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# Cleaning and asthma: A systematic review and approach for effective safety assessment

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ABSTRACT

Research indicates a correlative relationship between asthma and use of consumer cleaning products. We conduct a systematic review of epidemiological literature on persons who use or are exposed to cleaning products, both in occupational and domestic settings, and risk of asthma or asthma-like symptoms to improve understanding of the causal relationship between exposure and asthma. A scoring method for assessing study reliability is presented. Although research indicates an association between asthma and the use of cleaning products, no study robustly investigates exposure to cleaning products or ingredients along with asthma risk. This limits determination of causal relationships between asthma and specific products or ingredients in chemical safety assessment. These limitations, and a lack of robust animal models for toxicological assessment of asthma, create the need for a weight-of-evidence (WoE) approach to examine an ingredient or product's asthmatic potential. This proposed WoE method organizes diverse lines of data (i.e., asthma, sensitization, and irritation information) through a systematic, hierarchical framework that provides qualitatively categorized conclusions using hazard bands to predict a specific product or ingredient's potential for asthma induction. This work provides a method for prioritizing chemicals as a first step for quantitative and scenario-specific safety assessments based on their potential for inducing asthmatic effects. Acetic acid is used as a case study to test this framework.



## 1. Introduction

Asthma prevalence is rising globally. Approximately 7% of adults (17.7 million) and 8.6% of children (6.3 million) in the United States have been diagnosed with current asthma, increasing the burden on health care costs and impacting quality of life (Centers for Disease Control and Prevention (CDC), 2015). Asthma is a complex syndrome with multiple phenotypes (Bousquet et al., 2010) characterized by a combination of smooth muscle dysfunction and inflammatory responses (Lemanske and Busse, 2010; NHLBI, 2007) that commonly presents with symptoms of cough, wheeze, dyspnea, and chest tightness (Tarlo et al., 2008; Association of Occupational and Environmental Clinics (AOEC), 2008). Most cases of asthma are caused or triggered by specific (IgE–mediated) or non-specific (IgE-independent) inflammation (Mapp et al., 2005), but exposures to chemical irritants can also cause asthma-like syndromes, like Reactive Airways Dysfunction Syndrome (RADS; Bernstein, 1993; Vandenplas et al., 2014) or Low Intensity Chronic Exposure Dysfunction Syndrome (LICEDS; Baur et al., 2012). Thus, understanding the subtleties of evaluating asthma as an endpoint in the safety and risk assessment context is an important undertaking. However, risk assessors are hampered by limitations in both epidemiology and toxicology methods, specifically a lack of reliable *in vitro* or *in vivo* models for asthma or asthma-specific risk assessment guidance (Maier et al., 2014; 2015) and inadequate exposure characterization.

Interpretation of the potential for cleaning products or individual ingredients to induce asthma (i.e., cause new-onset asthma) or elicit an asthmatic response is an important driver for product formulation decisions and regulatory outcomes. The use of cleaning products in residential and commercial applications is implicated as a potential inducer of asthma or as a trigger for respiratory symptoms in asthmatics, which may contribute to the observed morbidity (Zock et al., 2010; Folletti et al., 2014; Jaakkola and Jaakkola, 2006; Siracusa et al., 2013). Current evidence is not sufficiently robust to accurately characterize the mixture of chemicals and exposures encountered during cleaning, nor to determine a clear relationship between specific cleaning product exposures and

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**Abbreviations**

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|---|---|
| AIHA | American Industrial Hygiene Association |
| AOEC | Association of Occupational and Environmental Clinics |
| CDC | Centers for Disease Control and Prevention |
| ETS | Environmental Tobacco Smoke |
| EU | European Union |
| HCL | Hydrochloric Acid |
| IgE | Immunoglobulin E |
| JEM | Job Exposure Matrix |
| LCL | Lower Confidence Limit |
| LICEDS | Low-Intensity Chronic Exposure Dysfunction Syndrome |
| LRTS | Lower Respiratory Tract Symptoms |
| NHBLI | National Heart, Lung, and Blood Institute |
| NTP | National Toxicology Program |
| OR | Odds Ratio |
| PR | Prevalence Ratio |
| RADS | Reactive Airways Dysfunction Syndrome |
| RR | Risk Ratio |
| SES | Socioeconomic Status |
| TERA | Toxicology Excellence for Risk Assessment |
| TRP | Transient Receptor Potential |
| UCL | Upper Confidence Limit |
| URTS | Upper Respiratory Tract Symptoms |
| WoE | Weight of Evidence |

the development of asthma, or asthma induction. Cleaning-related exposures are complex; cleaning can expose individuals to chemical irritants and also temporarily increases intake of dusts, pollen, dander, and molds while simultaneously reducing overall household allergen burdens over time (Nickmilder et al., 2007; Zock et al., 2009; Hernández-Cadena et al., 2015). Some studies have conducted quantitative exposure assessments of cleaning scenarios (Bello et al., 2010; Vincent et al., 1993; Nazaroff and Weschler, 2004; Singer et al., 2006; LeBouf et al., 2014; Bessonneau et al., 2013), but none measured asthmatic or asthma-like outcomes for determination of a quantitative exposure-response relationship.[1] Without linking quantitative exposure assessments to asthma response, the exposure-response relationship between cleaning product ingredients and asthma cannot be characterized and drawing conclusions about specific causal relationships is limited (Hill, 1965; Meek et al., 2014). Thus, the absence of definitive exposure-response data is hindering advances in risk management of cleaning-related asthma.

Due to the lack of specificity between cleaning activities and asthma induction and, more specifically, a lack of quality quantitative exposure-response estimations, risk assessors are limited to the use of ingredient-specific (i.e., single chemical) toxicological information. However, in the case of asthma, there is no single validated asthma animal model and assessments often use surrogate endpoint data (e.g., sensitization and irritation). This study aims to develop a weight-of-evidence (WoE) approach that can be used to integrate multiple lines of imperfect evidence. We developed a series of risk assessment tools to address this challenge, specifically a multi-step decision system with sequential data analysis techniques and a systematic framework for evaluating weight of evidence to inform hazard characterization and prioritization decisions (Fig. 1). This prioritization framework is divided into four key steps: systematic review, hazard characterization, safety assessment, and risk management. The procedure uses diverse lines of evidence, specifically human data on asthma and human and animal data on sensitization and irritation to establish a weight-of-evidence category. These tools include an objective study quality evaluation approach that rates epidemiological studies according to their reliability and relevance for asthma safety and risk assessment. Although many high-quality guidelines for evaluating the quality of epidemiological studies exist, they are generally tailored for specific uses (i.e., biomonitoring or exposure evaluation (LaKind et al., 2014)), disease outcomes (e.g., the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) for neurodevelopmental studies (Whiting et al., 2003)) or scenarios not relevant for asthma risk assessment. Other guidelines are complex and difficult to interpret and use in a WoE tool that integrates multiple lines of evidence because they lack a method for ranking studies by their quality. Examples include the BEES-C (LaKind et al., 2014), the PRISMA statement for reporting systematic reviews and meta-analyses (Liberati et al., 2009), the OHAT approach (NTP, 2013), the STROBE statement (Von Elm et al., 2008), and the RCGP three-star system (Nicholson et al., 2010; Baur, 2013). Our approach aligns with the underlying principles of such methods, but was customized to be flexible and simple in interpretation and easy to integrate with the Klimisch et al. (1997) scoring system widely used for toxicological study evaluation. The approach is expected to facilitate chemical safety assessment.

Our approach includes a systematic review of current epidemiology literature using the quality evaluation tool. The purpose for this review was two-fold: 1) to validate the proposed quality evaluation method and 2) to determine if persons (both adults and children) with and without a history of pre-existing asthma who actively use or are exposed to domestic cleaning products, both in occupational and domestic settings, at least one time per week are at increased risk for asthma or asthma-like symptoms during their lifetime. Domestic cleaning products are defined as products that are commonly available, can be purchased “off the shelf” at local stores, and are typically used in home cleaning scenarios. Specifically, we apply Bradford Hill's criteria for causal association in a chemical safety assessment context (Hill, 1965; Meek et al., 2014) to assess the strength, consistency, temporality, and coherence of the observed associations between cleaning product ingredient exposures and new-onset asthma.

In addition to our presentation of this systematic framework, we apply the methodology to a case study on acetic acid to test the robustness and accuracy of the method (refer to Supplemental Material 1). It is our goal that these methods can be used to enhance understanding of the possible relationship between cleaning product ingredients and asthma despite the knowledge gaps and lack of robust exposure-response information.

## 2. Methods

The proposed framework for characterizing and prioritizing chemicals based asthma hazard using a weight-of-evidence method is a multi-step process (see Fig. 1). The proposed methods provide guidance for navigating the first two steps of the

[1] Medina-Ramon et al. (2005) collected short term personal exposure measurements of airborne chlorine and ammonia in a subsample of 10 subjects (four cases and six controls). These ad-hoc measurements were used to describe common exposures and not to compare exposure levels between cases and controls or to determine a dose-response relationship.