

White petrolatum (Ph. Eur.) is virtually non-sensitizing. Analysis of IVDK data on 80 000 patients tested between 1992 and 2004 and short discussion of identification and designation of allergens

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Sporadic cases of contact allergy to white petrolatum, which is used as a vehicle in patch test preparations, have been reported. The quantitative relevance of the phenomenon remains yet to be elucidated. *Methods:* Retrospective analysis of patch test data of the Information Network of Departments of Dermatology (IVDK, <http://www.ivdk.org>) between 1992 and 2004. *Results:* Analysis of 79 365 patients patch tested with pure petrolatum yielded 27 '+' (0.03%) and 2 '+++' (0.003%) reactions. The majority of non-negative reactions (0.3%) was interpreted as doubtful (235) or mild irritant (32). The negative reaction index (RI) (−0.8), and the high positivity ratio (PR) (93%) especially a lack of concordance with patch test preparations containing ≥99% petrolatum indicate that many of the 'positive' (+) reactions have to be considered as irritant. There were 2 '+++' reactions. In 1 case, an 'angry back reaction' was confirmed. The other case is probably a reading or documentation error, as the majority of patch test reactions to preparations containing petrolatum remained negative in this case also. *Conclusions:* True allergic patch test reactions to white petrolatum are extremely rare and probably due to an individually increased susceptibility to allergens and/or irritants. This is in agreement with considering petrolatum as a non-sensitizer.

Key words: allergic contact dermatitis; CAS 8009-03-8 (unspecified, white or yellow); patch test; sensitization; white petrolatum. © Blackwell Munksgaard, 2006.

Accepted for publication 1 March 2006

White petrolatum (vaselinum album, soft paraffins, Vaseline[®], CAS 8009-03-8; unspecified, white or yellow) is a purified mixture of semisolid hydrocarbons obtained from petroleum distillation residues (1). The production process is the same for white and yellow petrolatum; however, to eliminate potentially toxic ingredients, the purification process is continued for white petrolatum until the product is free of yellow colour (2). In view of the differences in sensitizing properties and other toxicological properties between yellow and white petrolatum, only highly purified petrolatum, with the (carcinogenic) aromatic fraction eliminated, should be used, as regulated by the national and international pharmacopoeias (3). Yellow petrolatum may still be used in lubricating machinery, leather grease, shoe polish, rust preventives and modelling clays (1).

White petrolatum is used as ointment base in pharmaceuticals and cosmetics and as vehicle for most patch test allergens (4). Cases of contact sensitivity to yellow petrolatum have been described (5), and 2 of several possible allergens were putatively identified as phenanthrene derivatives (6), which apparently were present in yellow, but not white petrolatum (2). Although it was not possible to demonstrate sensitizing properties of white petrolatum in animal tests (7), different compounds of white petrolatum may still have sensitizing properties depending on its source and the purification process as required by a certain pharmacopoeia (2, 8). Moreover, rare cases in humans after patch testing were reported in the literature (8–10), occasionally combined with reactions to yellow petrolatum (11–14). The chemical nature, properties and various

reactions to petrolatum were briefly reviewed by Fisher (15). However, epidemiological analyses of reactions to highly purified white petrolatum to address the quantitative relevance of the phenomenon have not yet been performed. Therefore, we analysed patch test data with a certain species of highly purified white petrolatum (according to Ph. Eur.) obtained from a major manufacturer, collected in a large multi-centre surveillance network.

Methods

The multicentre project Information Network of Departments of Dermatology (IVDK) is an instrument of epidemiological surveillance of contact allergy and has been described in detail elsewhere (16, 17). Patch tests are performed in accordance with the recommendations of the ICDRG (18) and the German Contact Dermatitis Research Group (DKG) (19). Patch test material is obtained from Hermal/Trolab, Reinbek, Germany. Highly purified white petrolatum, purchased from the same supplier during the whole period and complying with the standards of the European Pharmacopeia (Ph. Eur.), according to the manufacturer, is used as allergen vehicle and negative control. Patch test preparations are applied for 24 h or 48 h. Readings are done until at least 72 h using the following grading based on international standards (20), further refined by the German Contact Dermatitis Group (19): neg., ?, +, ++, +++, irritant, follicular. The patch test results of every reading, a standardized history (comprising age, sex, atopic diseases, current and former occupation(s), presumptive causal exposures), along with final diagnoses and site(s) of dermatitis are assessed and documented. All data is transferred to the data centre in Göttingen in an anonymised format every 6 months.

Between 1992 and 2004, white petrolatum was applied in 41 departments of dermatology of the IVDK as a patch test preparation serving as negative control along with other allergens, such as those from the standard series.

Frequencies of sensitization (as percentage of patients tested) were calculated as crude proportions not further standardized for sex and age (21). The reaction index (RI), relating the number of allergic reactions to the number of doubtful or irritant reactions (22), and the positivity ratio (PR), relating the frequency of + reactions to the total number of allergic reactions (23), were calculated as parameters to assess the patch test preparation. As a standard measure of chance-corrected concordance between reactions to petrolatum and to selected petrolatum-based allergen preparations [potassium

dichromate, isopropylparaphenylenediamine, zinc diethyldithiocarbamate, *p*-tert butylformaldehyde resin (ptBF)], and for comparison, 1 water-based allergen (formaldehyde), Cohen's kappa value was calculated (Table 1) (24). For data management and analysis, the statistical software package SAS (version 9.1 SAS Institute, Cary, NC, USA) was used.

Results

Our present analysis of 79 365 patients patch tested with white petrolatum yielded 27 '+' (0.03%) and 2 '+++' (0.003%) reactions. In contrast, the majority of non-negative reactions (0.3%) were interpreted as doubtful: in 235 cases, erythema only was documented; in another 14 cases, a follicular reaction and in another 32 cases a mild irritant reaction was observed. The negative RI (−0.8, the majority of reactions being '?' or 'irrit') and the high PR (93%, the vast majority or allergic reactions being '+' reactions) are already indicating that many of the 'positive' reactions probably have to be considered as irritant (23).

The analysis of concordance of 'positive' reactions to petrolatum with a number of allergen preparations which contain $\geq 99\%$ petrolatum revealed a degree of concordance not exceeding chance (kappa values close to 0) throughout (Table 1). In other words, 'positive' reactions to 100% petrolatum were not related at all to positive reactions to (allergen preparations containing) 99% petrolatum.

An in-depth analysis of the 2 cases with documented +++ patch test reactions to petrolatum revealed the following: in 1 patient, testing of altogether 5 test series with a number of other allergens dissolved or dispersed in petrolatum yielded just 2 weak positive (to Bismark Brown R and glutardialdehyde) and 1 doubtful reaction to methylene bithiocyanate. In the other case, another 5 +++ reactions were observed in the immediate vicinity of the +++ reaction of petrolatum, including a very strong reaction to bufexamac. As an angry back reaction was suspected, the patient was re-tested some months later. On this occasion, a strong positive reaction to bufexamac but a negative reaction to petrolatum (and the other surrounding allergens) was found.

The analysis of proportions of 'positive' reactions to pure petrolatum across centres revealed 2 centres contributing a rather high share of such reactions, namely 5 of 2213 (0.2%; exact 95% CI = 0.07–0.5%) and 4 of 574 (0.7%; exact 95% CI = 0.2–0.7%), respectively, of the

patients tested. These 2 departments contributed only 3.5% of all patients tested. The remaining 20 patients were more or less equally distributed among 12 departments (covering 50% of all patients) while in 27 departments no reactions at all to the same highly purified petrolatum brand used by all IVDK members were observed.

Discussion

For decades, highly purified petrolatum is being used as a vehicle in patch test preparations applied to millions of patients throughout the world. Based on this tremendous experience, physicians feel certain about the non-sensitizing property of petrolatum used in patch testing ('face evidence'). However, the extremely rare case reports on contact allergy to white petrolatum, either due to a type of petrolatum meeting the requirements of high purity or not, seem to challenge such face evidence. The aim of our study was to put such sporadic results into the perspective of a large clinical data base, admittedly being able to assess just 1 particular brand of highly purified petrolatum as delivered by an important manufacturer of patch tests (Hermal/Trolab Germany), whereas other types of petrolatum were not tested (2, 8) and cannot be considered. Therefore, our results and conclusions cannot be generalized for all possible variants of white petrolatum as used, for example, in other commercial or non-commercial patch test preparations (8).

The possibility of false-positive reactions

Patch testing white petrolatum in almost 80 000 patients during a 12-year period yielded an exceedingly low number of 27 '+' and 2 '+++' reactions, respectively (0.03% and 0.003%). Even this prevalence may overestimate the actual frequency of sensitization for at least 3 reasons:

- (1) As the prevalence of true contact sensitization to pure petrolatum is presumably extremely low, if (i) the scarceness of case reports already quoted and (ii) the ubiquitous use of petrolatum as negative control in patch testing is taken into account, the *a priori* likelihood of true contact allergy to petrolatum will be extremely low. Thus, according to the formula of Bayes (24), the positive predictive value of the patch test will be negligibly low, that is the proportion of false-positive test reactions will be devastatingly high.
- (2) Petrolatum was always tested together with allergen preparations containing at least

99% petrolatum, which can be considered as multiple controls. Patch testing the same allergen in parallel yields normally a high concordance of reactions (25, 26). If petrolatum was an allergen, at least some concordance between reactions to pure petrolatum and other 'control' petrolatum preparations must be expected. However, virtually no concordance exceeding chance, similar to that found when comparing petrolatum with a water-based allergen, was observed.

- (3) The reaction profile (RI and PR) bears similarity to 'problematic' allergens (marginal irritants) such as phenylmercuric acetate or octyl gallate (23).

Consequently, a large proportion of the reactions classified as '+' has to be considered false positive.

The source of such misclassification may be either bias (systematic difference) or error (chance variation). A systematic difference must be suspected in the case of 1 particular department reading 0.7% of all negative control tests with pure petrolatum as weak positive, because this prevalence is extremely implausible, considering the literature and the results of further 40 departments. As a consequence and following further routine analysis of IVDK data for internal quality control (27) all results of this department had been excluded from further multicentre analyses of the IVDK.

As another source of misclassification, error on any level of the process of patch testing and the documentation of its results must be considered. While in 1 of the 2 cases with '+++' reactions, an 'angry back' phenomenon has been unequivocally proven, the other '+++' case (1/79 365 within 12 years; 0.0013%) may just have been a reading or documentation error, as most of test reactions to the many other petrolatum-based allergens remained completely negative. It is entirely possible that a certain, hopefully very low, number of the 27 '+' reactions were also erroneous. Such errors may presumably also happen with other allergens. However, while in the case of real and more common allergens correctly classified, test reactions will by far outweigh an occasional error, this is not the case with an extremely rare allergen.

The relevance of true-positive reactions for identification and designation of a chemical as an allergen

If (a small fraction of) the few '+' reactions had been true allergic reactions, e.g.

Table 1. Concordance of test reactions to pure petrolatum and patch test preparations containing =99% petrolatum and, for comparison, one water-based allergen. As indicated by kappa values around 0, 'positive' reactions to 100% petrolatum were not related at all to positive reactions to (allergen preparations containing) 99% petrolatum.

a) Potassium dichromate (0.5%), petrolatum (99.5%)				
	++ + +		neg., f., IR	kappa (95% CI)
Pure petrolatum	++ + +	7	22	0.003 (0.001–0.006)
	neg., f., IR	3363	75 734	
b) Isopropylparaphenylenediamine (0.1%), petrolatum (99.9%)				
	++ + +		neg., f., IR	kappa (95% CI)
Pure petrolatum	++ + +	3	25	0.008 (0.000–0.017)
	neg., f., IR	673	72 541	
c) Zinc diethyldithiocarbamate (1% pet.), petrolatum (99%)				
	++ + +		neg., f., IR	kappa (95% CI)
Pure petrolatum	++ + +	0	25	Not calculable
	neg., f., IR	371	67 608	
d) ptBF (1% pet.), petrolatum (99%)				
	++ + +		neg., f., IR	kappa (95% CI)
Pure petrolatum	++ + +	1	28	0.002 (0–0.006)
	neg., f., IR	800	78 293	
e) Formaldehyde (1%), water (99%)				
	++ + +		neg., f., IR	kappa (95% CI)
Pure petrolatum	++ + +	3	26	0.003 (0.000–0.006)
	neg., f., IR	1473	77548	

- (1) confirmed by a positive ROAT (which was unfortunately not done or documented) or
- (2) supported by marked concordance with other petrolatum-containing preparations (which was not the case).

The final question to be answered remains: Is highly purified white petrolatum, as tested in our series, an allergen, or not?

In the absence of a general agreement on an operational definition of a 'contact allergen', even a single case of unequivocal allergy could qualify the chemical as an 'allergen', disregarding the almost 100% of equally exposed cases where it was not an allergen. However, such a liberal definition not taking quantitative aspects into account would reduce 'sensitizer' and 'non-sensitizer' to meaningless terms.

Instead, classification of a substance as allergen has to consider several aspects, as existing evidence points to the fact that contact allergy is 'a graded phenomenon' (28), being the combined effect of (i) differing allergen potencies (29, 30), (ii) different doses of an allergen (31, 32) and (iii) differing individual susceptibility (33–36). Contact allergy is thus a phenomenon composed of different graded elements. Strong allergens like DNCB can cause contact allergy in a substantial number of exposed individuals (37), and, on the other

extreme, other substances almost never cause contact allergy, although exposure is abundant. Moreover, the extremely rare case of contact allergy observed under the conditions of abundant exposure and 'sufficient dose' would no longer be indicative of a 'contact allergen' but would indicate extreme susceptibility of the affected individual, as, vice versa, the role of susceptibility would be negligible in the case of a potent allergen.

Several proposals for the identification and designation of contact allergens have therefore adopted a multifaceted perspective of contact allergy (29, 38–40), alas, not yet considered in regulatory rules. According to these algorithms, petrolatum would clearly come out as a non-sensitizer.

Conclusion

Our data and further interpretation do not contradict previous evidence finding that certain preparations of petrolatum may very rarely cause contact allergy (8), possibly comparable to water. However, any apodictic statement that 'petrolatum is an allergen' must be rejected:

- (1) *Potency and exposure*: In view not only of experimental results but based on extensive human data (ours included), highly purified petrolatum must be regarded as

extremely weak allergen – if at all! Exposure to purified petrolatum is extensive – not only during patch testing, but also through cosmetics and topical medications. In view of such data, it is highly improbable that petrolatum is an allergen.

- (2) *Evidence*: The evidence to identify and designate petrolatum as an allergen is clearly insufficient. The contrary would be true: It is evident that petrolatum is a non-sensitizer, having in mind that almost every statement on ‘facts’ or ‘evidence’ in biological sciences, in particular in medicine (e.g. ‘diagnoses’), is not based on deterministic certainty but on probability (41). However, further epistemologic reasoning would go beyond the scope and intention of this article.
- (3) *Susceptibility*: Even if there is a sporadic, well-documented case of contact allergy to highly purified petrolatum, it could presumably not be explained by a particular property of the chemical (‘the chemical is an allergen’) but alternatively by the affected individual being highly susceptible – if a biological event such as sensitization is believed to follow rules of causality at all, and not merely to be ‘bad luck’. Such a view would, however, require a change of paradigm in the field of contact allergy, until now 1-dimensionally focused on the chemical.

In summary, purified white petrolatum in pharmaceutical quality meeting current pharmacopeial requirements (Ph. Eur) cannot be considered an allergen. The case of petrolatum could be used in the ongoing discussion on identification and designation of contact allergens.

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