Final Performance Report

(Summary Report)

Prediction of Irritation based on Exposure Duration

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ABSTRACT

Dermatitis is an extremely important occupational disease that can make the life of a worker miserable and cost the economy millions of dollars a year in medical treatment and lost time. Dermatitis is the second most frequent occupational disease. Appropriate identification of the contact time required for chemicals to cause irritancy would help ameliorate problems from dermal exposures. The broad, long-term objectives of this project are to develop a biologically-based mathematical modeling approach that can be used to derive duration-based standards for chemical irritancy. The specific objectives of this research were to mechanistically model the relationship between the duration of solvent exposure on the skin and the degree of irritation produced by chemicals representative of solvents and surfactants. Our approach was to use a rodent model to address the pharmacokinetics and pharmacodynamics of three known irritants. We exposed skin on the back of rats and guinea pigs to xylene, limonene and sodium lauryl sulfate for one hour and quantified the responses for up to 6 hours. We developed biologically-based models that can be used for distribution of chemicals in the skin. We measured temporal changes in IL-1α and iNOS proteins in the skin. We found histological changes in guinea pigs were more severe than in rats, but the molecular responses in guinea pigs were much more variable, so we focused on rats. We quantified oxidative species and low molecular weight DNA due to chemical exposure. We measured baseline gene expression and changes in gene transcripts due to exposure to the three chemicals. We found that the skin responded rapidly to chemical contact as evidenced by gene transcript and inflammatory cytokine changes. Gene responses and histological responses suggest that these chemicals may cause irritation by different mechanisms. We developed methods to expose dermal fibroblasts in a collagen matrix to a volatile chemical and quantify toxicity based on target tissue dose. Our conclusions are that our approach is an excellent model to study chemical irritation, but the temporal responses of proteins related to changes in mRNA we found need to be studied before the long-term objectives can be achieved.

SIGNIFICANT FINDINGS

1. **Normal gene expression in rat skin** – We investigated, for the first time, toxicity-related genes that are expressed in normal rat skin before any treatment with an irritating chemical [1][2][3]. Using the Affymetrix GeneChip protocol, we found there were 234 separate gene transcripts (of the 850 on the rat toxicology chip) present in at least 80% of the ten skin samples studied. Of these genes, the ones that were identified fell into the following categories: Metabolism (37%); oxidative/cellular stress (19%); signal transduction (14%); miscellaneous (11%); differentiation/cell division (6%); cell structure (5%); transporters/ligands (3%); cytokines/growth factors (2%); and extracellular matrix (2%).
2. **Changes in gene expression with brief exposures to irritating chemicals** – We found that gene expression in rat skin occurred very quickly in response to irritating chemicals[1][2][3]. A one-hour exposure to xylene, sodium lauryl sulfate and limonene caused changes (based on a two-fold increase or decrease) in transcripts that were present at the end of the exposure time. Neat limonene caused the largest number of gene expression changes, i.e. 38. 10% sodium lauryl sulfate caused 22 gene changes and xylene caused 19 changes. One percent and 10 percent sodium lauryl sulfate showed a does response with more genes responding at the higher concentration. The greatest gene response with limonene was at one hour and the greatest gene response with sodium lauryl sulfate was at four hours. Only one gene was upregulated from exposure to each of three chemicals, c-myc oncogene. The temporal differences and magnitude of changes suggest that these chemicals have different mechanisms of irritant action.
3. **Changes in oxidative species and low molecular wt DNA with brief exposures to xylene** – We investigated production of oxidative species (by oxidation of 2,7-dichlorofluorescin diacetate) and presence of low molecular weight DNA (by agarose gel electrophoresis) after one-hour exposures to rats[4]. We found that by one hour after the end of the exposure, oxidative species had increased. Low molecular weight DNA, an indication of injury to the skin, was also increased at one hour after the exposure. These responses serve as molecular indicators of skin irritation.
4. **Changes in IL-1α and iNOS protein levels** – We investigated changes in interleukin-1α (IL-1α) and inducible nitric oxide synthase (iNOS) after one-hour exposures of rats to xylene[5][6][7][8][9]. IL-1α levels were highest at the end of the exposure and slowly declined for the next 5 hours. iNOS levels peaked at about four hours and then slowly declined. These results show that inflammatory protein response is very rapid with these irritant chemicals. The earlier response of IL-1α compared to iNOS is consistent with the potential for the pool of IL-1α in the stratum corneum and epidermis to be the trigger for oxidative events caused by iNOS.
5. **Histological changes show differences in irritant treatments** – We investigated hematoxylin and eosin-stained sections of treated rat skin for up to five hours after a one hour exposure[1][5][10]. Histopathological changes at 3 hours after a one-hour exposure differed in severity, with limonene showing the most severe epidermal separation and granulocyte infiltration. Xylene showed moderate epidermal separation and granulocyte infiltration and 10% sodium lauryl sulfate showed the least. These results combined with the gene induction studies show that histological severity does not necessarily correlate with molecular response.

6. **Method developed for assessment of tissue concentrations** – We developed a method that we could use to try to understand the tissue distribution and toxicity of volatile organic irritants [11][12][13]. Traditionally, measurements of toxicity in cell cultures are reported as the concentration of chemical that is added to the culture media. For volatile organic chemicals, this number tremendously underestimates the toxicity because a large amount of the added chemical evaporates. We developed and validated a closed system for determinations of toxicity (LC_{50}) where the toxicity is expressed as the concentration of chemical inside the cell.
7. **Rats vs guinea pigs sensitivity for skin irritation** – We compared several molecular and histological parameters after equivalent exposures of rats and guinea pigs to xylene[6]. We found the histological changes were more severe in guinea pigs compared to rats. However, the molecular responses (IL-1α and iNOS protein and mRNA levels, nitrite production as an indication of NO, nitric oxide synthase activity, oxidative species and lipid peroxidation) of guinea pigs were generally of a lower magnitude and much more variable. [14]

USEFULNESS OF FINDINGS

These findings will be used to focus future studies on the molecular cascade in the skin that occurs with irritant chemical contact. These studies illustrated the rapid response of the skin to chemical irritants. Levels of IL-1α, an inflammatory protein, were increased at one hour after initiation of the exposure. Changes in gene expression were also found at one hour. Understanding of the early responses to skin irritation has the most potential for therapeutic intervention or prophylaxis. Baseline gene expression in normal skin will have a tremendous impact on our understanding of the structure and function of the skin. Differential changes in gene expression and histological responses with three skin irritants suggests that there is more than one pathway responsive to skin irritation. Demonstration of oxidative species and low molecular weight DNA will help in the understanding of the acute skin response to irritants. Taken together, the findings in this study will refine our understanding of the irritant cascade and ultimately lead to a biologically-based mathematical model that can be used to predict chemical irritancy in the workplace.

SCIENTIFIC REPORT

Specific aims: This proposed research was the first step in a series of planned studies to develop and demonstrate a mathematical approach that can eventually be used by industrial hygienists and other health professional to predict hazards of irritant contact dermatitis (ICD) from various durations of dermal exposures to solvents. We envisioned that a duration-based limit could be developed (i.e. minutes or hours of skin contact per week) analogous to a Threshold Limit Value® (except the limit value would be a time rather than a concentration) if the information were available. This approach would ultimately serve to better identify irritants prior to introduction of new processes into the workplace and provide better information about the safe use of current workplace chemicals. The specific objective of this research was to quantitatively understand the relationship between duration of surfactant and solvent exposures on the skin and the degree of irritation produced. A biologically based model to understand this relationship has

never been attempted. We hypothesized that for most chemicals, duration of exposure is an important determinant of the amount of chemical that enters the skin and subsequently causes irritation. We also hypothesized that the amount of chemical in the skin directly determines the severity of irritation. We proposed to refocus our extensive expertise in the biologically based modeling of chemical flux through the skin to understanding and predicting the immediate dynamic events that occur with the presence of an irritating chemical on the skin. The first focus was be to understand and predict the time course of the relationship between the concentration of chemical on the skin and the distribution of chemical in the skin based on physicochemical properties of the solvents. Next, we wanted to understand and predict the temporal relationship between the concentration in the skin and the cellular response of the skin. Finally, we wanted to develop the understanding required to predict the degree of irritation based on the duration of skin contact. Our specific aims are listed below with the publications that support them:

1. **Develop a predictive biologically based mathematical model for distribution of solvents in stratum corneum, viable epidermis and dermis.**
    a. Poet TS, McDougal JN: Skin Absorption and Human Risk Assessment. *Chemico-Biological Interactions*, 140:19-34, 2002.
    b. McDougal JN, Boeniger MF: Methods for Assessing Risks of Dermal Exposures in the Workplace. *Critical Reviews in Toxicology*, 32(4):291-327, 2002.
    c. McDougal JN: Methods in Physiologically-based Pharmacokinetic Modeling, In: Dermatotoxicology Methods: The Laboratory Worker's *vade mecum*, (eds. FN Marzulli HI Maibach), Taylor and Francis, Washington DC, pp51-69, 1998.
    d. McDougal JN: Prediction - Physiological Models. In: Dermal Absorption and Toxicity Assessment, (eds. MS Roberts, KA Walters), Marcel Dekker, New York, pp189-202, 1998.
    e. McDougal, J.N.: Physiologically-based Pharmacokinetic Modeling, in Dermatotoxicology, (eds. FN Marzulli, HI Maibach), 6th edition, Hemisphere Publishing Corporation, Washington DC, in press, 2003.
    f. Abstract #1 attached

2. **Identify a reliable biomarker pathway and extend our histopathological method for assessing irritant response in both the viable epidermis and the dermis in rats.**
    a. Rogers JV, Gunasekar PG, Garrett CM, McDougal JN: Dermal Exposure to m-Xylene Leads to Increasing Oxidative Species and Low Molecular Weight DNA in Rat Skin. *Journal Biochemical and Molecular Toxicology*, 15:228-230, 2001.
    b. Gunasekar PG, Rogers JV, Kabbur MH, Garrett CM, Brinkley WW, McDougal JN: Molecular and Histological Responses Related to Acute Skin Irritation from Exposure to m-Xylene. *Journal Biochemical and Molecular Toxicology,* in press, 2003.
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    d. Geiss, KT, Garrett CM, Rogers JV, McDougal JN: Improved Method for Obtaining RNA from Rodent Skin. AFRL-HE-TR-2001-0150, 2001.

e. Rogers JV, McCafferty JD, McDougal JN: Improved method for in vitro assessment of volatile organic chemical exposure using living dermal equivalents. AFRL-HE-TR-2002-0009, 2002.
f. Abstracts #2-9 attached.

3. **Understand and model the relationship between skin concentration and cellular response in a biologically based manner.**
   a. Rogers JV, McDougal JN: Improved Method for *in vitro* Assessment of Dermal Toxicity for Volatile Organic Chemicals. *Toxicology Letters*, 135:125-135 2002.
   b. McDougal, J.N.: Physiologically-based Pharmacokinetic Modeling, in Dermatotoxicology, (eds. FN Marzulli, HI Maibach), 6th edition, Hemisphere Publishing Corporation, Washington DC, in press, 2003.

4. **Understand the mechanistic relationship between exposure concentration and skin response well enough to be able to predict the irritant response profile based on duration of exposure to the surface, and the duration of exposure which would result in a specific skin response.**
   a. Coleman CA, Hull BE, McDougal JN, Rogers JV: The effect of m-xylene on cytotoxicity and cellular antioxidant status in rat dermal equivalents. *Toxicology Letters*, in press, 2003.

CITED PUBLICATIONS

[1] Rogers JV, Garrett CM, McDougal JN: Gene Expression in Rat Skin Induced by Irritating Chemicals. *Toxicology Letters*, submitted.

[2] Garrett, C., K Geiss, J. McDougal: Analysis of Gene Expression in F-344 Rats Following Dermal Exposure to Fuels and Solvents. The Toxicologist 54(1):217 (2000).

[3] J.N. McDougal, C.M. Garrett and J.V. Rogers: Molecular Changes in Skin Following Acute Dermal Exposures to Irritating Chemicals. US Army Medical Defense Bioscience Review. (2002).

[4] Rogers JV, Gunasekar PG, Garrett CM, McDougal JN: Dermal Exposure to m-Xylene Leads to Increasing Oxidative Species and Low Molecular Weight DNA in Rat Skin. *Journal Biochemical and Molecular Toxicology*, 15:228-230, 2001.

[5] Gunasekar PG, Rogers JV, Kabbur MH, Garrett CM, Brinkley WW, McDougal JN: Molecular and Histological Responses Related to Acute Skin Irritation from Exposure to m-Xylene. *Journal Biochemical and Molecular Toxicology*, in press, 2003.

[6] Gunasekar PG, Rogers JV, Kabbur MB, Garrett CM, Brinkley WW, McDougal JN: Comparative Study of Molecular Mechanisms of Skin Irritation after Acute Exposure to *m*-Xylene in Rats and Guinea Pigs. AFRL-HE-WP-TR-2001-0090, 2001.

[7] Kabbur, M., C. Garrett, K. Geiss, W. Brinkley and J. McDougal: Methods for Measuring Expression of IL-1 Alpha, Nitric Oxide Synthase, and Nitric Oxide in F-344 Rat Skin in Response to Dermal Exposures to Fuels or Solvents. The Toxicologist 54(1):254-255 (2000).

[8] Gunasekar, P.G., M.B. Kabbur, J.V. Rogers, C.M. Garrett and J.N. McDougal: Molecular Mechanism of Skin Irritation after Acute Exposure to m-Xylene in Rats and Guinea Pigs. The Toxicologist 60(1):59 (2001).

[9] P.G. Gunasekar, J.V. Rogers, M.B. Kabbur, W.W. Brinkley, C.M. Garrett and J.N. McDougal: Prediction of Molecular Mechanism of Skin Irritation after Acute Exposure to Sodium Lauryl Sulfate. The Toxicologist 66(1-S):162 (2002).

[10] W.W. Brinkley, J.V. Rogers, M.B. Kabbur, C.M. Garrett, K.T. Geiss, P.G. Gunasekar and J.N. McDougal: Histologic Assessment of Acute Dermal Exposure to m-Xylene, d-Limonene and Sodium Lauryl Sulfate in Rats. The Toxicologist 66(1-S):162 (2002).

[11] Rogers JV, McDougal JN: Improved Method for *in vitro* Assessment of Dermal Toxicity for Volatile Organic Chemicals. *Toxicology Letters*, 135:125-135 2002.
[12] Coleman CA, Hull BE, McDougal JN, Rogers JV: The effect of m-xylene on cytotoxicity and cellular antioxidant status in rat dermal equivalents. *Toxicology Letters*, in press, 2003.
[13] Rogers JV, McCafferty JD, McDougal JN: Improved method for in vitro assessment of volatile organic chemical exposure using living dermal equivalents. AFRL-HE-TR-2002-0009, 2002.

Attachment: 3 copies of publications

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Se
Centers for Disea
and Prevention

Memoran

Date: February 11, 2003

From: Lee M. Sanderson, Ph.D., Program Official
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 OH003654-03.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

McDougal JN: Physiologically-based Pharmacokinetic Modeling, in Dermatotoxicology, (eds. FN Marzulli, HI Maibach), 6th edition, Hemisphere Publishing Corporation, Washington, DC, in press, 2003

Gunasekar PG, Rogers JV, Kabbur MH, Garrett CM, Brinkley WW, McDougal JN: Molecular and Histological Responses Related to Acute Skin Irritation from Exposure to m-Xylene. Journal Biochemical and Molecular Toxicology, in press, 2003

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Title:	Prediction of Irritation Based on Exposure Duration
Investigator:	James N. McDougal, Ph.D.
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Telephone:	(937) 255-5150
Award Number:	5 R01 OH003654-03
Start & End Date:	9/30/1998–9/29/2002
Total Project Cost:	$777,420
Program Area:	Allergic and Irritant Dermatitis
Key Words:	

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