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REVIEW ARTICLE

Integrated ecological risk assessment of dioxin compounds

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Abstract Current ecological risk assessment (ERA) schemes focus mainly on bioaccumulation and toxicity of pollutants in individual organisms. Ecological models are tools mainly used to assess ecological risks of pollutants to ecosystems, communities, and populations. Their main advantage is the relatively direct integration of the species sensitivity to organic pollutants, the fate and mechanism of action in the environment of toxicants, and life-history features of the individual organism of concern. To promote scientific consensus on ERA schemes, this review is intended to provide a guideline on short-term ERA involving dioxin chemicals and to identify key findings for exposure assessment based on policies of different agencies. It also presents possible adverse effects of dioxins on ecosystems, toxicity equivalence methodology, environmental fate and transport modeling, and development of stressor-response profiles for dioxin-like chemicals.

Keywords Dioxins · Toxicity · Ecological risk assessment · Toxic equivalency factors

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Introduction

Dioxin-like compounds (DLCs) have been classified by the World Health Organization (WHO) as one of the persistent toxic chemical substances in the environment, and they are associated with several occupational activities and industrial accidents around the world (NSW 2013; Rezayi et al. 2014b; WHO 2002). The health effects of dioxin compounds and their exposure contaminates in the environment have been featured extensively in toxicological and epidemiologic studies as significant pollutants because of their resistance toward metabolism and hydrophobic nature, poisoning incident, long lifetimes, and high bioaccumulation in fatty tissues in humans and animals (Proestou et al. 2014; Rezayi et al. 2013a; Tavakoly Sany et al. 2014b; US EPA 2013b). The most toxic congener for this class is 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD), which has extensive toxicological effects such as modulation of the immune system, teratogenesis, and tumor promotion (Haffner and Schecter 2014; Rezayi et al. 2013b; US EPA 2010; US EPA 2012; Van den Berg et al. 1998, 2006).

Dioxin exposure to humans has not been reported prior to industrialization (Schecter et al. 2006; US EPA 2013b). But after industrialization, the most toxic dioxins have been commonly found in all environmental matrices at various spatial scales, with higher concentrations among chemical workers in industrialized countries (Abraham et al. 2015; Bigus et al. 2014; Saadati et al. 2013; Schecter 1994; Schecter and Constable 2013; Tavakoly Sany et al. 2014a; Tehrani et al. 2013; US EPA 2004; WHO 2002). DLCs contain 10 of the

polychlorinated dibenzofurans (PCDFs), seven of the polychlorinated dibenzodioxins (PCDDs), and 12 of the polychlorinated biphenyls (PCBs) (Olli et al. 2013; US EPA 2004). Increased PCDFs/PCDD concentrations were reported in North American lake sediments during 1920–1940 due to the commercial production of dioxin and PCBs in 1929. In 1957, toxic dioxins such as TCDD were frequently identified as unwanted pollutants. Common instances of dioxin exposure include the application of Agent Orange herbicide during the Vietnam War between 1961 and 1971 (IOM 2005; Schecter et al. 2005; Schecter et al. 2003). Dioxins were found at Love Canal (Smith et al. 1983), in chemical workers in the USA and Germany (Flesch-Janys et al. 1995; Steenland and Deddens 2003), in fly ash in Japanese incinerators (Olie et al. 1977), and in Seveso in Italy following an industrial accident in 1976 (Bertazzi et al. 2001).

Yucheng and Yusho disasters in Taiwan and Japan, respectively, were due to the ingestion of rice oil contaminated by PCDFs and PCBs (Masuda 1994). Thus, comprehensive government documents related to TCDD toxicity and its health effect have been provided by different agencies [such as WHO, the United States Environment Protection Agency (US EPA), Disease Registry of the Centers for Disease Control (CDC), and the Agency for Toxic Substances] based on the several toxicological and epidemiologic studies (US EPA 2010; US EPA 2012; US EPA 2013b; WHO 2002).

The present article will provide an integrated overview of available key studies with the objectives (i) to summarize a series of critical studies to describe a guideline to assess ecological risks associated with exposure to complex mixtures of DLCs and (ii) to highlight the key findings on issues concerning the risks such as toxicity equivalent factor, dioxins transfer in the environment based on the weaknesses, and strengths of the available evidence. This integrative review will give a synopsis of dioxin science and its key findings to characterize risk to use by environmental managers and risk assessors.

Chemical structure of dioxin-like compounds

Dioxin-like compounds are toxicologically and structurally related to halogenated aromatic hydrocarbons (HAHs) having similar chemical structure and mechanism of toxic action (Haffner and Schecter 2014; Long and Bonefeld-rgensen 2012; US EPA 2012), and they also induce a similar spectrum of biological responses via activation of a specific intracellular receptor such as aryl hydrocarbon receptor (AhR) (Guyot et al. 2013; Sorg 2013). DLCs contain polychlorinated dibenzo-p dioxins (PCDDs), polychlorodibenzo furans (PCDFs), polybrominated dibenzofurans (PBDFs), polybrominated dibenzo-*p*-dioxins (PBDDs), and dioxin-like biphenyls (PCBs) and their relevant compounds such as mono-ortho-substituted PCBs (PCB 105, 114, 118, 123, 156, 157, 189) and non-ortho coplanar PCBs (PCB 77, 81, 126, and 169) (Olli et al. 2013; US EPA 2004). PCDF and PCDD are by-products of incineration procedures and organic synthesis, whereas PCBs are used as coolant fluids and dielectric in capacitors, electric motors, and transformers (Sorg 2013; WHO 2002).

DLCs include two benzene rings connected by two oxygen atoms and consist of four to eight chlorine atom substitutions in the 2,3,7 and 8 positions with DLCs toxicity (Figure S1). DLCs contain 10 of the polychlorinated dibenzofurans (PCDFs), seven of the polychlorinated dibenzodioxins (PCDDs), and twelve of the polychlorinated biphenyls (PCBs) (Olli et al. 2013; US EPA 2004). These PCB compounds are known as coplanar PCBs because rotation ability of their rings into the same plane (US EPA 1994). Chemical basic structures of PCDFs, PCDDs, and a PCB were shown in figure S1.

Assessments of AhR-signaling pathways

In general, wildlife can be exposed to a mixture of dioxin congeners. Several molecular mechanisms of DLCs toxicity have been defined (Kulkarni et al. 2008; Long and Bonefeld-rgensen 2012; Sorg 2013). DLCs can cause the inappropriate pattern of interference or gene expression or with different signaling routes and cause the disruption and differentiation of tissue, cellular, and biochemical processes (Haffner and Schecter 2014; Schecter et al. 2006; Sorg 2013; van den Berg et al. 2013).

The most common bioassays for the estimation of dioxin toxicity including dioxin effects are mediated through the signal transduction pathway of the AhR and created a specific complex of atypical enzymes that induce several biological responses, induction or repression of gene expression and defects of the developmental and reproductive system (Kulkarni et al. 2008; Long and Bonefeld-rgensen 2012; Sorg 2013). The AhR is an intracellular ligand-dependent transcriptional factor in cytoplasm (Rice et al. 2008; Schecter et al. 2006). In the absence of agonists, this receptor is maintained in an inactive form by chaperone proteins: (a) the heat shock protein 90 (HSP90), (b) the prostaglandin E synthase 3 (cytosolic or p23), (c) the AhR-interacting protein (ARA9 or AIP), and (d) HBV X-associated protein 2 (XAP-2) (McIntosh et al. 2010; Möglich et al. 2009; Sorg 2013).

DLCs are formed as complex mixtures, and several congeners of DLCs activate AhR. These complications increase the difficulty to evaluate risks of DLCs because estimation of the concentration of each congener does not necessarily reflect whole AhR activation or signaling pathways (Long and Bonefeld-rgensen 2012; Rice et al. 2008; US EPA 2010; Van den Berg et al. 2006). Thus, the toxic equivalency factors

(TEFs) have been estimated experimentally for each congener of DLCs to estimate the total toxicity of dioxin and their relevant congeners based on a variety of responses, endpoints, and uncertainties in the available data (Parvez et al. 2013; US EPA 2008; US EPA 2010; Van den Berg et al. 2006). TEF is a factor showing the potential of each dioxin congener to induce AhR activation related to the reference substance, which TEF value for TCDD is fixed to 1.0 (Long and Bonefeld-rgensen 2012; Van den Berg et al. 2006). Whole activation of AhR receptors by different dioxin congeners is expressed as TCDD toxic equivalent (TEQ) based on the AhR signaling assessment. The classical method of TEQs is estimated based on multiplying the individual concentration of dioxin congeners (PCDFs/PCDDs/PCBs) in an environmental mixture by their respective TEF (Eq. 1) (US EPA 2008; Van den Berg et al. 2006). In complex mixtures, the TEQ is estimated by summing the TEQs of all congeners (Van den Berg et al. 1998).

$$\mathrm{TEQ} = \sum\nolimits_{i=1}^{n} (C_i \times \mathrm{TEF}) \quad (1)$$

C_i concentration of individual dioxin congeners.
$\mathrm{TEF_i}$ TEF values are estimated experimentally for individual congeners of DLCs (Table S1).
TEQ TCDD toxicity equivalence.
n number of individual dioxin congeners in mixture

These TEF and TEQ approaches for DLCs were defined based on the dose addition concept with several assumptions, under which the same toxicodynamics and toxicokinetics are considered for all DLCs (Kulkarni et al. 2008). The dioxin compounds bind to the AhR with the same toxic mode of action to induce AhR-mediated effects, and the dioxin and DLCs must accumulate and be persistent in the food web. Moreover, it is assumed that toxicological interactions (antagonism and synergism) do not occur between the DLCs in environmental samples (US EPA 2010; Van den Berg et al. 2006; van den Berg et al. 2013).

As stated in several studies, the use of TEF concept has been accepted as a "useful, interim method" to simplify the assessment of the potential risk of DLC mixtures because this method reduces the general uncertainties in the process of risk assessment (US EPA 2003; US EPA 2013b). Likewise, in this concept, TCDD equivalents are internationally being applied as a replacement for exposure estimates based on total PCBs or TCDD (US EPA 1994; US EPA 2003; US EPA 2010). The justifiable index was developed based on the last consensus values for TEFs, which has helped risk managers to better assess public health risks of DLCs, but its application depends on the availability of representative, reliable exposure data and TEFs (Long et al. 2006; Long and Bonefeld-rgensen 2012). Consequently, TEFs are applicable to provide a retrospective assessment from possibilities of pervious exposure to chemical stressors and to deliver prospective assessment of future adverse effects (Parvez et al. 2013; US EPA 2003).

Several drawbacks have also been indicated for using the TEF concept including very expensive, time-consuming gas chromatography mass spectrometry estimation and high sample volume requirements, presence of congeners not commonly estimated or unknown substances with AhR affinity, often low concentrations of congeners with the concentrations lower than detection limits, unknown or not routinely estimated AhR-active compounds available, the TEF values are not available for several HAHs, possible synergistic or antagonistic interactions between HAHs, the different shape of the dose–response curve, and differences in responsiveness of individual species (Long and Bonefeld-rgensen 2012; Long et al. 2003; US EPA 2008; US EPA 2013b). Therefore, it is essential to assess DLCs based on the integrated techniques.

The US EPA provides several comprehensive environmental reports in response to questions raised at the 2005 WHO expert meeting. The main question is whether the TEF values for DLCs for dermal and inhalation exposure pathways can be or not be used (US EPA 2010; US EPA 2013b). In addition to the ingestion routes, the TEFs can be used to calculate dermal or inhalation exposure pathways, assuming exposures to DLCs via these routes is estimated based on the fractional contribution of dermal, inhalation, and oral route exposures to identify the predicted TEQ value (US EPA 2013b). In the absence of toxicity factors for dermal routes, a simplified paradigm has been devised by the US EPA to convert a route-to-route (oral to dermal) extrapolation based on adjusting for absorption through skin and oral toxicity values. US EPA experts believe that slop factors and most oral reference doses (RfDs) are the specific values of substances administered per body weight and unit time, whereas the absorption dose is the appropriate amount to estimate exposure for dermal pathways. Thus, the dermal absorption factor was estimated for TCDD based on relationships between obtained dose–response of oral toxicity studied and adjusting for absorption dose through dermal contact. The dermal absorption factor (ABS) of TCDD has been considered, instead of TEFs, to evaluate dermal exposure (US EPA 2003; US EPA 2008). There is no toxicity value to assess the risk posed by inhalation of dioxin either via volatiles or particulates. The US EPA provides screening levels of dioxin for inhalation risk according to the particulate emission from soil, calculated by the California EPA reference concentration (RfC) for TCDD, where the contribution of the inhalation route compared to the ingestion route is well below 1 % (US EPA 2010). Other questions are related to the possibility of using dioxin TEFs to assess ecological risk and cancer and non-cancer risks. Based on several scientific reports from the US EPA and WHO, TEFs can be applied for all mediated effects through AhR binding by the dioxin compounds (US EPA 2010; US EPA 2013b; WHO 2002).

Ecological risk assessment

Ecological risk assessment (ERA) is performed to provide scientific information into meaningful data about the risk of the anthropogenic activities in environment (Tavakoly Sany et al. 2014c; Tavakoly Sany et al. 2014d; US EPA 2012). Four phases are considered to assess ecological risk: planning, problem formulation, analysis, and characterization of risk (Table 1) (Shea and Thorsen 2012; Glenn and Suter II 2006). The application of TEF is presented in the context of each phase to provide accurate estimation of the AhR-mediated risks (US EPA 2008; US EPA 2010).

Planning

The planning phase to assess ecological risks is preceded by the risk management decision that is related to make management goals, find appropriate methods, and determine the scope and size of the ecological risks (Shea and Thorsen 2012). The risk assessors also consider multiple parameters (other chemicals of concern, time, data adequacy, cost, scientific uncertainty, social conditions, or political) during the planning phase (Rezayi et al. 2014a; US EPA 2008). Identifying and quantifying scientific uncertainties is essential to perform successful risk assessment. The details of all the uncertainties inherent to the TEQ methodology and their application to risk assessment are described in all phases of ERA by US EPA and Van den Berg in 2006 (US EPA 2008; Van den Berg et al. 1998; Van den Berg et al. 2006).

The risk managers should verify that assumptions inherent in using the TEF concept are valid for the particular situation (e.g., the chemicals of concern are AHR agonists, congener-specific exposure data are available, and organisms are sensitive to an AHR-mediated mechanism of toxicity) to which the methodology is being used (Sorg 2013; van den Berg et al. 2013). In this framework, the TEF concept only applies for ecologically adverse effects associated with DLCs. It is essential to employ additional methods to account for other adverse effects associated with other chemicals that may be present (e.g., PCBs and furans) (US EPA 2008; US EPA 2010).

There are several bioanalytical methods that have the potential of accounting to estimate the adverse effects of chemical mixtures that act via the AhR. Such chemicals are not likely to be detected by a chemical method that estimates only PCDDs/Fs and PCBs (Shea and Thorsen 2012; Sorg 2013; US EPA 2008). The bioanalytical methods are faster methods with lower cost than chemical methods for TEF estimation. However, the experts at the US EPA do not recommend applying the bioanalytical tools as an alternative to the toxicity equivalence method and congener-specific analysis because of limitations in current technology, lack of consistent quality criteria relevant to recent bioanalytical tools, and lack of standard testing procedures (Rezayi et al. 2012; US EPA 2008; van den Berg et al. 2013).

The US EPA in 2008 listed the following important considerations for risk assessors for selecting the most appropriate analytical method to estimate risks from dioxin compounds (US EPA 2008):

1. The possibility of the presence of other chemicals, which could be expected to increase risk, posed by the dioxin congeners.
2. Aroclor standards usually cannot adequately present the environmental PCB mixtures because environmental weathering may significantly change the congeners' profiles of Aroclor standards (Aroclors are made by the congener profiles present in the original formulation). Thus, several uncertainties defined to assess effects and exposure during the toxicity tests based on the assumption that congener profiles of the Aroclor standard (as a commercial mixtures) are representative of PCB profiles in weathered environmental samples (either biota or exposure media).
3. The total PCDD/Fs and PCB concentration can be overestimated based on homologue (level-of-chlorination) analysis because of the overlapping of congeners, which may be measured in a specific or another homologue group analysis.
4. The determination of total PCBs, Aroclors, and homologues groups is not amenable to bioaccumulation modeling (fate and transport), and the toxicity equivalence method cannot be directly used for these groups. Since, large uncertainties are introduced in applying of TEFs to estimate concentration of PCB congeners based on Aroclor or homologue analyses due to differential weathering and bioaccumulation processes.
5. Regardless of the models or determination applied to assess risk, the chemical determination and characterization of the uncertainties associated with undetected chemicals should be clearly reported to the risk assessors or risk managers.
6. In all ERA, the dose metric (i.e., concentration of chemical compounds) should be constant among the effects assessment and the exposure assessment.

Problem formulation

Problem formulation is preliminary hypotheses to evaluate the adverse effects, which may occur, or have occurred, as a consequence of exposure to dioxin-like congeners (Dourson et al. 2013; US EPA 1998). In this phase, integration of available information (on stressor, sources and characteristics of the ecosystem, exposure characteristics and effects) is normally performed to evaluate ecological risk. This initial evaluation

Table 1 General view of ecological risk assessment (Shea and Thorsen 2012; Glenn and Suter II 2006)

Phases	Major element	Action
Planning	■ Roles risk managers and risk assessor and interested parties ■ Produce plan	■ Making management goals for ecological values. ■ Considering range of management options for multiple parameters. ■ Finding appropriate method. ■ Identifying the scope and size of the risk assessment. ■ Resource availability.
Problem formulation	■ Assessment of endpoints ■ Development of conceptual models ■ Analysis plan	■ Integration of available information. ■ Selecting the endpoint based on susceptibility, relevance to management target and ecological relevance. ■ This model is defined to show sources DLCs, affected media, potential or known environmental fate and endpoints receptors, and potential pathways of migration. ■ Providing clear description for the hypothesis, data needs, assessment design, limitations, and methods, assumptions and extrapolations.
Analysis	■ Characterization of exposure ■ Characterization of effects	■ By examining the distribution and sources of DLCs in environmental media, and the extension of contact. ■ By prediction and/or measurement of concentration of individual DLCs in sediment, water, diet, tissue and their bioaccumulation. ■ An accounting exposure pathway based on differential fate and transport of DLCs. ■ Estimation of TEQs that are defined with the dose metrics of the toxicity data. ■ Examining stressor-responses relationships based on the stressor-response profile for 2,3,7,8-TCDD. ■ Examining relationship between measures of effect and assessment endpoints.
Risk characterization		■ Estimate of risk based on the combination of stressor-response profile and exposure profile. ■ Making environmental decision.

provides the basis to select endpoints (any species that are both sensitive and exposure to toxicity of DLCs) and develop conceptual models and an analysis plan (Dourson et al. 2013; US EPA 1998; US EPA 2008).

Assessment of endpoints

It is necessary to consider the following principal criteria for selecting appropriate endpoints for risk assessment: susceptibility to potential chemical stressors, relevance to management targets, and ecological relevance (Shea and Thorsen 2012; Glenn and Suter II 2006). The following sections describe the unique characteristics and effects of dioxin-like congeners to identify organisms to assess endpoints based on the two criteria—susceptibility and ecological relevance (US EPA 2008).

Susceptibility Susceptibility includes two main parameters: sensitivity (how stressors affect an organism) and exposure (the intensity, duration, and frequency of contact among stressors and organisms) (Hung et al. 2013; US EPA 2008).

The US EPA 2003 evaluated the sensitivity of various animals to dioxin-induced toxicity based on the activation of AhR signaling pathways, which is known as a main toxicity indicator of potential susceptibility for organisms exposed to DLCs. One or more forms of the AhR have been detected in several fish, mammals, and birds especially in their embryonic or early-life stages (Farmahin et al. 2013; Ross et al. 2013; US EPA 2008; Van den Berg et al. 1998; Van den Berg et al. 2006; van den Berg et al. 2013). The presence of these receptors is sufficient to introduce these animals as most sensitive endpoints to DLCs toxicity, and they are considered to assess ecological risks of DLCs (Brown et al. 1997; Gendron 2013; Hahn 1998).

The toxicological significance of these organisms is still uncertain because their toxic effects data are extremely limited (Ross et al. 2013; US EPA 2008; US EPA 2010). Several studies recorded that dioxin congeners (mainly TCDD and PCBs) are commonly ineffectual at causing adverse effects on growth, reproduction, and survival in a wide variety of invertebrates including midges, amphipods, cladocerans, sandworms, snails, clams, purple sea urchin, oligochaete worms, mosquito larvae, and grass shrimp (Brown et al. 1997; Gendron 2013; Hahn 1998; Hahn 2002; US EPA 2008). Based on previous finding, the insensitivity of invertebrates to dioxin toxicity is due to lack of the ability of invertebrate AhR homologues to bind the ßeta-naphthol flavone and prototypical AhR ligands (TCDD) (Butler et al. 2001). Likewise, limited research has demonstrated that in spite of the significant accumulation of dioxin congeners (μg/g concentrations) in aquatic organisms (especially in algae and duckweed), they are insensitive to dioxin congeners, and no adverse effects of dioxin congeners were observed for these aquatic organisms (Kster et al. 2007; Spiegel et al. 2013; US EPA 2008). Based on these differences in sensitivity between endpoints and species, risk managers or risk assessors should consider the uncertainty to establish a successful risk assessment.

To assess ecological risk, the following alternative expressions should generally be considered as exposure to assess the relative susceptibility of species: (1) concentrations of DLCs in sediment, water, and species diet; (2) concentrations of DLCs in specific tissues of the species; and (3) concentrations of DLCs in the whole body of the species (US EPA 2008). As indicated in several studies, the endpoints must involve organisms that not only are susceptible in term of sensitivity but also are exposed through bioaccumulation of DLCs (US EPA 1998; US EPA 2010). It is essential to consider the following points to select appropriate exposure by risk assessors:

1. Spatial (life stages of endpoints) and temporal gradients of exposure when selecting species with the greatest bioaccumulation and exposure (Bain 2013; Diepens et al. 2014; US EPA 2008).
2. Benthic invertebrates whose food chains are connected to polluted sediments have greater exposures than pelagic invertebrates whose food chains are connected to surface water because of the high concentration of organic pollutants in sediments and the higher equilibrium of invertebrates with sediment than water (Burkhard et al. 2003; Weisbrod et al. 2007).
3. The ability of DLCs to be metabolized by the organisms that would reduce their bioaccumulation by increasing elimination. Invertebrates do not have enough ability to metabolize DLCs, while vertebrates significantly metabolize PCDFs, PCDDs, and to a limited extent of some PCBs (Norstrom 2002; Van Geest et al. 2011).
4. Dioxin congeners possessing chlorines at 2, 3, 7, and 8 positions (most toxic congeners) are significantly bioaccumulated by vertebrates due to their low ability to metabolize these dioxin congeners (Koenig et al. 2012; Lyons et al. 2014; US EPA 2008; US EPA 2012).

As explained in this section, species that are highly sensitive and experience high bioaccumulation and high exposure will be the species at greatest risk. Thus, it is essential to consider both sensitivity and exposure to evaluate species susceptibility.

Ecological relevance In 1992, the US EPA stated that, "ecologically relevant endpoints reflect important characteristics of the system and are functionally related to other endpoints" (Glenn and Suter II 2006; US EPA 2008). In 1998, the US EPA provided the guidelines for ERA, in which multiple "dioxin-sensitive" species were identified as ecologically relevant endpoints at any level of biological organization.

These species are relevant to the function and biodiversity of the ecosystems and sustenance of the natural structure. Thus, they are functionally related to other endpoints and have the ability to reflect main characteristics of an ecosystem (Shea and Thorsen 2012; US EPA 1998; Zwiernik et al. 2008).

For example, based on the results of several studies, piscivorous birds (herring gull, belted kingfisher, bald eagle) (Ngo et al. 2006; Seston et al. 2012), predaceous fish (lake trout) (Arcand-Hoy and Benson 1998; Giesy et al. 2002; King-Heiden et al. 2012), and mammals (mink, river otter) (Basu et al. 2007; Elliott et al. 1999; Zwiernik et al. 2008) have been considered as main classes of ecologically relevant species to assess the potential of ecological risks posed by TCDD to associated wildlife and aquatic organisms. Hence, they are employed as a keystone connection between trophic levels within the food web as well as representing both a sensitive and an ecologically relevant assessment endpoint in most ERA programs (Shea and Thorsen 2012; US EPA 1998). The guidelines for ERA identified five classifications to evaluate adverse effects or changes in assessment endpoints (US EPA 1998; US EPA 2008):

1. Nature of the effects: these effects include the mortality in a wide range of species due to developmental and reproductive toxicity because they are particularly ecologically relevant. Thus, they have potential to decrease the populations of organisms and to subsequently cause changes in the function, structure, and biodiversity of ecosystems.
2. Intensity of the effects: these effects have the potential to be great because of their potent developmental and reproductive toxicants.
3. Temporal and spatial scale effects: these effects are related to persist dioxin-like congeners in environmental matrices, for ecologically relevant time periods, making large potential effects in temporal and spatial scales of effects.
4. Potential for recovery: there is low or no opportunity for recovery due to the critical effects of AHR agonists on developmental stages of sensitive species.

Development of conceptual models

A conceptual model describes the movement of dioxin-like congeners (as stressors) from a source, the further exposure of ecological entities, subsequent exposure by bioaccumulation through food webs, and finally the hypothesized adverse ecological effects from these exposures (Shea and Thorsen 2012; US EPA 2008). As a matter of fact, the conceptual model is defined to show sources of DLCs, affected media, potential or known environmental fate and endpoints receptors, and potential or known pathways of migration (dermal, ingestion or inhalation) (EnHealth 2012; Tavakoly Sany et al. 2015; US EPA 2013b; US EPA 2014b).

DLCs are unwanted pollutants almost exclusively produced through industrial processes (Kruse et al. 2014; Lu et al. 2014; Proestou et al. 2014; Rezayi et al. 2011; WHO 2002). The US EPA has divided sources of DLCs into five groups (US EPA 2013a):

(i) Chemical manufacturing: PCDD/PCDFs are produced as chemical products from industrial manufacturing, including phenoxy herbicides (2,4,5-T), chlorinated phenols (pentachlorophenol, or PCP), PCBs, and chlorinated aliphatic compounds (ethylene dichloride), and chlorine-bleached wood pulp.
(ii) Combustion sources: PCDD/Fs are produced during combustion processes such as burning of various fuels (petroleum products, wood and coal), waste incineration (urban sewage sludge, solid waste, medical wastes, and hazards waste), uncontrolled and poorly combusted sources (open burning of wastes, building fires, and forest fires), and high temperature sources (cement kilns and incineration). Based on some evidence, very small amounts of PCBs are formed in combustion systems.
(iii) Metals refining and smelting: PCDD/Fs produced during various operations of industrial metals such as iron ore sintering, scrap metal recovery, and steel production.
(iv) Photochemical and biological processes: PCDD/Fs might be produced during photolysis of highly chlorinated phenols and formed during the action of microorganisms on chlorinated phenolic compounds.
(v) Reservoir sources: reservoirs are places with a high potential for circulation and redistribution of DLCs and PCBs, which are previously produced in environmental media.

In cases of environmental fate, it is essential to consider the individual DLC values because of the great variation in physicochemical properties of individual dioxin-like congeners in environmental media. The DLCs are essentially insoluble in water, they tend to bioaccumulate in the food chain, and they are generally classified as semi-volatile. Although some studies have reported that DLCs can degrade in environmental media, they are known as persistent and immobile in sediments and soil (Kruse et al. 2014; Lyons et al. 2014). The two main routes for dioxin congeners to enter the human diet and food chains are air-to-plant-to-animal and water/sediment-to-fish. DLCs are transported through the atmosphere as attached to airborne particle or vapors and deposited on sediment, soil, and plants by dry or wet deposition, which are the primary means of DLC dispersal in environmental media. The compounds are bioaccumulated in the fatty tissues of animals that feed on these plants. These compounds enter the aquatic food chains via direct atmospheric deposition or by surface erosion and runoff from watersheds. In aquatic systems, they can be volatilized out of the surface waters into the

atmosphere, they can be resuspended into the water bodies, or they can become buried in deeper sediments, which are considered as a permanent sink for DLCs. Moreover, fish are able to accumulate DLCs by direct contact with suspended particles in water and sediment and by their consumption of aquatic organisms (Lyons et al. 2014; US EPA 2008) (Figure S2). Humans could potentially be exposed via three exposure pathways: inhalation, dermal contact, and ingestion. In ambient air, intake of DLCs can be by general inhalation and inhalation of resuspended dust. Contact with the polluted sediment or soil may expose human to dioxins (dermal contact) (US EPA 2008; US EPA 2012).

Analysis plan

The analysis plan is the last step in the problem formulation phase that includes the clear description of the hypothesis, data needs, assessment design, measures, methods, assumptions, and extrapolations. The analysis plan leads to a clear understanding of the limitations, strengths, and transparent description of the assumptions associated with all methods (Bain 2013; Glenn and Suter II 2006).

In the application of the TEF concept to assess ecological risk, the analysis plan identifies suitable methods to provide: estimating dioxin-like congener concentrations in media and/or biota, exposure (frequency, duration, and intensity), toxicity effects (laboratory or field studies), selecting consensus TEFs and characterizing uncertainties (US EPA 2008).

Consideration in analysis

Analysis is a process that characterizes the exposure and effects and their relationships with ecosystem characteristics and between each other (Shea and Thorsen 2012; Glenn and Suter II 2006). The selection of TEF is a main connection between exposures and effects because this method fits well with the conceptual model and acts as a bridge among effects and exposures by accumulating exposure to complex mixtures of DLCs into a single value (US EPA 2008; van den Berg et al. 2013).

Characterization of exposure

Characterization of exposure provides a description of potential contact of a receptor species with chemical stressors (Shea and Thorsen 2012; US EPA 1998). Main considerations of an exposure profile for DLCs are the following (US EPA 2008; WHO 2002): (a) identification of receptors (the exposed ecological entity) based on predictions or measurements of DLC concentration in sediment, water, diet, and tissue (dose matric) in spatial and temporal scales; (b) an accounting exposure pathway (way a stressor taken from the sources by the receptors) based on the differential fate and transport of DLCs in the ecosystems; (c) predictions and/or measurements of the bioaccumulation for each DLC; and (d) estimation of TEQs based on dose metrics of the toxicity data being applied for risk estimation.

Transport and redistribution of DLCs on particles through water and atmospheric pathways are the main mechanisms that lead to spatial and temporal variations (Shields et al. 2010). Available scientific evidence shows that PCBs tend to be partitioned from water to air to a greater extent than PCDD/Fs, which are more likely removed from environmental media either by deposition or by photodegradation. In the environment, photodegradation of non-sorbed species at the water–air and soil–air interfaces (in the gaseous phase) is identified as the only significant transformation process for DLCs (Kruse et al. 2014; Shields et al. 2010).

Estimation of dioxin-like congeners in water is very difficult because of a high degree of water hydrophobicity especially for PCDD/Fs, which are in lower concentration in comparison with PCBs (Burkhard et al. 2004; Tavakoly Sany et al. 2014b; US EPA 2008). In abiotic media, concentrations of individual dioxin-like compounds usually cannot reflect the dioxin concentration profile calculated in the wildlife tissue samples (Burkhard et al. 2004; Lyons et al. 2014). Since individual dioxin congeners show the different physicochemical properties in bioaccumulation, biomagnification, bioavailability, and metabolism, their relative concentrations in organisms vary with trophic level and species (Burkhard 2003; Burkhard et al. 2004; US EPA 2012).

Thus, bioaccumulation factors (BAFs) are employed to PCDD/Fs and PCB concentrations in abiotic media to estimate predicted concentration of DLCs in organisms (biotic media) (Arnot and Gobas 2006; Burkhard 2003; US EPA 2008; US EPA 2009). It is essential to convert dioxin concentrations in abiotic media to concentrations in the organisms' tissues as well as their foods using scientific models or BAF or prior to employing TEFs to estimate TEQs (Arnot and Gobas 2006; Lyons et al. 2014; Tavakoly Sany et al. 2014a).

In ERA, if estimated concentrations of all dioxin congeners in tissues or diets of organisms associated with specific endpoints are available, then TEQs can be estimated directly based on Eq. 1. Otherwise, risk assessors have to consider how they will predict or estimate concentrations of all DLCs of concern in diets or tissues (Burkhard et al. 2004; Lyons et al. 2014). If the estimated concentrations in tissues and diets are not available, it will be necessary to estimate bioaccumulation for DLCs of concern in risk assessments involving the toxicity equivalence methodology (Arnot and Gobas 2006; US EPA 2008; US EPA 2009). The bio-concentration factors (BCFs) were previously applied to estimate bioaccumulation, but BCFs have poor applicability for hydrophobic chemicals especially PCDD/Fs and PCBs. In hydrophobic chemicals, application of BCFs leads to underestimation of uptake, bioaccumulation, and elimination of chemicals. This shows a net

uptake through all pathways of exposure because BCFs are estimated based on the uptake of the hydrophobic chemicals by aquatic species only from water via the gills (respiration) under laboratory conditions (Arnot and Gobas 2006; Lyons et al. 2014; US EPA 2008; US EPA 2009).

BAFs and biota-sediment accumulation factors (BSAFs) are applied as alternatives to BCFs and essential connectors of concentrations of dioxin congeners in the relevant tissues or diet of organisms with concentrations of DLCs in abiotic media (Lyons et al. 2014; Norstrom 2002; US EPA 2008). These factors are obtained from direct estimations from environmental media and an organism's tissue or prediction of elimination rates and uptake of chemicals as results of exposure pathways (Arnot and Gobas 2006; US EPA 2009).

When tissue concentrations of the chemicals are not available for the ecosystem and/or species of concern, it is possible to use a hybrid modeling approach to estimate BAFs and BSAFs by extrapolation from other ecosystems or species (Burkhard and Cook 2006; US EPA 2009). In addition, the US EPA has recently provided an extensive data (20,000) set of BSAFs from 20 locations for organic chemicals (US EPA 2014a).

Characterization of ecological effects

An ecological effect that characterization describes effects of DLCs (as stressor) based on stressor–response profiles. In the environment, PCDD/Fs and PCBs are generally present as complex mixtures. Thus, to assess their ecological risk, one needs to evaluate their cumulative effects and to quantify their individual exposures as well. The cumulative effects of DLCs are generally evaluated based on the stressor–response profile for TCDD because this profile is often the best or only available data to assess endpoints of concern for dioxin-like congeners (Shea and Thorsen 2012; US EPA 2008).

In recent decades, adverse health effects of DLCs have been characterized in wildlife species and humans (Goodman and Sauer 1992; Smith et al. 1976; Sparschu et al. 1971; Yang et al. 2000). Based on epidemiology data and on animal data (Table 2), TCDD is considered as "the most carcinogenic man-made chemical" (Keller et al. 2007; Keller et al. 2008). These results came from (1) theoretical animals models, (2) mutagenic metabolic conversions of other polycyclic aromatic hydrocarbons (PAHs), and (3) relationships between the expression of genes involved in oncogenesis and AhR signaling (Audebert et al. 2010; Santos 2009; Simon et al. 2009; Sorg 2013).

Results showed that acute exposure to TCDD leads to death even in tiny doses. The estimated LD_{50} value of TCCD was around 10,000 μg/kg body weight (bw) for hamsters, while it was 1 μg/kg bw for guinea pigs. Although the LD_{50} value of TCCD is unknown for humans, it is clearly higher than that of guinea pigs based on results of poisoning episodes (Schecter et al. 2006). Recent pharmacokinetic studies determined the biological half-life of TCDD based on its metabolism and bioavailability (Aylward et al. 2004; Aylward et al. 2005; Eadon et al. 1986; Emond et al. 2005; Hassoun et al. 2003; Sonne et al. 2014; Warner et al. 2013). The half-life of TCDD is dose-dependent with fast elimination at higher concentrations (Aylward et al. 2013; Warner et al. 2013). Likewise, they found a relationship between the body fat content and TCDD sensitivity and concluded that there is positive significant correlation between amounts of body fat and persistence of TCDD because accumulation of dioxin congeners in body fat is a detoxification mechanism that eliminate biologically active xenobiotics from their target organs (Aylward et al. 2004; Aylward et al. 2005; Eadon et al. 1986; Emond et al. 2005; Li et al. 1997). Following acute TCDD intoxication, biological half-life typically takes from 6 to 8 weeks in nonhuman primates and 2 to 4 weeks in rodents but it takes from 7 to 11 years in humans with wide individual variations (Birnbaum and Tuomisto 2000; Schecter et al. 2006).

The target organs show different kinetics in pathology and recovery. The pancreas and the liver are the first organs to be affected and recover within 6–10 weeks. The clinical manifestations of the skin following dioxin exposure start to develop numerous dermal hematoma only after several weeks, reaching a peak at 18 months and reduce slowly over a long period of time (3–5 years) (Schecter et al. 2006). A summary of effects associated with exposure to TCDD and other congeners of DLCs in wildlife is presented in Table 2.

Risk characterization

The risk characterization is the last step of ERA, in which the final estimate of risk is done based on the combination of exposure profile and stressor–response profile, which is developed during the analysis phase (Shea and Thorsen 2012; Glenn and Suter II 2006). The following techniques can be used to develop risk estimation: field observational studies, comparisons of effects estimates and single-point exposure, categorical rankings, comparisons relationships among the entire stressor-response, and process models based on theoretical approximations of effects and exposure (Shea and Thorsen 2012; Glenn and Suter II 2006).

In case of dioxin-like congeners, effects are usually measured based on toxicity studies of 2,3,7,8-TCDD. Exposure is defined by the TEQ to show the combined contribution of each dioxin-like congener that comprises the mixture. In risk assessment, the TEQ value is compared with toxicity of 2,3,7,8-TCDD to estimate the magnitude and likelihood effects. The quotient method is the simplest risk assessment method based on the ratio of the toxicity equivalence exposure point concentration divided by a toxicity reference value; with quotients more than 1 qualitatively indicating an increased probability effect (US EPA 2008; US EPA 2012).

Table 2 Some key adverse effects reported in animal bioassay studies

Endpoints	Exposure route and duration	Administered dose ng/kg/day[a]	
		NOAEL[b]	LOAEL[c]
Type of cancer			
Liver, lung, oral cavity, tongue, and adrenal (Goodman and Sauer 1992; Kociba et al. 1978)	Oral—lifetime feeding for rat, 2 years.	1	10
Liver, lung, pancreas, oral mucosa (NTP 2006).	Oral—gavage 5 days per week for rat; 2 years	N[d]	2.14
Developmental toxicity effect			
Reduced fetal body weight (Sparschu et al. 1971).	Maternal corn oil gavage in rat (GDs 6–15[e])	30	125
Increased relative liver weight, increased incidence of cleft palate (fetuses) (Smith et al. 1976).	Maternal corn oil gavage in mouse (GDs 6–15)	1000	3000
Reduced thymus weight (Seo et al. 1995).	Maternal corn oil gavage in rat (GDs 10–16)	25	100
Decreased spleen cellularity (immunotoxicity) (Nohara et al. 2000).	Maternal single corn oil gavage in rat (GD 15)	800	N
Increased endometrial implant survival, implant diameters, growth regulatory cytokine dysregulation (Yang et al. 2000).	Fed gelatin capsules in monkey, 5 days per week during 12 months	17.86	N
Increased organ weight (body weight, liver, thymus) (Franc et al. 2001)	Biweekly oral gavage for rat, 22 weeks.	10	30
Reduced serotonin in immune-reactive neurons (neurotoxicity) (Kuchiiwa et al. 2002).	Maternal olive oil gavage in mouse, weekly for 8 weeks prior to mating	N	0.7
Reduced anogenital distance (Ohsako et al. 2001).	Maternal single corn oil gavage in Rat (GD 15)	12.5	50
Reduced hormonal level such as progesterone serum estradiol (Li et al. 2006).	Maternal sesame oil gavage in mouse, daily for 8 days (GDs 1–8)	N	2
Increase cariogenic lesions (Miettinen et al. 2006).	Maternal single corn oil gavage in rat (GD 15)	N	30
Reduced mandibular molars shape and size (Keller et al. 2007; Keller et al. 2008).	Maternal single corn oil gavage in mouse (GD 13)	N	10
Reproductive toxicity effects			
Decrease in number of live pups and fertility index (Murray et al. 1979)	Daily dietary exposure in rat, during three generations	1	10
Neurobehavioral effects (Bowman et al. 1989; Schantz et al. 1985).	Daily dietary exposure in monkeys. 3.5–4 years.	N	0.12
Reduction in daily sperm production and caudal epididymal sperm reserves (Simanainen et al. 2004)	Maternal corn oil gavage (GDs 15) in rat	100	300
Decreased sperm production and weight of the reproductive organ (Latchoumycandane and Mathur 2002).	Olive oil gavage in rat, 45 days;	N	1
Decreased sex ratio and percentage of males (Ishihara et al. 2007)	Sesame oil gavage in mouse, weekly doses for 5 weeks	0.1	100
Decreased level of serum estradiol (Shi et al. 2007)	Maternal and offspring corn oil gavage in rat, weekly for 11 months	0.14	0.71
Embryotoxicity (Hutt et al. 2008)	Oral gavage for postpartum in rat, once per week during 3 months	N	7.14
Acute toxicity effects			
Liver, increase in hepatic EROD activity and CYP1A1 mRNA levels (Heuvel et al. 1994).	Corn oil gavage in rat (single dose)	0.1	1
Hormonal (increased serum FSH) (Li et al. 1997).	Corn oil dose via oral gastric intubation in rat (single dose)	3	10
Reduction in serum T4 levels changed in the EROD activities and reduced thymus weight (Simanainen et al. 2003).	Corn oil gavage in rat (single dose)	100	300

Table 2 (continued)

Endpoints	Exposure route and duration	Administered dose ng/kg/day[a]	
		NOAEL[b]	LOAEL[c]
Immunotoxicity (reduced antibody response to SRBCs) (Smialowicz et al. 2004).	Corn oil gavage in mouse (single dose)	300	1000
Thyroid (reduction in serum T4 levels) (Crofton et al. 2005).	Corn oil gavage in rat (4 days)	30	100
Sub-chronic toxicity effects			
Changed in body and organ weight (DeCaprio et al. 1986).	Daily dietary exposure in pig, 90 days	0.61	4.9
Changed in body and organ weight (Chu et al. 2001).	Corn oil gavage in rat, daily for 28 days	250	1000
Induction of biomarkers of oxidative stress at all doses in brain and liver (Hassoun et al. 2003).	Corn oil gavage in rat and mouse, 5 days per week for 13 weeks	N	0.32, 2.14, 7.14
Lesion in liver, thymus, and thyroid histopathology (Chu et al. 2007).	Corn oil gavage in rat, daily for 28 days	2.5	25
Decreased antibody response to SRBC (immunotoxicity), increased liver weight (Smialowicz et al. 2008).	Corn oil gavage in mouse, 5 days per week for 13 weeks	N	1.07
chronic toxicity effects			
Skin lesions and dermal amyloidosis (Toth et al. 1979).	Sunflower oil gavage mouse, weekly during 1 year	N	1
Increased body and organ weight, hepatocellular proliferation, clinical chemistry. Reduced serum T level in thyroid (Sewall et al. 1995).	Biweekly gavage in rat, 30 weeks	10.7	35
Reduced in EGFR maximum binding capacity (Sewall et al. 1995).	Biweekly gavage in rat, 30 weeks	N	3.5
Changed in body weight, PEPCK activity and IGF-I levels (Croutch et al. 2005)	Loading/maintenance dose in rat, every 3 days for different durations for 128 days	54.3	2.17

[a] The mass of a substance given to an organism and in contact with an exchange boundary (i.e., gastrointestinal tract) per unit wet body weight (BW) per unit time

[b] No observed adverse effect level

[c] Lowest observed adverse effect level

[d] Non-detected

[e] Gestation days (GD) 6–17 for rat and 6–15 for mouse

Conclusion

In this review, a set of key studies related to the perspective of developing toxicity values of DLCs were characterized based on exposure assessment and dose–response information to assess possible ecological risks to protect wildlife. The objective of this effort is to reduce the scope of analyses and models in relevant studies to a manageable size by focusing on the more relevant studies on the perspective of developing toxicity values of DLCs.

Based on several studies, a number of DLCs (PCDDs, PCDFs, and PCBs) can be described as bioaccumulative and persistent in the environment, and these compounds frequently occur as chemical mixtures in the environmental media with cumulative impacts. These chemicals have been shown to cause toxicity to fish, birds, and mammals through a mechanism of action mediated by the signal transduction pathway of the AhR.

The selection of a biologically relevant critical exposure is vital for risk assessment. The critical exposure needs to be quantifiable on an individual level and be susceptible to TCDD and other dioxin congeners for a specific health endpoints as well as availability of exposure information in the epidemiologic studies is a primary factor. In the case of animal studies, dose limits are considered as the most important criteria.

DLCs frequently occur as chemical mixtures in the environmental media with cumulative impacts. As described in this framework, the use of the toxicity equivalence methodology has several advantages to estimate ecological risks from chemical mixtures of DLCs. There is a growing body of evidence of the use of alternative methods (congener-specific analyses and Aroclor or homologue methods) that may result in underestimation or overestimation of the risks of chemical mixtures of DLCs due to the significant analytical uncertainties associated with those methods.

Thus, estimation of DLC concentrations, estimates of exposures (using the toxicity equivalence methodology), and bioaccumulation model predictions are likely to be more accurate compared to alternative methods. Another advantage of toxicity equivalence methodology is that the ecological risk assessor can select appropriate relative potency factors for DLCs. International TEF values have been established for fish, birds, and mammals based on practical approaches by WHO (Van den Berg et al. 2006; WHO 2002), and these values represent reasonable estimation of TEC. Several environmental agencies such as National Response Corporation (NRC), US EPA, and WHO have concluded that even with the inherent uncertainties associated with the application of the toxicity equivalence methodology, this methodology provides a scientifically justifiable, reasonable, and widely accepted method to measure the toxicological and biological potency of DLCs when the whole mixture data are not available for dioxin exposures. Furthermore, it is essential to understand that this methodology must be applied based on the appropriate chemicals, target species, and media which are consistent with underlying assumptions. Although, addressing key risk characterization is desirable, more studies are needed to update toxicity data for the DLCs and the TEF application considering the following issues: evaluating the fraction of the TEQ attributable to each chemical class of DLCs (PCDDs/Fs), TCDD, and dioxin-like PCBs; applying TEFs to several pathway (dermal, oral, and inhalation) exposure to assess the fractional contributions of each congeners within each route for prediction of TEQ; and performing a sensitivity analysis to characterize the application of TEF variability on the TEQ.

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