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Workshop Report

Approaches and considerations for the assessment of immunotoxicity for environmental chemicals: A workshop summary

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ABSTRACT

As experience is gained with toxicology testing and as new assays and technologies are developed, it is critical for stakeholders to discuss opportunities to advance our overall testing strategies. To facilitate these discussions, a workshop on practices for assessing immunotoxicity for environmental chemicals was held with the goal of sharing perspectives on immunotoxicity testing strategies and experiences, developmental immunotoxicity (DIT), and integrated and alternative approaches to immunotoxicity testing. Experiences across the chemical and pharmaceutical industries suggested that standard toxicity studies, combined with triggered-based testing approaches, represent an effective and efficient approach to evaluate immunotoxic potential. Additionally, discussions on study design, critical windows, and new guideline approaches and experiences identified important factors to consider before initiating DIT evaluations including assay choice and timing and the impact of existing adult data. Participants agreed that integrating endpoints into standard repeat-dose studies should be considered for fulfilling any immunotoxicity testing requirements, while also maximizing information and reducing animal use. Participants also acknowledged that *in vitro* evaluation of immunosuppression is complex and may require the use of multiple assays that are still being developed. These workshop discussions should contribute to developing an effective but more resource and animal efficient approach for evaluating chemical immunotoxicity.

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Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; ACD, allergic contact dermatitis; ACSA, agricultural chemical safety assessment; AFC, antibody forming cell; CP, cyclophosphamide; CT, carbon tetrachloride; DART, developmental and reproductive toxicology; DIT, developmental immunotoxicity; ELISA, enzyme linked immunosorbent assay; EOGRTS, extended one-generation reproductive toxicity study; EPA, environmental protection agency; EU, European union; FDA, food and drug administration; HESI, health and environmental sciences institute; ICH, international conference on harmonization; ILSI, international life sciences institute; KLH, keyhole limpet hemocyanin; LLNA, local lymph node assay; NK, natural killer; NIEHS, national institute of environmental health sciences; NIOSH, national institute for occupational safety and health; NOAEL, no observed adverse effect level; NRC, national research council; NTP, national toxicology program; OECD, organisation for economic cooperation and development; PND, postnatal day; RIVM, dutch national institute of public health and the environment; SRBC, sheep red blood cells; STS, standard toxicology studies; TDAR, T-cell dependent antibody reaction; US, United States; WoE, weight-of-evidence.

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1. Introduction

Evaluation of immunotoxicity is an important component of the hazard evaluation and safety assessment process for both pharmaceuticals and environmental chemicals, including pesticides. Although standard toxicity studies provide valuable data for evaluating immunotoxicity, endpoints such as organ weights, histopathology, hematology, and additional endpoints that involve characterization of the cellular and functional status of the immune system can provide additional information for the assessment of immunotoxic potential. Such studies may include assessment of the ability to respond to immunization (e.g., the T-cell dependent antibody response (TDAR)), the capacity to destroy neoplastic cells (e.g., the natural killer (NK) cell assay), the relative abundance of lymphocyte subpopulations, or a variety of other functional and observational assays. Due to the additional information these studies can provide, immunotoxicity testing guidance has been developed for pharmaceuticals and environmental chemicals, although with different requirements for incorporation into their respective testing paradigms (ICH, 2005; US EPA, 2007). Under chemical regulations, pesticide registrations require the completion of a substantial number of toxicity studies with a recent additional requirement for the conduct of specific immunotoxicity assays (US EPA, 2007). In contrast, guidance for pharmaceuticals uses a weight of evidence (WoE) approach that only requires specific immunotoxicity assays if there is cause for concern identified in standard toxicity studies.

While animal toxicity testing is a critical component for assessing the hazard potential of both environmental and pharmaceutical chemicals, it is recognized that the approach is time-consuming, expensive, requires extensive use of animals, and may not take full advantage of emerging technologies and biological knowledge. Such sentiments are conveyed in the National Research Council (NRC) report entitled: "Toxicity Testing in the 21st Century: A Vision and a Strategy" (NRC, 2007). This report has highlighted a potential strategy to move away from animal-focused testing to an approach that uses high-throughput methods with *in vitro* human model systems. While it will take years for such a vision to be completely developed, evaluated and effectively implemented, it has provided increased focus and discussion on the need for improving both the efficiency and effectiveness of our current testing approaches (Andersen and Krewski, 2010). In the shorter term, there are opportunities to refine our approaches to toxicity testing through progressive tiered-evaluation approaches and integrated testing approaches that can be used to refine and optimize animal use and data generation. Similarly, retrospective analyses can be valuable approaches to evaluate the impact of current testing strategies as a means to prioritize areas for improvement, guide and support changes in current data requirements and study designs, and to enhance our approaches to data interpretation and utilization. Recent examples that are relevant for pesticides include analyses and discussions on the one-year dog study requirement (Dellarco et al., 2010), the two-generation rat reproductive study (Piersma et al., 2011; Rorije et al., 2011), and the mouse carcinogenicity study (Billington et al., 2010).

As additional experience is gained with current testing requirements and as new assays and technologies are developed, it is critical for all stakeholders to engage in active dialog about potential opportunities to advance our current testing approaches. To facilitate these discussions in the area of immunotoxicology, a workshop hosted by the International Life Sciences Institute-Health and Environmental Sciences Institute (ILSI–HESI) was held on the evaluation of current practices for the assessment of immunotoxicity for environmental chemicals. The goal of this workshop was to share current perspectives from experts in the field on approaches for the assessment of immunotoxicity, with a focus on immunosuppression. Diverse perspectives were captured from various sectors to ensure a broad consideration of different approaches and experiences with the use of standard endpoints and functional assays, as well as tiered-based testing strategies and developing assays and study designs. Major themes of the workshop included discussions on current immunotoxicity assessment strategies and experiences, developmental immunotoxicity assessment, and integrated and alternative approaches to immunotoxicity testing. What follows is a summary of the key messages and discussions in these areas that took place during the workshop.

2. Current immunotoxicology assessment approaches and experiences

Immunotoxicity is a term used to describe the alteration of the normal structure and/or function of the immune system as determined by established immunological and toxicological approaches. Studies in laboratory animals have provided information on the types of immunotoxic effects that chemicals may induce, and that information has been used to assess the sensitivity and predictability of toxicological testing approaches for the identification of immunotoxicity (Luster et al., 1988; Luster et al., 1992a; Luster et al., 1993; Vos and Van Loveren, 1987). In 1979, under the auspices of the United States National Toxicology Program (US NTP), a panel of experts gathered to prioritize a list of immunological assays that would be suitable for use in rodent toxicology studies. Four laboratories participated in the ensuing validation effort to determine whether the tests selected by the panel had the required sensitivity and reproducibility to successfully detect subtle alterations in immune function and host resistance in mice (Luster et al., 1988). Subsequent studies used this testing panel to evaluate approximately 50 chemicals and established correlations between specific immune function and host resistance tests (Luster et al., 1993; Luster et al., 1992b). In addition to these comprehensive examinations with mouse models, the rat has also been a focus in immunotoxicity testing, primarily because of its standardized use in preclinical toxicity studies. In the late 1970s, a testing panel using the rat based on the Organisation for Economic Cooperation and Development (OECD) 407 guideline was developed at the Dutch National Institute of Public Health and the Environment (RIVM) (van Loveren and Vos, 1989; Vos, 1977; Vos, 1980). The utility of the rat model for immunotoxicity testing was further evaluated and validated through a number of inter-laboratory studies with known immunosuppressive agents (ICICIS Group Investigators, 1998; Richter-Reichhelm et al., 1995; White, 1992). Over time, the screening paradigms from both the NTP and RIVM have been updated to include additional endpoints, such as "enhanced histopathology" and routine enumeration of lymphocyte subsets, and new techniques (particularly *in vitro* methods) are continuously being considered and evaluated for their utility as predictors of potential toxicity to the immune system. Importantly, the early work from these groups, in terms of immunotoxicology assay development, evaluation and implementation, played a critical role in shaping the development of immunotoxicology guidelines for both pharmaceuticals and environmental chemicals.

2.1. Pharmaceutical industry guidelines for immunotoxicity and experience

Guidelines for the assessment of the immunotoxicity of pharmaceuticals emerged independently and differently within the European Union (EU) and the United States. The EU Committee

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