: nitrile, neoprene, and butyl. A closed-loop system, consisting of an Infrared analyzer (IR), an AMK 1-inch permeation cell, and a metal bellows pump, was used to obtain the data. The success of the decontamination was measured by the degree of resistance to permeation as determined by BT and SSPR. Following the exposure, the toluene contaminant was extracted from the matrix of the glove materials using consecutive washes of ethyl alcohol in three concentrations: 100%, 75%, and 50%, followed by a distilled water wash. The exposed sample of glove material and each wash solution was placed in a container which was in turn, incubated in an ultrasonic bath at 60° C for 30 minutes.

Chemical resistance (BT and SSPR) of the three materials was measured for eight consecutive cycles of exposure and subsequent decontamination. The results indicate that the resistance of the neoprene glove material was not compromised in any of the eight cycles. Chemical resistance for the nitrile material was compromised after two cycles, (BT decline = 33.6%, $p < 0.01$) while the butyl was compromised after the initial exposure (BT decline = 6%, $p < 0.01$). There was also an increase in SSPR values following the first exposure cycle.

In a separate study, the authors found that decontamination by heat extraction yielded good results with both neoprene and nitrile but was ineffective for the butyl. Thus, the authors concluded that no single method of decontamination is equally effective for all glove materials or all chemicals. Therefore, further studies are needed to determine the most effective decontamination methods for different material-chemical combinations.

An Evaluation of Dermal Exposures from an Engineering Perspective

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Researchers from the National Institute for Occupational Safety and Health (NIOSH) evaluated dermal exposure issues from an engineering controls perspective. The hierarchy of controls are: Chemical substitution, process modification, isolation of the process or workers, administrative controls, and use of personal protective devices. However, the primary solution to dermal exposures has often been selected from the bottom of the hierarchy, the recommendation to use chemical protective clothing (CPC). At best the recommendation to use CPC is accompanied with a recommended polymer type for construction of the CPC based on chemical compatibility with the hazardous chemical. There are often further recommendations to evaluate the possibility of chemical substitution, process change, or engineering controls, however, these recommendations are seldom carried out.

The latter recommendations require an in-depth knowledge of the chemistry and industrial processes but also provide a superior long-term solution. It is the responsibility of the occupational health community to team with the technical knowledge base within the industry to promote a long-term solution using intervention methods that are higher in the hierarchy of controls.

In a new NIOSH project, occupational health engineers, along with partners, will study the industrial processes and work practices in detail for each industrial site selected. Raw materials, intermediates, final products, unit operations, process equipment, worker interaction with the processes, plant drawings, and process flow diagrams will be reviewed and evaluated. Literature on chemical substitution, process changes, and engineering controls will be evaluated. Recommendations will be given. Interventions will be implemented. An engineering evaluation will be conducted to measure success including an economic impact.

Investigation of the Compatibility of a Skin Protection Gel and Natural Rubber Gloves

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When the hands cannot be protected by more effective engineering measures, gloves give the best possible protection. They are used to protect the hands mainly from chemical and biologic agents, but they can also be used against physical and mechanical hazards. Gloves may also be necessary for the protection of foodstuffs from contamination by the hands, or for the protection of patients against contamination by microbes on the hands of medical personnel.

However side effects from glove wearing are not uncommon. One major disadvantage of wearing gloves is skin occlusion, intense sweating and subsequently skin maceration. This can provoke skin irritation, while the barrier properties of the skin are reduced. Additionally, the prevention of evaporation of skin moisture by gloves creates a disagreeable skin feeling and reduces compliance with employer requirements to use this protective measure.

There are skin protection formulations available, which can reduce skin maceration induced by wearing gloves and therefore increase compliance and keep the skin in a healthy state. However, it is important to realize, that by using these formulations, interactions between the skin protection formulation and glove material occur.

Unfortunately, no standard test method is available to analyze this interaction. By modifying the standard test methods for gloves, which investigate the properties of glove materials, the influence of protection creams on glove materials can be investigated.

For evaluation of the impact of a skin protection gel on glove materials, two modified standard methods were used. One method is the determination of the tensile strength of the glove material (EN 455-2/ASTM D 412-98a).

Another method which can be applied is the electrical leakage test method, which is standardized for condoms (EN 4074). This method was preferred to the water leakage test which has been shown to be not very sensitive in that only holes with a diameter >50 um can be detected.

In both investigations, half of the natural rubber gloves were pretreated with a high amount of skin protection gel for a period of 2 hours. Subsequently, the tensile strength or the electronic resistance was determined in accordance with the methods mentioned above. Then the results were compared to the readings of the untreated gloves.

The results demonstrate that the skin protection gel reduces very slightly the tensile strength of the glove material. Based on the electronic method, no interaction between skin protection gel and natural rubber gloves could be found.

Both test results demonstrate the excellent compatibility of the skin protection gel with natural rubber gloves. Comparing both test results, the measurement of the tensile strength seems to be more appropriate to determine slight interactions between glove materials and skin protection formulations.

Diphoterine(R) and Hexafluorine(R): New Active Skin/Eye Decontamination Compounds

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Diphoterine(R) is an hypertonic, polyvalent, amphoteric, chelating compound with 6 active sites developed in France as an skin/eye chemical splash water-based decontamination solution. In vitro and in vivo, it decontaminates approximately 600 chemicals/chemical groups, including acids, alkalis, oxidizing and reducing agents, irritants, lacrimators, solvents, alkylating agents such as sulfur mustard, and radionuclides (238-U, 137-Cs, 90-Sr/Y, 60-Co); thus, the identity of the chemical involved in an exposure need not be known. Its chemical bond energy for such agents is greater than that of tissue receptors. Its hypertonicity impedes chemical tissue penetration and may remove some amount of skin/cornea-absorbed toxicants not already bound to tissue receptors. Chemical reactions with this decontamination solution are not exothermic (do not release significant amounts of heat). Its decontamination efficacy is greater than that of water, and for use against chemical warfare agents, it is at least as efficacious as dilute bleach solutions but is non-toxic and has no irritant potential. In experimental animals, this decontamination solution and its acid/alkali decontamination residues are not irritating to the eyes or skin. It is essentially nontoxic (LD50 [Rat] > 2000 mg/kg, oral /dermal routes). In human volunteers, it was not irritating in normal eyes. In European workplaces, decontamination of skin/eye acid, base, and other chemical splashes with this solution was associated with decreases in long-term sequelae, lost work time, and need for additional burn treatment or burn center/ophthalmology referral as compared with water lavage. It washes harmful chemicals off exposed tissues as well as neutralizing these substances. This decontamination solution cannot prevent systemic toxicity from chemicals that have already been absorbed through the skin and it is not a treatment for chemical burns. It can prevent or decrease the severity of skin/eye burns following nearly all chemical splashes and results in nearly immediate pain relief.

This decontamination solution can be used for mass chemical casualty decontamination in either civilian or military settings with the DRP-200 system which recycles the solution, requires little water and power, results in decontamination residues that are non-toxic and not harmful to the environment, and processes 200 persons per hour.

Hexafluorine(R) is a derivative of Diphoterine(R) specifically designed for decontaminating hydrofluoric acid (HF) skin/eye splashes. It has the same safety profile as the parent compound. In vitro, it returns the pH and pF (negative logarithm of the fluoride ion concentration) to levels that are not harmful, whereas either water or 10% calcium gluconate do not. In animal studies with 70% HF, this solution completely prevented burns, while water had no effect and water followed by calcium gluconate gel inunction only delayed the onset and decreased the burn severity. In 28 industrial HF (<20% to 70%) or pickling acid (6% HF/15% HNO3) exposures, decontamination with

this solution prevented or decreased the severity of burns and resulted in nearly immediate pain relief.

These decontamination solutions represent significant advances over simple water decontamination for nearly all chemical skin/eye splashes. Supporting references and short descriptions of experiments and studies will be presented in the poster.

Development of a Glove End of Service Life Indicator (ESLI) for Weak Organic and Inorganic Acids

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A commercially available colorimetric indicator used to detect permeation of acid/base compounds through chemical protective gloves was previously evaluated (Vo, The Analyst, 127:178-182, 2002) and was found to be insufficiently reactive toward weak organic acids. Exposure to propionic acid, acrylic acid and other weak acids was of sufficient concern to merit the development of an alternative indicator system that allows the detection of these chemicals.

A new indicator pad based on the use of 2-[4-(dimethylamino) phenylazo] benzoic acid, sodium salt was developed. This indicator produces a visible color change in a pH range of 5-6 allowing detection of these weak acids. In addition, a method to quantitatively determine the exposure dose of permeating chemicals to the indicator pad was developed using solvent desorption and gas chromatography.

The pad was used to detect both organic and inorganic acid permeation through six representative polymeric glove materials. A comparison of the indicator response to breakthrough times was determined by using a modified ASTM F-739 procedure with an infrared analyzer. The indicator proved highly sensitive and reliable in detecting and collecting acid permeation occurring through gloves and as use as a field validation method for glove performance.

Poster Session 5: "Developing Policy and Communicating Effectively"

5.1 **Prevention of Nickel Allergy - The EU Nickel Directive and European Standards**, Carola Lidén, Department of Occupational and Environmental Dermatology, Stockholm County Council and Karolinska Institutet, Stockholm, Sweden

5.2 **Methods for Analysis of Allergens - A European Standardisation Project**, Carola Lidén, Department of Occupational and Environmental Dermatology, Stockholm County Council and Karolinska Institutet, Stockholm, Sweden; Magnus Bruze and Birgitta Gruvberger, Malmö University Hospital, Malmö, Sweden; Roger Hooper, NiDI, UK; and Ann-Therese Karlberg, Göteborg University, Göteborg, Sweden

5.3 **NORA Dermal Exposure Research Program (DERP)**, Sidney C. Soderholm, PhD, National Institute for Occupational Safety and Health, Morgantown, WV, USA

Prevention of Nickel Allergy – The EU Nickel Directive and European Standards

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Nickel is the most frequent cause of contact allergy. At least 10-15% of women and 2-5% of men are allergic to nickel, and 30-40% of nickel-sensitive people develop hand eczema which may often be chronic with far-reaching consequences for both the individual and the society.

The Nickel Directive

The EU Nickel Directive was adopted in 1994, and it entered into full force in July 2001. The aim is to prevent sensitisation and also elicitation of allergic contact dermatitis. Nickel is limited:

(1) in posts used during epithelization after piercing (nickel content below 0.05%);
(2) in objects intended for direct and prolonged contact with the skin, such as jewellery, watches, buttons, zippers etc. (nickel release below 0.5 microgram/cm2/week);
(3) coated items under (2) must fulfil the criteria after "two years of normal use".

Test methods for nickel – European standards

CEN/TC 283/WG 4, convened by Sweden, has under a European Commission mandate developed the three reference test methods for showing compliance with the demands of part 1-3 of the Nickel Directive:

(1) EN 1810 – Nickel content by atomic absorption spectroscopy
(2) EN 1811 – Nickel release, one week in artificial sweat
(3) EN 12472 – Wear and corrosion test

The screening test for nickel release based on dimethylglyoxime (DMG) and ammonia has been further developed (CEN TR 12471). It has been made more sensitive and more specific than the simple DMG test. The standard describes a pre-test (the simple DMG test), a field application, and a laboratory application. The test is quick, cheap and simple to perform. It may be used by producers, retailers, consumers and authorities, as a guide concerning nickel release.

Effects of regulation

Denmark has since 1989 had a regulation limiting nickel release, similar to part 2 of the Nickel Directive. In Denmark, reduced sensitisation to nickel has been recorded among dermatitis patients (Duus Johansen J et al. Br J Dermatol 2000;142:490-5), and in schoolgirls with pierced ears (Jensen CS et al. Br J Dermatol 2002;146:636-42). This has been interpreted as a result of the regulation.

In Sweden, the market has started adaptation to the Nickel Directive (part 2) as shown by a study performed in 1999, two years before full entry into force. The largest market holders were aware of the coming demands and tried to introduce nickel policy in their

quality control system. 25% of 725 items tested with the simple DMG test were positive, and would not comply with the demands (Lidén C et al. Contact Dermatitis 2001;44:7-12).

Conclusions

Prevention of nickel allergy is of great concern. The EU Nickel Directive limits nickel in certain items known to be the most important causes of sensitisation. Part 2 of the Directive, limitation of nickel release from items in direct and prolonged contact with the skin, has already been shown to have an impact.

The nickel allergy problem will hopefully be much reduced in the future, provided that the market adapts to the requirements of the Nickel Directive. Information to increase understanding of the problem and effective control will be needed.

Methods for Analysis of Allergens – A European Standardisation Project

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Allergic reactions are a significant and increasing health problem. Several contact allergens that cause dermatitis, and some respiratory allergens that cause asthma and rhinitis, are chemical substances present in materials and products. The EU and national authorities try to prevent some of the problem by regulations concerning limitations in use and by labelling, such as the Nickel Directive, Cosmetics Directive, Directives on classification of dangerous substances, and on dangerous preparation, and limitation of chromium in cement (Lidén C, Contact Dermatitis 2001;44:65-69).

For many of these regulations, analytical methods are lacking for control of compliance with the legislation. Common European analytical methods in the form of European standards would represent a considerable improvement and increase possibilities for prevention of allergy. Such standards would prove useful in supporting existing and future European legislation. They would be useful also in tendering procedures.

A new European standardisation project (CEN BT/WG 132 "Methods for analysis of allergens") started in December 2001 and is convened by Sweden (convenor: C Lidén).

Aim
The aim of CEN BT/WG 132 is to examine the need to develop standards for analytical methods, applicable to known allergens in materials and products in both occupational and private life.

CEN BT/WG 132 shall examine the need to create a CEN/TC for executing possible future standardisation, prepare a work programme, set priorities, and identify needs for further research and development.

Current work programme
CEN BT/WG 132 participants are nominated experts from 8 European countries representing authorities, industry and science. Liaison partners represent the European Society of Contact Dermatitis (ESCD), European Federation of Asthma and Allergy Assoc. (EFA) and European Flavour and Fragrance Assoc. (EFFA). The European Commission has been approached also.

The work is focused on a selection of the most important allergens, mainly skin sensitisers. The following aspects are covered for each substance:

- Prevalence of allergy and major causes;

- Current and planned regulations;
- Available analytical methods, and their clinical relevance;
- Possibility for standardisation;
- Possibility for prevention by regulation.

Four project groups carry out the work and a nominated expert heads each project group:

PG1 - Metals: nickel, chromium in cement, chromium in leather, and cobalt (R Hooper);
PG2 - Plastics and rubber chemicals: isocyanates, acrylates, epoxy, PTBFR, carbamates, thiurams, and MBT (M Bruze);
PG3 - Preservatives etc: BIT, MCI/MI, formaldehyde, formaldehyde donors, MDBGN, formaldehyde in textiles and leather, and dyes (B Gruvberger);
PG4 - Perfumes and colophony: the most important fragrance allergens proposed for limitation by the Cosmetics Directive, and unmodified colophony (A-T Karlberg).

CEN BT/WG 132 shall avoid duplication of work, and is not engaged in the following:

- allergens in foods, medicaments or medicinal products;
- identification of new allergens;
- testing of sensitising potential of allergens.

Summary
CEN BT/WG 132 "Methods for analysis of allergens" is a new European standardisation project. Areas are identified, where future development of standardised analytical methods for specific allergens could support existing or planned European legislation aiming at prevention of allergy.

NORA Dermal Exposure Research Program (DERP)

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Estimates indicate that more than 13 million workers in the United States are potentially exposed to chemicals that can be absorbed through the skin. A worker's skin may be exposed to hazardous chemicals through direct contact with contaminated surfaces, deposition of aerosols, immersion, or splashes. When substantial amounts of chemicals are absorbed, systemic toxicity can result. Contact dermatitis can also result when chemicals are absorbed through a worker's skin. Contact dermatitis is one of the most common chemically induced causes of occupational illness, accounting for 10 to 15 percent of all occupational illnesses at an estimated annual cost of at least $1 billion.

The National Institute for Occupational Safety and Health (NIOSH) and approximately 500 external partners created the National Occupational Research Agenda (NORA) to guide occupational safety and health research into the next decade. The Agenda is made up of 21 priority research areas including allergic and irritant dermatitis. As part of NORA, NIOSH encouraged its intramural researchers to join together to develop large scale programs in and across NORA priority areas. One of the three interdisciplinary cross-divisional priority program areas funded in 2000 was the development of dermal policy based on laboratory and field studies. The overall goal of this program is to promote the development of improved NIOSH policies and recommendations for identifying and controlling dermal overexposures and dermatitis. This goal will be accomplished by (1) adding critical information to our current knowledge base through laboratory and field investigations and (2) developing and applying scientific decision-making processes for policy development using that knowledge base. For simplicity, this program is frequently called the NORA Dermal Exposure Research Program (NORA DERP).

There are currently eight research projects in the program contributing information in such areas as developing biomonitoring methods; developing colorimetric methods; conducting case studies in the field relating to exposure assessment, intervention evaluation and engineering controls; developing improved mathematical relationships to predict percutaneous penetration and sensitization potential; conducting laboratory studies of decontamination and penetration; and developing recommendations for improving current NIOSH skin notations. One core project applies the Local Lymph Node Assay (LLNA) to predict the sensitization potential of pure chemicals and mixtures. Another core project coordinates the program and encourages scientific forums on the topic.

Highlights of accomplishments include improved measurement and analysis methods, protocols for field studies, funding to encourage other researchers to enter this field, as well as leadership for this conference. Having completed approximately one-third of the proposed lifetime of this Program, we anticipate significant progress in the next few years

toward the improvement of NIOSH recommendations for identifying and controlling chemical over-exposures to the skin of workers.