Uncertainties in the Toxic Equivalency Factor concept: Future directions

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The recent consultation on the "Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI)" based the TDI on various adverse effects after exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in animal studies[1)]. These adverse effects included endometriosis, developmental neurobehavioral (cognitive) effects, developmental reproductive (sperm count, female urogenital malformations) effects and immunotoxic effects. In order to estimate human exposure to dioxin-like compounds as TCDD, the toxic equivalency factor concept is used[2)]. In this TEF concept, the total dioxin-concentration (TEQ) in an environmental biological sample is estimated by using toxic equivalency factors (TEFs) which are assigned to the individual dioxin-like compounds in the mixture and multiplied by the concentration in the specific matrix for various dioxin-like compounds, such as polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and co-planar and mono-ortho-substituted biphenyls (PCBs). A TEF value expresses the relative potency of the individual congener in comparison to TCDD.

By using a TDI derived from dose-response studies with TCDD, the consultation assumes that all dioxin-activity is captured by the TEF concept, which include PCDDs, PCDFs, co-planar and mono-ortho-substituted PCBs. However, some of the effects which drive the risk assessment of dioxin-like compounds, e.g., developmental neurobehavioral, developmental reproductive, and immunotoxic effects have also been observed after exposure to di-ortho-substituted PCBs, polybrominated diphenyl ethers (PBDEs), and hexachlorobenzene (HCB)[3-7)]. This indicates that by excluding di-ortho-substituted PCBs, PBDEs, and HCB in the assessment of a TDI, it is likely that the suggested TDI of 1 to 4 pg TEQ/kg/day is not protective enough. However, it might well be that in human exposure scenarios di-ortho-substituted PCBs, PBDEs, and HCB do not contribute considerably in order to overwhelm the effect of the pure dioxin-like compounds for the mentioned endpoints as has been estimated in environmental exposure scenarios with mink and PCBs[8)]. Nevertheless, is has recently been suggested that HCB could add considerably to the total TEQ based on only its dioxin-like properties[9)].

In addition, by using a TDI based on dose-response studies with TCDD, the consultation assumes dose-additivity for the used endpoints. Indeed, dose-additivity has been shown after exposure to mixtures resembling human or environmental exposure for various endpoints such a cytochrome P450 induction, immunotoxicity, a decrease in the concentration of hepatic retinoids, tumor promotion, and fish early life stage mortality[10-14)]. However, no information is available to date if this dose-additivity holds for the endpoints that drive the risk assessment. This is of concern since for example, permanent alterations in behavior and brain maturation in the offspring have been associated with decreased thyroid hormone levels[15)]. Di-ortho substituted PCBs, HCB, and PBDEs have been shown to accumulate in the food chain and have also been shown to interfere with thyroid homeostasis at various levels [5, 16-29)]. In addition, the thyroid toxicity of a mixture of dioxin-like compounds, including mono-ortho-substituted PCBs was underpredicted by approximately 2 orders of magnitude when compared to a dose-response study with TCDD[30)]. Hepatic and pulmonary cytochrome P4501A1 activities however, were similar in both studies,

indicating that the mixture predicted a pure Ah-receptor mediated effect very well[10]. This indicates that the thyroid system is vulnerable for interactive effects. In humans, pre- and postnatal exposure to dioxin-like compounds in the background population in the Netherlands and Japan have found alterations in circulating thyroid hormone concentrations and (neuro)developmental effects[31-39]. This indicates that after exposure to dioxin-like compounds, the thyroid system and (neuro)developmental behavior are among one of the more sensitive endpoints in humans.

Based on the above information, it is suggested that future studies should focus on dose-response studies with mixtures of dioxin-like compounds and non-dioxin-like compounds, including the mentioned groups. The ratio of the compounds in these mixtures should resemble human exposure. These studies would provide a base for the dose-additivity of the endpoints that drive risk assessment of dioxin-like compounds. In addition, these studies would also form a base for future risk assessments of dioxin-like and related compounds on a more realistic exposure scenario.

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