Mode of Action for 2,3,7,8-Tetrachlorodibenzo-p-dioxin Carcinogenicity

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Introduction

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) cancer bioassays primarily demonstrate liver, lung, and tumors of the oral cavity in both rats and mice (NTP, 1982; Kociba et al., 1978; NTP, 2006). In addition, there are a large number of initiation-promotion studies with TCDD and other dioxin-like compounds (DLCs) further elucidating the dose-response and toxicodynamic aspects of TCDD's carcinogenic potential (e.g., Pitot et al., 1980; Teeguarden et al., 1999; Maronpot et al., 1993). DLCs are widely recognized as tumor promoters and a number of review articles have examined this issue (Kohle et al., 2008; Knerr and Schrenk, 2006; Gasiewicz et al., 2008).

Methods

The human relevance framework and the key events dose-response framework provide a weight-of-evidence scaffold for examining the MOA behind TCDD-induced liver tumors and the dose-response characteristics (Meek et al., 2008; EPA, 2005; Boobis et al., 2006). The biology behind tumor promotion in the liver sets forth a number of basic biological principles by which chemicals promote liver tumors (e.g., Roberts et al., 1997; Fabregat et al., 2007). Literature searches for *in-vivo* and *in-vitro* TCDD studies, that provide data relevant to the known biological elements of tumor promotion, have been conducted to identify potential MOA information. The information from these published studies was evaluated against the human relevance framework to explore the weight of evidence for a MOA specific for rodent liver tumors.

Results

The proposed MOA for TCDD-promoted liver tumors covers multiple aspects of AHR cell biology, histopathological evidence, biochemical data, and now, genomics information. AHR activation is a central key event and modulation of AHR activation is directly, if not entirely coupled, to the tumor promotion outcome (e.g., Moennikes et al., 2004; Viluksela et al., 2000). AHR activation has also been shown to inhibit apoptosis in damaged cells, cells stimulated to undergo apoptosis, and in initiated liver cells (e.g., Stinchcombe et al., 1995). The early culmination of AHR activation and inhibition of apotosis in altered hepatocytes and foci leads to increases in the volume and number of altered hepatic foci (e.g., Teeguarden et al., 1999). As TCDD tissue levels sufficiently accumulate over time, hepatopathy arises as a key event that is associated with a number of abnormal histopathological findings (e.g., steatosis, inflammation) and other changes (mitochondrial injury, a role for estradiol, ROS and retinoid depletion) (Goodman and Sauer, 1992; Hailey et al.,2005; Forgacs et al., 2010). Regenerative repair of hepatopathy stimulates cell division as illustrated by increases in

BrDU labeling (NTP, 2006). The combination of these key events gives rise to the development of hepatocellular adenomas, carcinomas and cholangiolar carcinoma (NTP, 2006).

Dose-response considerations for the MOA were assessed in a number of studies that included low doses of TCDD in normal hepatocytes. AHR activation is responsible for normal development and physiology (as evidenced in AHR knockout mice), most likely in response to a plethora of naturally occurring AHR ligands that have been identified in humans and animals (Schecter et al., 1999; Connor et al., 2005). Presumably, any ligand interacting with the AHR would require sufficient mass action to overcome or interact with the naturally occurring AHR ligands. As the dose increases, a dose-transition occurs in the key event continuum that gives rise to reversible hormetic, or stress response changes, including induction of TiPARP, Nrf2, induction of a core battery of drug metabolizing enzymes, and slowing of the cell cycle (e.g., Bauman et al., 1995; Kohle and Bock, 2006; Tijet et al., 2006). Increasing dosages and continued administration eventually result in dose-transitions that directly affect the key events described above. An important element of the key event, especially with the dose-transition concept, is the zonal activation of the AHR where it is the polydiploid hepatocytes adjacent to the central vein that are the most sensitive and low-dose-responsive liver cells. As the dose increases, mid-zonal and then peri-portal hepatocytes are activated (e.g., Tritscher et al., 1992; Gaudio et al., 2009; Andersen and Conolly, 1998). This is significant since the stem cells and their differentiated daughter cells which are believed to be the cells most sensitive to initiation are near mid-zonal in location suggesting a higher dose required to affect these cells with the key events and dose-response factors described herein.

Discussion

This brief overview provides for only an example of the scientific literature and evidence available for examining the MOA for TCDD-promoted rodent liver tumors. At a higher hierarchical level the proposed MOA for dioxin-induced liver tumors is one of a nuclear receptor-mediated tumor promotion. As lower hierarchical levels of the MOA are examined, the key events supporting this proposed MOA include well-understood biological components involved with liver tumor promotion. The scientific evidence has provided good evidence for the MOA of TCDD-induced rodent liver tumors. While there are data-gaps in the proposed MOA, these data gaps are not sufficient to support the conclusion that there is insufficient scientific information for establishing a nuclear receptor-mediated tumor promotion MOA. Combined, the known biology of liver tumor promotion when examined against the human relevance framework and the published dioxin data, support a threshold basis for cancer dose-response modeling. The real challenge, and an interesting one, is how to take all the MOA data and key event elements to build a better tumor promotion model that is currently in use and to quantitatively model this information to better specify the threshold nature of dioxin-induced liver tumors in rats and mice.

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