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# Cumulative assessment of persistent organic pollutant toxicity in vivo

**AKADEMISK AVHANDLING**

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## **ABSTRACT**

Humans are continuously exposed to a multitude of compounds present in the environment and in food. A major challenge in risk assessment is to determine the degree of exposure to multiple chemicals and the hazards associated with such combined exposure. The simultaneous exposure to persistent organic pollutants (POPs), such as dioxins and dioxin-like (DL) compounds, polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), is one example of a complex group of chemicals which is of concern from a human health perspective.

To assess the cumulative risk related to DL compounds eliciting aryl hydrocarbon receptor (AhR)-mediated biochemical and toxic responses, the WHO TEF/TEQ concept has been developed. Congeners which are assigned a TEF value are thereby covered by the risk assessment for dioxins. The TEF values have been derived using scientific judgments of multiple relative potency values from different studies and for various endpoints including increased liver weight, considered an early and sensitive marker of exposure to organohalogen compounds, decreased liver vitamin A levels, which can be considered a marker of retinoid system modulation, and hepatic EROD induction, which is not a toxic effect per se but is considered an early and sensitive marker of AhR activation. These effects have also been observed after exposure to PCBs, PBDEs and commercial mixtures, but in contrast to the DL compounds several receptors have been suggested to be involved. The similarity in effects, i.e. modulation of a common system or tissue, observed after exposure to several types of POPs indicates that the combined exposure to these chemicals could contribute to cumulative toxicity and that a cumulative assessment based on the biological system or target tissue affected rather than on the mechanism of toxicity might be warranted as a complement to the established TEF concept for DL substances.

The aim of this thesis was to study the feasibility of developing an endpoint-specific cumulative assessment based on effects considered as markers of DL toxicity observed for different POPs in vivo. The studies focused on PCB 180 (Paper I), which is not included in the TEF concept, and the commercial penta-BDE mixture Bromkal 70-5DE (Paper II).

Effects on liver weight, hepatic vitamin A levels and hepatic EROD activity were observed after exposure to PCB 180 as well as observations indicating that the effects were not mediated via the AhR. In a comparison to a series of studies including both congeners assigned a TEF (PCBs 77, 105 and 118) and congeners not assigned a TEF (PCBs 28, 128 and 153) in the WHO concept, relative potency values has been estimated for all included congeners as compared to PCB 126 based on one or more of the endpoints increased liver weight, decreased hepatic vitamin A and hepatic EROD induction, indicating that the observed effects of these congeners were similar to the effects of PCB 126, regardless if they are assumed to act mainly via the AhR or not. Based on a whole mixture approach, Bromkal 70-5DE was found to contain DL contaminants to an extent that could explain the observed effects on liver weight, hepatic vitamin A levels and hepatic EROD induction.

In conclusion, the findings in this thesis support the suggestion to develop endpoint-specific systems for cumulative assessment of POPs based on the criteria to include chemicals with similar effects, i.e. modulating a common system or target tissue via multiple pathways and/or mechanisms of toxicity.