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REVIEW ARTICLE

## Phthalic anhydride: Illustrating a conundrum in chemical allergy

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### ABSTRACT

Although a substantial number of chemicals has the ability to bind covalently to proteins and thereby, given sufficient exposure, induce a state of sensitization, only a small minority appear to be able to cause allergic hypersensitivity of the respiratory tract; the great majority being exclusively skin sensitizers. The key mechanistic drivers for the differentiation between skin and respiratory sensitization are already well characterized at the cellular/cytokine level. However, at both the chemical level and in terms of predictive toxicology, matters are much less clear. In the present article, phthalic anhydride is used as an exemplar, since it displays a particularly differentiated profile as a chemical allergen. Whereas most respiratory sensitizers are known also to give rise to delayed skin reactions, evidence for phthalic anhydride suggests that it only causes immediate type allergy. Chemically, phthalic anhydride can be presumed to react similar to other respiratory sensitizing anhydrides; in predictive tests for skin sensitization, phthalic anhydride is clearly positive, a property it has in common with all other chemical respiratory allergens. Thus, in the context of interpreting predictive toxicology tests for skin sensitization, the inference is that negative results demonstrate an absence of both skin- and respiratory-sensitizing capacity.

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### Introduction

It is now clear that chemical allergens display heterogeneity with respect to the form of allergic disease with which they are primarily associated. Although many hundreds of chemicals that are known to cause skin sensitization associated with the development of allergic contact dermatitis, most of these have never been implicated as respiratory allergens. In contrast, other chemical allergens, much fewer in number, are associated primarily (but not necessarily exclusively) with sensitization of the respiratory tract and occupational asthma (Kimber et al. 2014a). Among the latter group, diisocyanates, acid anhydrides, chloroplatinate salts and some reactive dyes are included (Baur 2013; Baur & Bakehe 2014).

Data available from rodent studies suggest that the mechanistic basis for such differences is the preferential induction by contact and chemical respiratory allergens of discrete immune responses. Thus, contact allergens are associated primarily with T helper (T<sub>H</sub>)-1-type responses, whereas chemicals that cause sensitization of the respiratory tract preferentially elicit T<sub>H</sub>2-type responses (Dearman & Kimber 2001; Kimber et al. 2007; Boverhof et al. 2008). Although much of the evidence for differential immune responses being elicited by contact and chemical respiratory allergens is derived from studies in mice, and to a lesser extent rats, there are also some data from studies in humans that are consistent with this (Newell et al. 2013; Ouyang et al. 2013; Kimber et al. 2014b). However, although a clear separation between contact and chemical respiratory allergens based solely on the selective development of discrete functional subpopulations of Th cells is something of an over-simplification, the fact remains that these classes of allergen are associated with different qualities of immune response and is consistent with the form allergic reactions will take.

Despite this at least partial dichotomy between chemical allergens with respect to the quality of immune responses induced

and the type of allergic reactions they will elicit, it is the case that both contact and chemical respiratory allergens test positive in animal (guinea pig and mouse) models used for the identification of skin sensitizing chemicals. In fact, all confirmed chemical allergens that preferentially cause sensitization of the respiratory tract elicit positive responses in either or both mouse (local lymph node assay; LLNA) and guinea pig (maximization test or occluded patch test; GPMT) predictive test methods (Dearman et al. 2013). Indeed, it could be argued that the tests simply identify sensitizing chemicals and for practical purposes just happen to have used the dermal route of exposure.

Against this background the purpose of this article is to explore further: (a) the selectivity of chemical allergens with respect to the form in humans that allergic reactions will take, and (b) the apparent conundrum that different classes of chemical, that induce qualitatively different immune responses and that elicit allergic reactions of different types, both test positive in animal models for predicting skin sensitization. This will be explored by reference to a single and well known chemical respiratory allergen, phthalic anhydride.

### Allergy to phthalic anhydride in humans: (A) sensitization of the respiratory tract and occupational asthma

It is now well established that phthalic anhydride is able to cause sensitization of the respiratory tract and occupational asthma in a proportion of the exposed workforce and that this is not uncommonly associated with IgE antibody (Kern 1939; Maccia et al. 1976; Wernfors et al. 1986; Nielsen et al. 1988, 1991). Against the background of compelling evidence that in humans phthalic anhydride is a respiratory allergen and is known to cause occupational asthma, it is instructive to consider the potential of this

chemical to induce skin sensitization and allergic contact dermatitis (ACD).

### Allergy to phthalic anhydride in humans: (B) skin allergy

There are two potential types of allergic reaction in skin, immediate and delayed, the former mediated by IgE, the latter by T-lymphocytes. Immediate allergic skin reactions are usually referred to as immunologic contact urticaria (Basketter & Lahti 2011). A literature search with a mix of terms “contact urticaria, skin allergy, contact allergy and phthalic anhydride” reveals that contact urticaria to phthalic anhydride has been reported, albeit rarely. A single occupational case was detailed in Spain via a clearly positive skin prick test (Gutierrez-Fernandez et al. 2007). Two cases, diagnosed by skin prick test and the presence of specific IgE, were discussed in a 17-year review of occupational cases in Finland (Helaskoski et al. 2009). All of the patients had concomitant respiratory symptoms.

Delayed allergic skin reactions (ACD) to phthalic anhydride are similarly rare. The substance is mentioned in Cronin's classic textbook only as a cause of irritant dermatitis (Cronin 1980). The most recent edition of *Fisher's Contact Dermatitis* does not index phthalic anhydride at all (Rietschel & Fowler 2008). Furthermore, the latest edition of the only other standard textbook also fails to index the substance, but phthalic anhydride is mentioned [on Page 1222] as a potential cause of skin allergy when used as a pigment by ceramic workers. However, this is not referenced. Perhaps more importantly, the authors noted that phthalic anhydride was not responsible for the ACD occasionally associated with certain nail varnish resins (LeCoz & Lepoittevin 2011). That conclusion is consistent with patch test data from three patients with nail polish allergy, all of whom were negative to phthalic anhydride itself (Nassif et al. 2007). However, it conflicts with earlier results on four UK patients with ACD to phthalic anhydride/trimellitic anhydride/glycols copolymer, of whom three were 1+ positive to 1% phthalic anhydride at Day 4 (96 h) (Gach et al. 2005). It is worth noting that an earlier occupational case involving unsaturated polyester resin was patch test negative to 1% phthalic anhydride. The compilation of patch test concentrations for more than 4000 substances notes that 1% is suggested for phthalic anhydride (de Groot 2008). Also noted is the absence of any control data, which given the discordant data and low grade reactions does lead to the suspicion that at least some degree of skin irritation may be involved, a possibility that is supported by the comments from Cronin that phthalic anhydride can absorb skin moisture to produce burns (Cronin 1980).

In summary, there is a lack of persuasive evidence that phthalic anhydride causes skin sensitization or ACD. The limited data available are consistent with the theoretical expectation that chemical respiratory allergens (that are associated with T<sub>H</sub>2-type immune responses) can under the appropriate conditions of exposure, cause immunologic contact urticaria. The suggestion that phthalic anhydride can also cause ACD is not borne out by the limited and somewhat conflicting literature available. Although it has to be acknowledged that the absence of phthalic anhydride as a commercial patch test allergen does not encourage diagnostic testing, it could equally be argued that the reason for this is the absence of clinical suspicion that phthalic anhydride is a contact allergen, the latter perspective being supported by the current evidence. Therefore, it is interesting in this respect that most, if not all, of the other well characterized chemical respiratory allergens have shown at least some limited ability to cause delayed type hypersensitivity reactions clinically, with glutaraldehyde

being perhaps the most well known (Takigawa & Endo 2006; Dearman et al. 2013).

### Allergenic properties of phthalic anhydride in humans

Taken together, the data summarized above provides persuasive evidence that phthalic anhydride does display allergenic potential in humans, but that these allergenic properties are selective insofar as the chemical has been implicated as a respiratory allergen, but appears to lack the capacity to induce skin sensitization, resulting in ACD. There is evidence that phthalic anhydride is associated with contact urticaria, but this is likely a reflection of the fact that the properties that confer on chemicals the ability to induce allergic sensitization of the respiratory tract (eliciting a selective T<sub>H</sub>2-type immune response) also favor development in skin of IgE mediated immunologic contact urticaria. The induction by phthalic anhydride of selective T<sub>H</sub>2-type immune responses has been shown previously in mice (Dearman & Kimber 1992; Dearman et al. 2000). Phthalic anhydride therefore provides a particularly clear example of a chemical that displays selective allergenic potential, with in this instance a preference for allergic sensitization of the respiratory tract and occupational asthma.

### Behavior of phthalic anhydride in tests for skin sensitization

Having established the credentials of phthalic anhydride as a respiratory allergen with little or no potential in humans to cause ACD, it is relevant to consider the activity of this chemical in *in vivo* tests for skin sensitization (the LLNA, and two guinea pig methods – the occluded patch test of Buehler and the GPMT). It is clear that phthalic anhydride elicits positive responses in the LLNA (Dearman et al. 2000), the Buehler test (Botham et al. 2005) and the GPMT (Cronin & Basketter 1994; Gerberick et al. 2000). These data are therefore consistent with the view discussed previously (Dearman et al. 2013) that chemical respiratory allergens, including (as is illustrated here) those that have little or no potential to cause ACD in humans, elicit positive responses in skin sensitization test methods. The important aspect of this observation is the prediction that chemicals which fail to display positive responses in *in vivo* tests for skin sensitization will lack the potential for both skin sensitization and sensitization of the respiratory tract.

It is interesting also to consider the chemical reaction mechanism by which phthalic anhydride is likely to cause such sensitization responses. Several acid anhydrides are recognized as IgE-mediated allergens (e.g. Helaskoski et al. 2009; Baur 2013; Baur & Baheke 2014). Probable reaction types for a range of respiratory allergens have been described, with phthalic anhydride being attributed to an acylation mechanism (Enoch et al. 2009). The same mechanism is ascribed to some di-isocyanates and would be expected for other acid anhydrides. Thus, there is nothing yet at the chemistry level to distinguish phthalic anhydride from other members of the family of respiratory sensitizers. Furthermore, acylation is one of the more common mechanisms by which skin sensitizers cause allergy (Roberts et al. 2007).

### Conclusions

Two major subsets of chemical allergens can be identified: skin sensitizers and respiratory sensitizers. These subsets are not entirely exclusive, but phthalic anhydride provides perhaps the

most clear-cut example of a chemical that selectively induces sensitization of the respiratory tract rather than skin sensitization. Phthalic anhydride is a well-known human respiratory allergen, associated also with IgE-mediated dermal effects, but as evidenced above, is hardly ever associated with delayed type hypersensitivity in the skin. In terms of predictive toxicology, all types of chemical allergen give positive results in classic *in vivo* skin sensitization assays (Dearman et al. 2013). Consequently, there has been a long held view that negative results derived from skin sensitization testing involving the dermal route of exposure provides reliable evidence of the absence not only of skin sensitization hazard, but also of respiratory sensitizing potential (Dearman & Kimber 1992; Dearman et al. 2013). The immediate-type hypersensitivity polarization displayed by phthalic anhydride is fully consistent with this, as is the evidence that common inhalable skin sensitizers fail to cause respiratory allergy (Basketter & Kimber 2015).

### Disclosure statement

The authors declare no conflicts of interest. The authors alone are responsible for the content of this manuscript.

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