

# PROTOCOL FOR SYSTEMATIC EVIDENCE MAP OF BIOCIDES AND POTENTIAL RESPIRATORY HEALTH OUTCOMES

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### **BACKGROUND AND SIGNIFICANCE**

### Background

Biocides are commercial products used to kill or control the spread of harmful organisms by biological or chemical means. Biocides represent a broad range of products and uses including disinfectants, preservatives, antiseptics, pesticides, herbicides, fungicides, and insecticides.

Publications suggest work-related asthma and other respiratory illness may be associated with exposure to hard surface cleaning agents and disinfectants – collectively called biocides. Reports of work-related asthma symptoms with exposure to biocides have increased since the early 2000s. Respiratory illness has been reported in several occupations with high use of biocides including janitors, housekeepers, nurses, and health technicians.

#### Nomination

In May 2017, biocides were nominated to NTP by the EPA Office of Pesticide Programs (OPP) Antimicrobials Division for possible evaluation of the evidence for respiratory outcomes from occupational exposure to biocides commonly used for disinfection in occupational settings.

#### Scoping and Problem Formulation

The nomination was refined with EPA to focus on 10 major antimicrobial agents commonly used for disinfection in hospitals. EPA requested a scoping review to systematically collect and categorize the literature to develop an evidence map by biocide, respiratory health effect and type of evidence that can be used to identify areas of consistency as well as data gaps in the available literature.

### Significance

The U.S. Environmental Protection Agency (EPA) requested that NTP develop a scoping review of the scientific literature for evidence of respiratory illness from occupational exposure to biocides, with a specific focus on disinfectants used as hard surface cleaning agents. The identification and categorization of respiratory effects in studies of biocides is directly relevant to OPP at U.S. EPA to support decision making for an upcoming biocide assessment (U.S. EPA 2012). Rather than summarizing the literature, the output of this review will be to provide evidence tables or maps to support decision making regarding extent of evidence and data gaps.

### **OBJECTIVE AND SPECIFIC AIMS**

### Objective

The primary objective of this scoping review is to identify and characterize the literature relevant to respiratory effects (e.g., asthma, sensitization and irritation) from inhalation exposure to select biocides used as hard surface disinfectants. Evidence tables or maps will be developed to allow researchers to examine the literature collectively and by individual biocide, major respiratory effect categories, and evidence stream.

### **Specific Aims**

- Identify literature reporting respiratory effects (e.g., asthma, sensitization and irritation) from inhalation exposure to 10 major antimicrobial agents commonly used for hard surface disinfection in hospitals.
- Categorize data on the emerging evidence for respiratory effects (e.g., asthma, sensitization and irritation) from inhalation exposure to biocides.
- Create evidence tables or maps of relevant health effects data by exposure to hard-surface disinfectants.

### **PECO Statement**

A PECO statement (<u>P</u>opulation, <u>E</u>xposure(s), <u>C</u>omparator(s), and <u>O</u>utcome(s)) (<u>Table 1</u>) was developed to address and understand the potential effects of biocides on potential respiratory health effects reported in humans, animals, and *in* vitro model systems (<u>Table 1</u>). The PECO statement is used to help develop the specific research questions, search terms, and inclusion/exclusion criteria for the systematic review (Higgins and Green 2011).

Table 1. PECO (Population, Exposure, Comparator and Outcome) Statement	
Element	Evidence
Population	Human: All epidemiological studies
<u></u>	Animal: Experimental studies in non-human animals (restricted to mammals only.)
<u>E</u> xposure	Exposure to biocides based on administered dose or concentration, biomonitoring data (e.g., urine, blood, other specimens), environmental measures (e.g., air, water levels), or job title. Exposure route must be inhalation. Do not include ingestion or dermal exposures. Relevant biocides include: Alkyl dimethyl benzyl ammonium chloride Sodium Hypochlorite Trichloro-s-triazinetrione Chlorine Dioxide 1-Decanaminium, N-decyl-N, N-dimethyl chloride Hydrogen Peroxide Otho Phenyl Phenol Peracetic Acid p-chloro-m-cresol Poly (hexamethylene biguanide) hydrochloride
<u>C</u> omparators	Both experimental (controlled exposure or treatment) and observational studies should be included. Experimental studies should include an untreated or vehicle control.
<u>O</u> utcomes	Respiratory health- effects

### **METHODS**

The systematic review techniques in the protocol adhere to the framework developed by the Office of Health Assessment and Translation (OHAT) (Rooney *et al.* 2014). The OHAT systematic review framework consists of a 7-step process, and the first 3 are relevant to produce a scoping review to develop evidence tables; whereas the last 4 are relevant for assessing study quality and synthesizing evidence. Therefore, this protocol is restricted to the first 3 steps: 1) Problem Formulation, 2) Search and Select Studies for Inclusion, and 3) Data Extraction.

### **Step 1. Problem Formulation**

In May 2017, biocides were nominated to NTP by the EPA Office of Pesticide Programs (OPP) Antimicrobials Division for possible evaluation of the evidence for respiratory outcomes from occupational exposure to biocides commonly used for disinfection in occupational settings.

Given the public health and economic importance of hospital disinfectants/sanitizers, EPA/OPP plans to collaborate with NIEHS/NTP on developing evidence tables of available epidemiology, mammalian toxicity, and exposure studies available in the open literature for antimicrobial pesticides that act as potential inhalation irritants from products applied in health care settings. The information obtained from this literature review will be used to support the risk assessments developed during EPA's registration review process.

The nomination was refined with EPA (from May 2017 through Feb 2018) to focus on 10 major antimicrobial agents commonly used for disinfection in hospitals. EPA requested a scoping review to systematically collect and categorize the literature into evidence tables organized by biocide, respiratory health effect and type of evidence that can be used to identify areas of consistency as well as data gaps in the available literature.

Problem formulation focused on the goal of clarifying the types of data that would be most useful to EPA and outlining the plan to systematically collect and categorize the evidence of the key biocides related to respiratory health effects, types of evidence, and gaps in research.

#### **Chemical Selection**

Ten chemicals will be considered relevant biocide exposures:

- Alkyl dimethyl benzyl ammonium chloride
- Sodium Hypochlorite
- Trichloro-s-triazinetrione
- Chlorine Dioxide
- 1-Decanaminium, N-decyl-N, N-dimethyl chloride
- Hydrogen Peroxide
- Otho Phenyl Phenol
- Peracetic Acid
- p-chloro-m-cresol
- Poly (hexamethylene biguanide) hydrochloride

### Step 2. Search and Select Studies for Inclusion

### Literature Search Strategy

A literature search strategy was developed by an informationist familiar with systematic review methodologies to identify relevant published evidence on biocides and respiratory effects. The literature search strategy was designed using (1) the 10 biocides identified by EPA + Quaternary ammonium compound MeSH term (non-expanding), and (2) terms related to specific respiratory health outcomes (full details of the search strategy are presented in Appendix 1). A test set of relevant studies used to ensure that the developed search terms retrieved 100% of the test set. Search will be conducted in 3 databases, PubMed, Web of Science and Scopus with no publication year or language limits imposed.

#### **Screening Process**

The references identified by the literature search will be assembled in an Endnote library (Thomson Reuters, New York) and screened at both the title/abstract level for relevance, and full text level to confirm relevance. During full text screening, included references will also be characterized by: language type (e.g., English language, non-English language), publication type, evidence stream, exposure and category of respiratory health outcomes.

In order to be eligible for inclusion references must satisfy the criteria specified by the PECO statement **Table 1.** In addition to the PECO criteria, a reference will be excluded if the reference does not contain original data (e.g., reviews, editorials, or commentaries); or if a reference was not peer-reviewed (e.g., conference abstracts, technical reports, theses/dissertations, working papers from research groups or committees, and white papers). There are no limitations on the publication year or language of the article. The inclusion and exclusion criteria used to screen references for relevance and eligibility at both the title-and-abstract and full-text screening stages are summarized in Table 2.

References will be screened for relevancy using either Swift Active Screener (Sciome, Research Triangle Park, NC) or DistillerSR<sup>®</sup> (Evidence Partners, Ottawa, CA)<sup>1</sup>. Title and abstract screening with these software approaches use machine-learning and text-mining technology to prioritize the unscreened references in order of most relevant to least relevant based on the results of screened references. All references identified as potentially relevant at title and abstract will be confirmed at full text by an additional screening with structured forms and a searchable database of screening results.

#### Title/Abstract Review

Screening at the title and abstract level of studies from the literature search will be conducted such that two members of the evaluation design team will independently screen each reference to determine whether a reference meets the inclusion criteria. Screening will be conducted until the software predicts 95% of relevant references have been identified. References will be identified as either "yes, relevant or potentially relevant (e.g., unclear)" or "no, not relevant" at the title and abstract level. All relevant reviews will be included at the title and abstract screening. Screeners will be trained using project-specific instructions in a pilot phase undertaken to improve clarity of the inclusion and exclusion instructions and to improve accuracy and consistency among screeners. Screening conflicts will be resolved by the project lead (Walker). Any article with an unresolved screening conflict or that is unclear at the title and abstract phase will be included and reviewed in the full text screening phase.

<sup>&</sup>lt;sup>1</sup> DistillerSR<sup>®</sup> (http://systematic-review.net/) is a proprietary project management tool for tracking studies through the screening process and storing data extracted from these studies using user-customized forms.

Table 2. Detailed inclusion and exclusion criteria to determine study eligibility		
Evidence stream	Inclusion Criteria	Exclusion Criteria (or blank if none)
Participants/Popu	lation (Human Studies or Experimental Model Systems)	
Human	All epidemiological studies No restrictions on country of residence/origin, lifestyle, race/ethnicity, or occupation	None
Animal	Studies in animal models (mammals only) without restriction of species	Non-mammal animals
In vitro	<i>In vitro</i> models utilizing organs, tissues, cell lines, or cellular components	None
Exposure		
Human, animal, In vitro	Exposure to hard-surface disinfectants. Exposure to biocides based on administered dose or concentration, biomonitoring data (e.g., urine, blood, other specimens), environmental measures (e.g., air, water levels), or job title. Alkyl dimethyl benzyl ammonium chloride Sodium Hypochlorite Trichloro-s-triazinetrione Chlorine Dioxide 1-Decanaminium, N-decyl-N, N-dimethyl chloride Hydrogen Peroxide Otho Phenyl Phenol Peracetic Acid p-chloro-m-cresol Poly (hexamethylene biguanide) hydrochloride Inhalation route of exposure only	Non-inhalation exposure routes
Comparators		
Human, animal, In vitro	Individuals exposed to lower levels (or no exposure/exposure below detection levels) of biocides	None
Outcomes		
Human, animal, <i>In vitro</i>	Respiratory health outcomes only.	Non respiratory outcomes
Publications (e.g.,	language restrictions, use of conference abstracts, etc.)	
Human, animal, <i>In vitro</i>	Reference must contain original data and must be peer- reviewed References published in a language other than English will be identified, but not categorized by health effect and exposure; references will not be translated.	Articles with no original data (e.g., editorials, reviews, commentaries) Non-peer reviewed articles: Conference abstracts or other studies published in abstract form only, grant awards, and theses/dissertations

#### **Full-Text Review**

Articles will be screened for inclusion at the full text using one of the two web-based software programs described previously with structured forms and procedures to ensure standardization of the screening and data extraction process. Screening at the full-text level will be conducted such that two members of the evaluation design team will independently screen full-text of included articles from the title and abstract screening phase. Full text screening will confirm relevancy using the same inclusion criteria based on the PECO statement. Screening conflicts will be resolved by the project lead (Walker) if necessary, through consultation with EPA collaborators. The reason for exclusion at the full-text review stage will be recorded and reported in the study flow diagram.

### Tracking study eligibility and reporting the flow of information

The reason for exclusion at the full-text-review stage will be annotated and reported in a study flow diagram in the final report. Studies will be excluded if: (1) is a review, commentary, or editorial with no original data; (2) lacks relevant exposure information; (3) lacks relevant health outcome information; (4) is a conference abstract, thesis/dissertation, or (5) full text is "not available".

### Step 3. Study Characterization and Content Management

Study characterization will be conducted using structured forms in Distiller<sup>2</sup>. Data extraction elements are listed in appendices for human (Appendix 2) and non-human experimental animal (Appendix 3). Data will be extracted only for health effects that are relevant to the PECO. The references identified by the literature search will be characterized by publication type, evidence stream, exposure and category of respiratory health outcomes. Evidence stream will be categorized broadly to human or non-human animal study design and then further characterized by the specific study design features (e.g., cohort, case series) or models (e.g., mouse, rat, rabbit) used to conduct the study. Exposures will be categorized using a tiered approach, first to one of the ten biocide exposure groups, secondly, to the specific exposure if provided and finally, classifying each exposure into one of four exposure scenarios. Information related to co-exposures will also be extracted and the article recorded as having a co-exposure. Outcomes will be categorized using a tiered approach in a broad to specific manner using a controlled vocabulary. Specific outcomes reported in each article will be categorized to a controlled vocabulary list of respiratory outcomes. The outcomes will also be classified into three major health outcome categories; respiratory symptoms, respiratory function or respiratory disease (see Table 3 for outcome categories).

Study Characterization will be performed by one member of the evaluation team (primary extractor) and confirmed by a second member of the evaluation team (Quality Control (QC) extractor) for completeness and accuracy. Data extractors from the evaluation team will be trained using project-specific written instructions in an initial pilot phase using a subset of studies. Any discrepancies in data extraction will be resolved by discussion or consultation with a third member of the evaluation team.

#### OHAT Systematic Evidence Map of Biocides and Potential Respiratory Health Outcome

Table 3. Classification of Respiratory Outcomes		
Respiratory Outcome Category	Example of Broad Endpoints	
Respiratory symptoms	chest tightness or shortness of breath, labored breathing (dyspnea), lung sounds (crackling/rattling), mucous or phlegm production, coughing, wheezing, hyper-responsiveness of the airways, irritation, sore throat, mucosal swelling, nasal congestion, runny nose or sneezing, allergy symptoms, nasal mucociliary clearance, obstruction (lung/bronchial), thickening of bronchial walls	
Respiratory function	Lung function measures (FEV), lung inflammation, respiratory lesions, respiration/respiratory rate, BALF, lavage, edema (pulmonary), bronchospasm	
Respiratory disease	asthma (diagnosis or reported), COPD, pneumonia, respiratory distress/respiratory distress syndrome, bronchitis, sinusitis, rhinitis, common cold, influenza, emphysema, tonsillitis	

All extracted data will be used to develop evidence tables or maps. The evidence tables will be provided to EPA and also provide researchers and public health professionals a tool for exploring the evidence by major respiratory effect categories, evidence stream (i.e., human or animal studies), and either individual biocides or across multiple biocides collectively.

#### **Data Visualizations**

The data that have been extracted from all included human and animal studies will be collected in evidence tables or other visual formats to help characterize and show the extent of the evidence by health effect, biocide exposure, and types of evidence in available research.

#### **Quality Assurance and Quality Control Procedures**

Quality assurance (QA) and quality control (QC) procedures for study screening and study characterization will be followed as described previously in those methods sections and are summarized here for clarity. Inclusion and exclusion decisions during title and abstract screening will be reached after each study is independently screened in duplicate by two reviewers with QA input for any disagreements. All included studies will then be confirmed with additional review at full text level with decisions reached after full text of each study is independently screened in duplicate by two reviewers with QA input for any disagreements. QC verification for relevance of studies included at this stage will be performed prior to data extraction. Study characterization for each study will be performed by a primary extractor with QC review by a second experienced team member. Data exported from Distiller will undergo QC check for missing data or potential categorization errors as part of data transformation for evidence tables.

#### REFERENCES

- Heindel JJ, Skalla LA, Joubert BR, Kilworth CH, and Gray KA. 2017. Review of developmental origins of health and disease publications in environmental epidemiology. Reproductive Toxicology 68 (2017) 34-48.
- Higgins J, Green S. 2011. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). <u>http://handbook.cochrane.org/</u> [accessed 3 February 2013].
- Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122(7): 711-718.
- U.S. EPA (2012). Guidance for considering and using open literature toxicity studies to support human health risk assessment. http://www.epa.gov/pesticides/science/lit-studies.pdf

### **ABOUT THE PROTOCOL**

### Contributors

Evaluation teams are composed of federal staff and contractor staff. Contractor staff members are screened for potential conflicts of interest. Federal staff members should do a self-evaluation. Technical advisors were screened for conflict of interest prior to their service and did not report any conflicts of interest. Epidemiologists and toxicologists on OHAT evaluation teams should have at least three years' experience and/or training in reviewing studies, including summarizing studies and critical review (e.g., assessing study quality and interpreting findings). Team members should have at least a master's degree or equivalent experience in epidemiology, toxicology, environmental health sciences, or a related field.

#### Federal Staff

Name	Affiliation
Andrew A. Rooney	NIEHS/NTP, Project Lead
Vickie Walker	NIEHS/NTP, Project Lead
Anna Lowit	EPA/Office of Pesticide Programs
Timothy Leighton	EPA/Office of Pesticide Programs
Laura Parsons	EPA/Office of Pesticide Programs
Timothy Dole	EPA/Office of Pesticide Programs

#### Contract Support Staff: Will assist in screening and data extraction

Name	Affiliation	
Amanda Ross	ICF	
Anna Stamatogiannakis	ICF	
Chelsea Hunter	ICF	
Courtney Lemeris	ICF	
Devon Morgan	ICF	
Jeremy Frye	ICF	
Jessica Wignall	ICF	
Johanna Rochester	ICF	
Kate Helmick	ICF	
Kristen Magnuson	ICF	
Kelly Shipkowski	ICF	
Sean Robins	ICF	
Yousuf Ahmad	ICF	

#### **Technical Advisors**

Technical advisors are outside experts retained on an as-needed basis to provide individual advice to the NTP for a specific topic.

Although technical advisors may be added if necessary, during the project, no technical advisors were involved in development of the protocol other than the EPA staff listed above as project contributors.

### **Sources of Support**

National Institute of Environmental Health Sciences/Division of the National Toxicology Program

# **Protocol History and Revisions**

Activity or revision
Draft protocol developed
Peer-review and finalization of protocol
Protocol posted publicly at ( <u>https://ntp.niehs.nih.gov/go/biocides</u> )

# **APPENDICES**

# Appendix 1. Literature Search Strategy

### Pubmed database search terms

Results: 16,883	
Date of Search: January	17, 2018
Set	Search Strategy
Exposure/Biocides	<ul> <li>Search Strategy</li> <li>(Alkyldimethylbenzylammonium-Chloride[tiab] OR Alkyl-dimethyl-benzyl- ammonium-chloride[tiab] OR Asepsol[tiab] OR Benzalkonium[tiab] OR</li> <li>Benzalkonium-chloride[tiab] OR Benzalkonium-Compounds[mh] OR BTC-2125[tiab]</li> <li>OR osvan[tiab] OR Zephiran[tiab] OR 7681-52-9[rn] OR Antiformin[tiab] OR</li> <li>Bleach[tiab] OR Chloros[tiab] OR Chlorox[tiab] OR Clorox[tiab] OR Dakins- solution[tiab] OR Dakin's-solution[tiab] OR Deosan[tiab] OR Dispatch[tiab] OR</li> <li>Hyclorite[tiab] OR Hypochlorite-sodium[tiab] OR Javelle-water[tiab] OR Javel- water[tiab] OR Javex[tiab] OR Modified-dakin's-solution[tiab] OR NaClO[tiab] OR</li> </ul>
	<ul> <li>water[tiab] OR Javex[tiab] OR Modified-dakin's-solution[tiab] OR NaClO[tiab] OR</li> <li>NaOCl[tiab] OR Neo-cleaner[tiab] OR Sodium-Hypochlorite[tiab] OR Sodium-Hypochlorite[mh] OR 87-90-1[rn] OR Trichlorocyanuric-acid[tiab] OR</li> <li>Trichloroisocyanuric-acid[tiab] OR Trichloroisocyanuric-acid[m] OR Trichloro-s-triazinetrione[tiab] OR 10049-04-4[rn] OR Alcide[tiab] OR Alcide[tiab] OR</li> <li>Aseptrol[tiab] OR Chlorine-Dioxide[tiab] OR Chlorine-Dioxide[m] OR Chlorine-oxide[tiab] OR Chlorine-peroxide[tiab] OR ClO2[tiab] OR MicroClear[tiab] OR</li> <li>Purite[tiab] OR RenNew-D[tiab] OR Tristel[tiab] OR 7173-51-5[rn] OR Acticide[tiab] OR Astop[tiab] OR Bardac-22[tiab] OR Bardac-2280[tiab] OR deciquam-222[tiab]</li> <li>OR didecyldimethylammonium[tiab] OR didecyldimethylammonium[nm] OR</li> <li>didecyldimethylammonium-bromide[tiab] OR 7722-84-1[rn] OR Elawox[tiab] OR</li> <li>Hioxyl[tiab] OR Hydrogen-dioxide[tiab] OR Hydrogen-Peroxide[tiab] OR</li> <li>Peroxide[mh] OR Hydrogen-dioxide[tiab] OR Perhydrol[tiab] OR Superoxol[tiab] OR</li> <li>Oxydol[tiab] OR Deroxyde-d'hydrogene[tiab] OR Superoxol[tiab] OR</li> <li>Perone[tiab] OR Oxydol[tiab] OR Perhydrol[tiab] OR Perhydrol[tiab] OR</li> <li>Perone[tiab] OR Oxydol[tiab] OR 90-43-7[rn] OR Dowicide[tiab] OR Lyorthol[tiab] OR or</li> <li>phenylphenol[tiab] OR or phenylphenote[tiab] OR ortho-phenylphenate[tiab] OR</li> <li>orthophenylphenol[tiab] OR ortho-phenylphenote[tiab] OR</li> <li>orthophenylphenol[tiab] OR ortho-phenylphenote[tiab] OR</li> <li>orthophenylphenol[tiab] OR orgen-1[tiab] OR Peroxone-1[tiab] OR</li> </ul>
	acid[tiab] OR Peroxyacetic-acid[tiab] OR Peroxyacetic-Acid[tinl] OR PeroXoacetic- acid[tiab] OR Peroxyacetic-acid[tiab] OR Peroxyacetic-Acid[tiab] OR Peroxyethanoic-Acid[tiab] OR 3-Methyl-4-chlorophenol[tiab] OR 3-Methyl-4- chlorophenol[nm] OR 4-Chloro-3-cresol[tiab] OR 4-chloro-3-cresol[tiab] OR 4- Chloro-3-methylphenol[tiab] OR 4-chloro-3-methylphenol[tiab] OR 4-Chloro-3- methyl-phenol[tiab] OR 4-Chloro-m-cresol[tiab] OR 4-chloro-meta-cresol[tiab] OR 59-50-7[rn] OR 6-Chloro-3-hydroxytoluene[tiab] OR Aptal[tiab] OR Chloro-3- cresol[tiab] OR Chlorocresol[tiab] OR Parmetol[tiab] OR p-chloro-m-cresol[tiab] OR Preventol-CMK[tiab] OR Raschit[tiab] OR "poly(hexamethylene-biguanide)"[tiab] OR "poly(hexamethylenebiguanide)-hydrochloride"[tiab] OR 32289-58-0[rn] OR Baquacil[tiab] OR Cosmocil[tiab] OR Lavasept[tiab] OR PHMB-polymer[tiab] OR

Set	Search Strategy
Outeenee	Polihexanide[tiab] OR polihexanide[nm] OR polihexanide[tiab] OR polyhexamethylenbiguanid[tiab] OR polyhexamethylenbiguanide[tiab] OR polyhexamethylene-biguanide[tiab] OR polyhexamethylene-biguanide- hydrochloride[tiab] OR Polyhexanide[tiab] OR Prontoderm[tiab] OR Prontosan[tiab] OR Trigene[tiab] OR Vantocil[tiab] OR Vantocil-TG[tiab] OR Alkyl- dimethyl-benzyl[tiab] OR Alkyl-dimethyl-benzyl-ammonium-chloride[tiab] OR Alkyl-dimethyl-benzyl-ammonium-saccarinate[tiab] OR Alkyl-dimethyl-ethylbenzyl- ammonium-chloride[tiab] OR Dodecyl-dimethyl-benzyl-ammonium-chloride[tiab] OR Imidazolinium[tiab] OR Isoquinolinium[tiab] OR N-Ethyl-Morpholinium[tiab] OR Picolinium[tiab] OR QUAT[tiab] OR Quaternary-Ammonium- Compounds[mh:noexp] OR Quaternary-Ammonium-Compounds[tiab] OR
Outcome	AND (((cilia[mh] OR ciliary[tiab]) AND (dyskinesia[tiab] OR immotil*[tiab] OR motil*[tiab])) OR air-sac*[tiab] OR airway*[tiab] OR alveol*[tiab] OR asthma*[tiab] OR breath*[tiab] OR bronchi*[tiab] OR bronchopneumonia[tiab] OR bronchopulmonary[tiab] OR bronchus[tiab] OR Chronic-Airflow-Obstruction*[tiab] OR Chronic-Obstructive-Airway-Disease[tiab] OR Chronic-Obstructive-Lung- Disease[tiab] OR Chronic-Obstructive-Pulmonary-Disease[tiab] OR closing- volume[tiab] OR COPD[tiab] OR epiglottis[tiab] OR expiratory-reserve-volume[tiab] OR expiratory-flow[tiab] OR forced-expiratory-volume[tiab] OR functional-residual- capacity[tiab] OR glottis[tiab] OR goblet-cell*[tiab] OR (granuloma*[tiab] AND (respiratory[tiab] OR laryngeal[tiab])) OR granuloma, respiratory tratc[mh] OR hemopneumothorax[tiab] OR hemothorax[tiab] OR hydropneumothorax[tiab] OR hydrothorax[tiab] OR Inflammation[mh] OR inflammation mediators[mh] OR irritation[tiab] OR laryngeal[tiab] OR laryngeal cartilages[mh] OR laryngitis[tiab] OR laryngopharyngeal-reflux[tiab] OR laryngestenosis[tiab] OR larynx[tiab] OR lung[tiab] OR nase[[tiab] OR paranasal[tiab] OR (mucosa[tiab] AND (respiratory[tiab] OR nasel[tiab] OR olfactory[tiab]) OR masal[tiab] OR nasopharyn*[tiab] OR nose[tiab] OR paranasal[tiab] OR pharyngeal[tiab] OR pharynx[tiab] OR pneumothorax[tiab] OR proinflammat*[tiab] OR pneumonia[tiab] OR pneumothorax[tiab] OR proinflammat*[tiab] OR proving[tiab] OR pneumothorax[tiab] OR proinflammat*[tiab] OR proving[tiab] OR prespiratory-tract-diseases[mh] OR respiratory-tract- inflammat*[tiab] OR pulmonary-ventilation[mh] OR respiratory-physiological-phenomena[mh] OR respiratory-system[mh] OR respiratory-tract-diseases[mh] OR respiratory-tract- infections[mh] OR rhinits[tiab] OR signs-and-symptoms,-respiratory[mh] OR sinus[tiab] OR sinusitis[tiab] OR signs-and-symptoms,-respiratory[mh] OR sinus[tiab] OR sinusitis[tiab] OR signs-and-symptoms,-respiratory[mh] OR sinus[tiab] OR sinusitis[tiab] OR signs-and-symptoms,-respiratory[tiab] OR v

### Web of Science database search terms

### Results: 15,841

Date of Search: January 17, 2018

Exposure/Biocides	(Alkyldimethylbenzylammonium-Chloride OR Alkyl-dimethyl-benzyl-ammonium- chloride OR Asepsol OR Benzalkonium OR Benzalkonium-chloride OR BTC-2125 OR osvan OR Zephiran OR 7681-52-9 OR Antiformin OR Bleach OR Chloros OR Chloros OR Clorox OR Dakins-solution OR Dakin's-solution OR Deosan OR Dispatch OR Hyclorite OR Hypochlorite-sodium OR Javelle-water OR Javel-water OR Javex OR Modified-dakin's-solution OR NaClO OR NaOCl OR Neo-cleaner OR Sodium- Hypochlorite OR 87-90-1 OR Trichlorocyanuric-acid OR Trichloroisocyanuric-acid OR Trichloro-s-triazinetrione OR 10049-04-4 OR Alcide OR Alcide OR Aseptrol OR Chlorine-Dioxide OR Chlorine-oxide OR Chlorine-peroxide OR ClO2 OR MicroClear OR Purite OR RenNew-D OR Tristel OR 7173-51-5 OR Acticide OR Astop OR Bardac- 22 OR Bardac-2280 OR deciquam-222 OR didecyldimethylammonium-chloride OR Didecyl-dimethylammonium-bromide OR Didecyldimethylammonium-chloride OR Didecyl-dimethyl-ammonium-chloride OR Dimethyldidecylammonium-chloride OR Didecyl-dimethyl-ammonium-chornide OR Didecyldimethylammonium-chloride OR Perhydrol OR Perone OR Peroxide OR Peroxyde-d'hydrogene OR Superoxol OR 2- hydroxybiphenyl OR 2-hydroxydiphenyl OR 2-phenylphenol OR 90-43-7 OR Dowicide OR Lyorthol OR o-phenylphenol OR orylophenoate OR sodium- ortho-phenylphenate OR sodium-ortho-phenylphenol OR 90-43-7 OR Dowicide OR Desoxon-1 OR Desoxone-1 OR Ethaneperoxic-acid OR Peracetic-Acid OR Peroxacetic-acid OR Peroxyacetic-acid OR Peroxyacetic-Acid OR Peroxyethanoic-Acid OR 3-Methyl-4-chlorophenol OR 4-Chloro-3-cresol OR 4- Chloro-3-methyl-phenol OR 4-Chloro-3-cresol OR 4- Chloro-3-hydroxytoluene OR Aptal OR Chloro-3-cresol OR 4- Chloro-3-hydroxytoluene OR Prontosan OR Trigene OR Polihexanide OR polyhexamethylene-biguanide] OR "Polyhexamethylenebiguanide]- hydrochloride" OR "Poly-(hexamethylene-biguanide)- hydrochloride OR Prohtoderm OR Prontosan
Outcome	AND
	(((cilia OR ciliary) AND (dyskinesia OR immotil* OR motil*)) OR air-sac* OR airway* OR alveol* OR asthma* OR breath* OR bronchi* OR bronchopneumonia OR bronchopulmonary OR bronchus OR Chronic-Airflow-Obstruction* OR Chronic- Obstructive-Airway-Disease OR Chronic-Obstructive-Lung-Disease OR Chronic- Obstructive-Pulmonary-Disease OR closing-volume OR COPD OR epiglottis OR expiratory-reserve-volume OR expiratory-flow OR forced-expiratory-volume OR

#### OHAT Systematic Evidence Map of Biocides and Potential Respiratory Health Outcome

Set	Search Strategy
	functional-residual-capacity OR glottis OR goblet-cell* OR (granuloma* AND
	(respiratory OR laryngeal)) OR hemopneumothorax OR hemothorax OR
	hydropneumothorax OR hydrothorax OR hyperventilat* OR hypopharynx OR
	inflamed OR Inflammat* OR irritation OR laryngeal OR laryngitis OR
	laryngopharyngeal-reflux OR laryngostenosis OR larynx OR lung OR lungs OR
	mucociliary-clearance OR (mucosa AND (respiratory OR nasal OR olfactory)) OR
	nasal OR nasopharyn* OR nose OR paranasal OR pharyngeal OR pharynx OR
	pleura* OR pleural-diseases OR pleural-effusion OR pleurisy OR pneumoconiosis
	OR pneumocyte* OR pneumonia OR pneumothorax OR proinflammat* OR pro-
	inflammat* OR pulmonary OR residual-volume OR respiration OR respiratory OR
	rhinitis OR sinus OR sinusitis OR sneez* OR supraglottis OR trachea* OR tracheo*
	OR turbinate* OR ventilation-perfusion OR vital-capacity OR vocal-cord* OR
	vomeronasal)
Limits	Articles only

### Scopus

Results: 11,019 Date of Search: January 17, 2018

Set	Search Strategy
Set Exposure/Biocides	Search Strategy (Alkyldimethylbenzylammonium-Chloride OR Alkyl-dimethyl-benzyl-ammonium- chloride OR Asepsol OR Benzalkonium OR Benzalkonium-chloride OR BTC-2125 OR osvan OR Zephiran OR 7681-52-9 OR Antiformin OR Bleach OR Chloros OR Chlorox OR Clorox OR Dakins-solution OR Dakin's-solution OR Deosan OR Dispatch OR Hyclorite OR Hypochlorite-sodium OR Javelle-water OR Javel-water OR Javex OR Modified-dakin's-solution OR NaClO OR NaOCl OR Neo-cleaner OR Sodium- Hypochlorite OR 87-90-1 OR Trichlorocyanuric-acid OR Trichloroisocyanuric-acid OR Trichloro-s-triazinetrione OR 10049-04-4 OR Alcide OR Alcide OR Aseptrol OR Chlorine-Dioxide OR Chlorine-oxide OR Chlorine-peroxide OR ClO2 OR MicroClear OR Purite OR RenNew-D OR Tristel OR 7173-51-5 OR Acticide OR Astop OR Bardac- 22 OR Bardac-2280 OR deciquam-222 OR didecyldimethylammonium OR didecyldimethylammonium-bromide OR Didecyldimethylammonium-chloride OR Didecyl-dimethyl-ammonium-chloride OR Dimethyldidecylammonium-chloride OR Hydroperoxide OR Inhibine OR Lensept OR Oxydol OR Oxydol OR Perhydrol OR Perhydrol OR Perone OR Peroxide OR Peroxyde-d'hydrogene OR Superoxol OR 2- hydroxybiphenyl OR 2-hydroxydiphenyl OR 2-phenylphenol OR 90-43-7 OR Dowicide OR Lyorthol OR o-phenylphenate OR o-phenylphenoate OR sodium- ortho-phenylphenate OR orthophenylphenol OR sodium-o-phenylphenoate OR sodium- ortho-phenylphenate OR sodium-ortho-phenylphenol OR 79-21-0 OR Acetic- peroxide OR Desoxon-1 OR Desoxone-1 OR Ethaneperoxoic-acid OR Peracetic-Acid OR Peroxoacetic-acid OR Peroxyacetic-acid OR Peroxyacetic-Acid OR Peroxyethanoic-Acid OR 3-Methyl-4-chlorophenol OR 4-Chloro-3-cresol OR 4- chloro-3-cresol OR 4-Chloro-3-methylphenol OR 4-Chloro-3-cresol OR 4- Chloro-3-methyl-phenol OR 4-Chloro-m-cresol OR 4-chloro-3-cresol OR 59-50-7 OR 6-Chloro-3-methylphenol OR 4-Chloro-3-methylphenol OR 4- Chloro-3-methyl-phenol OR 4-Chloro-M-cresol OR 4- Chloro-3-methyl-phenol OR 4-Chloro-M-cresol OR 4- Chloro-3-methyl-phenol OR 4-Chloro-M-cresol OR 4- Chloro-3-methyl-phen
	Parmetol OR p-chloro-m-cresol OR Preventol-CMK OR Raschit OR
	"poly(hexamethylene-biguanide)" OR "poly(hexamethylenebiguanide)-

Set	Search Strategy
	hydrochloride" OR "Poly-(hexamethylene-biguanide)-hydrochloride" OR 32289-58- 0 OR Baquacil OR Cosmocil OR Lavasept OR PHMB-polymer OR Polihexanide OR polihexanide OR polyhexamethylenbiguanid OR polyhexamethylenbiguanide OR polyhexamethylene-biguanide OR polyhexamethylene-biguanide-hydrochloride OR Polyhexanide OR Prontoderm OR Prontosan OR Trigene OR Vantocil OR Vantocil- TG OR Alkyl-dimethyl-benzyl OR Alkyl-dimethyl-benzyl-ammonium-chloride OR Alkyl-dimethyl-benzyl-ammonium-saccarinate OR Alkyl-dimethyl-ethylbenzyl- ammonium-chloride OR Dodecyl-dimethyl-benzyl-ammonium-chloride OR Imidazolinium OR Isoquinolinium OR N-Ethyl-Morpholinium OR Picolinium OR QUAT OR Quaternary-Ammonium-Compounds OR QUATs OR trimethyl- ammonium-chloride)
Outcome	AND (((cilia OR ciliary) AND (dyskinesia OR immotil* OR motil*)) OR air-sac* OR airway* OR alveol* OR asthma* OR breath* OR bronchi* OR bronchopneumonia OR bronchopulmonary OR bronchus OR Chronic-Airflow-Obstruction* OR Chronic- Obstructive-Airway-Disease OR Chronic-Obstructive-Lung-Disease OR Chronic- Obstructive-Pulmonary-Disease OR closing-volume OR COPD OR epiglottis OR expiratory-reserve-volume OR expiratory-flow OR forced-expiratory-volume OR functional-residual-capacity OR glottis OR goblet-cell* OR (granuloma* AND (respiratory OR laryngeal)) OR hemopneumothorax OR hemothorax OR hydropneumothorax OR hydrothorax OR hyperventilat* OR hypopharynx OR inflamed OR Inflammat* OR irritation OR laryngeal OR laryngitis OR laryngopharyngeal-reflux OR laryngostenosis OR larynx OR lung OR lungs OR mucociliary-clearance OR (mucosa AND (respiratory OR nasal OR olfactory)) OR nasal OR nasopharyn* OR nose OR paranasal OR pharyngeal OR pharynx OR pleura* OR pleural-diseases OR pleural-effusion OR pleurisy OR pneumoconiosis OR pneumocyte* OR pneumonia OR pneumothorax OR pro- inflammat* OR pulmonary OR residual-volume OR respiration OR respiratory OR rhinitis OR sinus OR sinusitis OR sneez* OR supraglottis OR trachea* OR tracheo* OR turbinate* OR ventilation-perfusion OR vital-capacity OR vocal-cord* OR vomeronasal)
Limits	Articles only/ searched in title/abstract only

### Appendix 2. Data Extraction Elements for Human Studies

HUMAN				
Study Design	Control trial, retrospective cohort, prospective cohort, cross-sectional, case-control study or case report.			
Exposure	Biocide from relevant exposure list (including synonyms)			
	Alkyl dimethyl benzyl ammonium chloride (ADBAC QUAT)			
	Decanaminium, N-decyl-N, N-dimethyl chloride (DDAC QUAT)			
	Sodium Hypochlorite (Bleach)			
	Otho Phenyl Phenol (OPP)			
	Trichloro-s-triazinetrione (Chlorinated Isocyanurate)			
	Chlorine Dioxide (Chlorine Dioxide in solution)			
	Peracetic Acid (PAS)			
	Hydrogen Peroxide (hydrogen peroxide)			
	Poly (hexamethylene biguanide) hydrochloride (PHMB)			
	• p-chloro-m-cresol (PCMC)			
Exposure Scenario	Type of exposure scenario-			
-	occupational			
	<ul> <li>other (pools, parks or other public or private places)</li> </ul>			
	Experimental			
Outcomes	Respiratory outcomes evaluated categorized into one of three major outcome			
	categories (See Table 3 for the classification of specific outcomes):			
	Respiratory symptoms			
	Respiratory function			
	Respiratory disease			

Appendix 3.	Data	Extraction	Elements	for	Animal	<b>Studies</b>
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ANIMAL				
Animal Model	Mouse, Rat, Primate or Other			
Exposure	Biocide from relevant exposure list (including synonyms)			
	Alkyl dimethyl benzyl ammonium chloride (ADBAC QUAT)			
	<ul> <li>Decanaminium, N-decyl-N, N-dimethyl chloride (DDAC QUAT)</li> </ul>			
	Sodium Hypochlorite (Bleach)			
	Otho Phenyl Phenol (OPP)			
	Trichloro-s-triazinetrione (Chlorinated Isocyanurate)			
	Chlorine Dioxide (Chlorine Dioxide in solution)			
	Peracetic Acid (PAS)			
	Hydrogen Peroxide (hydrogen peroxide)			
	<ul> <li>Poly (hexamethylene biguanide) hydrochloride (PHMB)</li> </ul>			
	• p-chloro-m-cresol (PCMC)			
Exposure Scenario	Type of exposure scenario-			
	<ul> <li>other (pools, parks or other public or private places)</li> </ul>			
	Experimental			
Outcomes	Respiratory outcomes evaluated categorized into one of three major outcome			
	categories (See Table 3 for the classification of specific outcomes):			
	Respiratory symptoms			
	Respiratory function			
	Respiratory disease			