NORA Dermal Exposure Research Program Description

I. NORA DERP Overview

Developing Dermal Policy Based on Laboratory and Field Studies

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 a 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).

II. NORA DERP Specific Aims

Program Specific Aim 1: Develop policy documents and guidelines that make scientifically-based recommendations for recognizing and controlling occupational dermal hazards.

The Education and Information Division (EID) project "Development of Decision-Making Procedures and Documents" will provide the program focus for identifying critical chemical data and developing needed decision-making processes using those data in order to classify a chemical's potential to cause dermatitis or cause systemic toxicity after dermal exposure. This project also will provide the specific expertise needed to develop draft policy documents to provide both the classification of chemicals' dermal toxicity potentials and proven strategies for identifying and controlling dermal hazards on work sites. Although this project's personnel will be primarily responsible for this work, they will continuously draw upon the expertise of other researchers in the program and even elsewhere in NIOSH and outside NIOSH to develop the best possible policy documents given the available knowledge base. The researchers in this project have made significant progress in identifying critical data and developing a decision-making process for classifying chemicals with regard to their potential for causing local or systemic toxicity by the dermal route.

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Program Specific Aim 2: Apply widely-accepted methods for classifying the potential of chemicals to cause occupational dermatitis.

The Office of the Director, Agriculture and Immunotoxicology Group, (OD/AIG) project "Hazard Identification Core" will assure that the necessary chemical testing services related to characterization of a chemical's potential to cause allergic dermatitis will be available to the researchers in the program. Testing available will include the local lymph node assay (LLNA), a fairly new but widely-accepted animal test for assessing the allergic contact dermatitis potential of chemicals, as well as phenotypic analysis and cytokine evaluation for the differentiation of T cell mediated and IgE mediated sensitizers. In order to identify the probable cause of occupational dermatitis cases, such testing will be needed for both individual compounds and mixtures encountered in field investigations conducted as part of this program.

Program Specific Aim 3: Demonstrate effective interventions in workplace case studies conducted in a range of occupations and industries whose workers suffer from occupational dermatitis AND

Program Specific Aim 5 : Demonstrate effective interventions in workplace case studies in occupations and industries in which dermal absorption contributes to systemic toxicity.

Several projects in the program focus on conducting field investigations (and include essential complementary laboratory investigations) in order to develop a proven suite of strategies for anticipating, recognizing, evaluating and controlling hazards that could otherwise lead to either dermatitis or systemic toxicity by the dermal route.

The Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS) project "Field Studies to Assess and Prevent Dermal Over-Exposures" provides much of the expertise to conduct broad-based field investigations. The researchers also have experience through the Health Hazard Evaluation program in providing work site-specific recommendations for identifying and controlling dermal hazards. All of the field investigations will collect qualitative data about successful strategies for dealing with dermal hazards. In some very important cases, it will be possible to collect quantitative data, for example, relating the amount of chemical on surfaces, in the air, on skin and in the body. These types of data will be especially valuable in evaluating the effectiveness of hazard reduction strategies. In order to conduct such quantitative field investigations, it is almost always necessary to evaluate the exposure of a worker to a chemical using biological monitoring.

The Division of Applied Research and Technology (DART) project "Biomonitoring Analyses for Studies of Dermal Exposure" will provide the expertise needed to develop new or improve and apply existing biomonitoring measurements. Because these researchers will need to develop needed biomonitoring techniques before the field studies using them are started, the program investigators have chosen 2-butoxyethanol as one chemical for early development or improvement of biomonitoring analyses based on the chemical's widespread use and high potential for causing either dermatitis or systemic effects or both.

Another aspect of field studies that can acquire quantitative or semi-quantitative data is the measurement of the chemical of interest on surfaces, on the skin or under protective clothing. The National Personal Protective Technology Laboratory (NPPTL) project "Develop & Demonstrate the Use of Colorimetric Indicators" will develop and support the field use of colorimetric indicators for indicating the amount of chemical on surfaces, including under protective clothing.

A critical part of developing successful hazard reduction strategies is the consideration of other control options besides the traditional one of providing personal protective equipment. The Division of Applied Research and Technology (DART) project "Developing an Engineering Control Knowledge Base" will provide the specialized process and control engineering expertise needed to consider options of substitution, administrative controls, and engineering design improvement necessary to tailor a solution to the particular work site situation. Any of the work places investigated in the other field projects are potential sites for this work. This project started in fiscal year 2002.

Program Specific Aim 4: Improve the ability of mathematical models to predict systemic absorption through controlled laboratory studies and check the predictions for consistency with the results of field studies.

The Health Effects Laboratory Division (HELD) project "Predicting Skin Penetration: Model and Experiments" develops mathematical and computer models based on principles of mass transfer as well as comparisons with experimental results. Features of this work include a focus on realistic stratum corneum morphology, use of fluorescent tracer chemicals to define pathways through the stratum corneum and the collection of data from epidermal and stratum corneum permeation studies as well as from stratum corneum desorption studies.

The HELD project "Quantitative Structure Activity Relationship Modeling" uses state-of-the-art tools to elucidate relationships and begin to provide new types of tools for predicting percutaneous penetration and potential to cause allergic or irritant dermatitis. Preliminary work has focused on an existing set of in vitro human skin penetration data. The project is also building a database of information on the dermal sensitization potential of chemicals and on chemical properties in order to develop structure/sensitization relationships that are expected to be helpful in screening lists of chemicals to identify those with the highest sensitization potential for testing.

The HELD project "Developing Healthy and Dermatitis Skin Absorption Models" will provide a consistent set of data on penetration, absorption and decontamination of a variety of chemicals using in vitro animal and human models and in vivo animal models. In the later phases of the project, the in vivo model will include dermatitis.

Program Specific Aim 6: Document project impact and organize meetings and workshops with a variety of stakeholders and partners to exchange information.

The HELD core project "Coordinating Core" will facilitate interactions among the researchers in the program, including the facilitation of work groups helping to develop changes to NIOSH policy. This project will serve as the central contact for outside partners interested in the program, will facilitate the planning of workshops and conferences related to the program's research area, and will monitor and document program accomplishments and impact on the problem of dermal over-exposures.

III. NORA DERP Projects

Project 1. Development of Decision-Making Procedures and Documents

Project Officer: Heinz Ahlers, Education and Information Division

The overall goal of this project is to develop a series of documents aiming to inform workers and employers and setting forth NIOSH recommendations for classifying substances as contact or allergic dermatitis agents or

systemic toxins by the dermal route as well as methods for evaluating worker exposures and the effectiveness of potential exposure-reduction approaches.

The first specific aim is to develop and publish an initial decision-making process for classifying chemicals as potential systemic toxins by the dermal route with later improvement through collaboration with laboratory and field study researchers in a continuous feedback approach in which the decision-making process is refined.

The second specific aim is to evaluate the utility of possible approaches for estimating the allergenic and irritant dermatitis potential of suspected chemicals based on structural activity relationships developed in collaboration with the HELD Computational Biology Team and based on widely-accepted testing procedures, such as the Local Lymph Node Assay, implemented with the assistance of the HELD Core Project. In a continuous feedback approach, evaluations will be refined as critical data and the knowledge base are supplemented by information obtained in laboratory and field studies. The third specific aim is to develop documents for transferring information developed in the laboratory and field studies on cutaneous hazards to those who can act to control hazards in work places. The researchers in this project will take a key role in drafting the documents and procedures in consultation with NIOSH laboratory and field researchers through established working groups.

Project 2. Biomonitoring Analyses for Studies of Dermal Exposures
Project Officer: Kenneth L. Cheever, Division of Applied Research and Technology

A significant part of this program will be accomplished through field investigations of the occurrence of and intervention strategies for reducing dermal exposures. The overall goal of this project is to provide the biomonitoring analyses required by these investigations through development and application of new analytical methods and adaptation of published methods.

The specific aims are to develop biomonitoring methods for 2-butoxyethanol via urinary butoxyacetic acid and for 1-bromopropane via urinary n-propyl mercapturic acid. Other biomonitoring analyses will be developed as needed. Data on proper timing of collection of the specimens and specimen stability will be obtained, if not available elsewhere. The analytical methods will be verified as to precision, accuracy, and detection limit.

Project 3. Field Studies to Assess and Prevent Dermal Over-Exposures
Project Officer: Boris Lushniak, Division of Surveillance, Hazard Evaluations, and Field Studies

The overall goal of this project is to develop a scientific process and a knowledge base to evaluate and control occupational dermal exposures and systemic or dermal health effects using information and experiences from case (field) studies.

The specific aims of this project are to: 1) review, assess, and evaluate past NIOSH field reports dealing with dermal exposures and health effects in order to categorize specific exposures, health effects, and recommendations (emphasizing past Health Hazard Evaluation (HHE) reports, reporting trends and determining the basis of recommendations), 2) develop partnerships with industry, labor, academia, and Federal and State agencies and to utilize these partnerships in setting up field studies, 3) assess the usefulness of determining pre-clinical and clinical direct skin effects of occupational dermal exposures in the workplace, 4) assess the usefulness of measuring dermal exposures in the workplace by using a wide variety of approaches in biological, surface, and skin monitoring, 5) develop a broadly applicable protocol for the industrial hygiene and medical evaluation of dermal exposures and health effects in workplaces, 6) reduce or eliminate dermal exposures and health effects in the workplace by introducing and testing the effectiveness of interventions, and

7) participate in policy development work groups. This project will consist of the following three main activities: 1) review and partnership building, 2) field studies for exposure assessment and health effects studies (emphasizing the HHE program), and 3) field surveys for intervention studies.

Project 4. Developing an Engineering Control Knowledge Base
Project Officer: Leroy Mickelsen, Division of Applied Research and Technology

The overall goal of this project is to develop an engineering control knowledge base to address occupational dermal hazards that will be a basis for policy development. The specific Aims are: 1) develop partnerships with high dermal hazard industries, 2) evaluate workplaces that have dermal hazards and provide engineering solutions tailored to the individual sites, 3) integrate and develop the results of evaluations conducted at each site into an engineering knowledge base for policy development aimed at reducing dermal hazards in the workplace, and 4) participate in the work of appropriate NIOSH groups developing policy documents involving the control of occupational dermal hazards. In order to accomplish these aims, partnerships will be developed with industry engineers, so their knowledge base can be leveraged in the engineering control study. NIOSH engineers, along with their newly developed partners, will study the industry, process, and work practice in detail for each site. 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. Video will be taken to evaluate work practice and skin contact. Literature on chemical substitution, process changes, and engineering controls will be evaluated. Recommendations will be given. Interventions will be implemented. An engineering evaluation with be conducted. The engineering process from each of 4 or 5 sites will be integrated into a knowledge base for policy development.

Project 5. Develop & Demonstrate the Use of Colorimetric Indicators
Project Officer: Evanly Vo, National Personal Protective Technology Laboratory

The absorption of chemical agents through the skin varies widely among different chemicals and cannot be fully predicted from knowledge concerning the physical and chemical properties of the chemical agents, so the lack of a means whereby the worker can visually discern the chemical permeation may result in skin over-exposure. The overall goal of this project is to develop rapid and reliable colorimetric indicators to provide a method for field validation of chemical protective gloves and clothing.

The specific aims of this proposal are to: 1) synthesize colorimetric indicating compounds, 2) design and fabricate colorimetric-indicating pads for each indicator compound, 3) test each pad with the appropriate chemicals to provide a positive control and color reference, 4) evaluate the pads and demonstrate their ability to detect chemical permeation through glove and protective clothing materials in workplace studies, and 5) participate in the work of NIOSH groups developing policy documents involving colorimetric indicators and protective clothing. The general research plan includes the following steps: synthesize indicator compounds and test each indicator compound to determine if they have adequate response to these chemicals; fabricate and test indicator pads with target chemicals to provide a positive control and color reference. Conduct both laboratory and field evaluations to demonstrate each pad's ability to detect chemical permeation through glove and protective clothing materials in workplace condition in accordance with ASTM permeation standards.

Project 6. Predicting Skin Penetration: Model and Experiments
Project Officer: H. Frederick Frasch, Health Effects Laboratory Division

The overall goal of this study is to improve the ability of mathematical/computer modeling to predict both steady- and non steady-state penetration of chemicals through human skin. The underlying hypothesis is that

dermal penetration can most appropriately be predicted using a "random walk" approach. This model is unique in that it proceeds from first principles (diffusion) and explicitly accounts for the heterogeneous structural properties of stratum corneum (SC) which govern skin permeation. Diffusion is modeled at the micro level as a random walk, from which macro level diffusion properties, including permeability, can be derived. In-vitro penetration and diffusion studies will be performed using excised human cadaver skin. These results will be used for parameter optimization of the computer model and to evaluate the predictive ability of the model.

To achieve these goals, a number of specific aims have been identified: 1. To quantify the gross morphology and lipid lamellar organization of human stratum corneum. 2. To identify and quantify specific diffusional paths through stratum corneum using two model fluorescent compounds, one polar and one lipophilic. 3. To obtain data from in-vitro epidermal and SC permeability and SC desorption experiments. 4. To refine a computer model of penetration of chemicals through skin to account for human SC structural organization and for anisotropic lipid lamellar properties. 5. To derive mathematical relationships to enable the prediction of systemic chemical exposures from realistic occupational dermal exposure scenarios. These studies will supply needed data and modeling capabilities to DERP. Results from these studies will be applied by DERP in the process of science-based policy development.

Project 7. Developing Healthy and Dermatitis Skin Absorption Models
Project Officer: Sidney C. Soderholm, Health Effects Laboratory Division

The overall goal of this project is to develop suitable in vitro animal and human skin models and in vivo animal models and apply them to obtain data on the penetration, absorption and decontamination of skin by chemicals, in such a way that those data can be credibly applied to situations faced by workers in order to improve the identification and control of potential over-exposures. The specific aims are: 1) to develop an in vitro human skin model, 2) develop an in vitro hairless guinea pig skin model, 3) develop an in vivo hairless guinea pig skin model, including dermatitis, during the later phases of this project, 4) develop an artificial sweat/sebum mixture to be used as a "universal" vehicle and 5) apply all three models and the universal vehicle to obtain credible data on penetration, absorption and decontamination for chemicals of widely varying properties.

Project 8. Quantitative Structure Activity Relationship Modeling
Project Officer; Eugene Demchuk, Health Effects Laboratory Division

The overall goal of this project is to develop [Quantitative] Structure-Activity Relationships ([Q]SARs) for occupational dermal exposures and to contribute to understanding the mechanisms of skin permeation by chemicals and the mechanisms leading to dermatitis.

The first specific aim is to extend existing mechanistic approaches (e.g. Potts and Guy; Robinson) to mathematical modeling of skin permeation in order to achieve better understanding of the molecular mechanism(s) of skin permeation and to improve our ability to predict permeation rates. This is achieved by systematic analysis of QSAR descriptors significant for the skin permeation process; use of nonparametric modeling including hierarchical cluster analysis of topological descriptors; and neural networks.

The second specific aim is to develop QSARs for percutaneous permeation across diseased dermatitis skin using absorption and pharmacokinetic data for diseased skin generated by the Program. Success in achieving this specific aim may have significant impact on the third specific aim, which is to develop QSARs for occupational allergic contact dermatitis, including data generated by Local Lymph Node Assay, some within this program. The fourth specific aim is to participate in the work of appropriate NIOSH groups developing policy documents involving this or similar QSAR research.

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Project 9. Hazard Identification Core

Project Officer: Barbara Jean Meade, Office of the Director / Agriculture and Immunology Group

The overall goal of this core is to use validated and other published assays to provide hazard identification and dose response data that can be used by the individual projects and by the project "Development of Decision-Making Procedures and Documents (Ahlers)" and the Derm Policy Working Group for establishing guidelines and writing skin notations.

The specific aims are: 1) Evaluate the potential of a chemical or mixture to be a human sensitizer. A modified Local Lymph Node assay will be used to meet this specific aim. 2) Perform specific assays to aid in the differentiation of chemicals' or mixtures' potential for producing irritation, T cell-mediated or IgE-mediated hypersensitivity reactions. A modification of the LLNA which uses mouse ear swelling as an indicator of irritancy and draining lymph node cell phenotyping to differentiate between, T cell-mediated and IgE-mediated sensitizers, and a murine total serum IgE assay will be used. 3) If required, test individual components of mixtures to identify the chemical(s) responsible for eliciting the biological activity (i.e. irritant or sensitizing potential). 4) Establish in the core new methods related to specific needs arising from ongoing field studies. and 5) Participate in the work of appropriate NIOSH groups developing dermal policy based on the results obtained in the hazard identification core and other research in the Program.

Project 10. Coordinating Core

Project Officer: Sidney C. Soderholm, Health Effects Laboratory Division

The overall goal of this project is to provide a focal point for communication and coordination among program researchers and for communication with external partners and stakeholders. The specific aims are: 1) Establish an identifiable program location named "Coordinating Center for the Dermal Exposure Research Program", 2) Establish regular channels of communication and coordination among program researchers, 3) Monitor progress in individual projects and promote the solution of problems, 4) Foster the start-up of additional research projects and activities through the funding of small feasibility projects, 5) Plan meetings and workshops with a variety of stakeholders and partners to exchange information, 6) Facilitate and support the work of appropriate interdivisional NIOSH groups developing policy documents, and 7) Document and report the program's impact. The intended result is an effective research program, adoption of improved policies by NIOSH and successful tracking of the Program's impact on employers, workers, regulatory agencies and others.

IV. NORA DERP Personnel

Project Officer	NIOSH Division	Project
Heinz W. Ahlers, J.D.	Education & Information Division	Development of Decision-Making Procedures and Documents; Executive Committee
Mark F. Boeniger, M.S.	Division for Surveillance, Hazard Evaluations & Field Studies	Development of Decision-Making Procedures and Documents; Field Studies to Assess and Prevent Dermal Over-Exposures; Executive Committee
Kenneth L. Cheever, Ph.D.	Division of Applied Research & Technology	Biomonitoring Analyses for Studies of Dermal Exposures
Eugene Demchuk, Ph.D.	Health Effects Laboratory Division	Quantitative Structure Activity Relationship Modeling
H. Frederick Frasch, Ph.D.	Health Effects Laboratory Division	Predicting Skin Penetration: Model and Experiments
Boris D. Lushniak, M.D., M.P.H.	Division for Surveillance, Hazard Evaluations & Field Studies	Field Studies to Assess and Prevent Dermal Over-Exposures; Executive Committee
B. Jean Meade, D.V.M., Ph.D.	Office of the Director, Agriculture & Immunotoxicology Group	Hazard Identification Core
R. Leroy Mickelsen, M.S.	Division of Applied Research & Technology	Developing an Engineering Control Knowledge Base
Sidney C. Soderholm, Ph.D.	Health Effects Laboratory Division	Developing Healthy and Dermatitis Skin Absorption Models; Coordinating Core; Program Director; Executive Committee
Evanly Vo, Ph.D.	National Personal Protective Technology Laboratory	Develop & Demonstrate the Use of Colorimetric Indicators