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

William S. Beckett M.D., M.P.H.
Box EHSC, University of Rochester School of Medicine and Dentistry
575 Elmwood Ave.
Rochester, NY 14642
585 273 4964
bill_beckett@urmc.rochester.edu

Revised April 2005
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) 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, and 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.

b) 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 how best to define occupational asthma; this working definition is chosen not to settle those disagreements, but to provide a useful working definition suited to the needs of AOEC and SENSOR.

As detailed below, it is proposed that there will be two categories of the AOEC List of Exposures causing occupational asthma. The current list will be designated as the category “Sensitizing Causes of Asthma” and to this will be added a separate category “Non-Sensitizing Causes of Asthma” which will
include substances which cause reactive airways dysfunction syndrome and irritant asthma.

For the purposes of this project, occupational asthma will be defined as asthma which is acquired de novo from a specific workplace exposure. This may occur through an immunologic sensitization, another form of sensitization, or due to the induction of a chronic asthma state due to non-sensitizing inflammatory stimuli. This is limited to asthma which would not have occurred in the complete absence of that specific exposure. Asthma induced by pharmacological agents (e.g. recurrent exposure to cholinesterase-inhibiting pesticides or cotton dust) will be included as potential asthmagens. It is recognized that a much broader definition of occupational asthma which includes work-aggravated asthma is often appropriate, but for this project the objective is to develop a list of substances known to cause asthma de novo. 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 similar exposure and control groups would be exposed to a substance of interest, and disease outcome is observed. This is obviously not ethical for exposure of individuals to suspected asthma-causing substances, and so study designs with lesser degrees of certainty must be used to establish causation of occupational asthma. This can be done with a high degree of certainty, however (as for example, with establishing that smoking cigarettes causes lung cancer and emphysema).

2. Observational studies of exposed workers (cohort and case-control studies). Such epidemiological studies in which measures of exposure and asthma outcome are compared across gradients of exposure cannot definitively establish cause and effect. However, when observational studies repeatedly indicate an association between exposure and subsequent asthma in a variety of study groups, in circumstances where bias and confounding have been carefully evaluated, a presumption of causation can eventually be made with a high degree of certainty.

3. Case reports and case-series based on clinical experiences. These are important designs in designating new potential asthmagens. Because adult-onset asthma may occur in workers in the absence of an occupational cause, case
studies and small series do not necessarily determine causation. Nonetheless, this design is the most frequent study design that leads 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 been highly successful in establishing, and sometimes refuting, the importance of newly-hypothesized sensitizing asthmagens. Subjects with new-onset clinical asthma during workplace exposure to a substance not known to cause asthma are studied in a human challenge laboratory. These 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 but not after control challenges is considered to confirm the exposure substance as 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. One or particularly many positive challenge tests in an occupationally exposed group often help to establish a new asthmagen. Controlled workplace challenge tests with measurement of serial peak expiratory flow or spirometry can be similar to laboratory challenge tests and may implicate a complex workplace environment
(e.g. the aluminum pot room) without identifying a specific agent causing asthma. Such workplace challenge tests may be extremely helpful in establishing a diagnosis of occupational asthma. Laboratory challenge sometimes has the important advantage of allowing more precise measurement of the inhaled concentration of the substance in question.

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 (retrospective cohort design). Individuals with suspected occupational asthma may be challenged at work or in a laboratory with the implicated substance, and if bronchoconstriction occurs with exposure but not control conditions, it is often assumed that the substance is capable of causing occupational asthma. Confirmation from various kinds of observational studies, allergen testing and specific challenge testing lends strength to the association of a substance with causation of asthma.

III. The AOEC Exposure Codes, which now maintains an on-line instant look-up engine, currently lists 359 substances as asthmagens (causes of asthma). This is available at the URL www.aoec.org/aoeccode.htm.

A literature review for current criteria for acceptance of agents known or suspected to cause occupational asthma has been performed. Based on the above considerations, the following protocol is proposed for routinely updating the AOEC asthmagen designations, including substance-specific literature review, and consultations with SENSOR state representatives and with NIOSH personnel. It is proposed that the methodology for adding or removing asthmagens from the AOEC list use the following approach, which requires meeting scientific criteria based in peer-reviewed scientific publications.

A substance will meet criteria for inclusion 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 (it is present in the air of workplaces) and in
addition meets sufficient criteria as listed below. To be included as a Sensitizing
cause of asthma, it must meet one or more of the major criteria, or two or more of
the minor criteria. To be included as a Non-Sensitizing cause of asthma
(Reactive Airways Dysfunction Syndrome or Irritant Asthma), it must meet major
criterion 2 or two or more of the minor criteria numbered 1, 2, and 4. (Major
criterion 1 and minor criterion 3 do not apply to non sensitizing causes of
asthma).

A. Specificity. To be included in the AOEC asthmagen list, a substance must be
defined in such a way that, if it is a cause of asthma, it can be avoided
specifically by the patient without requiring unnecessary avoidance of non-
asthmagens. An example of this criterion is the current category on the AOEC
list, “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
broader than is practical. To be included, a substance need not be exactly
chemically characterized, since there are common occupational asthmagens
(e.g. rat urine) which are chemically complex but which, from a practical point of
view, can be avoided for medical reasons.
B. Clinical relevance. To be designated as AOEC asthmagens, substances must be currently used or have been used in workplaces where there is potential for inhalation 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 the possibility of this substance as an asthagen.

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. 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, but this design is not characteristic of many 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. Subjects tested should be reasonably considered to be without asthma prior to
testing in the workplace, to exclude work-aggravated asthma. Peer reviewed publication.

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 methacholine, histamine, or cold-air challenge, 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.
III. Substances to be initially evaluated by these criteria (after review of criteria by AOEC external reviewers):

On the advice of project officer Katherine Kirkland MPH, Director, AOEC, the opinions of three SENSOR project members for substances to be initially evaluated was sought.

CAPT Margaret S. Filios RN, ScM of the Division of Respiratory Disease Studies, NIOSH, recommended the following substances to be evaluated:

d-Limonene
heat shrink wrapping.
cosmetics (NOS)
Amino mercapto triazole
Shark cartilage
Isophorone diisocyanate
n-butyl acrylate
TMPAA (name not further specified), a coating, cross-linking agent
Status of Draft Review, (7/27/02):

This draft is edited in response to the comments of all reviewers. An additional NIOSH review (4/24/02) recommended broadening the AOEC Asthmagen list to include causes of Reactive Airways Dysfunction Syndrome and Irritant Asthma, and a number of editorial changes. These recommendations have in most cases been incorporated into the current draft. Additional revisions have also been made at the suggestions of SENSOR participants at the June ’02 SENSOR meeting.
III. Bibliography

Three useful lists of substances causing occupational asthma were attached to the first draft:

