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A tiered asthma hazard characterization and exposure assessment approach for evaluation of consumer product ingredients

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ABSTRACT

Asthma is a complex syndrome with significant consequences for those affected. The number of individuals affected is growing, although the reasons for the increase are uncertain. Ensuring the effective management of potential exposures follows from substantial evidence that exposure to some chemicals can increase the likelihood of asthma responses. We have developed a safety assessment approach tailored to the screening of asthma risks from residential consumer product ingredients as a proactive risk management tool. Several key features of the proposed approach advance the assessment resources often used for asthma issues. First, a quantitative health benchmark for asthma or related endpoints (irritation and sensitization) is provided that extends qualitative hazard classification methods. Second, a parallel structure is employed to include dose-response methods for asthma endpoints and methods for scenario specific exposure estimation. The two parallel tracks are integrated in a risk characterization step. Third, a tiered assessment structure is provided to accommodate different amounts of data for both the dose-response assessment (i.e., use of existing benchmarks, hazard banding, or the threshold of toxicological concern) and exposure estimation (i.e., use of empirical data, model estimates, or exposure categories). Tools building from traditional methods and resources have been adapted to address specific issues pertinent to asthma toxicology (e.g., mode-of-action and dose-response features) and the nature of residential consumer product use scenarios (e.g., product use patterns and exposure durations). A case study for acetic acid as used in various sentinel products and residential cleaning scenarios was developed to test the safety assessment methodology. In particular, the results were used to refine and verify relationships among tiered approaches such that each lower data tier in the approach provides a similar or greater margin of safety for a given scenario.

1. Introduction

The increasing prevalence of asthma in the United States, and worldwide, is a growing burden on health care costs and quality of life (Centers for Disease Control and Prevention (CDC), 2015a). Asthma is a chronic inflammatory disease of the lung characterized by a narrowing of the airways that commonly presents with symptoms of cough, wheeze, dyspnea, and chest tightness (Beckett, 2008). Numerous epidemiological studies have linked the use of cleaning products in residential and commercial settings to an increase in physician-diagnosed asthma (Zock et al., 2007), however the current evidence is not sufficient to determine a clear dose-response relationship between specific cleaning product exposures and the development of asthma. Most cases of asthma are caused or triggered by specific or non-specific inflammation. Specific inflammation is often the result of an immunoglobin E (IgE) mediated response, but some low-molecular-weight (LMW) chemicals (e.g., toluene diisocyanate), in some cases, may cause IgE independent inflammation (Mapp et al., 1994; Walker et al., 1992). Single exposures to high concentrations of chemical irritants (e.g., hydrogen chloride) can also cause an asthma-like condition called reactive airways dysfunction syndrome (RADS) (Bernstein, 1993). Since the pathological mechanisms of asthma are not fully understood, safety assessments for chemicals and products need to address uncertainties in estimating the dose-response relationship

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists®
ACI	American Cleaning Institute
ADI	acceptable daily intake
AIHA	American Industrial Hygiene Association
AOEC	Association of Occupational and Environmental Clinics
CDC	Centers for Disease Control and Prevention
EL	exposure limit
EGV	exposure guide value
DFG	German Research Foundation
DNEL	derived no-effect level
ECETOC	European Center for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
FSA	free surface area
GPMT	Guinea Pig Maximization Test
HBGV	health-based guidance value
IgE	Immunoglobin E
IPCS	International Programme on Chemical Safety
LLNA	Local Lymph Node Assay
LMW	low molecular weight
MAK	Maximale arbeitsplatz-konzentration (maximum workplace concentration)
MCCEM	Multi-Chamber Concentration and Exposure Model
MOE	margin of exposure
MOS	margin of safety
NIOSH	National Institute for Occupational Safety and Health
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
OEB	occupational exposure band
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PHBGV	provisional health-based guidance value
POD	point of departure
ppm	parts per million
RADS	Reactive Airways Dysfunction Syndrome
REACH	Registration Evaluation Authorization and Restriction of Chemical Substances
RfC	reference concentration
RIVM	National Institute for Public Health and the Environment (Netherlands)
rLLNA	Respiratory Local Lymph Node Assay
SAF	sensitization assessment factor
SCOEL	European Union Scientific Committee on Occupational Exposure Limits
SP	sentinel product
STEL	short-term exposure limit
TDI	Toluene-2, 4-Diisocyanate
TLV	Threshold Limit Value®
TTC	threshold of toxicological concern
TWA	time-weighted average
UF	uncertainty factor
UNECE	United Nations Economic Commission for Europe
U.S. EPA	U.S. Environmental Protection Agency
VOC	volatile organic compound
WOE	weight of evidence

for both irritation and sensitization, and the relationship between these effects and asthma responses.

Residential consumer product use represents a complex variety of exposure scenarios, and cleaning product use is no exception. Exposures may be single events, a series of repeated events, or a continuous exposure to: (a) a single chemical from a single product, (b) a single product containing multiple chemicals, (c) a single chemical in multiple different products, or (d) multiple chemicals from multiple products. Product use and application (e.g., spraying, wiping, or pouring) also affects the overall emission and, therefore, exposure levels of the various chemicals within a product (Saito et al., 2015). For example, chemicals from a cleaning product applied via a spray applicator will be suspended in the air and present in the breathing zone longer than chemicals from other applications (Singer et al., 2006). The air concentration is also impacted by product parameters such as viscosity and delivery properties of the nozzle. Additionally, cleaning product users may inhale product ingredients as vapors, dry product particulates, or liquid aerosols, which affects lung deposition rates. Some of these ingredients may induce toxicological endpoints related to asthma or asthma-like responses, such as respiratory sensitization or irritation, through multiple modes of action (Maier et al., 2014). Furthermore, some chemicals have the potential to induce sensitization following dermal exposure, and subsequent inhalation challenges may result in asthma-like responses (Arts et al., 2008; Maier et al., 2014). For these chemicals, it is important that aggregate exposure from both dermal and inhalation exposures be conducted in an exposure assessment since, in some cases, both pathways may contribute to overall risks of asthma responses.

The primary focus of this effort is to create a set of preferred methods for estimation of systemic and respiratory tract exposure and dose based on differing levels of sophistication that are tailored for cleaning product use scenarios relevant for respiratory tract responses. Thus, this approach can be viewed as a refinement of current cleaning product exposure guidance that is tailored to the exposure pathways most relevant to asthma or bronchial irritation as a health endpoint of interest. We array a suite of methods for application to scenarios that address the unique character of asthma etiology and pathophysiology and exposures to cleaning products. The resulting approach is a tiered assessment framework that provides a margin of safety estimate for cleaning product use and asthma responses (Fig. 1). In arraying the available tools for exposure assessment and dose–response assessment, three possible tiers (or categories) would be identified broadly as (1) empirical data, (2) vetted model estimates, and (3) worse-case estimates from basic physiochemical models. Using a suite of tools arrayed in a tiered approach maximizes the interplay between confidence in the assessment outcome and data availability and assessment resources. The idea of using a tiered safety assessment approach is becoming increasingly formalized in risk assessment protocols (e.g., Meek et al., 2011) and is of particular utility for endpoint specific assessments for which data sets of variable completeness are likely to be encountered.

2. Methods

The three-tiered approach, shown in Fig. 2 was developed for conducting an exposure and hazard characterization assessment for the different scenarios identified for cleaning product use. The tiers start with the gathering of available information, such as direct