

RESOURCES FOR HEALTH PRACTITIONERS TO IDENTIFY EXPOSURES THAT CAN CAUSE WORK-RELATED ASTHMA

There is an excellent resource available for clinicians to help determine whether a work place exposure could be related to their patient's asthma. The Association of Occupational and Environmental Clinics (AOEC) provides an interactive list of agents known to cause work-related asthma (WRA). The list of agents can be found at: www.aoecdata.org/ExpCodeLookup.aspx.

The AOEC is a non-profit, 501(c) 3 organization made up of approximately 60 occupational and environmental clinics. In addition to providing a forum for collaborative research, the AOEC provides a mechanism for practitioners and clinics to share information on occupational and environmental health. In Michigan, Michigan State University and Wayne State University have the only two occupational/environmental clinics that are members of the AOEC. AOEC encourages and has open access to the information and resources it has developed for all practitioners.

For WRA specifically, the AOEC provides a listing of asthmagens. Currently, there are 319 unique substances on the list that have been classified as causing asthma in the work place. AOEC has a mechanism in place to update this list on a regular basis through a specified set of criteria; the AOEC regularly reviews the medical literature and updates the list twice a year.

The AOEC Exposure Code List was originally developed in 1994, for use by AOEC members in order to help identify emerging occupational and environmental health concerns, not just those related to WRA exposures (1). However, to meet the increasing use of the list as a standardized source on occupational asthma-causing agents, it was further enhanced in 2002.

Beginning in 2002, the AOEC developed a formal review process with set criteria to evaluate agents already on the list that had been previously designated as asthmagens, as well as adding newly-identified agents to the list. Agents historically on the list with an asthma-causing designa-

tion were those that had been reported in the medical literature by experts in WRA; many of those agents have been re-reviewed through the formal review process, applying the set criteria developed in 2002. For the remaining historically listed agents, the AOEC has established an ongoing process to determine which exposures meet the criteria. In addition, each year, new exposures are selected for review based on recommendations from AOEC members, asthma experts, industry representatives, or other stakeholders.

The AOEC Exposure Code List was developed as a tool to help clinicians. It does not replace the user's obligation to assess each situation on its individual merits and to make an independent clinical judgment. The list is not exhaustive; it is likely that there are exposures on the list not yet designated as asthmagens that are capable of inducing asthma. Furthermore, the AOEC asthmagen criteria do not take into account the level of exposure or 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 (e.g. encapsulated or airborne form, enclosed or open process, low or high concentration). It should be noted, the AOEC Exposure Code List is not an official document of any governmental agency.

Clinicians are encouraged to regularly consider whether there is a work component in their adult patients with asthma. The use of the AOEC list can help them determine whether their patient's exposure has previously been reported in the published medical literature as causing asthma.

Most of the medical literature on new causes of WRA 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).

This next section outlines the criteria that are used for asthma-causing agents on the AOEC Exposure Code List. There are two sets of criteria— those for Sensitizer-Induced Asthma, developed in 2002, and those for acute, Irritant-Induced Asthma, also known as Reactive Airways Dysfunction Syndrome (RADS), developed in 2008. These criteria were developed in collaboration with experts 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 of whom are clinic representatives, usually physicians, and four individual members, for whom at least two must be non-physicians (i.e. nurse, industrial hygienist).

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 who 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] Work place 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 work place, to exclude work-aggravated asthma.

OR

MINOR CRITERIA (at least two & must be published in a peer-reviewed journal):

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

Regardless of whether the agent is a sensitizer or irritant, any agent determined to be asthma-causing is given a code of “A” in the Asthmagen field on the AOEC Exposure Code List. The original agents designated with an “A” were based on a table from the second edition of Asthma in the Workplace (2). A second field in the List indicates the specific criteria used for determining the asthma-causing designation. For substances formally reviewed: those meeting criteria for sensitizer-induced asthma are designated “Rs”; those meeting criteria for RADS are designated “Rr”; those meeting both sets of criteria are designated “Rrs”; and, those not meeting either set of criteria are designated “R”. Exposures that are generally accepted as asthmagens where a formal review was not felt to be necessary are designated “G”, for example the isocyanates.

Criteria for Reactive Airways Dysfunction Syndrome (RADS)

- [1] There is a documented exposure to a specific 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. The magnitude of the exposure is not further quantified.
- [3] Symptoms appear within 24 hours of most recent acute exposure and persist for at least 3 months following the exposure.
- [4] Pulmonary function tests (PFT) demonstrate obstruction, when done within 1-2 months of symptom onset.
- [5] Nonspecific bronchial hyper-responsiveness is present, measured by methacholine or histamine challenge tests. Obstruction on PFT can usually be demonstrated soon after the acute exposure. Over time (i.e. 1-2 months) away from further exposures, routine PFTs may normalize, even though symptoms may persist and airway hyper-responsiveness may be demonstrated with challenge testing.

FOR a substance to be included in the AOEC RADS list, it must meet all of the above criteria 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. Unlike asthma caused by sensitizers, there is no basis to re-challenge the individual with the substance to verify causation.

One of the key differences in sensitization compared to RADS is latency. Latency refers to the time between the beginning of exposure to a substance and the onset of symptoms. 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 patients relates to the severity of initial pulmonary injury, rather than to prolonged or continued exposure as it does with a sensitizing agent.

What should a clinician do when they suspect their patient’s respiratory symptoms are related to their job? Routinely asking adult patients with new-onset asthma about possible work-related triggers is the initial step in identifying the agents. Once an agent or agents are identified, using the AOEC Exposure Code List to determine if the agent(s) are listed as asthmagens will help further clarify the diagnosis and treatment plan. For more detailed information on the medical literature related to a particular agent, the AOEC maintains reports on the agents that have been reviewed, and these annual reports are available from the AOEC office by request ([aoec @ aoec.org](mailto:aoec@aoec.org)).

Dr. Rosenman has been involved with the AOEC asthma review process and is happy to discuss an individual patient and/or provide the articles that are the basis for the AOEC’s asthma classification. He can be reached at 1-800-446-7805 or by email at Rosenman@msu.edu.

References:

1. Hunting KL, McDonald SM. Development of a Hierarchical Exposure Coding System for Clinic-Based Surveillance of Occupational Disease and Injury. *Applied Occupational and Environmental Hygiene* 1995; 10: 317.
2. Chan-Yeung M and Malo JL. Table of Major Inducers of Occupational Asthma in *Asthma in the Workplace, 2nd Ed.*, eds. Bernstein IL, Chan-Yeung M, Malo JL, and Bernstein DI. New York: Marcel Decker, Inc. 1999; 683-720.

AOEC Exposure Code	Primary Name	Synonym	P=Pesticide S=Solvent	A=Asthmagen	R= Sensitizer R= RADS R= Both R= Meets neither G= Generally accepted	RTECS	CAS
260.22	Tetrazene	Tetrazene		A	Rs	XF6864000	31330-63-9
260.30	3-Amino-5-mercapto-1,2,4-triazole	3-Amino-5-mercapto-1,2,4-triazole		A	Rs	XZ53575000	16691-43-3
260.30	3-Amino-5-mercapto-1,2,4-triazole	AMT		A	Rs	XZ53575000	16691-43-3
270.02	Latex, Natural Rubber	Latex Gloves, NOS		A	G		
270.02	Latex, Natural Rubber	Latex, Natural Rubber		A	G		

This is an example of what the AOEC Exposure Code List looks like. One can search for a specific agent by name or synonym (or partial word) or select “Display All Asthmagens” to view the agents listed in the database.

www.aoec.org is the link to the Exposure Code List as well as numerous other resources for health clinicians.

A new review article on Occupational Asthma was published in February 2014 in the *New England Journal of Medicine*—

Tarlo SM, Lemiere C. Occupational Asthma *NEJM* 2014; 370: 640-649.

Occupational asthma continues to be a frequent topic in medical journals. The condition is relatively common, and has been estimated as the cause in 15% of adults with asthma and as a trigger in 25% of adults with asthma. Yet, despite these estimates, occupational asthma remains under-diagnosed.

*Project
S E.N.S.O.R. News

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*PS Remember to report all cases of occupational disease!

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