Title

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Journal

Applied occupational and environmental hygiene, 20(8)

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Publication Date

2023-08-01

DOI

10.1080/15459624.2023.2221712

Peer reviewed

HHS Public Access

Author manuscript

J Occup Environ Hyg. Author manuscript; available in PMC 2023 December 05.

Published in final edited form as:

J Occup Environ Hyg. 2023 August ; 20(8): 350–363. doi:10.1080/15459624.2023.2221712.

Exposure frequency, intensity, and duration: What we know about work-related asthma risks for healthcare workers from cleaning and disinfection

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Abstract

The objective of this review was to scope the current evidence base related to three exposure assessment concepts: frequency, intensity, and duration (latency) for cleaning and disinfection exposures in healthcare and subsequent work-related asthma risks. A search strategy was developed addressing intersections of four main concepts: (1) work-related asthma; (2) occupation (healthcare workers/nurses); (3) cleaning and disinfection; and (4) exposure. Three databases were searched: Embase, PubMed, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database. Data were extracted related to three main components of risk assessment: (1) exposure frequency, (2) exposure intensity, and (3) exposure duration. Latency data were analyzed using an exponential distribution fit, and extracted concentration data were compared to occupational exposure limits. The final number of included sources from which data were extracted was 133. Latency periods for occupational asthma were exponentially distributed, with a mean waiting time ($1/\lambda$) of 4.55 years. No extracted concentration data were above OELs

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Competing interests

The authors have no competing interests to disclose.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15459624.2023.2221712. AIHA and ACGIH members may also access supplementary material at http://oeh.tandfonline.com.

except for some formaldehyde and glutaraldehyde concentrations. Data from included sources also indicated some evidence for a dose-response relationship regarding increased frequency yielding increased risk, but this relationship is unclear due to potential confounders (differences in role/task and associated exposure) and the healthy worker effect. Data priority needs to include linking concentration data to health outcomes, as most current literature does not include both types of measurements in a single study, leading to uncertainty in dose-response relationships.

Keywords

Chemical; hygiene; inhalation; latency; occupational health; respiratory; review

Introduction

It is estimated that 17% of asthma onset among adults is associated with occupational exposures (NIOSH 2017). Among adults with asthma, the work-exacerbated asthma prevalence may be as high as 58%, with the burden of work-related asthma varying by occupation and industry (NIOSH 2017). Work-related asthma includes adult-onset "occupational asthma" (also referred to as "OA") and work-exacerbated asthma.

The risks of work-related asthma from inhalation of vapors or dermal contact with chemicals used in cleaning and disinfection products have been established through several epidemiologic studies (Mirabelli et al. 2007; Arif et al. 2009; Arif and Delclos 2012; Gonzalez et al. 2014; Patel et al. 2020; Dumas et al. 2021). Dumas et al. (2021) demonstrated a greater incidence of asthma among early- to mid-career U.S. and Canadian nurses for those using high-level disinfectants relative to those who are not. In a European study, an increased risk (RR 4.63, 95% CI: 1.87, 11.5) of reported new-onset asthma was observed for hospital technicians relative to those who had not performed activities that would pose asthma risk (e.g., cleaning, disinfection, nursing, metal working) (Mirabelli et al. 2007).

While multiple occupations can experience an increased risk of work-related asthma due to cleaning and disinfection exposures, exposures in healthcare environments are unique for several reasons: (1) heightened awareness and effort toward cleaning, disinfection, and sterilization efforts to curb healthcare-associated infection risks (Agency for Healthcare Research and Quality 2014); (2) the use of sterilizing agents for equipment (e.g., glutaraldehyde or ortho-phthalaldehyde (OPA) for endoscopes) (Gannon et al. 1995; Fujita et al. 2006); and (3) a wide variety of tasks, roles, and environment types (LeBouf et al. 2014; Quinot et al. 2017; Su et al. 2018) that can lead to highly variable exposures and risks.

Despite evidence that cleaning and disinfection can increase work-related asthma risk for healthcare workers, the exposure-response relationships remain poorly understood. More collective data are needed describing the frequency of cleaning and disinfection, the intensity of exposure to cleaning and disinfection chemicals (e.g., chemical concentrations), and the latency period (defined here as the time from initial occupational exposure to occupational asthma onset, Table 1) for nonirritant induced occupational asthma. These three areas directly relate to the three components of exposure assessment: frequency,

intensity, and duration (related to latency period) (Zartarian et al. 2005; Nicas and Neuhaus 2022).

There is uncertainty about whether the latency period captures time between an initial exposure, alone, and the expected health outcome (occupational asthma) or a duration of continuous exposure that is then followed by occupational asthma onset. In this study, we use the following operational definition: time in role with exposure to cleaning/disinfection product before occupational asthma onset. This theoretically includes cases where only the initial exposure served as the "dose" that triggered the delayed "response" (occupational asthma) or cases where continuous exposures (and therefore multiple doses) resulted in the eventual development of occupational asthma. In this way, latency in this review overlaps with the concept, of "exposure duration," or "the length of time over which continuous or intermittent contacts occur between an agent and a target" (Table 1) (Zartarian et al. 2005). Operational definitions for other terms used throughout can be found in Table 1.

The frequency and intensity of exposures to cleaning/disinfection chemicals for healthcare workers are important because they can inform definitions of "safe" cleaning/disinfection practices that limit work-related asthma risks. While the importance of frequency and intensity is recognized in the literature on work-related asthma among healthcare workers (Arif et al. 2009; LeBouf et al. 2014), the importance of latency period for occupational asthma is not as broadly discussed. Latency periods can occur for both immunological occupational asthma and irritant-induced asthma, especially in cases of several intense or chronic but relatively low exposure levels (Cormier and Lemière 2020; Lemiere et al. 2022) (Table 1). Latency can affect risk perceptions of health outcomes, especially chronic diseases. For example, behavioral economics research has demonstrated that latency affects risk valuation within the context of cancer, (Van Houtven et al. 2008; McDonald et al. 2016) and there is preliminary evidence that latency of occupational asthma may influence the rationale of healthcare workers when considering the tradeoffs between the risk of infection and risk of occupational asthmas associated with cleaning/disinfection (Wilson et al. 2022).

Risk perceptions can affect risk acceptability or acceptability of risk management strategies. A better understanding of latency for immunological asthma can inform educational materials for those with occupational exposures to cleaning and disinfection chemicals and identify where to prioritize monitoring for the development of occupational asthma. Additionally, because latency information can feed into risk-risk tradeoff studies intended to quantify a population's acceptable risk, characterizing distributions of latency periods will advance current capabilities for accurately assessing acceptable risk levels.

Study objective

While data exist describing relationships between exposures during cleaning and disinfection activities for healthcare workers and work-related asthma, collected evidence relating to frequency, intensity, and duration (latency) of exposure to work-related asthma risk is limited. Using an exposure assessment lens to evaluate relationships between exposures during cleaning and disinfection in healthcare and work-related asthma will allow for the development of quantitative exposure guidelines and/or standards to achieve work-related asthma risk thresholds. The objective of this review was to elucidate how

exposure frequency, intensity, and duration (latency) are related to work-related asthma risks for healthcare workers engaging in cleaning and disinfection activities. This objective was addressed by scoping the current evidence base of exposures to cleaning, disinfection, and sterilizing products for healthcare workers. Through this review, environmental measurements and statistical data on exposure-response relationships (e.g., odds ratios, hazard ratios, and relative risks) and latency periods for occupational asthma cases were extracted from published literature and synthesized through description and/or meta-analysis. Strengths and limitations of the current evidence are addressed in the Discussion.

Methods

Key scoping areas

The topics are the three main components of risk assessment: (1) exposure frequency; (2) exposure intensity; and (3) exposure duration (comparable to latency period for latency occupational asthma, or immunological occupational asthma (Table 1)).

Search strategy and concepts

A scoping review was conducted as opposed to a systematic review due to anticipated heterogeneity of collected evidence for which assessing certainty and bias would be highly variable across studies (e.g., direct measurements of volatile organic compounds vs. epidemiological studies focused only on health outcomes and frequency of exposure vs. case studies). While not a systematic review, we utilized a systematic approach scoping review and achieved many of the checklist items for the 2020 PRISMA statement (Page et al. 2021), except checklist items relating to evaluation and reporting study risk of bias, certainty assessments, and review protocol registration. Three databases were searched: Embase, PubMed, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database. The search strategy was developed by using four overall larger concepts to organize related words: (1) work-related asthma; (2) occupation (healthcare workers/nurses); (3) cleaning and disinfection; and (4) exposure. Controlled vocabulary related to these concepts was identified in Emtree for the Embase search, MeSH for the PubMed search, and CINAHL Subject Headings. Keywords were identified using the controlled vocabulary and discussion with coauthors about relevant terms per concept. The final search strategy can be seen in the supplemental materials. Searches were conducted, and results were imported into Rayyan, an open-source tool for conducting systematic literature reviews (Ouzzani et al. 2016), for inclusion/exclusion screening. Duplicates were removed before screening.

Inclusion/exclusion criteria and screening

Sources were screened using Rayyan as an inclusion/exclusion screening tool (supplemental materials), and sources were reviewed by at least two team members. Disagreements were resolved with discussion and senior researcher input. Sources were included if they were written in English or had an English translation and if they included information regarding (1) cleaning and disinfection activities posing asthma risks to healthcare workers, (2) measurements of cleaning/disinfection exposures during cleaning and disinfection in healthcare environments, or (3) asthma among healthcare workers with cleaning and disinfection activities as a potential risk factor. They were excluded if they did not meet

the inclusion criteria and (1) did not relate specifically to asthma or cleaning/disinfection exposures; for example, studies about dermatitis related to latex exposure from gloves would be excluded, or (2) if they merely provided guidance on how to clean/disinfect without information regarding asthma risks. Even though glutaraldehyde use has been discontinued in some countries, sources describing exposures to this chemical were included, as this is one of the most researched chemicals in the healthcare industry with known asthma risks. Sources were not excluded based on article type, such that research abstracts or articles in trade journals were included. The references of included sources were also investigated for sources that may not have been captured by the initial search. These sources were also screened by at least two team members following the same screening process.

Data extraction and analysis

Data were extracted from included papers using a data extraction tool developed by the research team based on the study objective (supplemental materials), where sources were divided amongst researchers who participated in article screening. Before data extraction, practice with several articles and discussion of consistency in data extraction across researchers were qualitatively compared.

Data for latency were only extracted from articles that specified occupational asthma as the outcome. The determination of occupational asthma in reviewed sources was taken at face value, due to such limited data providing latency periods. This is addressed as a limitation in the Discussion. Extracted data were analyzed using R (R Core Team 2021). An exponential distribution was fit to these data because exponential distributions are typically used to represent “interarrival” and waiting times in other contexts (Cho et al. 2017; Lim 2021). Goodness of fit was investigated visually and through three goodness of fit tests (Cramer-Von Mises, Kolmogorov-Smirnov, Anderson-Darling) using the *fit-distrplus* R package, where a rejection of the null hypothesis (the data come from the exponential distribution) indicates lack of fit.

While a survival analysis approach, such as the use of a Cox proportional hazards model, could provide insights regarding the relative contributions of risk factors to occupational asthma onset risk, this approach was not taken due to an anticipated small sample size of latency period data and lack of data needed to account for important factors per individual, such as age, role type, task types, etc. This type of analysis would help account for the healthy worker bias (Picciotto et al. 2013) that likely affects the distribution of latency periods extracted from the literature in this study. We address the need for this as future work in the Discussion.

Airborne chemical concentrations measured in healthcare environments were converted to ppm to make them comparable. For those in units of mg/m^3, conversions to ppm assumed 25 °C and 1 atm. These concentrations were then compared to available occupational exposure limits (OELs): Occupational Safety and Health Administration (OSHA) permissible exposure levels (PELs), Threshold Limit Values (TLVs®) from the American Conference of Governmental Industrial Hygienists (ACGIH®) or recommended exposure levels (RELs) from the National Institute of Occupational Safety and Health

(NIOSH), and “target concentrations” that were not associated with the other threshold types.

Results

Search yields and included works

The initial search was conducted on 19 October 2021, yielding seven hundred ninety-three sources, with the largest count originating from Embase (Figure 1). One-hundred fifty-six sources were removed due to being duplicates. Of the 637 screened sources, 493 were excluded either due to not being able to be found ($n = 4$) or not matching the inclusion criteria ($n = 489$). Upon data extraction, another 17 sources were removed due to not meeting the inclusion criteria after a full reading of the source ($n = 9$) or not having access to the full version of the source ($n = 8$). During the data extraction process, six sources were found that were not previously identified during the literature search. The final number of included sources from which data were extracted was 133.

Exposure duration (latency period)

Overview of sources with data—Thirty-eight percent (51/133) of the sources: (1) described the number of years that a healthcare worker worked in the healthcare industry before asthma onset; (2) described the number of years of working in the healthcare industry and its relationship with asthma rates among participants; or (3) described or mentioned the word “latency.” Key data extracted from latency-related sources are summarized in Table 2 with additional data in supplemental materials.

Years of experience and respiratory symptoms relationship—Greater odds of respiratory symptoms for those with greater years of work experience have been observed in multiple studies (Gonzalez et al. 2014; Patel et al. 2020; Stoeva 2021). These data provide some insights into potential latency durations, but the studies do not have data about the periods or duration of exposure across HCWs’ careers. Owing to the use of different outcomes and categories for years of experience, these data could not be combined into a single meta-analysis and are simply summarized in (Table 2).

In a study of dentists, the most commonly reported (65.7%) cause of respiratory reactions was disinfectants, and greater years of work experience was an identified risk factor, where those with 11–20 years of experience had 1.45 OR (95% CI: 1.13–.86) and those with >20 years of experience had 2.19 (95% CI: 1.78–2.70) greater odds of respiratory symptoms than those with less than five years of experience (Stoeva 2021). Among those who reported respiratory symptoms, the greatest proportions of reported respiratory symptom onset were for 2–5 years after graduation (33.2%, 72/217 of men with respiratory symptoms) and 6–10 years after graduation (18.6%, 140/752 of women) (Stoeva 2021). In a study of certified nursing assistants (CNAs), those with 17–26 years at the job had 2.83 (95% CI: 1.24, 6.48) greater odds of bronchial hyper responsiveness (BHR) symptoms than those with 0–9 years at the job (Patel et al. 2020). However, those with 10–16 years (OR: 1.97, 95% CI: 0.81, 4.84) and with 27 or more years of experience (OR 2.19, 95% CI: 0.86, 5.55) did not have statistically significantly higher odds of BHR symptoms relative to those with 0–9 years at

the job (Patel et al. 2020). Age, as a continuous variable, did not statistically significantly increase BHR odds (OR: 1.01, 95% CI: 0.99, 1.03), but did increase the odds for new-onset asthma (OR: 1.04, 95% CI: 1.01, 1.08) (Patel et al. 2020). Although Patel et al. (2020) also investigated risk factors for new-onset asthma, the number of years on the job was not included due to a low number of new-onset asthma cases ($n = 11$) (Patel et al. 2020).

In a study of nurses, auxiliary nurses, cleaners, and administrative staff, there were not statistically significantly increased odds of physician-diagnosed asthma, new-onset asthma, or nasal symptoms at work among those with 10–19 or 20+ years of experience relative to those with 0-9 years (Gonzalez et al. 2014). Those who had worked 10–19 in healthcare had decreased odds (0.07, 95% CI: 0.01, 0.52) of new-onset asthma relative to those with 0–9 years of experience, where this inverse relationship may be due to the healthy worker effect, a limitation acknowledged by the authors (Gonzalez et al. 2014).

Latency periods for occupational asthma and chemicals—The sources that included durations of exposure before occupational asthma reported durations that spanned the orders of weeks to years (Figure 2). Data described glutaraldehyde exposures for nurses in endoscopy (Gannon et al. 1995) or exposures to peracetic acid, chloramines, quaternary ammonium compounds, or unspecified chemicals for HCWs in a variety of environments (Walters et al. 2017). Upon request, Walters provided raw data from their study (Walters et al. 2017), including latency data and job roles for 36 participants in healthcare who used a cleaning/disinfection agent (Table S1). These data were combined with other data extracted from the literature. Latency periods with a value of zero were removed (i.e., some values from the Walters data set where zero indicated <1 month). The exponential distribution fit to the pooled data was not rejected by three out of the three tests. A comparison of this distribution to the data can be seen in Figure 2, and the distribution parameter fit yielded a rate (λ) of 0.22, which gives a mean waiting time until occupational asthma onset of 4.55 years ($1/\lambda$).

Other data were extracted from sources that described the time from initial exposure to onset of other asthma-related outcomes, including unspecified asthma symptoms (Massachusetts Department of Public Health 2001; Adisesh et al. 2011), hospitalization (Chen et al. 2019), chest tightness (Corrado et al. 1986; Cristofari-Marquand et al. 2007), rhinorrhea (Cristofari-Marquand et al. 2007), rhinitis (Corrado et al. 1986), conjunctivitis (Cristofari-Marquand et al. 2007), lower respiratory tract symptoms (Vyas 2000), and nasal symptoms (Corrado et al. 1986), with times ranging from 0.04–14 years (Corrado et al. 1986; Adisesh et al. 2011). This full data set is available in supplemental materials (Table S2); pooled analyses were not performed owing to the variety of outcomes.

Exposure intensity and frequency

Overview of sources with data—Sixty-three percent (84/133) of sources provided information on the frequency of cleaning/disinfection, concentrations of exposures (including in animal studies), information on relationships between frequency or concentration of exposure and an asthma-related outcome, and/or included the term “dose-response.”

Exposure intensity—Concentration data were extracted from fifteen sources (Jachuck et al. 1989; Binding and Witting 1990; Campbell and Cripps 1991; Leinster et al. 1993; Gannon et al. 1995; Vyas 2000, 2001; Fujita et al. 2006; Nayebzadeh 2007; LeBouf et al. 2014; Chen et al. 2015; Hawley et al. 2017; Vincent 2017; Su et al. 2018; Mwanga and Jeebhay 2020) representing a variety of occupation types and/or types of healthcare facilities (LeBouf et al. 2014; Hawley et al. 2017; Su et al. 2018). Represented facility types included operating rooms (Binding and Witting 1990; Hawley et al. 2017; Su et al. 2018), women's care and birth center (WCBC) (Hawley et al. 2017), WCBC triage, WCBC OR, acute and postpartum, medical/surgical, surgery/orthopedics, ICU, oncology, NICU, outpatient clinic, public BR, float, and floors (LeBouf et al. 2014; Hawley et al. 2017), where most of the sources that included concentration data were of studies conducted in endoscopy units (Jachuck et al. 1989; Campbell and Cripps 1991; Leinster et al. 1993; Gannon et al. 1995; Vyas 2000, 2001; Fujita et al. 2006; Nayebzadeh 2007; LeBouf et al. 2014; Su et al. 2018). Represented health-care roles included clinical laboratory technician, nursing assistant, central supply worker, operating room technician, dental assistant or laboratory technician, endoscopy technician, floor stripper/waxer, housekeeper or environmental services personnel, licensed practical nurse, medical appliance technician, medical equipment preparer, pharmacist/pharmacy technician, registered nurse, respiratory therapist, and surgical technologist (LeBouf et al. 2014; Su et al. 2018; Caridi et al. 2019). Some compared concentrations of chemicals (e.g., glutaraldehyde) across different ventilation conditions (Vyas 2000), work practices (Nayebzadeh 2007), or different areas within the same unit (e.g., near a bench in a hallway in an endoscopy unit vs. a personal sample from a nurse (Jachuck et al. 1989) or near an endoscopy disinfection bucket vs. another point in the endoscopy room (Fujita et al. 2006)).

Measurements were found for the following chemicals: 2-propanol (Su et al. 2018); acetic acid (Hawley et al. 2017); acetone (Su et al. 2018); α-Pinene (Su et al. 2018); benzene (LeBouf et al. 2014); chloroform (Su et al. 2018); *d*-Limonene (Su et al. 2018); didecyl-dimethylammonium chloride (DDAC) (Vincent et al. 2007); ethanol (Su et al. 2018); ethylbenzene (LeBouf et al. 2014); formaldehyde (Binding and Witting 1990; Vyas 2000); glutaraldehyde (Jachuck et al. 1989; Binding and Witting 1990; Campbell and Cripps 1991; Leinster et al. 1993; Gannon et al. 1995; Vyas 2000, 2001; Nayebzadeh 2007); hydrogen peroxide (Hawley et al. 2017); *m*, *p*-xylene (LeBouf et al. 2014); *o*-xylene (LeBouf et al. 2014); ortho-phthalaldehyde (OPA) (Fujita et al. 2006; Chen et al. 2015; Mwanga and Jeebhay 2020); peracetic acid (Hawley et al. 2017); succinaldehyde (Vyas 2000); and toluene (LeBouf et al. 2014). Some studies overlapped in measurements and study design (LeBouf et al. 2014; Hawley et al. 2017; Su et al. 2018; Caridi et al. 2019), where different analyses were conducted. In this case, data were checked so that they were only recorded once for data analysis (Figure 3).

Among sources that provide measured concentrations, measured concentrations were below OELs, except for formaldehyde and glutaraldehyde (Figure 3). One of the measurements from Vyas (Vyas 2000) (0.02 ppm) and all measurements from Binding and Witting (1990) (Binding and Witting 1990) (0.18, 0.23, and 0.43 ppm) were above the formaldehyde REL (0.016 ppm). Concentrations of glutaraldehyde above the TLV (0.05 ppm) were measured in

3 studies (Jachuck et al. 1989; Campbell and Cripps 1991; Nayebzadeh 2007) and ranged from 0.051 to 0.17 ppm. No measured glutaraldehyde concentrations were above the REL (0.20 ppm).

Exposure frequency—How the frequency of cleaning was measured varied. Studies used: (1) several exposures to different chemicals or allergens experienced at least once a month for a period of 6 months or longer (Arif and Delclos 2012); (2) whether a product was used at least once in some given period (e.g., weekly use of sprays or daily disinfection activities) (Cristofari-Marquand et al. 2007; Arif and Delclos 2012; Dumas et al. 2019); or (3) implemented job exposure matrices (JEMs) (Arif et al. 2009; Delclos et al. 2009; Quinot et al. 2017). A JEM utilized in multiple studies included combinations of jobs and practices and five main classes of exposure, where one of these was the use of cleaning products or disinfectants (Delclos et al. 2007; Arif et al. 2009; Delclos et al. 2009). Experts used these JEMs to assign a code, where a larger code translates to a probability of most workers being "occupationally exposed at least once per week" (Delclos et al. 2007).

While this JEM includes other exposures related to asthma (e.g., latex glove use) (Delclos et al. 2007; Arif et al. 2009; Delclos et al. 2009), others have used JEMs devoted solely to cleaning and disinfection exposures (Quinot et al. 2017). Quinot et al. (2017) compared a JEM to a job-task exposure matrix (JTEM), where a job-task axis was introduced with combinations of types of nursing and types of cleaning tasks. This JTEM combined a category of frequency (number of days per week) with a category of "intensity" (hours/day). However, note that this measure of "intensity" may be more closely related to the operational definition of exposure duration used in this study, which was not a concentration but rather several exposure events over a given period (Table 1). The comparison of the JEM and JTEM elucidated that the inclusion of task type in JEMs may increase their accuracy (Quinot et al. 2017). This JTEM has been applied in research on asthma control among nurses exposed to disinfectants (Dumas et al. 2017).

Relationship between frequency and outcome—Information on relationships between frequency (either in increasing levels or as a binary exposure) of cleaning/disinfection and outcomes were available for asthma (Dimich-Ward et al. 2004; Gonzalez et al. 2014; Dumas et al. 2020, 2021), work-related asthma (Arif and Delclos 2012), post-hire asthma (Caridi et al. 2019), occupational asthma (Arif and Delclos 2012), new-onset asthma (Gonzalez et al. 2014), current asthma (women, specifically) (Dumas et al. 2012), current asthma (men, specifically) (Dumas et al. 2012), current asthma (no gender specified) (Caridi et al. 2019), asthma symptom score (Caridi et al. 2019), asthma control test (ACT) score (Dumas et al. 2017), asthma attack (Dimich-Ward et al. 2004), BHR (Arif et al. 2009; Caridi et al. 2019), asthma exacerbation (Arif and Delclos 2012; Caridi et al. 2019), and symptoms (e.g., chest tightness, usual cough, wheezing, nasal symptoms) (Dimich-Ward et al. 2004; Gonzalez et al. 2014; Lee et al. 2014; Caridi et al. 2019). While there is potential overlap in these definitions (post-hire asthma or new-onset asthma could overlap with occupational asthma if caused by exposures in the workplace, for example, Table 1), these categories were not combined due to uncertainty in their interchangeability. One source described relationships between cleaning and disinfection exposures and COPD (Dumas et al. 2019),

but these data were not included in this review as they did not focus on risks for asthma. However, it is acknowledged that COPD and asthma can co-occur in some individuals, known as asthma-COPD Overlap Syndrome (ACOS) (Leung and Sin 2017).

Most studies that included odds ratios, risk ratios, or hazard ratios described exposure as a binary variable (e.g., “weekly use of sprays” or “weekly use of disinfectant to clean surfaces”) (Dumas et al. 2017) as opposed to including levels of frequency (Figures S1-S7). Arif and Delclos (2012), however, included levels of exposure (e.g., disinfectants/sterilants and levels of “more than once a day,” “every day,” “at least once a week”) and several exposures, related to having been in contact with a given material at least once a month for a period of 6 months or longer. Adjusted ORs increased as the number of exposures increased for work-related asthma (0–2 exposures as the reference group; 3–5 exposures: 1.66, 95% CI: 0.40, 6.83; 6 or more exposures: 4.45, 95% CI: 1.25, 15.86). However, this did not hold for work-exacerbated asthma or occupational asthma, individually, where the adjusted OR of work-exacerbated asthma (0.51, 95% CI: 0.07, 3.74) was smaller relative to 0–2 exposures (Arif and Delclos 2012). The adjusted OR of occupational asthma for those with 6 or more exposures (1.09, 95% CI: 0.22, 5.48) was less than for those with 3-5 exposures (1.25, 95% CI: 0.18, 8.84) relative to those with 0–2 exposures (Arif and Delclos 2012). The fact that 6 or more exposures posed lesser odds than 3–5 exposures could indicate a healthy worker effect or confounding by task/role type or other differences among workers with 6 or more exposures vs. 3–5. Dumas et al. (2019) demonstrated a dose-response relationship, where increased frequency relative to the “never” frequency category resulted in a greater adjusted hazard ratio (AHR) of COPD, using frequency levels of <1 day per week, 1–3 days per week, and 4–7 days per week (Dumas et al. 2019). These HRs were calculated for use of any disinfectant, use of sprays, cleaning surfaces, and cleaning instruments, separately. For the use of any disinfectants and the use of disinfectants to clean instruments, a frequency of 4–7 days per week resulted in significant AHRs (any disinfectant: 1.43, 95% CI: 1.13–1.80; disinfectant to clean instruments: 1.37, 95% CI: 1.09–1.72) (Dumas et al. 2019).

Discussion

Latency – is it “exposure duration”?

The range of latency periods for occupational asthma in healthcare settings extracted from the literature varied greatly (Figure 2), from 0.08 to 21 years (median = 3 years), following an exponential distribution. While the operational definition of exposure duration here is “the length of time over which continuous or intermittent contacts occur between an agent and a target,” (Zartarian et al. 2005) there is a disconnection between this concept and exposure frequency (“the number of exposure events in an exposure duration”) in work-related asthma literature for healthcare worker exposures to cleaning and disinfection products. For example, while there may be data on the number of exposure events over the course of a week (Cristofari-Marquand et al. 2007; Arif and Delclos 2012; Dumas et al. 2019), this does not capture exposures over the total latency period, or the total number of exposures over the course of an entire career in the industry.

More data are needed linking the frequency of exposure events on the scale of years and how this relates to the latency period for immunological occupational asthma. Analyzing

time-to-event for occupational asthma onset may provide insights regarding the relative contributions of task type, chemical type, demographics, and other factors that could contribute to the risk of asthma onset. Latency period data available in the literature are currently sparse in comparison to data regarding exposure frequency or intensity. Latency data with the intensity of exposure, even indicated categorically using job-exposure-matrices (JEMs) or job-task-exposure-matrices (JTEMs), could provide semi-quantitative exposure-response insights.

Exposure intensity

There are data describing concentrations of cleaning/-disinfection or sterilizing chemicals in healthcare environments, but there is a lack of data linking these concentrations to health outcomes. Therefore, while some of the measured concentrations in Figure 3 are below limits or thresholds, it is unknown whether these concentrations pose work-related asthma risks or not. More quantitative exposure assessment data are needed in epidemiological studies to describe relationships between exposure intensity and frequency of work-related asthma outcomes.

Exposure frequency

There is some evidence that increased frequency of cleaning/disinfection may increase risks of work-related asthma (Arif and Delclos 2012) and COPD (Dumas et al. 2019). However, frequencies of exposure can be difficult to quantify accurately, due to recall bias and ambiguity or inconsistencies in definitions of a single “exposure event” (Table 1). While our operational definition of “exposure event” is “the occurrence of continuous contact between an agent and a target,” (Table 1) defining continuous contact with exposure intensity measurements can be difficult, costly, and time intensive. The use of JEMs to categorize low, medium, and high exposure levels may therefore be useful, and these have been applied in epidemiologic studies of healthcare workers and exposures to cleaning and disinfection products (Delclos et al. 2009; Quinot et al. 2017). However, cleaning protocols may vary across facilities, making comparisons and generalizability of findings across studies uncertain. Whether low, medium, and high exposure levels as determined by JEMs or JETMs result in concentrations above or below specific thresholds is unknown and may be study- or site-specific. This limits the ability of these studies to influence OELs unless they can be linked to a range or order of magnitude of exposure.

Limitations

One of the limitations of this study was a focus on healthcare workers, alone, as opposed to including all literature relating to cleaning/disinfection product exposure and asthma outcomes. However, this approach was taken due to the unique exposures (e.g., glutaraldehyde in endoscopy units) (Corrado et al. 1986; Jachuck et al. 1989; Gannon et al. 1995) and unique culture (i.e., strong emphasis on cleaning and disinfection to protect patient health) (Agency for Healthcare Research and Quality 2014) of this population. Increasing the scope of the review would have likely led to larger data sets for analyses of latency period and concentrations relative to OELs, but this would increase challenges in

addressing generalizability, as task and environment are large contributors to variability in exposure intensity and frequency (LeBouf et al. 2014; Quinot et al. 2017).

Another limitation is the data themselves, as they are not recent in some cases. Exposures to glutaraldehyde measured 34 years ago (Jachuck et al. 1989) may not be relevant to the magnitude of exposures or the chemical used in many endoscopy units today (Figure 3). Additionally, due to such few sources including information on latency for occupational asthma cases, the determination of occupational asthma was taken at face value as opposed to using minimum diagnostic requirements. In this case, there is likely increased sensitivity at the cost of specificity, and more recent research is needed to evaluate distributions of observed latency periods for more consistently diagnosed occupational asthma cases. These limitations emphasize the need for more research to relate consistently defined work-related asthma outcomes to exposure assessment research on cleaning and disinfection exposures for healthcare workers, where exposure intensity, frequency, and duration data are collected.

Conclusions

An exposure assessment lens (i.e., a focus on frequency, intensity, and duration (latency)) was used to scope current literature related to exposures during cleaning and disinfection for healthcare workers and associated work-related asthma. The study results highlight that much of the current evidence relating exposures to cleaning and disinfection products for healthcare workers to work-related asthma lacks either quantitative exposure information or does not relate health outcomes to quantitatively measured exposures. There are uncertainties and inconsistencies in how exposure intensity and frequency are defined and measured. While there is evidence that increased frequency is linked to an increased risk of work-related asthma outcomes, the intensity of individual exposure events and whether increased exposure always means increased risk (assumed monotonic relationship) is uncertain. Systematic incorporation of exposure assessment principles in studies of asthma and cleaning and disinfection exposures in healthcare is needed to inform our understanding of exposure-response relationships. One key finding, however, is that latency periods for occupational asthma (comparable to the exposure assessment concept, “duration,”) are likely exponentially distributed, with a median period of multiple years. However, more data are needed to understand how demographic variables; and task, role, and chemical type vary this distribution. Characterizing contributions of latency to risk will inform work-related asthma monitoring efforts and risk perception research that has the potential for connecting exposure intensity, frequency, and duration to probabilities of work-related asthma outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Gareth Walters for providing data for the meta-analysis related to latencies. The authors have no competing interests to disclose. AM Wilson, LB Gerald, and PI Beamer are members of the Southwest Environmental Health Sciences Center (NIEHS P30 ES006694).

Funding

AM Wilson and was supported by a University of Arizona Health Sciences Career Development Award.

Data availability statement

Code and data for the analysis are available at https://github.com/awilson12/scoping_review via a Creative Commons license. Other data are available in the supplemental materials and from the corresponding author by reasonable request.

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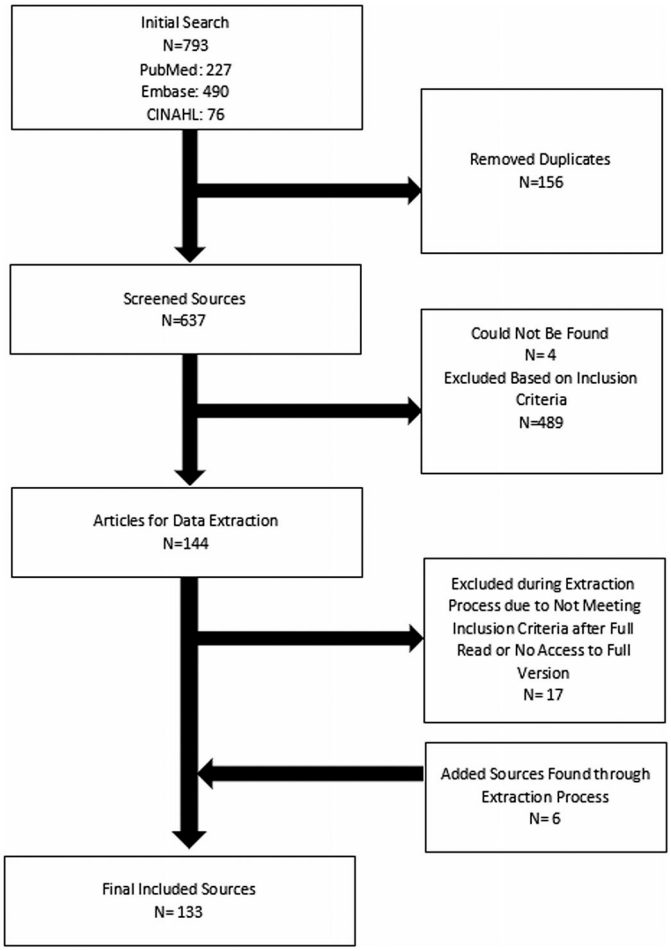

Figure 1.
Inclusion tree of screened sources.

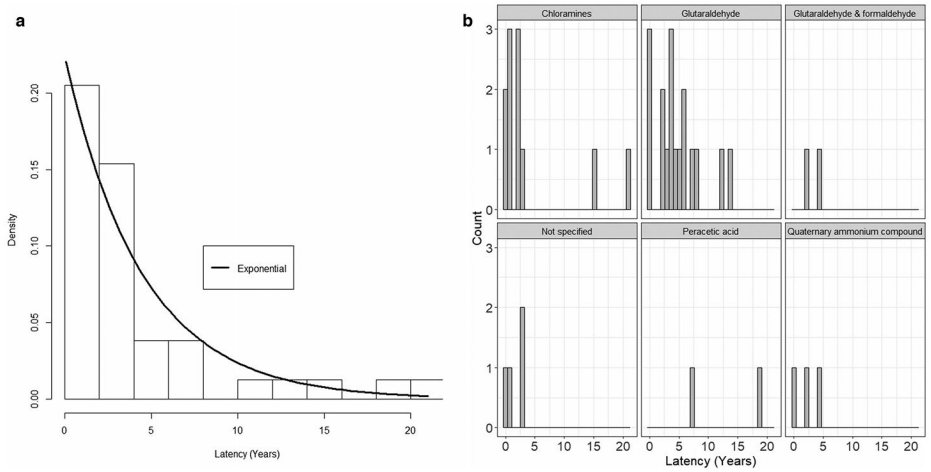

Figure 2.

Latency distributions (A) with exponential distribution fit and (B) all extracted data and stratified by chemical type.

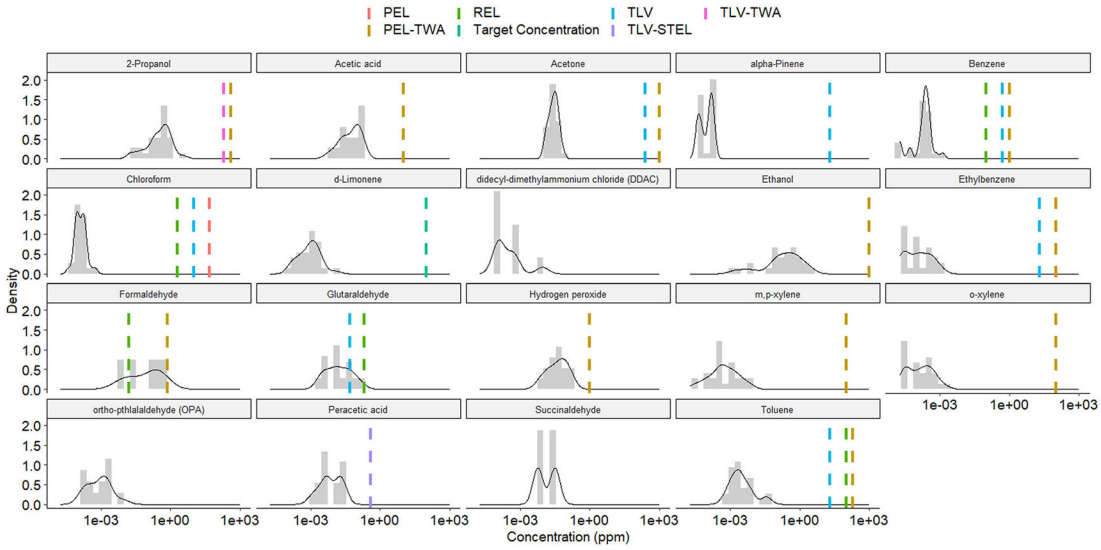

Figure 3.
Concentrations measured in healthcare environments in comparison to threshold values.

Table 1.

Operational definitions.

Term	Operational Definition	Source
Asthma	A chronic disease involving inflammation of the lung airways, resulting in narrowing of the airways, tightening of muscles around the airways, and/or increased mucus production	(Hashmi et al. 2022)
Work-related asthma	Encompasses occupational asthma or work-exacerbated asthma (see definitions below)	(Friedman-Jimenez et al. 2015)
Occupational asthma	Asthma that onsets due to exposures in the work environment and not due to exposures outside the work environment	(Vandenplas and Malo 2003)
Respiratory symptoms consistent with asthma	Wheezing, shortness of breath, frequent cough, chest tightness, bronchial hyperresponsiveness (BHR)	(Borak and Lefkowitz 2016)
Irritant induced asthma	Nonimmunological occupational asthma that onsets after one (RADS) or more “high-level irritant exposure(s)”; may have a latency period, especially in cases of multiple and intense or chronic but low exposure events	(Vandenplas and Malo 2003; Cormier and Lemière 2020; Lemiere et al. 2022)
Reactive airways dysfunction syndrome (RADS) or acute irritant-induced asthma	Immediate onset of symptoms related to asthma after a single “high-level” occupational exposure to an irritating vapor, fume, or gas	(Vandenplas and Malo 2003)
Occupational asthma with latency	Asthma that onsets after some duration (latency period) following a work exposure, typically an immunological occupational asthma but may also be irritant-induced asthma (see definition above)	(Vandenplas and Malo 2003; Cormier and Lemière 2020; Lemiere et al. 2022)
Occupational asthma without latency (IIA and RADS)	Asthma that onsets immediately after exposure, a nonimmuological occupational asthma	(Vandenplas and Malo 2003)
Work-exacerbated asthma (also known as work aggravated asthma)	Asthma that is already present before occupational exposures and is exacerbated by occupational exposures	(Vandenplas and Malo 2003)
Latency period	Time from initial occupational exposure to symptom development	(Friedman-Jiménez et al. 2000)
Exposure duration	The length of time over which continuous or intermittent contacts occur between an agent and a target	(Zartarian et al. 2005)
Exposure frequency	The number of exposure events in an exposure duration	(Zartarian et al. 2005)
Exposure event	The occurrence of continuous contact between an agent and a target	(Zartarian et al. 2005)
Exposure intensity	Relating to the magnitude (concentration) of the exposure	(Nicas and Neuhaus 2022)

Table 2.

Extracted latency data, including relationships between years of work experience and respiratory symptoms and latency data per healthcare worker role, outcome, and chemical.

Evidence for Years of Work Experience and Respiratory Symptoms

Source	Healthcare Worker Role	Outcome	Reference Group Years Experience	Years Experience Category	Odds (95% CI)
(Stoeva 2021)	Dentists	Respiratory reactions	<5	11-20	1.45 (1.13–1.86)
				>20	2.19 (1.78–2.70)
(Patel et al. 2020)	Certified nursing assistants (CNAs)	BHR	0-9	10-16	1.97 (0.81, 4.84)
				17-26	2.83 (1.24, 6.48)
(Gonzalez et al. 2014)	Nurses, auxiliary nurses, cleaners, administrative staff, and those in other roles	Physician-diagnosed asthma	0–9	10–19	1.34 (0.68, 2.62)
				>20	0.87 (0.45, 1.68)
		New-onset asthma	0–9	10–19	0.07 (0.01, 0.52)
				10–19	0.88 (0.35, 2.16)
		Nasal symptoms at work	0–9	10–19	0.84 (0.54, 1.31)
				>20	0.78 (0.52, 1.16)

Latency Data

Source	Healthcare Worker Role	Years Before Outcome	Outcome	Chemical
(Chen et al. 2019)	Regional hospital nurse	3	Hospitalization with severe asthma	Denatonium benzoate
(Cristofari-Marquand et al. 2007)	Auxiliary nurse	2.5	Chest tightness, rhinorrhea, conjunctivitis	Peracetic acid-hydrogen peroxide
	Anesthetist nurse in endoscopy unit	0.42	Rhinorrhea, conjunctivitis and dry cough without wheezing	Peracetic acid-hydrogen peroxide
(Vyas 2000)	Endoscopy nurse	0.257	Lower respiratory tract work-related symptom	Glutaraldehyde and/or succinaldehyde-formaldehyde
Massachusetts Department of Public Health 2001)	Dental hygienist	1	Asthma symptoms	Sterilizing solution and glutaraldehyde
(Corrado et al. 1986)	Endoscopy nurse	0.04	severe nasal symptoms, increasing chest tightness	Alkaline glutaraldehyde
		0.25	Asthma episodes and perennial rhinitis	Alkaline glutaraldehyde
		0.04	Asthma and rhinitis	Not specified
(Stenton et al. 1994)	Endoscopy nurse	4	Asthma-like symptoms (unclear diagnosis)	Glutaraldehyde

Evidence for Years of Work Experience and Respiratory Symptoms

Source	Healthcare Worker Role	Outcome	Reference Group Years Experience	Years Experience Category	Odds (95% CI)
(Gannon et al. 1995)	Endoscopy nurse	4	Occupational asthma	Glutaraldehyde and formaldehyde	
	Endoscopy nurse	7		Glutaraldehyde	
	Endoscopy nurse	6		Glutaraldehyde	
	ENT nurse	4		Glutaraldehyde	
	Theatre nurse	2		Glutaraldehyde and formaldehyde	
(Walters et al. 2017) *	Variety of healthcare roles	4.18 (mean for $n = 36$)		Variety of chemicals (not specified)	
(Di Stefano et al. 1999)	Healthcare worker (role not specified)	6.7		Glutaraldehyde	
(Adisesh et al. 2011)	Sterile services department technician	14	Asthma symptoms	Enzyme products	
(Fujita et al. 2006)	Endoscopy nurse	0.75	Dyspnea and dry cough	Ortho-pthalaldehyde (OPA)	
(Quirce et al. 1999)	Nurse in renal dialysis unit	10	Chest tightness and shortness of breath	Formalin	
	Nurse in renal dialysis unit	4	Eye irritation, irritation of the upper respiratory tract, dyspnea on exertion, dry cough, episodic attacks of wheezing	Glutaraldehyde	
(Hendrick and Lane 1977)	Nurse in dialysis unit	0.25	Dry cough and wheezing attacks	Formalin	
	Nurse in dialysis unit	0.5	Wheezing attacks		
	Technician in dialysis unit	2	Redness and watering eyes, bronchitis attacks		
(Copeland sand Nugent 2015)	Endoscopy nurse	1	Chronic and persistent cough, shortness of breath	Glutaraldehyde	

* Data by individual from the Walters et al. (2017) data set are available in supplemental materials. BHR = bronchial hyperreactivity.