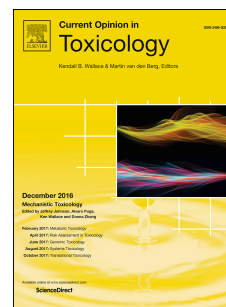


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Current status of alternative methods for assessing immunotoxicity: A chemical industry perspective

Raja S. Settivari^a, Shannon M. Krieger^a, Stuart Hindle^b, Sean C. Gehen^c, Heli M. Hollnagel^b, Darrell R. Boverhof^{a,1}

^aThe Dow Chemical Company, Midland, MI, USA

^bDow Europe GmbH, Bachtobelstrasse 3, CH-8810 Horgen, Switzerland

^cDow AgroSciences LLC, Indianapolis, IN, USA

¹Corresponding author: RBoverhof@dow.com

Abstract

Assessment of potential adverse effects on the immune system is an important component of the chemical safety evaluation process. As alternative testing methods are rapidly evolving, there is a progressing interest to determine their practical implementation for reducing or replacing existing *in vivo* studies without compromising chemical safety. There has been considerable progress in the development of alternative testing methods for dermal sensitization, however, the methods for evaluating respiratory sensitization and immunosuppression are still at various stages of development and validation. This review highlights the current status of alternative testing methods and practical considerations for implementation from a chemical industry perspective.

1. Introduction

Evaluation of immunotoxicity is an important component of chemical safety assessment. In the chemical sector, evidence of immunotoxicity is usually assessed through a range of direct and indirect assays including acute assays and evaluation of immune organs and hematology endpoints in repeat dose toxicology studies. However, endpoints of immunotoxicity that are assessed more routinely as part of the safety evaluation process, and for which *in vitro* assays have been the subject of active research, include dermal sensitization, respiratory sensitization, and immunosuppression. Current perspectives on the status of these approaches as well as remaining challenges are discussed below. In addition, specific areas that require further improvement to allow for the practical application of *in vitro* methods in immunotoxicity evaluation are discussed.

2. Endpoints: Status and Opportunities

2.1. Dermal Sensitization

Assessing skin sensitization potential of chemicals is important for defining safe handling and use practices. Therefore, this endpoint is a routine requirement for global registration of chemicals and serves to establish product classification and labeling. Historically, Guinea pig tests (1) and the mouse local lymph node assay (LLNA) (2) served as the gold-standard *in vivo* animal tests for assessing dermal sensitization (3-8). However, over the past decade, advances in our mechanistic understanding of the key events in the adverse outcome pathway (AOP) for skin sensitization have led to development of promising *in silico* (e.g., TOPKAT, DEREK, TIMES-SS), *in chemico* (the direct peptide reactivity assay; DPRA

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