Dihydroxydiphenyl – a historical rubber contact allergen?

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4,4′-Dihydroxydiphenyl (DOD; CAS no. 92-88-6), also known under the synonyms 4,4′-biphenyldiol, p,p′-diphenol, dihydroxybiphenyl, and dihydroxydiphenyl (CAS SciFinder), see Fig. 1, has been in the rubber patch test series of Trolab/Hermal for many years (0.1% in pet.), while other patch test suppliers have not marketed this allergen. There is no recent literature as searched for by use of PubMed®. DOD is mentioned in a few textbooks, but without further comments on its importance (1, 2). In Cronin’s classic textbook, DOD is listed as dioxydiphenyl; it was tested at 1% pet. at that time, and only one case of ‘rubber sheet dermatitis’ was described (3). Polano reported four surgeons who had reacted to rubber gloves and to one of the constituents, namely DOD (tested at 1% pet.) (4). In the old German literature, DOD was linked to one case of axillary dermatitis – DOD was present in ‘sweat pads’ used at that time against perspiration (5). Moreover, a case of occupational dermatitis caused by DOD and diphenylthiourea in neoprene gloves was reported (6).
According to information provided by Hermal, DOD is used in the vulcanization process for rubber items and as an antioxidant added to light rubber products. Moreover, it is mentioned as an antioxidant in phenol formaldehyde resins. DOD is not present in any of the manufacturers’ ‘plastic series’, and is not recommended as a diagnostic tool for identifying cases of contact dermatitis caused by plastic materials, either in the production process or by contact with the finished product (7). Bruze and Zimerson (8) reported on contact allergy to a dihydroxydiphenyl methane (bisphenol F), which is obviously different from DOD.

In recent publications on contact allergy to rubber, DOD was not listed at all (9–14). However, in the large data pool of the Information Network of Departments of Dermatology (IVDK), the results obtained with DOD have been recorded since 1996. We therefore analysed these and other clinical data, and also tried to obtain information on the current use of DOD from the rubber industry.

Methods

IVDK data
Details on the network collecting patch test data from over 50 departments of dermatology in Germany, Austria and Switzerland can be found in a recent publication (15) and on the internet (www.ivdk.org). Test results obtained with DOD in the time period 1996–2013 were analysed. DOD is part of the rubber series of the German Contact Dermatitis Research Group, and was provided by Hermal (Reinbek) at 0.1% pet.

Information from other departments of dermatology
Seven European centres with a focus on contact dermatitis and occupational dermatology and one centre in the United States were contacted with a questionnaire with regard to testing of DOD and available information on the presence of DOD in rubber products.

Information on the use of DOD in rubber products from manufacturers
Major manufacturers of rubber gloves and rubber tyres were contacted with regard to whether DOD was used in the production process of their products. Two organizations collecting product information as provided by the manufacturers of gloves for various applications were asked about DOD: Bundesverband Handschutz (BVH, Oberhausen, Germany) and GISBAU (Berufsgenossenschaft der Bauwirtschaft, Frankfurt, Germany).

Results

IVDK data
A total of 36 338 patients were tested with DOD 0.1% pet. between 1996 and 2013. There were 42 positive reactions (0.12%) on day (D) 3 or 4, the overwhelming majority [88.1% (positivity ratio)] being 1+ reactions (37/42). The number of doubtful, follicular and irritant reactions amounted to a total of 148 (0.41%); thus, the ‘reaction index’ was −0.56. A comparison of the MOAHLFA index between DOD-positive and DOD-negative patients yielded no relevant differences regarding sex, anatomical site of eczema (hands: 50% DOD-positive versus 57% DOD-negative), atopic dermatitis, and occupational causation. However, the final diagnosis was more often ‘allergic contact dermatitis’ (45% versus 29% in DOD-negative patients). The duration of application of patches (1 versus 2 days) had no significant impact on the occurrence of positive test reactions (p = 0.9, χ² test). The pattern of occupations did not differ in any relevant way between DOD-negative and DOD-positive patients. In 17 of 42 (40%) DOD-positive patients, rubber materials were suspected as cause of dermatitis, in contrast to 27.9% of DOD-negative patients (p = 0.1, χ² test). All DOD-positive patients also reacted to at least one other allergen from the rubber series; on average, 2.8 allergens. Among DOD-negative patients, 31 998 had no positive reaction to another allergen from the rubber series. Among DOD-negative patients with another positive reaction to a rubber series allergen (n = 4 298), 1.8 reactions to rubber allergens were observed on average (all excluding the rubber markers from the baseline series).

Nearly 40% of all positive cases were observed in Erlangen (5/1807), Lübeck (4/838), Rostock (4/437), and Bern (3/1210). The remaining cases were observed in 19 centres (2 cases or 1 case each). There was no clear relationship between the prevalence of DOD sensitization and geographical region. The department (specialized in

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Fig. 1. Chemical structure of 4,4′-dihydroxydiphenyl.
occupational dermatology) with the highest number of patients tested with DOD was Osnabrück in North Germany, where only 1 of 3496 patients was DOD-positive.

Detailed information was obtained on the 5 DOD-positive cases in Erlangen; all 5 had a history of rubber exposure at one time or another (gloves, tyres, and swimming goggles). In 2 patients, the DOD reaction was seen on an angry back; retesting gave a negative result in one case, and is still pending in the other. In 2 patients, clinical relevance to DOD was clearly ruled out, because other sources explained the dermatitis (p-phenylenediamine in black leather shoes, and monoethanolamine in metal-working fluids). In a 51-year-old worker with various jobs [cleaning, driver (delivery of tyres), and warehouse], the clinical relevance of the DOD reaction was considered as 'possible' owing to intensive exposure to various rubber items (during loading and unloading of rubber tyres as a driver, and wearing rubber gloves as a warehouse worker) over many years. There were three bouts of severe hand eczema after intensive rubber contact. However, the patient also had a total of five reactions to other rubber compounds in the baseline and rubber series. Therefore, previous exposure and sensitization to DOD is just possible, as detailed information on the ingredients of the rubber products was not available.

**Information from other departments**

Eight departments provided information on DOD testing. Only three centres had experience with it, using DOD 0.1% pet for patch testing. In Odense (Denmark) – also collecting data of dermatologists in practice – 3 of 168 tested patients were positive (1.7%); another 3 patients showed a + reaction on D2, without further readings being documented. Of the 3 patients with positive reactions at two readings, 2 had also reacted to diphenylthiourea and dibutylthiourea, 1 to diphenylguanidine, and 1 to zinc dimethyl dithiocarbamate and fragrance mix I. All patients had hand eczema. No further data on clinical relevance and causative products were available. In Leuven (Belgium), 699 patients were tested, without any positive reactions. Therefore, testing was stopped in 2004. In Coimbra (Portugal), 63 patients were tested in 2012 and 2013, and no reactions were seen. Taking all tested patients together, there were only 3 of 930 positive patients (0.32%). DOD was not tested in the following five departments: Lund and Malmö (Sweden), Gentofte (Denmark), Leeds (UK), and Cleveland (USA). None of the investigators remembered any product containing DOD.

**Information from manufacturers**

Three major manufacturers of rubber products of various kinds – Continental (Hannover/Hamburg, Germany), Semperit (Windpassing, Austria), and Michelin (Clermont Ferrand, France) – denied using DOD in any manufacturing process. This was also confirmed by a leading manufacturer of gloves, MAPA (Zeven, Germany). SmartPractice (Phoenix, AZ, USA) produces and distributes various gloves for medical professions, mainly in the United States. DOD is not added to their product line at any stage of production, including processing of the raw material in Malaysia. The BVH, an association of manufacturers of products for occupational skin protection (gloves, skin care, etc.), could not identify DOD as a constituent in any of the rubber products produced by its members. The same information was obtained by the Statutory Employers’ Liability Insurance Institution of the Building Industry (GISBAU), which collects information on skin protection equipment and health hazards caused by construction materials. DOD is listed as a ‘potential allergen’ in the database on gloves, but is not found in any commercial product.

**Discussion**

On the basis of the extensive IVDK data, it can be concluded that DOD is currently a very rare contact allergen. When it was tested at 0.1% pet., most reactions were only weakly positive. The number of doubtful, follicular and irritant reactions greatly outnumbered the total of reactions read as positive. In view of the much higher test concentration used in the past (1.0%), the presently used test concentration may be too low; we are not aware of any efforts to establish a valid patch test concentration for DOD. In the de Groot textbook, DOD is listed with 0.1% pet., with only further textbooks and no original publications on DOD being cited (2). Specifically, no data on dose–response curves in proven cases of contact dermatitis caused by DOD are available, and no animal data on experimental sensitization with DOD have been found.

In the 42 DOD-positive patients of the IVDK, the clinical relevance remained unclear, although exposure to rubber products was assumed to have occurred in the past or present, particularly in those patients also showing positive reactions to other rubber constituents. However, in the routine documentation of the IVDK, no particular rubber product containing DOD, possibly being the cause of the sensitization, could be identified by the investigators.

In view of the ‘historical’ case reports, it may be considered that we have detected mainly old sensitizations. Major manufacturers of rubber products denied the current use of DOD as an antioxidant. Cross-reactions with other rubber chemicals may be considered. However, the molecular structure of DOD is quite different from that of...
the major rubber constituents used for patch testing, and true cross-reactions are unlikely (J-P Lepoittevin, pers. comm. 2014). The observed associations with sensitizations to rubber chemicals probably have to be considered as concomitant sensitizations.

The three European departments that had tested DOD for a short period found very few DOD-positive cases, and these were of unclear clinical relevance. The majority of contacted departments had not included DOD in the rubber series.

In conclusion, DOD is a very rare contact allergen. Major manufacturers of rubber products deny its current use. It may therefore be omitted from the patch test series used for screening for rubber contact allergy. However, according to the CAS database (https://scifinder.cas.org/scifinder, last accessed 15 June 2015), DOD is used in the production of particular plastic resins, and exposure may therefore still occur in this context.

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