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# A comprehensive list of asthmagens to inform health interventions in the Australian workplace

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## **Abstract (200 words)**

**Objective:** To develop a comprehensive list of asthmagens to which exposure may occur in occupational settings in Australia.

**Methods:** Potential asthmagens considered for this list were identified through work health and safety classification databases in Australia and through lists developed by professional associations in other countries. Inclusion criteria were; there is evidence that the agent is asthmagenic; it is used in occupational settings; and is available in Australia.

**Results:** The final list contained 277 asthmagens in 27 groups that may be found in occupational circumstances in Australia. Three other agents which have been documented as asthmagens in Australia were included: almond dust, fluoride (in aluminium pot room fumes) and sawdust from the Australian Blackwood.

**Conclusions:** This is the first comprehensive and inclusive list of Australian occupationally relevant asthmagens to have been compiled.

**Implications:** This list is specific for Australian workplace exposure to asthmagens. It will help focus policy and preventative practices and reduce the burden of occupational asthma. It will also be useful in future studies to identify who is exposed to the asthmagens and provide information to assist regulators to identify industries, occupations, specific activities and existing exposure standards that can be targeted to improve worker health and welfare.

## Introduction

It has been estimated that between 1,000 and 3,000 new cases of asthma in Australia could be attributed to workplace exposures annually.<sup>1</sup> However, precise information on the nature and extent of occupational asthma (OA) in Australia is not currently available to inform policy development. Estimates of adult-onset asthma cases that can be attributed to occupational exposures range from 9 to 17% in Australia.<sup>1, 2, 3</sup> Internationally, a recent study of more than 41,000 workers in 19 broad occupational groups in the United States, reported a prevalence of OA of 8.1% (95%CI 7.8 to 8.5%). When compared to a reference group of administration workers, the highest prevalence ratios (PR) were reported for health workers (PR 1.5, 95%CI 1.2 to 1.9) and teachers (PR 1.3, 95%CI 1.1 to 1.6).<sup>4</sup>

Australia does not have a national notification scheme for OA. A small number (n=292 since 2008) of cases are reported to the state based Surveillance of Australian Workplace Respiratory Events (SABRE) in New South Wales, Victoria and Tasmania together.<sup>5, 6</sup> Similarly, only a few cases are compensated through workers' compensation schemes; 15 claims per million employees over the most recent seven year period.<sup>7</sup>

The first step in understanding occupational asthma in Australia is to understand the potential causes. Currently there is no body or document that lists confirmed or reported asthmagens encountered in Australia. While there are a great number of confirmed asthmagens that have been linked to OA, there is currently no over-arching internationally established and peer-reviewed list of occupational asthmagens. Although various lists are available from bodies such as the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)<sup>8</sup> which is the Australian Government authority responsible for the evaluation of new and existing chemicals based on their health and environmental impacts<sup>8</sup> or the Health and Safety Executive (HSE) in the United Kingdom, and the Association of Occupational and Environmental Clinics (AOEC) in the United States, these bodies produce widely varying lists of asthmagens. Not all of these asthmagens are related to occupation and some are encountered in Australia where others are not.

This paper describes how we have assembled a list of occupational asthmagens relevant to Australian workplaces. We limited our list to those asthmagens that are most relevant to working conditions in Australia. The aim of this list is to provide a comprehensive catalogue of occupational asthmagens that may contribute to OA in Australia and that could be further used to focus policy and to improve understanding of the extent of exposure.

## Methods

For the purposes of this study, an asthmagen was defined as any substance that is causally related to the development or exacerbation of asthma symptoms. Occupational asthma was defined as 'new-onset asthma in which the underlying cause is exposure to an asthmagen while at work'.<sup>1</sup> OA excludes work-*aggravated* asthma which is asthma that occurs where workplace exposures provoke or exacerbate symptoms of existing asthma. OA can further be classified as *sensitiser*-induced or *irritant*-induced<sup>9</sup> and most cases (approximately 90%) of OA are sensitiser-induced.<sup>9</sup> Sensitiser-induced asthma is characterised by the existence of a latency period between the first exposure to a respiratory sensitiser and the development of immunologically-mediated symptoms such as may be seen with latex exposures where the latency period maybe weeks or months.<sup>10</sup> *Irritant*-induced asthma typically occurs after months or years of exposure to a respiratory irritant e.g. sulphur dioxide, chlorine or ammonia. This type of reaction is commonly associated with low molecular weight astmagens such as diisocyanates or cyclic amines. Reactive airways dysfunction syndrome (RADS) is a subclass of irritant-induced asthma characterised by the sudden onset of asthma symptoms days after a single intense exposure to a respiratory irritant such as chlorine gas.<sup>11</sup>

Potential astmagens which could be included in this list were identified through existing work health and safety classification databases in Australia and from a number of published articles by European, American or other agencies and professional associations. NICNAS<sup>8</sup> lists 108 agents that may cause serious irritation to the respiratory system based on observations in humans. The HSE's 'Asthma Compendium' includes 45 substances as respiratory sensitizers. In the United States, the AOEC has the largest and most comprehensive list of identified astmagens and currently (as at March 2015) contains 438 occupationally-related astmagens.<sup>12</sup> In addition, and most recently, Baur and Bakehe have published a wide-ranging review of 372 separate astmagens.<sup>13</sup> All of the reference lists consulted while constructing our list had some astmagens in common although not all were work-related or were encountered in Australia.

Our criteria for the inclusion of an agent to be selected for this asthmagen list were:

1. There is good evidence that the agent is asthmagenic
2. The agent is used in occupational settings
3. The agent is encountered in Australia

*Evidence that the agent is asthmagenic*

The absence of a routinely available test for asthma means that the available information for evaluating potential agents to induce asthma is largely based on clinical, incidental or epidemiological findings. Often clinical studies have focused on diagnosis of asthma in a patient, with identification of the asthmagen(s) being less specific or less clearly stated.

Almost all regulatory or other available lists of asthmagens focus on agents that are respiratory sensitisers and must be shown to induce respiratory hypersensitivity and subsequently trigger asthmatic episodes. However, the most extensive currently available list of asthmagens, produced by the US-based AOEC, includes agents designated as 'sensitizing causes of asthma' and/or 'non-sensitising causes of asthma' which includes substances which cause RADS or irritant-induced asthma. We initially included all occupational asthmagens listed by AOEC.<sup>14</sup>

Additionally, we included all substances labelled according to the Australian Hazardous Substances Information System (HSIS)<sup>15</sup> as either R37 "Substances which cause serious irritation of the respiratory system based on practical observations in humans or positive results from appropriate animal tests" or R42 "Substances which may cause sensitisation by inhalation, may induce specific respiratory hypersensitivity in the form of asthma based on human experience".

We added any agents labelled as H334 by the Globally Harmonised System for Classification and Labelling of Chemicals (GHS) which were not already included. The GHS is maintained by the European Chemicals Agency.<sup>16</sup> The H334 label identifies agents that "may cause allergy or asthma symptoms or breathing difficulties if inhaled".

We then compared our list with recently published literature reviews of allergens causing OA by Chan-Yeung and Malo<sup>17</sup> and by Baur and Bakehe.<sup>13</sup> These extensive reviews resulted in a list of 372 separate agents, which were initially included in our list.

#### *Evidence that the agent is used in occupational settings*

From the combined list of potential asthmagens and in consultation with occupational hygienists, we removed exposures not deemed to be primarily work-related.

#### *Evidence that the agent is used in Australia*

We consulted a number of data sources including NICNAS which maintains the Australian Inventory of Chemical Substances (AICS), listing data on chemicals manufactured or imported for use in Australia. In consultation with the occupational hygienists, any listed agents that were not likely to be found or permitted to be used in an Australian workplace were excluded.

## **Results**

The AOEC list of 438 occupational asthmagens known to have a causal link to OA<sup>12</sup> was reduced to 309 agents by the removal of duplicate agents or agents listed under several common names, such as cutting oils, metal working fluids, and oil mist; and those agents which could be considered a sub-category of another agent, for example, sericin is a by-product of silkworms and is included under the silkworm listing, and carene is a constituent of turpentine and is included under the turpentine listing.

The only agent excluded as being non-occupationally related was gluten, a dietary agent through which exposure occurs primarily by ingestion rather than through respiratory or dermal exposure.

A further 34 agents were considered unlikely to be encountered in Australia based on expert opinion, and included some arthropod species (specifically, screw worm fly and Mexican bean weevil), some specific wood dusts (i.e. those derived from iroko and kejaat tree species), and agents which are no longer in common use or not legally available in Australia like enflurane, the explosive tetrazene, and medications such as diacetyl morphine.

We excluded Carmine red dye (E120 food additive) as it is now banned in the US and rarely used in Australia. We also excluded Northern hemisphere marine species such as the Snow crab (*Chionoecetes opillilis*), as this is not available in Australia, although Southern hemisphere crabs were included (Blue Swimmer Crabs (*Portunus pelagicus*), Giant Mud Crab (*Scylla serrata*) and Spanner Crabs (*Ranina ranina*)).

There were agents on the original lists to which occupational exposure is unlikely to be frequent (such as quillaja bark or isolyser). However, as there was limited information available about exposure prevalence, these agents have been included with the aim of refining this list once more definitive exposure prevalence information becomes available.

The remaining 274 agents were then supplemented with three agents previously documented to cause OA in Australia, namely: almond dust,<sup>18</sup> fluoride (as a constituent of aluminium pot room fumes)<sup>19</sup> and sawdust from the Australian Blackwood (*Acacia melanoxylon*) timber.<sup>20</sup>

The final list of 277 agents were then categorised into 27 occupationally associated groups (following the groupings used by Kennedy et al).<sup>21</sup> Two asthmagens, latex and ethylene oxide, were identified as stand-alone specific agents. Other groups included isocyanates (n=9), pesticides (n=21), and metals (n=22). The complete list of 277 occupational asthmagens in 27 groups can be found in Table 1.

## **Discussion and Conclusions**

The aim of this project was to assemble a comprehensive list of substances that may be encountered in an Australian workplace and for which there is good evidence that they could lead to the development of OA. To limit or prevent OA, it is important to understand which asthmagens are encountered in the workplace. Our final list contained 277 known or probable occupational asthmagens separated into 27 groups. This list was designed to be broad and inclusive, and therefore should enable a wide range of research and policy aims to be met.

The list will permit the future estimation of the number of Australian workers who may be exposed to asthmagens at work. The list will help to identify industries and occupations with a high prevalence of exposure to asthmagens and therefore where occupational health and safety interventions can be targeted to have the greatest effect. The process followed in establishing this list was transparent and reproducible, and could be used in establishing similar lists for other disease outcomes and in other countries.

Our list was closely aligned with the Canadian list prepared by Chan-Yeung and Malo<sup>17</sup> but omitted agents such as tetrazene, some medications, several non-Australian arthropods and twelve types of wood or timber not available in Australia. Our metal group was more extensive and included aluminium, rhodium, titanium, tin and vanadium not mentioned by Chan-Yeung et al.

A number of factors limited the collation of an Australian specific list of occupational asthmagens. The information sources, and the breadth and depth of information available for each of the listed agents varied. Estimates of the nature and extent of exposures to workplace hazards may be based on data derived from self-reported information about workplace exposures. The 2008 National Hazard Exposure Worker Surveillance (NHEWS) survey is an example of this approach.<sup>22</sup> However, the NHEWS survey provided limited information on specific asthmagens because it relied on respondents being able to identify the agents that may have been contained in chemical fumes or dusts that they were exposed to. NHEWS did not collect information on exposures to a range of non-chemical and biological asthmagens, such as occurs with pot room fumes in aluminium smelting plants<sup>19</sup> or mouse urine in animal cages.

The specific asthmagenic agents are difficult to identify in such circumstances. High quality studies of prevalence of exposure are rare and available reports are often case-studies of affected individuals. Prevalence studies may underestimate exposure because of the Healthy Worker Effect where individuals affected by asthma symptoms may choose to work in jobs in which the potential for asthmagen exposure is low; they may be excluded from being hired; or they may seek transfer to less exposed jobs or leave that workplace.<sup>23</sup> The list will help

future researchers identify workplaces where low prevalence of asthma is observed due to the presence of identified asthmagens.

A high quality survey of prevalence of exposure to occupational asthmagens is now needed in Australian workplaces.

### **Implications**

We have collated a practical and relevant list of occupationally related asthmagens which is inclusive and relevant for Australian workplaces. This list will permit regulators to identify industries, occupations, specific activities and existing exposure standards that can be targeted to improve worker health and welfare. This list could form the foundation of future studies to better describe and understand the extent of exposure to occupational asthmagens in Australia, and in particular to identify both those occupations where the greatest number of workers are at risk of exposure and also where exposure to asthmagens is most likely to occur. The list would also be useful as a reference for medical or occupational Health and Safety organisations who currently have no comprehensive reference list to refer to when considering a diagnosis of OA.

Table 1 Twenty seven groups of 277 occupational asthmagens.

Agent Group	Agent
1 ARTHROPODS OR MITES	Acarian, Barn mite, Caddis flies, Cricket, Ephestia kuehniella (Mediterranean flour moth), Fowl mite, Fruit fly, Grain/Flour mites, Lesser mealworm, Locust, Mites NOS, Sheep blowfly, Silkworm
2 ACIDS	Dodecanedioic acid, Glacial acetic acid, Hydrochloric acid, Peroxyacetic acid, Sulfuric acid/sulphur dioxide
3 ACRYLATES	Acrylic acid, Cyanoacrylates, NOS (glues), Methyl methacrylate, Polymethyl methacrylate (plexiglass), Trimethylolpropane triacrylate/2-Hydroxypropyl Acrylate
4 ALDEHYDES	Formaldehyde, Gluteraldehyde, Paraformaldehyde, Urea formaldehyde
5 AMINES	Aminoethyl ethanolamine, Diethanolamine, Dimethylethanolamine, Ethanolamines, NOS, Ethylenediamine, Monoethanolamine, Surfactant-specific amines, Triethanolamine, Triethylenetetramine, Trimethylhexane-1,6-diamine/Isophorondiamine mixture.
6 AMMONIA	Anhydrous ammonia, Ammonium hydroxide, Ammonia solution 10% and 29%
7 ANHYDRIDES	Hexahydrophthalic anhydride, Himic anhydride, Maleic anhydride, Methyl tetrahydrophthalic anhydride, Phthalic anhydride, Tetrachlorophthalic anhydride, Trimellitic anhydride
8 BIO AEROSOLS	Alternaria, Chrysonilia sitophilia, Neurospora, Penicillium, Cutting oils
9 BIOLOGICAL ENZYMES	Bacillus subtilis enzymes, Bromelain, Egg lysozyme, Esperase, Flaviastase, Fungal amylase, Fungal amyloglucosidase, Fungal hemicellulose, Pancreatin, Papain, Pepsin, Trypsin
10 DERIVED FROM ANIMALS	Bat guano, Bovine serum albumin, Casein, Cat, Chicken, Cow dander, Frog, Guinea Pig antigens, Lactoserum, Mice, Pig, Rabbit antigens, Rat antigens
11 DERIVED FROM FISH/SHELLFISH	Anisakis simplex (herring worm), Clam, Crab, Cuttlefish, Fish feed, Nacre dust, Octopus, Prawn, Red soft coral, Salmon, Shrimp meal, Trout
12 DERIVED FROM PLANTS - OTHER	Almond dust, Arabidopsis thaliana, Chlorella algae, Grain dust, Gum Arabic, Henna, Kapok, Linseed oilcake, Pinellia ternate, Quillaja bark, rice dust, Tall oil crude, Tall oil – Rosin, Tobacco leaf, Tragacanth, Turpentine, Vicia sativa (vetch), Weeping fig.
13 EPOXY	Adhesive, Epoxy
14 ETHYLENE OXIDE	Ethylene oxide
15 FLOUR	Buckwheat, Flour NOS, Rye flour, Soya flour, Wheat flour
16 FLOWERS	Baby's breath, Freesia, Limonium tataricum, Sunflower
17 FOODS	Brazil ginseng, Castor bean, Chamomile, Cinnamon, Dioscorea batatas (Chinese yam), Egg protein, Fenugreek, Garlic dust, Green beans, Guar, Hops, Paprika, Pectin, Rose hips, Soybean lecithin, Tea, Thiamine (vitamin B), Thyme
18 INDUSTRIAL CLEANING AND STERILISING AGENTS	Alkyl dimethyl benzyl ammonium chloride, Benzyl-C10-16-alkyldimethyl, chlorides, Benzyl-C12-16-alkyldimethyl, chlorides, Benzyl-C12-18-alkyldimethyl, chlorides, Benzyl-C16-18-alkyldimethyl, chlorides, Benzyl dimethylstearyl ammonium chloride, BTC 776, BTC 927, Cetalkonium chloride, Chlorhexidine, Chlorine, Dialkyl methyl benzyl ammonium chloride, Dicumyl-peroxide, Didecyl dimethyl ammonium chloride, Dimethyl ethyl benzyl ammonium chloride, Dodecyl-dimethyl-benzylammonium, Fluorine, Persulphate salts, Quarternary ammonium compounds NOS, Sodium hypochlorite, Sodium metabisulfite
19 ISOCYANATES	Diisocyanates, NOS, HDI Prepolymers, Hexamethylene diisocyanate HDI, Isophorone diisocyanate, Methylene bisphenyl diisocyanate, Naphthalene

		diisocyanate NDI, Polymethylene polyphenylisocyanate, TDI Prepolymers, Toluene diisocyanate
20	LATEX	Latex, natural rubber
21	MEDICATIONS	Ampicillin, Amprolium, Cimetidine, Codeine, Colistin, Hydralazine, Ipecacuanha, Hydrocodone, Isonicotinic acid hydrazide, Methyl dopa, Morphine, Opiate compounds, Oxycodone, Papaverine, Penicillamine, Penicillins, Phenylglycine acid chloride, Psyllium, Salbutamol intermediate, Spiramycin, Tetracycline, Thebaine, Tylosin tartrate, Vancomycin
22	METALS	Aluminium, Aluminium chloride, Aluminium oxide, Aluminium compounds, Ammonium dichromate or hexachloroplatinate (IV), Chromium NOS, metal, hexavalent and, non-hexavalent, Cobalt, Cobalt compounds, Gas metal arc welding on uncoated mild steel, Nickel, Nickel compounds, Platinum, Rhodium, Soluble halogenated platinum compounds NOS, Titanium oxide/dioxide, Tributyl tin oxide, Tungsten carbide, Tungsten carbide/cobalt, Vanadium, Welding fume, stainless steel, Zinc oxide
23	OTHER REACTIVE CHEMICALS	Fluoride, Freon heated, Furfuryl alcohol mixed with a catalyst, Isolyzer, Polyethylene terephthalate/Polybutylene terephthal, Polyfunctional Aziridine (PFA), Polypropylene heated, Polyvinyl chloride heated or non-heated or thermal decomposition, Radiographic fixative, Resin containing furfuryl alcohol, Styrene, Triglycidyl isocyanurate
24	PESTICIDES	3-Amino-5-mercapto-1,2,4-triazole, Acephate, Chloramine T, Chlorothalonil (Bravo, Echo), Diazinon, Dimethoate, Fenthion, Malathion, Nema-cur, Piperazine, Piperazine citrate, Piperazine hydrochloride, Pyrethrins, Pyrfon, Safrotin, Tetramethrin
25	REACTIVE DYES	Cibachrome Brilliant Scarlet 32, Drimarene Brilliant Blue K-BL, Drimarene Brilliant Yellow K-3GL, Lanazol Yellow 4G, Levafix Brilliant Yellow E36, Methyl Blue, Reactive Dyes, NOS, Rifacion Orange HE 2G, Rifafix Yellow 3 RN, Rifazol Black GR, Rifazol Brilliant Orange 3R
26	SOLDERING FLUXES	Colophony, soldering flux (heated) Alkyl aryl polyether or Zinc
27	WOOD DUSTS	African Maple (Triplachiton scleroxylon), Blackwood (Acacia melanoxylon), California Redwood (Sequoia sempervirens), Central American Walnut (Juglans olanchana), Eastern White Cedar (Thuja occidentalis), Mahogany (Shorea sp.), Oak (Quercus robur), Western Red Cedar (Thuja lpicata).

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