

Phosphite esters: a novel class of contact allergen

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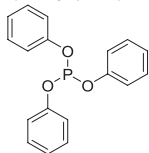
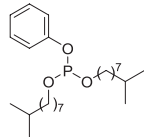
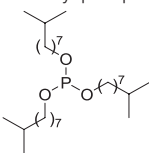
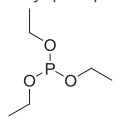
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Phosphite ester compounds are utilized as stabilizers and anti-oxidants in industrial polymers [e.g. poly(vinyl chlorides)] and lubrication oils. Establishing the skin sensitization hazard for this class of compounds would currently be challenging, as these compounds are not represented in public datasets of *in vivo* skin sensitizers [e.g. Cronin and Basketter (1), Gerberick et al (2), and Urbisch et al (3)].

Table 1. Reports of skin sensitization for four representative phosphite ester compounds in humans, the murine local lymph node assay (LLNA) and the guinea pig maximization test (GPMT).

Chemical	CAS no.	Number of positive reports			LLNA potency category (EC3) [†]
		Human*	LLNA [†]	GPMT [†]	
Triphenyl phosphite 	101-02-0	5	1	–	Moderate sensitizer (EC3 = 1.4%)
Diisodecyl phenyl phosphite 	25550-98-5	–	1	1	Weak sensitizer (EC3 = 41%)
Triisodecyl phosphite 	25448-25-3	–	1	–	Weak sensitizer (EC3 = 20%)
Triethyl phosphite 	122-52-1	–	–	1	–

*Reported skin sensitization in humans following accidental or occupational exposure, confirmed by patch test rechallenger (4–8).

[†]Positive reported LLNA and GPMT data from submissions for registration to the European Chemicals Agency (accessible through www.echemportal.org, last accessed 17 October 2016). No negative reported skin sensitization data were identified for the compounds shown.

Methods and Results

A detailed literature review showed five reports of allergic contact dermatitis in humans following accidental or occupational exposure to triphenyl phosphite (TPP) (CAS no. 101-02-0), confirmed by subsequent human patch test rechallenger (4–8). Additionally 12 reports on the skin sensitization effects of TPP and other phosphite ester compounds in the murine local lymph node assay (LLNA) or guinea pig maximization test (GPMT) were found in submissions for registration to the European Chemicals Agency (representative examples are shown in Table 1). Generally, a stronger skin sensitization response has been reported for triaryl-substituted phosphite esters than for dialkyl-substituted or trialkyl-substituted analogues in the LLNA. For example, TPP has been reported to give positive results with moderate potency in the LLNA, whereas both diisodecyl phenyl phosphite and triisodecyl

phosphite have been reported to have weak potency in this assay (Table 1).

These toxicity data were deemed to be of sufficient quality to classify phosphite ester compounds as alerting for skin sensitization, if a plausible mechanistic rationale could be provided. Unlike many skin sensitizers, phosphite esters are not electrophilic; in fact, their use as antioxidants is driven by their nucleophilic and reducing properties (9). Therefore, haptenation reactions, including the formation of protein adducts, may occur by unusual nucleophilic reactions with disulfide bonds present in skin proteins (10, 11), although phenolic phosphite esters may generate reactive species following hydrolysis or metabolism (12). The broad range of skin sensitization potencies reported for phosphite esters can therefore be attributed to potential mechanistic differences and the influence of physicochemical property variation (e.g. compound lipophilicity). This

information was used to support the implementation of a toxicity alert for skin sensitization in Derek Nexus version 5.0 (Lhasa, Leeds, UK), which includes a quantitative potency prediction based on experimental EC3 values and similarity.

Discussion

The evidence presented indicates that phosphite esters constitute a novel class of skin sensitizing compounds. The absence of such compounds from the commonly used datasets of skin sensitizers highlights gaps in our current knowledge. This has implications for the applicability

of some of the animal and/or newer *in vitro* test methods (e.g. the direct peptide reactivity assay), which are based on a skin sensitization adverse outcome pathway that is driven by an electrophilic molecular initiating event. As such some compounds, including phosphite esters, may not be represented in the integrated testing strategies that are being developed for risk assessments. It therefore seems likely that *in silico* methods built on an understanding of all publicly available *in vivo* data, as well as an understanding of metabolism and a mechanistic rationale, may act to complement extrapolations made from the validated animal replacement *in vitro* assays (13) to human contact allergy risk assessment.

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