A. COVER PAGE

Project Title: Deciphering Occupational Asthma Pathogenesis Caused by Isocyanate	
Grant Number: 5R01OH010941-04	**Project/Grant Period:** 08/01/2016 - 07/31/2020
Reporting Period: 08/01/2019 - 07/31/2020	**Requested Budget Period:** 08/01/2019 - 07/31/2020
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Program Director/Principal Investigator Information: ADAM WISNEWSKI , BS PHD **Phone Number:** (203) 737-2544 **Email:** adam.wisnewski@yale.edu	**Recipient Organization:** YALE UNIVERSITY YALE UNIVERSITY OFFICE OF SPONSORED PROJECTS, PO BOX 208327 NEW HAVEN, CT 065208327 **DUNS:** 043207562 **EIN:** 1060646973A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: ANDREA LOZANO 25 Science Park - 3rd Floor 150 Munson St New Haven, CT 06520 **Phone number:** **Email:**	**Signing Official:** CATHERINE VOLPE 150 Munson Street, 3rd floor New Haven, CT 065113572 **Phone number:** **Email:**
Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The major goals of the project have not changed since the application was awarded. The specific Aims are the following:

Specific Aim 1. Determine the influence of endogenous GSH levels on isocyanate immune sensitization and exposure induced airway inflammation.

(1A.) Determine the effect of GSH suppression on isocyanate immune sensitization and airway inflammation in naïve and previously sensitized mice.11
(1B.) Evaluate the affect of GSH supplementation on isocyanate immune sensitization and airway inflammation in naïve and previously sensitized mice.

Specific Aim 2. Elucidate the isocyanate-stimulated cell types, cytokines, and signal transduction cascades critical to immune sensitization and exposure-induced airway pathology.

(2A.) Evaluate the presence of B-cells, T-cells, and innate lymphoid cells (ILCs) in the inflamed airways of a mouse MDI asthma model and their necessity for pathogenic allergic responses to exposure.
(2B.) Determine the source and role of airway IL-12/IL-23 beta in isocyanate-induced airway inflammation.
(2C.) Elucidate the role of IL-4/IL-13 receptors and major signaling molecule (STAT6) in isocyanate's ability to induce alternative macrophage activation.

Specific Aim 3. Identify biomarkers of isocyanate exposure and disease.

(3A.) Generate and characterize metabolites of MDI, GSH-MDI, and transcarbamoylation products with albumin.
(3B.) Quantitate with amount of MDI metabolites and MDI-conjugated proteins in the peripheral blood and urine of exposed mice and determine their association with isocyanate exposure dose and route (lung/skin).
(3C.) Identify protein and molecular changes in the respiratory tract that differentiate isocyanate-induced airway inflammation from that induced by common protein allergens (ovalbumin).

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

We have completed the three specific aims of the R01 and published our findings in16 manuscripts listed in the Publication List. The major findings are reported below.

AIM 1. Determine the influence of endogenous GSH levels on diisocyanate immune sensitization andexposure induced airway inflammation.

` Based on rapid reactivity of MDI with glutathione (GSH), we tested the hypothesis that GSH levels might affect the uptake and pathogenic response to diisocyanate. To test this hypothesis, we used traditional approaches to suppress or augment glutathione levels; buthionine sulfoximine (BSO) in drinking water and i.p.injections of N-acetyl cysteine (NAC) and S-adenosyl methionine (SAM). BSO reduced MDI-triggered airway inflammation (total BAL cell numbers and eosinophils) however the differences were not statistically significant. Treatment with NAC+SAM had no discernible protective effect against diisocyanate induced lung pathology.

Thus, while GSH is an effective vehicle for delivery of reactive diisocyanate into the airways, with experimentally well-defined pathogenic potential, it represents a complicated target for disease intervention, with potentially adverse outcomes from perturbation that outweigh limited, if any, protective effect against MDI.

AIM 2. Elucidate the diisocyanate-stimulated cell types, cytokines, and signal transduction cascadescritical to immune sensitization and exposure-induced airway pathology.

(2A) Necessity of B & T-Cells for diisocyanate asthma pathology.

We found mature B-cells and antigen-specific IgE were not required for the development of diisocyanate-induced asthma pathology in our mouse model, consistent with clinical diisocyanate asthma (without antigen specific IgE). These studies were performed using mice lacking an immunoglobulin constant region gene, which arrests B cell development and IgE production. We went on to further define a core set of IgE-independent diisocyanate induced genes and molecular changes central to asthma pathology through lung mRNA microarray studies in multiple mouse strains. The data support the long held hypothesis that diisocyanate asthma is an IgE-independent disease and were published (Wisnewski et at, Am J Res CellMol Biol 2020), along with microarray data in the NCBI Gene Expression Omnibus, GSE136146.

We confirmed that T-cells are essential to diisocyanate-induced airway pathology using 2 different T- cell deficient mouse strains. Nude mice (lacking the transcription factor $Foxn1^{nu}$ required for thymus development) fail to develop systemic diisocyanate immune sensitization or asthmatic pathology following respiratory tract exposure. Mice lacking antigen-receptor recombinase ($Rag2^{-/-}$) exhibited similar “resistance” todiisocyanate airway pathology. The studies demonstrate an essential role for T cells in pathogenic responses to diisocyanate and identifies them as potential targets for intervention.

(2B) Source and role of airway IL-12/IL-23 beta associated with diisocyanate-induced airway inflammation.

Prior published studies (Wisnewski et al, Chem Res Toxicol) demonstrated selective increase in cytokines IL-12 and IL-23’s shared beta subunit in the airways in association with diisocyanate-induced pathology. We identified $CD11b^{+}$ macrophages in lung tissue as the major source for diisocyanate-induced- airway IL-12/IL-23 beta, consistent with data demonstrating alternative macrophage activation as an importantcomponent of diisocyanate immune sensitivity. Our data further suggest a protective role of IL-12 / IL-23 beta,as mice exhibit increased asthma pathology (airway eosinophils, mucus) in its absence. The studies were accomplished using fluorescent reporter and knockout mice as described in our initial R01. The findings suggest caution in using certain immune-modulating FDA-approved biologics (Ustekinumab/Stelara®, which target IL-12/IL-23 beta) in individuals exposed to diisocyanate.

(2C) Role of IL-4/IL-13 receptor-STAT6 signaling pathway.

IL-4 is the major driving cytokine for IgE-isotype switching in B cells Since antigen-specific IgE is associated with environmental asthma but not diisocyanate-induced asthma, we hypothesized IL-4 receptor may not be required for diisocyanate-induced pathology. Instead, we found the IL-4 receptor critical to diisocyanate-induced airway pathology, with complete lack of asthma-related endpoints (airway eosinophils, mucus) in its absence. The studies were performed in mice lacking the alpha subunit of the IL-4 receptor, which is also part of the IL-13 receptor, both of which signal though STAT6, indicating an essential role for this pathway in pathology. The lack of diisocyanate-induced airway pathology in IL4 receptor alpha deficient mice (a) doesn’t appear to result from lack of systemic immune sensitization, (b) further implicates IL4/IL13- dependent alternatively activated macrophages (CD11b+) in diisocyanate asthma pathogenesis as initiallyhypothesized, and (c) suggests potential targets for intervention, such as DUPIXENT® (dupilumab).

Aim 3. Identify biomarkers of diisocyanate exposure and disease.

(3A) Generate and characterize metabolites of MDI, GSH-MDI, and transcarbamylation products with albumin.

Our progress is detailed in 7 manuscripts in the Publication List and briefly summarized below. (1) We observed rapid reactivity of GSH with each of the 3 different MDI isomers (2,2', 2,4', and 4,4') currently used in commercial products and extensively characterized the reaction products through LC-UV, LC-MS, MS-MS, and FTIR in Wisnewski et al, EC Pharm 2019. (2) We identified cyclized GSH-MDI, and oxidized GSSG-MDI metabolites formed from MDI incubated with microsomes vitro in Wisnewski et al, Toxicol In Vitro, 2016. (3) We identified GSH-diisocyanate in intubated vapor exposed rabbits Wisnewski et al Xenobiotica, 2018, (4) dimers of partially hydrolyzed diisocyanate in cell culture in Wisnewski et al, Anal Biochem, 2018, and (5) changes in metabolites and lipids in Nassar et al, Drug DiscovToday, 2017, (6) In MDI aerosol exposed mice we identified MDI-albumin in the airways in Hettick et al, Xenobiotica, 2018, (7) In vivo in urine of exposed mice we identified MDI-albumin, GSH-MDI adducts and anovel MDI metabolite (di-lysine-MDI), which was extensively characterized by LC-MS/MS, $^{1}H/^{13}C$-NMR, and synthetically produced as described in Wisnewski et al, Chem Res Toxicol, 2019.

(3B) Quantitate with amount of MDI metabolites and MDI-conjugated proteins in the peripheral blood and urineof exposed mice and determine their association with diisocyanate exposure dose and route (lung/skin).

As detailed in Wisnewski et al, Chem Res Toxicol, 2019, we successfully quantitated 3 different metabolites in the urine of mice exposed to MDI via the skin or the respiratory tract, MDI-albumin, cyclized GSH-MDI, and di-lysine-MDI, a 543.29 m/z $[M+H]^{+}$ ion. The excretion of the biomarkers occurs in anexposure dose and time dependent manner. Di-Lysine-MDI, likely arising from MDI-albumin, was a major urinary metabolite regardless of the route (skin/airway) or formulation (1% acetone/GSH adduct) of exposure. Cyclized GSH-MDI was found in the urine of mice exposed to GSH-MDI via the respiratory tract, but not from mice exposed to MDI in acetone via the skin. GSH-MDI conjugates were cleared rapidly (within 24 hours) whiledi-lysine-MDI and albumin conjugates were cleared at a much slower rate (days to weeks).

(3C) Identify protein and molecular changes in the respiratory tract associated with diisocyanate-induced airwayinflammation and compare with that induced by common protein allergens (ovalbumin).

As published in Wisnewski et al, Am J Res Cell Mol Biol, we have extensively characterized molecularchanges in the lungs of naïve and sensitized mice exposed to MDI. Our microarray data is freely available under the NCBI Gene Expression Omnibus, GSE136146. The data indicate a primary role for alternatively activated macrophages, chemokines, and chloride channels, the latter of which was verified through studies with a unique inhibitor, the FDA-approved anti-diarrheal drug Mytesi®, generic name crofelemer. While more similarities than differences in lung gene transcripts were noted in MDI vs. ovalbumin-induced asthma, differentially expressed gene transcripts include the dendritic cell specific receptor (XCR1) and the interferon-like, myeloid cell nuclear differentiation antigen (MNDA), consistent with our hypothesis involving alternatively activated macrophages in diisocyanate-induced pathology.

Perhaps equally exciting are findings of differences in gene expression of MDI exposed naïve mice. A distinct pattern of type I interferon expression is triggered by respiratory tract exposure to MDI only in naïve, and not in sensitize mice. The gene expression profile is consistent with a deficiency in adenosine deaminase acting against RNA (ADAR1), with roughly ½ of the genes in the pathway effected (24 increased, 3 decreased), IRF-7 being the most prominent. The data define a molecular gene expression pattern that differentiates pathologic asthmatic responses in sensitized hosts from non-pathogenic responses observed in naïve hosts. The cellular source and biological explanation for these differences remain to be elucidated and may form the basis of future therapies or preventative measures.

Summary: The data from the project to date identify important characteristics of diisocyanate asthma in a mouse model that parallel human disease. The data point to new potential avenues for treatment and prevention and describe differences vs. "environmental asthma" that may not be treatable with new biologics, e.g., Dupixent, Stelara etc. The data also identify important aspects of biochemical reactivity and identify biomarkers of exposure that will likely be applicable to human exposure surveillance and disease prevention in the future, to help enable safety of workers exposed to diisocyanate on the job.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Wisnewski AV, Liu J, Colangelo CM. Glutathione reaction products with a chemical allergen, methylene-diphenyl diisocyanate, stimulate alternative macrophage activation and eosinophilic airway inflammation. Chemical research in toxicology. 2015 April 20;28(4):729-37. PubMed PMID: 25635619; PubMed Central PMCID: PMC4667722; DOI: 10.1021/tx5005002.
N/A: Not NIH Funded	Wisnewski AV, Liu J. Immunochemical detection of the occupational allergen, methylene diphenyl diisocyanate (MDI), in situ. Journal of immunological methods. 2016 February;429:60-5. PubMed PMID: 26690039; PubMed Central PMCID: PMC4753098; DOI: 10.1016/j.jim.2015.12.008.
N/A: Not NIH Funded	Nassar AF, Wisnewski AV, Raddassi K. Progress in automation of mass cytometry barcoding for drug development. Bioanalysis. 2016 July;8(14):1429-35. PubMed PMID: 27323800; DOI: 10.4155/bio-2016-0135.
N/A: Not NIH Funded	Nassar AE, Wisnewski AV, King I. Biotransformation and Rearrangement of Laromustine. Drug metabolism and disposition: the biological fate of chemicals. 2016 August;44(8):1349-63. PubMed PMID: 27278961; DOI: 10.1124/dmd.116.069823.
N/A: Not NIH Funded	Wisnewski AV, Liu J, Nassar AF. In vitro cleavage of diisocyanate-glutathione conjugates by human gamma-glutamyl transpeptidase-1. Xenobiotica; the fate of foreign compounds in biological systems. 2016 August;46(8):726-32. PubMed PMID: 26678254; PubMed Central PMCID: PMC4848134; DOI: 10.3109/00498254.2015.1118576.
N/A: Not NIH Funded	Wisnewski AV, Liu J, Nassar AF. Identification of novel reaction products of methylene-bis-phenylisocyanate ("MDI") with oxidized glutathione in aqueous solution and also during incubation of MDI with a murine hepatic S9 fraction. Toxicology in vitro : an international journal published in association with BIBRA. 2016 October;36:97-104. PubMed PMID: 27453132; PubMed Central PMCID: PMC5010927; DOI: 10.1016/j.tiv.2016.07.011.
N/A: Not NIH Funded	Hagerman LM, Law BF, Bledsoe TA, Hettick JM, Kashon ML, Lemons AR, Wisnewski AV, Siegel PD. The influence of diisocyanate antigen preparation methodology on monoclonal and serum antibody recognition. Journal of occupational and environmental hygiene. 2016 November;13(11):829-39. PubMed PMID: 27124286; PubMed Central PMCID: PMC5016257; DOI: 10.1080/15459624.2016.1183013.
N/A: Not NIH Funded	Nassar AF, Wu T, Nassar SF, Wisnewski AV. UPLC-MS for metabolomics: a giant step forward in support of pharmaceutical research. Drug discovery today. 2017 February;22(2):463-470. PubMed PMID: 27919805; PubMed Central PMCID: PMC5721520; DOI: 10.1016/j.drudis.2016.11.020.
N/A: Not NIH Funded	Nassar AF, Wisnewski AV, King I. Population pharmacokinetic (PK) analysis of laromustine, an emerging alkylating agent, in cancer patients. Xenobiotica; the fate of foreign compounds in biological systems. 2017 May;47(5):394-407. PubMed PMID: 27440490; DOI:

	10.1080/00498254.2016.1201703.
N/A: Not NIH Funded	Wisnewski AV, Liu J. Molecular Characterization and Experimental Utility of Monoclonal Antibodies with Specificity for Aliphatic Di- and Polyisocyanates. Monoclonal antibodies in immunodiagnosis and immunotherapy. 2020 June;39(3):66-73. PubMed PMID: 32302507; PubMed Central PMCID: PMC7310211; DOI: 10.1089/mab.2020.0006.
N/A: Not NIH Funded	Wisnewski AV, Liu J, Redlich CA. Analysis of Lung Gene Expression Reveals a Role for Cl^- Channels in Diisocyanate-induced Airway Eosinophilia in a Mouse Model of Asthma Pathology. American journal of respiratory cell and molecular biology. 2020 July;63(1):25-35. PubMed PMID: 32101465; PubMed Central PMCID: PMC7328250; DOI: 10.1165/rcmb.2019-0400OC.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

Category	Explanation
Protocols	Protocol for detecting Diisocyanate (asthma causing chemical) In situ Wisnewski AV, Liu J. Immunochemical detection of the occupational allergen, methylene diphenyl diisocyanate (MDI), in situ. J Immunol Methods. 2016 Feb;429:60-5. doi: 10.1016/j.jim.2015.12.008. Epub 2015 Dec 12. PMID: 26690039; PMCID: PMC4753098.
Protocols	Protocol for preparing di-lysine-MDI, and protocol for measuring levels in blood and urine: Wisnewski AV, Nassar AF, Liu J, Bello D. Dilysine-Methylene Diphenyl Diisocyanate (MDI), a Urine Biomarker of MDI Exposure? Chem Res Toxicol. 2019 Apr 15;32(4):557-565. doi: 10.1021/acs.chemrestox.8b00262. Epub 2019 Feb 18. PMID: 30724074; PMCID: PMC6465083.

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Other	Identification of new biomarker for exposure surveillance/disease prevention Wisnewski AV, Nassar AF, Liu J, Bello D. Dilysine-Methylene

	Diphenyl Diisocyanate (MDI), a Urine Biomarker of MDI Exposure? Chem Res Toxicol. 2019 Apr 15;32(4):557-565. doi: 10.1021/acs.chemrestox.8b00262. Epub 2019 Feb 18. PMID: 30724074; PMCID: PMC6465083.
Models	Model of occupational asthma in mice Wisnewski AV, Liu J, Redlich CA. Analysis of Lung Gene Expression Reveals a Role for Cl- Channels in Diisocyanate-induced Airway Eosinophilia in a Mouse Model of Asthma Pathology. Am J Respir Cell Mol Biol. 2020 Jul;63(1):25-35. doi: 10.1165/rcmb.2019-0400OC. PMID: 32101465; PMCID: PMC7328250.
Interventions (e.g., clinical or educational)	Experimental Asthma Intervention Wisnewski AV, Liu J, Redlich CA. Analysis of Lung Gene Expression Reveals a Role for Cl- Channels in Diisocyanate-induced Airway Eosinophilia in a Mouse Model of Asthma Pathology. Am J Respir Cell Mol Biol. 2020 Jul;63(1):25-35. doi: 10.1165/rcmb.2019-0400OC. PMID: 32101465; PMCID: PMC7328250.
Research Material	New Monoclonal Antibodies for Diisocyanates Wisnewski AV, Liu J. Molecular determinants of humoral immune specificity for the occupational allergen, methylene diphenyl diisocyanate. Mol Immunol. 2013 Jun;54(2):233-7. doi: 10.1016/j.molimm.2012.11.017. Epub 2013 Jan 4. PMID: 23295252; PMCID: PMC3563841. Wisnewski AV, Liu J. Molecular Characterization and Experimental Utility of Monoclonal Antibodies with Specificity for Aliphatic Di- and Polyisocyanates. Monoclon Antib Immunodiagn Immunother. 2020 Jun;39(3):66-73. doi: 10.1089/mab.2020.0006. Epub 2020 Apr 17. PMID: 32302507; PMCID: PMC7310211. Wisnewski AV, Liu J. Immunochemical detection of the occupational allergen, methylene diphenyl diisocyanate (MDI), in situ. J Immunol Methods. 2016 Feb;429:60-5. doi: 10.1016/j.jim.2015.12.008. Epub 2015 Dec 12. PMID: 26690039; PMCID: PMC4753098.

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
AWISNEWSKI	Y	WISNEWSKI, ADAM	BS,PHD	PD/PI	0.0	0.0	0.0			NA
REDLICH	N	REDLICH, CARRIE A	BA,MD,DOTH,MPH,MPH,MD,DMD	Co-Investigator	0.0	0.0	0.0			NA
MEREDITHSTOWE	N	Stowe, Meredith	BS,PHD	Co-Investigator	0.0	0.0	0.0			NA
	N	Nassar, Ala		Co-Investigator	0.0	0.0	0.0			NA
	N	Liu, Jian	MS	Technician	0.0	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

NOTHING TO REPORT

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT
No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE
Not Applicable
G.11 PROGRAM INCOME
Not Applicable
G.12 F&A COSTS
Not Applicable

I. OUTCOMES

I.1 What were the outcomes of the award?

Summary: The studies focused on important industrial chemicals necessary to make polyurethane, which is important to our economy and our culture and safety. An important chemical needed to make polyurethane is diisocyanate, which is known to cause asthma. Currently workers must use protective equipment to work with the chemical and there are no tests widely available to establish chemical sensitivity (asthma). The data from the project to date identify important characteristics of asthma caused by diisocyanate in a mouse model that parallels human disease. The data identify new potential avenues for treatment and prevention and describe differences vs. "environmental asthma" that may make the disease intractable to treatment with new anti-inflammatory biologics. The data also identify important aspects of biochemical reactivity of diisocyanate with self-molecules and identify biomarkers of exposure that will likely be applicable to human exposure surveillance and disease prevention in the future, to help enable safety of workers exposed to diisocyanate on the job. Important outcomes of the award are

- Multiple medical journal manuscripts describing underlying biochemistry of exposure, reactivity with self
- New insight into basic mechanisms of disease (importance of chloride channels, and "innate" immune system)
- Identification of exposure biomarker for surveillance of workplace exposiure
- Chemical Methods for synthesizing standard for biomonitoring chemical exposure at work