



# Animal Allergens & Endotoxins

## A Recommended Control Strategy

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NJAIHA & MASOT Joint Meeting

# Background

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- Merck's global research-driven pharmaceutical operations:
  - Several facilities house research animals
  - Large proportion of animal population are rodents (mice & rats)
- ∴ Use 'surrogate approach' for other allergens & focus efforts on rat & mouse allergens:
  - Rat Urinary Protein (RUP)
  - Mouse Urinary Protein (MUP)

# Select Animal Allergens & Endotoxin

NOTE: Mus m 1 levels in serum and urine are 4X higher - ♂ mice : ♀ mice

## Mouse (MUP)



Serum - Albumin

Hair, dander - Mus m2

Endotoxin - feces

Hair, dander, urine - Mus m 1 (prealbumin)

## Rat (RUP)

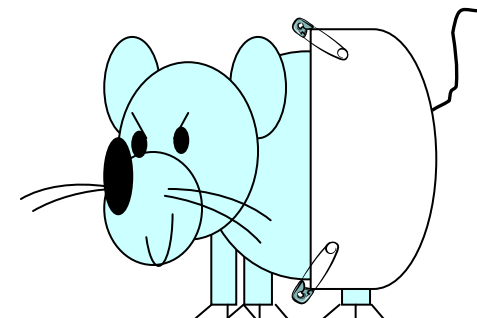


Hair, dander, urine - Rat n 1 A/ Rat n 1B

Endotoxin - feces

Albumin - Serum

Saliva - Rat n 1A/ Rat n 1B



# Defining the Problems

## Complex

- Adverse health effects
  - Individual susceptibility
- Lack of clear & specific regulations / guidance
  - No formal OEL / OEB
  - Respiratory protection worn
- Complex exposure issues
  - No S&A methods for some allergens
  - Workplace / Personal
- NIOSH lags in S & A methods
- Multiple variables influencing exposures
- Once 1° LAA develops, typical controls are not effective for preventing 1° symptoms / 2° allergy



## Simple

- Corporate S & OH policies & governance
- Regulatory - “General Duty Clause” to protect employees from serious occupational hazards & risks
- Robust & reliable S & A methods available for select allergens / contaminants
- Control strategies
  - LAA is potentially preventable
  - Significant reductions in airborne exposures with ‘at source controls’
- Medical Surveillance & Testing
- Comparing pre / post data:
  - IH data – post control upgrade
  - Incidence data

# Background – Regulatory & Corporate

- “General Duty” type of clauses:
  - OSHA: Employer must furnish ....[workplace] free from recognized hazards that are causing or are likely to cause death or serious physical harm
    - NIOSH Alert to OSHA Regional Offices – Preventing Asthma in Animal Handlers, Jan 1998
  - European Union (EU – Article 5): Employer shall have a duty to ensure the safety and health of workers in every aspect related to the work...
  - UK COSHH: Animal allergens covered as Substance Hazardous to Health
    - Pharmaceutical Industry led need for specific guidance / methods
- Global regulatory requirements specify same “*IH Control Strategies*”
  - Hierarchy of IH control measures
  - PPE / RPE - acceptable only as 1<sup>o</sup> control, when engineering & administrative are not feasible
- Respiratory Protection (RPE) / Personal Protective Equipment (PPE)
  - Inconsistent policies & practices for respirator use
  - Number of sites required primary RPE use for at least 1 task, some required for all tasks
  - Exposures not always evaluated
- Corporate Safety & Occupational Health Policies
  - Protect safety & well being of employees
  - Assess workplace health hazards & prevent health effects

# Resolving Problems – Overall Approach

- Ensure all affected sites established “IH Review Plans”
  - Conduct qualitative and quantitative exposure assessments
  - As necessary conduct feasibility analyses to identify “feasible” engineering controls
- Conducted extensive literature review & sought expert advice
- Benchmarked with key Leaders
  - Pharmaceutical companies
  - Select research institutes
- Formulated Position / Control Strategy:
  - External peer review – WOEL Monograph + support documentation
  - Input from select internal stakeholders
  - Presented to Animal Allergen Subcommittee of ITAC & ITAC (Merck’s OEL / OEB committee) for endorsement

# Summary of Key Health Effects

- Medical tests indicate < ~ 50% are sensitized to lab animal allergens<sup>1</sup>
  - Non-symptomatic sensitized workers may go on to develop allergy
- 20-50% of “animal workers” report respiratory & skin symptoms<sup>1</sup>
  - Symptoms → Allergy = Lab Animal Allergy (LAA)
- Nearly 1/3 animal workers lose work time due to symptoms or are permanently removed from animal work (NIH study)<sup>1</sup>
- Airborne endotoxins major risk factor for nasal, chest, & skin symptoms in non-sensitized workers<sup>2</sup>
  - Co-exposure may be important in development of LAA sensitization<sup>2</sup>
  - Peak exposure may be more important in triggering symptoms & immunologic sensitization<sup>2</sup>
- Animal allergens & endotoxins - adverse health hazards for pharmaceutical animal workers
  - Lab Animal Allergy (LAA) → potential health risk

<sup>1</sup>Bland, S. et al, *JOM*: 1986: 28

<sup>2</sup>Pacheco, K. et al, *Amer J of Resp & Critical Care Medicine*: 2003: 167

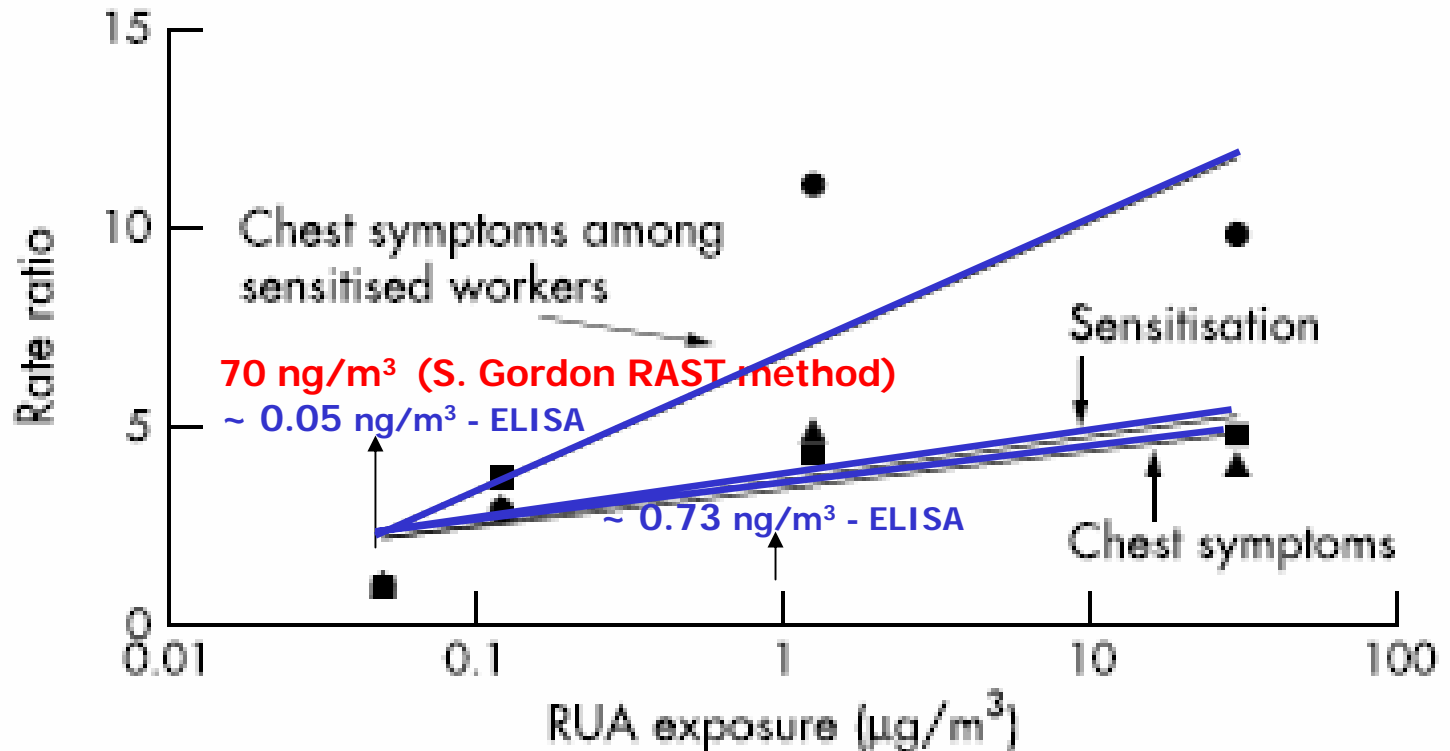
# Exposures - Sampling & Analytical Methods

- Need to understand Sampling & Analytical Methods → critical relationship to establishing OEL
- S. Gordon's old AA Method (RAST) measured more allergens
  - Recommended OEL based on method
  - No longer available
  - Conversion factor RAST → ELISA ( $\sim 7.26 \times 10^{-4}$ ) ∴ higher airborne allergen concentrations measured with S. Gordon's method<sup>1</sup>
- Endotoxin S & A Methods:
  - Inconsistencies between methods / labs
    - Lack of universally standardized method
  - S. Spaan (Netherlands) – optimized S & A methods

<sup>1</sup>Heederik, D. et al, *J Aller Clin Immunol* 1999:103

<sup>2</sup>Spaan S. et. al, *Appl Environ Microbiol*: 2007:73

NOTE: S. Gordon's S & A Method, ∴ higher allergen concentrations



**Figure 1** Exposure-response relations for chest symptoms (triangles), skin prick test (squares), and sensitised chest symptoms (circles), including a best fit line.

<sup>1</sup>Nieuwenhuisen, M., et. al, *OEM* 2003: 60

<sup>2</sup>Values in red calculated based on corrections to RAST concentrations Heederik, D. et al, *J Allerg Clin Immunol* 1999:103 (RAST → ELISA Correction ( $7.33 \times 10^{-4} \times$  RAST conc))

# Endorsed Recommendations

- Use ‘surrogate’ exposure approach for AA / endotoxin exposures:
  - Focus on tasks involving exposures to rat / mouse allergens
  - Endotoxin (primarily tasks involving feces exposures)
- “Working” OELs = WOELs
  - Animal Allergens (i.e., RUP / MUP) = Ceiling Limit = 5 ng/m<sup>3</sup>
  - Endotoxin = OEL-TWA = 50 EU/m<sup>3</sup> for 8-hour TWA (~ 4.5 ng/m<sup>3</sup>)
    - Incorporate Activity Multiplier (1- 5 based on duration of task)
  - Re-assess WOELs based on health outcome & exposure data
- Wipe sampling for AA
  - Evaluate effectiveness of administrative controls, e.g., poor hygiene practices
- Conduct risk-based IH sampling
  - Complete correlation study (IOM to Open face cassette) to improve user friendliness

# Endorsed Recommendations

- Adhere to Risk Management Control Strategy:
  - Install engineering controls for disposal of waste bedding (“high risk” exposure task)
    - Conduct IH monitoring post engineering control installation
  - Conduct IH sampling for other “high risk” to “medium risk” exposure tasks; focus on engineering controls if not already present
    - Washing cages
    - Box changing
    - Shaving fur
    - Changing of filters (HVAC / LEV systems)
    - Injections & other invasive procedures

# Waste Dumping Control Measures



# Endorsed Recommendations

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- Adhere to Risk Management Control Strategy (continued):
  - Establish Engineering Task Force
    - LAR, R&D, Engineering, Safety & IH
    - Focused reviews for “high risk” tasks / exposure potentials
  - Monitor exposures before control installation to confirm need & post installation to verify effectiveness
  - Follow Control Banding Strategy for all other exposure potentials
    - Monitor employees’ exposures based on highest risk first + Health-related triggers
    - Investigate feasible engineering controls
    - Involve Corporate Feasibility Analysis Committee to provide assistance with initial feasibility analyses

# Control Banding Strategy – Animal Allergens

Exposure Category	Airborne Concentration	Engineering Controls	Work Practice Controls	PPE
Low	< 5 ng/m <sup>3</sup>	No further controls required*	✓ SOPs Maintenance Bedding, etc.	✓ Per risk assessment
Medium	5 - 50 ng/m <sup>3</sup>	✓ Feasibility Analysis required Control at Source	✓ “ “	✓ “ “ RPE required; if disposable, need QNTF
High	> 50 ng/m <sup>3</sup>	✓ Control at Source	✓ “ “; Additional Admin Controls	✓ “ “; RPE with higher APF

**Special**

**\*Newly identified sensitized / allergic worker(s) triggers formal investigation with protocol / team & include identified corrective & preventive actions**

# Control Banding Strategy – Endotoxin

Exposure Category	Airborne Concentration	Engineering Controls	Work Practice Controls	PPE
<b>Low</b>	< 50 EU/m <sup>3</sup> for 8-hour TWA or below corresponding AWOEL	No further controls required*	✓ SOPs Maintenance, Bedding Type, etc.	✓ Per risk assessment
<b>Medium</b>	>50-100 EU/m <sup>3</sup> – 4-8 hrs .....up to ..... >250-750 EU/m <sup>3</sup> – 10 min based on activity multiplier	✓ Feasibility Analysis required Control at Source	✓ “ “	✓ “ “ RPE required; if disposable RPE, need QNTF
<b>High</b>	>100 EU/m <sup>3</sup> – 8 hours ..... to..... >750 EU/m <sup>3</sup> – 10 min based on activity multiplier	✓ Feasibility Analysis required Control at Source	✓ “ “; Additional Admin Controls	✓ “ “; RPE with higher APF

**Special**

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# Endorsed Recommendations

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- Leverage Research Safety Network:
  - IH Data & information –
    - Share task data & eliminate sampling same tasks wherever possible
  - Identified successful control measures
  - Incident investigation data, including any new cases
  - Lessons Learned
- Provide training to all medical personnel:
  - Proper LAA classification
  - LAA incident investigation & notification protocol / requirements

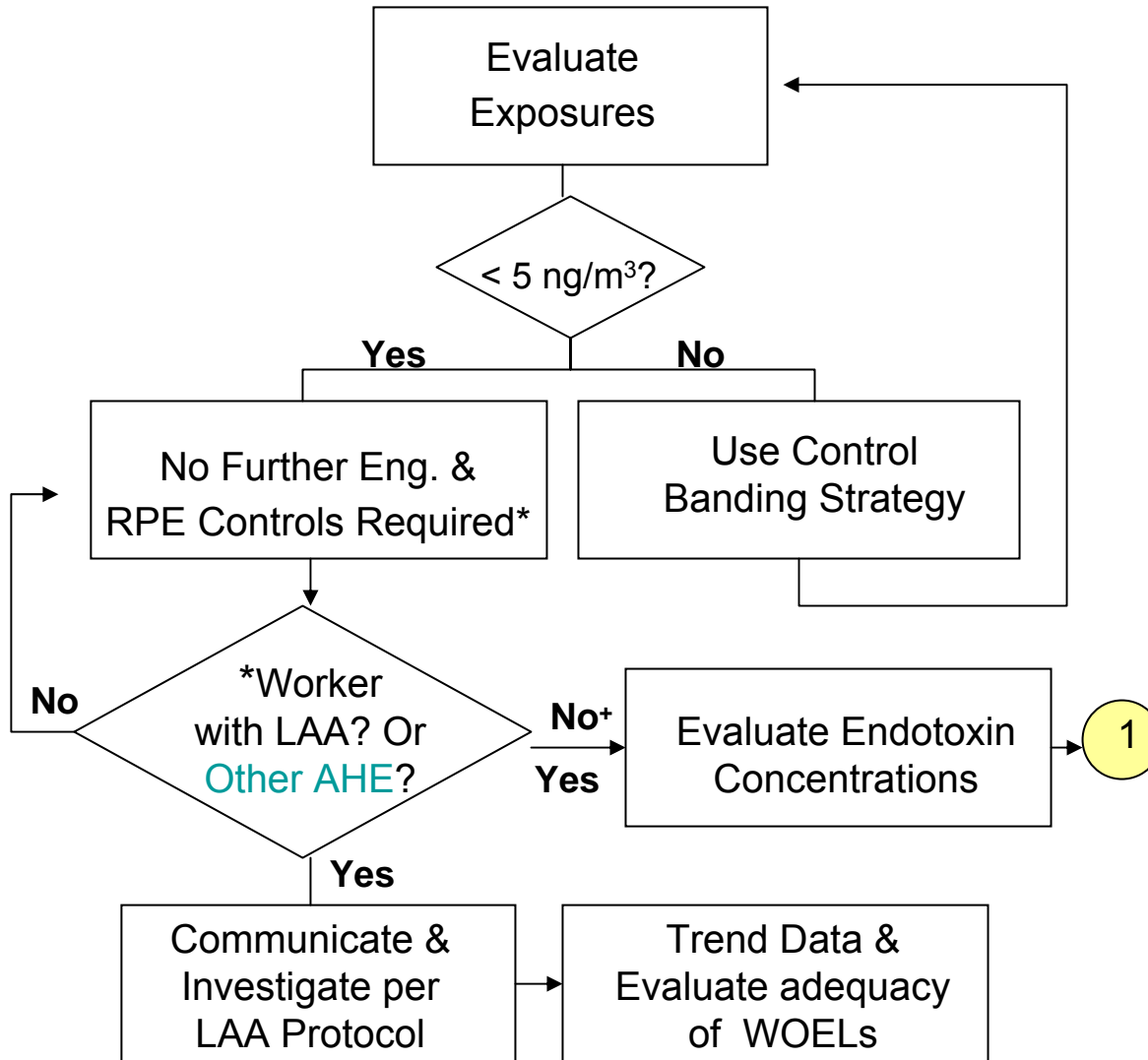
# Endorsed Recommendations

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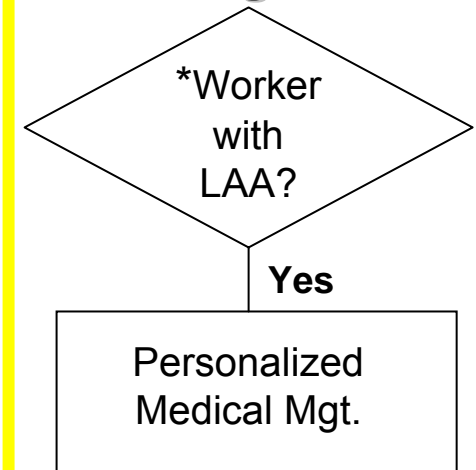
- Evaluate suspected sensitization / LAA cases
  - Notify Global Occupational Health (GOH)
  - Investigate incident
    - Incident Investigation Team – Site S&E, LAR, R&D, Health Services, GOH as appropriate
- Document & share incident investigation report
- Trend appropriate illness data
  - 1° LAA
  - 2° LAA, etc.
  - Endotoxin-related
- Re-evaluate Working OELs based on health data & exposures

# Animal Allergens – Risk Management Approach

## IH / Risk Management

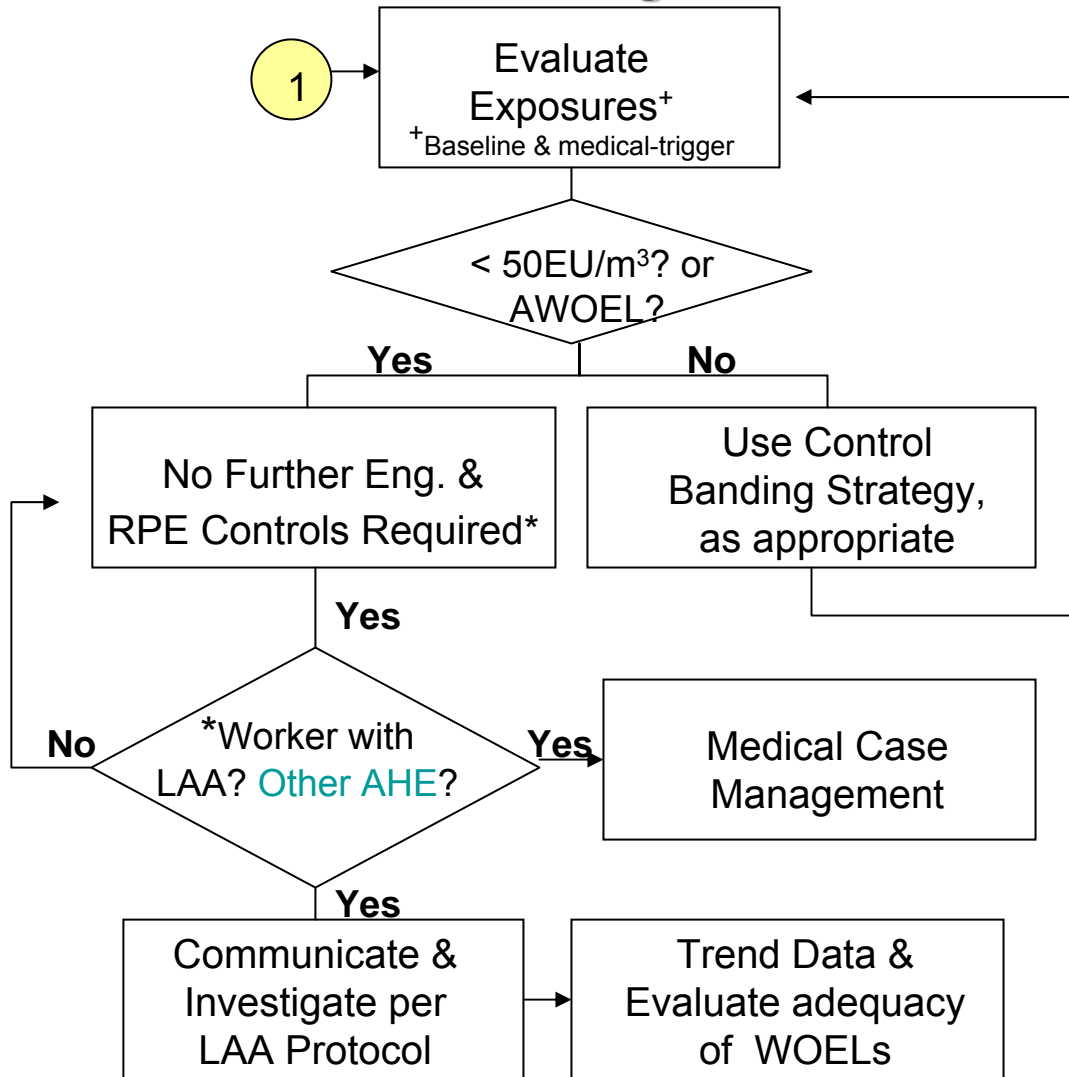


## Medical Management

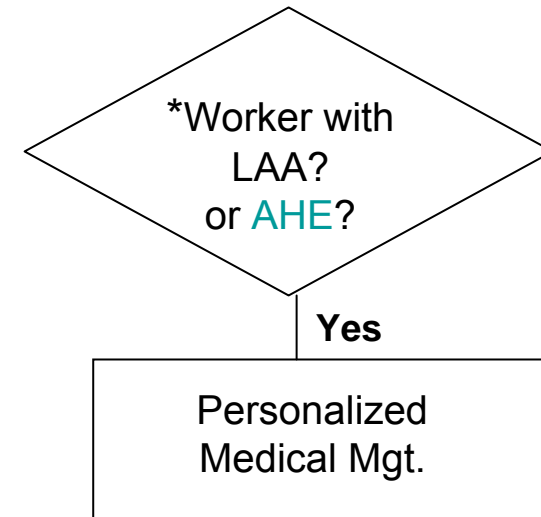


# Endotoxin – Risk Mgt. Approach

## IH / Risk Management



## Medical Management



# Path Forward

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- Improve IH Sampling & Analytical Method
  - Issued S&A Method (based on open face cassette)
  - Complete correlation study of IOM & Open Face Cassette to determine any required correction factor (correlation between methods)
- Assure QA/QC of External IH Lab
  - Complete QC/QA spike recovery studies
  - Provide QC/QA spike samples to sites prior to sampling
  - Quality Audit – prioritize recommendations & track to completion
- Sites to complete IH Review Plan

# Path Forward

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- Communicate & Share Best Practices
  - Data
  - Control measures
- Evaluate & Interpret data
  - Trend Injury / illness statistics
  - Trend IH data
  - Re-evaluate WOELs based on trends & revise as necessary

# Merck's Control Strategy - Balanced Approach to Improving Workers' Health

## Complex

- Establish WOELs
  - Evaluate exposures & controls and prioritize risks
  - Ensure effective control strategy
  - Drive continuous improvement
- Establish improved IH S&A Methods
  - Improves accuracy, consistency, & reproducibility
  - Improves user friendliness & cost effectiveness
- Control at source
  - Prevent distribution / redistribution
  - Investigate dilution ventilation (ACH) reduction opportunities



## Simple

- Effective Control Strategies
  - LAA is **mostly preventable** by reducing exposures < WOEL
  - Reduce overall concentrations & ∴ improve health outcomes
- Medical Surveillance & Testing
  - Identify new cases
  - Trend data
- Leverage Safety Network:
  - Share data & information
- Assure compliance
  - Regulatory requirements
  - Company requirements
- Reduce overall costs (direct / indirect)

# Acknowledgements

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Dr. Pete Nigro – Global Sr. Occupational Physician

# Questions ?

