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CONTACT DERMATITIS

Editorial

Metabolism *versus* chemical transformation or pro- *versus* prehaptens?

Since the landmark article of Landsteiner and Jacobs (1) published in 1935 on the sensitizing potential of 2,4-dinitrohalobenzene derivatives, it has been hypothesized that small molecular weight molecules should have some kind of chemical interaction with proteins to act as skin sensitizers. This hypothesis has been largely expanded by Dupuis and Benezra (2) and confirmed by subsequent studies on protein modifications by haptens [for more details and references, see a recent review (3) published in this journal]. The hapten concept has been the base for the understanding of relations between the chemical structure of a molecule and its sensitizing potential leading to the development of Structure Activity Relationships, Quantitative Structure Activity Relationships as well as predictive expert systems such as DEREK and non-biological alternative tests based on reactivity (4). However, not all sensitizing molecules are fitting with the hapten model, as they are not *per se* protein reactive. This observation led to the introduction of the prohapten concept based on the metabolic transformation of protein non-reactive low molecular weight molecules into true effective haptens (2). This prohapten concept has been strengthened by our increased knowledge on the metabolic activity of skin cells and tissues (5). Since this original classification of sensitizing molecules into 'haptens' and 'prohaptens', no significant revision has been proposed to take into account more recent developments of the chemical understanding of the sensitization mechanism. Molecules are not inert substances but can be subjected to chemical transformations/modifications following exposure to their environment (heat, light, oxygen, etc.). Hellerström and colleagues (6) have already described in 1957 such chemical transformations in the field of skin sensitization showing that Δ^3-carene was not the actual sensitizer of turpentine but a precursor auto-oxidized into an allergenic hydroperoxide. Since that pioneering work, several other examples of non-reactive molecules transformed into true haptens by air-oxidation have been reported. This is the case for example of colophony and abietic acid (7) as well as other terpenes shown to be involved in fragrance sensitivity (8). Similar observations can be applied to molecules easy to oxidize such as, *p*-phenylenediamine (PPD), and derivatives that can rapidly be transformed into hapten-reactive *p*-quinonediimine derivatives by simple contact with air.

So far, these non-reactive molecules have been referred to as 'prohaptens', even if no specific metabolic enzyme is needed to activate them into 'haptens'. Recent efforts made to develop alternative methods to animal experimentation in the perspective of the EU ban on *in vivo* testing of cosmetic and toiletry ingredients (9) have shown that this 'prohapten' classification was in fact a break to their development and acceptance. Indeed, the very often unknown or non-existing metabolic capacity of these new systems is raised as a major pitfall: 'What about prohaptens in your system?' In fact, what is the proportion of the real prohaptens that do need a specific metabolic activation to become reactive versus molecules that are just oxidized by contact with air? Anyone who has experimentally worked with PPD, often considered as the model of prohapten, knows that the rapid colour change of the solutions signs the formation of reactive intermediates able to activate *in vitro* systems or modify peptides without any further specific enzymatic activation.

To make it more clear and stimulate further research on how non-reactive molecules are reacting with proteins to form antigens, it is may be time to revise our classification and introduce a third category named 'prehapten' for non-reactive sensitizing molecules transformed into 'haptens' by simple chemical transformation and without requirement of a specific enzymatic system. This would also make more easy the development and validation of alternative methods for the identification of sensitizers.

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