Mechanistic Dermal PBPK Modeling for the Dermatokinetic Risk Assessment of Persistent Pigment Particles

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Evaluating the risk of persistent particles deposited in the skin remains a critical gap within New Approach Methodologies (NAMs), primarily due to the lack of regulatory-ready models describing the long-term transport and accumulation of insoluble materials. Tattoo formulations containing TiO_2 and Cu-phthalocyanine represent ideal model systems for addressing this limitation, as these pigments reside long-term in the dermis while undergoing partial migration toward regional lymph nodes. In this study, we developed a mechanistically grounded physiologically based pharmacokinetic (PBPK) framework to quantitatively evaluate dermal particle kinetics.

The model was built on a multi-compartment differential equation architecture compatible with the PK-Sim/MoBi suite. It incorporates key nano-specific mechanisms, such as macrophage phagocytosis saturation, local tissue persistence, lymphatic clearance, and lymph node retention. Model input parameters, including particle size, surface charge, protein binding, and biopersistence, were extracted from literature and dedicated databases.

The resulting simulations effectively captured reported *in vivo* dermatokinetic trends, demonstrating progressive dermal clearance alongside systemic and nodal redistribution. Under standard tattoo exposure conditions, simulated TiO_2 dynamics yielded a 0.8–3.2% accumulation in regional lymph nodes over a 12-week timeframe, whereas Cu-phthalocyanine pigments displayed higher rates of lymphatic transfer.

Overall, this PBPK framework illustrates how *in silico* approaches can integrate physicochemical properties and experimental parameters to simulate target tissue exposure, supporting non-animal safety assessment strategies for dermally applied particulate systems.