Industry Sponsored
Asthma Science Forum

Report of Workshop held May 10, 2011
Renaissance Capital View, Arlington, Virginia

Submitted to:
Asthma Science Forum Steering Committee

Submitted by:
Toxicology Excellence for Risk Assessment
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Executive Summary

An industry-sponsored Asthma Science Forum was held on May 10, 2011 in Arlington, Virginia to provide a platform for industry participants to review and discuss data and issues relevant to the relationship between asthma and exposure to consumer products and product ingredients. The goal was to provide information and guidance on methodological and analytical approaches that could be used to address the issues and data gaps associated with current asthma research. The workshop was organized by a Steering Committee that included representatives from several industry associations, which represent an array of chemical and consumer product businesses.

Nine expert speakers provided a review of the clinical and biological basis for asthma and other asthma-like respiratory responses and their causation, and presented reports on investigations into asthma, as related to consumer and commercial products. Methods for assessing exposure and current research efforts were also highlighted. Speakers discussed three key issues: 1) which data and methods are the most helpful in characterizing whether exposure to a consumer chemical or product can cause or exacerbate asthma or asthma-like respiratory responses and if so what biological mechanisms may be responsible, 2) the most impactful data gaps and areas of uncertainty that need to be addressed to better characterize the relationships between consumer exposures and asthma, and 3) additional research approaches and methodological developments that are needed to facilitate the effective use of safety assessment and mitigation approaches.

The speakers formed a panel to answer attendees’ questions and further discuss some of the key questions related to asthma and consumer products and ingredients. A number of key points were made and individual experts identified data gaps and research needs pertinent to their particular field. These points are listed below:

- **Asthma is a chronic inflammatory disease of the conducting airways: it is a syndrome whose typical features of episodic cough, wheezing, dyspnea, reversible airflow obstruction and airway hyperreactivity belie considerable heterogeneity with respect to pathogenesis, natural history and response to treatment.** There is an increased incidence of asthma in the U.S., which does not appear to be simply attributable to greater awareness of the disease. Some of the leading hypotheses for the increased incidence in children were identified. For example, the “hygiene hypothesis,” initially proposed by David Strachan in 1989, stated that infections and unhygienic contact somehow conferred protection from allergic diseases, including asthma. Other hypotheses include greater exposures to environmental pollutants, maternal folic acid
supplements, and childhood vaccinations leading to fewer infections. There is not likely one single cause for the increased incidence of asthma in children. Prevalence rates have been shown to shift in genetically similar populations in less than one generation (i.e., from a TH-1 chronic bronchitic phenotype to a TH-2-type allergic phenotype). Early effect biomarker information shows promise and should be further explored to help diagnose asthma.

- **The TH-1 type phenotype is associated with chronic bronchitis with fixed airflow obstruction; while TH-2-type is an allergic asthma phenotype.** Immune responses are either innate (rapid and non-specific) or acquired (recognize specific antigens). The acquired response of hypersensitivity/allergy is a two-stage process that distinguishes allergy from irritation. Generally a higher dose is needed for sensitization, with lower doses subsequently eliciting the effect. Many researchers believe that some substances that cause sensitization through dermal contact may later elicit a response via respiratory tract exposures. However, additional research is needed to make a definitive statement as to whether respiratory tract response elicitation can arise from dermal sensitization (i.e., that sensitization is a systemic response) whether sensitization must occur via respiratory tract exposure (i.e., sensitization and elicitation are driven by mechanisms at the local tissue level), or whether both pathways can occur (and if so, under what circumstances). Better tools and generalized models for identifying contact and respiratory sensitizing agents, and the relationship between them, would be helpful. Also needed is a better understanding of the underlying immunology and critical events, such as dysregulation of inflammation, specific immune responses and immune tolerance, and quantitative relationships between response and effect. Basic research to investigate the role of nonspecific inflammation should be a priority as a complement to researching specific allergic responses. The mechanisms of the irritant response, including determinants of its severity and amplification, also need study, particularly as the irritant response is likely to be important for work-exacerbated asthma with respect to cleaning products.

- **The database of epidemiology studies is not sufficiently robust to demonstrate a causal relationship between cleaning product exposures and new-onset asthma, although the case was stronger for triggering asthma-like symptoms.** Current epidemiological studies lack the ability to pinpoint whether specific exposures lead to asthma onset. Animal toxicology studies provide information on effects seen with individual chemicals and immunologic and respiratory parameters associated with the asthma phenotype, but their ability to predict the ability of a chemical to cause human asthma or asthma-like responses has not been fully validated. In the absence of a suite of definitive assays, a weight-of-evidence approach can help characterize asthma exacerbation by pooling the existing data into a single and more robust evaluation.
• There is ample evidence that irritants can exacerbate existing asthma, but it is not known whether irritants alone can cause asthma. There is general acceptance of RADS (reactive airway dysfunction syndrome), an asthma syndrome occurring after a brief high level irritant exposure, but this case is far less common with respect to cleaning products or recurrent lower level exposure to irritants. While there is some evidence that chronic low-level occupational exposures to substances producing irritation are associated with the start of asthma, there is not a causal link. Data to address potential mechanisms are fragmentary, primary relating to epithelial dysfunction in asthma with reduced amounts of intracellular toxicant buffers. Transient receptor potential (TRP) receptors and bitter receptors in smooth airway muscles mediate the response to some irritant compounds, and there may be other receptors not yet identified. Nearly all volatile chemicals can be irritants at high concentrations. Odor may play a role in eliciting or exacerbating asthmatic symptoms for some people (and not for others). Many asthmatics report airway symptoms upon exposure to odors and airborne irritants, but it is not known if this is a conditioned psychogenic response and multiple mechanisms are thought to contribute to these symptoms. Clinical tests do not distinguish between a conditioned psychogenic response or a local tissue or airway response; “perceived” hazard/stress from a non-irritant can trigger symptom reports and airway inflammation. Additional research is warranted on how genetic polymorphisms in metabolic capacity, TRP channel density and bitter receptors in airways impact the asthmatic response to irritants.

• The rodent is a useful model for the human respiratory tract, but has limitations and when using rodent data attention should be paid to matching epithelium and cell types, as well as dosing regimens. There are no current regulatory testing guidelines for respiratory sensitization, and although a number of animal models have been used, protocols and endpoints for these approaches are often inconsistent, costly and difficult to reproduce. In vitro approaches have potential for identifying respiratory sensitizers, but none of them are validated. In vitro and in silico models show promise for use in characterization of exposure and potential contact sensitization. A more specific understanding of essential physiochemical properties that can distinguish between respiratory and contact sensitizers is needed.

• There is a need for better exposure assessment, with measurements of actual exposures (rather than surrogates) and good source characterization. Assessing a variety of potential exposures in an occupational or residential setting requires an understanding of sources, a systematic sampling strategy, and specialized equipment and data interpretation skills. In evaluating the exposure situation, it is critical to know the
agent of interest in order to design an efficient sampling strategy and determine the appropriate exposure metric (e.g., breathing zone concentration). The utility of current exposure models could be improved with additional data on air and particle movement, as well as metabolism and fate of dermal and inhalation exposures. Data are often lacking for the biological fate of materials inhaled from consumer products requiring extrapolations from dermal studies, but this is an area of active data collection. Many cleaning products are used in sequence with, or in conjunction with, other materials. Exposure assessments need to consider the possibility of reactions among materials and their degradation products in typical usage situations.

- **Evaluating exposure and identifying asthma causation and exacerbation is complicated because people are exposed to mixtures of products, environmental contaminants, and/or microbial agents.** People are exposed to many substances at sub-threshold levels that individually do not induce an irritation or sensitization response; however, co-exposure to multiple substances might lead to an adjuvant effect resulting in sensitization at otherwise sub-threshold doses, or result in perceived irritation that could exacerbate asthma or asthma-like responses. Many compounds react or degrade over time and individuals may be reacting to something other than the original parent material, contributing to uncertainty in understanding the causation of any biological effect. Whether volatile non-irritant chemicals amplify the sensory and inflammatory response to irritants is an outstanding unanswered question.

- **Some exposure situations require evaluating benefits of products’ use with potential risks.** Multi-disciplined groups of experts are needed to evaluate these situations and there may be some lessons to learn from pharmaceuticals on comparing benefits and risks. Consensus on terminology and definitions as they are used across disciplines would be helpful to insure understanding and effective risk communication. And finally, educating consumers on safe usage of products and materials is very important to minimize exposure and potential for harm.
# Table of Contents

**Executive Summary** .................................................................................................................................................................................. 3

**Introduction** ......................................................................................................................................................................................... 9

*Steering Committee Members* ................................................................................................................................................................. 11

**Presentations** ....................................................................................................................................................................................... 13

**Session I: Clinical and Biological Basis for Asthmagenic Responses** .................................................................................................................. 13
  - Clinical Perspectives in Asthma Etiology and Diagnosis .................................................................................................................... 13
  - Immunologic Basis for Allergic Asthma and Current Tools for Assessing Potential Chemical Risks... 16
  - Sensory Irritation and the Respiratory Tract Response .................................................................................................................. 19

**Session II: Investigations into Asthma and Consumer and Commercial Products Use** .................................................................................................. 23
  - Asthma Related Exposure Assessments ........................................................................................................................................ 23
  - New Weight of Evidence Approaches: Cleaning Products and Asthma .......................................................................................... 25
  - Swimming and asthma: What does the current research say? ......................................................................................................... 28

**Session III: Research and New Evaluation Initiatives** ......................................................................................................................................... 31
  - *In Silico, In Vitro, and In Vivo* Approaches to Identify Respiratory Sensitizers .................................................................................. 31
  - Landscape of New Research Initiatives ......................................................................................................................................... 34
  - Exposure Assessment Modeling for Consumer Products ............................................................................................................. 37

**Discussion** ............................................................................................................................................................................................................ 41

*Prevalence/incidence changes* ...................................................................................................................................................................... 41

*Mixtures - complex and cumulative exposures, exposome, adjuvants* ......................................................................................................... 42

*Irritation as a cause of asthma* ................................................................................................................................................................. 43

*Odor: How to investigate further* ................................................................................................................................................................. 44

*Bitter and other receptors* ........................................................................................................................................................................... 45

*Animal models and species* ........................................................................................................................................................................ 45

*Dermal penetration model* ......................................................................................................................................................................... 46

*Early effects biomarkers* ............................................................................................................................................................................ 46

*Contact and respiratory sensitizers* ........................................................................................................................................................ 47

*Comparative risk assessment* ..................................................................................................................................................................... 48

*Consensus on definitions* ........................................................................................................................................................................... 49

*Parting comments* ................................................................................................................................................................................... 49

*References* ............................................................................................................................................................................................ 51
Appendix A – List of Sponsors and Affiliates................................................................. 57
Appendix B – List of Attendees.................................................................................. 59
Appendix C – Biographical Sketches ........................................................................ 69

Rebecca Bascom M.D., M.P.H., FAAAAI, FACCP ...................................................... 69
Fred W. Boelter, CIH, PE, BCEE ............................................................................... 71
Pamela Dalton, Ph.D., MPH ...................................................................................... 72
Jon Hotchkiss, Ph.D. ................................................................................................. 73
Michael A. Jayjock, Ph.D., CIH ................................................................................ 74
Judy S. LaKind, Ph.D. ................................................................................................ 76
Andrew Maier, Ph.D., CIH, DABT ............................................................................ 78
MaryJane Selgrade, Ph.D., ATS ................................................................................ 79
Madhuri Singal, Ph.D., R.R.T. .................................................................................. 81
Introduction

The increased prevalence of asthma is a growing public health concern. Significant scientific efforts have increased our understanding of the physiological basis of asthma, the causes of asthmatic responses, and the implementation of practices for assuring safety. An industry-sponsored Asthma Science Forum was held on May 10, 2011 in Arlington, Virginia to provide a platform for industry participants to review and discuss data and issues relevant to the relationship between asthma and exposure to consumer products and product ingredients. The goal was to provide information that could be used to guide development of approaches to address the issues and data gaps associated with current asthma research. The workshop was organized by a Steering Committee that included representatives from several industry associations, which represent an array of chemical and consumer product businesses (see list below).

The workshop program provided a review of the clinical and biological bases for asthma and other asthma-like respiratory responses and their causation, and included focused reports on investigations into asthma, as it is related to consumer and commercial products. Current research efforts were also highlighted. Over 50 scientists from member companies participated.

The Steering Committee designed the workshop program to help address several overarching questions:

- What data and methods are the most helpful in characterizing whether exposure to a consumer chemical or product can cause or exacerbate asthma or asthma-like respiratory responses?
- What are the most impactful data gaps and areas of uncertainty that need to be addressed to better characterize the relationship between consumer exposures and asthma?
- What additional research approaches and methodological developments or improvements are needed to facilitate the effective use of safety assessment and mitigation approaches?

The workshop was divided into four sessions. The first three sessions consisted of presentations by a diverse group of experts addressing a broad range of issues relevant to evaluating asthma potential and risk.

Session I: Clinical and Biological Basis for Asthma Responses

- Clinical Perspectives in Asthma Etiology and Diagnosis: Rebecca Bascom, M.D., MPH, FAAAAI, FACCP (Penn State Hershey Medical Center)
- Immunologic Basis for Allergic Asthma and Current Tools for Assessing Potential Chemical Risks: MaryJane Selgrade, Ph.D., ATS (ICF International)
• Sensory Irritation and the Respiratory Tract Response: Pamela Dalton, Ph.D., MPH 
(Monell Chemical Senses Center)

Session II: Investigations into Asthma and Consumer and Commercial Products Use
• Asthma Related Exposure Assessments: Fred W. Boelter, CIH, PE, BCEE (ENVIRON International Corporation)
• New Weight of Evidence Approaches: Cleaning Products and Asthma: Andrew Maier, Ph.D., CIH, DABT (TERA)
• Swimming and Asthma: What Does the Current Research Say?: Judy S. LaKind, Ph.D. (LaKind Associates, LLC)

Session III: Research and New Evaluation Initiatives
• In Silico, In Vitro, and In Vivo Approaches to Identify Respiratory Sensitizers: Jon A. Hotchkiss, Ph.D. (The Dow Chemical Company)
• Landscape of New Research Initiatives: Madhuri Singal, Ph.D, RRT (Research Institute for Fragrance Materials, Inc.)
• Exposure Assessment Modeling for Consumer Products: Michael A. Jayjock, Ph.D, CIH (The LifeLine Group)

In addition to the broad questions, the speakers were asked to address session-specific questions. From Session I, the panelists were asked to address, from a clinical and health risk assessment perspective, what is asthma, and what are the underlying chemical toxicity mechanisms (e.g., sensitization, irritant responses, and others) that can trigger asthmatic responses. Session II panelists were asked to address what is known about consumer product use and levels of assurance of safety, based on current health effects studies, and what information is needed to resolve open questions regarding causality that can guide safety assessment and management procedures. Panelists from Session III were asked to identify current research developments that will likely impact the ability to characterize the relationship between consumer exposures and asthma and ultimately enhance the effectiveness of safety assessment and management.

The workshop concluded with a facilitated panel discussion and audience questions. Panel members were asked to comment on what is known about the prevalence and incidence of asthma and whether the increase is reflective of environmental causes or increased awareness. The panel discussion covered a number of key topics, including: changes in the prevalence and incidence of asthma, mixture and adjuvant exposures, receptors that may play a role in asthma (e.g., bitter or TRP receptors), the role of irritation in causing asthma, the appropriateness of using rodent nasal and pulmonary airways as surrogate models for the human respiratory tract (and which animal models are best to use), the efficacy of current contact and respiratory sensitizer models, the potential benefits of a dermal penetration model, consensus on definitions
of key terms (e.g. non-specific irritation and sensitization), early effects biomarkers, the status of comparative risk assessment tools, and how to further investigate the role of odor on exacerbation of asthma and/or asthma-like symptoms.

This report is organized in three parts:
- Brief summaries of each speaker’s presentation and key data gaps and references for the topic
- A summary of the audience questions and the panel discussion
- Appendices (Lists of Sponsors and Attendees, Speaker Biographical Sketches)

The Asthma Forum was sponsored by several industry associations that represent an array of chemical and consumer product businesses, including the American Chemistry Council, the American Cleaning Institute, the American Petroleum Institute, the Chemical Producers and Distributors Association, the Consumer Specialty Products Association, CropLife America, the Personal Care Products Council, and the Society of Chemical Manufacturers and Affiliates (SCOMA). Affiliated organizations included the Grocery Manufacturers Association, the Research Institute for Fragrance Materials, and the Styrene Information and Research Center. Toxicology Excellence for Risk Assessment (TERA) helped organize the program content, facilitated the sessions, and prepared this report. The American Cleaning Institute provided meeting management support.

**Steering Committee Members**

- Jay Ansell, Personal Care Products Council
- Richard Becker, American Chemistry Council
- Steven Bennett, Consumer Specialty Products Association
- Sarah Brozena, American Chemistry Council
- Carol Eisenmann, Personal Care Products Council
- Doug Fratz, Consumer Specialty Products Association
- Tucker Helmes, Society of Chemical Manufacturers and Affiliates
- Wendelyn Jones, CropLife America
- Francis Kruszewski (Chair), American Cleaning Institute
- Timothy O’Brien, Ecolab
- Will Ollison, American Petroleum Institute
- Mary Ostrowski, American Chemistry Council
- Richard Sedlak, American Cleaning Institute
- Madhuri Singal, Research Institute for Fragrance Materials
- Danielle Vitale, Research Institute for Fragrance Materials
- Russell White, American Petroleum Institute
Presentations

Session I: Clinical and Biological Basis for Asthmagenic Responses

Clinical Perspectives in Asthma Etiology and Diagnosis
Rebecca Bascom M.D., M.P.H., FAAAAI, FACC, Penn State College of Medicine

Key Points
- Asthma is a syndrome.
- Asthma is an important public health issue because of its prevalence and morbidity.
- It is important for industry to understand asthma because patients with this disease are identified as a susceptible subpopulation, characterized by increased reactivity, and increasing in the population.
- Asthma occurrence follows a biphasic distribution with peaks in childhood and mid-life.
- Clinical diagnosed by characteristic patient history, variable airflow obstruction, and exclusion of other conditions.
- Atopy, viral infections, and brief, high level exposure to an irritant are important factors in asthma development.
- Established asthma may be exacerbated by respiratory infections, irritant exposures, stress, and obesity.

Asthma is a chronic inflammatory airways disease whose common clinical features include variable symptoms of wheezing, cough, chest tightness and shortness of breath, variable airflow obstruction (usually reversible), and increased airway reactivity. It is increasing in prevalence worldwide with international epidemiological studies seeking to measure the health burden and to understand associated risk factors. Its societal importance is measured by the National Institute of Health (NIH) commitment to the National Asthma Education and Prevention Program, which has had three statements, most recently in 2008. A review of these documents (http://www.nhlbi.nih.gov/about/naepp/) shows the importance attributed to small point source exposures from products manufactured by industries represented at this workshop, as well as the gaps in information and science to guide this area.

There is a biphasic distribution of asthma occurrence, with peaks in childhood (male predominance) and mid-life (female predominance). Asthma is the leading cause of lost school days in children and its greatest burden is the associated morbidity (illness, health care utilization, medication costs, lost time and activities); mortality rates are generally low. Studies have shown that prevalence rates of asthma in genetically similar populations can shift in less than one generation (e.g. East-West Germany studies of the 1990s). This shift from a TH1-type, chronic bronchitic, fixed airflow obstruction phenotype to a TH2-type allergic asthma phenotype occurred against a background of widespread societal and environmental changes.
Asthma is a syndrome, meaning that it is a recognizable symptom complex, but is likely the final common pathway (or similar presentation) for more than one pathogenetic sequence. One factor important in the development of asthma is atopy, which is the inherited tendency to form IgE antibody when presented with environmental allergen, and is manifest in the diseases of asthma, allergic rhinoconjunctivitis and allergic eczema. Another factor is viral infections, particular in infancy. Brief, high level exposure to an irritant can lead to permanent asthma, a condition known as Reactive Airway Dysfunction Syndrome (RADS). Established asthma may be exacerbated by respiratory infections, irritant exposures, stress, and obesity.

There is general acceptance of RADS, an asthma syndrome occurring after a brief high level irritant exposure, but this case is far less common with respect to cleaning products or recurrent lower level exposure to irritants. While there is some evidence that chronic low-level occupational exposures to substances producing irritation are associated with the start of asthma, there is not a causal link. Data to address potential mechanisms are fragmentary, primary relating to epithelial dysfunction in asthma with reduced amounts of intracellular toxicant buffers (Holgate, 2007; Cookson, 2004; Leikauf, 2010).

Biopsy specimens obtained from the airways of asthmatic patients show histopathologic changes, with abnormalities present in clinically asymptomatic patients. Examples of remodeling of structural cells include epithelial injury, shedding and metaplasia, mucus cell and glandular hyperplasia, and subepithelial fibrosis. A mixed inflammatory cell influx of eosinophils, neutrophils, and lymphocytes are typically present. Expectorated sputum collection is a method used to assess inflammatory cell patterns, and measurement of exhaled breath NO correlates well with airway inflammation, leading to its use as a disease marker.

Toxicology assessments of commonly used chemicals using rodent inhalation models have shown portal of entry effects as the sole endpoint for many compounds. It is generally thought that the human tracheobronchial tree is the anatomic analogue of the rodent nose. There is a great need for research about pathways of toxicity in the human airway of normal and susceptible populations (e.g., children, people with asthma) to guide clinical management and risk assessment.

The clinical diagnosis of asthma is made in patients with a characteristic history, demonstrated variable airflow obstruction (response to bronchodilators or positive methacholine challenge) and exclusion of other conditions including laryngoesophageal reflux, bronchiectasis, parenchymal lung disease and cardiac disease. Common clinical variants include cough-variant asthma, nocturnal asthma and exercise induced asthma.

Current medical management of asthma is aimed at preserving lung function and a full range of daily activities, while minimizing side effects from medications/treatments. The mainstay of
controlled treatment in persistent asthma is inhaled corticosteroids. Short-acting bronchodilators relieve symptoms. Anti-IgE is a relatively new treatment that blocks the release of inflammatory mediators from basophils and mast cells, and is indicated for patients with moderate to severe persistent allergic asthma. Other pharmaceutical treatments include leukotriene pathway modifiers and receptor antagonists, long-acting beta agonists and theophylline related products. Lifestyle modification is an important component of asthma management. Smoking cessation and avoidance of passive smoke exposure is strongly advised. Avoidance of allergens and triggers is likewise advised.

Data and Research Gaps

- Research on pathways of toxicity in the human airway of normal and susceptible populations (e.g., children, people with asthma) to guide clinical management and risk assessment.

Key References/Resources

The immune system protects the body against infectious agents and some tumor cells, but may also react to otherwise relatively innocuous foreign substances, including chemicals. The resulting allergic reactions can produce an array of pathologies ranging from skin rashes and rhinitis to more life-threatening asthmatic and anaphylactic reactions. Immune responses can be divided into innate and acquired. Innate responses are rapid and non-specific. Acquired responses recognize specific foreign substances (antigens) and selectively eliminate them. On re-encountering the same antigen the response is more rapid and heightened. There is cross-talk between the innate and acquired response, and both involve inflammation, a hallmark of asthma. This talk focused on acquired immune responses associated with the development and expression of allergic asthma, the potential contribution of chemicals to this disease, and tools currently available for assessing such risks.
the dose required for elicitation and vice versa. In some cases sensitization may take place via exposure through the skin, but later elicitation may occur via the respiratory tract.

Chemicals may be involved in allergic reactions/asthma either as the specific allergen or as an adjuvant that promotes allergic sensitization to other allergens or enhances the elicitation response. Chemical allergens can be complete allergens (usually proteins) or haptens, small molecules which are not immunogenic on their own but are reactive enough to conjugate to a carrier protein; this conjugate then can induce an immune response.

When a sensitized asthmatic is exposed to the offending allergen, there is an immediate response that occurs because IgE is attached to mast cells, and the antigen cross-linking of IgE molecules releases preformed mediators (e.g. histamine) that cause bronchoconstriction (there is also release of denovosynthesized mediators such as leukotriene C, also a bronchoconstrictor). There is also a late phase response (6-8 hours after exposure) characterized by hyper-responsiveness to non-specific stimuli and eosinophilic inflammation in the lung, which is mediated, at least in part, by a type 4 cell mediated response. A number of immune mediators (cytokines) are involved in these responses.

Initial attempts to use animal models to assess chemicals for potential to induce allergic reactions in the lung relied on lung function endpoints. This is very cumbersome and costly, and whereas such methods have been useful research tools, none have been widely accepted or validated as a means of testing chemicals. Other endpoints that have been explored in laboratory rodents (but have yet to be validated or accepted) include assessment of cytophilic antibodies (IgE) and T helper cell (Th)2 cytokine profiles. Similar endpoints have been explored to assess potential adjuvant effects of chemicals, but again tests to assess chemicals for adjuvant effects have not been validated or widely accepted. In addition, because low molecular weight chemicals must be reactive enough to conjugate with a protein in order to cause either skin or respiratory reactions, in vitro reactivity with a protein or a positive result in a rodent assay for allergic contact dermatitis have been proposed as a first tier in testing for potential to induce respiratory sensitization. Negative results can be used to exclude a chemical; positive results suggest further testing is needed. Because a well-validated rodent model to assess chemical for potential to cause allergic reactions in the respiratory tract is lacking, classification of chemicals as respiratory sensitizers is largely dependent on human data. If available, animal data can contribute to the weight of evidence. Dr. Selgrade shared a decision tree for identifying and classifying substances as respiratory sensitizers based on human and animal data, as well as a second tree that evaluates specific types of clinical and epidemiology data to determine evidence for respiratory sensitizers.
Data and Research Gaps

- Better understanding of underlying Immunology/Critical Immune Events, such as “misregulation of inflammation,” specific immune responses and immunologic tolerance, and quantitative relationships between response and effect.
- A well-validated rodent model to assess chemical for potential to cause allergic reactions in the respiratory tract would be helpful, as well as in vitro and in silico models.
- Better understanding of sensitization versus elicitation: Two dose responses or cumulative dose? What situations lend themselves to one approach over the other?
- Cross-Reactivity among multiple chemicals
- Currently, there are almost no tools for evaluating adjuvant effects (exposures that enhance immune sensitization); non-specific inflammation is often a key aspect and hence markers of such inflammation could be candidate indicators.
- More quantitative biomarkers of effect and better screening tools

Key References/Resources

Sensory Irritation and the Respiratory Tract Response
Pamela Dalton, Ph.D., MPH, Monell Chemical Senses Center

Key Points

- Afferents of 3 cranial nerves (V, IX & X) innervating the respiratory tract respond to a wide range of chemical irritants, mediated by specific TRP channels.
- TRPA1 is key in development of neurogenic inflammation & triggering asthma.
- Dissociations between surveys, epidemiological studies and controlled exposure studies suggest other factors, such as ‘dose,’ genetic polymorphisms, or co-exposures (mixtures) may play a role in eliciting asthma symptoms in response to irritants.
- Novel ‘bitter’ receptors in human airways may mediate the response to some irritants.
- ‘Perceived’ hazard/stress from a non-irritant can trigger symptom reports AND airway inflammation; this may involve both asthmagenic and psychogenic mechanisms.

Asthma is characterized by airflow obstruction and bronchoconstrictor responses to a wide variety of stimuli, including dust mites, pollens, mold, irritant gases, and dusts. In addition, however, increased levels of psychological stress have been associated with decreases in pulmonary function (FEV₁) and increases in airway inflammation among patients with asthma. That many asthmatics report airway symptoms upon exposure to odors and airborne irritants is not a matter of dispute. However, the mechanisms by which such exposures elicit adverse responses are likely to be varied and may involve both asthmagenic and psychogenic mechanisms.

As the sentinel portal to the respiratory system, the nose and upper respiratory tract subserves a number of critical functions in humans, including: (1) warming and humidifying incoming air, (2) trapping and desorbing particulates and vapors, and (3) providing the sensory functions of olfaction (smell) and chemical somatosensation (irritation or chemesthesis). These functions include a critical protective role as the nasal epithelium has an unmatched ability to detect, trap, and detoxify many pollutants prior to their passage to the lower airways. This protective function does not come without cost; however, as exposure to volatile irritants can elicit direct reactions through contact with trigeminal, glossopharyngeal or vagal nerve endings in the nose, nasopharynx, or throat. Such activation has been shown to stimulate reflex sensations in the upper respiratory airways that lead to bronchoconstriction or bronchodilation in the lower airways. Exposure may also lead to release of inflammatory mediators, such as substance P which can modulate the response of airway smooth muscles. In addition, evidence exists to suggest that pre-existing airway inflammation can lower the threshold for trigeminally-based irritant response.

Dr. Dalton discussed sensory irritation and chemosensory innervation of the upper airways. Sensory irritation (also known as pungency or chemesthesis) refers to the broad range of physiological responses (sensory, secretory, respiratory, cellular and biochemical) when airborne chemicals stimulate free nerve endings in the airway mucosa. For typical healthy individuals
most sensory and many of the physiological responses abate quickly when exposure is removed. The respiratory tract is innervated by sensory afferents of CN, V, IX and X, notably chemically-sensitive non-myelinated C-fibers. She noted that afferents of three cranial nerves (V, IX & X) innervating the respiratory tract are responsive to a wide range of chemical irritants, mediated by specific TRP channels. “Chlorine” tingle and burn of the CN V trigeminal nerve is the first to be stimulated. Nearly all volatile chemicals can be irritants at sufficiently high concentrations.

Cation channels of TRP class mediate chemosensory responses to irritant ligands and appear to play a role in triggering asthma. Some example ligands include capsaicin, camphor, formaldehyde, acrolein, and menthol. TRPA1 is a promiscuous receptor and responds to many ligands. It is a key player in the development of neurogenic inflammation and triggering asthma. The TRP channels appear to play a role in the exacerbation of asthma - inflammatory and allergic response of sensitized mice to ovoalbumin challenge can be blocked by genetic or pharmacological inhibition of TRP1A. The mouse models do not demonstrate all of the same symptomology as humans, but are good for cellular and respiratory responses. For example, TRPA1 knock-out mice exposed to hydrogen peroxide or sodium hypochlorite showed less respiratory depression than wild-type mice. Dr. Dalton discussed the role of TRP channel ligands in eliciting airway inflammation and cough and presented some results of human studies on TRP channels and cough reflex sensitivity. Cough reflex sensitivity to capsaicin (a TRPV1 ligand) is elevated among individuals with asthma and chronic obstructive pulmonary disorder (COPD) (Doherty et al, 2000); exposure to tobacco smoke reduces cough reflex sensitivity to a TRV1 ligand, but not a TRPA1 ligand; and menthol (a TRPM8 ligand) decreases sensitivity of cough to a TRPA1 ligand (citric acid). The last example might also just cause irritation to be perceived and not always be a sensitization response.

Dr. Dalton reviewed the role of psychogenic airway responses to odorous volatiles below the irritant threshold and how learned responses and expectations can elicit asthma symptoms in the absence of irritation. Observational and epidemiological studies have supported the possibility of a relationship between exposure to volatile irritants and asthma exacerbation, with significant correlations found between asthma symptoms and indoor concentrations of volatile organic compounds (VOCs) such as CO2, formaldehyde, benzene, ethylbenzene, toluene and limonene. At odds with these results, however, is the consistent pattern of results from controlled exposure studies evaluating response to VOC concentrations at or above residential levels, in which investigators have repeatedly failed to find a causal link between VOC exposures and asthma symptoms.

Dr. Dalton also discussed the recent discovery of bitter receptors in smooth airway muscle (in both rodents and humans) and the implications this may have for asthmatics.
Data and Research Gaps

- There is ample evidence that chemical irritants found in many consumer products can initiate airway responses that trigger or exacerbate asthma symptoms, but we lack sufficient data to evaluate whether acute or chronic exposure to those low-level chemical irritants can induce asthma.
- How do genetic polymorphisms in metabolic capacity, TRP channel density, and bitter receptors in airways impact the asthmatic response to irritants?
- Can volatile non-irritant chemicals amplify the sensory and inflammatory response to irritants (the mixture question)?

Key References/Resources

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Session II: Investigations into Asthma and Consumer and Commercial Products Use

Asthma Related Exposure Assessments
Fred W. Boelter, CIH, PE, BCEE, ENVIRON International

Key Points

- Exposure assessments should be designed so that the results will be relevant to the endpoint of interest.
- Researchers need to determine whether an assessment is practical and applicable.
- Knowledge of the agent of interest is critical for implementing an efficient sampling strategy.
- Assessing the variety of potential exposures in an occupational or residential setting requires an understanding of sources, a systematic sampling strategy, specialized equipment, and data interpretation skills.

Exposure assessments are a systematic scientific process. Assessments seek to understand the symptoms experienced by a recipient, possible contaminants or agents, and the pathway and quantities, frequencies, and durations by which exposure may occur. The updated National Academy of Sciences (NAS) framework for risk assessment (NRC 2008) states that, when designing an assessment, it is important to know what the purpose of the results will be so that the endpoint is relevant. It also states that researchers should articulate the value of the information being gathered, as it relates to the question(s) being addressed, and evaluate whether the assessment design has a practical application. Ideally, there are three phases of an exposure assessment: scope, assessment, and management. Fundamentally, an assessment related to asthma is an undertaking to assess the risk that exposures may correlate with immunological or nonimmunological asthmatic symptoms such as cough, wheezing, chest tightness, and breathlessness, be they clinically confirmed or self-reported.

Sampling may be appropriate, but rarely can an efficient sampling strategy be implemented without some knowledge of contaminants or agents of interest. Judgments need to be made regarding conditions under which to sample, instrument types, and analytic detection capabilities. Importantly, no sampling strategy should be undertaken without some understanding of how to interpret or evaluate the data which is generated. There are many challenges in evaluating data of poor quality, data which are censored, and data which may produce unintended consequences.

A number of contaminants have been suggested as being related to asthmatic symptoms. Irritants such as chlorine, ammonia, sulfuric acid are often cited example. There are also
workplace stimuli such as diisocyanates, proteins, and resin fumes which can result in occupational asthma. In residential settings, molds and volatile organic carbons (VOCs) have been suggested as causing allergic reactions and asthma. Exposure pathways include direct ingestion, inhalation and dermal contact; an exposure can be assessed visually, through airborne sampling, testing surfaces and materials and/or observing activities spatially. Air sampling equipment includes SUMMA canisters for whole air sampling, coated filter cassettes and sorbent tubes for chemical analysis, as well as equipment that measures particles continuously or collect them on microscope slides. Data collection involves balancing cost versus quality. Assessing such a variety of potential exposures from consumer products and their ingredients requires an understanding of sources, a systematic sampling strategy, specialized equipment, and data interpretation skills.

**Key References/Resources**

New Weight of Evidence Approaches: Cleaning Products and Asthma
Andrew Maier, Ph.D., CIH, DABT, Toxicology Excellence for Risk Assessment (TERA)

Weight of evidence (WOE) approaches provide a useful context for evaluating complex data sets, which include multiple lines or types of research evidence. Application of systematic data evaluation techniques is particularly useful for determining causal relationships between exposure and disease when a wealth of conflicting information is available. Dr. Maier described efforts to adapt current WOE and data quality evaluation concepts to assess the relationships between cleaning product use and asthma or asthma-like responses.

Dr. Maier and colleagues used a systematic scoring approach (adapted from the Klimisch et al. 1997 scoring technique used by many agencies for toxicology evaluation literature) to assess the reliability and relevance of epidemiology studies. The study scoring relied on the degree to which the epidemiology studies had been internally and externally validated – building from the concepts enumerated in the Bradford-Hill considerations. The study scoring approach was applied to a set of nearly 100 studies investigating the link between the use of residential and commercial cleaning products and the onset of asthma or the exacerbation of asthma-symptoms. The results from a sub-set of the most reliable of these studies were pooled and evaluated using a newly developed weight-of-evidence framework. The systematic data scoring approach allowed for greater weight to be placed on higher quality studies and provided for better linkage with data quality evaluations typically done for toxicology studies.

Overall, the database of epidemiology studies was not sufficiently robust to demonstrate a causal relationship between cleaning product exposures and new-onset asthma, although the case was stronger for exacerbation of asthma-like symptoms. There are many caveats in using epidemiology studies to determine the causal role of cleaning product ingredients in asthma induction that were considered in the analysis. Asthma-like symptoms are typically non-specific and can be associated with various other respiratory disorders (e.g., bronchitis). Moreover, common household exposures (e.g., pet allergens, molds, etc.) and common ambient pollutants (e.g., ozone, nitrogen oxides, and formaldehyde) also induce or exacerbate asthma, and can
confound the cleaning exposures measured in these studies. Bronchoprovocation can typically be used to identify the insulting chemical, or to diagnose RADS, but sensitization to multiple other chemicals may also occur especially in people who are atopic, or susceptible to allergy.

A complementary approach to evaluate the relationship between cleaning product use and asthma is through hazard evaluations of component ingredients. Robust epidemiology studies with exposure measurements from individual product ingredients or types were not available. However, hazard characterization can be supplemented with results from animal studies. Thoughtful integration of the complex collection of human and animal data required the development of a second weight-of-evidence system that could account for the relative value of information for various study types. The resulting weight of evidence approach was developed to qualitatively characterize the potential asthmagenicity of specific cleaning product ingredients based on both human and animal data related to asthma, sensitization, and irritation. Because in vivo animal models for asthma have not been validated, evidence of respiratory irritation and sensitization in animals was considered an important input to the overall decision approach. Respiratory irritation was categorized into one of two categories 1) none or mild or 2) moderate or severe, to reflect the intended goal of prioritizing product ingredients that are most likely to induce asthma or exacerbate asthma symptoms without refining the approach beyond a reasonable amount of precision. The embedded assumption was that asthma or asthma-like responses would correlate best with moderate or severe irritants. Respiratory sensitization was categorized as either present or not present. Skin irritation or sensitization data were used to predict respiratory irritation or sensitization in the absence of adequate respiratory effects information taking into consideration caveats in extrapolating findings across exposure routes. When dermal application data were used they were given less weight than evidence from inhalation exposures. Each of the three endpoints addressed using this approach (asthma, respiratory irritation, respiratory sensitization) were assigned a descriptor of the likelihood for a causal relationship that reflects the robustness of the database. Such qualitative descriptors are used in other complex hazard characterization schemes (e.g., for cancer) and similar terminology was used to increase the familiarity of the general scheme to risk assessment scientists. After determining the appropriate category for each of the individual endpoints (asthma, respiratory irritation, and respiratory sensitization), the individual descriptors were integrated to develop a unified descriptor for the overall weight of evidence for the potential of an individual chemical to induce asthma or exacerbate asthma responses.

Key References/Resources

- Adami HO, Berry, SC, Breckenridge, CB, Smith, LL, Swenberg, JA, Trichopoulos, D, Weiss, NS, Pastoor, TP. 2011. Toxicology and epidemiology: improving the science

Swimming and asthma: What does the current research say?

Judy LaKind, Ph.D., LaKind Associates

Key Points

- Disinfecting pools inactivates pathogens, but also results in the formation of disinfection byproducts (DBPs).
- Swimming can lower asthmagenicity and can reduce asthma symptoms or exercise-induced asthma.
- Disinfection byproducts are associated with an increase in asthma among elite swimmers, but not for children or adults who used swimming pools during childhood.
- Little is known about non-chlorine-based disinfectants.

Despite the popularity of swimming in the United States and other countries, important data gaps related to swimming pool chemistry, human exposure to disinfection byproducts (DBPs), and potential health risks have yet to be filled. Because of these data gaps, and for reasons associated with the complexity of the problem (i.e., both in terms of pool chemistry and related human exposures and the complex etiology of asthma), it is difficult to state with certainty whether swimming in pools is associated with asthma etiology. However, research to date allows us to begin to answer this question and to identify research that will best move us toward an understanding of how to maintain a healthy pool environment.

This talk addressed the following topics: (1) Why disinfect pools and what happens when we do? (2) Why asthma and swimming? (3) Evidence that swimming is a healthy activity (4) Evidence regarding whether DBPs may be associated with certain adverse health effects (5) Non-cancer health effects other than asthma (6) Non-chlorine-based disinfectants (7) What can be done now to improve pool and swimmer health.

Pool disinfection inactivates most waterborne pathogens including fecal-borne ones - it is essential for protection of public health. Pathogens that have been found in pool water include bacteria such as *E. coli*, viruses such as hepatitis A, and protozoa such as *Cryptosporidium* and *Giardia*. These pathogens can cause numerous adverse health effects; thousands of pathogen/pool-related illnesses in the US have been reported over the past few decades. The introduction of disinfectants to pool water destroys most of these pathogens but results in reaction with various substances in the pool water to form DBPs, some of which have been associated with adverse health effects.

Several studies found higher rates of asthma in elite and Olympic swimmers. Other studies looking at associations between infant and childhood pool attendance and asthma led to the “chlorine hypothesis” - that asthma may be induced by chlorine-related compounds from swimming pools (http://en.wikipedia.org/wiki/Pool_chlorine_hypothesis). This hypothesis...
postulates that long-term attendance at indoor chlorinated swimming pools, especially by children up to about 6-7 years old, is a major factor in the rise of asthma in first world countries since the late 20\textsuperscript{th} century.

Swimming exercise is associated with lower asthmagenicity, as compared to other types of exercise, possibly due to a lower pollen count over water, higher hydrostatic pressure on the chest, controlled breathing, and/or greater air humidity above pool water. Some studies have reported beneficial health effects associated with swim training, such as reduction in exercise-induced asthma (EIA) severity, emergency room visits or hospitalizations, the number of asthma attacks, wheezing days per person, and asthma medicine use.

A meta-analysis of the available data found an association between swimming in pools and asthma for elite swimmers but not for children and adults who used swimming pools during childhood (Goodman and Hays 2008). Moreover, an association was found between people with no swimming activity during the first year of life and higher rates of asthma (Schoefer et al. 2007). The most recent studies (Font-Ribera et al. 2009, 2011) reported that swimming pool attendance was related to a slightly lower prevalence of current asthma and was associated with increased lung function. These studies do not answer all of our questions, however. Research is still needed on levels of DBPs in the air at swimming pools, development of validated questionnaires related to pool attendance, better measurements of physical activity at pool environments, and other health effects thought to be associated with swimming pools and DBPs.

Most research on pool disinfectant efficacy, DBP formation, and association with adverse health effects has been conducted for chlorine-based disinfectants. While other disinfectants are available and in use, less is known about efficacy, related DBPs and potential health effects.

Even without a full understanding of pool chemistry or DBP exposures or hazard, actions can be taken to reduce unwanted DBP formation and human exposures. Education and outreach with pool operators and the swimming public is needed as is additional focused research.

**Key References/Resources**

• LaKind, JS, Richardson, SD, Blount, BC. 2010. The good, the bad, and the volatile: can we have both healthy pools and healthy people? Environ Sci Technol. 44(9):3205-10.
Session III: Research and New Evaluation Initiatives

In Silico, In Vitro, and In Vivo Approaches to Identify Respiratory Sensitizers
Jon A. Hotchkiss, Ph.D., The Dow Chemical Company

There are currently no accepted regulatory models or predictive tests for assessing the potential of a substance to cause respiratory sensitization and allergy. The European Commission (EC) recommends using a weight of evidence approach to consider both human experiences and animal data and developed an evaluation strategy for REACH. Although a number of animal models have been used for researching respiratory sensitization and allergy (e.g., guinea pig intratracheal test, GPIT), protocols and endpoints for these approaches are often inconsistent, costly and difficult to reproduce, thereby limiting meaningful comparisons of data between laboratories and development of a consensus approach. In vitro approaches (e.g. cell culture systems) have potential for identifying respiratory sensitizers, but no single system can accurately predict respiratory sensitization potential. Emerging in vitro and in silico models (e.g., Quantitative Structure Activity Relationships, QSAR) show promise for use in the characterization of contact sensitization potential.

In contrast, a number of models exist for the assessment of contact sensitization and allergic contact dermatitis (ACD). Research indicates that respiratory sensitizers may be identified through contact sensitization assays such as the local lymph node assay, although only a small subset of the compounds that yield positive results in these assays are actually respiratory sensitizers. There may be subtle but important differences in the pathogenesis of respiratory allergy and ACD that may be exploited by in silico, in vitro and in vivo approaches that are currently being applied or could be further developed to identify compounds capable of causing
respiratory allergy. Due to the increasing health concerns associated with occupational asthma and the impending directives on the regulation of respiratory sensitizers and allergens, an approach which can identify these compounds and distinguish them from contact sensitizers is required. Ultimately, the development of a consistent, accurate and cost-effective model will likely incorporate a number of these approaches and will require effective communication, collaboration and consensus among all stakeholders.

In order to develop an acceptable model for respiratory sensitization, several key data gaps need to be filled. Developing a robust, broadly applicable, challenge-based, in vivo model to identify respiratory sensitizers is a critical but challenging goal. Current in vivo models need to be refined so that they address key questions of 1) exposure route, timing, dose, and frequency of exposures during sensitization; 2) selection of predictive endpoints and characterization of the exposure-response profile during elicitation; 3) allergenic potency and identification of elicitation response thresholds; and 4) selection and characterization of negative control substances. There are several promising in vitro models, but none of them are validated. Continued research to improve methods of identification and characterization of contact sensitizers may provide essential data necessary to discriminate between potential contact and respiratory sensitizers. However, de novo identification of respiratory sensitizers will still need to be tied to results from in vivo models. In silico models are an attractive solution for identifying respiratory sensitization potential, but they are not yet ready. We still need a more specific understanding of essential physiochemical properties that can distinguish between respiratory and contact sensitizers, especially since the impact of misclassification is high. These models will also need to be anchored to in vitro and in vivo model predictions.

Data and Research Gaps

- Tiered approach for detecting LMW respiratory sensitizers
- Design a robust, broadly applicable, challenge-based, in vivo model to identify respiratory sensitizers
- Continued research to improve methods of identification and characterization of contact sensitizers may provide essential data necessary to discriminate between potential contact and respiratory sensitizers
- A more specific understanding of essential physiochemical properties that can distinguish between respiratory and contract sensitizers.

Key References/Resources


Landscape of New Research Initiatives
Madhuri Singal, Ph.D., R.R.T., Research Institute for Fragrance Materials

The respiratory tract is a highly complex and diverse organ system that not only functions to exchange oxygen and carbon dioxide and assist with acid-base balance, but also to filter materials in the air that we breathe. With each successive generation down the respiratory tract the physical geometry becomes increasingly complicated and the cell types change from the upper respiratory tract (nose, sinuses, and pharynx) to the lower respiratory tract (trachea, bronchi/bronchioles, and alveolar spaces). As the cell types change so does the functionality of those various cell types and their respective response to airborne stimuli that may enter the respiratory system. In the landscape of new research initiatives, the Respiratory Science Program at the Research Institute for Fragrance Materials, Inc. (RIFM) has developed, in collaboration with industry and academic partnerships, a comprehensive 5-year research plan to systematically approach and answer critical questions regarding fragrance impact on asthma and airway hypersensitivity that may lead to respiratory allergy development. Dr. Singal presented examples of current research and initiatives to address exposure and bioavailability, protein reactivity and immune system stimulation, and clinical responses, as they relate to products and asthma.

Based on the presentations preceding this talk, five important steps moving from exposure to clinical response must be addressed in concert with one another. These five steps have been integrated into a series of studies designed to feed data into each other such that a complete picture can be assembled regarding the impact of exposure on bioavailability, the effect of bioavailability on protein reactivity, subsequent immune system stimulation, and finally, the potential clinical outcome resulting from the exposure event. All of the models described are universally applicable to the assessment of multiples types/categories of air care products.

**Key Points**

- RIFM designed an integrated series of studies to assemble a complete picture regarding the impact of exposure on bioavailability, the effect of bioavailability on protein reactivity, subsequent immune system stimulation, and the potential clinical outcome event.
- 2-Box Air Dispersion Model software calculates peak air concentrations of individual materials from different air care product types.
- Respiratory Cellular Cytokine Profiling Project developed an immune-competent, 3-dimensional human *in vitro* model system of the main cell types present at the air-tissue interface in the deep lung and are responsible for inflammatory and/or allergic events in the respiratory system.
- Dosimetry/Deposition Project is a computational modeling software system corroborated with *in vivo* data exposures to develop a picture of inhalation exposure and potential effects to validate a predictive computational model.
Building from previously conducted simulated exposure studies, the Dosimetry/Deposition Project is comprised of two studies, computational modeling and in vivo correlative exposures. The data from these two studies allow for the development of a picture of inhalation exposure and potential effects while simultaneously building a predictive computational model. Preliminary data using non-fragrance materials have shown excellent correlation with previously published in vivo data. As of May 2010, the in vivo correlation exposure studies began with a well-established Organisation for Economic Co-operation and Development (OECD)-based testing protocol to evaluate a variety of endpoints following inhalation exposure to selected fragrance materials. The fragrance materials were selected to represent a wide range of vapor pressures (high, medium, and low) as well as their high global use in fragranced products worldwide. These materials have been tested in the computational model to predict deposition patterns in the airway and determine/quantify the deposited dose. Based on knowledge of the cell types in the regions of greatest deposition, the computational model will allow for the prediction of potential physiological effects we may anticipate in the correlative in vivo inhalation exposure study. Once the dose deposited in the airways of the animal computational model is quantified, the results can be extrapolated, mathematically, to the airways of the human model. The data from the limited in vivo study will support use of the computational model as a strong alternative to animal methods for inhalation risk assessment. For aerosol products, this will be an important tool to understand the behavior/kinetics of any particular material from the product in the air, especially in conjunction with the use of validated single or multi-chamber air dispersion models.

In addition to this research, recently completed is the model development/feasibility phase of the Respiratory Cellular Cytokine Profiling Project. The goal of this project was to develop an immune-competent, 3-dimensional human in vitro model system containing the three main cell types that are present at the air-tissue interface in the deep lung and responsible for inflammatory, and potentially allergic, events in the respiratory system. What is particularly unique about the model is the CULTEX aerosol generation system. This system provides the “inhaled” material of interest at a set flow rate and concentration in a life-like manner by maintaining the air-liquid interface that is present during breathing. In the next phase of the project, currently in progress, the cells will be exposed to eight non-fragrance irritants or sensitizers. Samples collected from these exposures will be screened for the expression of different chemical mediators (cytokines). Cytokine profiles differ depending on whether the stimulus causes inflammation as an irritant or a potential allergen. By characterizing the trends observed in these profiles, we will obtain valuable information for distinguishing new and existing fragrance materials as potential sensitizers.
Recently debuted is the 2-Box Air Dispersion Model software. The model is a web-based software program with templates programmed for users to calculate peak air concentrations of individual fragrance materials following intended consumer use of finished products from three air care product categories: Aerosol Air Fresheners/Fine Fragrance Sprays, Candles/Incense, and Heated Oil Plug-In Air Fresheners/ Reed Diffusers.

These categories are defined by the similarity in air dispersion patterns and consumer use habits. An individual using the program would simply need the percentage of the final concentration of the material of interest in the product of interest. Upon entering this value into the pre-programmed template for the product of interest chosen, the program will generate a graph depicting the inhalation exposure profile for that material and calculate a cumulative available inhalation exposure concentration for a period of 24 hours. Currently being built is a fourth template that will allow for nearfield (personal) exposure analysis. Experienced users can also build custom scenarios with parameters specific to their product and use characteristics. This software will assist product safety scientists and regulatory toxicologists by producing valuable exposure assessment data for application to inhalation risk assessment purposes.

Overall, the program is designed such that data from each project will provide data integral to the success of the following project. Although each project can also stand independently, the comprehensive collection of data will seamlessly tie together the various aspects of inhalation exposure following the paradigm of exposure assessment to risk, or safety, assessment.

Key References/Resources

Exposure Assessment Modeling for Consumer Products

Michael A. Jayjock, Ph.D., CIH, The LifeLine Group

Exposure assessment modeling starts with the identification of the specific etiologic agent (either as a parent or a metabolite) causing sensitization. This specification of agent should also render the residence time (biological half-life) of the chemical (and any of its etiologically relevant metabolites) in the body. This, in turn, will drive the proper averaging time of the exposure events. Typical averaging times for exposure modeling include instantaneous, or peak, values (C or ceiling), 15 minutes (short term exposure limit, STEL or a 15 minute time weighted average, TWA), 8 hours (8 hr TWA) or 24 hours (Daily Average).

Knowledge of the agent also helps determine the appropriate exposure metric. Exposure metrics are defined as the measureable or estimated physical quantity that best correlates with the adverse health outcome of overexposure. Inhalation exposure metrics include breathing zone concentration, which is estimated in a hemisphere that extends approximately 30 cm in front of the face from a midpoint of an imaginary line that joins the ears. Vapor is relatively simple to estimate because it always moves with, and is mixed in, the air. Particulates, however, are more problematic; each airborne particle is a relatively massive collection of the substance of interest and they are typically not all the same size. Moreover, the size of the particle determines whether or how fast it will settle to the ground or where in the respiratory tract it will deposit. The site of respiratory tract deposition depends on aerodynamic particle size or diameter (aerodynamic diameter, or AD). The somewhat unit primary dermal exposure metric for Type IV contact allergens is typically measured as mg/cm²/day the standard metric for dermal exposure to systemic toxicants is mg/kg/day.

Inhalation exposure can be estimated with monitoring the breathing zone or modeling. Specific inhalation models include the 1-Zone (or Well Mixed Box) and 2-Zone (or Near-Field/Far Field), and eddy diffusivity models. The input variables as well as the strengths and weaknesses of each model were discussed. The 1 Zone model is relatively simple, while the 2-Zone is considerably more complicated incorporating mass balance equations with constant or decreasing source rate for calculating breathing zone concentrations in both the near and far fields. Eddy diffusion modeling is an advanced and competent theoretical model, but awaits further research. IH MOD is a user friendly freeware spreadsheet form the American Industrial Hygiene Association that provides the ability to run these models and others. The complete mathematical basis for each
model was presented along with Internet links to freeware resources that allow the complicated mathematical operations of these modeling tools to be done with relative ease.

Dermal exposure assessment as a potentially important route for the development of asthma was presented in some detail. The primary elements of assessing this route of exposure are:

- How much agent goes onto the skin
- The surface area of skin exposed to the substance
- The rate at which the substance goes through the top layer of skin (the stratum corneum or SC) and into the systemic circulation

The structural elements of human skin were presented and discussed within the context of currently used dermal exposure modeling. A freeware resource to estimate the actual rate of dermal penetration (Kp) can be found at http://home.planet.nl/~wtberge/home.html and a general dermal exposure algorithm that allows the aggregation of the total dermal dose over various body zones is software called STICK PERSON, which is available at http://www.thelifelingroup.org/cbas/index.htm.

The overall current precision and utility of the various models was presented along with areas of research that could provide cost effective improvements to these important tools. The models are all essentially first-principle models and are therefore as good as their input. The dermal models will provide estimates within a factor of 10 of the actual value; this range of uncertainty is based primarily on the uncertainty associated with the permeation rate through the skin. One-Zone models significantly under-predict exposures that occur within the near-field. Two-Zone models do a better job at prediction, but require a good input for the air exchange rates between the near and far fields. The Eddy Diffusivity Model is highly uncertain due to a lack of knowledge about the turbulent diffusion coefficient (D_T). All of these models can be improved by having good data on source strength (wt/time) and the time course of emissions.

**Data and Research Gaps**

- Data needed to improve inhalation models
  - All of the models could use good data on source strength (wt/time) and the time course of emissions.
  - 2-Zone – a comprehensive data set on random air movement extant within residences as a function of activities within the rooms of interest and the general ventilation rate (air changes per hour, or ACH).
  - Eddy Diffusivity – research into the determinants of D_T that would allow it to be predicted within typical scenarios.
- Data needed to improve dermal exposure models
  - Dislodgeable residue data set for chemicals of interest.
• Studies on metabolism and fate (e.g., irreversible binding) within the stratum corneum. For example, the stratum corneum is full of residual hydrolase activity for esters and amides.
• Metabolism studies of the viable epidermis relative to how much and which chemical species are formed.
• Standardization of protocols and careful control of in-vitro experiments of Kp.
• Creation of a database of simultaneous in-vivo with in-vitro penetration studies

Key References/Resources

• American Industrial Hygiene Association (AIHA). Freeware resources for Well Mixed Box, Near-Field/Far Field, and eddy diffusivity models
  (http://www.aiha.org/insideaiha/volunteergroups/Pages/EASC.aspx)
• A freeware resource to estimate the actual rate of dermal penetration (Kp) can be found at http://home.planet.nl/~wtberge/home.html
• A general dermal exposure algorithm that allows the aggregation of the total dermal dose over various body zones is software called STICK PERSON, available from The LifeLine Group http://www.thelifelinegroup.org/cbas/index.htm.
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Discussion

The speakers formed a panel for the final workshop discussion session. Members of the audience asked panel members a number of questions. In addition, the Facilitator, Dr. Andrew Maier, posed additional questions for the panel to address. The following is a summary of the panel’s responses, grouped into a number of key topics.

**Prevalence/incidence changes**

David Nuber of Colgate-Palmolive asked the panel to comment on what is known about the prevalence for asthma incidence and whether incidence is actually increasing or if the increase reflects more awareness. Dr. Bascom thought that there is an increased incidence of asthma overall (Asher et al., 2006) and also an increase in awareness of the disease, but noted that no one has apportioned how much of the increase to attribute to each. Dr. Selgrade added that a recent Centers for Disease Control and Prevention (CDC) study found that the greatest increase in asthma prevalence is in the 0-5 and 5-12 year old age groups (Mannino et al., 1998). Dr. Bascom noted that the “wheezy” phenotype can be subdivided (Savenije et al., 2011 and Von Mutius, 2011). One group is small boys with smaller airways who are exposed to viral infections; these children generally grow out of their asthma. There is a bimodal distribution in populations: more boys than girls have asthma, and more women than men (but to a smaller extent).

Dr. Maier asked the panelists to identify the leading hypotheses for the increased incidence in children. Dr. Bascom identified a number of hypotheses. She noted that the “hygiene hypothesis” is commonly cited (von Mutius, 2007). It attributes increased incidence of asthma with a cleaner personal environment, resulting in fewer challenges to the immune system and therefore, less stimulation of the TH1 pathway. Another leading hypothesis is that there is something different in the modern environment, which leads to different expressions in incidence. For example, exposure to bacterial pathogens stimulates and amplifies asthma symptoms for TH1-types. Scientists now realize there are more subsets of T cells than thought in the past, which complicates understanding. Another aspect is the environment in which the antibody/antigen is presented to lymphocytes. For example, diesel particles increase primary allergic sensitization; the particles are thought to be a contributor because they serve as an adjuvant (Auten et al., 2011; Porter et al., 2007). Maternal supplements of folic acid is an additional hypothesis (Hollingsworth et al., 2008; Whitrow et al., 2009). Dr. Selgrade identified some additional common hypotheses: tighter indoor environments; more people living near roadways and thereby exposed to particulates from exhaust, nitrous oxides, and, ozone; and,
more childhood vaccinations leading to fewer infections. Dr. Bascom concluded that it is not likely that there is just one single cause for increased incidence of asthma in children, rather there is a broad list of causes.

**Mixtures - complex and cumulative exposures, exposome, adjuvants**

Dr. Maier asked the panel to consider the question of mixed exposures and they provided their thoughts from a number of different perspectives. Dr. Selgrade noted that risk assessment has trouble assessing mixtures and other panelists agreed, noting some of the problems and issues involved relate to the understanding of biological interactions (at the level of toxicokinetic and toxicodynamic responses) and the resulting challenges in predicting responses in the absence of whole mixture data. Dr. Dalton noted that in terms of respiratory tract responses, mixtures need to be considered in light of the odor trigger issue that was discussed earlier; a strong odor may be present with hundreds of other compounds, and a response may be triggered by the odor event at subthreshold doses for the individual biological irritants. Thus, in addition to additive effects of chemical irritants at the level of local tissue biology (e.g., TRP receptor activation) – chemical mixtures need to account for such effects of varying sensations on the mixture response. Dr. LaKind added that the presence of microbiological agents could add further complexity to assessing mixtures. In their research of the swimming pool environment, they have not yet begun to examine exposure to factors other than chemicals present. She noted that a pool is also a warm and wet environment with microbes and biological agents that could also trigger asthma responses.

Dr. Dalton and Dr. Singal noted that indoor air is a complex mixture and that it changes with many compounds reacting or degrading over time; the parent material may not be what the person is exposed to or the cause of the symptoms or observed effects. Moreover, Dr. Boelter added that the products themselves also may change over time, citing diesel as an example of changing emissions due to different uses and applications. Existing technologies include ultra-low sulfur fuels, particulate filters and either an SCR catalyst, an NOx absorber, or recirculation of the exhaust gas. New technologies continue to be developed including low compression diesel engines and electrochemical flue gas purification. In addition, tighter buildings with reduced ventilation compared to well-ventilated spaces may also have different profiles of the chemicals present over time. Information on all of these factors helps us understand the mixture of chemicals and environmental factors that need to be considered in investigating cause and effect within a particular setting. Dr. Boelter remarked, however, that this array of considerations can be complex, and a more complicated model may not be necessarily better, for example using a 3-Zone, rather than 2-Zone model. The tools for estimation of relevant exposures should only be as complex as needed to answer the risk assessment question at hand.
Dr. Selgrade mentioned current work on the “exposome” - a recent initiative to explore and identify total lifetime exposure. She explained that EPA and others are currently exploring ways to use systems biology to combine exposures to gain a better understanding of overall lifetime of exposure and how different life stages and activities contribute to health risk. Dr. Boelter added that more prospective epidemiological work will complement the exposome project to provide a prospective picture of health risk impacts arising from cumulative exposures over a lifetime. This can then be coupled with the dose-response to provide what is needed for more robust risk assessment.

Dr. Maier asked the panel to clarify what is the adjuvant response and biological mechanism behind it. Dr. Hotchkiss explained that people are exposed to many substances at subthreshold doses. Individually these exposures may not result in an irritant response or result in sensitization, but, co-exposure to a subthreshold dose of an allergen plus an airway irritant may result in sensitization. Dr. Selgrade provided an example. Animals exposed to diesel, fly ash, or NO₂ with a common allergen such as dust mite, exhibit heightened responses (characteristic of asthma) upon subsequent challenge with the allergen in the absence of air pollutant, suggesting that the air pollutant acted as an adjuvant to promote sensitization. She noted that adjuvants are used in vaccinations to promote protective immune responses. As with allergic sensitization, a number of animal models have been used to demonstrate adjuvant effects in research settings, but there are no validated test models. She thought some of the consumer product chemicals might be in this group.

Russell White of the American Petroleum Institute (API) asked if there are thresholds for adjuvants and how one would calculate dose-response. Dr. Hotchkiss explained that they can develop good dose-response profiles for sensitizing agents in current models, but the impact of an adjuvant can be unpredictable; its impacts are often dependent on the amount present, the nature of the material (particle or gas; organic or inorganic) and the interaction with the airway epithelium. Moreover, dosimetry will be different and timing of exposure can enhance or suppress expression of the allergic response.

**Irritation as a cause of asthma**

Athena Jolly of Huntsman Corporation asked the panel whether there is sufficient knowledge to say that irritation alone can cause asthma, not just exacerbate an asthma response. Dr. Dalton commented that there is ample evidence that irritants can exacerbate existing asthma. Dr. Bascom mentioned that chronic low level occupational exposure to substances that produce irritation (but not the inflammation associated with reactive airway disorder [RAD]) is associated with the onset of asthma, but this is not a demonstrated causal link and the data are not adequate to resolve this question. Mr. Boelter agreed that the mechanisms for low-grade irritation or inflammation being a cause of asthma or making a person more susceptible are not known. Dr.
Bascom noted that some studies demonstrate that chronic exposure to ozone results in changes from a neutrophilic to an eosinophilic response (Peden et. al., 1997); and wondered if it is the constant low grade irritation via TRP channel responses. Dr. Dalton thought this plausible, clearly TRP1α is involved in the production of eosinophilic infiltration (Caceres, et al., 2009), but she did not know of any studies looking at chronic low-grade irritation.

Dr. Bascom added that data from controlled human studies show that not all irritants are equivalent in their tissue inflammatory response (Bascom et. al., 1990; Bascom et. al., 1991) Furthermore, Dr. Bascom added that irritation data from human studies are not all equivalent; nasal, tracheal or bronchial areas see different results from different substances due to differences in tissue dosimetry. She thought that variability in TRP receptor localization may explain some differences in response. Dr. Dalton thought better understanding of the role of TRP receptors might provide a way to more fully characterize differences in relative potency.

Dr. Bascom noted that Dr. Selgrade in her talk distinguished between innate immunity and acquired immunity. She asked Dr. Selgrade if continued stimulation of innate response could cause asthma. Dr. Selgrade said it could, that dysregulation of inflammation may play a role (Dietert, 2011). Constant inflammation of the lung will not be healthy; some people are more susceptible to ozone than others and there is some indication that genetics explain why some are more resistant than others (Bauer and Kleeberger 2010). Dr. Bascom also noted that EPA studies showed variation among subjects, but there was consistency within subjects (McDonnell et. al., 1985).

**Odor: How to investigate further**

Angela Hofstra of Syngenta Crop Protection asked panel members to comment on the role of odor in the induction and exacerbation of asthma and asthma symptoms. Dr. Dalton clarified that it is known that odor plays a role in exacerbation of asthmatic symptoms for some people, but it is not known how a purely olfactory stimulus causes a reflexive respiratory tract response. The odor may cause a conditioned response; that is, the odor serves as a signal for exposure to the chemical and provides a basis for a psychogenic response to the stimulus. Odor is clearly a signal for perceived harmful exposure - whether this is a conditioned response or an unexplained mechanism is not known. The odor stimulus is not the same for all patients; some asthmatics are bothered by certain odors, while others are not.

Dr. Bascom thought that teasing out the role of odor might be investigated in a fashion similar to that used by Steve Holgate’s group (Johnston et al. 1996) to determine the role viruses play in asthma. She explained that Holgate and colleagues interviewed patients reporting asthma symptoms in real time and found rhinovirus was an important factor. She suggested that perhaps a similar technique can be used to investigate odors - a real time follow up with those reporting
odor induced symptoms to determine if there are chemical exposures accompanying the odor. Remote sensing and a way to record symptom events might be used to provide a real time monitoring of the air to identify triggers for these reflexive responses to odors. Dr. Boelter noted that there are personal monitors that can measure air concentrations with specific activities and events. He was not aware of current technology to record events, but thought one would need visual information and direct real time instrumentation to help to determine if there is a causal relationship. Video tape might be used to correlate activity and concentrations, with reported symptoms and events.

**Bitter and other receptors**

Dr. Russell White of API asked the panel to discuss further the novel “bitter” receptors. Dr. Dalton explained that sweet and salt receptors have not been found in airways, although they have been found in other parts of the body. Dr. Maier asked how likely there may be other receptors, that have not yet been identified, that may be key drivers for asthma. He noted that we know TRP family of receptors and apparently the bitter receptors play a role, leading one to believe there may be other receptors. Dr. Dalton agreed, given the uncertainty of predicting asthma, there are probably still other receptors yet to be identified. Asthma response may reflect a role of a combination of gene products.

**Animal models and species**

Angela Hofstra of Syngenta Crop Protection asked the panel how good they thought the rodent respiratory tract is as a model for the human respiratory tract and if the Brown Norway rat is a better species for asthma research than the Sprague Dawley rat. Dr. Singal noted that there has been a lot of work over the past 20 years looking at rodent species and allometric scaling to humans. She noted that it is recognized that the rodent upper airway is not an exact replica, but correlations can be made with the human respiratory tract, based on lesions observed and computational fluid dynamic modeling. She thought the rodent and human models developed do a reasonably good job of providing a place to start an evaluation. Dr. Hotchkiss explained that one would need to look at specific locations of the upper or lower respiratory tract and focus on the same types of epithelium and cell types, and similar dosing regimens, to make comparisons and determine how well models can predict responses between species.

Dr. Bascom noted that the rat nose does not compare directly to the human respiratory system, because the rat nose is the portal of entry in that species. However, she agreed with other panelists that progress has been made in correlating rodent and human respiratory tract responses and one can make some correlations between the two. Dr. Singal also cautioned that since rodents are obligate nose breathers and humans have oral and nasal breathing these differences impact how substances deposit in the airways. Dr. Bascom asked Dr. Singal whether the model she showed in her presentation also covers the tracheal region. Dr. Singal confirmed that the
model she discussed covers the entire respiratory system and that there are mathematical models available as well to assist in evaluating species tissue dosimetry differences.

Dr. Ralph Perod of BASF Corporation raised the question of the best animal models for sensitization. He noted that panel members mentioned the guinea pig might be a little oversensitive. With diisocyanates, Dr. Karol could elicit response with inhalation challenge in the ppb range, leading one to ask what would we expect in humans? What is the advantage of moving away from the guinea pig? Dr. Hotchkiss explained that there are advantages with other animal models; for example, one can better examine mechanisms underlying immune-, irritant- or injury-mediated airway remodeling using mouse or rat model systems, information which can then be fed into in vitro and in silico models to be make them more predictive. The Brown Norway rat is useful when one is interested in specific molecules when looking for a No-Observed-Effect-Level (NOEL) for elicitation - something he was not sure could be done reliably using the guinea pig. Dr. Perod asked about the value of a NOEL in rats in and its relevance for assessing human risk. Dr. Hotchkiss noted the work by Pauluhn and colleagues (2011), which measured tissue dose and doses to specific target organs that were similar to that seen in humans. He thought that the guinea pig may be restrictive to the diisocyanates, rather than wider range of materials. Further considering the different rat species, Dr. Singal noted that the results from the Brown Norway rat are skewed because it is a species sensitive to producing a higher magnitude of these immunological responses. Dr. Hotchkiss added that the Brown Norway rat is often used when investigating potential immune-mediated (allergic) responses to explore exposure-response relationships in what is considered a more sensitive rat species. He noted that Fischer 344 and Sprague-Dawley rats are strains that are commonly used in toxicology studies which may be less responsive to allergenic stimuli.

**Dermal penetration model**

Dr. Perod asked Dr. Jayjock to comment further why he thinks more work is needed on dermal penetration data. Dr. Jayjock explained that the best database currently available from Wil ten Berge’s web site (http://home.wxs.nl/~wtberge/qsarperm.html). This database is limited because it comes from a number of different sources using defined and applied protocols. Given this limitation in data quality ten Berge has expressed to Jayjock that he believes that the data and subsequent models are good within a factor of 10. Drs. Jayjock and ten Berge think a concerted effort for a standardized test applied to a broad range of hundreds of compounds is needed to narrow the uncertainty to a factor significantly less than 10.

**Early effects biomarkers**

Dr. Maier asked the panel to comment on the utility of early biomarkers for asthma, in light of current efforts to more fully use systems biology data for health risk assessments (NRC, 2007). He asked the panel whether the current science is close to being able to use early effect
biomarkers for assessing asthma. Panel members identified a number of areas where biomarkers show promise and could be further explored.

Dr. Bascom noted that people who are not atopic, when presented with an antigen in the workplace, respond at a rate of 5-10%, while those with a family history of atopy (the inherited tendency to form IgE antibody when presented with environmental allergens) respond at a rate of 30% (Bush et al, 1998, see Table III). But the prevalence of asthma is less than 40%, indicating that immunologic sensitization may be a step in disease pathogenesis, but that immunologic sensitization is not a specific marker for asthma. Dr. Bascom thought however, that this information could be used for establishing workplace control strategies, citing the reduced prevalence of latex sensitization among nurses with the reduced use of latex gloves in recent years. In addition, the rate of new occupational asthma cases among nurses has also gone down (Niggemann, 2010; Charous et. al., 2002; Tarlo, 2007; LaMontagne et. al., 2006).

Dr. Singal suggested that at this point biomarkers could provide directionality, giving an indication of a potential problem situation, but not serve as a definitive predictive measure. She thought that in the occupational setting better medical surveillance could help elucidate how causation or sensitization occurs. She noted that Association of Occupational and Environmental Clinics (AOEC) utilize a very long list of “asthmagens,” but not all of these have been defined as causing de novo asthma, and include common items like loose leaf tea. She said that there are diagnostic tests (e.g., bronchial provocation testing) but that these have been developed for specific materials and those that have been developed do not include commonly used consumer product ingredients.

Dr. LaKind added that the use of Clara cell protein (CC16) has been investigated and may hold promise, but that at present there are several critical areas where additional information is needed before CC16 can be used as a robust biomarker of effect or exposure (LaKind et al. 2007). For example, there are no data currently on the range of concentrations for a healthy population. Dr. Bascom reflected that the field of cardiology has validated blood markers for heart muscle injury and suggested exploring the possibility of identifying markers for asthma as there is not currently a test of this type that is adequately validated for respiratory effects related to asthma.

**Contact and respiratory sensitizers**

Dr. Maier asked the panel to comment on the effectiveness of the current suite of topical and respiratory sensitizer models in identifying chemicals that cause asthma. Dr. Bascom commented that the primary distinction between contact and respiratory sensitizing agents is whether they can get into the lung. Dr. Singal noted, however, that there are mechanical and chemical interaction differences; for example aerosols and particulates will interact with the cells of the respiratory system differently. An aerosol of a water soluble substance will be handled by
the cells in a different manner than an insoluble particulate that has been aerosolized and inhaled. For example, with silica, the crystalline form is persistent and causes chronic inflammatory injury in the lung, hence the development of silicosis. However, amorphous silica has no defined crystalline structure, has lower residence time in the lung, and causes an acute inflammatory event that clears quickly.

Dr. Hotchkiss thought that there is a need for more robust endpoints for sensitizers in general to allow for differentiation and to classify chemicals as contact sensitizers and respiratory sensitizers. He thought that in the future there will be powerful in vitro and in silico tools for differentiating route specific sensitization, but this will take some time and the tools will need to be validated. At this time there is no good generalized model; each scientist is focused on his or her own molecule of interest and highlights the response of that molecule. He explained that when they have tried to generalize such chemical class specific models from these specific investigations to a group of chemicals, it has not worked, citing his own company’s work on evaluating QSAR predictions of dermal sensitization potential of a group of 65 industrial and agricultural chemicals previously evaluated by Guinea pig sensitization, LLNA, or human patch testing (Sosinski et al., 2009).

Dr. Bascom asked the other panelists if Industrial Hygienists differentiate respiratory and contact sensitizers simply on accessibility to the respiratory tract. Dr. Jayjock confirmed that the field identifies substances as contact sensitizers versus respiratory sensitizers. Mr. Boelter added that much of the workplace inhalation exposure evaluations performed in the past were based on total mass per unit volume of air (for example, total dust measurements), but it is more common now to use sampling techniques that mimic the inhalable or respiratory fractions of the ambient exposure. For nano-particles he noted that we do not know whether there are significant uncertainties regarding their unique toxicity, but we do know how to control exposure to particles in this size range. From the exposure assessment standpoint, he explained that sophisticated modeling can be done, but a better understanding of the dose-metric and what part of respiratory system is of interest is needed to use the results for a robust risk assessment.

**Comparative risk assessment**

Dr. Maier asked the panel to comment on the status of comparative risk tools given current issues surrounding trade-offs between cleaner environments (less illness from microbial exposure) and the interplay with asthma risk (due to the hygiene hypothesis or proposed impacts of cleaning product exposures). Dr. LaKind noted that the pool research she reported on was conducted by a multidisciplinary group of researchers, and that this approach of bringing the different experts together has been very valuable in examining the risk issue from different perspectives and in gaining new insights. She thought that the study of exposure and asthma would benefit from the evaluation and comparison of risks, and that this type of multidisciplinary
effort should be done more often. She noted a recent World Health Organization (WHO) approach for quantitative risk-benefit analysis for fish consumption, and supported consideration of both risk and benefit for decision-making, rather than just risk-risk comparisons. Dr. Selgrade noted that the EPA does not do much with comparative risk and thought that there are lessons to learn from the pharmaceutical arena on risk-benefit approaches.

Consensus on definitions
Gary Minsavage of Exxon-Mobil Biomedical Research asked whether there is consensus on the definitions for key terms in this area; for example, non-specific irritation and sensitization. Dr. Bascom suggested that a diagram defining and clarifying terms and usage across disciplines; showing where they are interchangeable and where they are specific, would be helpful. Dr. Bascom noted that the separation between innate and specific immune response is something all generally agree about and that within the specific immune response, there are Types 1 through 4. Dr. Selgrade noted that all four types are bad for health; the distinction is that the Type 1 response is immediate and tied to exposure and an immune antibody response, while the same cannot be said for Type 4. Dr. Selgrade noted that there is a need to separate Type 1 from Type 4 responses, but she cautioned that by putting terms into boxes we may miss the big picture.

Parting comments
At the end of the discussion session, Dr. Maier asked the panel one final question: “If you were trying to clarify the relationship between asthma and consumer products use – what would be your highest priority for research?” Below are the individual responses.

- Dr. LaKind thought that the highest priorities would be to better capture exposure information and to assess mixtures in a more sophisticated way. She explained that without specific quantifiable exposure information we are left to make judgments based on qualitative surrogates (e.g., time in environment, product use or no use, etc.).

- Dr. Dalton agreed that exposure assessment and actual measurements are critical and that the problem with evidence in real world associations is that they are not capturing real exposures, but surrogate measures. She recommended better exposure monitoring and medical monitoring to correlate the two.

- Dr. Jayjock thought the biggest single need is more robust source characterization, which would provide valuable information for quantitative exposure estimation.

- Dr. Hotchkiss identified as priority, the need to establish potency thresholds for exposure and dosimetry. He thought available tools, such as QSAR in vitro, and in vivo models can provide data for hazard characterization purposes. However, risk management
measures would be better informed with exposure and dose-response information. Risk can then be minimized through smart exposure controls to limit exposure to subthreshold levels for de novo sensitization, elicitation responses in previously sensitized populations or potential exacerbation of pre-existing chronic respiratory disease.

- Mr. Boelter reminded the attendees not to forget the obvious need to educate people to understand safe usage of materials, such as use of personal protection, following label instructions, not mixing chemicals, understanding the concept of reservoirs (e.g., carpet collects substances and is difficult to clean), and recognizing the importance of ventilation (particularly since many energy efficiency measures reduce ventilation).

- Dr. Singal agreed with what the others said and would put exposure data and consumer education as high priorities.

- Dr. Selgrade thought there should be a priority on basic immunology research and in particular to investigate the role of nonspecific inflammation response rather than focusing solely on specific allergic responses.

- Dr. Bascom recommended research into situations where there are apparent contradictions in data (e.g. small estimated exposure) and outcomes (e.g. large self-reported response), as such scenarios can provide a greater opportunity to learn. For example, point sources with small exposures may cause large reactions in some patients. One research approach would be to evaluate pathways of toxicity for common cleaning chemicals in normal airway epithelium compared with epithelium derived from patients with asthma. Another would be to compare pathways of toxicity to specific chemicals in patients with asthma who did and did not report adverse responses to cleaning chemicals. The use of in vitro models would remove the question about psychogenic response and focus on seeking biomarkers of the subjective response.
References


Appendices

Appendix A – List of Sponsors and Affiliates ................................................................. 56

Appendix B – List of Attendees ...................................................................................... 58

Appendix C – Biographical Sketches ............................................................................. 69

  Rebecca Bascom M.D., M.P.H., FAAAAI, FACCP ..................................................... 69
  Fred W. Boelter, CIH, PE, BCEE .................................................................................. 71
  Pamela Dalton, Ph.D., MPH ......................................................................................... 72
  Jon Hotchkiss, Ph.D. .................................................................................................... 73
  Michael A. Jayjock, Ph.D., CIH ................................................................................... 74
  Judy S. LaKind, Ph.D. .................................................................................................. 76
  Andrew Maier, Ph.D., CIH, DABT ............................................................................... 78
  MaryJane Selgrade, Ph.D., ATS .................................................................................. 79
  Madhuri Singal, Ph.D., R.R.T. ..................................................................................... 81
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Rebecca Bascom M.D., M.P.H., FAAAAI, FACCP

Rebecca Bascom MD MPH is Professor of Medicine at Penn State College of Medicine and a member of the Penn State Graduate Faculty. She has an active clinical practice in pulmonary and critical care medicine at the Milton S. Hershey Medical Center in Hershey, Pennsylvania, and expertise in occupational and environmental respiratory disorders. She mentors pulmonary/critical care fellows and research trainees. She served on the Asthma Oversight Team for the Penn State Geisinger Health System, aligning the System's policies and practice with the NAEPP guidelines. She served on the ACCP Consensus Conference: "Assessment of Asthma in the Workplace" and the ATS Statement "What Constitutes an Adverse Health Effect of Air Pollution".

For 16 years, she has served on the board of directors and research review committee for the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), a center devoted to advancing toxicological sciences with founding support from the cosmetics and personal products industry. She was a member of the organizing committee for the CIIT conference "The Nose Knows Workshop" and session chair for clinical pathology and epidemiological topics. She currently serves on the National Academy of Sciences/Institute of Medicine Committee on Scientific Standards for Studies on Reduced Risk Tobacco Products. Previous National Academy service include the Committee on the Health Effects of Indoor Allergens(IOM), and Occupational Health and Safety in the Care and Use of Research Animals.(ILAR) She has served on National
Institutes of Health study sections, and reviewed for scientific journals. Her research interest in inhalation toxicology led to controlled human challenge studies evaluating the mechanisms and markers of upper respiratory tract environmental tobacco smoke sensitivity, evaluating interactions with exposures to antigen and tobacco smoke, antigen and ozone, and formaldehyde. She led the analysis team for an epidemiologic study of New York Police Officers' cardiorespiratory status following 9/11, and served on the data analysis team for the Indoor Air Quality and Work Environment Study: EPA Headquarters Building.

Active research projects include clinical-engineering collaborations for development of image guided bronchoscopy systems, measurement and modeling of toxicant uptake and deposition in the human respiratory tract, and evaluating the impact of outdoor air pollution on patients with idiopathic pulmonary fibrosis.
Fred W. Boelter, CIH, PE, BCEE

Fred W. Boelter, CIH, PE, BCEE, is a Principal with ENVIRON International. Fred has 38 years of industrial hygiene, environmental engineering and risk management experience. He was trained as an Environmental Engineer at Purdue University, and has investigated and designed controls for a wide range of issues involving air, water, soil, and occupational hygiene from the perspective of both private industry and federal regulatory agencies. Mr. Boelter is also a Fellow of the American Industrial Hygiene Association and a recipient of the Edward J. Baier Technical Achievement Award.
Pamela Dalton, Ph.D., MPH

Dr. Dalton received her PhD from New York University in Experimental Psychology and her MPH from Drexel University. Her research program is focused on the human perception of odor and irritation from volatile chemicals. This work is supported by grants from the National Institutes of Health, with additional funding from the DOD and industry collaborations. The research utilizes both laboratory chamber studies and field studies to investigate the sensory, cognitive, and psychophysiological response to odors and irritants. Current investigations include effects of long-term occupational and residential exposure to volatile chemicals on olfactory sensitivity; the role played by expectations and beliefs about chemicals on odor and irritant perception and the ability of odors to trigger reports of irritation and health effects, particularly among sensitive subpopulations such as asthmatics.

Dr. Dalton is a senior member at the Monell Chemical Senses Center in Philadelphia—the world’s only nonprofit, multidisciplinary, basic research institute devoted to the study of smell, taste and chemical irritation. She has published extensively on the human perception and response to odors and given numerous talks and presentations at scientific and industry conferences. She also serves as a consultant to many groups in the chemical, food, household products, and fragrance industries, as well as government and community organizations involved in odor issues.
Jon Hotchkiss, Ph.D.

Dr. Hotchkiss has over 25 years of experience in respiratory cell biology and inhalation toxicology. His graduate research to develop immunoreagents to label, isolate, and quantitate pulmonary epithelial and capillary endothelial cells was conducted at the Oak Ridge National Laboratory. He gained experience in aerosol science and inhalation toxicology at the (Lovelace) Inhalation Toxicology Research Institute in Albuquerque, NM. He has conducted numerous inhalation exposure studies to environmental pollutants (ozone, endotoxin), tobacco smoke, and industrial chemicals, to study mechanisms of epithelial injury, adaptation, and repair including upper and lower airway enzyme and mucin gene expression. As an Assistant professor at Michigan State University (MSU) he examined the role epithelial/inflammatory cell interactions in upper and lower airway remodeling using rodent models of chronic human respiratory diseases. He developed an inhalation-exposure laboratory at MSU and participated in the design, construction and operation of a mobile laboratory designed to expose laboratory animals to concentrated ambient air particulate matter. Dr. Hotchkiss is currently the Sr. Inhalation Toxicologist and technical leader of Respiratory Toxicology of the Toxicology and Environmental Research and Consulting Laboratory of The Dow Chemical Company, Midland, MI. The laboratory conducts acute, subchronic, and chronic guideline and mechanistic studies in support of product registration, product stewardship, and human risk assessment activities for all Dow businesses as well as external consortia. His laboratory has active research programs in pulmonary allergenicity and asthma and nanoparticle dosimetry, clearance, dissolution kinetics in vitro and in vivo.
Michael A. Jayjock, Ph.D., CIH

Mike Jayjock is former Senior Research Fellow of the Rohm & Haas Company and currently Senior Analyst for The LifeLine Group, a non-profit organization dedicated to the development of state-of-the-science tools in human health exposure/risk assessment. He has an M.S. and Ph.D. from Drexel University in Environmental Engineering & Science and he is board certified (ABIH) in the Comprehensive Practice of Industrial Hygiene. Mike is a former member of the US EPA’s Science Advisory Board (SAB) and the Board of Scientific Councilors subcommittee reviewing the USEPA’s research program. His principal research interests include the development of better-estimating and more cost-efficient exposure models with a primary focus on sources. To that end he has been active in the publication of his work and in participating on various projects and committees of the EPA, Health Canada, The European Commission, American Chemistry Council, International Society of Exposure Assessment, American Industrial Hygiene Association and the National Academy of Science. Recent publications of note include:


- Jayjock, M.A., C.F. Chaisson, Claire A. Franklin, S. Arnold, Paul S. Price: Using publicly available information to create exposure and risk-based ranking of chemicals
used in the workplace and consumer products, Journal of Exposure Science and Environmental Epidemiology, 19, 515-524 (2009)

Judy S. LaKind, Ph.D.

Judy S. LaKind, Ph.D., President of LaKind Associates, LLC; Associate Professor, Department of Epidemiology and Public Health, University of Maryland School of Medicine; and Adjunct Associate Professor, Department of Pediatrics, Pennslyvania State University College of Medicine, Milton S. Hershey Medical Center. Dr. LaKind is a health and environmental scientist with expertise in strategic risk management, assessment of human health risks, biomonitoring, scientific and technical analysis for regulatory and litigation support, and state-of-the-science reviews.

She has spoken and published extensively on risk-related issues, including children’s exposures to environmental chemicals, the implications of uncertainty in the risk assessment process, weighing potential risks and benefits related to chemical use (for example, use of MTBE in gasoline, glycols in de-icing formulations, and chlorination of swimming pools for disinfection), the presence of environmental chemicals in human milk, and time-dependence and distributional analysis of exposure. Dr. LaKind has evaluated the use of human health risk assessment in the development of water quality criteria, and has critically analyzed the environmental fate, behavior, and bioavailability of pollutants in the context of setting regulatory criteria. She has developed risk assessments for a variety of urban industrial sites, military bases, and firing ranges, and has utilized state-of-the-science models for estimating blood lead levels in adults and children.

Previously, Dr. LaKind was a geologist at the US EPA’s Office of Federal Activities, where she was responsible for the evaluation of Environmental Impact Statements and legislative reports. Dr. LaKind has taught graduate level courses at The Johns Hopkins University and the University of Maryland in risk assessment and aquatic chemistry and serves on the editorial
boards of the Journal of Toxicology and Environmental Health and the Journal of Exposure Science and Environmental Epidemiology. Dr. LaKind is a member of the World Health Organization Survey Coordinating Committee for the WHO Global Survey of Human Milk for Persistent Organic Pollutants (POPs), and a former member of Maryland’s Children’s Environmental Health and Protection Advisory Council and the Lead Poisoning Prevention Commission. She currently serves on the Institute of Medicine Committee on Blue Water Navy Vietnam Veterans and Agent Orange Exposure. Dr. LaKind received her B.A. in Earth and Planetary Sciences from The Johns Hopkins University, her M.S. in Geology from the University of Wisconsin, Madison, and her Ph.D. in Geography and Environmental Engineering from The Johns Hopkins University.
**Andrew Maier, Ph.D., CIH, DABT**

Dr. Maier has 18 years of professional work experience in the areas of environmental health, industrial hygiene, and toxicology. He is currently the Director for the non-profit organization Toxicology Excellence for Risk Assessment (TERA) where he leads efforts in developing occupational and environmental exposure guidelines. He completed his PhD in toxicology from the University of Cincinnati, where he currently holds a position as an Adjunct Associate Professor of Environmental Health. He earned a M.S. in Industrial Health from the University of Michigan and is Board certified in both toxicology and comprehensive industrial hygiene practice. Dr. Maier is active in communicating his findings to the broader scientific community through active participation in professional societies and through publication of his work. His areas of research interest include developing and applying new methods for safety and risk assessment for occupational and environmental exposures. He also is actively engaged in methodology development for setting occupational exposure guidelines. He is the immediate past-chair of the American Industrial Hygiene Association Workplace Environmental Exposure Levels Committee, the Vice-President Elect of the Society of Toxicology Occupational and Public Health Specialty Section, and is currently serving as a Toxicology Fellow with the National Institute for Occupational Safety and Health.
MaryJane Selgrade, Ph.D., ATS

Dr. MaryJane Selgrade earned her M.S. and Ph.D. in Medical Microbiology from the University of Wisconsin, Madison, after which she spent a year doing research in viral immunology as a National Research Council fellow at the Naval Medical Research Institute in Bethesda, MD and two years as a Public Health Service NRSA postdoctoral fellow at the University of North Carolina at Chapel Hill. She was a visiting assistant Professor in the Microbiology Department at North Carolina State University before joining the U.S. EPA as a Research Microbiologist in 1979. During her 32 year career at EPA she gained broad technical and managerial experience in environmental health, toxicology, and risk assessment culminating in her position as Chief of the Cardiopulmonary and Immunotoxicology Branch of the Environmental Public Health Division within the National Health and Environmental Effects Research Laboratory. Her responsibilities at EPA included developing research strategies to meet particular EPA regulatory needs related to health effects in diverse areas including biotechnology, Libby asbestos (superfund), particulate matter air pollution, air toxics, indoor air, susceptible populations (primarily children), and pesticides. She joined ICF International in August 2010 as a senior toxicologist working in the Environmental Risk and Toxicology line of business. She serves as a consultant for both government and industry (largely related to REACH) clients and has major responsibilities in the development of risk assessment documents. In addition to her current position at ICF, she is an adjunct professor in the Curriculum of Toxicology, University of North Carolina, Chapel Hill and in the Departments of Toxicology and Population Health and Pathobiology at North Carolina State University. She recently completed an 8-year term as an associate editor for Toxicological Sciences.

Dr. Selgrade’s research interests involve effects of xenobiotics on the immune system and consequences for infectious, neoplastic, and allergic diseases, underlying mechanisms, and
biomarkers of effect. In particular, she has been interested in the effects of environmental pollutants on the induction, elicitation, and exacerbation of allergic asthma and other types of allergic diseases. She has published over 100 research papers and book chapters covering an array of topics in toxicology and risk assessment, and has organized workshops on important topics in toxicology for EPA, Society of Toxicology, World Health Organization (WHO), and others.
**Madhuri Singal, Ph.D., R.R.T.**

Dr. Madhuri Singal, RRT is Manager of the Respiratory Science Program at the Research Institute for Fragrance Materials, Inc. (RIFM). Since joining RIFM in May 2007, Dr. Singal has assumed responsibility for completion of the clinical exposure study, has re-invigorated the Respiratory Science Working Group and has developed a multiple pathway approach, that includes unique alternative research methods, to answer important questions regarding inhalation safety and fragrance material use in air care products.

Dr. Singal has clinical critical care experience in neonatal, pediatric, and adult intensive care and emergency medicine as a Registered Respiratory Care Practitioner at medical centers in New York, Pennsylvania and New Jersey. She received her doctorate in Molecular Toxicology and Environmental Medicine, her masters in Environmental Medicine from the University of Rochester School of Medicine, and her B.S. in Respiratory Care, with honors, from the State University of New York Upstate Medical University.

Dr. Singal has published papers in international scientific journals including *Inhalation Toxicology*, *Experimental Lung Research*, the industry journal *Household and Personal Care Today* and, most recently, in the *Annals of Biomedical Engineering*. In July 2010, her dissertation, regarding nanoparticle-induced inflammatory signaling in the lung, was published as a textbook by VDM Publishing. Dr. Singal is also an invited member of the Scientific Editorial Review Board for *Household and Personal Care Today*.

Among her professional affiliations, Dr. Singal is an active member of the American Thoracic Society, the Society of Toxicology, the National Board for Respiratory Care and the American Association for Respiratory Care.