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One TEF concept does not fit all: the case for human risk assessment of Polychlorinated Biphenyls.

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Abstract

Human risk assessment of dioxins and dioxin-like compounds relies heavily on toxic equivalency factors (TEFs) that are mainly based on *in vivo* rodent studies. However, especially for the PCBs there are many uncertainties with respect to the actual dioxin-like activities and subsequent health effects in humans. For example, the relative effect potencies (REPs) for PCB126 are consistently up to two orders of magnitude lower in human cell models than in rodents and rodent cell cultures. For other dioxin-like (DL) PCBs, REPs can often not be obtained in human models due to a lack of AHR-mediated responses. In addition, DL-PCB-related effects such as thyroid disruption are largely attributed to mechanisms that are not (directly) AHR-mediated. Consequently, the AHR-mediated risk in humans for DL-PCBs is likely overestimated in the current TEF concept. The increasing availability of *in vitro* models using human cells will provide great opportunities to determine human-specific REP/TEFs based on toxicologically relevant endpoints. A better understanding of human-specific responses should lead to more reliable potency estimates of human effects and ultimately improved human risk assessment for DL-PCBs.

Highlights

- Current TEF concept overestimates AHR-mediated risk of DL-PCBs in humans.
- *In vitro* studies with human cells will provide human-relevant REPs for DL-PCBs.
- The human-TEF for PCB126 should probably be around 0.003 for AHR-mediated effects.

Keywords (max 6): dioxins, PCBs, human risk assessment; toxic equivalency factor.

1. PCBs and the WHO-TEF concept

Human risk assessment of exposure to dioxin-like compounds (DLCs) remains a continuous challenge for toxicologists and regulators. This is especially true for polychlorinated biphenyls (PCBs) that have been used until mid-70s as coolants, coatings and lubricants. While production and use of PCBs has been prohibited for over forty years, they are still abundantly present in the environment and in tissues of birds, fish and mammals, including humans, due to their highly persistent and bioaccumulative properties. In addition, disposal of PCB-containing equipment and materials still contributes to PCB release in the environment leading to accumulation in the food chain. Consequently, human exposure to PCBs remains an issue of concern [1,2]. There are 209 possible PCBs, of which 12 are traditionally considered to have dioxin-like properties via AHR-mediated processes and have been assigned a toxic equivalency factor (TEF). TEFs reflect the potency of a

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