

Evaluating 1,3-Propanediol for Potential Skin Effects

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ABSTRACT: *In the present article, the authors assess the skin irritation and sensitization potential of 1,3-propanediol (INCI: Propanediol). Results in animals and humans by acute or repeat exposure support a low potential of skin reactivity for the material. In addition, the skin reactivity potential in humans was found to be lower with 1,3-propanediol than 1,2-propanediol (INCI: Propylene Glycol).*

Glycols have been used in cosmetics and personal care products to impart beneficial properties such as humectancy, solvency, moisturization and emulsification. One such ingredient is 1,3-propanediol (PDO), which is manufactured either by a chemical process using petroleum feedstock or by a fermentation (bio-based) process using corn sugar. Since PDO became commercially available only recently, it does not yet have a widespread history of use for properties such as humectancy, moisturization or emulsification. However, a substance structurally similar to PDO, propylene glycol (PG) (see **Figure 1**), does have widespread use and distribution in personal care products—but it also has a history of some dermal irritation and to a lesser extent, sensitization.^{1,2}

Obviously, besides the efficacy properties of a raw material, another critical property is the lack of or low potential for dermal irritation and sensitization of skin. Therefore, an evaluation of the potential for new ingredients to cause adverse skin reactions is essential.³ Information from previous animal

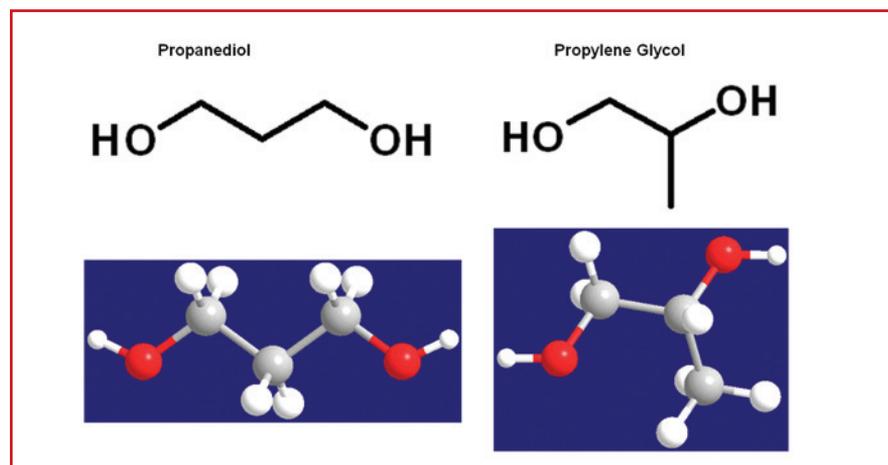


Figure 1. PDO and PG structural depictions

Table 1. Summary of skin reactions in the described 200-person RIPT

Test concentration, pH and test material	Severity of response according to the test grading system	No. subjects with a response/total subjects	Final clinical observation/conclusion
Control pH 4	0	0/207	Negative
Control pH 7	0	0/207	Negative
Control pH 9	0	0/207	Negative
25% PG pH 7	+ to 2	17/207	Positive for irritation/cumulative irritation
50% PG pH 7	+ to 3	45/207	Positive for irritation/cumulative irritation
75% PG pH 7	+ to 2	47/207	Positive for irritation/cumulative irritation
25% PDO pH 7	+	2/207	Negative (clinically insignificant ^{**})
50% PDO pH 7	+ to 1	3/207	Negative (clinically insignificant)
75% PDO pH 7	+	6/207	Negative (clinically insignificant)
75% PDO pH 4	+ to 1	6/207	Negative (clinically insignificant)
75% PDO pH 9	+ to 1	6/207	Negative (clinically insignificant)

Score	Description of Effect
0	No visible skin reaction
+	Barely perceivable or spotty erythema
1	Mild erythema covering most of the test site
2	Moderate erythema, possible presence of mild edema
3	Marked erythema, possible edema
4	Severe erythema, possible edema, vesiculation, bullae and/or ulceration

^{**}Mild redness occurring once during nine induction applications or transiently at challenge was considered clinically insignificant
 PDO = 1,3-propanediol; PG = 1,2-propanediol

studies following exposure to chemically-produced PDO suggests a low potential for human skin reactions. This historical information includes a study in rabbits (Draize method), showing neat PDO is mildly irritating;⁴ and a study in guinea pigs (Landsteiner/Draize method), showing no dermal irritation or sensitization.⁵

To build on existing information for PDO, humans have been tested for effects to the skin using bio-based PDO of similar purity. For example, an acute dermal irritation study was conducted on 40 healthy Japanese volunteers, who received a single application of neat bio-based PDO, and no significant skin irritation was observed.⁶ However, acute animal and single exposure human studies are limited in their ability to predict skin reactions in humans exposed repeatedly to PDO. Therefore, human repeat-insult patch test (RIPT) dermal studies were conducted using bio-based PDO in comparison with PG to understand the potential to cause irritation and sensitization. The RIPT studies, described here, were designed using a range of concentrations and pH levels to

cover a wide variety of potential personal care applications.

Materials and Methods

Test substances: PDO^a (> 99.8%; CAS # 504-63-2) and PG^b (USP grade purity 99.5%; CAS# 57-55-6) were obtained for the described studies. PDO

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was tested in two separate human RIPT involving 100 and 200 subjects, respectively. In the 200-person RIPT, PG served as a reference compound for comparison.

Modified Draize RIPT in Humans

Substance application and panel: The tested PDO^a was diluted in 0.22 µm-filtered deionized water to 5%,

25% and 50% for the 100-person RIPT^c; and 25%, 50% and 75% at pH 4, 7 and 9, respectively, for the 200-person RIPT^d. The test solution (0.1 mL) was applied to one-inch absorbent pads and covered with a clear adhesive dressing. The strip was then pressed into place on the upper left arm^c or upper back^d of volunteer panelists. PG at concentrations of 25%, 50%, and 75% was used for comparison with PDO in the 200-person RIPT, as noted.

Experimental design: The method for both RIPTs was similar to that described by Draize.⁷ For the induction phase, patches were applied to the contact sites and remained in place for 24 hr. At the end of this period, the patches were removed and the sites were examined for dermal response. An additional observation was made 24 hr later. New patches were applied and remained in place for 24 hr.

^a Zemea Propanediol (INCI: Propanediol) is a product of DuPont Tate & Lyle Bio Products, LLC.

^b Propylene Glycol (INCI: Propylene Glycol) was purchased from Sigma-Aldrich.

^c The 100-subject RIPT was conducted by ConTox Ltd., Philadelphia, PA.

This procedure was repeated on Mondays, Wednesdays and Fridays for a total of nine applications. The same sites were used throughout the study. Following the 9th application and a 2-week rest period, a challenge application was applied in the same manner as described in the induction phase. A duplicate challenge application also was applied to a previously untreated site on the other arm^c or on the back^d. The sites were examined for irritation and sensitization at 24 hr and 48 hr, post-removal.

Results

The 100-person RIPT study evaluated only PDO and a deionized water control. No skin reactions were observed in any study participant exposed to 5%, 25% or 50% PDO or vehicle controls during either the induction or challenge phases. Under the conditions of this study, PDO was not found to be a skin irritant, fatiguing agent or skin sensitizer.

In the 200-person RIPT, no clinically significant skin reactions were observed for PDO (see **Table 1**). High and low pH did not impact the skin results even at 75% PDO. A few subjects exposed to 25%, 50% and 75% PDO did exhibit barely perceivable or mild redness (erythema) at 24 hr or 72 hr post-challenge, but the sites were considered clinically insignificant at the final observation. No erythema was observed throughout the induction period for 25% and 50% PDO. At 75% PDO, four individuals expressed mild erythema after one of nine applications.

Allergic contact dermatitis or sensitization was not induced by PDO or PG. However, mild, moderate and marked skin irritation and cumulative skin irritation reactions were observed throughout the testing period for all three test concentrations of PG (see **Table 1**). These reactions occurred during the nine applications of the induction phase and 24 and 72 hr after challenge with different degrees of severity. Some individuals exhibited a response after six of the nine applications. These results represented irritant or cumulative irritant responses in 8.2%, 21.7% and 22.7% of the test population exposed to 25%, 50% and 75% PG, respectively.

Discussion

As has been described, the potential of PDO to cause dermal effects in humans was explored in two repeat insult human studies to build upon existing animal tests and short-term human studies. Taken collectively, the data from these studies showed that PDO has low potential to irritate or sensitize human skin; additionally, its potential for these effects was lower than an incumbent glycol, PG.

PDO has low potential to irritate or sensitize human skin and its potential for these effects was lower than PG.

A few panelists exposed to PDO in the 200-person RIPT produced barely perceptible to mild redness only once during the nine applications in the induction period, or a transient, barely perceptible to mild redness following the challenge application. The infrequent appearance of minor reactions with recovery after challenge was considered clinically insignificant by the study physician. Due to the hygroscopic nature of higher PDO concentrations, drying of the skin may explain the mild, sporadic and transient reddening observed.

The observations in the 200-person RIPT for PG were described as irritant or cumulative irritant reactions but were not characteristic of dermal sensitization. PG is a widely used ingredient that occasionally can produce contact dermatitis in a small portion of the population. While predictive animal tests did not detect potential sensitizing properties of PG for human skin, human patch tests have provided more consistent results.⁸ Patch test surveys aimed at evaluating patients with existing allergic contact dermatitis reported a 2–4% occurrence of sensitization to PG in the general population.^{9, 10, 11} The reactions observed in response to PG topical exposure in the above

reported RIPT are indicative of irritation rather than sensitization, and it is not clear how many of these “irritation responses” may have represented a prior sensitization to PG from exposure to consumer products containing it.

Conclusion

PG and PDO are different molecules that have similar structures and physicochemical properties. The RIPT results described here suggest that PG may be more likely to cause skin reactions than PDO. Factors that may influence this difference in response include chemical structure and the extent and nature of exposure. It has been hypothesized^{12, 13, 14} that dipole moment may influence skin irritation responses, which could provide one explanation for this difference since PDO and PG have different dipole moments—the PDO molecule having greater flexibility.

The human population includes individuals with sensitive skin that are more likely to react to ingredients that are inactive for the majority of the population.^{15, 16} Since a larger portion of the population has already been exposed to PG through personal care products, cosmetics and food, it is possible that more consumers with sensitive skin have been exposed to PG than PDO, which could account for the relatively high incidence of contact dermatitis.

The search for cosmetic ingredients that do not produce skin reactions in humans, including sensitive subpopulations, is a continuing challenge. It is essential to introduce ingredients that have minimal potential for skin reactivity to reduce the risk of adverse skin reactions.

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^d The 200-subject RIPT was conducted by Consumer Product Testing Co., Fairfield, NJ.

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Lab Practical: Using PDO

- When replacing another glycol with PDO, substitute it 1:1 in the formulation.
- When formulating solid deodorants, increase the blending temperature.
- If cloudiness or solubility issues arise, adjust the order of addition and mix PDO into the aqueous phase and/or increase the blending temperature.
- 60% maximum PDO is recommended for solid deodorant sticks with sodium stearate; if shrinkage occurs, a solubilizing agent is recommended.

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