



The National Institute for Occupational Safety and Health (NIOSH)



Alice B. Hamilton Awards 2003

Biological Science Category

Winner:

- **Title:** A Role of tumor necrosis factor (TNF) in toluene diisocyanate (TDI) asthma
- **Authors:** Joanna Matheson, Ranulfo Lemus, Robert W. Lange, Meryl H. Karol, Michael I. Luster
- **Source:** American Journal of Respiratory Cell and Molecular Biology 2002; 27:396-405
- **Abstract:** Nearly 9 million workers are exposed to chemical agents associated with occupational asthma, with isocyanates representing the chemical class most responsible. Isocyanate-induced asthma has been difficult to diagnose and control, in part because the biologic mechanisms responsible for the disease and the determinants of exposure have not been well defined. Isocyanate-induced asthma is characterized by airway inflammation, and we hypothesized that inflammation is a prerequisite of isocyanate-induced asthma, with tumor necrosis factor (TNF)- α being critical to this process. To explore this hypothesis, wildtype mice, athymic mice, TNF- α receptor knockout (TNFR), and anti-TNF- α antibody-treated mice were sensitized by subcutaneous injection (20 μ l on Day 1; 5 μ l, Days 4 and 11), and challenged 7 d later by inhalation (100 ppb; Days 20, 22, and 24) with toluene diisocyanate (TDI). Airway inflammation, goblet cell metaplasia, epithelial cell damage, and nonspecific airway reactivity to methacholine challenge, measured 24 h following the last challenge, were reduced to baseline levels in TNF- α null mice and athymic mice. TNF- α deficiency also markedly abrogated TDI-induced Th2 cytokines in airway tissues, indicating a role in the development of Th2 responses. Despite abrogation of all indicators of asthma pathology, TNF- α neutralization had no effect on serum IgE levels or IgG-specific TDI antibodies, suggesting the lack of importance of a humoral response in the manifestation of TDI-induced asthma. Instillation studies with fluorescein-conjugated isothiocyanate and TDI suggested that TNF- α deficiency also resulted in a significant reduction in the migration of airway dendritic cells to the draining lymph nodes. Taken together, these results suggest that, unlike protein antigens, TNF- α has multiple and central roles in TDI-induced asthma, influencing both nonspecific inflammatory processes and specific immune events.



[Link to abstract in NIOSHTIC-2](#)

Honorable Mention:

- **Title:** Chemoprotection by phenolic antioxidants: Inhibition of tumor necrosis factor alpha induction in macrophages
- **Authors:** Qiang Ma, Krista Kinneer
- **Source:** The Journal Of Biological Chemistry 2002;277:2477-2484
- **Abstract:** Phenolic antioxidants exhibit anti-inflammatory activity in protection against chemical toxicity and cancer. To investigate the molecular mechanism of antiinflammation, we analyzed the regulation of tumor necrosis factor α (TNF- α) expression in macrophages, a key step in inflammation, by the antioxidants. Whereas lipopolysaccharide (LPS), an inflammatory inducer, stimulates rapid synthesis of TNF- α protein, phenolic antioxidants, exemplified by tert-butyl hydroquinone and 1,4-dihydroquinone, block LPS-induced production of TNF- α protein in a time- and dose-dependent manner. Inhibition of TNF- α induction correlates with the capacity of the antioxidants to undergo oxidation-reduction cycling, implicating oxidative signaling in the inhibition. The antioxidants blocked LPS-induced increase of the steady-state mRNA of TNF- α but did not affect the half-life of the mRNA. Electrophoretic mobility shift assay reveals a total inhibition of LPS-induced formation of nuclear factor κ B-DNA binding complexes by phenolic antioxidants. Finally, 1,4-dihydroquinone blocks the induction of TNF- α target genes interleukin 1 β and interleukin 6 at both mRNA and protein levels. Our findings demonstrate that phenolic antioxidants potently inhibit signal-induced TNF- α transcription and suggest a mechanism of anti-inflammation by the antioxidants through control of cytokine induction during inflammation.

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Engineering and Physical Sciences Category

Winner:

- **Title:** A random walk model of skin permeation
- **Authors:** H. Frederick Frasch
- **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 twodimensional 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 ($R^2 = 0.84$; $SE = 0.0076$; $F = 154$; $N = 94$). 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.

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Honorable Mention:

- **Title:** Studies of the measurement of respirable coal dusts and diesel particulate matter
- **Authors:** Charles D. Litton
- **Source:** Measurement Science and Technology 2002;13:365-374
- **Abstract:** Experiments were conducted to determine the optical scattering properties of respirable coal dusts and diesel particulate matter (DPM) at discrete angles in the forward direction and at light source wavelengths of 632.8 and 635 nm. In addition to the scattering data, simultaneous measurements were made of the total mass concentration of dust, DPM or mixtures of the two, and the responses of a unipolar ion chamber and a simpler, more common bipolar ion chamber typical of residential smoke detectors. The results of these experiments indicate, for respirable coal dusts, that the intensity per unit mass concentration at discrete angles in the range of 15–30 varies linearly with mass concentration independent of the volatility of the dust, but that at larger scattering angles, intensities per unit mass concentration are affected by dust volatility. For DPM, the intensities per unit mass concentration are significantly lower. The results also indicate that the ion chambers respond significantly to DPM while there is no response to respirable coal dust, and that when



Honorable Mention:

- **Title:** A derived association between ambient aerosol surface area and excess mortality using historic time series data
- **Author:** Andrew D. Maynard, Robert L. Maynard
- **Source:** . Atmospheric Environment 2002;36:5561-5567
- **Abstract:** Although aerosol mass concentration is widely associated with ill health following inhalation; there is increasing evidence that it is a poor indicator of .ne and ultra.ne particle toxicity. Research has indicated that biological response to such particles is closely associated with particulate surface area; although no epidemiology data currently exist to validate the association. By applying a simple model to historic mass-based time series data, we have been able to estimate mortality rate as a function of ambient aerosol surface area. Within the simplifying assumptions of the model, a linear association is indicated between mortality rate and surface area concentration for coalescing particles. The analysis also indicates the existence of a threshold aerosol concentration, below which particulate mass and surface area are linearly related. Below this threshold, we suggest that mass concentration measurements may provide a good indicator of health effects, although for high exposures found in the developing world and industry, the model indicates that aerosol exposure may be more appropriately characterized by surface area. Further experimental validation of the model should establish the applicability of derived relationships between aerosol mass and surface area concentration to ambient and occupational exposures.

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Human Studies Category

Winner:

- **Title:** The impact of mental processing and pacing on spine loading
- **Author:** Kermit G. Davis, William S. Marras, Catherine A. Heaney, Thomas R.Waters, Purnendu Gupta
- **Source:** Spine 2002;27:2645-2653
- **Abstract:Study Design**
The impact of various levels of mental processing and pacing (during lifting) on spine loading was monitored under laboratory conditions. **Objectives**
To explore how mental demands and pacing influence the biomechanical response and subsequent spine loading and, to determine whether individual characteristics have a modifying role in the responses. Summary of Background Data Modern work often requires rapid physical exertions along with demands of mental processing (both psychosocial stressors). While the effect of physical workplace factors on spine loading has been widely documented, few studies have investigated the impact that interaction of psychosocial factors and individual factors has on spine loads. **Methods**
For this study, 60 subjects lifted boxes while completing two types of mental processing tasks: 1) series tasks with decisions occurring before the act of lifting, and 2) simultaneous tasks with decisions occurring concurrently with the lift. For both of these mental processing conditions, two intensities of mental load were evaluated: simple and complex. Task pacing was also adjusted under slow and fast conditions. Finally, individual characteristics (personality and gender) were evaluated as potential modifiers. An electromyographically assisted model evaluated the three-dimensional spine loads under the experimental conditions. **Results**
Simultaneous mental processing had the largest impact on the spine loads, with the complex intensity resulting in increases of 160 N with lateral shear, 80 N with anteroposterior shear, and 700 N with compression. Increased task pace produced greater lateral shear (by 20 N), anteroposterior shear (by 60 N), and compression loads (by 410 N). Gender and personality also influenced loadings by as much as 17%. **Conclusions**
Mental processing stress acted as a catalyst for the biomechanical responses, leading to intensified spine loading. Mental stress appeared to occur as a function of time pressures on task performance and resulted in less controlled movements and increases in trunk muscle coactivation. These adjustments significantly increased spine loading. These results suggest a potential mechanism for the increase in low back pain risk resulting from psychosocial stress caused by modern work demands.

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Honorable Mention:

- **Title:** Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant
- **Authors:** Kathleen Kreiss, Ahmed Gomaa, Greg Kullman, Kathleen Fedan, Eduardo J.Simoes, Paul L. Enright
- **Source:** The New England Journal of Medicine 2002;347:330-338
- **Abstract:Background**
In May 2000, eight persons who had formerly worked at a microwave-popcorn production plant were reported to have severe bronchiolitis obliterans. No recognized cause was identified in the plant. Therefore, we medically evaluated current employees and assessed their occupational exposures. **Methods**
Questionnaire responses and spirometric findings in participating workers were compared with data from the third National Health and Nutrition Examination Survey, after adjustment for age and smoking status. We evaluated the relation between exposures and health-related outcomes by analyzing the rates of symptoms and abnormalities according to current and cumulative exposure to diacetyl, the predominant ketone in artificial butter flavoring and in the air at the plant. **Results**
Of the 135 current workers at the plant, 117 (87 percent) completed the questionnaire. These 117 workers had 2.6 times the expected rates of chronic cough and shortness of breath, according to comparisons with the national data, and twice the expected rates of physician-diagnosed asthma and chronic bronchitis. Overall, the workers had 3.3 times the expected rate of airway obstruction; those who had never smoked had 10.8 times the expected rate. Workers directly involved in the production of microwave popcorn had higher rates of shortness of breath on exertion and skin problems that had developed since they started work than workers in other parts of the plant. There was a strong relation between the quartile of estimated cumulative exposure to diacetyl and the frequency and extent of airway obstruction. **Conclusions**
The excess rates of lung disease and lung-function abnormalities and the relation between exposure and outcomes in this working population indicate that they probably had occupational bronchiolitis obliterans caused by the inhalation of volatile butter-flavoring ingredients. (N Engl J Med 2002;347:330-8.)

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