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Review

In vitro bioassays for detecting dioxin-like activity — Application potentials and limits of detection, a review

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HIGHLIGHTS

- Bioassays with LODs of up to 0.1 pM 2,3,7,8-TCDD may compete with GC–MS.
- Assay applications are diverse (sediment, soil, water, tissue, food, feedstuff).
- Recombinant cell lines achieve lower LODs than there wild type counterparts.
- A bioassay LOD decides on its application (i.e. serum samples need low LODs).
- In vitro studies should list EC_x, linear working range and the LOD of an assay.

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ABSTRACT

Use of in vitro assays as screening tool to characterize contamination of a variety of environmental matrices has become an increasingly popular and powerful toolbox in the field of environmental toxicology.
While bioassays cannot entirely substitute analytical methods such as gas chromatography–mass spectrometry (GC–MS), the increasing improvement of cell lines and standardization of bioassay procedures enhance their utility as bioanalytical pre-screening tests prior to more targeted chemical analytical investigations. Dioxin-receptor-based assays provide a holistic characterization of exposure to dioxin-like compounds (DLCs) by integrating their overall toxic potential, including potentials of unknown DLCs not detectable via e.g. GC–MS. Hence, they provide important additional information with respect to environmental risk assessment of DLCs.
This review summarizes different in vitro bioassay applications for detection of DLCs and considers the comparability of bioassay and chemical analytically derived toxicity equivalents (TEQs) of different approaches and various matrices. These range from complex samples such as sediments through single reference to compound mixtures. A summary of bioassay derived detection limits (LODs) showed a number of current bioassays to be equally sensitive as chemical methodologies, but moreover revealed that most of the bioanalytical studies conducted to date did not report their LODs, which represents a limitation with regard to low potency samples.
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1. Introduction

Since the middle of the 20th century there has been an increasing concern about exposure of humans and wildlife to certain xenobiotics that were released into the environment due to diverse anthropogenic activities. One group of environmental toxicants that is of particular interest relative to potential environmental health effects are dioxin-like chemicals (DLCs). These ubiquitous compounds are hydrophobic, lipophilic and resistant to biological and chemical degradation, properties that impart persistency and a propensity to bio-accumulate and biomagnify to concentrations that can cause harmful effects. DLCs include polychlorinated dibenzo-*p*-dioxins and dibenzo furans (PCDD/Fs), dioxin-like polychlorinated biphenyls (DL-PCBs), polycyclic aromatic hydrocarbons (PAHs), as well as a multitude of other partially known and unknown compounds (Giesy et al., 2006, 1994b; Larsson et al., 2013; Poland and Knutson, 1982; Song et al., 2006; Van den Berg et al., 2006; Van der Plas et al., 2001). The in vivo behavior of these compounds depends on their uptake, distribution and metabolism (Behnisch et al., 2001a; Safe, 1986) as well as modifying factors such as species, age and reproductive status (Whyte et al., 2000). Hence, the range of biological effects across different organisms is broad. Effects may include thymic atrophy, hepatotoxicity, certain types of cancer, immunotoxicity, wasting syndrome, reproductive toxicity and the induction of monooxygenase enzymes (Brouwer et al., 1995; Denison and Heath-Pagliuso, 1998; Denison and Nagy, 2003; Giesy et al., 1994a; Poland and Knutson, 1982; Van den Berg et al., 1998).

1.1. The aryl hydrocarbon receptor (AhR)

Many studies have proven that most of these toxic effects are mediated via the aryl hydrocarbon receptor (AhR) (Bittner et al., 2006; Hankinson, 1995; Olsman et al., 2007a). More specifically, the AhR, a cytosolic receptor protein, which belongs to a subclass of helix–loop–helix-containing transcription factors (Giesy and Kannan, 1998; Goldstein and Safe, 1989), binds co-planar aromatic compounds with high affinity and translocates them into the nucleus where the complex forms a heterodimer with the AhR nuclear translocation (ARNT) protein and possibly additional factors (Hahn, 1998). The ligand–AhR–ARNT complex binds to dioxin responsive elements (DRE) in genomic sequences, which leads to transcriptional activation and synthesis of responsive genes like cytochrome P_{450}1A (CYP1A) (Hilscherova et al., 2000). Cytochromes represent a multigene family of heme-containing proteins, which are mainly present in the liver, but also in kidney, gastrointestinal tract, gills and other tissues of many organisms. They possess the ability to metabolize xenobiotics via Phase-I-reactions (oxidation, hydrolysis or reduction reactions), which may lead to a detoxification or to a so-called bioactivation (toxification) (Castell et al., 1997).

1.2. CYP and reporter gene based in vitro assays

The specific and naturally occurring mechanism of CYP1A induction by DLCs has been used in in vitro bioassay techniques for the characterization of dioxin-like potentials of e.g. environmental samples (Tillitt et al., 1992, 1991a). However, as for in vivo effects, the responsiveness of in vitro systems is species or cell-line specific (Keiter et al., 2008). This is due to differing binding affinities, structures, quantities and physicochemical properties of the AhR of different cell lines (Hilscherova et al., 2001; Sanderson et al., 1996). Regarding functional AhR-based bioassays for quantification of CYP1A activity (such as the 7-ethoxyresorufin-O-deethylase assay, EROD), the dioxin-like potential of DLCs present in a certain sample is determined by quantifying the induction of the cytochrome P_{450} (CYP) monooxygenase system (in the present case: the activity of the EROD enzyme) (Sanderson et al., 1996). The EROD assay has been applied using different cell lines, such as permanent fish cell line RTL-W1 (rainbow trout liver - waterloo 1) or rat hepatoma cell line H4IIE (here the assay is called “micro EROD”), which led to the title “golden standard of in vitro bioassays” (as reviewed by Behnisch et al. (2001b)).

In some cases, however, CYPs like EROD can be inhibited by their own substrates (e.g. in the presence of high concentrations of PCBs) (Sanderson and Giesy, 1998), which may lead to false-negative results. Moreover, the linear working range of EROD activity based test systems is often limited (Behnisch et al., 2001b). To overcome these issues, the process of AhR mediated activation of genes has been genetically engineered by connecting the DRE of various cell lines with certain reporter genes (Lee et al., 2013). These genes may originate from firefly (*Photinu spyralis*) or from sea pen (*Renilla reniformis*) and by activation are capable of producing the light emitting enzyme luciferase (Denison et al., 1988b, 1988a; Garrison et al., 1996; Thain et al., 2006).

Examples for those reporter gene based assays are the DR CALUX® (Dioxin Responsive-Chemical Activated LUciferase gene eXpression) with mammalian hepatoma cell lines transfected with plasmid pGudLuc1.1, the H4IIE-luc assay using an eponymous cell line, the CALUX assay (mostly performed by using Hepa 1 mouse hepatoma cell line) (Villeneuve et al., 1999) and the P_{450} reporter gene system (RGS) assay, which constitutes a related methodology by using HepG2 cells, stably transfected with a human CYP1A1 promoter sequence fused with the already mentioned firefly luciferase reporter gene (101

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