

## Review

# Primary Prevention of Occupational Asthma: Identifying and Controlling Exposures to Asthma-Causing Agents

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**Background** Primary prevention of occupational asthma requires timely identification and regulation of asthma-causing agents.

**Methods** We examined 39 substances identified as causing allergic occupational asthma in the US to determine the basis for their identification and their regulatory status. We compared them with occupational asthmagens identified and regulated in the UK and Germany.

**Results** US regulatory agencies have not established consistent, evidence-based methods to identify and control exposures to substances that cause occupational asthma. Occupational asthmagens are identified primarily by non-regulatory US organizations, and most are not regulated to prevent asthma.

**Conclusions** Implementing an evidence-based identification and regulatory process for occupational asthmagens will help to ensure primary prevention of occupational asthma in the US. This should include: establishing consistent identification criteria; publishing a list of occupational asthmagens; collecting use, exposure, and health effects information on asthma-causing substances; requiring medical surveillance and medical removal protection in addition to exposure limits; and stimulating development of safer alternatives. Am. J. Ind. Med. 51:477–491, 2008. Published 2008 Wiley-Liss, Inc.<sup>†</sup>

**KEY WORDS:** occupational asthma-causing agents; ACGIH; NIOSH; AOEC; Cal/OSHA; OSHA; UK; Germany

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## INTRODUCTION

Occupational asthma [Toren et al., 2000] is a serious and sometimes fatal disease [Gassert et al., 1998; Chester et al., 2005; Labrecque et al., 2006] that accounts for up to 15% of adult-onset asthma [Balmes et al., 2003]. As one of the most common occupational diseases in industrialized countries [Chan-Yeung and Malo, 1994], it can lead to deterioration of health, inability to work, and lost productivity [Gannon et al., 1993; Eisner et al., 2006]. Estimated medical costs for occupational asthma in the US were \$1.5 billion in 1999 [Leigh et al., 2003]. Occupational asthmagens emitted from workplaces potentially can add to the asthma burden in

communities [Leikauf, 2002; White et al., 2002]. Occupational asthma can be caused by exposure to both sensitizing agents and to irritants. Our study is focused on allergic occupational asthma, which develops after a variable period of time during which “sensitization” to a workplace substance occurs [Youakim, 2001].

Controlling and eliminating exposures to workplace substances that cause asthma can be effective in decreasing asthma morbidity and the associated costs [Allmers et al., 2002; LaMontagne et al., 2006; Tarlo, 2007]. However, in contrast to agent-induced, work-related cancer and other chronic health conditions, there is no standard, validated animal model for identifying asthma-causing agents and establishing safe exposure levels based on risk assessments [Fairhurst, 2003]. This poses a significant barrier to primary prevention of occupational asthma.

In this article, we examine workplace asthmagen policies of government agencies in the UK and Germany that identify, publicize, and control exposures to workplace agents that cause asthma. We make recommendations for implementing similar policies in the US to augment our ongoing efforts to prevent asthma in workplaces and communities.

## METHODS

We compiled a list of US occupational asthmagens comprised of substances identified primarily by the American Conference of Governmental Industrial Hygienists (ACGIH), which provides current and readily available information on recommended exposure limits and their health bases, and secondarily by the National Institute for Occupational Safety and Health (NIOSH), the Association of Occupational and Environmental Clinics (AOEC), and the Hazard Evaluation System and Information Service (HESIS), California Department of Public Health.

The ACGIH-identified occupational asthmagens for the purpose of this study are those substances for which the “Threshold Limit Value (TLV) Basis” published in the 2007 ACGIH TLV Booklet [American Conference of Governmental Industrial Hygienists (ACGIH), 2007] is identified as “asthma” or “respiratory sensitization,” or substances that have been assigned a respiratory sensitizer (SEN) notation. The TLV Documentations [American Conference of Governmental Industrial Hygienists (ACGIH), 2001] for specific substances were reviewed to provide additional information on the basis of TLVs and to distinguish respiratory and dermal sensitizer (SEN) notations. The NIOSH-identified asthmagens are substances that are identified as causing symptoms of “asthma” and/or “respiratory sensitization” in the 2005 NIOSH Pocket Guide to Chemical Hazards [National Institute for Occupational Safety and Health (NIOSH), 2005]. The AOEC occupational asthmagens included in the study were limited to substances

that have been identified by the AOEC using posted criteria [Beckett, 2005]. These substances are a subset of the AOEC list of approximately 350 Occupational Asthmagens, which consists of sensitizing and non-sensitizing agents, previously identified based on expert opinion [Association of Occupational and Environmental Clinics (AOEC), 2007]. The HESIS asthma-causing agents are substances for which HESIS has recommended regulations to protect against asthma as a part of legislatively mandated program work [Hooper, 1982].

We compared the list of US occupational asthmagens we compiled to lists of occupational asthmagens published by the United Kingdom Health and Safety Commission (UK HSC) [Health and Safety Executive (HSE), 2007] and by the Commission of the Deutsche Forschungsgemeinschaft for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) [Deutsche Forschungsgemeinschaft (DFG), 2006].

To examine methods that can be used to identify occupational asthmagens, we reviewed the ACGIH Documentations of TLVs [American Conference of Governmental Industrial Hygienists (ACGIH), 2001] for substances identified as respiratory sensitizers, and identification criteria posted by the AOEC [Beckett, 2005], and published by the UK HSC [European Commission, 1996; Health and Safety Executive (HSE), 2001] and German MAK Commission [Deutsche Forschungsgemeinschaft (DFG), 2006]. The identification criteria and methods used by the various organizations to identify occupational asthmagens are summarized in Table I.

To assess the regulatory status of, and recommended exposure limits for, the identified occupational asthmagens, we reviewed the California Division of Occupational Safety and Health (Cal/OSHA) Permissible Exposure Limits (PELs) [California Division of Occupational Safety and Health (Cal/OSHA), 2007], US Occupational Safety and Health Administration (OSHA) PELs [Occupational Safety and Health Administration (OSHA), 2007], UK HSC Workplace Exposure Limits (WELs) [Health and Safety Executive (HSE), 2007a], German MAK Commission exposure limit (MAK) values [Deutsche Forschungsgemeinschaft (DFG), 2006], ACGIH TLVs [American Conference of Governmental Industrial Hygienists (ACGIH), 2007], and NIOSH Reference Exposure Levels (RELs) [National Institute for Occupational Safety and Health (NIOSH), 2005].

## RESULTS

### US Organizations

Table II lists 39 substances identified as causing occupational asthma by US organizations. The ACGIH identifies 19 asthmagens and other US organizations identify

**TABLE I.** Criteria or Basis for Designating Agents as Occupational Asthmagens

| Organization  | Criteria or identification method  | Criteria publicly available/published? | Exposure limit health basis publicly available/published? |
|---|--|--|---|
| American Conference of Governmental Industrial Hygienists <sup>a</sup> (US) | Substances for which "respiratory sensitization" or "asthma" is the "TLV Basis" published in the 2007 ACGIH TLV Booklet, or substances assigned a respiratory sensitizer (SEN) notation  | No                                     | Yes   |
| Association of Occupational and Environmental Clinics <sup>b</sup> (US)     | <b>MAJOR CRITERIA</b> (at least one) 1. Specific inhalation challenge test positive; 2. Workplace challenge with physiologic response (spirometry or peak flow) shows reversible expiratory airflow obstruction. <b>OR MINOR CRITERIA</b> (at least 2); 1. Non-specific airways hyperreactivity demonstrated in patients while employed (peer reviewed publication); 2. Reversible wheeze heard, with repeated exposures (peer reviewed publication); 3. Positive specific IgE in two or more patients (peer reviewed publication); 4. Remission/recurrence with stop-resume work test (peer reviewed publication)   | Yes                                    | Yes   |
| Hazard Evaluation System and Information Service <sup>c</sup> (US)          | Expert opinion based on review and evaluation of published toxicological, medical, industrial hygiene and other relevant data  | No                                     | Yes   |
| Health and Safety Executive <sup>d</sup> (UK)                               | A substance may cause sensitization by inhalation (risk phrase R 42) if there is: evidence that the substance or preparation can induce specific respiratory hypersensitivity; where there are positive results from appropriate animal tests; or if the substance is an isocyanate, unless there is evidence that the [isocyanate] substance does not cause respiratory hypersensitivity. Hypersensitivity is normally seen as asthma, but rhinitis and alveolitis are also considered. When considering the evidence from human exposure, it is necessary for a decision on classification to take into account in addition to the evidence from the cases: the size of the population exposed and the extent of the exposure. <b>HUMAN EVIDENCE:</b> Clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include: a chemical structure related to substances known to cause respiratory hypersensitivity, in vivo immunologic test (e.g., skin prick test), in vitro immunologic test (e.g., serological analysis), studies that may indicate other specific but non-immunological mechanisms of action, e.g., repeated low-level irritation, pharmacologically mediated effects, or data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction. Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and the development of respiratory hypersensitivity. Positive bronchial challenge tests provide sufficient evidence for classification on their own. <b>ANIMAL STUDIES:</b> May include IgE measurements (e.g., in mice), specific pulmonary responses in guinea pigs | Yes                                    | Yes   |
| MAK Commission <sup>e</sup> (Germany)                                       | <b>SUFFICIENT EVIDENCE:</b> (1) studies or case reports of a specific hyperreactivity of the airways or the lungs which are indicative of an immunologic mechanism from more than one patient and at least two independent testing centers. In addition the (clinical) symptoms or adverse effects in the function of the upper or lower airways or lungs must be shown to be associated with the exposure to the substance. <b>PROBABLE EVIDENCE:</b> one single case report of a specific hyperreactivity of the airways or the lungs <b>AND</b> other indications of sensitizing effects, e.g., a close structure—effect relationship with known airway allergens. <b>NOT SUFFICIENTLY DOCUMENTED BUT NOT EXCLUDED:</b> (1) epidemiological studies which demonstrate an increased incidence of symptoms or impaired function in exposed persons; (2) studies or case reports of a specific hyperreactivity of the airways or lungs in only one patient; (3) studies or case reports of sensitization (e.g., detection of IgE) without accompanying symptoms or impairment of function causally associated with exposure; (4) positive results of animal studies; <b>OR</b> (5) structure—effect relationships with known respiratory allergens   | Yes                                    | Yes   |
| National Institute for Occupational Safety and Health (US) <sup>f</sup>     | Based on information in NIOSH criteria documents, Current Intelligence Bulletins, and other technical publications; published testimony; and evaluation of information from recognized references in the fields of industrial hygiene, occupational medicine, toxicology, and analytical chemistry   | No                                     | Yes   |

<sup>a</sup>American Conference of Governmental Industrial Hygienists (ACGIH) [2001]. Documentation for Threshold Limit Values and Biological Exposure Indices, 7th ed., suppl. Cincinnati, OH.

<sup>b</sup>Beckett W S. Criteria for designating substances as occupational asthmagens on the ADEC List of Exposure Codes. [www.aoc.org/content/asthma/asthma\\_protocol4-9-05\\_revision.doc](http://www.aoc.org/content/asthma/asthma_protocol4-9-05_revision.doc).

<sup>c</sup>Hazard Evaluation System and Information Service (HESIS), Occupational Health Branch, California Department of Public Health. Available: [www.dhs.ca.gov/ohb/hesis/default.htm](http://www.dhs.ca.gov/ohb/hesis/default.htm).

<sup>d</sup>Health and Safety Executive (HSE), UK. Asthmagen? Critical assessments of the evidence for agents implicated in occupational asthma. Available: [www.hse.gov.uk/asthma/asthma/asthma.pdf](http://www.hse.gov.uk/asthma/asthma/asthma.pdf).

<sup>e</sup>Commission for the Investigation of Health Hazard of Chemical Compounds in the Work Area Deutsche Forschungsgemeinschaft. *List of MAK and BAT values 2006*. Weinheim: Wiley-VCH, 2006.

<sup>f</sup>National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards. September 2005. DHHS (NIOSH) Publication No. 2005-149.

**TABLE II. Occupational Asthma-Causing Agents Identified by Selected US Non-Regulatory Organizations and Agencies, Cal/OSHA, and OSHA\***

| No. | Agent  | ACGIH TLV <sup>a</sup>  | TLV basis <sup>b</sup>   | NIOSH REL <sup>c</sup>  | Cal/OSHA PEL <sup>d</sup>   | Cal/OSHA PEL basis <sup>e</sup>                           | OSHA PEL <sup>f</sup>   | OSHA PEL basis <sup>g</sup>                                  |
|-----|--|---|--|---|---|---|---|--|
| 1   | Alternaria <sup>h</sup> (common outdoor mold)                        | None  | NA   | None  | None  | NA  | None  | NA   |
| 2   | Caprolactam <sup>i</sup>   | 5 mg/m <sup>3</sup> inhalable fraction and vapor  | URT irritation   | 1 mg/m <sup>3</sup> (dust), 5 ppm (vapor)   | 1 mg/m <sup>3</sup> (dust), 5 ppm (vapor)   | Not available   | None  | NA   |
| 3   | Chromium <sup>iii</sup> metal, chromium III Chromium VI (hexavalent) | 0.5 mg/m <sup>3</sup> , 0.5 mg/m <sup>3</sup><br>0.05 mg/m <sup>3</sup> (water soluble)<br>0.01 mg/m <sup>3</sup> (insoluble) | URT and skin irritation<br>URT irritation; cancer<br>Lung cancer     | 0.5 mg/m <sup>3</sup><br>0.001 mg/m <sup>3</sup> (all compounds)<br>0.001 mg/m <sup>3</sup> | 0.5 mg/m <sup>3</sup><br>0.005 mg/m <sup>3</sup> (all compounds)<br>0.005 mg/m <sup>3</sup> | Not available<br>Cancer<br>Cancer                         | 1.0 mg/m <sup>3</sup> , 0.5 mg/m <sup>3</sup><br>0.005 mg/m <sup>3</sup> (all compounds)<br>0.005 mg/m <sup>3</sup> | None<br>pulmonary disease; toxic effects<br>Cancer<br>Cancer |
| 4   | Cobalt and inorganic compounds as cobalt <sup>j</sup>                | 0.02 mg/m <sup>3</sup>  | Asthma; pulmonary function; myocardial effects                       | 0.05 mg/m <sup>3</sup> (metal dust and fume)  | 0.02 mg/m <sup>3</sup> (metal dust and fume)  | Myocardial effects (same as 1994 TLV)                     | 0.1 mg/m <sup>3</sup> (metal dust and fume)   | Interstitial pneumonitis                                     |
| 5   | Cotton dust, raw   | 0.2 mg/m <sup>3</sup> (measured using vertical elutriator, cotton dust sampler)   | Asthma   | <0.2 mg/m <sup>3</sup>  | 1 mg/m <sup>3</sup>   | Bysinosis   | 1 mg/m <sup>3</sup>   | Bysinosis  |
| 6   | Cyanoacrylate <sup>k</sup> NDS                                       | 0.2 ppm methyl-2-cyanoacrylate  | URT and eye irritation   | 2 ppm methyl-2-cyanoacrylate  | 0.2 ppm methyl-2-cyanoacrylate  | Not available   | None  | NA   |
| 7   | Diazonethane <sup>l</sup>  | 0.2 ppm   | URT and eye irritation   | 0.2 ppm   | 0.2 ppm   | Not available   | 0.2 ppm   | LRT irritant; other toxic effects                            |
| 8   | Diethanolamine <sup>h</sup>  | 2 mg/m <sup>3</sup> , skin  | Liver and kidney damage; headache                                    | 15 mg/m <sup>3</sup>  | 2 mg/m <sup>3</sup> , skin  | Growth rate depression in rats (consistent with 1994 TLV) | None  | NA   |
| 9   | Ethylenediamine <sup>l</sup>   | 10 ppm; skin  | Not stated   | 10 ppm  | 10 ppm  | Not available   | 10 ppm  | Respiratory sensitization                                    |
| 10  | Flour dust   | 0.5 mg/m <sup>3</sup> , inhalable fraction; SEN <sup>m</sup>  | Asthma; URT irritation; bronchitis                                   | None  | 0.5 mg/m <sup>3</sup>   | Pulmonary function; asthma                                | None  | NA   |
| 11  | Formaldehyde <sup>k</sup>  | C <sup>n</sup> 0.3 ppm SEN  | URT and eye irritation   | 0.016 ppm   | 0.75 ppm  | Cancer; asthma  | 0.75 ppm  | Cancer; asthma   |
| 12  | Freon, heated <sup>h</sup>   | None  | NA   | None  | None  | NA  | None  | NA   |
| 13  | Glutaraldehyde <sup>n</sup> activated and inactivated                | C 0.05 ppm  | URT and eye irritation; CNS impairment; skin irritation              | C 0.2 ppm   | C 0.05 ppm  | Same as current TLV                                       | None  | NA   |
| 14  | Grain dust (oat, wheat, barley) <sup>o</sup>                         | 4 mg/m <sup>3</sup> (no asbestos and <1% crystalline silica)  | bronchitis; URT irritation; pulmonary function                       | 4 mg/m <sup>3</sup>   | 10 mg/m <sup>3</sup>  | Not available   | 10 mg/m <sup>3</sup>  | Adverse respiratory effects                                  |
| 15  | Hexahydrophthalic anhydride, all isomers                             | C 0.005 mg/m <sup>3</sup> inhalable fraction and vapor; SEN   | Respiratory sensitization; eye, skin, and URT irritation             | None  | None; C 0.005 mg/m <sup>3</sup> based on 2004 TLV (proposed)                                | NA  | None  | NA   |
| 16  | Hexamethylene diisocyanate <sup>l</sup>                              | 0.005 ppm   | URT irritation; respiratory sensitization                            | 0.005 ppm   | 0.005 ppm   | Not available   | None  | NA   |
| 17  | Isophorone diisocyanate <sup>l</sup>                                 | 0.005 ppm   | Respiratory sensitization  | 0.005 ppm skin  | 0.005 ppm; skin   | Not available   | None  | NA   |
| 18  | Maleic anhydride <sup>l</sup>  | 0.1 ppm SEN   | Eye; URT, and skin irritation  | 0.25 ppm  | 0.1 ppm   | Not available   | 0.25 ppm  | Irritation; respiratory sensitization                        |
| 19  | Methylene bisphenyl isocyanate (MDI) <sup>l</sup>                    | 0.005 ppm   | Respiratory sensitization  | 0.005 ppm   | 0.005 ppm   | Not available   | C 0.02 ppm  | Respiratory sensitization                                    |
| 20  | Methyl isocyanate <sup>l</sup>                                       | 0.02 ppm; skin  | URT irritation   | 0.02 ppm; skin  | 0.02 ppm; skin  | Not available   | 0.02 ppm; skin  | Irritation   |
| 21  | Methyl methacrylate <sup>h</sup>                                     | 50 ppm  | URT irritation; body weight effects; pulmonary edema; eye irritation | 100 ppm   | 50 ppm  | Pulmonary and olfactory effects (same as 2000 TLV)        | 100 ppm   | Irritation; systemic effects                                 |
| 22  | Naphthalene diisocyanate <sup>l</sup>                                | None  | NA   | 0.005 ppm   | C 0.01 ppm  | Not available   | None  | NA   |
| 23  | Nickel, and nickel compounds <sup>h,i</sup>                          | None  | NA   | 0.015 mg/m <sup>3</sup> (all except nickel carbonyl)  | None  | Not available   | None  | NA   |
|     | Elemental  | 15 mg/m <sup>3</sup> inhalable fraction   | Dermatitis; pneumoconiosis   | 0.015 mg/m <sup>3</sup>   | 10 mg/m <sup>3</sup>  | Not available   | 10 mg/m <sup>3</sup>  | Dermatitis; sensitization                                    |
|     | Soluble inorganic (NOS)  | 0.1 mg/m <sup>3</sup> , inhalable fraction  | Lung damage; nasal cancer  | 0.015 mg/m <sup>3</sup>   | 0.1 mg/m <sup>3</sup>   | Not available   | 1.0 mg/m <sup>3</sup>   | Dermatitis; sensitization                                    |
|     | Insoluble inorganic (NOS)  | 0.2 mg/m <sup>3</sup> , inhalable fraction  | Lung cancer  | 0.015 mg/m <sup>3</sup>   | 10 mg/m <sup>3</sup>  | Not available   | 1.0 mg/m <sup>3</sup>   | Dermatitis; sensitization                                    |
|     | Nickel subsulfide as nickel  | 0.1 mg/m <sup>3</sup> , inhalable fraction  | Lung cancer  | 0.015 mg/m <sup>3</sup>   | None  | Not available   | None  | NA   |
| 24  | Penicillium <sup>h</sup>   | None  | NA   | None  | None  | NA  | None  | NA   |
| 25  | p-Phenylenediamine <sup>l</sup>                                      | 0.1 mg/m <sup>3</sup>   | URT irritation; skin sensitization                                   | 0.1 mg/m <sup>3</sup> , skin  | 0.1 mg/m <sup>3</sup> , skin  | Not available   | 0.1 mg/m <sup>3</sup> , skin  | Asthma   |
| 26  | Phthalic anhydride <sup>l</sup>                                      | 1 ppm; SEN  | URT, eye, and skin irritation  | 1 ppm   | 1 ppm   | Not available   | 2 ppm   | Skin, eye, URT irritation                                    |
| 27  | Piperazine dithionchloride <sup>l</sup>                              | 5 mg/m <sup>3</sup>   | Eye and skin irritation; skin sensitization; asthma                  | 5 mg/m <sup>3</sup>   | 5 mg/m <sup>3</sup>   | Not available   | None  | NA   |

|    |  |   |   |  |  |      |  |                                      |   |
|----|--|---|---|--|--|------|--|--------------------------------------|---|
| 28 | Platinum metal   | 1 mg/m <sup>3</sup>   | Asthma; URT irritation  | 1 mg/m <sup>3</sup>                                | 1 mg/m <sup>3</sup>  | None | Not available  | None                                 | NA  |
|    | Soluble salts, as platinum                                   | 0.002 mg/m <sup>3</sup>   | Asthma; URT irritation  | 0.002 mg/m <sup>3</sup>                            | 0.002 mg/m <sup>3</sup>  | None | Not available  | 0.002 mg/m <sup>3</sup>              | Asthma; respiratory distress                  |
| 29 | Polymetric isocyanates <sup>1</sup>                          | None  | NA  | None   | None   | None | None   | None                                 | NA  |
| 30 | Pyrethrum <sup>1</sup>                                       | 5 mg/m <sup>3</sup>   | Liver damage; LRT irritation  | 5 mg/m <sup>3</sup>                                | 5 mg/m <sup>3</sup>  | None | Not available  | 5 mg/m <sup>3</sup>                  | Systemic effects                              |
| 31 | Rhodium metal and insoluble compounds <sup>1</sup>           | 1 mg/m <sup>3</sup>   | URT irritation (metal); LRT irritation (insoluble)                  | 0.1 mg/m <sup>3</sup>                              | 0.1 mg/m <sup>3</sup>  | None | Not available  | 0.1 mg/m <sup>3</sup>                | Possible allergic effects (based on platinum) |
|    | Soluble compounds  | 0.01 mg/m <sup>3</sup>  | Asthma  | 0.001 mg/m <sup>3</sup>                            | 0.001 mg/m <sup>3</sup>  | None | Not available  | 0.001 mg/m <sup>3</sup>              | Possible allergic effects (based on platinum) |
| 32 | Rosin core solder thermal decomposition products (colophony) | None; exposure by all routes should be controlled as low as possible; SEN | Skin sensitization; dermatitis; asthma                              | 0.1 mg/m <sup>3</sup> (as formaldehyde)            | 0.1 mg/m <sup>3</sup> (as formaldehyde)  | None | Not available  | None                                 | NA  |
| 33 | Rice dust <sup>1</sup>                                       | None  | NA  | None   | None   | None | NA   | None                                 | NA  |
| 34 | Subtilisins, crystalline active enzyme <sup>1</sup>          | C 0.00006 mg/m <sup>3</sup>   | Asthma; skin, URT, and LRT irritation                               | ST <sup>1</sup> 0.00006 mg/m <sup>3</sup> [60 min] | ST 0.00006 mg/m <sup>3</sup> (higher volume sampler for 60 min)                  | None | Not available  | None                                 | NA  |
| 35 | Toluene-2,4-or 2,6-disocyanate or as mixture <sup>1</sup>    | 0.005 ppm; SEN (intended change)  | Respiratory sensitization; asthma; eye irritation (intended change) | Ca (cancer) lowest feasible                        | 0.005 ppm (toluene-2,4-disocyanate)  | None | Not available  | C 0.02 ppm (toluene-2,4-disocyanate) | Respiratory sensitization                     |
| 36 | Triethanolamine <sup>1</sup>                                 | 5 mg/m <sup>3</sup>   | Eye and skin irritation   | None   | 5 mg/m <sup>3</sup>  | None | Contact dermatitis; skin and eye irritation (same as 1993 TLV) | None                                 | NA  |
| 37 | Trimellitic anhydride <sup>1</sup>                           | C 0.04 mg/m <sup>3</sup> (intended change)                                | Respiratory sensitization   | 0.04 mg/m <sup>3</sup>                             | 0.04 mg/m <sup>3</sup>   | None | Allergic sensitization (consistent with 1993 TLV)              | None                                 | NA  |
| 38 | Wood dust Western Red Cedar <sup>1</sup>                     | 0.5 mg/m <sup>3</sup> , inhalable fraction; SEN                           | Asthma  | 1 mg/m <sup>3</sup>                                | 2.5 mg/m <sup>3</sup> , 0.5 mg/m <sup>3</sup> ; SEN (proposed based on 2005 TLV) | None | Not available  | None                                 | NA  |
| 39 | Wood dust hardwoods and softwoods <sup>1</sup>               | 1 mg/m <sup>3</sup> (all other species except Western Red Cedar)          | Pulmonary function  | 1 mg/m <sup>3</sup> (includes Western Red Cedar)   | 5 mg/m <sup>3</sup> , 1 mg/m <sup>3</sup> (proposed based on 2005 TLV)           | None | Not available  | None                                 | NA  |

URT, upper respiratory tract; NOS, not otherwise specified; CNS, central nervous system; LRT, lower respiratory tract; NA, not applicable.

<sup>1</sup>Primarily agents for which ACGIH lists respiratory sensitization or asthma as the TLV basis, or assigns a respiratory sensitization (SEN) notation. Additional agents identified by other US organizations are indicated by footnotes, i, h, k, and l.

<sup>2</sup>ACGIH [2007], TLVs<sup>(k)</sup> and BEIs<sup>(k)</sup>. ACGIH Worldwide Signature Publications. Cincinnati, OH. Time-weighted average concentrations for a 8-hr workday and a 40-hr workweek, except as indicated.

<sup>3</sup>Information published in ACGIH [2007] TLVs<sup>(k)</sup> and BEIs<sup>(k)</sup>. ACGIH Worldwide Signature Publications. Cincinnati, OH.

<sup>4</sup>NIOSH [2005]. Pocket guide to chemical hazards. DHHS (NIOSH) Publication No. 2005-149. Except as indicated, time-weighted average concentrations for up to a 10-hr workday during a 40-hr workweek.

<sup>5</sup>Cal/OSHA [2007]. Title 8, California Code of Regulations, § 5155, Table AC-1, Permissible Exposure Limits for Chemical Contaminants. Available: [www.dir.ca.gov/title8/5155table.ac1.html](http://www.dir.ca.gov/title8/5155table.ac1.html). Except as indicated, time-weighted average concentrations for up to an 8-hr workday during a 40-hr workweek.

<sup>6</sup>California Occupational Safety and Health Standards Board [2007]. Archives. Approved Regulations. Title 8, § 5155, Airborne Contaminants. Available: [www.dir.ca.gov/osh/sb/archives.html](http://www.dir.ca.gov/osh/sb/archives.html) and footnote d.

<sup>7</sup>OSHA [2007]. 29 Code of Federal Regulations, Table Z-1. Limits for Air Contaminants. 1910.1000. Available: <http://www.osha-slc.gov/plis/oshaweb/owadisp/showdocument?p1table=standards&p1id=9992>.

<sup>8</sup>Documentation of Threshold Limit Values for Substances in Workroom Air. American Conference of Governmental Hygienists, Third Edition, 1971.

<sup>9</sup>AOEC occupational asthmagens based on established criteria. (Table 1). Available: [www.aoc.org/content/asthmagen.protocol.4-9-05.revision.pdf](http://www.aoc.org/content/asthmagen.protocol.4-9-05.revision.pdf).

<sup>10</sup>NIOSH [2005]. Pocket guide to chemical hazards. DHHS (NIOSH) Publication No. 2005-149. Substances identified as causing symptoms of asthma and/or respiratory sensitization.

<sup>11</sup>NIOSH also identifies substance as causing asthma and/or respiratory sensitization.

<sup>12</sup>Regulated to prevent respiratory and dermal sensitization by Cal/OSHA and Federal OSHA.

<sup>13</sup>HESIS recommended regulation by Cal/OSHA to prevent asthma.

<sup>14</sup>SEN = potential for an agent to produce sensitization as confirmed by animal or human data. It does not imply that sensitization is the critical effect on which the TLV is based, nor does it imply that this effect is the sole basis for that agent's TLV. ACGIH, 2007. TLVs<sup>(k)</sup> and BEIs<sup>(k)</sup>. ACGIH Worldwide Signature Publications. Cincinnati, OH.

<sup>15</sup>Ceiling limit. The concentration that should not be exceeded during any part of the working exposure.

<sup>16</sup>Short-term exposure over a 60 min period.

an additional 21 (includes rhodium metal and insoluble compounds) asthmagens. Of the substances not identified by ACGIH, NIOSH identifies 12 substances, AOEC identifies 10 substances, and HESIS identifies two substances. Nickel and nickel compounds are identified by both AOEC and NIOSH, and glutaraldehyde is identified by NIOSH and HESIS. Formaldehyde is the only substance regulated by Cal/OSHA and OSHA to prevent occupational asthma through a comprehensive standard [California Division of Occupational Safety and Health (Cal/OSHA), 2007a; Occupational Safety and Health Administration (OSHA), 2007a].

The ACGIH, a nongovernmental, not-for-profit professional organization, identifies and provides guidance to practicing industrial hygienists on controlling exposures to occupational substances, including those that cause asthma. As new scientific information becomes available which may affect TLVs, substances are reevaluated. The Threshold Limit Values for Chemical Substances Committee reviews existing scientific information in various occupational health and safety disciplines and develops health-based, non-regulatory guidelines known as TLVs. The TLVs are developed for use by professionals in the practice of industrial hygiene, and are not intended to be used as enforceable health standards. The basic rationale for the establishment of occupational exposure limits for substances reviewed by the Committee are published in Documentations of the Threshold Limit Values (TLVs<sup>®</sup>) and Biological Exposure Indices (BEIs<sup>®</sup>) [American Conference of Governmental Industrial Hygienists (ACGIH), 2001]. Threshold Limit Values are set according to the lowest airborne concentration at which a health hazard is present, and the TLV basis is identified as the hazard which occurs at that level. As shown in Table I, there are no a priori criteria defining the characteristics of specific health effects (such as sensitization or asthma).

Review of the TLV Documentations [American Conference of Governmental Industrial Hygienists (ACGIH), 2001] for the ACGIH-identified substances in Table II indicate that human data, primarily from peer-reviewed, published studies, but also from government and industry reports, and animal data, were used in establishing respiratory sensitization. Limited data were available for many of the substances. In some cases, agents were identified as respiratory sensitizers based on structure–activity relationships. In other cases, agents were identified as respiratory sensitizers even though there were insufficient exposure or toxicity data to guide the recommendation of a TLV to protect against sensitization.

Due to data limitations, the TLVs for only eight of the 19 agents identified by the ACGIH are based on minimizing the potential for developing asthma. The recommended TLV possibly will protect against asthma for five other agents. For example, due to insufficient data for four of the diisocyanate

substances (hexamethylene diisocyanate (HDI), isophorone diisocyanate, methylene bisphenyl diisocyanate (MDI), and methylene bis (4-cyclohexylisocyanate)), the TLVs will possibly protect against asthma on the basis of analogy to toluene diisocyanate (TDI), the only diisocyanate for which quantitative data were available. Direct evidence for rhodium soluble compounds causing respiratory sensitization is also lacking—the TLV is by analogy to platinum soluble compounds. The cotton dust TLV is intended to minimize the potential for Monday morning “chest tightness,” a symptom of byssinosis, and the platinum TLV is intended to minimize the potential for respiratory tract irritation and dermatitis. There were no relevant data upon which to base a TLV for piperazine dihydrochloride to reduce potential respiratory sensitization, so the level of protection provided by the TLV is unknown. Due to the lack of available data on workplace exposure, a TLV was not recommended for rosin core solder thermal decomposition (colophony).

There does not appear to be a consistent correlation between ACGIH assignments of SEN (potential to produce respiratory sensitization) notations and “asthma” and “respiratory sensitization” descriptions (TLV Basis) for agents in Table II. For example, hexamethylene diisocyanate and isophorone diisocyanate (TLV Basis is “respiratory sensitization”) and cobalt (TLV basis is “asthma”) do not have SEN notations. Formaldehyde, maleic anhydride, and phthalic anhydride (TLV Basis is “URT irritation”) have SEN notations. The basis for assigning the SEN notation is the expert opinion of the TLV Chemical Substances Committee applied to each substance individually based on review of scientific and medical literature.

Based on expert opinion (Table I), NIOSH identifies 12 additional asthmagens. NIOSH also identifies 11 of the ACGIH-identified asthmagens—four of which are diisocyanate compounds [National Institute for Occupational Safety and Health (NIOSH), 2005]. NIOSH is a federal agency charged with recommending occupational safety and health standards and describing exposure concentrations that are safe for various periods of employment—including but not limited to concentrations at which no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience. The NIOSH scientific evaluations and proposed standards or Recommended Exposure Levels (RELs) are communicated to regulatory agencies (such as OSHA) and to others in the occupational safety and health community in a variety of publications, including criteria documents and current intelligence bulletins, and also in published testimony [National Institute for Occupational Safety and Health (NIOSH), 2006, 1992].

Review of the RELs for the 23 substances NIOSH identifies as causing asthma indicates that the majority were adopted during the 1989 OSHA PEL Update Project [Occupational Safety and Health Administration (OSHA),

1989; National Institute for Occupational Safety and Health (NIOSH), 2005] and are the same as RELs published for the substances in 1992 [National Institute for Occupational Safety and Health (NIOSH), 1992]. Asthma and/or respiratory sensitization is identified as a health effect for the RELs for 15 substances. Non-asthma health effects are identified for caprolactam, cobalt, glutaraldehyde, maleic anhydride, methyl isocyanate, nickel and nickel compounds, piperazine dihydrochloride, pyrethrum, and toluene diisocyanate. NIOSH identified platinum metal and soluble compounds as causing asthma in 1992 [National Institute for Occupational Safety and Health (NIOSH), 1992], but not in 2005 [National Institute for Occupational Safety and Health (NIOSH), 2005]. The RELs for 14 of the NIOSH-identified substances are the same as the current TLVs for the substances. With the exception of nickel and nickel compounds, toluene diisocyanate, and Western Red Cedar, RELs for the nine remaining substances are the same as TLVs that were adopted by ACGIH before 1986. This is consistent with the widespread use of ACGIH TLVs as a source for occupational health exposure limits in general [Hansson, 1998; Topping, 2001], and with the specific use of the 1986 ACGIH TLVs as the basis for updating PELs during the OSHA PEL Update Project [Occupational Safety and Health Administration (OSHA), 1989]. As shown, nine of the agents in Table II do not have RELs.

Differences in NIOSH and ACGIH assessments regarding the asthma potential of nine substances (caprolactam, diazomethane, ethylenediamine, grain dust, methyl isocyanate, *p*-phenylenediamine, platinum metal and soluble salts, pyrethrum, and wood dusts), suggest that the two organizations use different criteria to determine whether workplace substances cause asthma.

Table II shows 10 occupational asthmagens identified by AOEC based on published criteria (Table I). These substances have not been identified by ACGIH. The AOEC, a non-profit organization, reviews and evaluates peer-reviewed, published human studies and case reports, and uses established criteria to review and revise the AOEC List of Occupational Asthmagens which includes sensitizing and non-sensitizing agents, and originally was based on expert opinion [Association of Occupational and Environmental Clinics (AOEC), 2007]. Through the Sentinel Event Notification Systems for Occupational Risks (SENSOR), NIOSH funds state health departments to conduct surveillance of occupational asthma [Jajosky et al., 1999; Goe et al., 2004]. NIOSH SENSOR Asthma states recommend agents for review by the AOEC, and use the AOEC list in conducting state-based surveillance. The designation of chromium compounds, diethanolamine, methyl methacrylate, and triethanolamine as occupational asthmagens by the AOEC, but not by ACGIH and NIOSH, may be due to evaluation of different information, and/or use of different identification criteria or rationales.

The Hazard Evaluation System and Information Service (HESIS), based on expert opinion (Table I), identifies two asthmagens, glutaraldehyde and polymeric isocyanates, that have not been identified by ACGIH. Established by the California Legislature, HESIS identifies, evaluates, provides practical information on, and recommends protective standards for workplace chemicals that can cause chronic disease and other health damage [Hooper, 1982]. HESIS recommended a PEL of 0.015 ppm for glutaraldehyde, and medical surveillance and medical removal requirements consistent with the Cal/OSHA Formaldehyde Standard. A 1995 HESIS publication on glutaraldehyde informed employees and employers about the asthmagenic potential of this substance and how to minimize exposures [Hazard Evaluation System and Information Service (HESIS), 1995]. HESIS recommends a total reactive isocyanate group (TRIG)-based standard for polymeric isocyanates, which is consistent with others [Bello et al., 2004].

We reviewed Cal/OSHA and OSHA PELs to determine the regulatory status of the asthmagens identified by US organizations. As shown in Table II, limited information on the basis of the Cal/OSHA PELs was available for review [California Occupational Safety and Health Standards Board, 2007]. Cal/OSHA identifies asthma and/or respiratory sensitization as the PEL basis for three of the substances (flour dust, formaldehyde, and trimellitic anhydride). Asthma is not identified as the basis for the Cal/OSHA PEL for cobalt although the current TLV, which has the same value, is based on asthma. The Cal/OSHA PEL for glutaraldehyde, like the TLV, is based on animal data and is intended to prevent irritation. The TLV was adjusted to account for the greater irritancy potency of glutaraldehyde compared to formaldehyde [American Conference of Governmental Industrial Hygienists (ACGIH), 2001a]. Cal/OSHA documents (in a footnote to the PEL) that the glutaraldehyde PEL may not protect against asthma, and provides information regarding the respiratory and dermal sensitization potential of glutaraldehyde and protective measures [California Division of Occupational Safety and Health (Cal/OSHA), 2007]. Most of the Cal/OSHA PELs for which information on the health bases was not available are the same as current or previously adopted TLVs, and probably have the same health bases. This congruence reflects the process Cal/OSHA has used to update PELs. Using the TLVs as a starting point, a Cal/OSHA-appointed, Airborne Contaminants Advisory Committee periodically reviews and updates existing Cal/OSHA PELs and evaluates proposals for new PELs. Based upon independent scientific assessments, the Committee often has recommended revised PELs that are consistent with TLVs [California Occupational Safety and Health Standards Board, 2005]. There are no Cal/OSHA PELs for seven of the asthmagens in Table II. As shown, Cal/OSHA has proposed new PELs for hexahy-

diphthalic anhydride and isocyanate-containing compounds, and revisions to the existing PELs for Western Red Cedar and wood dusts [California Division of Occupational Safety and Health (Cal/OSHA), 2007b].

The majority of the OSHA PELs in Table II were adopted when the agency was established in 1970, and are based on 1968 ACGIH TLVs [Occupational Safety and Health Administration (OSHA), 1989]. New and revised PELs (based on 1986 TLVs) were adopted by OSHA during the PEL Update Project [Occupational Safety and Health Administration (OSHA), 1989], but were later vacated [Occupational Safety and Health Administration (OSHA), 1993]. As shown, the OSHA PELs for nine substances are the same as 1968 TLVs that are based on asthma or respiratory sensitization. There are no OSHA PELs for 23 of the asthmagens in Table II.

As noted earlier, formaldehyde is the only agent that is regulated by OSHA and Cal/OSHA to prevent asthma with a comprehensive standard that includes requirements for medical surveillance to detect early signs of asthma, and medical removal protection if employees' exposure to formaldehyde results in occupational asthma. In contrast, respiratory sensitization or asthma is not the basis of the formaldehyde TLV or REL. The formaldehyde SEN notation is based on reports of allergic reactions/sensitization following occupational and non-occupational exposure [American Conference of Governmental Industrial Hygienists (ACGIH), 2001]. OSHA identified asthma as a non-cancer health hazard of hexavalent chromium in the recently adopted, comprehensive standard [Occupational Safety and Health Administration (OSHA), 2006]. The PEL, however, is not based on protecting against asthma, and there are no requirements for medical surveillance and medical removal protection related to hexavalent chromium-induced asthma similar to the requirements of the formaldehyde standard.

In summary, NIOSH identifies a total of 23 of the 39 asthmagens in Table II, ACGIH identifies 19, and AOEC identifies 10. HESIS has recommended PELs or identified asthma as a health concern (in fact sheets and other publications) for nine of the substances. Cal/OSHA recognizes five of the agents as causing asthma, and possibly nine others (PELs are the same as TLVs for ACGIH-identified asthmagens), which would result in a total of 14. In addition, Cal/OSHA has proposed PELs based on asthma for three additional substances. OSHA presumably recognizes nine of the substances in Table II as asthmagens since the PELs are the same as 1968 TLVs for which the basis is asthma or respiratory sensitization.

The 39 asthmagens in Table II may represent the "tip of the iceberg" since the total number of sensitizing agents on the original AOEC List of approximately 350 occupational asthmagens [Association of Occupational and Environmental Clinics (AOEC), 2007] has not been determined.

Based on the outcome of this determination, the number of US-identified asthmagens may increase substantially.

## The UK

Table III lists substances designated as causing occupational asthma by the UK HSC using established criteria (Table I) consistent with those of the European Union [European Union, 1996; Health and Safety Executive (HSE), 2001]. Less than half of the UK substances are industrial chemicals—seven of which are not on the US List (Table II). A large number of the occupational asthmagens are naturally occurring substances and biological agents. Groups of structurally similar substances such as isocyanates and reactive dyes are listed instead of individual substances in the group. Eight substances—*isocyanates, flour and grain dusts, glutaraldehyde, wood dust, latex, laboratory animals, glues and resins, and rosin-based solder flux fume*—account for most cases of occupational asthma in the UK [Health and Safety Executive (HSE), 2005, 2007b]. As indicated, 16 of the 45 UK-identified substances are also on the US list (Table II). Three substances (formaldehyde, methyl methacrylate, and cyanoacrylates) on the US list did not meet the UK asthmagen criteria and are not listed [Health and Safety Executive (HSE), 2001].

Relatively few of the UK-identified agents have Workplace Exposure Limits (WELs). Five of the eight substances that generate the most asthma cases (*isocyanates, flour dust, glutaraldehyde, wood dust, and solder/colophony*) however, do have established WELs. For these substances, exposures must never exceed the WEL, and must be kept as low as possible below the WEL. Except for flour dust (UK review of the exposure limit is planned), most of the WEL values are the same as, or not substantially different from current and previously adopted TLVs. Similar to Cal/OSHA and OSHA PELs and NIOSH RELs, ACGIH TLVs are the original basis for many of the UK exposure limits [Topping, 2001]. Some of the agents in Table III have SEN notations and/or R42 (respiratory sensitization) or R42/43 (respiratory and dermal sensitization) risk phrases [European Union, 1996; Health and Safety Executive (HSE), 2001]. We could not determine the basis upon which these identifiers were assigned to some agents and not others.

## Germany

Table IV shows the substances designated by the MAK Commission as respiratory allergens. The MAK designations are based upon established criteria (Table I) that are an extended version of the European Union identification criteria [Schnuch et al., 2002]. Similar to the US, and in contrast to the UK, the majority of the identified respiratory allergens are industrial chemicals. As shown, 18 of the 32 asthmagens identified by the MAK Commission are

**TABLE III.** Substances That Can Cause Asthma-UK Health and Safety Commission\*

| No. | Agent   | Workplace exposure limit (WEL) <sup>a</sup>               | US asthmagen list (Table II) |
|-----|---|---|------------------------------|
| 1   | Alpha amylases                                | None  | No                           |
| 2   | Azodicarbonamide                              | 1.0 mg/m <sup>3</sup> SEN <sup>b</sup> R42 <sup>c</sup>   | No                           |
| 3   | Bromelains                                    | None  | No                           |
| 4   | Carmine                                       | None  | No                           |
| 5   | Castor bean dust                              | None  | No                           |
| 6   | Cephalosporins                                | None  | No                           |
| 7   | Chloramine-T                                  | None  | No                           |
| 8   | Chloroplatinates and other halogenoplatinates | 0.002 mg/m <sup>3</sup>                                   | Yes                          |
| 9   | Chromium (VI) compounds (as chromium)         | 0.05 mg/m <sup>3</sup> SEN                                | Yes                          |
| 10  | Cobalt (metal and compounds)                  | 0.1 mg/m <sup>3</sup> SEN                                 | Yes                          |
| 11  | Cockroach material                            | None  | No                           |
| 12  | Coffee bean dust                              | None  | No                           |
| 13  | Cow epithelium/urine                          | None  | No                           |
| 14  | Crustacean proteins                           | None  | No                           |
| 15  | Diazonium salts                               | None  | No                           |
| 16  | Egg proteins                                  | None  | No                           |
| 17  | Ethylenediamine                               | None  | Yes                          |
| 18  | Fish proteins                                 | None  | No                           |
| 19  | Flour dust                                    | 10 mg/m <sup>3</sup> SEN (review planned)                 | Yes                          |
| 20  | Glutaraldehyde                                | 0.05 ppm SEN R42/43 <sup>d</sup>                          | Yes                          |
| 21  | Some hardwood dusts                           | 5 mg/m <sup>3</sup> SEN (review planned)                  | Yes                          |
| 22  | Henna   | None  | No                           |
| 23  | Isocyanates                                   | 0.02 mg/m <sup>3</sup> (all as -NCO) SEN (review planned) | Yes                          |
| 24  | Ispaghula                                     | None  | No                           |
| 25  | Laboratory animal excreta/secretata           | None  | No                           |
| 26  | Latex (natural rubber)                        | None  | No                           |
| 27  | Maleic anhydride                              | 1 mg/m <sup>3</sup> SEN R42/43                            | Yes                          |
| 28  | Methyltetrahydrophthalic anhydride            | None  | No                           |
| 29  | Nickel sulfate                                | 0.1 mg/m <sup>3</sup> SEN                                 | Yes                          |
| 30  | Opiates                                       | None  | No                           |
| 31  | Papain  | None  | No                           |
| 32  | Penicillins                                   | None  | Yes                          |
| 33  | Persulfates                                   | None  | No                           |
| 34  | Phthalic anhydride                            | 4 mg/m <sup>3</sup> SEN R42/43                            | Yes                          |
| 35  | Piperazine                                    | 0.1 mg/m <sup>3</sup> SEN R42/43                          | No                           |
| 36  | Psyllium                                      | None  | No                           |
| 37  | Some reactive dyes                            | None  | No                           |
| 38  | Rosin-based solder flux fume (colophony)      | 0.05 mg/m <sup>3</sup> SEN                                | Yes                          |
| 39  | Some softwood dust                            | 5 mg/m <sup>3</sup> SEN (review planned)                  | Yes                          |
| 40  | Soybean dust                                  | None  | No                           |
| 41  | Spiramycin                                    | None  | No                           |
| 42  | Storage mites                                 | None  | No                           |
| 43  | Subtilisins                                   | 0.00004 mg/m <sup>3</sup> SEN R42                         | Yes                          |
| 44  | Tetrachlorophthalic anhydride                 | None  | No                           |
| 45  | Trimellitic anhydride                         | 0.04 mg/m <sup>3</sup> R42/43                             | Yes                          |

\*UK occupational asthmagens list is available at: <http://www.hse.gov.uk/asthma/substances.htm>.

<sup>a</sup>2007 Workplace Exposure Limits (WELs) approved by the UK Health and Safety Commission (HSC). Available at: <http://www.hse.gov.uk/coshh/table1.pdf>.

<sup>b</sup>SEN = Capable of causing respiratory sensitization. The identified substances are those which: (a) are assigned the risk phrase "R42: May cause sensitization by inhalation"; or "R42/43: May cause sensitization by inhalation or skin contact" in the *Approved supply list*; or (b) which are listed in Section C of HSE publication "Asthmagen? critical assessments of the evidence for agents implicated in occupational asthma" as updated from time to time, or any substances which the risk assessment has shown to be a potential cause of asthma.

<sup>c</sup>R42 = May cause sensitization by inhalation.

<sup>d</sup>R42/43 = May cause sensitization by inhalation or skin contact.

**TABLE IV.** List of Respiratory Allergens\*-German MAK Commission

| No. | Agent  | MAK <sup>a</sup>  | US asthmagen list (Table II) | UK asthmagen list (Table III) |
|-----|--|---|------------------------------|-------------------------------|
| 1   | Alkali persulfates   | None, establishment of a MAK value <sup>b</sup>                       | No                           | No                            |
| 2   | Ammonium persulfate  | None, establishment of a MAK value                                    | No                           | No                            |
| 3   | $\alpha$ -Amylase  | None  | No                           | No                            |
| 4   | Animal hair, epithelia and other materials derived from animals        | None, establishment of a MAK value                                    | No                           | Yes                           |
| 5   | Beryllium and its compounds  | None, carcinogen—exposure equivalent cannot be evaluated <sup>c</sup> | No                           | No                            |
| 6   | Bromelain  | None  | No                           | Yes                           |
| 7   | Cellulases   | None, establishment of a MAK value                                    | No                           | No                            |
| 8   | Cereal flour dusts (rye, wheat)  | None, examination for sensitization potential <sup>b</sup>            | Yes                          | Yes                           |
| 9   | Cobalt and cobalt compounds (as inhalable fraction)                    | None, carcinogen—no value possible <sup>d</sup>                       | Yes                          | Yes                           |
| 10  | Ethylenediamine  | None, no MAK value can be established at present <sup>e</sup>         | Yes                          | Yes                           |
| 11  | Glutaraldehyde   | 0.05 ppm  | Yes                          | Yes                           |
| 12  | Hard metal containing tungsten carbide and cobalt (inhalable fraction) | None  | No                           | No                            |
| 13  | Hexahydrophthalic anhydride  | None, establishment of a MAK value <sup>b</sup>                       | Yes                          | No                            |
| 14  | 1,6-Hexamethylene diisocyanate (HDI)                                   | 0.005 ppm   | Yes                          | Yes                           |
| 15  | Isophorone diisocyanate  | 0.005 ppm   | Yes                          | Yes                           |
| 16  | Maleic anhydride   | 0.1 ppm, examination of MAK value <sup>b</sup>                        | Yes                          | Yes                           |
| 17  | 4,4'-Methylene diphenyl isocyanate (MDI) (inhalable fraction)          | 0.05 mg/m <sup>3</sup>  | Yes                          | Yes                           |
| 18  | Methyltetrahydrophthalic anhydride                                     | None, establishment of a MAK value                                    | No                           | Yes                           |
| 19  | 1,5-Naphthylene diisocyanate   | None  | No                           | Yes                           |
| 20  | Natural rubber latex   | None  | Yes                          | Yes                           |
| 21  | Nickel and nickel compounds  | None, carcinogen—no value possible <sup>d</sup>                       | Yes                          | No                            |
| 22  | Nickel alloys  | None  | No                           | No                            |
| 23  | Papain   | None  | No                           | Yes                           |
| 24  | Phenyl isocyanate  | None, establishment of a MAK value <sup>b</sup>                       | No                           | Yes                           |
| 25  | Phthalic anhydride   | None, no MAK value can be established at present <sup>e</sup>         | Yes                          | Yes                           |
| 26  | Piperazine   | None, no MAK value can be established at present                      | No                           | Yes                           |
| 27  | Platinum compounds (chloroplatinates)                                  | None, no MAK value can be established at present                      | Yes                          | Yes                           |
| 28  | Polymeric MDI  | None  | Yes                          | Yes                           |
| 29  | Ricinus protein (castor bean)  | None, establishment of a MAK value                                    | No                           | Yes                           |
| 30  | Soya bean constituents   | None, establishment of a MAK value                                    | No                           | Yes                           |
| 31  | Subtilisins  | None  | Yes                          | Yes                           |
| 32  | 2,4- and 2,6-Toluene diisocyanate                                      | None  | Yes                          | Yes                           |
| 33  | Trimellitic anhydride  | 0.04 mg/m <sup>3</sup> , examination of MAK value <sup>b</sup>        | Yes                          | Yes                           |
| 34  | Woods  | None, examination for sensitization potential <sup>b</sup>            |                              |                               |
|     | <i>Terminalia superba</i>  | None  | Yes                          | No                            |
|     | <i>Thuja plicata</i> (includes Western Red Cedar)                      | None  | Yes                          | Yes                           |
|     | <i>Triplochiton scleroxylan</i>  | None  | Yes                          | No                            |
| 35  | Xylanases  | None  | No                           | No                            |
| 36  | Zirconium and insoluble compounds                                      | 1 mg/m <sup>3</sup>   | No                           | No                            |
| 37  | Zirconium, soluble compounds   | None, no MAK value can be established at present <sup>e</sup>         | No                           | No                            |

\*Substances designated "Sa" (airway sensitization) or "Sah" (airway and skin sensitization), German Deutsche Forschungsgemeinschaft (DFG) Report No. 42, List of MAK and BAT Values 2006.

<sup>a</sup>Maximum Concentrations at the Workplace, DFG Report No. 42, List of MAK and BAT (Biological Tolerance) Values 2006.

<sup>b</sup>Appendix VII, MAK Values (Changes and New Entries), DFG Report No. 42, List of MAK and BAT Values 2006.

<sup>c</sup>Section XIII.2, Carcinogenic substances for which "exposure equivalents for carcinogenic substances" cannot be evaluated, DFG Report No. 42, List of MAK and BAT Values 2006.

<sup>d</sup>Section XIII, Carcinogen Substances, DFG Report No. 42, List of MAK and BAT Values 2006.

<sup>e</sup>Section IIb, Substances for which no MAK value can be established at present, DFG Report No. 42, List of MAK and BAT Values 2006.

also on the US List (Table II), and 25 are on the UK List (Table III). Consistent with their criteria, isocyanate compounds are listed individually, not as a group.

Only seven of the 32 agents in Table IV currently have MAK values. With the exception of zirconium and insoluble compounds, and consistent with their initial origin [Topping, 2001], MAK values for the asthmagens are the same as current TLVs. In conjunction with changes recommended for discussion for 2007, two of the seven current MAK values may be examined, and MAK values may be established for nine additional substances. Beryllium, cobalt, and nickel and nickel compounds will not have MAK values based on MAK Commission policy that safe limits cannot be determined for carcinogens. A MAK value has not been established for toluene diisocyanate, which is identified as a non-genotoxic and low potency carcinogen, because the database is considered insufficient. Due to insufficient data at the present time, the MAK Commission has determined that it is not possible to establish values for ethylenediamine, phthalic anhydride, piperazine, platinum compounds (chloroplatinates), and soluble zirconium compounds [Deutsche Forschungsgemeinschaft (DFG), 2006]. We could not determine the status of establishing exposure limits for the remaining 12 respiratory allergens.

## DISCUSSION

To assist employers in providing healthful and safe workplaces, and to protect the health of communities, government agencies play a key role in identifying and evaluating chemicals and other substances that can cause chronic disease. Examples include the identification of carcinogens and reproductive and developmental toxicants, and publication of carcinogen lists by the National Toxicology Program [NTP, 2007, 2007a], and the evaluation of chronic toxicants and publication of the Proposition 65 List by the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (Cal/EPA) [Office of Environmental Health Hazard Assessment (OEHHA), 2007]. Due, in part, to the absence of standardized animal tests, primary prevention of occupational asthma through government-based identification and evaluation of asthma-causing agents has lagged behind primary prevention efforts for other chronic diseases. In spite of these barriers, our review of existing approaches used to identify and control exposures to asthma-causing agents show that regulatory agencies in the UK and Germany play an essential role in developing evidence-based and transparent processes for the primary prevention of occupational asthma.

An important first step is to develop, publish, and use established criteria to identify occupational respiratory sensitizers. Developing and disseminating a list of occupational asthmagens based on the established criteria can help

employers eliminate or reduce exposures to asthma-causing substances, help employees recognize and report asthma symptoms early, help health care providers improve diagnosis of occupational asthma, and improve surveillance of occupational asthma.

The importance of using established criteria to determine which agents cause occupational asthma appears to be reflected in the lack of overlap in the identification of occupational asthmagens by the US, UK, and Germany. As shown in Table V, only 21% (18 of 85) of the total occupational asthmagens were identified by all three countries. Six of the overlapping asthmagens are isocyanates. Only 12 of 85 or 14% of non-isocyanate compounds were identified by the US, UK, and Germany. Many of the designation differences appear to be related to use of different criteria (Table I). It is clear, for example, based on their published criteria, why isocyanates are listed as a group on the UK list and as individual isocyanate compounds on Germany's list. Cyanoacrylates and methyl methacrylate are asthmagens based on AOEC criteria, but not based on the UK criteria. Other differences in the lists also appear to be criteria-based. Glutaraldehyde, one of the leading causes of reported occupational asthma in the UK, is also identified as a respiratory allergen by the MAK Commission, NIOSH, HESIS, and Cal/OSHA. The ACGIH, however, does not designate glutaraldehyde as a respiratory sensitizer due to insufficient evidence. Formaldehyde, the only substance regulated with a comprehensive standard to prevent asthma in the US, is not designated as an occupational asthmagen by NIOSH, the UK, and Germany. In addition to establishing identification criteria, periodic evaluation of the criteria to determine if they are effective in meeting occupational asthma prevention goals, and making necessary adjustments [Schnuch et al., 2002] is also critical.

The initial selection of substances to which criteria subsequently are applied may also influence which occupational asthmagens are identified. The predominance of industrial chemicals identified as asthmagens by the US and Germany probably reflects a focus on hazard surveillance in which substances are selected for evaluation of health hazards in general, as opposed to their asthmagenic potential, in particular. In the UK, substances are selected for evaluation based, in part, on reports of occupational asthma to the UK Surveillance of Work-related Occupational Respiratory Disease (SWORD) system [McDonald et al., 2001]. This surveillance-based selection of substances for evaluation may explain the large number of naturally occurring substances and biological agents identified as occupational asthmagens on the UK list.

Regulatory approaches and policies regarding control of exposures to occupational asthmagens have not been developed in the US except for promulgation of the formaldehyde standard, and appear to be in a state of transition in the UK and Germany where few identified

**TABLE V.** US, UK, and Germany Occupational Asthmagens (Tables II–IV)

| No. | Asthmagen   | US | UK | Germany | No. | Asthmagen                                 | US | UK | Germany |
|-----|---|----|----|---------|-----|---|----|----|---------|
| 1   | Alpha amylase   |    | ✓  | ✓       | 43  | Maleic anhydride†                         | ✓  | ✓  | ✓       |
| 2   | Alternaria  | ✓  |    |         | 44  | Methylene bis (4-cyclohexyl-isocyanate)   | ✓  | ✓  |         |
| 3   | Ammonium persulfate   |    | ✓  | ✓       | 45  | Methylene bisphenyl isocyanate (MDI)*     | ✓  | ✓  | ✓       |
| 4   | Animal hair, epithelia & other materials derived from animals |    | ✓  | ✓       | 46  | Methyl isocyanate                         | ✓  | ✓  |         |
| 5   | Azodicarbonamide  |    | ✓  |         | 47  | Methyl methacrylate                       | ✓  |    |         |
| 6   | Beryllium & its compounds                                     |    |    | ✓       | 48  | Methyltetrahydrophthalic anhydride        |    | ✓  | ✓       |
| 7   | Bromelains  |    | ✓  | ✓       | 49  | 1,5-Naphthalene diisocyanate*             | ✓  | ✓  | ✓       |
| 8   | Caprolactam   | ✓  |    |         | 50  | Natural rubber latex                      |    | ✓  | ✓       |
| 9   | Carmines  |    | ✓  |         | 51  | Nickel & nickel compounds                 | ✓  |    | ✓       |
| 10  | Castor bean dust  |    | ✓  | ✓       | 52  | Nickel sulphate†                          | ✓  | ✓  | ✓       |
| 11  | Cellulases  |    |    | ✓       | 53  | Nickel alloys                             |    |    | ✓       |
| 12  | Cephalosporins  |    | ✓  |         | 54  | Opiates                                   |    | ✓  |         |
| 13  | Chloramine-T  |    | ✓  |         | 55  | Papain                                    |    | ✓  | ✓       |
| 14  | Chloroplatinates & other halogenoplatinates <sup>a</sup>      |    | ✓  | ✓       | 56  | Penicillins                               | ✓  | ✓  |         |
| 15  | Chromium metal and Chromium III and IV                        | ✓  | ✓  |         | 57  | Persulfates                               |    | ✓  |         |
| 16  | Cobalt and cobalt compounds as cobalt†                        | ✓  | ✓  | ✓       | 58  | Persulfates, alkali                       |    | ✓  | ✓       |
| 17  | Cockroach material  |    | ✓  |         | 59  | Persulfate, ammonium                      |    | ✓  | ✓       |
| 18  | Coffee bean dust  |    | ✓  |         | 60  | p-Phenylenediamine                        | ✓  |    |         |
| 19  | Cotton dust, raw  | ✓  |    |         | 61  | Phenyl isocyanate                         |    | ✓  | ✓       |
| 20  | Cow epithelium/urine  |    | ✓  |         | 62  | Phthalic anhydride†                       | ✓  | ✓  | ✓       |
| 21  | Crustacean proteins   |    | ✓  |         | 63  | Piperazine                                |    | ✓  | ✓       |
| 22  | Cyanoacrylates, not otherwise specified                       | ✓  |    |         | 64  | Piperazine dihydrochloride                | ✓  |    |         |
| 23  | Diazomethane  | ✓  |    |         | 65  | Platinum metal & soluble compounds        | ✓  |    |         |
| 24  | Diazonium salts   |    | ✓  |         | 66  | Polymeric isocyanates                     | ✓  | ✓  |         |
| 25  | Diethanolamine  | ✓  |    |         | 67  | Polymeric MDI*                            | ✓  | ✓  | ✓       |
| 26  | Egg proteins  |    | ✓  |         | 68  | Psyllium                                  |    | ✓  |         |
| 27  | Ethylenediamine†  | ✓  | ✓  | ✓       | 69  | Pyrethrum                                 | ✓  |    |         |
| 28  | Fish proteins   |    | ✓  |         | 70  | Reactive dyes (some)                      |    | ✓  |         |
| 29  | Flour dust†   | ✓  | ✓  | ✓       | 71  | Rhodium & compounds                       | ✓  |    |         |
| 30  | Formaldehyde  | ✓  |    |         | 72  | Rice dust                                 | ✓  |    |         |
| 31  | Freon, heated   | ✓  |    |         | 73  | Rosin-based solder flux fume              | ✓  | ✓  |         |
| 32  | Glutaraldehyde†   | ✓  | ✓  | ✓       | 74  | Softwood dust <sup>c</sup>                | ✓  | ✓  | ✓       |
| 33  | Grain dusts   | ✓  |    |         | 75  | Soya bean constituents                    |    | ✓  | ✓       |
| 34  | Hard metal containing tungsten carbide & cobalt               |    |    | ✓       | 76  | Spiramycin                                |    | ✓  |         |
| 35  | Hardwood dust <sup>b</sup> †                                  | ✓  | ✓  | ✓       | 77  | Storage mites                             |    | ✓  |         |
| 36  | Henna   |    | ✓  |         | 78  | Subtilisins                               | ✓  | ✓  | ✓       |
| 37  | Hexahydrophthalic anhydride, all isomers                      | ✓  |    | ✓       | 79  | Toluene-2,4 or 2,6- diisocyanate*         | ✓  | ✓  | ✓       |
| 38  | 1,6-Hexamethylene diisocyanate*                               | ✓  | ✓  | ✓       | 80  | Tetrachlorophthalic anhydride             |    | ✓  |         |
| 39  | Isocyanates   |    | ✓  |         | 81  | Triethanolamine                           | ✓  |    |         |
| 40  | Isophorone diisocyanate*                                      | ✓  | ✓  | ✓       | 82  | Trimellitic anhydride†                    | ✓  | ✓  | ✓       |
| 41  | Ispaghula   |    | ✓  |         | 83  | Western Red Cedar†                        | ✓  | ✓  | ✓       |
| 42  | Laboratory animal excreta/secret                              |    | ✓  | ✓       | 84  | Xylanases                                 |    |    | ✓       |
|     |   |    |    |         | 85  | Zirconium & soluble & insoluble compounds |    |    | ✓       |

<sup>a</sup>Germany = chloroplatinates, only.

<sup>b</sup>UK = about 40 species of hard woods. Germany = *Terminalia superba* and *Triplochiton scleroxylon*, only.

<sup>c</sup>UK = a wide variety derived from mainly coniferous trees. Germany = *Thuja plicata* (includes Western Red Cedar)

☐ = asthmagens identified by US, UK, and Germany (18 of 85 or 21%)

\* = isocyanate compound identified by US, UK, and Germany (n=6)

† = non-isocyanate asthmagens identified by US, UK, and Germany (12 of 85 or 14%)

occupational asthmagens currently have exposure limits. Most of the US-identified occupational asthmagens have exposure limits, the majority of which originate from ACGIH TLVs. Due to data limitations, however, only a few of the exposure limits are based on protecting against asthma. Regulations similar to the comprehensive formaldehyde standard have not been developed in the US for toluene diisocyanate and other well-recognized asthmagens, and Cal/OSHA and OSHA do not currently use identifiers such as SEN notations to distinguish respiratory sensitizers from other regulated substances. Cal/OSHA established a Sensitizers Advisory Committee to provide input on how to effectively regulate respiratory and dermal sensitizers [California Division of Occupational Safety and Health (Cal/OSHA), 2005]. However, this committee has not yet established written criteria upon which to base regulatory action.

The UK workplace exposure limit framework is under review [Health and Safety Commission (HSC), 2003]. WELs have been established for five of their eight top asthma-causing agents. In addition, as a part of a comprehensive effort to reduce the incidence of occupational asthma, the UK developed specific guidance, *Control of Substances that Cause Asthma*, to augment the existing Control of Substances Hazardous to Health (COSHH) regulations [Health and Safety Executive (HSE), 2002]. The guidance includes requirements such as: conducting workplace assessments to identify potential asthma-causing agents, identifying which workers are exposed and how they are exposed, assessing control measures and good working practices for substances which cause asthma, placing all employees who are exposed or likely to be exposed under health surveillance, and providing suitable information and training to employees who may be exposed to agents that cause asthma. Specific prevention strategies also are being developed to address the top eight asthma-causing substances for which the highest numbers of cases are reported each year.

As in the UK, only a few of the identified occupational asthmagens in Germany have exposure limits. However, based on the MAK Commission's current activities, control of exposures to asthma-causing agents appears to be an integral part of Germany's occupational asthma prevention strategy. The MAK Commission's activities related to exposure limits for occupational asthmagens include examining existing MAK values, establishing new values, evaluating new health information for identified respiratory allergens, and determining which asthma-causing substances will not have MAK values due either to their carcinogenic potential, or to insufficient data at the present time. The unique role, related to overseeing compliance with occupational exposure limits, of the institutions for statutory accident insurance and prevention (Berufsgenossenschaften or BGen), in which both employers and trade unions are

involved, may explain Germany's apparent emphasis on establishing occupational exposure limits for substances that cause asthma.

## RECOMMENDATIONS

Based on our review, we recommend that US government agencies take the following actions to ensure a primary prevention approach to protecting against occupational asthma:

- Develop, publish, and use criteria that ensure consistent and early identification of occupational agents that cause asthma. At a minimum, these criteria should: (1) be based on a precautionary approach such as use of structure–activity relationships for known respiratory sensitizers like isocyanates and acid anhydrides; (2) address minimum requirements for scientific and medical evidence and required sources of the evidence (e.g., peer-reviewed publications; reliable reports from government agencies, clinicians, or employers) to ensure a timely, science-based, and comprehensive identification process; and (3) be reviewed and evaluated on an ongoing basis to ensure effectiveness. Existing identification criteria developed by the European Union, the German MAK Commission, and the AOEC should be evaluated as potential models.
- Publish, disseminate, and regularly update a list of occupational asthma-causing agents that are identified using the established criteria. Wide dissemination of the list to employees and their representatives, employers, health care providers, and government agencies will assist educational efforts to promote early symptom reporting by employees, provide the scientific and medical bases that can be used by health care providers to diagnose occupational asthma, establish criteria for case definitions used in the surveillance of occupational asthma, and may result in collecting new exposure and health effects data on asthma-causing agents.
- Identify and address existing data gaps for agents currently identified as occupational asthmagens to ensure appropriate protection for workers. Existing data gaps include lack of relevant environmental exposure information for agents such as piperazine hydrochloride, colophony, and ethylenediamine, and insufficient and/or dated medical and scientific information on agents such as *p*-phenylenediamine and phthalic anhydride.
- Develop, based on defined criteria, new occupational health standards, or revise existing standards, for identified occupational asthmagens. The standards should include protective exposure limits as well as medical surveillance and medical removal protection requirements (consistent with the existing formaldehyde

standard). Assignment of time-weighted average (TWA), short-term exposure limit (STEL), and Ceiling values should be based on defined criteria. Notations such as R SEN and D SEN should be used to identify the agents as respiratory and dermal sensitizers, respectively. The German MAK should be consulted regarding their process for establishing and revising exposure limits for occupational respiratory allergens, and their information used to the extent possible.

- Research, identify, and ensure the efficacy and cost-effectiveness of safer alternatives and other control strategies for agents identified as causing asthma.
- Conduct targeted education and outreach on the risks of occupational asthma, workplace agents that can cause asthma, safer alternatives and other occupational and environmental asthma prevention strategies, and other relevant information to workers and their representatives, employers, community-based organizations, health care providers, government agencies, and other affected stakeholders.

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