Current Clinical Perspectives in Evaluating Chemical Induced Asthma, or “What Caused My Asthma?”

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Objectives

• To describe complexities in defining asthma as a clinical syndrome
• To describe methods used to diagnose asthma
• To describe future directions in clinical research of chemically-induced asthma
Asthma Pathophysiology

Smooth Muscle Dysfunction

- Bronchoconstriction
- Bronchial hyperreactivity
- Hypertrophy/hyperplasia
- Inflammatory mediator release

Airway Inflammation

- Inflammatory cell infiltration/activation
- Mucosal edema
- Cellular proliferation
- Epithelial damage
- Basement membrane thickening

Symptoms/Exacerbations

Pathophysiological Features Associated With Asthma

- Variable airflow obstruction
- Bronchoconstriction
- Edema
- Airway hyperreactivity
- Airway inflammation
  - Eosinophils
  - Mast cells
  - Lymphocytes
  - Neutrophils
- Mucus hypersecretion
  - Goblet cell metaplasia
  - Submucosal gland hypertrophy
- Impaired mucus clearance
- Smooth muscle hypertrophy/hyperplasia
- Subepithelial matrix protein deposition
- Collagen deposition
Inflammation in Asthma

- Acute Response
  - Bronchoconstriction
  - Edema
  - Secretions
  - Cough

- Chronic Inflammation
  - Cell recruitment
  - Epithelial damage
  - Early structural changes

- Airway Remodeling
  - Cellular proliferation
  - Extracellular matrix increase
  - Structural changes
Bronchoconstriction

Before

10 Minutes After Allergen Challenge
Inflammation’s Vicious Circle

1. Epithelial damage, apoptosis: epithelial cell desquamation
2. Basal epithelial cells attempt to repair: over-expression of Bcl-2
3. Failure to repair: low proliferative ability/ low expression of PCNA
4. Basal epithelial cell over-activation: high NF-κB release
5. High release of mediators (TGF-α, etc)
6. Exaggerated thickening of extracellular matrix

Adapted from Vignola et al. Chest. 2003;123:417S
Airway Inflammation

Acute symptoms

- Histamine
- Tryptase
- PGD2
- LTs
- Cytokines
- TNF
- ILF

MAST

- IgE

B

- IgE antibody
- IgE

CD4+

CD25+

IL-4/IL-13

Eos

IL-5/IL-3

Basic proteins
- LTs
- Cytokines

Histamine
- LTs
- Cytokines

Bas

Th0

Th2

Th1

CD4+

IL-1

Antigen

presenting cell

Chronic symptoms, inflammation

Allergen

Class II
MHC

T cell
receptor

fragments
Risk Factors for Asthma

• Atopy
• Family history
• Passive/Active smoke exposure
• Bronchiolitis < 2 y/o
• Persistent wheezing as a child
• Environmental determinants
• Frequent use of antibiotics?
• Breast feeding?
Diagnosis of Asthma: History

- Course of the disease – management history
- Typical episode – treatment and outcome
- Social/environmental setting
- Impact on patient/family
- Family history
- Review of systems
- Allergy history (allergic rhinitis, atopic dermatitis?)
- Occupational history
Diagnosis of Asthma: Pattern of symptoms and nature of triggers

• Episodic
• Nocturnal
• Prompted by specific triggers
  – Allergens (seasonal vs. perennial)
  – Viral infections
  – Exercise
  – Other (i.e., cold air, stress)
  – Environmental irritants
  – Occupational exposures
Work-related asthma

Irritants (moderate/high levels)

Work-exacerbated asthma

Irritants (toxic levels) (no latency)

Irritant-induced occupational asthma

Allergens/sensitizers

Latency

Sensitizer-induced occupational asthma
Etiologies of Occupational Asthma
Examples OF Low and High Molecular Weight Agents

Low molecular weight agents
- Cleaning agents
- Isocyanates (HDI, MDI, TDI, IPDI)
- Woods (red cedar, exotic, sawmills)
- Antibiotics
- Glues (methacrylates, cyanoacrylates)
- Epoxies (acid anhydrides, amines...)
- Colophony
- Dyes

High molecular weight agents
- Flour - cereals
- Animal danders
- Latex
- Psyllium
- Crab processing
- Enzymes
## Occupations and Potential Exposures

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Irritant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agricultural workers</td>
<td>Ammonia, nitrogen dioxide, hydrogen sulfide</td>
</tr>
<tr>
<td>Custodians</td>
<td>Ammonia, bleach (hypochlorite), chloramines</td>
</tr>
<tr>
<td>Firefighters</td>
<td>Smoke, hazardous materials releases</td>
</tr>
<tr>
<td>Food service workers</td>
<td>Cooking vapors, cigarette smoke</td>
</tr>
<tr>
<td>Health professionals</td>
<td>Glutaraldehyde, formaldehyde</td>
</tr>
<tr>
<td>Laboratory workers</td>
<td>Solvent vapors, inorganic acid vapors/mists</td>
</tr>
<tr>
<td>Military personnel</td>
<td>Zinc chloride smoke</td>
</tr>
<tr>
<td>Power plant and oil refinery workers</td>
<td>Sulfur dioxide</td>
</tr>
<tr>
<td>Printers, painters</td>
<td>Solvent vapors</td>
</tr>
<tr>
<td>Pulp mill workers</td>
<td>Chlorine, chlorine dioxide, hydrogen sulfide</td>
</tr>
<tr>
<td>Railroad workers, miners, truck drivers</td>
<td>Diesel exhaust</td>
</tr>
<tr>
<td>Refrigeration workers (commercial)</td>
<td>Ammonia</td>
</tr>
<tr>
<td>Roofers, pavers</td>
<td>Asphalt vapors, PAHs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Swimming pool service workers</td>
<td>Chlorine, hydrogen chloride, nitrogen trichloride</td>
</tr>
<tr>
<td>Waste water treatment workers</td>
<td>Chlorine, hydrogen sulfide</td>
</tr>
<tr>
<td>Welders</td>
<td>Metallic oxide fumes, nitrogen oxides, ozone</td>
</tr>
<tr>
<td>Woodworkers</td>
<td>Wood dust</td>
</tr>
</tbody>
</table>
Immunologic assessment

- Skin prick tests and occasionally intracutaneous testings
- *In vitro* specific IgE tests (Immunocap, ELISA)
- Testing assesses allergen sensitization but need to confirm symptoms elicited after exposure to confirm “allergy”
Non-Allergic Rhinitis Environmental Exposure Chamber Responses: Mono- Or Pluri- Responsive

- No Triggers: 22%
- 1 Trigger: 25%
- 2 Triggers: 11%
- 3 Triggers: 31%
- 4 Triggers: 11%

Inflamax research, unpublished data
Irritant Index Scale

**Irritants**

- 1. Perfume
- 2. Hair spray
- 3. Cosmetics (including after-shave lotion)
- 4. Antiperspirants/Deodorants
- 5. Fresh newsprint
- 6. Cooking/frying odors
- 7. Bleach (Clorox®)
- 8. Soap powders (i.e. laundry soap)
- 9. Ammonia (i.e. Lysol®, Windex®)
- 10. Household cleaners (i.e. Tilex®, Comet®)
- 11. Christmas tree odors or Pine-Sol®
- 12. Varnish
- 13. Solvents (turpentine, alcohol, nail polish remover)
- 14. Paints
- 15. Saw dust
- 16. Crude oil (gasoline, diesel, kerosene)
- 17. Periods of high air pollution
- 18. Cold air
- 19. Weather (rain, dampness, temperature changes)
- 20. Tobacco smoke/Wood smoke (burning logs)
- 21. Mold/mildew odors

**Upper respiratory Symptoms**

**Headache**

**INSTRUCTIONS:** Please rate on a scale of 0-10 scale the degree in which the following irritants cause or aggravate any upper respiratory symptoms or headaches.

0 means that the irritant has no effect on creating or aggravating upper respiratory symptoms or headache, and 10 means that the irritant has a maximal effect. If it does not provoke the disease at all, write “0”.

If you avoid the irritant because it aggravates your symptoms, please rate what your reaction was when you were exposed to the irritant in the past.

Upper respiratory symptoms may include: Stuffy nose; runny nose; itching of the nose; sneezing; itchy, red, watery eyes; post-nasal drainage
Clinical Characteristics Of Chronic Rhinitis Patients With High Vs Low Irritant Trigger Burdens

Table 3
Demographic and clinical characteristics of AR and MR patients by physician diagnosis and ILQ reclassification categories

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Physician diagnosis</th>
<th>IlQ reclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AR (n = 404)</td>
<td>MR (n = 129)</td>
</tr>
<tr>
<td>Female</td>
<td>231 (57)</td>
<td>85 (66)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>39.7 (0.58)</td>
<td>44.7 (1.16)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>White</td>
<td>347 (86)</td>
<td>111 (86)</td>
</tr>
<tr>
<td>Family history of atopy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>169 (49)</td>
<td>58 (51)</td>
</tr>
<tr>
<td>Mean positive allergy test results, %</td>
<td>42</td>
<td>23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>216 (54)</td>
<td>26 (20)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physician-diagnosed asthma</td>
<td>109 (27)</td>
<td>53 (21)</td>
</tr>
<tr>
<td>No. of rhinitis symptoms, mean (SE)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.3 (0.06)</td>
<td>3.2 (0.10)</td>
</tr>
<tr>
<td>Seasonality of rhinitis symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perennial only</td>
<td>47 (12)</td>
<td>25 (19)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Seasonal only</td>
<td>126 (32)</td>
<td>23 (18)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Both perennial and seasonal</td>
<td>216 (54)</td>
<td>79 (61)</td>
</tr>
</tbody>
</table>

Table 4
Demographic and clinical characteristics of 123 patients with physician-diagnosed NAR by ILQ reclassification category<sup>d</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-burden NAR (n = 44)</th>
<th>Low-burden NAR (n = 79)</th>
<th>Total NAR (n = 123)</th>
<th>P values for high-burden vs low-burden NAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>37 (84)</td>
<td>60 (76)</td>
<td>97 (79)</td>
<td>.29</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>49.6 (1.59)</td>
<td>45 (1.30)</td>
<td>46.6 (1.03)</td>
<td>.03</td>
</tr>
<tr>
<td>White</td>
<td>40 (91)</td>
<td>72 (91)</td>
<td>112 (91)</td>
<td>.97</td>
</tr>
<tr>
<td>Family history of atopy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (50)</td>
<td>25 (37)</td>
<td>43 (41)</td>
<td>.19</td>
</tr>
<tr>
<td>Physician-Diagnosed asthma</td>
<td>15 (34)</td>
<td>10 (13)</td>
<td>25 (20)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No. of rhinitis symptoms, mean (SE)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.2 (0.16)</td>
<td>2.5 (0.16)</td>
<td>2.8 (0.12)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Seasonality of rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perennial only</td>
<td>11 (25)</td>
<td>26 (33)</td>
<td>37 (30)</td>
<td>.34</td>
</tr>
<tr>
<td>Seasonal only</td>
<td>5 (11)</td>
<td>16 (21)</td>
<td>21 (17)</td>
<td>.20</td>
</tr>
<tr>
<td>Both perennial and seasonal</td>
<td>27 (61)</td>
<td>26 (33)</td>
<td>53 (43)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

<sup>b</sup>p<.01

Patients and Surface Disinfectants Survey

• 440 respondents
• 1/3 had treated pts. with disinfectant-related symptoms
• Settings: work > home > school > community
  • Jobs: health care > custodians > personal care > office / financial services > food services
• Conditions: Asthma > eye, nose, throat irritation > dermatitis > rhinitis > ocular allergy > urticaria
• 1/3 had difficulty obtaining chemical information
• 1/2 could not ID chemical class of product(s)

Source: Bernstein J. and Shusterman D., AAAAI Survey
Population-based Studies Have Confirmed Health Risks Of Cleaning Occupations

  - Most common work-related exposures were to SO2, chlorine and cleaning-agents
  - Most common non-work related discharges were due to smoke exposure from fires and household cleaners
- **Ng et al.** showed OR 1.91 (95%CI 1.22-2.99) between cleaners and the risk of asthma in Singapore (1994)
- **Arif et al.** analyzed associations between occupation and work-related asthma and work-related wheezing among US workers
  - Cleaning agents and equipment cleaners showed the highest risk in both categories
- **Reinisch et al** surveyed physician reports of work-related asthma in California 1993-6
  - Janitors and cleaners (625/million) had the highest reporting rates of work-related asthma
- **Jaakkola et al** conducted a population case-control study to examine occupational risk of developing asthma in adulthood in Finland
  - Women cleaners (OR=1.42, 95% CI: 0.81-2.48)
- **Forastiere et al** evaluated the role of occupational factors on the prevalence of self-reported asthma among women >55 yo. in Sonoma, CA (5/93-12/94)
  - Service occupations & asthma (OR=2.4 [1.0-5.8])
  - Homemakers & asthma-like symptoms (OR=2.4 [1.0-6.0])

Evaluation Of Cleaning Activities On Respiratory Symptoms In Asthmatic Female Homemaker

- **Objective:** To compare health effects of cleaning among asthmatic and nonasthmatic women who are the primary cleaners in their homes.

- **Methods:** A 12-week, prospective, parallel-group study assessing the effects of cleaning on peak expiratory flow rates and upper and lower respiratory tract symptoms in women with and without asthma.

- **National Institutes of Health (NIH) health rating:** 0, minimal; 1, slight; 2, moderate; 3, serious; and 4, severe (eg, 0 = Fantastik and dish soaps; 1 = Pledge, Windex, Glass plus, Murphy’s oil soap, Mr. Clean, Formula 409; 2 = chlorine-based products; 3 = Lysol, ceramic countertop cleaners, oven cleaners).

Table 1. Baseline Demographic Characteristics of Patient Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Asthmatic (n = 25)</th>
<th>Nonasthmatic (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>49 (11)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>23 (92)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Education higher than high school diploma, No. (%)</td>
<td>18 (72)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Allergic and/or nonallergic rhinitis, No. %</td>
<td>21 (84)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Atopic status, No. %</td>
<td>22 (88)</td>
<td>6 (32)</td>
</tr>
<tr>
<td><strong>Chest symptoms with exertion, No. (%)</strong></td>
<td>19 (76)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Stops exercising activity due to symptoms, No. (%)</td>
<td>12 (63)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Stops exercising due to overexertion, No. (%)</td>
<td>12 (48)</td>
<td>5 (26)</td>
</tr>
<tr>
<td><strong>Cleaning activity (NIH health rating), No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet mopping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrosive floor cleaner (2 or 3)</td>
<td>4 (16)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Floor cleaner with chlorine (2)</td>
<td>4 (16)</td>
<td>5 (27)</td>
</tr>
<tr>
<td>Floor cleaner without chlorine (0 or 1)</td>
<td>19 (76)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Vinegar (1)</td>
<td>3 (12)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Water (0)</td>
<td>5 (20)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Dusting, waxing, or polishing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrosive cleaner (2 or 3)</td>
<td>1 (4)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Isopropanol (1) or potassium hydroxide (1)</td>
<td>3 (12)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Wood polish and dust remover (0 or 1)</strong></td>
<td>23 (92)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Lemon oil (0)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Humid or dry cloth (0)</td>
<td>4 (16)</td>
<td>5 (27)</td>
</tr>
<tr>
<td>Toilet and bathroom cleaning</td>
<td></td>
<td></td>
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<tr>
<td>Corrosive disinfectant (2 or 3)</td>
<td>12 (48)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Other disinfectant with chlorine (2)</td>
<td>14 (56)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Disinfectant without chlorine (1)</td>
<td>5 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Kitchen cleaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrosive cleaners (2 or 3)</td>
<td>11 (44)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>All purpose cleaner with chlorine (2)</td>
<td>14 (56)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>All purpose cleaner without chlorine (0 or 1)</td>
<td>14 (56)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Windows and mirrors cleaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrosive cleaner (2 or 3)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Isopropanol (1)</td>
<td>22 (88)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Vinegar (1)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Dish soap (0)</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Damp cloth (0)</td>
<td>1 (4)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>All cleaning activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>103</td>
<td>69</td>
</tr>
<tr>
<td>2 or 3</td>
<td>61</td>
<td>45</td>
</tr>
<tr>
<td><strong>Duration of cleaning activity, mean (SD), hours per week</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet mopping</td>
<td>2.4 (0.5)</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>Dusting, waxing, or polishing</td>
<td>2.7 (0.7)</td>
<td>2.8 (0.7)</td>
</tr>
<tr>
<td>Toilet and bathroom cleaning</td>
<td>2.8 (0.6)</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td>Kitchen cleaning</td>
<td>2.4 (0.6)</td>
<td>2.2 (0.4)</td>
</tr>
<tr>
<td>Windows and mirrors cleaning</td>
<td>3.2 (0.5)</td>
<td>3.0 (0.7)</td>
</tr>
<tr>
<td>All cleaning activities</td>
<td>13.4 (1.9)</td>
<td>12.4 (2.4)</td>
</tr>
</tbody>
</table>
### Table 2. Summary of Data Obtained From Cleaning Diaries of 25 Asthmatic and 19 Nonasthmatic Patients

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic (n = 25)</th>
<th>Nonasthmatic (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. of diaries per patient</td>
<td>10.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Mean No. of cleaning hours per day per patient</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean (SD) peak flow before and after cleaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>338.9 (95.9)</td>
<td>370.2 (60.4)</td>
</tr>
<tr>
<td>After</td>
<td>326.7 (93)</td>
<td>358.9 (57.6)</td>
</tr>
<tr>
<td>Mean (SD) morning-evening peak flow difference before minus after cleaning</td>
<td>-12.2 (26.4)</td>
<td>-11.3 (33.3)</td>
</tr>
<tr>
<td>Mean (SD) upper respiratory tract symptoms before and after cleaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1.6 (1.8)</td>
<td>1.0 (1.4)</td>
</tr>
<tr>
<td>After</td>
<td>2.7 (2.5)</td>
<td>2.1 (2.3)</td>
</tr>
<tr>
<td>Mean (SD) upper respiratory tract symptoms after minus before cleaning</td>
<td>1.2 (1.8)</td>
<td>1.1 (1.8)</td>
</tr>
<tr>
<td>Mean (SD) lower respiratory tract symptoms before and after cleaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1.4 (2.3)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td>After</td>
<td>2.6 (2.9)</td>
<td>0.9 (1.3)</td>
</tr>
<tr>
<td>Mean (SD) change in lower respiratory symptoms after minus before cleaning</td>
<td>1.2 (1.8)</td>
<td>0.3 (0.8)</td>
</tr>
</tbody>
</table>

### Table 3. Estimated Change in Peak Expiratory Flow Rate (PEFR) After Minus Before Cleaning and Lower Respiratory Tract and Upper Respiratory Tract Symptoms for Asthmatic and Nonasthmatic Patients Controlling for Chemical Severity Exposure and Cleaning Duration

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Change in PEFR, L/sec</th>
<th>P value</th>
<th>Change in lower respiratory tract symptoms</th>
<th>P value</th>
<th>Change in upper respiratory tract symptoms</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (yes/no) adjusted means</td>
<td>-3.6</td>
<td>.48</td>
<td></td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Adjusted means</td>
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<td></td>
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</tr>
<tr>
<td>Asthmatic (4.3%)</td>
<td>13.0</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonasthmatic (1.5%)</td>
<td>9.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical exposure index (high vs low)</td>
<td>+0.5</td>
<td>.88</td>
<td></td>
<td>.68</td>
<td></td>
<td>.91</td>
</tr>
<tr>
<td>Cleaning duration (change per 1 hour of cleaning)</td>
<td>-1.9</td>
<td>.06</td>
<td></td>
<td>.21</td>
<td></td>
<td>.11</td>
</tr>
</tbody>
</table>
Estimated Atmospheric Emissions Of VOCs From Use Of Household And Commercial Cleaning Products And Air Fresheners In California, 1997a

<table>
<thead>
<tr>
<th>Product</th>
<th>VOC emissions (tonnes/d)</th>
<th>Per capita VOC emissions (mg·d⁻¹·person⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpet and upholstery care: cleaners and deodorizers</td>
<td>1.07</td>
<td>32</td>
</tr>
<tr>
<td>Spot removers</td>
<td>0.64</td>
<td>20</td>
</tr>
<tr>
<td>Fabric protectants</td>
<td>0.37</td>
<td>11</td>
</tr>
<tr>
<td>Floor care: wax, wax strippers, polish</td>
<td>5.6</td>
<td>170</td>
</tr>
<tr>
<td>General purpose cleaners</td>
<td>7.4</td>
<td>220</td>
</tr>
<tr>
<td>General purpose degreasers</td>
<td>2.1</td>
<td>64</td>
</tr>
<tr>
<td>Glass cleaners</td>
<td>3.4</td>
<td>100</td>
</tr>
<tr>
<td>Oven cleaners and metal polishes/cleansers</td>
<td>0.87</td>
<td>26</td>
</tr>
<tr>
<td>Bathroom cleaners: toilet bowl, tub, tile, and sink</td>
<td>0.74</td>
<td>22</td>
</tr>
<tr>
<td>Furniture waxes and polishes; dusting aids</td>
<td>2.4</td>
<td>71</td>
</tr>
<tr>
<td>Air fresheners</td>
<td>7.5</td>
<td>230</td>
</tr>
</tbody>
</table>

Source: CARB, 2003; per capita emissions based on 1997 population estimate of 33 million (http://www.dhs.ca.gov/hs Populatio/dis/per index.htm).
Volatile and Non-Volatile Organic Compounds

- Cleaning products are divided into substances that can evaporate into the air as a gas or vapor (volatile) and those that cannot (non-volatile)
- The most toxicologically significant fraction are volatile organic compounds (VOCs)
  - Defined as organic compounds with boiling points between 0-400°C
  - Ubiquitous in indoor air
- Many different sources contribute to indoor air VOC’s
  - Building products
  - Machines
  - Outdoor air
  - Mold (microbial VOCs)
  - Cleaning products
- Increasing VOC domestic exposure, below currently accepted recommendations, linked to increasing risk of childhood asthma *(Rumchev, et al Thorax 2003;59:746-51)*
- Depending on substrate and concentration of the cleaning agent, very volatile substances will usually evaporate from the cleaned surface resulting in short-term peak concentrations of VOCs
  - Both cleaner and occupant can be exposed immediately
  - Semi-volatile compounds (>200°C) will show a delayed emission over time, increasing the probability of exposure *(Wolkoff, et al Sci Tot Env 1998;215:135-156)*
Cleaning Products: Active Components

- **Surfactants** (detergents, tensides) are the main constituents of most cleaning agents
  - Often classified as anionic, cationic, non-ionic or amphoteric according to the charge of the hydrophilic part of the molecule
  - Function is to enhance the effect of the cleaning agent by lowering the surface tension of water
  - Considered to be responsible for a range of skin and eye problems as well as mucous membrane irritation
- **Acidic and alkaline substances** have a dissolving effect on calcium and fatty substances, respectively
  - Enhance the effect of other substances (e.g. surfactants) by regulating the pH of the solution
  - Alkaline compounds (e.g. metalosilicates, disilicate, Ca carbonate, sodium carbonate, potassium and sodium hydroxide) inhibit the corrosion of metal surfaces
  - Some acids also act as disinfectants (e.g. phosphoric, acetic, oxalic, citric, formic or sulphamic acids)
- **Complexing agents or water softeners** are added to dissolve and bind calcium, magnesium and other metal ions
  - Prevent the lowering of the surfactant’s effect
  - Include tripolyphosphates, zerolite, citrates, polycarboxylates, nitrilotriacetic acid (NTA) and ethylenediamine tetraacetic acid (EDTA)
- **Disinfectants’** main purpose is to destroy bacteria and other microorganisms; **active compounds include**:
  - Chlorine-releasing compounds (hypochlorite and Chloramine-T) – corrosive; can cause asthma and contact dermatitis
  - Alcohols (ethanol, isopropanol) – in solvents
  - Aldehydes (formaldehyde, glutaraldehyde) – well known asthmagens
  - Quaternary ammonium compounds (benzalkonium chloride aka BKC)
  - Oxygen-releasing compounds and enzymes
- **Other components** – perfumes, scents, film formers, polishers

Asthma And Exposure To Cleaning Products –
A European Academy Of Allergy And Clinical
Immunology Task Force Consensus Statement

**Key Messages**

- Professional and domestic cleaning is associated with work-related asthma.
- Cleaning sprays, bleach, ammonia, disinfectants (e.g., chloramine-T, quaternary ammonium compounds, and ethanolamine), mixing products, and specific job tasks have been identified as specific causes of or exacerbation for asthma.
- Low-volatility liquid cleaning products has been associated with less asthma.
- Inhalation accidents (e.g., mixing bleach with ammonium salts or acid detergents) are associated with acute irritant-induced asthma (RADS) and WEA.
- Most cleaning agents have an irritating effect on airways, although occasionally a few agents (e.g., chloramine-T and enzymes) show an IgE-mediated mechanism.
- Cleaning, a women-dominated occupation, might partly explain gender differences in asthma control.
- Possible preventive measures encompass avoidance of aerosolization of cleaning products, bleach, and ammonia, minimizing the use of disinfectants, avoidance of mixing products, the use of respiratory protective devices, worker education, and medical surveillance.
- Information activities and collaboration between scientific communities and safety and health agencies are urgently needed.

Diagnosis of Asthma: Spirometry, A Simple, Basic Objective Measurement

• Essential to initial evaluation to confirm diagnosis
• Helps assess severity of airflow obstruction
• Aids in differential diagnosis
  – Obstructive versus restrictive airway disease
  – Reversibility of airflow obstruction
• Confirms periodic home PEFR measurements in selected patients
• Symptoms alone are insufficient to determine asthma severity
Spirometry: Volume–Time Curves in Asthma Demonstrating Reversal of Airflow Obstruction Following a Beta-Agonist

Pre-
- FVC = 3.6 l
- FEV₁ = 2.0 l
- FEV₁/FVC = 56%

Post-
- FVC = 4.0 l
- FEV₁ = 3.0 l
- FEV₁/FVC = 75%
**Spirometry:** Flow-Volume Loops in Asthma
Demonstrating Non-obstructed Pattern & Reversal of Airflow Obstruction Following a Beta-Agonist
PEFR Monitoring in Asthma

- Monitors response to therapy
- Monitors response to illness
- Identifies variation in disease severity, >20% suggests worsening asthma
- May help identify environmental triggers
- Important clinical tool in home
Non-Specific Provocation: To confirm or exclude airway hyperresponsiveness

- Methacholine challenge – assess smooth muscle dysfunction
- Histamine challenge
- Exercise
- Mannitol
Monitoring of PEF & PC$_{20}$

To objectively confirm exacerbation of asthma

Exhaled Nitric Oxide: A Non-invasive Measurement Of Airway Inflammation – correlates with asthma control*

• To compare eNO with the clinical assessment of asthma control
• 73 children with asthma were enrolled. Control based on β-agonist use, day-night time symptom scores, spirometry
  -Good Control (n=21): eNO 11 ppb
  -Acceptable Control (n=31): eNO 15 ppb
  -Inadequate Control (n=21): eNO 28 ppb
• An eNO value >21 ppb is a reliable predictor of poor asthma control based on symptoms, β-agonist use, and spirometry
• Similar results seen with β-agonist reversibility

Indications for Controlled Challenge with a Specific Agent

• Diagnostic uncertainty
  – Poor history, confounding factors
  – Diagnostic dispute
  – Physicians, employers, insurance companies, attorneys
  – Research
Asthma Management

• Reduce / avoid exposure in home and workplace

• Medications

• Address any concomitant illnesses
  – Chronic rhinitis subtypes
  – GERD
  – Chronic sinusitis
  – CHF, chronic PE, VCD, Tracheobronchiomalacia...
### NHLBI Expert Panel Report II: Guidelines for the Diagnosis & Management of Asthma

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptoms</th>
<th>Nocturnal Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1: Mild Intermittent</strong></td>
<td>≤ 2 times per week, no symptoms &amp; normal PEF between exacerbations</td>
<td>≤2 times per month</td>
<td>FEV$_1$ or PEF ≥80%; PEF variability &lt;20%</td>
</tr>
<tr>
<td><strong>Step 2: Mild Persistent</strong></td>
<td>&gt;2 times/wk but &lt;1/ d Exacerbations may affect activity</td>
<td>&gt;2 times a month</td>
<td>FEV$_1$ or PEF ≥80%; PEF variability 20%–30%</td>
</tr>
<tr>
<td><strong>Step 3: Moderate Persistent</strong></td>
<td>Daily. Daily use of SABAs, attacks affect activity. Exacerbations ≥2 x /wk</td>
<td>&gt;1 time per week</td>
<td>FEV$_1$ or PEF &gt;60 to ≤80%, PEF variability &gt;30%</td>
</tr>
<tr>
<td><strong>Step 4: Severe Persistent</strong></td>
<td>Continual symptoms, Limited physical activity. Frequent exacerbations</td>
<td>Frequent</td>
<td>FEV$_1$ or PEF ≤60%, PEF variability &gt;30%</td>
</tr>
</tbody>
</table>
Asthma Prognosis: 

**Excellent if...**

- Early diagnosis
- Environmental control measures implemented
- Appropriate medications prescribed
  - Good inhaler technique
  - Good adherence
- Assessment and management of concomitant disease
- Long term monitoring for asthma control (ACT, ACQ)
  - Risk vs. control
  - No symptoms and no loss of lung function over time
  - Medication step down or step up
  - Asthma education
Future Research Directions To Better Understand Irritant Induced Asthma

• Research
  • Epidemiologic studies
  • Specific provocation using an environmental exposure chamber
  • Mechanistic studies (human ex vivo and in vivo)

• Consumer and Employer Education
• Product Development