Allergens in the Workplace: A Case Study of Animal Allergens and the Development of an Occupational Exposure Limit

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OVERVIEW

- Workplace Allergens
- Lab Animal Allergy
  - Epidemiology
  - Scope
  - Impact
- Lab Animal Allergens
- Mechanism
  - Immunology
  - Symptoms
- Medical Surveillance
- Setting an Exposure Limit
- LAA Assessment and Treatment
- Exposure Control / Prevention

Workplace Allergens

- High molecular weight compounds
  - Animal proteins (rat/mouse urinary protein)
  - Plant proteins (latex)
- Low molecular weight compounds
  - Pharmaceuticals (beta lactams)
  - Acid Anhydrides
  - Isocyanates (TDI)
- Impact
  - Social and economic consequences of resultant diseases

Occupational Asthma

- **OCCUPATIONAL ASTHMA -** Asthma is a chronic inflammatory disorder of the airways, often reversible, characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and/or cough due to airways obstruction.
- Adversely affects life (work, ADLs) – may be disabling
- The literature lists over 350 agents, industries, or processes that have been epidemiologically or clinically reported to be associated with the development of asthma.
- The diagnosis of asthma should be supported by appropriate testing (FEV1 more than 10% below predicted, and showing >12% improvement after inhalation of short acting bronchodilator) and confirmed by a Pulmonary Specialist.

Occupational Dermatitis

- **OCCUPATIONAL DERMATITIS** – Occupational-related skin disorders have been recognized since the 1700's, including observations by Ramazzini in 1700 and Pott in 1775.
- accounts for almost half of all occupational diseases
- one of the leading causes of days lost from the job.
- Occupational Dermatoses can be:
  - Allergic
  - irritant

Laboratory Animal Allergy

- **LABORATORY ANIMAL ALLERGY-** Laboratory Animal Allergy is an allergy to laboratory animals such as mice, rats, guinea pigs, & dogs used in research laboratories.
- the development of allergen-specific IgE antibodies that react with allergens after exposure
- symptoms:
  - rash,
  - rhinnorhea,
  - sneezing,
  - conjunctival irritation,
  - wheezing,
  - asthma,
  - life-threatening anaphylaxis.

OTHER

- Allergic conjunctivitis
- Allergic rhinitis
- Anaphylaxis
- Hypersensitivity Pneumonitis (e.g., TDI)

Clinical Case Example

- Hx: 25 yo staff biologist working primarily with rodents. Over past 3 months, developed increasingly severe upper respiratory allergic symptoms (sneezing, nasal congestion, watery eyes) whenever works with rodents. Denies rash, wheezing, or history of asthma. PPE – surgical mask.
- PMHx: On Zyrtec for seasonal allergies. NKDAs. Non-smoker. No pets. Exercises regularly without symptoms.
- PE: 25 yo female, NAD. HEENT: grossly normal, lungs: clear. Skin: no rash.
- Allergy Test Results:
  - Skin Testing- suggestive of rat allergy
  - RAST Testing: Positive for Rat Urine and Cat Dander
- Disposition:
  - Treated short term with nasal steroids, antihistamine, removal from exposure to rat at work
  - Final Disposition: permanently restricted from work with rats

LAA - Introduction

- POPULATION AT RISK: Workers exposed to furred lab animals – resulting condition termed Lab Animal Allergy (LAA)
- LAA - a major Occupational Illness to:
  technicians,
  animal caretakers,
  veterinarians,
  physicians
  scientists
- **Goodno and Stave, in JOEM, 2002**, - 125,000 workers in U.S., and 15,000 in U.K. regularly work with laboratory animals,
- -33% may develop symptoms of LAA
- **Wolfle and Bush**, in **Institute for Laboratory Animal Research (ILAR)**
  - 46% of lab animal workers will develop allergic symptoms, and of those , more than 10% develop Occupational Asthma
- **NIH**-Manifestations of LAA cause more than **one third** of lab animal workers to lose time from work.
- Lab Animal Allergy= important health problem for animal workers, and an administrative and financial burden on the research institutions due to lost productivity and health care costs.

Epidemiology – cont'd

- **Prevalence** – Goodno and Stave- cross sectional studies estimate prevalence of LAA to be as high as 44%
- **Incidence** – estimates range from 10% - 37%
- **Cullinan et al**
  - Mean duration of employment before symptoms to rat exposure
    - Respiratory = 365 days
    - Nose and eye = 214 days
    - Skin = 335 days
- **Animals and allergenicity** –
  - many authors report mice and rats are most allergenic
  - **Bush, Wood, and Eggleston** report in **J Allergy Clin Immunol** that allergy to other animals in the workplace is less common than allergy to rats and mice **primarily because other animals are used less**

- In a large Japanese epidemiologic study, allergy symptoms reported in:
  - 26% workers exposed to mice or hamsters
  - 25% for rats or dogs,
  - 31% for Guinea Pigs,
  - 30% for rabbits or cats, and
  - 24% for monkeys.

Epidemiology (cont'd)

- Risk of LAA is in part due to **activity** of worker – cage cleaning exposes worker to higher airborne allergen level than other activities
- LAA is preventable – Goodno and Stave – 2002 study – reduced exposure with PPE led to LAA incidence of zero
- Secondary LAA - Goodno and Stave reported in JOEM Dec 2002 that for those workers with primary LAA who remained in the workplace, up to 8% developed allergy to a second species (10 year Secondary LAA Incidence rate =11(95% CI, 7.4 -14.6) cases per 100 person- years

SCOPE

- **Source of animal allergens** – animals shed allergens through **urine, dander**, **hair**, **serum**, and **saliva**,
  - but not all species or strains do so equally
- **Gender inequity** – in general, females shed fewer allergens than males
- Allergen exposure related to:
  - Size of allergen particle
  - Environmental conditions in cage
    - Type of bedding
    - Density of animals
    - Ventilation of rooms
  - Job/task responsibility
  - Duration of exposure

The Allergens

- Belong to family of proteins called ***lipocalins***
- Lipocalins - produced in **liver** or **secretory glands**
- Lipocalins share biological and structural properties that elicit similar responses from the human immune system
- Proteinuria in rodents - persistent proteinuria results in urine as major source of allergen production and worker exposure
- Other rodent sources of allergens - hair, dander, saliva (less allergenic)
- Cats and dogs - hair, dander, and saliva all major sources of allergen production

The Allergens-Mouse

- **Mus m 1** - pre albumin protein , molecular weight 19 kd
  - Gene molecularly cloned, and amino acid sequence has been deduced
  - Mus m 1 found in urine, hair follicles, and dander
  - Produced in liver cells
  - Levels in serum and urine are four times higher in male mice compared to females
    - Due to testosterone dependence of gene expression

- **Mus m 2** – glycoprotein, molecular weight 16 kd
  - Originates in hair follicles and dander
  - Not found in urine

- **Albumin** – third major allergen
  - Found to be allergenic in 30% of individuals exposed to mice

The Allergens – other animals

- **Rats** –
  - When produced in **liver** – androgen dependent
  - When produced in **exocrine glands** (salivary, mammary, meibomian, preputial), not androgen dependent
- Rabbits
- Cats
  - Minimum 12 proteins of cat origin found to be allergenic
  - Fel d 1 most allergenic by far
  - Molecular weight 38kd
  - Produced in hair follicles and to lesser extent saliva
  - Male cats produce more Fel d 1 than females
- Dogs
  - Can f 1, most important Dog allergen
  - Polypeptide, molecular weight 25kd
  - Produced in hair follicles, dander, ad saliva
- Other
  - Non-human primates – conflicting data

Environmental Distribution

- Animal allergens carried on relatively small particles
  - Studies show airborne mouse allergen particles range from 3.3 to 10 microns in one study, 6 -18 microns in second study
- Small particles can remain airborne for extended periods of time, and are easily respirable
- Airborne mouse allergen studies
  - Levels range from 16.6 to 563 ng/m3 in rooms with mice and from 1.2 to 2.7 ng/m3 in rooms without mice
  - Another study showed airborne levels ranged from 1.8 to 825 ng/m3, and **varied with number of mice and degree of work activity in room**
  - Another study showed **higher allergen levels in rooms with male mice** compared to rooms with female mice (Mus m 1, 13,050 pg/m3 vs. 317 pg/m3)

Airborne rat studies also showed levels highly dependent on type of activity being performed

-cleaning and feeding associated with highest levels of exposure

Mechanism of LAA

- Activation of innate immune response pathways by bioaerosols such as animal allergens, endotoxins, peptidoglycans, and B-glucan
  - Pathogen-associated molecular pattern (PAMP) recognition molecules (e.g., toll-like receptors (TLRs)
  - Initiation of inflammatory responses
  - Initiation of adaptive immune response
- Laboratory Animal Allergy – **Type 1, immediate hypersensitivity reaction** according to Gel and Combs
  - Involves production of Immunoglobulin (IgE) antibodies formed in response to protein LAA antigen
  - CD4+ T – helper lymphocytes play central role in generation of IgE antibodies
  - LAA exposure occurs primarily through inhalation of allergen proteins
  - Skin contact a minor exposure route

Development of IgE Antibodies

- *Sensitization* – development of IgE antibodies to the specific allergen

- Allergenic protein taken up by ***Antigen-Presenting Cells (APC)*** *Lung APCs*
  - *Monocytes*
  - *Alveolar macrophages*
  - *Dendritic cells*
  - *Skin APCs*
    - *Langerhans cells*
    - *Dendritic cells*

Development of IgE Abs

- *Antigen - processed into small peptide fragments and presented on the surface of APC in association with Major Histocompatibility (MHC) class II molecules*
- *Naïve T Cells recognize the complex of the MHC molecule and the allergenic antigen*
- *With this recognition signal, and other costimulatory signals (B7 and CD28 interaction), T cell becomes **activated***
- *Activated T cell undergoes multiple rounds of replication under effect of the cytokine Interleukin 2 (IL2)*
- *Result is multipotential population of T cells (Th0)*

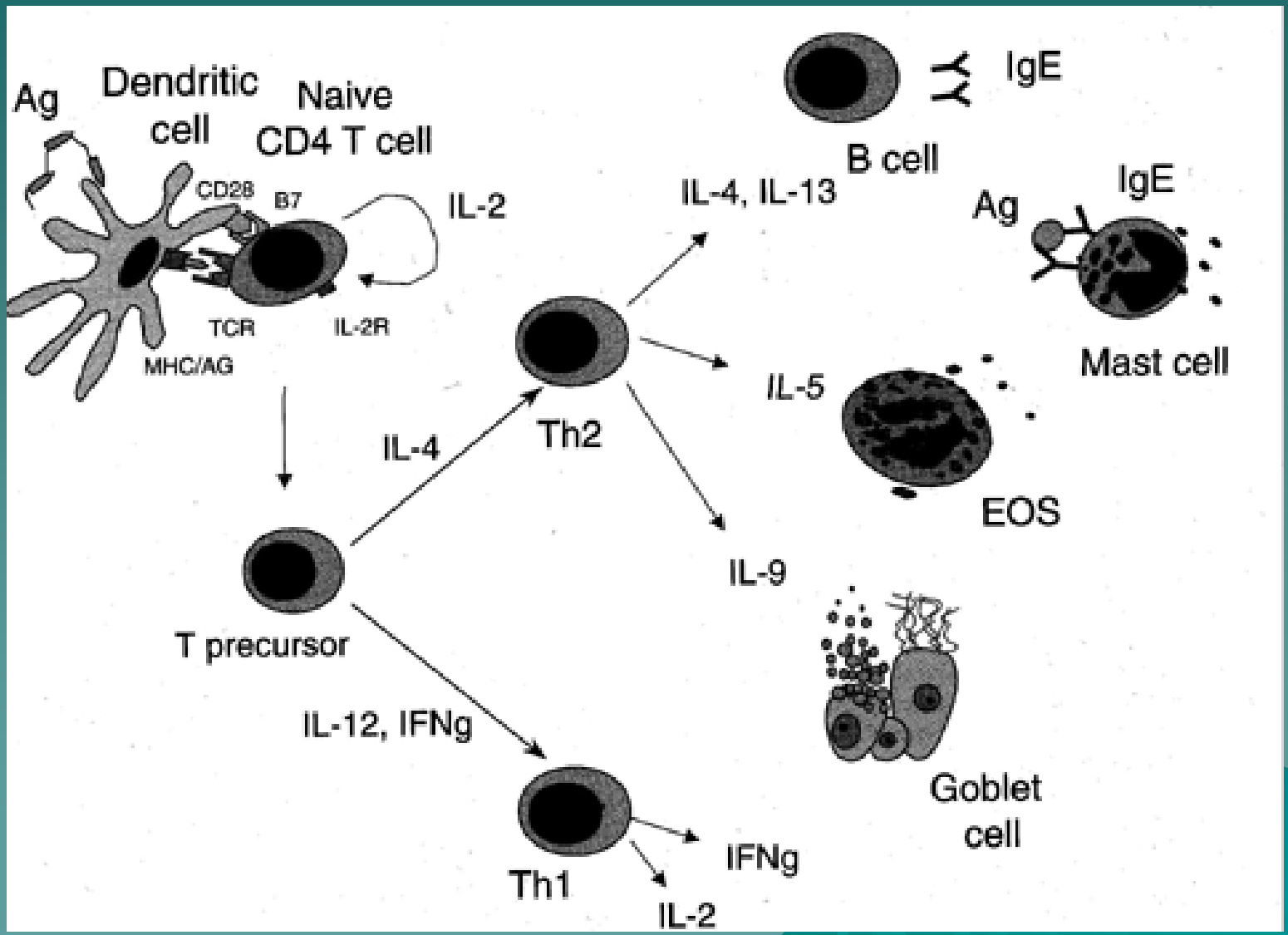
IgE Antibody Development – cont'd

- Th0 T cells serve as progenitors of two different types of ***Effector Cells-***
  - Th1 lymphocytes – develop in presence of IL12 and Interferon gamma (IFNg)
  - Th2 Lymphocytes – develop in presence of IL4
- **Th1** cell produces IFNg, which **suppresses** the formation of IgE antibody production
- **Th2** response is the typical feature of immediate-type allergic diseases
  - The production of cytokines (IL-4,IL-13) **stimulates** B Lymphocytes to produce antibodies specific to the allergen presented
- Subsequent exposure (even years later) to the initial sensitizing allergen elicits a rapid and vigorous response

Allergy mechanism – cont'd

- PREDISPOSITION – for many allergic diseases, a genetic predisposition (Atopy) is present
- Individuals are defined as being atopic if they, or close relatives, have manifestations such as
  - Allergic rhinitis
  - Asthma
  - Eczema
- **Current theory of allergy** – lack of production (or imbalance) of IFNg vs IL4 and IL13 in atopic individuals causes production of IgE to allergenic protein
- Intended role of IgE in human health – unknown
  - May be related to body's response to Parasitic infections
  - IgE production causes recruitment of Eosinophils, which have been shown to kill parasites such as schistosomes in culture
- Role of IgE antibody in allergy – binds to Fc receptors on mast cells and basophils
- Causes release of chemical mediators of allergic symptoms in these cells in:
  - Respiratory tract,
  - GI tract,
  - Skin,
  - Conjunctiva

Sensitization / Allergy Mechanism (ILAR 2003)



Development of Allergic Symptoms

- Early Phase Reaction –
  - Specific allergen interacts with IgE antibodies on surface of mast cell or basophil
  - Results in release of preformed biochemical mediators
    - histamine,
    - leukotrienes,
    - activation of arachidonic acid cascade causing production of prostaglandins,
    - generation of cytokines (TNF-a, IL-1, IL-4, IL-5, IL -6, IL -8, & IL -16)
    - and generation chemokines (MIP -1a, MIP -1b, MCP-1, and RANTES)

  Resulting pathophysiology -

  - tissue edema (nasal congestion, bronchial edema,hives)
  - increased mucous secretion(rhinitis, bronchi)
  - nerve stimulation causing itching (skin,eyes),sneezing, bronchospasm
  - systemic allergic reaction (anaphylaxis) – pruritis, urticaria, angioedema, edema of larynx, acute asthma, hypotension and shock

Medical Surveillance

The major objective for **health** and **safety =** eliminate and reduce exposures ***(Primary Prevention).*** Examples:

- Reducing the use of use of animals in experimentation
- Controlling the environment in the animal facility to reduce exposures
- Limiting the number of personnel with access

- **Medical surveillance** is ***Secondary Prevention*** *– purpose is to identify early signs of disease, hopefully at a stage in which intervention will improve the outcome*
- Basis for Medical Surveillance program – no formal legal requirement (OSHA)
  - Ethical responsibility of employer to minimize disease risk & burden on employees
  - Good business to prevent disease in employees
- Elements
  - Preplacement testing- limited in value due to lack of predictive value for developing LAA
  - Baseline History- useful as baseline for changes in future- also identifying higher risk individuals to watch closely for S/S early allergic disease
  - Periodic questionnaires with appropriate follow-up(physical exam, testing) of changes to facilitate early identification of allergy
  - Education of lab animal workers on risks, signs and symptoms of interest valuable
  - Statistical analysis of population data to detect trends

ASSESSMENT

- History of symptoms in conjunction with exposure
  - Nose- chronic congestion and rhinorrhea, sneezing, pruritic nose and throat
  - Skin – eczematous rash (scaly, pruritic, red rash in flexural areas of arms and legs)
  - Lungs- wheezing, cough, chest tightness, SOB; occurring episodically, especially after allergen exposure, exercise, irritants such as smoke, URIs
- Tests for IgE-mediated allergy
  - Skin testing
    - Drop of allergen extract is placed on skin, which is pricked with small lancet
    - Diameter of wheal and flare that result within 15 minutes is measured and compare to histamine control
  - RAST Testing
    - Allergen binding by IgE antibody, if present, is detected by second antibody
  - Both tests correlate; RAST is more expensive and not affected by medications, but less sensitive
  - Both tests are dependent on composition of extract of allergen
    - Concentration of allergen extracts of different lots of same allergen can vary by as much as 1,000 fold
    - Concentration of allergenic proteins decreases with time due to proteases present
    - Standardized, stable extracts for ANIMAL allergens are very limited
- Clinical Testing
  - Pulmonary Function Testing (daily peak flows – looking for changes 15%, cross-shift spirometry looking for changes in FEV1 and FVC after exposure, Methacholine Challenge Testing, Specific Inhalational Challenges)
- Genetic Testing (HLA-B16 an HLA-DR4 association with animal allergy risk?)- Utility?

TREATMENT

- Emergency treatment of anaphylactic reactions (epinephrine, ACLS system)
- Exposure reduction / avoidance
  - administrative controls
  - Improve Engineering controls
  - Change Lab animal care practices
  - PPE
- Corticosteroids (topical, oral, inhaled, IV)
- leukotriene receptor antagonists
- Antihistamines
- Inhaled Beta Agonists
- Immunotherapy
  - Immunotherapy to cats and dogs successful in a few reports, but only in workers intermittently exposed rather than chronically exposed
  - Uncontrolled studies of immunotherapy to lab animals (mice, rats, and rabbits) have demonstrated some improvement
  - Insufficient study to recommend immunotherapy as a means to protect workers from developing symptoms with exposure
- Risk of treating with continued exposure
  - Asthma development risk – 3-6% of 1 LAA
  - Secondary LAA development - (Goodno & Stave, Hazard Ratio (HR) for developing 2 LAA =8.21

    95% CI, 7.33-8.83, P < 0.001)

PREVENTION

- CONVENTIONAL WISDOM: *no clearly established threshold for allergen exposure supports a minimum safe exposure level*
- Goal: Defy CW & Establish a Working Exposure Limit

ANIMAL ALLERGENS (AA)
&
ENDOTOXINS

A RECOMMENDED CONTROL STRATEGY

Terry Lane & Dr. Pete Nigro

Selection of AA Exposure Limit

- Clear exposure-response relationship at ~100 ng/m^3
  - ~ 2.5-4X risk of + skin prick test & chest symptoms[1]
- Clear exposure response relationship between RUA exposure & specific IgE antibodies to lab rat allergens
  - Exposure-response relationship robust[2]
- Suarthana et al in AJIM 2005: "Exposure level to High Molecular Weight allergens is strong predictor of sensitization"

[1]Nieuwenhuisjsen M., et. al, *JOEM*, 1999: 60

2 Heederik D., et. al, *J Allerg Clin Immunol* 1999:103

Dose-response relationship

- 1990, Eggleston and Ansari reported 12 volunteers symptoms with exposure for one hour to Rat n 1 levels ranging from 1.5 ng/m3 to 310 ng/m3
- All 12 (100%) experienced nasal symptoms by end of one hour exposure
- 5 of 12 (42%) showed decrease in FEV1 over 10% within one hour exposure
- In a follow up study, high allergen levels (cage cleaning, mean Rat n 1 = 166 ng/m3) were compared to low allergen exposure levels (quiet sitting in rat vivarium, mean Rat n 1 = 9.6 ng/m3) in 17 subjects.
  - **A clear dose-response was demonstrated with both upper and lower airway responses being dependent on airborne allergen levels.**

AA Exposure Limit (cont'd)

- Discussions with G. Evans & HSL peer review experts
  - Health / exposure data
  - Peak vs. TWA comparisons
- Institute of Occupational medicine (2005)–
  - Carried out studies on correlation of airborne concentrations of mouse and rat urinary proteins vs. allergic response
  - Concluded concentrations above **6 ng/m3**

    increased likelihood of sensitization
- Nieuwenhuijsen et al in *Occ & Env Med* 2003, as well as Pacheco et al, in 2006 *Annals Occupational Hygiene* – "peak exposures more important than mean exposures in triggering sensitization

Literature supporting AA exposure limit

- Hollander, Heederik & Doekes – 1997 Am J Respir Care Med
  - reported prevalence rate of sensitization to lab animal allergens clearly associated with exposure levels
  - Clearest association with “high level exposure” at **4.2 ng/m3**

- Eggleston & Wood, 1992 Allergy Proc.
  - Environmental exposure challenges performed to find allergic threshold concentration
  - Found statistical correlation between exposure concentration and allergic mediator release
  - Significantly smaller allergic responses with exposures below **10 ng/m3**

AA Exposure Limit

- S. Gordon (formerly IOM) recommended maintaining exposures at or below 5 ng/m^3
  - Feasible controls for rodent allergens
  - Reduced risk of LAA at this level - study of 458 workers newly exposed workers to MUP
  - Similar reduced risk of LAA to rats anticipated at this level of exposure[1]
  - LAA risk reduced but not eliminated; still risk that a small number of people will develop LAA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S. Gordon - Other

[1]Cullinan P., et. al, *Eur Respir J*, 1999: 13 & Elliot L., et al. *Occup Envir Med* 2005: 62

Problem Resolution Approach

- Extensive literature review (+ 50 papers)
- Benchmarked with key pharmaceutical companies; obtained other benchmarking data from research institutes
- Formulated Position / Control Strategy
- External peer review of position paper/slides by UK's Health & Safety Lab (HSL) experts
- Internal stakeholder review - WP LAR & Safety

Setting AA Exposure Limits - Challenges

- Variability LAA Cases
  - (GSK 10-year Study)[1]:
  - Most occur in first 3 years of exposure
  - At least 36.5% cases did not occur until > 5 years
  - 9.2 % cases occur after 20 years exposure
  - 33% of workers with 1° allergy (1 species), developed 2° allergy to at least 1 more animal species
    - Increase incidence of 2° allergy increased to ~ 50% > 10 years[2]; workers more likely to be atopics & some had up to 6 allergies[2]
- Confounding Factors
  - Individual susceptibility –
    - Subset of population will not develop sensitization regardless of exposure
    - Increased risk for atopics, +/- smokers 3
    - Endotoxin co-exposure[4]

[1]Goodno L. et al, *JOEM 2002: 44*

[2]GSK Data – *Practical Approaches to Managing OH Programs in Your Animal Facility Conf:* 1996

[3]Cullinan P., et. al, *Eur Respir J*, 1999: 13 & Elliot L., et al. *Occup Envir Med* 2005: 62

[4]Pacheco, K. et al. *Amer J of Resp & Critical Care Medicine:* 2003: 167

Setting Exp Limit – Challenges (cont'd)

- Choosing endpoint
  - **Allergy**
    - Pro – easy to detect; accepted medical management
    - Con – acting "late" less defensible
      - Goodno, 2002 JOEM – exposure levels against primary LAA not sufficiently protective against secondary LAA
      - Gordon & Preece 2003 *Occ Med* – suggest sensitization to allergens ay levels < allergy symptomatic level
  - **Sensitization**
    - Pro – "early" detection can prevent disease progression
    - Con – logistical difficulties in detecting sensitization
      - ? Legality of actions based upon sensitization

Background – Endotoxin Exposures

- Numerous studies linking various health effects (e.g., fever, joint pain, respiratory effects) with exposures to endotoxins
- Key endotoxin exposures from animals & feces
- Co-exposure of AA & endotoxin may be important in development of sensitization[1]
  - Peak exposure vs. mean TWA exposure may be more important in triggering symptoms & immunologic sensitization[1]
    - Chronic exposure may alter susceptibly to sensitization & may reduce the dose at which the allergens can trigger allergic responses

[1]Pacheco, K. et al, *Ann Occup Hyg:* 2006: 50
[2] Spaan S. et. al, *Appl Environ Microbiol:* 2007:73

Endotoxin - Health Effects

- Inhaled endotoxins – respiratory & systematic inflammatory responses[1]
- Acute Health Effects (high exposures - e.g., pig farms):
  - Systemic & respiratory
    - Dry cough/shortness of breath, decreased lung function
    - Fever reactions & malaise
    - Occasional dyspnea, headache & joint aches
- Chronic Health Effects:
  - May cause chronic bronchitis & reduced lung function
  - Co-exposure may be important in development of LAA sensitization

[1]Rietschel E. et al 1994 *FASEB J:* 8, Rylander R. et al *Int J Occ Env Hlth* 1997: 3; & Liebers V. et al *Am J Ind Med* 2006: 49

Endotoxins – Hazard Assessment

- No Effect Levels – calculated to range from 90 - 1700 EU/m^3 (9 – 170 ng/m^3)
- Dutch Expert Committee on Occupational Standards recommended a health based OEL-TWA = 50 EU/m^3 (~ 4.5 ng/m^3)
  - Changed to 200 EU/m^3 – to address 'feasibility' within agricultural industry
  - Measured as "inhalable dust"
  - Now looking at as a Threshold Value – industry sector

Castellan RM, et al *Ann Int Med* 1984, 101 & *N Eng J Med* 1987, 317
Rylander R, et al. *Am Rev Resp Dis* 1985, 131 & *Organic Dusts: Exposure, Effects, and Prevention,* Lewis Publishers 1994

Prevention (Cont'd)

- ENGINEERING CONTROLS
  - Material Change / substitution
    - Animals (less allergenic species or strain, juvenile or younger animals, female gender)
    - Bedding (non contact pads or corncobs vs wood chips or sawdust reduces allergen levels in air by 57 – 68%)
  - ventilation changes to reduce amount of airborne allergens and duration of exposure
    - Filtering air with HEPA filters (local controls)
    - Increased room air exchanges (general dilutional)
  - Filter topped cages
  - Process Change (e.g., automation using robots for cage washing)
  - Isolation / enclosure
  - Exposure limits (peak exposures)

Prevention (cont'd)

- ADMINISTRATIVE CONTROLS
  - limiting access to animal care areas
  - limiting animal stock density in rooms
  - limiting duration of work in animal care rooms
  - regular housekeeping such as wet mopping and water-hosing

- PERSONAL PROTECTIVE EQUIPMENT
  - Respirator
    - Dust masks approved by NIOSH shown in studies to remove up to 98% of rodent urinary allergens from inhaled air – probably OK for asymptomatic animal care workers
    - Better allergen reduction for asymptomatic, and possibly for symptomatic – ½ face negative pressure respirator, PAPR with hood, or better
    - NOTE: the use of respirators has **not** been shown to reduce progression of disease and is not a substitute for removing severely allergic individuals from exposure.
  - Gloves
  - Hats
  - Gowns
  - Shoe covers
  - Eye protection

Prevention (cont'd)

- Disposition question: Whether to allow individual with established LAA to continue working using PPE, or to remove from position?
  - Portengen, Hollander, Doekes, & Heederik. *Lung Function decline in laboratory animal workers: the role of sensitization and exposure*. Occupational and Env Med 2003;60: 870-875.
  - Studied relation between sensitization and subsequent lung function decline in working populations exposed to allergen(s).
  - Method: longitudinal study (median follow up 2.0 years) – 319 lab animal workers- excluded subjects with over 4 years exposure
  - Results:
    - Multiple regression analyses-
    - Lung function decline most pronounced in sensitized subjects who continued to work in contact with lab animals
    - Average excess declines FEV1= 83 ml/y ($p<0.05$)
    - FVC = 148 ml/y ($p<0.01$)
    - MMEF = 7 ml/s/y ($p=0.9$)
  - Results corroborate findings of other studies
    - Renstrom et al(*Eur Respi J* 1995)
    - Sjosted et al (*Am J Ind Med,1993*)
  - Proposed mechanism: Malo et al, (*J Allergy Clin Immunol* 1992) – chronic inflammation develops after sensitization, but before development of symptoms
  - Low level inflammation leads to decline in lung function with continued exposure
  - Study flaws- short follow up, ? Small sample size, unclear if workers "continually exposed" used PPE

General

- Trend illness data
  - 1°/ 2° LAA incidence
  - AHE & endotoxin co-exposure where no LAA sensitization
  - Prevalence
- Compare illness trend data to exposure (IH) data
- Re-evaluate Working OELs as needed

Future Prevention?

- Immune modulation - increasing suppression of abnormal immune response?
- Summers, Elliott, & Weinstock- University of Iowa
  - *Trichuris suis* in Therapy of Inflammatory Bowel Disease
  - Theory: Hyper-reactive immune response may be diminished by intake of parasites
  - Stimulates suppressor arm of immune system
  - Study showed significant response of individuals with IBS to intake of Helminths
  - ? Possible application to other allergies such as LAA?