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Review

Review and recommendations on criteria to evaluate the relevance of pesticide interaction data for ecological risk assessments

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HIGHLIGHTS

- We review published scientific criteria to evaluate data quality, relevance and interpretation of interaction studies.
- We recommend criteria reflecting consensus from decades of research in pharmacology and toxicology.
- Examples demonstrate how the criteria may be used to evaluate whether mixture data can inform regulatory decision-making.
- Examples are presented to assess combined exposure and/or effects and interpreting data in the context of risk assessment.

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ABSTRACT

Mixing pesticides with different modes of action can provide a wider spectrum of control with fewer applications compared to using single active ingredients and is essential for comprehensive management of pest resistance. Mixture studies with pesticides are performed to assess compatibility, combined efficacy, and potential for toxicological interactions that damage crops. The purpose of this paper is to review and recommend previously published scientific criteria for evaluating the quality, relevance and interpretability of data on toxicological interactions and to demonstrate a methodology for applying them objectively to mixtures studies used in ecological risk assessment. The recommended criteria reflect the consensus of the literature on interaction analysis from decades of research in pharmacology and toxicology and are broadly applicable to mixtures of drugs, pesticides, industrial chemicals and food additives. They are useful for researchers who design and analyze interaction studies, for risk assessors who use interaction data in risk assessments, and for those who make risk management decisions pertaining to pesticides. This paper describes our methodology for assessing data on the combined activity of pesticides and then discusses how to interpret such data in the context of an ecological risk assessment. Examples have been drawn primarily from studies with herbicides and nontarget plants, and several example analyses have been included that can inform whether mixture data are sufficiently reliable and relevant for use in regulatory decision making.

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1. Introduction

The practice of mixing pesticides, either as pre-mixes or as tank-mixes, is routinely performed to provide practical, economic and agronomic benefits to farmers. For example, the practice of mixing pesticides that work via different modes of action is an essential component of a comprehensive pest resistance management program (Norsworthy et al., 2012; Owen et al., 2014; Denholm and Rowlan, 1992). Commonly, bioassays are performed with pesticide mixtures to assess compatibility and efficacy against target species, for the possibility of crop damage and for potential impacts to the existing ecological risk assessments for individual active ingredients. In pesticide mixture assessments, the key question is whether the mixture response differs from that expected based on additivity of the individual components and does the combined activity impact an existing risk assessment for the individual components. An informed prediction of the toxic effect of a mixture requires information on the toxicity of each component, the component ratios in the mixture and the concentrations to which the organism of interest is exposed.

The purpose of this paper is two-fold. First, we review the principles for evaluating results from mixture assays in the context of an ecological risk assessment. Examples of approaches to evaluate mixture results have primarily been drawn from studies on herbicides and nontarget plants. Second, the paper reviews and adapts previously published criteria that can be used to objectively evaluate data quality, interpretations of mixture data, and relevance to an ecological risk assessment. Such criteria can easily be applied to interaction data for drugs, pesticides, industrial chemicals, and food additives. We describe how these criteria can also be used to assist risk assessors and risk managers who must evaluate interaction studies and then put the results into the context of a risk assessment. The criteria can also assist researchers to better design and analyze interaction studies used to inform ecological risk assessments. We conclude by demonstrating how the criteria can be used to determine whether a greater than additive response observed between pesticides will impact the conclusions of existing ecological assessments or risk mitigation decisions, which are largely based on single active substances or products.

2. Concepts in mixture toxicology

There has been an ongoing and reasonably successful effort to codify interaction terms and definitions within the field of interaction pharmacology and toxicology. However, the terminology is even less standardized outside those fields. Authors often neglect to define the terms they use, yet apply them to different concepts (Greco et al., 1992; Greco et al., 1995; Henschler et al., 1996; U.S. EPA, 1990; U.S. EPA, 1999). This creates significant ambiguity because making an interpretation about interactions depends on how one defines non-interaction (Berenbaum, 1989). In short, the same data points can be interpreted as synergistic under one set of concepts and methods, but antagonistic under another. The resulting confusion is responsible, in part, for the limited amount of interaction data useful for risk assessment, and for the ineffectiveness of the term “synergism” (Hertzberg and MacDonnell, 2002). To avoid confusion, this paper employs the following terminology and concepts widely accepted in the fields of pharmacology and toxicology.

The term “synergy” has many definitions and carries pejorative connotations in some fields. “Greater than additive” (GTA) is more precise and objective and will be used herein instead of synergy. In the toxicological literature, a GTA interaction occurs when the combined effects of two components are greater than the sum of the effects of each component given alone (example: $2 + 2 = 20$) (Casarett et al., 1996). A less than additive interaction (LTA; often termed antagonism) occurs when the combined effect of two components is less than the sum of their individual effects (example: $2 + 2 = 3$) and an additive response occurs when the combined effect of two components is equal to the sum of their individual effects ($2 + 2 = 4$) (Casarett et al., 1996). Data that are consistent with additivity do not represent an interaction and is commonly termed zero-interaction or no-interaction (Könemann and Pieters, 1996).

Components in a mixture can interact through two primary types of mechanisms, either toxicokinetic (e.g., affecting uptake, distribution, metabolism, and excretion) or toxicodynamic (e.g., affecting action molecular, cellular or organ targets). Könemann and Pieters (1996) concluded that toxicokinetic and toxicodynamic interactions are rare when chemicals are present below their individual no-effect levels. In most instances where one compound has changed the action of another, it has been due to toxicokinetic mechanisms (Krishnan and Brodeur, 1991; Cassee et al., 1998; Belden and Lydy, 2006; Cokol et al., 2011). An example of this would be the addition of a surfactant to a formulation to increase the uptake of a pesticidal active ingredient by a target organism. An example for interactions in the toxicodynamic phase is induction or inhibition of biotransformation enzymes (Cassee et al., 1996).

The most accurate way to measure the toxicity of a mixture is to test the mixture, but the number of possible permutations of mixture constituents and their concentrations and ratios, either for tank mixes or mixtures observed in the environment, often makes this approach impractical. However, when adequate data exist on the toxicity of the mixture components and their binary combinations lack evidence of an interaction, predictive models that assume no-interaction - either the response addition model or concentration addition model - can be used to predict toxicity of the mixture. The key concepts of those models and rationale for choosing one model over another are reviewed below.

Response addition, historically known as independent action (Bliss, 1939), is a no-interaction model widely accepted in mixture toxicology (U.S. EPA, 1986). Due to its simplicity, it is by far the more popular model, particularly in the weed science literature where it is commonly referred to as the “Colby equation” (Colby, 1967). It assumes that each chemical exerts its effects as if other mixture components were not present. Thus, the toxicity of the mixture is the sum of the responses to each component and simply calculates the sum of the two fractional responses minus their product. It is the only non-interaction model that can be used when a single dose level of each component has been tested. Although it makes no assumptions about the mechanisms by which individual components exert their effects, its basis in independence of biological