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Review article

Developmental neurotoxicity of succeeding generations of insecticides

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ABSTRACT

Insecticides are by design toxic. They must be toxic to effectively kill target species of insects. Unfortunately, they also have off-target toxic effects that can harm other species, including humans. Developmental neurotoxicity is one of the most prominent off-target toxic risks of insecticides. Over the past seven decades several classes of insecticides have been developed, each with their own mechanisms of effect and toxic side effects. This review covers the developmental neurotoxicity of the succeeding generations of insecticides including organochlorines, organophosphates, pyrethroids, carbamates and neonicotinoids. The goal of new insecticide development is to more effectively kill target species with fewer toxic side effects on non-target species. From the experience with the developmental neurotoxicity caused by the generations of insecticides developed in the past advice is offered how to proceed with future insecticide development to decrease neurotoxic risk.

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1. Introduction

Insecticides control insect attacks on crops, livestock and pets and prevent transmission of insect-borne diseases. However, insecticide exposures can also have adverse off-target effects including neurotoxicity. Over the past seven decades, a variety of insecticide classes has been introduced. The organochlorines (OCs), introduced in the market in the early 1940s, were the first insecticides active against a wide variety of pests, and effective for long periods of time (Casida and Quistad, 1998). These were succeeded by organophosphates (OPs) and carbamates (CAs), pyrethroids (PIs), and most recently in the 1990s, by neonicotinoids (NEs) (Casida and Durkin, 2013b). It is instructive to compare the risks posed by insecticides in all of these classes in the quest to develop safer strategies to maximize insecticidal actions while minimizing off-target toxic effects. One of the most prominent risks, and a source of intense regulatory activity, is developmental neurotoxicity (Grandjean and Landrigan, 2014). This is the focus of the current review.

Each of the classes of insecticides was considered safe when introduced into the market; however, none is completely specific for insect pests. Indeed, insecticides primarily target the nervous system and similarities between the insect and human nervous systems often lead to cross-toxicity. Accordingly, experimental animal studies and epidemiological findings point to the health hazards associated with exposure to all of these classes of insecticides.

The developing nervous system is highly susceptible to the neurotoxicity of insecticides as it is for many types of environmental toxicants. This enhanced sensitivity occurs not only during prenatal development but also postnatally, extending into adolescence (Connors et al., 2008). Impacts on the developing nervous system can have deleterious effects that last a lifetime, long after the end of exposure, because the toxicant causes malformations of the nervous system. This review will consider the targets and mechanisms of action of the main insecticide classes during brain development, highlighting morphological and neurochemical effects that culminate in behavioral dysfunction. Finally, we will suggest future directions for insecticide research that could lead to development of safer products.

For each class of insecticides, *in vitro*, experimental studies in animal models and epidemiological findings were included. Deleterious neural outcomes of developmental exposure are summarized in the main body of the review; tables [provided as supplementary material (SM)] also include studies that failed to find significant alterations. Dose effects for adverse neurodevelopmental effects in animal models are shown in figures plotted doses as proportions of the no-observed-adverse-effect level (NOAEL) as a common point of toxicodynamic potency and periods of exposure for representative insecticides on each class. For epidemiological findings, with few exceptions, we included only those studies in which exposure was quantified through measurement of parent compounds or metabolites in biological samples. Detailed information on insecticidal and off-target toxicity is provided as SM.

2. Organochlorines (OCs)

The Austrian chemist, Othmar Zeidler, first synthesized the prototypic OC DDT (dichlorodiphenyltrichloroethane) in 1874. However, more than 60 years later, it was the Swiss chemist, Paul Müller, who first demonstrated the effectiveness of DDT as an insecticide and, for that, he was awarded the 1948 Nobel Prize in Physiology or Medicine (Casida and Quistad, 1998). Subsequently, other chlorinated compounds were identified as effective insecticides and, for decades, OCs dominated the market of insect control in both agriculture and home formulations. They were widely used over the span from 1940s, until they were largely restricted and banned in most countries during the 1970s and 1980s (Costa, 2015), largely because of their persistence in the environment, bioaccumulation and emerging evidence of adverse effects on wildlife off-target species. Rachel Carson's landmark book "Silent Spring", published in 1962 (Carson, 2002), played a major role in the decision to ban DDT and other OCs for agricultural uses in the US and, subsequently, in many other countries, and led to increased regulation of pesticides (for review: (Epstein, 2014).

2.1. Developmental toxicity of OCs

Even though neurotoxicity was not among the most important reasons that led to regulation of OCs subsequent studies identified the developing brain as a sensitive target. Because of their lipophilicity, OCs bioaccumulate in adipose tissue where they can remain for decades (Mrema et al., 2013). When mobilized from adipocytes to the blood stream, OCs are readily secreted into breast milk (Mrema et al., 2013; Shen et al., 2007). OCs also can cross the placenta and the blood brain barrier and accumulate in the brain (Morrison, 1971; Tebourbi et al., 2006). OCs such as DDT are still permitted for use against mosquito-borne transmission of malaria in several countries due to their higher efficacy versus other insecticides (Bouwman et al., 2011). Due to their persistence and continued use, developmental exposure to OCs still affects public health. Due to their lipophilicity and accumulation in the brain, neurotoxicity is a major concern.

In Subtopic 2.1.1 and in SM Table 1 we summarize data showing that OCs cause developmental behavioral and neurochemical disruption in experimental models. The mechanisms associated with neurotoxicity do not appear to be restricted to the blocking of sodium channels and γ-aminobutyric acid receptors that are involved in acute toxicity (see SM for a detailed description). As detailed below, these additional actions include altered neurotransmitter levels and endocrine disruption. Fig. 1 further makes it clear that even very low levels of OC exposure during gestation and/or lactation of rodents cause deleterious neurobehavioral effects. Subsequently (Subtopic 2.1.2 and SM Table 2), parallel results from epidemiological studies that implicate early OCs exposure in adverse neurodevelopmental outcomes are presented.

2.1.1. Evidence of OCs developmental neurotoxicity from in vitro and animal models

In vitro studies show that OCs affect neuronal differentiation, function and survival. At nanomolar concentrations, dieldrin, lindane and endosulfan inhibit voltage-gated calcium channels, decreasing the intracellular calcium concentration in pheochromocytoma (PC12) cells (Heusinkveld and Westerink, 2010; Heusinkveld and Westerink, 2012; Meijer et al., 2015). At higher (micromolar) concentrations, dieldrin decreases cell viability and cell proliferation in undifferentiated PC12 cells (Slotkin et al., 2007a) and in mouse neuroprogenitor cells