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Effects of pesticide mixtures in human and animal models: An update of the recent literature

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ABSTRACT

This review aims to provide an update on our current knowledge of the various effects of pesticide cocktails. We have collected data from studies conducted in mammalian models *in vitro* and *in vivo* that was published between 2000 and 2014. All ecotoxicological studies were voluntarily excluded. Cocktail effects were classified according to how they had been classified by each author. The frequency of the various cocktail effects and the classes and chemical families of pesticides involved in the observed effects were assessed. When focusing on the function of pesticides (i.e. herbicide, insecticide or fungicide), 46% of the mixtures contained insecticides alone, 15% fungicides alone, and 4.5% herbicides alone. Mixtures with effects associated with neurotoxicity were mainly composed of insecticides, and most studies on the effects of fungicide mixtures (90%) were associated with effects on endocrine regulation and/or reproduction. Dose addition was observed with each kind of mixture except herbicide combinations. In contrast, synergic interactions or greater-than-additive effects were mainly reported for insecticide mixtures. There were few examples of potentiating and antagonistic interactions. We have identified chemical families of compounds specifically involved in synergy, addition, potentiation and antagonism, and those that do not interact when combined. The chemical families identified as being involved in synergy are in agreement with data from another recently published compilation of ecotoxicological studies. For most mixtures investigated, further validation data is still needed from experiments using other compounds and other experimental models but this update provides useful information to help in human health risk assessments.

Contents

Abbreviations: Dicarbo, dicarboximide; NEO, neonicotinoid; OP, organophosphorous; OC, organochlorine; CARB, carbamate; PYR, pyrethroid; AZ, azole; IMI, imidazole; A-PYR, anilopyridine; BenzIMI, benzimidazole; DITHIOCARB, dithiocarbamate; Bi-Pyr, bi-pyridilium; TRIA, triazine; TriAz, triazole; UC, unclassified: i.e. different from the other chemical families listed; I, insecticide; H, herbicide; F, fungicide; I+H, mixture of insecticides and herbicides; I+F, mixture of insecticides and fungicides; F+H, mixture of fungicides and herbicides; I+F+H, mixture of insecticides, fungicides and herbicides.

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1. Introduction

There is increasing concern over the health effects associated with the use of pesticides for both agricultural and residential purposes. In recent years, several studies have reported the occurrence of pesticides in a variety of matrices, such as food, water, soil, outdoor and indoor air and house dust, meaning that both general and professional populations are often exposed to compounds from different sources [1–4]. The effects of this combination of pesticides on human health need to be evaluated because the regulatory assessment of pesticide toxicity is currently only performed on selected single compounds.

One of the difficulties in assessing the effect of pesticide cocktails from the literature is the inconsistency of terms used to qualify these effects, which varies between authors. Therefore, we must first clarify that in this review we define the cocktail effects of chemical mixtures to be the result of two distinct situations: (i) where there is no direct interaction between compounds, which may or may not be associated with dose-dependent addition, and (ii) where there is an interaction between compounds. Addition is used to describe situations whereby chemicals do not interact but act together to produce effects without enhancing or diminishing each other's actions [5]. Dose addition is the term usually applied to chemicals that exert their effects through the same target and have similar modes of action. For interacting compounds, the resulting toxicities can be synergic (higher than expected from the additive effect of the doses, greater-than-additive or supra-additive effects are also classed as synergic), antagonistic (lower than expected), or potentiating (when the effect of one compound is increased by another/others). When compounds do not interact and no dose addition is observed, the toxicity of the mixture is either null or equal to that of the most efficient product(s) in the mixture.

Other reviews have already collated information on different aspects of the effects of pesticide cocktails. Carpy et al. [6] examined the available data published between 1985 and 1998 regarding the health risk assessments of the residual concentrations of pesticide mixtures found in human food and drinking water. They reported that both synergy and antagonism occurred within the same organism depending on the organ or target, and that interactions between compounds did not appear to be a common event at these levels. In 2007, Kortenkamp et al. [5] published a review of studies that assessed endocrine disrupter (ED) mixtures in terms of additivity, antagonism or synergy. They concluded that combined effects occur even when all the individual mixture components are present at doses that are below those causing observable effects. To identify the greatest synergic effects of pesticide mixtures, Boobis et al. conducted a critical analysis of the literature from 1990 to 2008 on low-dose synergic effects of mixtures composed of a variety of chemicals (toluene, hydroquinone, pesticides, xylene) [7]. They defined synergy as a mixture response that significantly exceeds that predicted by a non-interaction model. Their search identified 90 studies that in total reported the effects of combinations of 204 different chemicals in mammals. Six of these studies provided useful quantitative estimates of synergy, and from these the authors concluded that the magnitude of synergy at low doses varied from 1.5 to 3.5. From a number of other positive studies, they concluded that the occurrence of synergy was dose-dependent and was observed only at higher doses.

In another review, Hernandez et al. [8] assessed a number of toxicological interactions in pesticide mixtures at the molecular level and their relevance to human health. They reported several examples of cocktail effects, such as the potentiation of the toxicity of some pesticides by others (e.g. malathion by isomalathion, pyrethroids (PYRs) by anticholinesterase insecticides, organophosphorous (OP) by organochlorine (OC), carbaryl by OP, and OP by triazines (TRIAs)), the synergy between PYR and carbamate (CARB) compounds, and the antagonism between TRIA herbicides and prochloraz.

Very recently, Cedergreen [9] published a very interesting review of ecotoxicological studies that aimed to identify groups of chemicals that are overrepresented in synergic mixtures and define the molecular mechanisms underlying the observed synergy. Three groups of chemicals were studied, including pesticides, and synergic mixtures were defined as those with a minimum 2-fold difference between the observed and predicted effect of the individual concentrations, using the concentration addition model (CA) as a reference model and including lethal and sub-lethal endpoints. Synergy occurred in 7% of the 136 binary pesticide mixtures, which included mainly cholinesterase inhibitors or azole (AZ) fungicides, both of which are known to interfere with the metabolic degradation of other xenobiotics.

In the present review we provide an update of the recent literature on the impact of pesticide mixtures. We compiled 78 studies published between 2000 and 2014 that were conducted in mammalian model systems (both *in vitro* and *in vivo*). Ecotoxicological data were excluded although ecotoxicology and mammalian toxicity are linked to each other. From these studies, we identified those which had experimentally assessed the associated effects of simultaneous exposure to a combination of two or more pesticides and which had clearly reported the joint toxic effects of the pesticide mixtures. The cocktail effects were grouped into five classes according to the classifications made by the authors of the studies without recalculation of their results: (i) Addition, when authors clearly reported dose addition or additive effects; (ii) Synergy,