



Web based listing of agents associated with new onset work-related asthma



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Summary

Background: Work-related asthma is common and yet remains a challenge to diagnose. Access to a listing of agents associated with work-related asthma has been suggested as useful in assisting in the diagnosis.

Methods: The Association of Occupational and Environmental Clinics (AOEC) developed criteria that were used to review the peer-reviewed medical literature published in English. Based on this review, substances were designated either as a sensitizing agent or an irritant. The reviews were conducted by a board certified internist/pulmonologist/occupational medicine specialist from 2002 to 2007 and a board certified internist/occupational medicine physician from 2008-date. All reviews were then reviewed by the nine member AOEC board of directors.

Results: The original list of agents associated with new onset work-related asthma was derived from the tables of a text book on work-related asthma. After 13 years of review, there are 327 substances designated as asthma agents on the AOEC list; 173 (52.9%) coded as sensitizers, 35 (10.7%) as generally recognized as an asthma causing agent, four (1.2%) as irritants, two (0.6%) as both a sensitizer and an irritant and 113(34.6%) agents that still need to be reviewed.

Conclusions: The AOEC has developed a readily available web based listing of agents associated with new onset work-related asthma in adults. The listing is based on peer-reviewed criteria. The listing is updated twice a year. Regular review of the peer-reviewed medical literature is conducted to determine whether new substances should be added to the list. Clinicians should find the list useful when considering the diagnosis of work-related asthma.

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Introduction

Work exposures are an important component of the development of asthma in adults, and controlling them represents an opportunity for prevention [1]. In 2003, the American Thoracic Society published a consensus statement that concluded: "A careful review of the literature demonstrates that approximately 15% of both asthma and COPD is likely to be work related," [2]. Work-related asthma remains a challenge for physicians to diagnose and manage. To assist physicians, the American College of Chest Physicians published a consensus statement on the Diagnosis and Management of Work-Related Asthma, which included the statement that clinicians "should focus particularly on exposures occurring at the time that asthma started or worsened at work" [3]. To assist clinicians in assessing the work exposures of their patients, the consensus statement referred to the ASMANET website that contained a listing of "workplace sensitizers" based on reports in the published literature up to 2002. Although the ASMANET website can still be found on the internet, the list of "workplace sensitizers" has not been available for the past four years.

This paper describes an active web site, which is regularly updated, that lists substances that meet specified criteria for causing work related asthma by sensitization or acute irritant-induced asthma. This manuscript also describes the criteria used for a substance being included on the listing as a sensitizer or irritant. Clinicians can use this web site to assist them when evaluating patients they suspect have new onset work-related asthma.

Methods

The Association of Occupational and Environmental Clinics (AOEC) maintains an exposure code list (<http://www.aoeccdata.org/ExpCodeLookup.aspx>). The AOEC Exposure Code List was first developed in 1995, for use by AOEC members in order to help identify emerging occupational and environmental health concerns [4]. The AOEC Exposure Code List is not an official document of any governmental agency. The AOEC is registered with the United States Internal Revenue Service as a non-profit, 501(c) 3 organization made up of approximately 60 occupational and environmental clinics. AOEC encourages use and has open access to all practitioners for all the information and resources it has developed.

A supplemental designation for asthmagens (indicated by an "A") was added the same year the AOEC list was developed to facilitate analysis of data by the four states in the United States doing work-related asthma surveillance [4]. The designation of an "A" was mainly derived from substances listed in either of the two tables in Chapter 35 of the second edition of the medical textbook *Asthma in the Workplace*, which was published in 1999, Agents Causing Occupational Asthma with Key References or Low-Molecular-Weight Agents Causing Occupational Asthma [5]. The chapter was written by two experts in occupational asthma, Moira Chan-Yeung and Jean-Luc Malo. No formal criteria were described by the authors for the agents included in these two tables. Inclusion was based on

published journal articles "derived mostly from English-language journals, but other languages were also included." (The most recent edition of this text was published in 2013, which includes an updated listing of substances causing occupational asthma, as well as detailed chapters on selected categories of substances). This table can be found at http://www.asthme.csst.qc.ca/document/Info_Med/IdCauses/Bernstein/AgentsAnglais.pdf.

The AOEC developed formal criteria for the asthmagen designation for sensitizer-induced asthma in 2002 (Table 1) and for acute irritant-induced asthma (RADS) in 2008 (Table 2). These criteria were developed by the second author in consultation with others in occupational and pulmonary medicine. Both sets of criteria were reviewed and approved by the AOEC Board of Directors, which consists of nine members: five are clinics representatives, usually physicians and four individual members, at least one of whom must be non-physicians (i.e. nurse, industrial hygienist).

Beginning in 2002, with the development of these criteria, a formal review process was begun to use the new criteria to evaluate substances on the list previously designated as causing occupational asthma and to add new substances that met the criteria. The reviews have been conducted by the two authors, one a board certified internist/pulmonologist/occupational medicine specialist did the reviews from 2002 to 2007 and second a board certified internist/occupational medicine physician did the reviews from 2008- date. Not all of the substances reported to be asthmagens in the 1995 AOEC list have yet been formally evaluated against the AOEC criteria, however the AOEC has been reviewing approximately 20 substances per year to determine which substances meet the criteria. Each year, exposures are selected for review based on recommendations from AOEC members, asthma researchers, industry representatives, or other stakeholders. These annual reports are available from the AOEC office by request (aoec@aoec.org). The Exposure Code List has two columns to identify asthmagens. The first column indicates an "A" once a substance has been designated as an asthmagen. The second column indicates which criteria were used for determining that designation. Substances reviewed and meeting criteria for sensitizer-induced asthma are designated "Rs"; those reviewed and meeting criteria for RADS are designated "Rr"; those reviewed and meeting both sets of criteria are designated "Rrs"; those reviewed and not meeting either set of criteria are designated "R". A substance that has an "R", meaning it has been reviewed but does not meet either criteria, will not have an A in the first column. Substance may not have originally had an "A" in the first column because a review may have been requested and conducted on a substance never previously designated as an asthmagen. Exposures that are still scheduled to be reviewed will be blank in the second column. Exposures that are generally accepted as an asthmagen, such as toluene diisocyanate where the medical evidence is so extensive that a review is not felt to be needed, have a "G" in the second column.

A systematic search of the English peer reviewed medical literature is conducted for each agent. This search consists of a U.S. National Library of Medicine (NLM) PubMed search including a search of TOXNET (NLM Toxicology Data Network), review of references in the articles identified and

Table 1 AOEC criteria for sensitization.**Major criteria (at least one)**

1. Specific inhalation challenge indicates occupational asthma (i.e. immediate or delayed fall in FEV1 after exposure) in at least one patient with asthma that appears to have developed the asthma as a result of exposure to the implicated substance. The peer-reviewed study should indicate a response to sub-irritant levels of sensitizing substances. Ideally, a positive challenge will be controlled by negative challenges in asthmatic patients who are not believed to be sensitized to the particular substance, though such a design is not routinely used for specific exposure challenges.
2. Workplace challenge with physiologic response (serial spirometry or serial peak expiratory flow) showing reversible expiratory airflow obstruction or changing airway reactivity in relation to exposure, with a comparable control period without significant variable airflow obstruction or airway reactivity, published in a peer-reviewed journal. Patient(s) tested should be reasonably considered to be without asthma prior to testing in the workplace, to exclude work-aggravated asthma.

OR

Minor criteria (at least two):

1. Non-Specific airway hyper-responsiveness is demonstrated in at least one patient with suspected occupational asthma while still employed at the workplace in question, based on non-specific challenge with agents such as methacholine or histamine, published in a peer-reviewed journal.
2. Work-exposure related reversible wheezing heard with repeated exposures in at least one patient with a compatible clinical picture, published in a peer-reviewed journal.
3. Positive IgE antibody (skin test or serologic test) for the suspected antigen in at least one patient, indicating potential IgE sensitization, published in a peer-reviewed journal.
4. Clinical response of remission of symptoms with cessation of exposure and recurrence of symptoms with re-exposure in at least one patient, published in a peer-reviewed journal.

review of all references associated with the current listing of an agent on the AOEC exposure list. The medical literature that is reviewed to assess whether a substance meets the AOEC criteria must be in English and must be in a peer-reviewed publication. Letters to the editor are not considered sufficient since they are not peer reviewed.

Review of the literature is performed to determine if a substance meets the criteria developed for sensitization (Table 1) and the criteria developed for an acute irritant (Table 2)

We have used the term work-related asthma in this manuscript, which encompasses both occupational asthma

(new onset asthma caused by a sensitizer or an irritant) and work-exacerbated asthma (pre-existing asthma aggravated by work), when discussing the broader topic of asthma in adults and occupational asthma when discussing the specific substances on the AOEC list.

No IRB approval was sought as the work consisted of reviewing published medical literature.

Results

There are 2091 substances on the AOEC exposure list but after accounting for synonyms only 1293 substances with

Table 2 AOEC criteria for acute irritant-induced asthma.

- 1 There is a documented exposure to a specifically identified substance (chemical or compound).
- 2 The circumstances (level, frequency and extent) of the exposure are described, and the level of the single high exposure, or multiple somewhat-high exposures, is likely to have been higher than either TLV or PEL concentrations.
- 3 Symptoms appear within 24 h of most recent acute exposure and are persistent for at least three months following the exposure.^a
- 4 Pulmonary function tests demonstrate obstruction, when done within one to two months of symptom onset.^b
- 5 Nonspecific bronchial hyper-responsiveness is present, as measured by methacholine or histamine challenge tests.

For a substance to be included on the AOEC as an acute irritant causing RADS, it must meet all of the above criteria in Table 2 as reported in at least one peer-reviewed article describing at least one patient. The linkage of a specific substance with RADS is based on the temporal sequence of exposure to that substance followed by the onset of symptoms, and by the lack of any other evident cause. Important to this definition is the magnitude of exposure (concentration of substance in air times duration) which is described as high, though not further quantified. Unlike with asthma caused by sensitizers, there is no basis to re-challenge the individual with the substance to verify causation.

^a Onset of exposure refers to the time between the beginning of exposure to a substance and the time symptoms begin. Unlike the situation with sensitizer-induced asthma, for which prior exposure to an allergen or immunogenic substance is required to produce an immunologic response leading to asthma, RADS typically occurs following one or more acute, high level exposures (e.g. accidental spills). The likelihood of improvement for RADS relates to the severity of initial pulmonary injury, rather than to prolonged or continued exposure as it does with a sensitizing agent.

^b Obstruction on pulmonary function testing can usually be demonstrated soon after the acute exposure. However, over time (i.e. 1–2 months) away from further exposures pulmonary function (spirometry) testing may normalize, even though symptoms may persist and airway hyper-responsiveness may be demonstrated with challenge testing.

unique codes. There are 492 substances with an occupational asthma designation but again accounting for synonyms, 327 (25.3%) unique substances with an occupational asthma designation. Table 3 shows the review status of these 327 substances. Another 60 substances have been reviewed and do not meet the AOEC criteria for an occupational asthma agent; 34 were on the original AOEC list as an occupational asthma agent and another 16 were reviewed for possible addition. One hundred thirteen substances still need to be reviewed, of which 20 are chemicals and 93 are plant, animal and microbial material. Table 4 shows the listing from the AOEC website of the first ten occupational asthma agents. The references and which specific criteria each substance met are not on the web site. As an example, the review of glutaraldehyde, which has this information, is in Appendix I. Copies of the individual write ups of all the substances reviewed can be obtained by contacting the AOEC office.

Discussion

The diagnosis and management of work-related asthma has proven difficult. It requires the clinician to consider the possible association with work in adult patients with asthma, routinely include screening questions in their assessment and if these initial questions are positive to ask detailed questions about the onset of the patient's respiratory symptoms, what the patient does and what they may be exposed to. Where the question of work-related asthma has been raised, the clinician must make recommendations to the patient and employer about whether to continue or change the current workplace exposures.

The availability of a comprehensive list of substances previously reported to cause occupational asthma can be a useful adjunct to the clinician who has taken the initial steps to consider the possibility of work-related asthma. The AOEC list is readily available (<http://www.aoecdata.org/ExpCodeLookup.aspx>) and identification that an adult patient with asthma has an exposure listed to an agent classified on the AOEC list as an occupational asthma agent should be an indication the clinician needs to spend more

time considering occupational asthma in the differential or making a referral to a specialist with more expertise in evaluating patients for occupational asthma. The AOEC Exposure Code List was developed as a tool to help clinicians who are evaluating patients whose asthma may be occupational in nature. It does not replace the obligation of the physician using the listing to assess each situation on its individual merits and to draw an independent judgment taking into account all possible risk factors for the patient's asthma. It is very important to understand that the AOEC occupational asthma criteria do not take into account the level of exposure and do not reflect any specific exposure scenario. The level of exposure and how the substance is being used will alter the risk of asthma from a particular substance and the likelihood of an association in a specific workplace setting (e.g. encapsulated or airborne form, enclosed or open process, low or high concentration of substance in a product).

The AOEC list is not exhaustive. It is likely that some exposures not yet designated as occupational asthma agents are capable of inducing asthma. There are 327 unique substances on the list that have been associated with new onset asthma in the work place. Given the identification of new associations between work exposures and asthma recognized each year and although AOEC regularly reviews the medical literature and updates the list twice a year, there is still an approximate one year lag time for a new substance to be reviewed, designated and posted as an occupational asthma agent on the AOEC list. Additionally, there are agents in the workplace associated with new onset asthma that have yet to be recognized. Finally, there are innumerable substances that may significantly aggravate a patient's preexisting asthma, work-exacerbated asthma that will not be listed as an occupational asthma agent on the AOEC list. The potential for the AOEC list to not be all inclusive despite regular updates means a clinician should still consider occupational asthma in the differential if an adult asthma patient has a temporal relationship between their symptoms and work.

There is an understanding of the importance of irritant induced asthma [6] and we were surprised that only six substances on the AOEC list have been identified that meet the criteria for RADS. We attribute this small number to the lack of reports in the peer reviewed medical literature (i.e. substances may be listed in book chapters or letters) of follow up beyond the immediate acute care with inclusion of pulmonary function tests for chemicals that cause acute respiratory illness.

What other resources are available to clinicians? Review articles and book chapters continue to include listings of agents associated with occupational asthma [1,6–9]. There are also web based resources, which include reports listing agents associated with occupational asthma, that provide assistance on the diagnosis and management of work-related asthma. A 2011 listing of 374 substances associated with asthma, based on reviews of a variety of government and non-government sources (including the current AOEC list) is available online [10]. This listing was compiled by consultants to the US National Institutes of Health in support of efforts to promote health in the built environment and cites the sources of information for the

Table 3 Review status of 327 substances designated as an asthma causing agent on the AOEC exposure list.^a

Status	#	%
Coded Rs	173	52.9
Coded Rr	4	1.2
Coded Rrs	2	0.6
Coded G	35	10.7
Not reviewed	113	34.6
Total	327	100.0

Rs = reviewed, classified as meeting criteria as a sensitizer; Rr = reviewed, classified as meeting criteria as an irritant; Rrs = reviewed, classified as meeting criteria as a sensitizer and an irritant; G = generally accepted as a sensitizer and no future plans to review.

^a (34 substances designated "A" in the 1995 AOEC Exposure listing were subsequently reviewed using the AOEC asthmagen criteria and as a result of not meeting the criteria, had removal of the "A" designation.).

Table 4 Screen shot of the first ten asthma causing agents on the AOEC website.

AOEC exposure code	Primary name	Synonym	P = Pesticide S = Solvent	A = Asthmagen	Rs = Sensitizer Rr = RADS Rrs = Both R = Meets neither G = Generally accepted	RTECS	CAS
020.010	Aluminum Compounds	Aluminum Compounds		A	Rs		
020.011	Aluminum	Aluminum		A	Rs	BD0330000	7429-90-5
020.012	Aluminum Chloride	Aluminum Chloride		A	Rs		7446-70-0
020.02	Aluminum Oxide	Alumina		A	Rs	BD1200000	1344-28-1
020.02	Aluminum Oxide	Aluminum Oxide		A	Rs	BD1200000	1344-28-1
020.021	Aluminum Oxide, Corundum	Aluminum Oxide, Corundum		A	Rs	GN0231000	1302-74-5
020.140	Chromium Compounds	Chromium Compounds		A	Rs		
020.141	Chromium Metal	Chromium Metal		A	Rs		
020.142	Chromium, Not Hexavalent	Chromium, Not Hexavalent		A	Rs	GB4200000	7440-47-3
020.150	Cobalt Compounds	Cobalt Compounds		A	G		

RTECS = Registry of Toxic Environmental Chemical Substances, <http://www.cdc.gov/niosh/rtecs/default.html>.

CAS = Chemical Abstracts Service registry numbers, unique numerical identifiers assigned by the Chemical Abstracts Service of the American Chemical Society to every chemical substance described in the open scientific literature (currently including those described from at least 1957 through the present) Rs = reviewed, classified as meeting criteria as a sensitizer; Rr = reviewed, classified as meeting criteria as an irritant; Rrs = reviewed, classified as meeting criteria as a sensitizer and an irritant; G = generally accepted as a sensitizer and no future plans to review.

Rs = reviewed, classified as meeting criteria as a sensitizer; Rr = reviewed, classified as meeting criteria as an irritant; Rrs = reviewed, classified as meeting criteria as a sensitizer and an irritant; G = generally accepted as a sensitizer and no future plans to review.

substances listed, but does not specify criteria for inclusion.

The Répertoire Toxicologique website developed for Québec's employers and workers provides a list of occupational asthma agents grouped by high and low molecular weight and by classes of agents, i.e. plants, pharmaceuticals, etc. Clicking on a limited number of substances connects to another website with documentation about the material in French. Occupations/industries are listed alongside each agent [11].

The World Allergy Organization has a listing on their web site, last updated January 2014, of sensitizing agents inducers of occupational asthma, hypersensitivity pneumonitis and eosinophilic bronchitis [12]. The listing includes generally one but up to three references per listing. The criteria used to include an agent are not delineated.

In 2014, a systematic review of publications in the English, French and German literature was published that identified and then graded the evidence for allergic cause of occupational asthma for 372 agents or worksites [9]. This review used the Scottish Intercollegiate Guidelines Network (SIGN) Grading system [13] and the Royal College of General Practitioners (RCGP) three-star system [14]. These

evaluation systems require high quality cohort or case control studies to be rated as strong evidence and consider case reports or case series even with specific antigen challenge testing to have limited, very limited or no scientific evidence. Most publications in the medical literature on new causes of work-related asthma are case reports which include a description of the patient's symptoms, exposure, documentation of hyper-reactivity, skin testing and pulmonary function testing specific to the exposure or workplace (specific antigen challenge testing). Using the RCGP evaluation system, only 36 substances or worksites were rated having moderate or strong evidence, 61 had limited or contradictory evidence while 275 agents, worksites or professions were rated as having no scientific evidence. This contrasts with the AOEC criteria, which highly value well done specific antigen challenge testing even in a single subject and do not accept analytical cohort or case control studies that do not include pulmonary function testing to document with objective testing physician diagnosed asthma or self-reported respiratory symptoms. Users of the AOEC list should be aware of the criteria for the agents on the AOEC occupational asthma list. These criteria differ from epidemiological criteria used to determine causality.

In summary, the AOEC list of agents associated with the new onset of work-related asthma has well developed criteria, a peer review process and regular updates. In addition to its use in clinical practice it has been useful in classifying agents reported to work-related asthma surveillance systems in the United States [15–17]. Future improvements to the web site that have been suggested are having the references used to classify the agents and the common occupations/industries where these substances are used included on the web site. The list is recommended as a resource to clinicians evaluating patients with adult onset asthma.

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Appendix I

Glutaraldehyde CAS # 111-30-8

Glutaraldehyde is a saturated dialdehyde widely used as a disinfectant and chemical sterilant. It is also used in water treatment, as a preservative in cosmetics, a biocide in metal working fluids, a tanning agent, a tissue fixative in pathology labs, a hardening agent in the development of radiographs, and in embalming solution. Glutaraldehyde is used in solutions that range from 1 to 50% glutaraldehyde in water. Disinfectant solutions approved by the FDA are 2.4%–3.4% glutaraldehyde.

Health effects reported from exposure to glutaraldehyde are irritation of the eyes, nose and throat, contact and allergic dermatitis, and asthma. There are at least 44 well-documented cases of occupational asthma from seven peer-reviewed publications.

The first report of occupational asthma from glutaraldehyde was on two endoscopy nurses; one had a positive bronchial specific antigen test 80 min after exposure and one had a positive nasal airways resistance test at 20 and 120 min after exposure. Two other symptomatic endoscopic nurses had negative challenge tests ([Corrado et al., 1986]).

A 33 year respiratory technician had worsening of her asthma after beginning to work in a bronchoscopy suite where she was responsible for cleaning bronchoscopes with a solution containing 3.6% glutaraldehyde, 7% phenol and 1.2% sodium phenolate. She had a 23% drop in her FEV₁ on a post shift spirometry after cleaning the bronchoscopes and only a 1% drop on a day she only performed administrative duties. Her FEV₁ improved and she required a higher dose of methacholine to demonstrate a significant drop in her FEV₁ after a two week vacation. She then had a positive workplace challenge test where she had spirometry every 1/2 hour throughout the work day ([Chan-Yeung et al., 1993]).

Five workers involved with endoscopy and two workers from radiography had positive bronchial specific antigen challenge testing to glutaraldehyde (three also had a positive test to formaldehyde) and peak expiratory flow records over multiple weeks showing a pattern consistent with occupational asthma. Increased responsiveness to methacholine was recorded after the positive bronchial specific antigen challenges ([Gannon et al., 1995]).

Twenty-one cases of occupational asthma to glutaraldehyde were confirmed in the West Midlands area of England. Eight individuals had positive bronchial specific antigen challenge testing to glutaraldehyde. Three of the eight, in addition to 13 others who did not have bronchial specific antigen testing performed, also had peak flow testing consistent with occupational asthma. Seven individuals had positive specific IgE to glutaraldehyde ([DiStefano et al., 1999]).

A 61 year old renal dialysis nurse developed asthma four years after glutaraldehyde was substituted for formaldehyde. She had a positive bronchial specific antigen challenge to glutaraldehyde ([Quirce et al., 1999]).

Eleven hospital workers (eight nurses, one laboratory technician, one radiographer and one ward attendant) had positive bronchial specific antigen challenge testing to glutaraldehyde. These individuals had an increase in eosinophil number and percentage, in eosinophil cationic protein, in tryptase and in albumin in nasal lavage fluid after challenge ([Palczynski et al., 2001]).

The most recent case report with a positive bronchial specific antigen challenge test to glutaraldehyde was on a pulmonary technician ([Ong et al., 2004]).

Summary

Glutaraldehyde meets both major AOEC criteria and minor criteria #1, #3 and #4 for sensitization and therefore meets the AOEC criteria for an asthmagen.

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