

Letter to the Editor

Paradoxical asthma hazard of short-acting β 2-agonists

Bonnaud et al. (1) report a case of bronchoconstriction in a patient caused by inhalation of short-acting β 2-agonists. In an occupational setting, exposures to such agents can be even greater than those encountered therapeutically and there have been at least two reported cases of occupational asthma attributed to salbutamol exposure in pharmaceutical process workers (2). However, in the above-mentioned report the authors postulated that the mechanism might be tachyphylactic rather than IgE-mediated. Thus, salbutamol was one of the 78 low molecular weight (LMW)

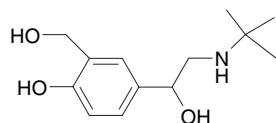
organic chemicals known to cause occupational asthma from which a quantitative structure-activity relationship (QSAR) model was developed (3). This asthma hazard prediction program is freely available through the internet (4), and we have previously illustrated how a positive 'asthma hazard index' can help corroborate evidence of potential asthmagenicity of LMW organic chemicals (3, 5).

Although designed for the purpose of predicting the asthma hazard of industrial chemicals, this QSAR model has been used by others, in clinical pharmacology. Thus an

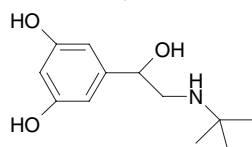
independent user of the model found that a chemical ingredient of salmeterol inhalers, xinafoate, had an asthma hazard index of 0.73. This index is expressed on a scale of 0–1 with a value of 0.5 or higher indicating asthmagenic potential. Based on a validation set containing 21 astmagens this cut-point results in a sensitivity of 86% and specificity 99%. It was postulated that xinafoate might be the cause of severe asthma exacerbations observed in some patients using this long-acting β 2-agonist (6).

In the case reported by Bonnaud et al. (1) the β -agonist drugs themselves were clearly demonstrated to cause bronchoconstriction, perhaps through an IgE-mediated mechanism. Salbutamol has an asthma hazard index of 0.84. Interestingly, terbutaline, and pirbuterol, which were not in the QSAR model development set, have hazard indices of 0.79 and 0.97, respectively. Common structural features might explain why these three chemicals are capable of sharing reactive features potentially leading to asthmagenicity (Fig. 1), such as by reacting with native proteins resulting in IgE neoepitopes. Proof (or otherwise) that the mechanism is IgE-mediated would however require *in vivo* and *in vitro* studies to search for specific IgE antibodies.

Salbutamol (CAS 18559-94-9) *Asthma hazard index 0.84*



Terbutaline (CAS 23031-25-6) *Asthma hazard index 0.79*



Pirbuterol (CAS 38677-81-5) *Asthma hazard index 0.97*

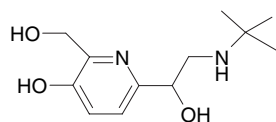


Figure 1. Chemical structures and asthma hazard indices of salbutamol, terbutaline, and pirbuterol.

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M. J. Seed, R. M. Agius
Centre for Occupational & Environmental
Health, University of Manchester,
Manchester, UK