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Regulatory Toxicology and Pharmacology 41 (2005) 150–158
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Conference report

# Proceedings of the international conference on occupational and environmental exposures of skin to chemicals: science and policy—session II: health effects and hazard identification [1]

Dermal risk assessment is becoming an important issue in regulatory toxicology. As the inhalational exposure to hazardous substances is more effectively controlled, the exposure through the skin contributes increasingly to the overall exposure. It is estimated that over 13 million workers in the United States are potentially exposed to chemicals that can be absorbed through the skin. By route of percutaneous penetration, toxic chemicals may cause systemic health effects as well as localized skin injuries such as irritation, corrosion, and hypersensitivity. Occupationally, contact dermatitis is one of the most frequently reported illnesses, accounting for 10–15% of all occupational diseases at an estimated annual cost in the US of at least $1 billion.

While the problem of skin exposure continues to magnify, there is little guidance regarding its anticipation, recognition, evaluation, and control. In practice, a skin notation (SN) on the list of occupational exposure limits (OELs) represents a major regulation in existence to alert the workers of the skin absorption hazards present in the workplace. The SN traditionally indicates chemicals that may induce systemic health effects by uptake through the skin. However, the definition of this notation in operation differs from country to country. Furthermore, by its original design the SN is not a tool to indicate chemicals that provoke localized skin injuries in which the skin itself is a target organ. The other limitations in the notation system as a warning of the hazard include the lack of ability to distinguish the severity of health impact and the uncertainty in the criteria selected to facilitate the SN assignment.

A strategy that may improve the evaluation and risk communication of occupational skin exposure is the development of a quantitative standard such as the dermal occupational exposure limits (DOELs). The development of DOELs requires reliable measurements of dermal exposure, and at the moment is the aim of occupational hygienists and researchers involved in the assessment of skin exposure risks. Also required for setting DOELs is a good knowledge of toxicology for the target compounds, including the percutaneous penetration and kinetics data. The main obstacles that currently impede the use of DOELs in quantitative risk assessments are the lack of general agreement on how to measure skin contamination and the lack of percutaneous penetration data generated following standardized and validated methods.

On September 8–11, 2002, the National Institute for Occupational Safety and Health (NIOSH) organized the International Conference "Occupational and Environmental Exposures of Skin to Chemicals: Science and Policy" in Washington, DC. The aim was to bring together scientists with many different areas of expertise (dermatologists, occupational hygienists, laboratory researchers, policy makers, and occupational physicians) to focus on the science, knowledge gaps, and policy opportunities related to occupational and environmental exposures of the skin to chemicals. The Conference was divided into five concurrent sessions to present issues pertinent to occupational and environmental skin exposures, with the major themes in these sessions being "Defining the Problem," "Health Effects and Hazard Identification," "Measuring and Predicting Exposures," "Controlling Exposures and Prevention," and "Developing Policy and Communicating Effectively." All sessions shared a common goal of exploring research and policy developments that may serve as or promote effective actions for the prevention and control of occupational and environmental skin exposures.

Session II of the Conference was dedicated to health effects and hazard identification. Hazard identification is the first step in the dermal risk assessment that consists in comparing the exposure levels with the no-observed-adverse-effect levels (NOAELs) usually obtained using animal models. The session planning committee [formed by H. Ahlers, P. Elsner, P. Engasser, F. Gerberick, G. Kennedy, and P. Sartorelli (Coordinator)] in accordance with the NIOSH organizers (S. Soderholm and M. Boeniger) determined and arranged for the main subjects and the speakers for plenary presentations.

[1] Hilton Crystal City, Washington, DC, USA, September 8–11, 2002.

doi:10.1016/j.yrtph.2004.10.004

## 1. Plenary presentations

The plenary presentations in Session II (chaired by P. Sartorelli and F. Gerberick) focused on several aspects of dermal uptake of chemicals, including penetration, absorption, distribution, and scientific approaches associating risk with chemicals when exposure occurs by the dermal route.

Faith Williams (Skin Toxicology Unit, Department of Environmental and Occupational Medicine, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne, UK) discussed *Percutaneous Penetration Studies for Risk Assessment*. To predict systemic health risks 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 (SARs), and physiologically based pharmacokinetic (PBPK) models, and increasingly from measurements of percutaneous penetration using isolated human or animal skin maintained in an in vitro diffusion system. The findings from animal studies can be related to available toxicology data whereas the results from studies using human skin provide the most relevant information for human risk assessment. It is important to standardize the in vitro penetration studies and to validate them with parallel in vivo studies. Many different in vitro systems are in use and a number of organizations have produced guidelines. A standardization study with 10 European laboratories has recently been conducted as part of the research project ''Evaluations and predictions of dermal absorption of toxic chemicals'' (EDETOX) funded by the European Union, assessing the robustness of the in vitro approach in prediction of percutaneous penetration of chemicals. A protocol was developed in line with the OECD Guidelines and agreed among participants, and an inter-laboratory comparison was conducted for the absorption of three marker chemicals: caffeine, testosterone, and benzoic acid. Despite that a range of techniques were used (e.g., flow-through and static diffusion cells), the predictions were robust and variation within laboratories was small. Greater variation was found among laboratories, with a major determinant of the spread being the inter-individual differences in penetration of chemicals.

Howard Maibach (Department of Dermatology, University of California at San Francisco, San Francisco, CA, USA) described the *Factors Influencing Percutaneous Penetration in the Workplace and General Environment*. Factors for which data exist include: regional variation (~50× from the least to the most permeable areas), effect of clothing, washing, soil, mass/unit area, and ''delivery'' vehicle (matrix). The following areas are of particular interest in understanding the factors affecting the skin-penetrating behaviours of chemical substances:

- relevant and non-predictable differences of in vivo vs. in vitro studies;
- dramatic effect of occlusion;
- regional variation of percutaneous penetration;
- stratum corneum reservoir;
- decrease in the percentage of absorption by increase in the applied dose;
- effectiveness of decontamination for hydrophilic and hydrophobic substances;
- metabolic reactions in the skin;
- evaporation of volatiles;
- skin damage;
- relationship between percutaneous penetration and the size of stratum corneum.

John Corish and Dara Fitzpatrick (Department of Chemistry, Trinity College, University of Dublin, Dublin, Ireland) deliberated upon *Theoretical Models of Percutaneous Absorption*. To estimate the skin absorption of toxic chemicals, risk assessors need a realistic and flexible model compatible with available computational resources and capable of making discriminatory predictions. There are three principal aspects of percutaneous absorption essential to the modeling approach, and a complete model should allow the parameters that control each of them to be adjustable so to reflect the conditions of exposure during model simulation. The first aspect is the exposure itself, for which the variables may include the formulation and mode of application, the duration and number of exposures, the use of protective clothing, and personal hygiene. The second is the percutaneous penetration process in which the complex nature of the skin, the reservoir effect, and the influences of penetration enhancers and of damage to the skin should be considered. Finally, the representation for systemic disposition of the substance should include consideration of its half-life, the metabolic processes that it may undergo, the elimination kinetics, and its toxicity.

Models of percutaneous absorption that share a primary objective of predicting the skin permeability coefficient ($K_p$) are commonly developed by two techniques. The first is the use of quantitative SARs (QSARs) that relate statistically the measured biological activity of a series of compounds to their physicochemical and/or structural properties (such as the octanol–water partition coefficient of the substance and some measures of its molecular bulk, e.g., molecular weight or molecular volume). The second technique is to develop mathematical equations based on the theories available for the process under study and to solve the equations either analytically or using numerical methods. For percutaneous penetration, the equations originating in the partition of the diffusing substance between layers of skin and the macroscopic theories for the substance's transport along the resulting pathways are utilized.

The development of an integrated model of dermal exposure and absorption, capable of providing realistic predictions on which risk assessments could be based, will require that the limitations in evidence be overcome. These limitations include the quality, reliability, and consistency of the data used in the development and validation of QSARs and other models. In particular, accurate and reproducible data must be generated under conditions that reflect typical occupational exposures. Such data would enable decisions on the choice of optimum QSAR models and of the ranges of chemicals to which such models may apply. More reliable and flexible models will then be required to encompass variables such as formulation/vehicle/phase and the detailed exposure regime, including the non-steady-state events. Simulations based on these models will need to integrate the specific types of information relating to the different processes of exposure, adsorption, and disposition to realistically assess the risk. The EDETOX project is currently addressing some of these deficiencies and issues.

Frank Gerberick (Procter and Gamble, Cincinnati, OH, USA) outlined *The Importance of Exposure and Potency in the Assessment of Skin Sensitization Risk*. Essential elements for conducting a sound risk assessment for new chemicals introduced into the workplace or marketplace involve the development of an understanding of the sensitization potential of the contact allergen and the likely dose, nature, extent, and duration of exposure. One area of difficulty in the development of a quantitative risk assessment for a contact allergen is the lack of objective information regarding its relative potency compared with other skin sensitizers. The development of a novel predictive assay in the mouse, the Local Lymph Node Assay (LLNA), provides new opportunities for obtaining objective and quantitative estimation of skin sensitization potency. For the purpose of hazard identification, the LLNA measures the sensitization potential as a function of the lymphocyte proliferative responses induced in draining lymph nodes by test chemicals. The chemicals that at one or more test concentrations provoke a threefold or greater increase in lymphocyte proliferation compared with vehicle controls are classified as potential contact allergens. This method has been applied recently to the determination of relative potency, with comparisons between chemicals based on the mathematical derivation of an EC3 value, an estimated concentration of chemical necessary to cause a threefold 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. This latter correlation is of the greatest significance in evaluating the accuracy of relative potency determinations made using the LLNA. It is anticipated that the quantitative estimates of relative skin-sensitizing potency (EC3 values), in combination with an understanding of the exposure, will be of considerable utility in the development of sound risk assessments for skin-sensitizing chemicals.

Jesper Bo Nielsen and Philippe Grandjean (Institute of Public Health, University of Southern Denmark, Odense, Denmark) were among the first to point out the limits of SNs and the uncertainties linked to the assignment criteria. They discussed the *Criteria for Skin Notation in an International Perspective*. The SNs were originally introduced as a qualitative indicator (i.e., a warning sign) of hazards related to dermal absorption. As a qualitative hazard warning, SNs do not allow the differentiation of the chemicals recognized as skin exposure hazards by their toxicity or percutaneous penetration rates. The SNs have not been applied as intended: only few new SNs have been added even when respiratory exposure limits were substantially lowered. To be useful in most practical settings, SNs need to be supplemented by some kind of quantitative measure to classify or categorize the skin exposure hazards.

As the understanding of percutaneous absorption processes improved, some countries/organizations developed alternative and more sophisticated guidelines for assigning SNs to chemicals. These guidelines also aim at taking into account the relative importance of the dermal absorption compared to the pulmonary absorption of chemicals present in the air at a level equal to the airborne exposure limit. In this instance, a SN is assigned to a substance if its dermal absorption is expected to significantly increase the total systemic exposure. Several relevant issues must be considered. First, how much is a 'significantly' increased absorption? Second, should this assessment account for potential increase in percutaneous absorption of chemicals as a result of dermatological diseases or skin defattening? Third, many skin exposures involve chemical mixtures in which one agent may enhance or attenuate the skin penetration of another. Should the SNs include substances that enhance the penetration of other chemicals of greater toxicological potency? These issues have not yet been resolved appropriately and may be difficult to address with a simple administrative instrument as a notation in the official lists of OELs.

The use of different criteria in assigning SNs and the fact that some countries include skin irritation in SNs have resulted in a very uneven distribution of SNs among countries that have comparable OELs. A continuing source of uncertainty impeding the SN assignment is the availability of proper data on dermal penetration of chemicals and the questionable quality of existing data. Furthermore, when available the penetration data are largely provided for pure compounds, not for their

mixtures as often present in the commercial formulations. The lack of information that elucidates the penetration characteristics of mixtures has caused regulatory authorities to strengthen the requirements for approval of new commercial products. The needs for SN improvement and preventive measures in this regard have expanded rapidly in the recent years.

In their conclusions Nielsen and Grandjean recommended to improve the SNs by including a (semi) quantitative measure in the assignment process, and that the issues with SNs are taken up by international organizations with an ultimate goal of obtaining an improved tool to facilitate the prevention of occupational skin exposures.

## 2. Poster presentations

In addition to the plenary talks a total of 13 posters were presented in Session II of the Conference. These posters introduced a broad spectrum of topics representative of current trends in research for dermal hazard identification and evaluation, ranging from investigating skin absorption of chemicals present in different physical states, vehicles, and environmental conditions to developing QSARs and PBPK models predicting skin permeability, systemic toxicity attributed to skin absorption, and skin sensitization potency. New in vitro bioassays and analytical methods were developed to identify the irritation, sensitization, and metabolism of biologically relevant compounds in the skin, as were the biomonitoring techniques to determine the accumulation and elimination of dermally absorbed chemicals in the body. These presentations include:

- *Dermal Exposure to Powdered Solids and Aqueous Solutions: Are the Risks Different?* by Annette L. Bunge and Eugene E. Ley (Colorado School of Mines, Golden, CO, USA);
- *A Mathematical Approach for Evaluating Dermal Exposure and Facilitating Assignment of Skin Notations* by Chen-Peng Chen, Mark F. Boeniger, and Heinz W. Ahlers (NIOSH, Cincinnati, OH, USA);
- *Use of Real-Time Breath Analysis and PBPK Modeling to Evaluate Dermal Absorption of Aqueous Toluene in Human Volunteers* by Karla D. Thrall, Karl K. Weitz, and Angela D. Woodstock (Battelle Pacific Northwest Division, Richland, WA, USA);
- *Molecular Changes in Skin Following Acute Dermal Exposures to Irritating Chemicals* by James N. McDougal (Wright State University School of Medicine, Dayton, OH, USA), Carol M. Garrett and James V. Rogers (Operational Toxicology (AFRL/HEST), Air Force Research Laboratory, Wright Patterson AFB, OH, USA);
- *Dermal Absorption of Vapours: Comparison of In Vivo and In Vitro Data* by Kate Jones, Ian Dick, John Cocker, and Martin Roff (Health and Safety Laboratory, Sheffield, UK);
- *Factors Affecting Dermal Absorption of Vapours* by Kate Jones[1], John Cocker[1], Lisa Dodd[1], Isla Fraser[2], and Martin Roff[1] ([1]Health and Safety Laboratory, Sheffield, and [2]Health and Safety Executive, Liverpool, UK);
- *Active Ingredients in Sunscreens Act as Topical Penetration Enhancers for the Herbicide 2,4D* by Adam R. Pont (University of Nebraska, Lincoln, NE, USA), Anna R. Charron and Rhonda M. Brand (Evanston Northwestern Hospital, Evanston, IL, USA);
- *Dry Trimellitic Anhydride (TMA) Powder Dermal Sensitization Induces Specific IgE and Airway Responses Following Challenge in Brown Norway Rats* by Xing-Dong Zhang, Jeff S. Fedan, Daniel M. Lewis, and Paul D. Siegel (NIOSH, Morgantown, WV, USA);
- *Biologically Based Environmental Exposure Levels (BEELs): The Case for 4,4′-Methylene Dianiline (MDA)* by Shane S. Que Hee (Department of Environmental Health Sciences and UCLA Center for Occupational and Environmental Health, University of California at Los Angeles, Los Angeles, CA, USA);
- *One NIOSH Approach to Estimating Dermal Absorption* by H. Fred Frasch and Ana M. Barbero (NIOSH, Morgantown, WV, USA);
- *Development of New QSAR Approaches in Occupational Contact Dermatitis* by Adam Fedorowicz[1], Hamed Afshari[1,2], Lingyi Zheng[2], Harshinder Singh[1,2], and Eugene Demchuk[1,2] ([1]NIOSH and [2]West Virginia University, Morgantown, WV, USA);
- *Determination of Caffeine and Its Metabolites in Human Skin Homogenate by High-Performance Liquid Chromatography* by Lun-Yi Zang, Jean I. DeHaven, and Sidney C. Soderholm (NIOSH, Morgantown, WV, USA);
- *Percutaneous Absorption of Neat and Water Solutions of 2-Butoxyethanol in Man* by 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).

Additional information including the abstracts and extended abstracts for the podium and poster presentations in Session II and in the other Sessions can be found at a permanent Internet website maintained by the NIOSH Safety and Health Topic Page "Skin Exposures and Effects" (http://www.cdc.gov/niosh/topics/skin/conference/index.html).

## 3. Workshop report

The Conference was followed by a one-day Workshop divided into five individual sessions, with an overarching goal of exploring the effective actions for reduction of health burden from skin exposure to hazardous chemicals and examining the guidance available/needed to encourage implementation of effective actions. In the *Workshop of Session II* "*Health Effects and Hazard Identification,*" led by F. Gerberick, discussions encompassed the current understanding in evaluation of skin absorption, adverse health effects resulting from skin exposure, and prevailing methods of hazard identification and exposure assessment. A Workshop Discussion Paper with organized questions for facilitating the discussions was distributed via the Internet (http://www.cdc.gov/niosh/topics/skin/conference/ws_discuss.html) prior to the Conference. Summarized here are the primary issues discussed in the Session II Workshop and recommendations made on research and public health opportunities for reduction of skin exposure.

### *3.1. Methods and information sources for communication of skin exposure risk*

#### *3.1.1. Skin notations and symbols of dermal exposure hazards*

The Workshop discussed mechanisms currently available for dermal risk communication, with a focus on the SNs and symbols alerting workers of potential skin exposure hazards. The participants recognized the misuses of SNs and the need of a unified international standard for SN assignment as suggested by Jesper Bo Nielsen and Philippe Grandjean in their presentation. In addition, the Workshop discussed possible strategies for improvement of SNs. One approach that has been practiced is to expand the current system to comprise multiple designations, each aiming at a category of health effects of major significance. Examples include the risk phrases prepared by the International Programme on Chemical Safety and the Commission of the European Communities in the International Chemical Safety Cards that denote the specific adverse effects arising from skin exposure, such as toxicity, burns, skin irritation, and sensitization (ILO, 2002a). The American Conference of Governmental Industrial Hygienists also assigns a designation "SEN" as part of the Threshold Limit Value to indicate chemical agents of allergenic potential (ACGIH, 2003) in addition to the conventional "Skin" designation.

The hazard symbols are graphic presentation of the dangers involved in exposure to hazardous substances. By using hazard symbols the message is conveyed to the chemical users in a simple and straightforward manner. They are often used as a warning in the labeling of consumer products and/or of chemical containers. Examples include the labeling symbols used in the European Union and the European Economic Area (ILO, 2002b) for indicating toxic, irritating, and corrosive substances and the symbols incorporated in the hazard labels of the Workplace Hazardous Materials Information System of Health Canada (WHMIS, 2003). The hazard symbols are an effective tool of communication; however they are not always developed by sufficiently established scientific knowledge.

#### *3.1.2. Sources of information for adverse health effects from dermal exposure*

In addition to using tools such as SNs and hazard symbols to alert workers and stakeholders the presence of risk from dermal exposure, an equally important task is to disseminate the information of health effects due to skin exposure to industrial hygienists and occupational medicine practitioners. Several databases provide summaries of adverse health effects as observed in animal studies or reported from occupational incidents, and they are mostly accessible on the Internet or through vendors. Examples include the Hazardous Substances Data Bank in the Toxicology Data Network (TOXNET) (NLM, 2004a) and Haz-Map database (Information on Hazardous Chemicals and Occupational Diseases) (NLM, 2004b) developed by the US National Library of Medicine and the Registry of Toxic Effects of Chemical Substances (RTECS) (NIOSH, 2004) developed by NIOSH. However, it should be noted that these databases collect and report the health effects observed in humans or test animals following the exposure to chemicals by all potential routes of exposure rather than only those explicitly as consequences of skin exposure. The Workshop recognized that the information on skin exposure characterization, health hazard identification, and risk assessment and management may appear in different literature sources, and that there is not a standardized approach to explore pertinent information. The scope and extent of literature search for the purpose of characterizing chemical hazards in the workplace will vary depending on the chemical agents in question and should be determined case-by-case.

### *3.2. Techniques for dermal hazard identification and health effect evaluation*

Substantial discussions in the Workshop were devoted to the techniques used and/or recommended in the identification of health effects resulting from dermal exposure and of skin absorption and permeation of toxic substances. Examples of standardized methods include the Guidelines for Testing of Chemicals developed by the Organisation for Economic Co-operation and Development, the Health Effects Test Guidelines developed by the US Environmental Protection Agency, Of-

fice of Prevention, Pesticides and Toxic Substances, and the protocols established by the US National Toxicology Program (NTP) for determining pre-chronic/chronic toxicity and carcinogenicity. Summarized below are some representative protocols for evaluating the potentials of chemical agents inducing systemic toxicity by route of dermal absorption or causing localized skin injuries.

#### *3.2.1. Protocols for identification of systemic effects due to skin exposure*

Harmonized protocols that examine the systemic toxicity from skin exposure in animals are available and well accepted in research. They study the acute toxicity following single dermal exposure (OECD, 1987; USEPA, 1998a), the repeated-dose toxicity from repeated exposure for a period up to 28 days (OECD, 1981a; USEPA, 1998b), the subchronic toxicity from exposure for at least 90 days (OECD, 1981b; USEPA, 1998c), the chronic toxicity from exposure for at least 12 months (OECD, 1981c; USEPA, 1998d), and the carcinogenicity due to skin exposure (OECD, 1981d; USEPA, 1998e). Laboratory studies conducted using these protocols often report clinical/pathological findings associated with the systemic effects and present quantitative results if and when available. In the acute toxicity testing the mortality rates of animals at different test doses are determined and the results presented as the lethal dose by topical application at which 50% of the test animals expire ($LD_{50}$). In the repeated-dose, subchronic and chronic toxicity and carcinogenicity testing, the no-observed-effect level(s) (NOELs) may be determined for the most sensitive endpoint(s) selected from examined health effects. In addition, methods are available for testing the destruction or disruption of target organ systems and/or specific biological functions.

#### *3.2.2. Protocols for identification of irritation/corrosion due to skin exposure*

Methods for identifying primary skin irritation (non-immunologically mediated) and corrosion include the in vivo animal tests and in vitro bioassays. Most in vivo procedures are based on the Draize patch test (NRC, 1977) and evaluate acute irritancy and corrosivity, with modifications in the exposure duration, test animal species/number, and observation interval. In the standardized in vivo protocols (OECD, 2002a; USEPA, 1998f) the albino rabbits are topically dosed with the test substance, and the appearance of inflammatory reactions (e.g., erythema and edema) and their reversibility are examined over time and scored to provide semi-quantitative results. The in vitro assays assess the dermal corrosivity potentials of chemical substances using human or animal skin models. Examples of in vitro methods include those recommended for regulatory acceptance by the US Interagency Coordinating Committee on the Validation of Alternative Methods and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, including the Corrositex (measuring the pH-sensitive destruction of biobarrier material) (NTP, 1999), the EPISKIN and EpiDerm (measuring the decrease in viability of human skin cells) and the Rat Skin Transcutaneous Electrical Resistance (TER) assay (measuring the TER reduction) (NTP, 2002). The Workshop noted that the in vivo methods based on the Draize procedure in design examine the acute irritancy of a substance and do not provide prediction on the effects following cumulative or repeated exposure.

#### *3.2.3. Protocols for identification of sensitization due to skin exposure*

Standardized protocols available for identifying the potential of sensitization or allergic contact dermatitis include the guinea pig sensitization tests (e.g., the Guinea-Pig Maximization Test and Buehler Test) (OECD, 1992; USEPA, 2003) and the more recently developed murine LLNA (OECD, 2002b; USEPA, 2003). The guinea pig sensitization tests examine the development of a hypersensitive state in animals, as evidenced by the elicitation of disease-analogous skin reactions following the induction of immune responses by a test substance and the challenge exposure. In comparison, the LLNA examines the induction phase of sensitization and determines the sensitization potential by measuring the cell proliferation in the lymph node draining the site of chemical application. Semi-quantitative or quantitative results are often available from these tests.

#### *3.2.4. Protocols for evaluation of skin absorption and permeation*

Experimentally the percutaneous absorption and permeation of chemicals can be investigated either utilizing the whole animals or the cadaver skin coupled with diffusion determination. In the in vivo approach (OECD, 2000a; USEPA, 1998g) the penetration of a test substance through the skin and its systemic circulation and disposition are determined, and the study output typically consists of a quantitative description on the distribution of test chemical in animals following percutaneous absorption, including its presence in the treated skin, blood, excreta, carcass, and any specifically examined organs, and a calculated skin absorption rate. In addition to the basic elements, in vivo studies may include specific designs to investigate the formation of toxicologically significant metabolites, kinetics in blood/plasma, absorption of volatile compounds, or absorption from an infinite source.

In comparison, the in vitro approach focuses on measuring the diffusion of a test substance into and across the excised skin consisting of epidermal membranes or split thickness skin to a fluid reservoir (OECD, 2000b; USEPA, 2004). In the in vitro studies a static or a

flow-through diffusion cell is employed; the former is used to measure diffusion alone while the latter can be used with fresh, metabolically active skin to simultaneously measure diffusion and skin metabolism. The absorption of test substance is measured by analyzing the substance in the receptor fluid over a sampling period sufficient to characterizing the temporal profile of absorption. When an infinite dose is utilized, the permeation constant $K_p$ (cm/h) is reported to quantitatively describe skin diffusion at the steady state. If a finite dose is used in the exposure event, the residues of chemical washed from and stored in the skin at the end of exposure can also be quantified. Alternatively, a short-term absorption rate may be measured if the $K_p$ cannot be obtained, for example, for harsh chemicals that may severely damage the skin after prolonged contact. The short-term absorption rate ($\mu g/cm^2/h$) is determined from the total amount of the test chemical found in the receptor fluid and in the skin.

The Workshop noted that these protocols provided means of dermal hazard identification but did not all serve as tools of risk characterization. In addition, their usefulness in predicting and describing the biological responses elicited by skin exposure to chemical mixtures requires validation, as many of them were not designed specifically to investigate the adverse effects resulting from skin exposure to mixtures. As a conclusion from the Workshop, it is a priority task to develop guidelines of dermal risk assessment that incorporates the hazard identification methods already established. These guidelines should also include protocols for characterization of exposure factors (e.g., concomitant exposure to mixtures) and conditions (e.g., frequency and intensity); such information is crucial in determining if an adverse effect would occur following occupation- or task-specific skin exposures.

The Workshop also examined the current progress in the development of predictive algorithms such as (Q)SARs that identify skin exposure hazards and suggest potential adverse effects based on physicochemical properties of chemical substances. This approach provides a useful mechanism of dermal hazard identification, particularly considering it does not demand animal sacrifice. However, cautions should be exercised when applying these tools to derive at negative conclusions on potential interactions between toxic agents and living tissues, as many of these interactions are not sufficiently realized from laboratory studies and accordingly accounted for in the predictive tools currently available.

### *3.3. Research on effective actions for reduction of skin exposure and health risk*

Within the scope of Session II, the Workshop participants discussed the research likely to significantly improve the actions for reduction of skin exposure and subsequent health threats. The research addressed by the Workshop includes (not listed in the order of priority):

- Studies on the skin permeability of chemical substances related to worker's exposure, especially those:
  - generating experimental data pertinent to occupational exposure;
  - improving the in vivo and in vitro approaches used in hazard identification and the understanding in their limitations;
  - applying standardized protocols of hazard identification to examine chemical substances of higher impacts (e.g., those of wide industrial applications or significant environmental distribution);
  - identifying influences from physicochemical properties of compounds on their skin permeation behaviors.
- Studies on the elicitation of skin injuries or systemic toxicity as a result of dermal exposure to mixtures and the biological/chemical mechanisms involved.
- Studies on the modification of dermal barrier functions resulting from exposure to chemical substances of occupational relevance, including those:
  - investigating physiological changes of skin in association with reduced barrier functions and capability;
  - evaluating absorption of chemicals through damaged/abraded skin vs. healthy skin.
- Studies to refine the methods of hazard identification currently applied in the investigation of skin irritation and sensitization.
- Studies utilizing biological monitoring as a surveillance tool in evaluation of skin exposure and as an investigation technique to provide data on absorption, disposition, and excretion of chemicals following exposure.
- Studies on the effectiveness of personal protective equipments (PPEs) in shielding workers from skin exposure, including those:
  - emphasizing PPE resistance against chemical permeation and degradation;
  - examining the adverse effects such as occlusion effect and allergic reactions in association with chemical breakthrough, PPE deterioration, and/or improper uses.
- Studies to develop methods evaluating skin contamination and decontamination.
- Studies to advance the communication with and education of workers, stakeholders, occupational professionals, and policy makers on the health risk arising from skin exposure to hazardous substances.

The Workshop concluded that, to improve the hazard identification process as an effective action for prevention of skin exposure, it is a top priority to develop guidance of hazard identification and evaluation through analysis of existing data and application

of standardized decision-making logics. This guidance should consider practical utility to both experts and non-experts and for adoption in workplace practices. Also important is to promote collaboration among physicians and dermatologists, occupational and environmental hygienists, and toxicologists in the tasks of identifying potential skin hazards. To achieve these goals, continuous efforts are necessary to increase the interactions among professionals playing different roles in the efforts of exposure prevention and to disseminate the information on occupational and environmental skin exposures. One mechanism to facilitate these efforts is an easily accessible, centralized database or a similar system, serving as a platform for the exchange of knowledge on factors and conditions leading to skin exposures, adverse health effects due to such exposures, and recommendations of intervention strategies. An effective action is attainable only when all actors of diverse backgrounds in relevant fields collaboratively contribute to its design, demonstration, and implementation.

## Acknowledgments

The authors thank Drs. Heinz W. Ahlers, Charles L. Geraci, and Sidney C. Soderholm of NIOSH, Dr. Rhonda M. Brand of Evanston Northwestern Healthcare Research Institute, Northwestern University, and Dr. Sanja Kezic of Coronel Institute of Occupational and Environmental Health, University of Amsterdam, for their reviews of the proceedings during its development. Their valuable input greatly improved the quality and scope of this report.

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Available online 9 December 2004