中文摘要

二氧化鈦 (TiO_2) 為典型之低溶解性微粒 (Poorly Soluble Particles)，全球 TiO_2 產量之 70% 使用於塗料產品中，近年來 TiO_2 常添加於化妝品、防曬油中及製作光催化劑。生產 TiO_2 之包裝、研磨、混合及機械維修過程皆可能產生高吸入暴露，國際癌症研究署 (International Agency for Research on Cancer, IARC) 於 2006 年將 TiO_2 重新歸類為可能對人類產生致癌性之物質。本研究目的為以風險評估架構為基礎結合暴露與效應評估，推估 TiO2 工廠工作人員肺泡組織嗜中性白血球 (Polymorphonuclear 或 Leukocytes, PMN) 上升及肺腫瘤 (Lung Tumor) 產生率之超越風險。本研究採用之風險評估資料以美國及歐洲境內 TiO_2 工廠工作人員之暴露數據為主。本研究首先應用對數常態分佈模式擬合 TiO_2 工廠之氣懸 TiO_2 奈米微粒 (TiO_2 NPs) 粒徑分佈，並以生理為基礎之肺部模式 (Physiologically Based Lung Model) 推估 TiO_2 工廠工作人員吸入不同粒徑銳鈦礦 (Anatase) 及金紅石 (Rutile) 之暴露程度，最後再以 Hill 模式重建 PMN 上升及肺腫瘤產生率之毒理效應曲線。以對數常態分佈模式擬合 TiO_2 工廠內之氣懸 TiO2 NPs 粒數分佈，得知幾何粒徑平均數為 24.81 nm，幾何標準偏差為 1.38 (r^2 = 0.95)；而工廠外氣懸 TiO_2 NPs 之幾何粒徑平均為 42.71 nm，幾何標準偏差為 1.45 (r^2 = 0.88)。效應分析結果顯造成 50% 之 PMN 上升效應劑量 (EC50) 為 0.11 m^2 g^{-1} (n = 2.1, r^2 = 0.88)，造成 50% 之肺腫瘤發生率劑量為 1.15 m^2 g^{-1} (n = 5.32, r^2 = 0.85)。暴露評估結果顯示美國包裝工人肺泡表面負荷銳鈦礦及金紅石之最高值分別為 0.1744 及 0.122 m^2；肺泡間隙累積最高值分別為 0.9804 及 0.6856 m^2，而歐洲表面處理工人肺泡表面負荷銳鈦礦及金紅石之最高值則分別為 0.4 及 0.28 m^2；肺泡間隙累積之最高值分別為 2.25 及 1.57 m^2。TiO2 引起

PMN 上升效應之風險曲線指出，美國包裝工人暴露於銳鈦礦及金紅石製程中引發 PMN 上升的 50 % (Risk = 0.5) 超越風險值分別為標準值之 67.33 及 35.9 倍；而歐洲表面處理工人分別為標準值之 84.94 及 71.28 倍。TiO2 引起肺腫瘤產生效應之風險曲線指出，歐洲表面處理工人暴露於銳鈦礦及金紅石製程中肺腫瘤產生的 50 % 超越風險值分別為 2×10^{-4} 及 1.81×10^{-6}，而歐洲境內其餘之工作族群及美國境內所有之工作族群皆無因銳鈦礦及金紅石暴露而引發肺腫瘤之風險。

關鍵詞：二氧化鈦；比表面積；肺部生理模式；奈米微粒；奈米毒理；風險評估

Abstract

Titanium dioxide (TiO_2) is a typical poorly soluble particles which was accounted for 70% of the total production volume of pigments worldwide. TiO_2 is appied to produce cosmetics, sunscreens and catalytic agen in recently. High inhalation exposures occur in TiO_2 production during packing, milling, mixed, and maintenance. International Agency for Research on Cancer (IARC) has recently classified TiO_2 as possibly carcinogenic to humans in 2006. The purpose of this thesis is to combine the assessments of exposure and related effect to estimate the exceedence risks for workers in TiO_2 manufacturing factories. This study used two datasets related to TiO_2 dust concentrations in TiO_2 plants in the United States (US) and Europe (EU), respectively,to explore the risk assessment. We apply the lognormal probabilistic model to fit particle size distribution data of airborne TiO_2 in the TiO_2 manufacturing factories. We estimate the inhalation risk of different size ranges of TiO_2 natase and Rutile.in the TiO_2 manufacturing factories by application physiologically based lung model (PB Lung Model). Three-parameter Hill model is used to reconstruct the dose-response profiles for polymorphonuclear leukocyte (PMN) elevation and lung tumor effects induced by TiO_2 dust. The optimal fit of the lognormal probabilistic model (r^2 = 0.95) resulting in a geometric mean (gm) of 24.81 nm with a geometric standard deviation (gsd) of 1.38. The optimal fit model (r^2 = 0.91) for outside of factory with a gm of 42.71 nm and a gsd of 1.45. The results show the median effect (EC50) for PMN elevation is 0.11 m^2 g^{-1} (n = 2.1, r^2 = 0.88) and EC50 for lung tumor proportion is 1.15 m^2 g^{-1} (n = 5.32, r^2= 0.85). The highest alveolar surface burden of packers in US factories are 0.1744 and 0.122 m^2 for anatase and rutile, whereas that are 0.4 and 0.28 m^2 for surface treatment workers in EU. The highest interstitial burden of packers in US were 0.9804 and 0.6856 m^2 for anatase

and rutile, whereas that were 2.25 and 1.57 m^2 for surface treatment workers in EU. The exceedence risks curve of PMN elevation effect at risk = 0.5 of packers in US show the highest 67.33 and 35.9 fold of standard PMN counts for TiO_2 anatase and rutile, whereas that are 84.94 and 71.28 fold for surface treatment workers in EU. The lung tumor risk results show 2×10^{-4} and 1.81×10^{-6} of lung tumor proportion for TiO_2 anatase and rutile of surface treatment workers in EU. Then the lung tumor proportion are lower than 10^{-4} for all of the work categories in US and EU (except for surface treatment) for anatase and rutile that unlikely induce lung tumor effect .

Keywords： Titanium dioxide ; Specific surface area ; Physiologically based lung model ; Nanoparticle ; nanotoxicology ; risk assessment