Revised Protocol:

Criteria for Designating Substances as Occupational Asthmagens on the AOEC List of Exposure Codes

Revised September 2008

I. Introduction

This is a project to evaluate the current AOEC listing of occupational asthmagens, and to develop a protocol for AOEC to routinely update this listing. In order to develop such a protocol, we must first define the terms to be used in this process.

A working definition of Asthma

For the purposes of this project, asthma will be defined as a condition of variable airflow obstruction, commonly presenting with symptoms of cough, wheeze, dyspnea, or chest tightness. In most cases wheezing is heard in the chest during active episodes, but wheezing may resolve completely between episodes. Asthma is a clinical diagnosis since there is no single test, biomarker, or gene specific for asthma.

A working definition of Occupational Asthma

The purpose of the AOEC list is to provide clinical guidance about previously demonstrated causes of asthma. Some disagreement exists among experts as to the best definition of occupational asthma. The AOEC working definition is chosen not to settle those disagreements, but to help develop a list of substances known to cause asthma *de novo*.

As detailed below, the AOEC List of Exposures will identify substances that cause occupational asthma. After review, substances will be designated as "Sensitizing Causes of Asthma" and/or "Non-Sensitizing Causes of Asthma" which will include substances which cause reactive airways dysfunction syndrome (RADS) or irritant-induced asthma.

For the purposes of this project, occupational asthma will be defined as asthma which is acquired *de novo* from a workplace exposure to a specific substance. This may occur through an immunologic sensitization or by the induction of a chronic asthma state due to an inflammatory response to a non-sensitizing exposure. Although a much broader definition of occupational asthma could include work-aggravated asthma, this working definition focuses on asthma which would not have occurred but for that specific exposure. Work-aggravated asthma will be included only insofar as it refers to a new sensitization or a markedly greater severity of asthma resulting from a new irritant airways response in subjects with previous asthma. Work-aggravated asthma will be excluded where this refers to pre-existing asthma which is not caused, but made symptomatically worse, by inhalation exposures to non-specific substances such as nuisance dust (particles not otherwise classified) or cold, dry air.

II. Background: Methodology of establishing criteria for causation of disease.

Different study designs carry different degrees of certainty in considering whether a disease is caused by an occupational exposure.

1. Controlled clinical trials. The study design with the highest degree of certainty is the controlled clinical trial, in which a group of subjects would be exposed to a substance of interest, and the likelihood of disease outcome in that group is compared to the likelihood in a similar but non-exposed group. It is obviously not ethical to expose individuals to suspected asthma-causing substances, and so study designs with lesser degrees of certainty must be used to establish causation of occupational asthma.

2. Observational studies of exposed workers (cohort and case-control studies). Epidemiological studies in which measures of exposure and disease outcome are measured simultaneously cannot definitively establish cause and effect. However, when exposures are measured prospectively, or when they involve gradients of exposure that address dose-response relationships, they can provide strong evidence supporting a causal relationship. Furthermore, when observational studies repeatedly indicate an association between exposure and disease in a variety of study groups, a conclusion of causation can eventually be made with a high degree of certainty. Of course, it is always important to carefully evaluate the potential for bias or confounding which can obscure true relationships between exposure and disease.

3. Case reports and case-series based on clinical experiences. Despite the inherent limitations in studies that lack a comparison group, these are important designs for identifying candidate substances as asthmagens, and they frequently lead to the eventual identification of new asthmagens.

4. Allergy testing and inhalational challenge testing. Initial hypotheses in case reports and case series are often supported by allergy testing (measurement of antigen-specific IgE) and inhalation challenge testing. The inhalation challenge has successfully established, and sometimes refuted, the importance of newly-hypothesized sensitizing asthmagens. Controlled workplace challenge tests with measurement of serial peak expiratory flow or spirometry can implicate a complex workplace environment (e.g. the aluminum pot room) without identifying a specific agent causing asthma. Positive challenge tests in an occupationally-exposed group have helped to establish a new asthmagen. Such workplace challenge tests may be extremely helpful in establishing a diagnosis of occupational asthma. Subjects with new-onset clinical asthma during workplace exposure to a substance not known to cause asthma are sometimes studied in a specific inhalation challenge laboratory. Laboratory challenge has the important advantage of allowing more precise identification of candidate asthmagens, as well as accurate measurement of the inhaled concentration of the substance. Test subjects receive inhalation challenges with low doses of the suspected substance to simulate workplace exposures, usually with a blinded control challenge. Serial measures of airflow (usually FEV_1) are taken over a period of about 12 hours after exposure to test for immediate or delayed bronchoconstriction. Significant bronchoconstriction after exposure to the substance, but not after control challenges, is considered confirmation that the specific substance is a cause of asthma. The inhalation challenge test is sometimes referred to as the “gold standard” for determining whether a specific exposure has caused asthma in a given individual.

4. Animal exposure studies. In many cases, animal inhalation or other exposure studies are used to examine mechanisms of occupational asthma (e.g. T-cell vs. humoral immunity). Because there are few animal models of asthma closely similar to human asthma, inter-species comparisons have not been as helpful in supporting or refuting causation as they have been for some other toxic diseases. However, similar airway inflammatory effects may sometimes be seen in animal exposure studies. For example, ovalbumin (egg white) was used for many years to sensitize guinea pigs by the peritoneal route with subsequent enhancement of respiratory responses and bronchoconstriction by airway challenge. Only relatively recently was the human correlate to this animal model observed—occupational asthma from inhalation of dried eggs in food workers.

A common sequence of events in identifying new asthmagens begins with the recognition through a case report or case series of a potential causative substance. Particularly if multiple cases are reported from the same exposure at multiple locations, the association is strengthened. This may be followed by a cross-sectional survey of asthma prevalence in the exposed and a similar unexposed group. Prospective studies of working populations can identify associations between asthma incidence and occupational exposures. Individuals with suspected occupational asthma may be challenged at work or in a laboratory with the candidate substance, and bronchoconstriction that occurs with exposure but not with control conditions strengthens the association of a substance with causation of asthma. Consistent findings from various observational studies, case reports, allergen testing, and specific challenge testing, support the conclusion that a candidate substance is a cause of occupational asthma.

III. The AOEC Exposure Code System

The AOEC Exposure Code List was first developed in 1994, for use by AOEC members in order to help identify emerging occupational and environmental health concerns (Hunting and McDonald, "Development of a Hierarchical Exposure Coding System for Clinic-Based Surveillance of Occupational Disease and Injury", *Appl. Occup. Environ. Hyg*. 10(4), April, 1995.). The AOEC Exposure Code List is not an official document of any governmental agency. The AOEC is a non-profit, 501(c)3 organization and encourages open access to the information and resources it has developed.

A supplemental designation for asthmagens (indicated by an "A") is included on the list. Formal criteria for the asthmagen designation (see section IV below) were first established for sensitizer-induced asthma in 2002 and for irritant-induced asthma (Reactive Airways Dysfunction Syndrome, RADS) in 2008. These criteria were developed in collaboration with experts in occupational and pulmonary medicine. Both sets of criteria have been reviewed and approved by the AOEC Board of Directors.

The AOEC Exposure Code List includes substances that have been reported as asthmagens by experts in occupational asthma (Chan-Yeung M and Malo JL. Tables 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.). Although not all of the substances reported to be asthmagens have

yet been formally evaluated against the AOEC criteria, the AOEC has established an ongoing process to determine which exposures meet the criteria. Each year, several exposures are selected for review based on recommendations from AOEC members, asthma experts, industry representatives, or other stakeholders. These annual reports are available from the AOEC office by request. The Exposure Code List has two columns to identify asthmagens. The first column indicates an "A" once an exposure has been designated as an asthmagen. The second column indicates which criteria were used for determining that designation. Exposures 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. Exposures that are generally accepted as asthmagens are designated "G".

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 draw independent judgments. In particular, the list is not exhaustive. It is likely that some exposures not yet designated as asthmagens are capable of inducing asthma. Furthermore, the AOEC asthmagen criteria do not reflect a specific exposure scenario, which will alter the risk of asthma from a particular substance (e.g. encapsulated or airborne form, enclosed or open process, low or high concentration).

IV. Process for designating a substance as an Asthmagen

After conducting a scientific literature review of accepted criteria for identifying substances that cause occupational asthma, and in consultation with representatives from the Sentinel Event Notification System for Occupational Risks (SENSOR) program and the National Institute of Occupational Safety & Health (NIOSH), the AOEC has adopted specific methodology for adding or removing asthmagens from the exposure list. This methodology requires that a candidate substance meet specific criteria based on peer-reviewed scientific publications.

A substance will meet criteria for designation as a cause of occupational asthma if it first meets the test of specificity (it can be identified as a discrete workplace substance) and clinical relevance (there is the potential for human exposure because of its use in workplaces) and in addition meets the criteria listed below. To be included as a Sensitizing cause of asthma, it must meet at least one of the major criteria or at least two of the minor criteria. To be included as a Non-Sensitizing cause of asthma (Reactive Airways Dysfunction Syndrome or Irritant-induced Asthma), it must meet the criteria established for RADS.

A. Specificity. To be designated as an asthmagen, a substance must be defined in such a way that it can be specifically avoided by the patient without requiring unnecessary avoidance of non-asthmagens. For example, the AOEC list includes "Cosmetology chemicals, not otherwise specified." Such a broad category encompasses a large variety of common and uncommon substances, ranging from the acetone in nail polish to the talc

in body powders, to animal and plant extracts in perfumes. For the purposes of the AOEC listing, such a category is too broad to be practical. Nonetheless, a substance need not be precisely characterized, since some occupational asthmagens (e.g. rat urine) are chemically complex but, from a practical point of view, can be specifically avoided.

B. Clinical relevance. To be designated as an asthmagen, a substance must be currently used or have been used in workplaces where there is potential for exposure. A peer-reviewed case report, outbreak report, or case series report is also required to establish clinical relevance where circumstances described in the report indicate that the substance is likely to be an asthmagen.

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. 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. Subjects 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 hyperresponsiveness is demonstrated in patients with suspected occupational asthma while they are 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 two patients, 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 one or more patients in each of two or more subjects published in a peer-reviewed journal.

Criteria for Reactive Airways Dysfunction Syndrome (RADS)

The term RADS has been used to describe an "irritant induced non-immunological asthma without a latency period" (Gautrin DF, Bernstein IL, Brooks S, Henneberger P. Reactive airways dysfunction syndrome and irritant asthma. Chapter 25, in *Asthma in the Workplace and Related Conditions, 3rd Ed*. Taylor & Francis, New York, London.). These authors have proposed the following Cardinal Diagnostic Features of RADS for diagnosing individual clinical cases:

1. Identification of date, time, frequency and extent of exposure, which may be single high or multiple somewhat high exposures (yet still higher than either TLV or PEL concentrations).
2. Symptoms appear within 24 hours
3. No latency period between exposure and symptoms
4. Symptoms less likely to improve away from work
5. Objective (pulmonary function) tests demonstrate obstruction
6. Presence and persistence of nonspecific bronchial hyper-responsiveness (as measured by methacholine or histamine challenge tests).

These clinical criteria can be potentially applied to any exposure, regardless of the chemical nature of the substance. 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. These authors also list more than 30 substances for which published reports (in most instances case reports) support causation of RADS, with fulfillment of one or more criteria that include clinical history, spirometry, bronchial hyper-responsiveness, and pathology. Most but not all of the substances listed could be described as acids, bases, or strong irritants. Not all the substances are defined by their specific chemical nature (e.g. case reports are cited for "bleaching agent, spray paint, paint fumes, and cleaning agents"). 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 with asthma caused by sensitizers, there is no basis to re-challenge the individual with the substance to verify causation.

Considerations in developing modified criteria:

The criteria used to evaluate specific substances as candidates for inclusion in a list of causes of RADS is somewhat different than clinical diagnostic criteria, although a peer reviewed publication of one or more case reports fulfilling the clinical diagnostic criteria above would certainly support inclusion in such a list.

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). In that situation, prior low level exposures become irrelevant, and the concept of latency is immaterial. Also unlike sensitizer-induced asthma, RADS may be less likely to improve once exposure ends. However, this reflects mechanistic differences between the two disorders, in which the likelihood of improvement for RADS relates to the severity of initial pulmonary injury, rather than to prolonged or continued exposure to the sensitizing agent.

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, routine pulmonary function testing may normalize, even though symptoms may persist and airway hyper-responsiveness may be demonstrated with challenge testing.

AOEC will use the following modified clinical criteria for the purpose of evaluating specific candidate substances as causes of RADS:

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 hours of most recent acute exposure and are persistent for at least 3 months following the exposure.
4. Pulmonary function tests demonstrate obstruction, when done within 1-2 months of symptom onset.
5. Nonspecific bronchial hyper-responsiveness is present, as measured by methacholine or histamine challenge tests.

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 two or more cases, or in two or more peer-reviewed articles describing single cases. This differs slightly from the AOEC criteria for sensitizer-induced asthma, where one case report is sufficient, as long as airway hyper-responsiveness is demonstrated under certain conditions which are typically not possible with RADS.

Acknowledgements:

AOEC wishes to acknowledge the efforts of William Beckett, MD, MPH who developed the initial document **Explanatory Protocol: Criteria for Designating Substances as Occupational Asthmagens on the AOEC List of Exposure Codes**. The initial document developed by Dr. Beckett and his subsequent document regarding RADS, has been revised by the AOEC Board of Directors with input from various AOEC members and was officially adopted by the Board September 22, 2008.