

The substantial differences between photoallergic and phototoxic reactions

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Re: Jakubowicz O, Żaba C, Nowak G, Jarmuda S, Żaba R, Marcinkowski JT. *Heracleum sosnowskyi* Manden. *Ann Agric Environ Med.* 2012; 19(2): 327-328.

With great interest, yet growing concern, I read the article published by Jakubowicz et al. in a recent issue of the journal AAEM [1], in which the authors addressed phototoxic reactions caused by *Heracleum sosnowskyi*. Without any doubt, this is a relevant challenge to public health in Poland, for the plant is spreading across the country in an uncontrolled way and people exposed to this plant and sunlight may suffer severe adverse cutaneous reactions. However, the scientifically incorrect terminology used by the authors throughout this article cannot be left without comment, as it fosters misunderstandings about this very important topic.

Phototoxic reactions resulting from exposure to plants were first described in France by Maurice Oppenheim in 1932, and then reinforced by his further observations in the USA [2]. The disease was then referred to as *dermatitis striata pratensis bullosa* (grass or meadow dermatitis), which typically presented as bullous eruptions on the areas of the skin which have been in contact with certain plants and subsequently exposed to sunlight. This historical name so accurately depicts the clinical picture and circumstances of the emergence of this disease that it is still preferred by some authors even today [3], although 'phototoxic dermatitis' seems much more sound scientifically. The road to understanding of the underlying mechanisms was paved in 1938, when Hans Kuske isolated from various plants with known sun-sensitizing properties compounds responsible for phototoxicity, including psoralens [4]. We now know that there are 2 types of phototoxicity: photodynamic, which requires oxygen, and non-photodynamic, which is not oxygen-dependent. The reactions induced by psoralens, for the most part, are non-photodynamic [5]. By 1959, the relationship between the structures of furocoumarins and their biological effect were quite well-known [6], and the therapeutic use of their phototoxic properties had begun. 'Phototoxic' indeed, and certainly not 'photoallergic' as Jakubowicz et al. have put it. The differences between photoallergic and phototoxic reactions (Table 1) are substantial – as substantial as are those between allergic contact dermatitis and irritant contact dermatitis in the skin, or allergy and toxicity in general [7]. Thus, calling the archotypically phototoxic psoralens in *Heracleum* as 'photoallergic' agents is as incorrect scientifically as would be referring to arsenic poisoning as 'arsenic allergy'.

Table 1. The most important differences between phototoxic and photoallergic reactions [8-14].

Phototoxic reactions	Photoallergic reactions
All exposed people will react (risk to whole populations)	Only predisposed people will react (risk to isolated individuals)
Reaction predictable	Reaction unpredictable (no possibility of indicating who will develop allergy before the occurrence of first symptoms)
Reaction may develop upon first encounter	First encounter symptom-free, a "silent" induction period of varying length (weeks – years) is required
Clinical appearance of phototoxic reactions are characterized by erythema and edema, and formation of bullae (large blisters), followed by hyperpigmentation. Bizarre, often streaked shapes suggesting a "running drop" are indicative. In chronic subclinical courses chloasma-like hyperpigmentation in the face can develop.	Erythema and oedema with subsequent development of small vesicles and scaling. Eyelid oedema in case of facial (e.g. sunscreens or airborne agents) or systemic exposure to photohaptens (e.g. oral drugs). Typically, skin inflammation is evenly distributed upon whole sun-exposed areas like face, neck, décolleté or hands with forearms. Due to similar distribution pattern, differential diagnosis to airborne dermatitis is necessary.
Development of symptoms within a couple of hours after exposure	In already sensitized individual, development of the disease takes 1 day or more (up to several weeks) after exposure
Skin inflammation due to the unspecific damage caused by free radicals (nonphotodynamic reactions), reactive oxygen or nitrogen species (photodynamic reactions). Mechanisms involved are basically not different from sunburn (though stronger), no involvement of the adaptive immune system.	Hapten specific reaction – photobinding of a specific photohaptens to body's own proteins alters their spatial conformation leading to a recognition as "non-self" and provoking an delayed type allergic reaction driven by antigen-specific effector lymphocytes. In rare cases also immediate type photoallergy to exogenous haptens possible.
Phototoxic potential of compounds can be easily detected by means of in vitro assays.	(At present) photoallergic potential of compounds can be assessed only by means of in vivo assays.

Photoallergic reactions depend on individual predispositions and involve specific immunologic reactions, including antigen recognition by specific T-cells. These reactions, as a rule, are unpredictable, but very rare. Therefore, photoallergies seem not well suited to be addressed with the means of public health, health policy or consumer protection. Simply put, a great effort would bring benefit to a very small group of affected people. It would be like e.g. imposing a ban on terbinafine – a safe and effective antifungal drug that has already been on the market for several decades, just because of a single recently diagnosed case of photoallergic reaction to terbinafine [15]. Thus, photoallergies remain a domain of specialized clinicians keen on tracking down rare and unusual cases. Having said that, 'endemics' of photoallergic reactions may sometimes occur

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in occupational settings [16,17], or even require health policy measures, such as the restrictions on over-the-counter sales of ketoprofen in Europe due to the relatively high frequency of photoallergy to this drug. 'Relatively high' meaning here that ketoprofen photoallergy has been found in 12% of all people with suspected photoallergy [18], who altogether account for less than 1% of the general population [19] – thus still a rare entity. On the other hand, 12–23% of all patients undergoing diagnosis for allergic contact dermatitis are ill with photoallergy [20], which leads to the conclusion that all dermatologists and allergists should be aware of the problem and trained to recognize cases of photoallergy among their patients. Agricultural chemicals and food preservatives are another examples of photoallergic agents of importance to public health [14,21].

In contrast to photoallergy, phototoxic reactions are predictable to such extent that some of the plant derivatives (e.g. 5-methoxypsoralen) have been used for decades as therapeutic drugs to augment the effects of phototherapy [22]. Unfortunately, this predictability is also observed in case of adverse reactions to psoralens and other furocoumarins, unintentionally and in an uncontrolled way transferred from plants to people during outdoor activities. Unlike photoallergy, phototoxic reactions will rapidly manifest as acute dermatitis in virtually all people exposed to the phototoxicant, and subsequently to UV light (either from the sun or artificial sources). Therefore, phototoxicity to outdoor plants indeed constitutes a challenge to environmental medicine and requires public health actions, as virtually whole populations may be affected. A possible preventive action to stop phototoxic reactions from *Heraclium* in Poland could involve an informational educational campaign on how to effectively evade contact with the offending plants, addressed to groups at the highest risk, e.g. farmers and forestry workers, hunters, fishers, campers, and mountain hikers [23–25]. Farmers' insurance and authorities responsible for agriculture and forestry, occupational safety and health authorities, and sanitary authorities seem natural partners for such a campaign. On the other hand, a concerted action should be undertaken aimed at eradication of the plant, through cutting or aimed herbicides. Also, natural insect enemies or diseases specific to this species might be considered. I hope that the above elaboration has made it clear why we should differentiate between photoallergic and phototoxic reactions, and has helped in clarifying the misunderstanding caused by the improper use of terminology in this otherwise interesting article.

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