Abstracts of Recent NIOSH Peer-Reviewed Publications from Methodological Studies for Improved Chemical Analyses and Risk Analyses

2003

TITLE: In vivo sensitization to purified Hevea brasiliensis proteins in health care workers sensitized to natural rubber latex

AUTHORS: Bernstein DI, Biagini RE, Karnani R, Hamilton R, Murphy K, Bernstein C, Arif SAM, Berendts B, Yeang HY

SOURCE: J Allergy Clin Immunol 2003; 111:610-616

ABSTRACT: Background: Thirteen proteins of natural rubber latex (Hevea brasiliensis) known to bind human IgE have been isolated and characterized as Hev b allergens. However,the in vivo importance of native Hev b allergens has not been defined in health care workers (HCWs) with natural rubber latex (NRL) allergy.
Objectives: The principal aim of this study was to identify the major in vivo Hev b allergens in HCWs with NRL allergy confirmed by percutaneous sensitivity to nonammoniated latex (NAL).
Methods: Skin prick testing was performed with 7 (native) proteins purified from NAL (Hev b 1, 2, 3, 4, 6.01, 7.01, and a newly described Hev b 13) and recombinant Hev b 5 in 62 HCWs with histories of NRL allergy (group 1) confirmed by percutaneous reactivity to NAL and in 49 atopic HCWs without NRL allergy (group 2). Serial 10-fold concentrations of Hev b proteins (5 x 10(-5) mug/mL to 50 mug/mL) were tested; serum samples of subjects were assayed for serum specific IgE by immunoassays.
Results: Hev b 2, Hev b 5, Hev b 6.01, and Hev b 13 produced skin reactions in more than 60% of group I subjects, with Hev b 1, 3, 4, and 7.01 eliciting reactions in less than 50%. Only I of 49 group 2 workers reacted to a single Hev b antigen (Hev b 13). Specificity of 7 Hev b allergens was 100% and 98% for Hev b 13 in identifying workers with confirmed NRL allergy. Specific IgE by AlaSTAT and CAP immunoassays was elevated in 40 of 60 (67%) and 33 of 62 (53%) of NAL-reactive workers and produced false-positive test results in 4 of 49 (8%) and 3 of 48 (6%) group 2 subjects, respectively.
Conclusion: Hev b 2, 5, and 6.01 are major in vivo allergens and Hev b 13 is a new major in vivo allergen among HCWs with allergy to NRL.

TITLE: Steady-State Flux and Lag Time in the Stratum Corneum Lipid Pathway: Results from Finite Element Models

AUTHORS: Frasch HF, Barbero AM

SOURCE: J Pharm Sci 2003; 92:2196-2207

ABSTRACT: Finite element model (FEM) solutions of the diffusion through two dimensional representations of the stratum corneum (SC) lipid pathway are presented. Both simplified, regular "brick and mortar" models and a more complex, irregular model are analyzed. It is assumed that diffusion occurs only within the SC lipids and the lipids are isotropic. The steady-state flux and lag time are solved and compared with the corresponding values for a homogeneous membrane of the same thickness consisting of lipid material. Results confirm that the heterogeneous SC model behaves like a homogeneous membrane, meaning that FEM diffusion simulations are well approximated by an appropriate solution of the diffusion equation for a homogeneous membrane. Additionally, both steady-state flux and lag time (relative to these values in a homogeneous membrane) can be predicted from algebraic equations based on simple dimensionless descriptors of SC geometry. However, values for diffusivity derived from homogeneous membrane approximations to the FEM solutions (effective diffusivity, D*) are not equal to the intrinsic diffusivity of the chemical in lipid. Furthermore, the pathlength

derived from homogeneous membrane approximations to FEM solutions (effective pathlength, l*) is not equal to the lipid pathlength and is not dependent on SC tortuosity. Whereas l* is not a function of corneocyte overlap, D* is. These model results suggest that diffusion properties of the SC lipid pathway can be correlated to SC geometry, but intrinsic diffusion coefficients and SC tortuosity cannot be derived from common diffusion cell experiments. Use of the model equations to predict permeability and lag time of lipophilic solutes is described.

2002

TITLE: A Critique of Assumptions About Selecting Chemical-Resistant Gloves: A Case for Workplace Evaluation of Glove Efficacy

AUTHORS: Klingner TD, Boeniger MF

SOURCE: Appl Occup Environ Hyg 2002; 17:360-367

ABSTRACT: Wearing chemical-resistant gloves and clothing is the primary method used to prevent skin exposure to toxic chemicals in the workplace. The process for selecting gloves is usually based on manufacturers' laboratory-generated chemical permeation data. However, such data may not reflect conditions in the workplace where many variables are encountered (e.g., elevated temperature, flexing, pressure, and product variation between suppliers). Thus, the reliance on this selection process is questionable. Variables that may influence the performance of chemical-resistant gloves are identified and discussed. Passive dermal monitoring is recommended to evaluate glove performance under actual-use conditions and can bridge the gap between laboratory data and real-world performance.

TITLE: A New Technique to Determine Organic and Inorganic Acid Contamination

AUTHORS: Vo E

SOURCE: Analyst 2002; 127:178-182

ABSTRACT: A new acid indicator pad was developed for the detection of acid breakthrough of gloves and chemical protective clothing. The pad carries a reagent which responds to acid contaminant by producing a color change. The pad was used to detect both organic and inorganic acids permeating through glove materials using the modified ASTM F-739 and direct permeability testing procedures. Breakthrough times for each type of glove were determined, and found to range from 4 min to > 4 h for propionic acid. from 3 min to > 4 h for acrylic acid. and from 26 min to > 4 h for HCl. A quantification was performed for propionic and acrylic acids following solvent desorption and gas chromatography. Both acids exhibited > 99% adsorption {the acid and its reactivity (the acid reacted with an indicator to contribute the color change)} on the pads at a spiking level of 1.8 µL for each acid. Acid recovery during quantification was calculated for each acid. ranging from 52-72% (RSD less than or equal to 4.0%) for both acids over the spiking range 0.2-1.8 µL. The quantitative mass of the acids on the pads at the time of breakthrough detection ranged from 260-282 and 270-296 µg cm-2 for propionic acid and acrylic acid, respectively. The new colorimetric indicator pad should be useful in detecting and collecting acid permeation samples through gloves and chemical protective clothing in both laboratory and field studies, for quantitative analysis.

TITLE: A Random Walk Model of Skin Permeation

AUTHORS: Frach HF

SOURCE: Risk Analysis 2002; 22:265-276

ABSTRACT: A new mathematical model for permeability of chemicals in aqueous vehicle through skin is presented. The rationale for this model is to represent diffusion by its fundamental molecular mechanism, i.e., random thermal motion. Diffusion is modeled as a two-dimensional random walk through the biphasic (lipid and corneocyte) stratum corneum (SC). This approach permits calculations of diffusion phenomena in a morphologically realistic SC structure. Two concepts are key in the application of the model to the prediction of steady-state skin permeability coefficients: "effective diffusivity" and "effective path length," meaning the diffusivity and thickness of a homogeneous membrane having identical permeation properties as the stratum corneum. Algebraic expressions for these two variables are developed as functions of the molecular weight and octanol-water partition coefficient of the diffusing substance. Combining these with expressions for membrane-vehicle partition coefficient and permeability of the aqueous epidermis enables the calculation of steady-state skin permeability coefficients. The resulting four-parameter algebraic model was regressed against the "Flynn data base" with excellent results (R2=0.84;SE=0.0076; F=154;N=94). The model provides insight into the contributions of stratum corneum diffusivity and effective path lengths to overall skin permeability and may prove useful in the prediction of non-steady-state diffusion phenomena.

TITLE: In-Use Testing and Interpretation of Chemical-Resistant Glove Performance

AUTHORS: Boeniger MF, Klingner TD

SOURCE: Appl Occup Environ Hyg 2002; 17:368-378

ABSTRACT: Issuing gloves to workers is the most common approach to protecting against skin contact with hazardous chemicals. Typically, glove materials are selected and duration of wear is estimated based on comparisons of laboratory test data. Those who select the glove materials often fail to verify their selections by testing the glove during actual use. This failure poses a common but potentially serious hazard to workers. Although methods are available for assessing permeation rates during actual use, such testing is unlikely without acceptable exposure guidance criteria for decision making. This document reviews methods for testing glove performance during actual use and suggests an approach for estimating acceptable exposure guidance criteria for evaluation of chemicals that are systemically absorbed. It is the authors' opinion that as of now an approach to estimating exposure criteria for chemical irritants and sensitizers may not be feasible. With available data resources, acceptable glove exposure criteria could be generated for use in assessing the risk of using specific gloves for handling many compounds in occupational settings.

TITLE: Regarding the Sources of Data Analyzed with Quantitative Structure-Skin Permeability Relationship Methods

AUTHORS: Frasch HF, Landsittel DP

SOURCE: Eur J Pharm Sci

ABSTRACT: We investigated the sources of data used in recently published predictive models of skin permeability. It was found that skin permeability coefficients for 63 compounds are poorly documented. We hypothesized that these coefficients were calculated using the simple two variable, three parameter `Potts and Guy' regression equation and hence were not derived from experimental measurements. We therefore examined the distribution of residuals of these reported coefficients compared with the Potts and Guy predictions. The residuals cannot be described by a normal distribution. A substantial (51%) number of residuals equaled 0.00. Further analysis demonstrated that 89% (56 out of 63) of the skin permeability coefficients can be explained as being calculated by the Potts and Guy equation using different documented

octanol–water partition coefficients, and/or transcription errors. The results strongly suggest that these 63 skin permeability coefficients are calculated and not experimentally determined—a conclusion subsequently confirmed by one of the developers of the data set. Continued use of these data would lead to biased model selection, underestimation of experimental variability, and overestimation of model predictive ability.

2001

TITLE: Development of Sampling and Analytical Methods for Concerted Determination of Commonly Used Chloroacetanilide, Chlorotriazine, and 2,4-D Herbicides in Hand-wash, Dermal-patch, and Air Samples

AUTHORS: Tucker SP, Reynolds JM, Wickman DC, Hines CJ, Perkins JB

SOURCE: Appl Occup Environ Hyg 2001; 16:698-707

ABSTRACT: Sampling and analytical methods were developed for commonly used chloroacetanilide, chlorotriazine, and 2,4- D herbicides in hand washes, on dermal patches, and in air. Eight herbicides selected for study were alachlor, atrazine, cyanazine, 2,4-dichlorophenoxyacetic acid (2,4-D), metolachlor, simazine, and two esters of 2,4-D, the 2-butoxyethyl ester (2,4-D, BE) and the 2-ethylhexyl ester (2,4-D, EH). The hand-wash method consisted of shaking the worker'shand in 150 mL of isopropanol in a polyethylene bag for 30 seconds. The dermal-patch method entailed attaching a 10-cm × 10-cm × 0.6-cm polyurethane foam (PUF) patch to the worker for exposure; recovery of the herbicides was achieved by extraction with 40 mL of isopropanol. The air method involved sampling with an OVS-2 tube (which contained an 11-mm quartz fiber filter and two beds of XAD-2 resin) and recovery with 2 mL of 10:90 methanol:methyl t-butyl ether. Analysis of each of the three sample types was performed by gas chromatography with an electron-capture detector. Diazomethane in solution was employed to convert 2,4-D as the free acid to the methyl ester in each of the three methods for ease of gas chromatography. Silicic acid was added to sample solutions to quench excess diazomethane. Limits of detection for all eight herbicides were matrix-dependent and, generally, less than 1 microgram per sample for each matrix. Sampling and analytical methods met NIOSH evaluation criteria for all herbicides in hand-wash samples, for seven herbicides in air samples (all herbicides except cyanazine), and for six herbicides in dermal-patch samples (all herbicides except cyanazine and 2,4-D). Speciation of 2,4-D esters and simultaneous determination of 2,4-D acid were possible without losses of the esters or of other herbicides (acetanilides and triazines) being determined.

TITLE: Random Sampling or 'Random' Model in Skin Flux Measurements? [Commentary on "Investigation of the Mechanism of Flux Across Human Skin In Vitro by Quantitative Structure Permeability Relationships"]

AUTHORS: Poda GI, Landsittel DP, Brumbaugh K, Sharp DS, Frasch F, Demchuk E

SOURCE: Eur J Pharm Sci 2001; 14:197-200

ABSTRACT: Transdermal therapy receives increasing attention as an attractive alternative to traditional drug delivery. Unfortunately the exact algorithm of transdermal permeation that could guide medicinal chemists towards delivery optimization at an early stage of the drug design process still remains to be decoded. This paper discusses some major hurdles on the way to full understanding of Quantitative Structure–Activity Relationships (QSAR) of skin permeation. From the statistical perspective, a recently published combined data set is found to be inappropriate with respect to the distribution of major molecular descriptors, and therefore should be approached cautiously as a source for QSAR model training and in modelling of occupational and environmental skin exposures.

TITLE: Receiver Operating Characteristics Analyses of Food and Drug Administration-cleared Serological Assays for Natural Rubber Latex-specific Immunoglobulin E Antibody

AUTHORS: Biagini RE, Krieg EF, Pinkerton LE, Hamilton RG

SOURCE: Clin Diagn Lab Immunol 2001; 8:1145-1149

ABSTRACT: Receiver operating characteristics (ROC) analyses to evaluate and compare the diagnostic accuracy of Food and Drug Administration (510K)-cleared natural rubber latex (NRL)-specific immunoglobulin E (IgE) antibody immunoassays have not been performed using well-characterized skin-testing reagents. Sera were collected from 311 subjects (131 latex puncture skin test [PST] positive and 180 PST negative). All masked, coded sera were analyzed for latex-specific IgE antibodies in the Diagnostic Products Corporation microplate AlaSTAT, HYCOR HY-TEC RAST, and Pharmacia-Upjohn CAP System RAST FEIA (CAP). Diagnostic accuracy was evaluated using GraphRoc for Windows software to construct and analyze ROC curves in relation to the subjects' PST status and the results of the immunoassays. The ROC areas under the curve (AUCs) ± standard error based on PST for the three diagnostic tests were 0.858 ± 0.024, 0.869 ± 0.024, and 0.924 ± 0.017, respectively, for AlaSTAT, CAP, and HY-TEC. The HY-TEC system had a significantly greater AUC based on PST than those observed for AlaSTAT ($P < 0.05$) and CAP ($P < 0.05$) analyses. When the diagnostic tests were probed as to the cutoffs giving maximal diagnostic efficiency compared to PST, CAP and AlaSTAT yielded values of <0.35 kU of allergen IgE (kUA)/liter and <0.35 kU/liter while the HY-TEC assay yielded 0.11 kU/liter. The diagnostic efficiencies based on PST in our cohort at these cutoffs were 87.1, 88.1, and 88.7%, respectively. The HY-TEC assay had a significantly greater AUC than CAP and AlaSTAT using PST as a diagnostic discriminator in our cohort. When the HY-TEC system was probed at its maximally efficient cutoff (0.11 kU/liter) versus HYCOR's recommended cutoff of 0.05 kU/liter, a loss of sensitivity of 8.4% was observed with a gain in specificity of 19.5%.

2000

TITLE: A Laboratory Comparison of Two Media for Use in the Assessment of Dermal Exposure to Pesticides

AUTHORS: Lorberau CD, Pride JL

SOURCE: Appl Occup Environ Hyg 2000; 15:946-950

ABSTRACT: In a laboratory study, gauze pads and Empore filters were compared for their ability to assess the dermal exposure of two insecticides (chlorpyrifos and diazinon) and five herbicides (atrazine, alachlor, metolachlor, cyanazine, and 2,4-D ethylhexyl ester). The analytes, when analyzed by gas chromatography with flame ionization detection, were found to have a linear dynamic range to at least 250 µg/mL. While a number of different solvents were examined for the desorption of the analytes, methanol was found to be the best solvent for the recovery of all the analytes from 16-ply gauze pads, while 20 percent ethyl acetate in hexane was the preferred solvent for the styrene divinylbenzene impregnated Empore filters. Limits of detection (LODs) for the analytes were comparable for both media. For Empore filters, the LODs were 50 µg/sample for atrazine, alachlor, chlorpyrifos, diazinon, and 2,4-D ethylhexy ester, with 30 µg/ sample for metolachlor, and 80 µg/sample for cyanazine. For gauze pads, the LODs were 40 µg/sample for metolachlor, 50 µg/sample for alachlor, diazinon, and 2,4-D ethylhexy ester, 60 µg/sample for atrazine and chlorpyrifos, and 80 µg/sample for cyanazine. Both gauze pads and Empore filters gave quantitative recovery for all analytes except chlorpyrifos and 2,4-D ethylhexyl ester under ambient conditions (18°C, 70% relative humidity) for up to 30 days; these analytes required refrigeration for that period to reach over 90 percent recovery. To assess the effect of environmental conditions on the recovery of the analytes, samples of each media were spiked at about 125 µg

per analyte/sample (except cyanazine which was spiked at 190 µg) and challenged for 8 hr under high (80%) and low (20%) humidity and high (40°C) and low (5°C) temperature conditions in an environmental chamber. While the Empore samples gave quantitative recovery after being challenged, recovery from the gauze pads was affected by environmental conditions, especially high temperature. Recovery from gauze pads was below 30 percent for some analytes under high temperature/high humidity conditions.

TITLE: A Quantitative Study of Aromatic Amine Permeation Through Protective Gloves Using Amine Adsorptive Pads

AUTHORS: Vo E, Berardinelli SP, Hall RC, El Ayouby N

SOURCE: Am Ind Hyg Assoc J 2000; 61:837-841

ABSTRACT: A quantitative study of aromatic amine permeation through a glove material using Permea-Tec aromatic amine pads, used for the detection of chemical breakthrough of protective clothing, was performed for aniline following the microwave extraction process and gas chromatographic analysis. Aniline exhibited >99% adsorption on the pads at a spiking level of 1.94 mg (1.9 µL). Aniline showed recoveries from 65 to 89% (RSD less than or equal to 5.6%) over the range 1.1-1.9 µL (1.12-1.94 mg) of aniline applied to pads. The modified ASTM F739 and direct permeability testing procedures were used to determine breakthrough times for five protective glove materials using aniline as a challenge chemical. Breakthrough times for six protective gloves were determined, ranging from 182 sec to 82 min. The quantitative concentration of aniline on the pads following permeation through the gloves also was determined, ranging from 0.53 to 0.55 mg/cm2 (1.79-1.88 mg/pad).

TITLE: A Robust Structure-Activity Relationship (SAR) Model for Esters that Cause Skin Irritation in Humans

AUTHORS: Smith JS, Macina OT, Sussman NB, Luster MI, Karol MH

SOURCE: Toxicol Sci 2000; 55:215-222

ABSTRACT: A structure-activity relationship (SAR) model has been developed to discriminate skin irritant from nonirritant esters. The model is based on the physicochemical properties of 42 esters that were tested in humans for skin irritation. Nineteen physicochemical parameters that represent transport, electronic, and steric properties were calculated for each chemical. Best subsets regression analysis indicated candidate models for further analysis. Regression analyses identified significant models ($p < 0.05$) that had variables that were also significant ($p < 0.05$). These candidate models were evaluated using linear discriminant analysis to determine if the irritant esters could be discriminated from nonirritant esters. The stability of the model was evident from the consistency of parameters among ten submodels generated using multiple random sampling of the database. The sensitivity of the ten models, evaluated by "leave-one-out" cross-validation, ranged from 0.846 to 0.923, with a mean of 0.885 ± 0.025 (95% CI). The specificity ranged from 0.615 to 0.923, with a mean of 0.738 ± 0.06 (CI). Compared with nonirritant esters, irritant esters had lower density, lower water solubility, lower sum of partial positive charges, higher Hansen hydrogen bonding parameter, and higher Hansen dispersion parameter. The results indicate that physicochemical features of esters contribute to their ability to cause skin irritation in humans, and that chemical partitioning into the epidermis and intermolecular reactions are likely important components of the response. This model is applicable for prediction of human irritation of esters yet untested.

TITLE: Comparison of Solvents for Removing Pesticides from Skin Using an In Vitro Porcine Model

AUTHORS: Campbell JL, Smith MA, Eiteman MA, Williams PL, Boeniger MF

SOURCE: Am Ind Hyg Assoc J 2000; 61:82-88

ABSTRACT: This study compared four solvents (1-propanol, polyethylene glycol [avg. MW 400], 10% Ivory® Liquid and water, and D-TAM®) for their ability to remove selected pesticides from and in vitro porcine skin model using a solvent-moistened wipe. Wipes were performed 90 min after pesticide was applied to the skin. The four pesticides selected (glyphosate, alachlor, methyl parathion, and trifluralin) were chosen because of their differences in water solubility. This study also determined whether pretreatment of skin with a solvent prior to pesticide application would either increase or decrease recovery of the pesticide. Recovery efficiencies for all solvents and pesticides were affected by the amount of contaminant on the skin. Although pesticide recoveries from all four solvents were similar (range: 45-57%) on average 1-propanol had significantly higher recoveries, followed by soap and water. There was no significant difference between polyethylene glycol and D-Tam. When skin was pretreated with any of the four solvents before pesticide application, the recoveries of the more water soluble compounds, glyphosate and alachlor, decreased. When pretreatment with solvent preceded application of trifluralin, the pesticide with the lowest water solubility, recoveries increased. 1-Propanol or soap and water were more effective in removing pesticides from skin than polyethylene glycol or D-TAM, but the amount of pesticide recovered from skin was affected by the chemical characteristics of the pesticide recovered from was affected by the chemical characteristics of the pesticide (such as water solubility) and the amount of pesticide originally on the skin. This study provides information useful to the interpretation of skin wipe sample results collected in field studies.

1999

TITLE: Determination of Alkylamine Permeation Through Protective Gloves Using Aliphatic Amine Pads

AUTHORS: Vo E, Berardinelli SP

SOURCE: J Environ Monit 1999; 1:545-548

ABSTRACT: A quantitative study of alkylamine permeation through a glove material using Permea-Tec aliphatic amine pads, used for the detection of chemical breakthrough of protective clothing, was performed for triethylamine following a microwave-extraction process and gas chromatographic analysis. Triethylamine exhibited >99% adsorption on the pads at a spiking level of 729 μg (1.0 μl). Triethylamine showed recoveries from 63 to 90% (RSD less than or equal to 5%) over the range 0.2-1.0 μl (146-729 μg) applied to pads. The ASTM F739 standard and direct permeability testing procedures were used to determine breakthrough times for five protective glove materials using triethylamine as a challenge chemical. Breakthrough times for six protective gloves were determined ranging from 40 s to >4 h. The quantitative concentration of triethylamine on the pads following permeation through the gloves was also determined, ranging from 101 to 103 μg cm-2 (382-386 μg per pad). [Editor's note: Many of the units were incorrectly printed in the original and have been corrected here.]

TITLE: Recovery of Some Common Solvents from Protective Clothing Breakthrough Indicator Pads by Microwave-Solvent Extraction and Gas Chromatography

AUTHORS: Vo E, Berardinelli SP, Hall RC

SOURCE: Analyst 1999; 124:941-944

ABSTRACT: The efficiency of solvent adsorption using Permea-Tec general solvent pads, used for the detection of chemical breakthrough of protective clothing, was determined for methanol, acetone, ethyl methyl ketone, trichloroethylene (TriCE), tetrachloroethylene (TetCE), toluene, m-xylene, and D-limonene. Known volumes of single or mixed solvents were added to pads in the range 0.2-5.0 µl (0.16-8.13 mg). After microwave-solvent extraction (ME) into hexan-1-ol, the samples (0.5-3.0 µl) of the filtered and extracted solutions were analyzed by gas chromatography. All solvents exhibited > 97% adsorption on the pads at spiking levels of 0.48-0.98 mg for each solvent. The solvent recovery for the system was calculated for each solvent, with solvents with boiling points below 110 °C showing recoveries of > 90%, and with solvents with boiling points above 110 °C showing recoveries from 80% to 90%. The recovery precision was good (RSD less than or equal to 4%) for all solvents over the range 1.0-2.5 µl of applied solvents to pads for ME and 1.0 µl of extracted solutions for GC analysis. [Editor's note: Two of the mass units were incorrectly printed in the original and have been corrected here.]