以量化結構－活性關係為基礎之化學物皮膚滲透係數預測模式

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工業化學毒物之皮膚暴露可對作業人員生命或健康構成重大威脅，然而因確切毒害效應測試資料缺乏，其皮膚暴露可形成之危害難以有效評估。化學物經皮膚暴露吸收之潛能常利用該物質穿透角質層速率，亦即皮膚滲透係數(Kp)量化表示。此數值可經由活體外實驗測試而得，但受到實驗材料與技術之限制，Kp 迄今未能大規模透過實驗方式產生。本研究嘗試透過化學物之分子結構特徵，建立以量化結構－活性關係(QSAR)爲基礎之 Kp 預測模式。研究所建立之 QSAR 模式分析化學物之分子結構特徵，建立對應之分子描述符，繼而探討 158 個工業化學物 Kp 實驗值與描述符間之關係。模式發展過程首先利用 HyperChem®軟體進行化學物分子結構繪製及結構優化，而後使用 DRAGON®軟體依據優化分子結構進行描述符計算，並透過逐步迴歸法挑選最具代表性之描述符。研究結果發現：當模式篩選分子描述符之統計顯著水準達 $p < 0.05$ 時，預測模式之線性可達 $R^2 = 0.83$。模式共包含 4 個與 Kp 高度相關之描述符，分別爲：分子間凡德瓦爾力之四偶極矩靜電吸引力、辛醇–水分配係數、抗腫瘤增生藥物 80%相似指數、及碳–氮原子間拓撲距離爲六鍵之頻率。本研究所建立之 Kp 預測模式，可在生物實測數據缺乏時，作爲提供預測化學物皮膚滲透潛能及其危害之工具。

關鍵字：皮膚滲透係數、定量結構－活性關係

Quantitative Structure-Activity Relationship-Based Model for Predicting Skin Permeation Coefficient of Chemical Substance

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The exposure of skin to toxic industrial chemicals (TICs) poses a threat to health of workers. However, limited by lack of sufficient data from toxicological testing, health hazard from skin exposure to TICs has not been effectively assessed. Conventionally the potential of TIC uptake via dermal route is quantitatively expressed as the rate of TIC permeating through stratum corneum, the skin permeation coefficient (Kp). The Kp may be determined in vitro but due to limitations in technique has not yet been so produced steadily. This study aimed to develop a quantitative structure-activity relationship (QSAR) for Kp estimation. A total of 158 TICs were analyzed for development of molecular descriptors; the descriptors were then statistically investigated for their correlations with Kp. In the QSAR development, the molecular structures of chemical were graphically presented and geometrically optimized using HyperChem® and the corresponding descriptors calculated by DRAGON®. Step-wise regression was employed to determine the descriptors that were most correlated to Kp estimation. As the findings show: four molecular descriptors were highly associated with Kp ($p < 0.05$; $R^2 = 0.83$), including the electrostatic interactions between electric quadrupoles of van der Waals forces, octanol-water partition coefficient, antineoplastic-like index at 80%, and frequency of C-N at topological distance of 06. This QSAR model may be used as an alternative in evaluating Kp when the biologically determined Kp is not available.

Keywords: skin permeation coefficient, quantitative structure-activity relationship