Structure-Activity Relationships for Respiratory Sensitisation and Occupational Asthma Caused by Low Molecular Weight Chemicals

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Introduction

Asthma is a chronic inflammatory condition of the airways clinically characterised by symptoms of coughing, wheezing, chest tightness and dyspnoea (difficulty in breathing). Occupational asthma is asthma acquired through workplace exposures to low or high molecular weight chemicals (including allergens of biological origin). The latter is generally IgE antibody mediated, but low molecular weight (<1000) chemicals exhibit a diversity of mechanisms. Low molecular weight occupational asthma is commonly divided into “immunological” (sensitiser) and “non-immunological” irritant-induced asthma. Recent work has shown that the two may not be clinically distinguishable.

The knowledge base expert toxicity prediction program Derek Nexus (Lhasa Limited) has a range of alerts covering well-established classes of asthmatics that recognises mechanistic differences with a division between three endpoints “respiratory sensitisation”, specifically (non-immunological) “occupational asthma” and the more general “respiratory tract irritation”. The aim of the present work was to develop a curated asthmagen dataset, and to understand and to use this, in the first instance, to examine the potential for improved prediction by adding or modifying alerts to Derek Nexus. Comparison has been made with published work [1-9].

Method

A database of low molecular weight asthmagens was compiled in Excel format using the tabulations of Jarvis et al [5], supplemented by substances in recent compilations of new asthmagens [6,7] or published in MEDLINE literature since 2010. Chemicals were processed through Derek Nexus 2.1 using a recently updated knowledge base (KB 2015_1.0). The evidence for each chemical as an inhalation route asthmagen was briefly reviewed. To provide mechanistic insight information was also acquired relating to chemical reactivity, immunological sensitisation (allergy) of any kind, irritant or corrosive properties, known effects on mast cells and pharmacology. For comparison a dataset of 82 non-asthmagenic chemicals was employed, based on substances with workplace exposure limits, from Enoch et al. [2].

Results: Review of the Asthmagen Dataset

The evidence for many individual chemicals reported as asthmagens has been reviewed by others (e.g. by UK HSE). Several, such as formaldehyde, methyl methacrylate, and ethanolamine do not satisfy EU criteria for classification as respiratory sensitisers. However, such chemicals are retained for our SAR analysis since the non-classification is generally indicative of low potency rather than a complete absence of activity and we are considering the activity of a structural class as a whole. About 40% of the chemicals reported as asthmagens only had a single report and about 25% had asthma reported in only one individual. This raises the possibility of idiosyncratic reactions with a low general incidence level in the exposed human population. However some of these isolated reports included a range of clinical and laboratory investigations, including specific provocation and airways reactivity studies, and cannot be so easily discounted.

My compilation initially included 140 chemicals, 12 of which were inorganic chemicals (including particulates) and will not be considered further here. On review, at least 8 did not have good evidence for the production of occupational asthma following chronic exposure via the inhalation route leaving 120 putative occupational asthmagens. For example, dibutylamine was reported to produce asthma but only after “continuous infusion” not inhalation and Paul’s reagent caused hypersensitivity pneumonitis not asthma. For a few chemicals the “asthmagenicity” was clearly based on mixed exposures with little evidence for causality, e.g. polymethylmethacrylate and hydroquinone. Acetic acid and chloroxylenol (p-chloro-m-cresol) rarely produced asthma and only after high concentration exposures.

Discussion: SARs and Mechanisms

Of the 120 “shortlisted” chemical asthmagens 47 were predicted by Derek Nexus which are many of the better known compounds that cause the most disease, such as isocyanates, acid anhydrides and reactive dyes. Examples are shown in Figure 1. Beta-lactam antibiotics, reactive dyes and acid anhydrides are generally considered to act by IgE antibody mediated respiratory sensitisation. Polar groups, such as carboxylic or sulphonic acids or their anions, are a frequent occurrence in such compounds or their likely reaction products with proteins. For asthmagens such as disocyanates additional mechanisms are considered to contribute and polarity is a less conspicuous feature, at least in the initial reagent. The presence of two reactive groups giving cross-linking properties is a common feature of asthmagens. This may facilitate immunological sensitisation and inflammation by self-reaction to larger and more immunogenic oligomers and by the cross-linking of intact molecules such as for FcEγ receptors or IgE on mast cells. The resulting cellular degranulation releases inflammatory mediators including histamine, protamines and cytokines which are known to play a major role in the development of asthma.

Many of these 47 compounds were confirmed as experimental skin sensitisers but are also associated with other allergic reactions such as Type I and Type III hypersensitivity e.g. anaphylaxis, urticaria, allergic alveolitis, and drug induced auto-immune reactions. In general only a subset of skin sensitisers are respiratory sensitisers. The required reactivity level for the latter appears to be higher and there are more specific structural requirements. Some asthmagens may act mainly by non-immunological mechanisms such as mast cell degranulation (e.g. morphine and persulfates) or irritant mechanisms (e.g. bis(2-ethylhexyl) phthalate). Enoch et al. [1,2] suggested that lysine reactivity is required, on the assumption that the oxidative environment of the lung lowers the availability of cysteine thiol nucleophiles and identified similar alerts to the above. Chemical mechanisms of metabolic activation can be postulated (as in Figure 3). However such proposals require testing and validation. An example is provided by “asthmagenic” organophosphorus compounds, for instance fenthion or dioxan, which have alerts as alkylating agents. These compounds, in addition to direct cholineserine inhibition, have been reported to produce bronchospasm and wheezing (a) by inhibition of neuronal M2 muscarinic receptors that normally limit acetylcholine release from parasympathetic nerves supplying airway smooth muscle, and (b) by producing the inflammatory cytokine TNF-α from pulmonary macrophages.

Conclusions

The number of reported low molecular weight asthmagens has grown considerably over the past 30 years and structure-activity based models have been produced to make predictions. This is particularly significant in the absence of a reliable and acceptable animal model. However the published dataset requires greater scrutiny for reliability. The mechanistic heterogeneity also limits the accuracy of global SAR models. Despite these caveats, overall the structure-activity analysis shows a strong influence of electrochemistry and cross-linking properties which provides potential for expanding the scope and accuracy of Derek Nexus predictions to areas of new chemical space likely to be associated with the highest frequencies of occupational asthma.

References