TARGET ORGAN TOXICITY DOSES FOR CDDs AND PCBs

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Abstract

The derivation of target organ toxicity doses (TTDs) for chlorinated dibenzo-p-dioxins CDDs) and polychlorinated biphenyls (PCBs) is described. TTDs were derived for several critical effects including hepatic, endocrine, immunologic, neurodevelopmental, and reproductive effects. The Agency for Toxic Substances and Disease Registry (ATSDR) uses the TTDs approach as a refinement of the hazard index method to accommodate the assessment of mixtures whose components do not all have the same critical effect

Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) has developed a program to evaluate the risk associated with exposures to chemical mixtures at or around hazardous waste sites. The evaluation is guided by ATSDR's "Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures" (1). If no information is available on the whole mixture, ATSDR recommends the weight-of-evidence approach (WOE) for binary combinations of chemicals in the mixture (2). WOE is a qualitative judgment, based on empirical observations and mechanistic considerations, which categorizes the most plausible nature of any potential influence of one compound on the toxicity of another for a given exposure scenario. The hazard index (HI) approach is then used to assess the whole mixture (1). HI approach uses the assumption of dose additivity to assess the noncancer health effects of a mixture from the data on the components. The target organ toxicity dose (TTD) method is a refinement of the HI to accommodate the assessment of mixtures whose components do not all have the same critical effect. Finally, a qualitative adjustment of the HI based on the WOE results is recommended. TTDs for chlorinated dibenzo-p-dioxins CDDs) and polychlorinated biphenyls (PCBs) were derived for several critical effects.

Methods and Materials

TTDs were based on information compiled in the toxicological profiles for the respective chemicals (3,4). The derivation of TTDs for use in assessment of the joint toxic action of chemical mixtures is the same as the derivation of ATSDR's health based guidance values called minimal risk levels (MRLs) and follows the ATSDR MRL guidance (5). MRL or TTD based on the 2,3,7,8-tetrachlorodibenzo-p-dioxin applies also to total toxicity equivalents or TEQs (3).

Results and Discussion

Hepatic Effects - CDDs. Numerous studies have observed liver effects in laboratory animals exposed to 2,3,7,8-TCDD for acute, intermediate, and chronic durations (3). A $TTD_{HEPATIC}$ can be derived for 2,3,7,8-TCDD by applying an uncertainty factor (UF) of 300 (10 for use of a LOAEL, 3 for extrapolation from rats to humans, and 10 to protect sensitive individuals) to the chronic hepatic LOAEL of 0.001 μg/kg/day from the (6) study. This yields a $TTD_{HEPATIC}$ of 0.000003 μg/kg/day. The use of an uncertainty factor of 3 rather than 10 for extrapolation from rats to humans follows the MRL derivations in ATSDR's toxicological profile (3) and is based on a comparison of sensitivity to 2,3,7,8-TCDD among animal species.

Endocrine Effects- CDDs. The lowest LOAEL was reported by(7), who found a 50% decrease in serum T4 in male Sprague-Dawley rats treated with 0.03 μg/kg/day of 2,3,7,8-TCDD by gavage in oil once per week for 10 weeks, with a NOAEL of 0.003 μg/kg/day. Applying an uncertainty factor of 30 (3 for extrapolation from rats to humans and 10 to protect sensitive individuals) to the NOAEL of 0.003 μg/kg/day yields a $TTD_{ENDOCRINE}$ of 0.0001 μg/kg/day.

Immunological Effects-CDDs. Based on the available database, the intermediate oral MRL of 0.00002 μg/kg/day is protective also to chronic exposure and is adopted as the TTD_{IMMUNO} for 2,3,7,8-TCDD. More details on the MRL can be found in (3).

Neurological Effects-CDDs. The chronic MRL of 0.000001 μg/kg/day was based on a LOAEL for neurobehavioral effects (changes in social behavior in the offspring) following the exposure of female monkeys to 2,3,7,8-TCDD in the diet throughout the mating period, gestation, and lactation and an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) (3).

Reproductive Effects-CDDs. The lowest LOAEL for reproductive effects was for the development of endometriosis in Rhesus monkeys 10 years after the end of a 4-year exposure period during which the monkeys received 2,3,7,8-TCDD in the feed daily. The incidence and severity of the effect were dose-related, with a LOAEL of 0.00012 μg/kg/day (8). These are the same monkeys that were used in the developmental study upon which the chronic oral MRL is based. ATSDR (3) considered using the reproductive LOAEL of 0.00012 μg/kg/day as the basis for the oral MRL. An uncertainty factor of one for extrapolation from monkeys to humans was proposed by (3) because monkeys appear to be more sensitive to endometriosis than humans (30% background incidence in monkeys and 10% background incidence in humans), along with uncertainty factors of 10 for use of a LOAEL and 10 to protect sensitive individuals. Applying these uncertainty factors (total UF = 100) to the LOAEL of 0.00012 μg/kg/day yields a TTD_{REPRO} of 0.000001 μg/kg/day for 2,3,7,8-TCDD, which is the same as the chronic oral MRL.

Developmental Effects-CDDs. As described under neurological effects above, the chronic oral MRL for 2,3,7,8-TCDD (3) is based on neurodevelopmental effects (changes in social behavior in offspring of monkeys exposed during the mating period, gestation, and lactation). Thus, the chronic oral MRL of 0.000001 μg/kg/day for 2,3,7,8-TCDD is suitable to assess the potential for developmental effects.

Hepatic Effects – PCBs. The lowest exposure levels associated with liver changes in available animal studies (4) are 0.04 mg/kg/day (no NOAEL was identified) for decreased serum cholesterol in Rhesus monkeys exposed to Aroclor 1254 for 37 months), 0.08 mg/kg/day (with a NOAEL of 0.04 mg/kg/day) for increased relative liver weight in Rhesus monkeys exposed to Aroclor 1254 for 72 months , 0.2 mg/kg/day (no NOAEL was identified) for hepatocyte necrosis and biliary tract hypertrophy in Rhesus monkeys exposed to Aroclor 1254 for 12 or 28 months, and 1 mg/kg/day (no NOAEL was identified) for hepatocellular hypertrophy and increased levels of serum enzymes in male rats exposed to Aroclor 1254 or 1260 for 24 months. Applying an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from monkeys to humans, and 10 for human variability) to the LOAEL of 0.04 mg/kg/day for decreased serum cholesterol in Rhesus monkeys (9) yields a $TTD_{HEPATIC}$ of 0.1 μg/kg/day for PCB mixtures.

Endocrine Effects- PCBs Animal studies firmly establish causal relationships between PCB exposures and several types of endocrine effects including disruption of thyroid structural integrity, disruption of thyroid hormone homeostasis, and impaired reproductive function and development that may involve disruption of steroid hormone homeostasis (ATSDR 2000). Dividing the rat LOAEL of 0.09 mg/kg/day for decreased serum thyroid hormone levels produced by intermediate-duration exposure (10) by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolating from rats to humans, and 10 for human variability) yields a $TTD_{ENDOCRINE}$ of 0.1 μg/kg/day. This value is expected to be protective of chronic-duration exposure because of the large uncertainty factor.

Immunological Effects-PCBs The lowest exposure level associated with immune effects in animals orally exposed to PCB mixtures is 0.005 mg/kg/day for decreased IgM and IgG antibody responses to sheep red blood cells in female Rhesus monkeys exposed to Aroclor 1254 for 23 months (11). No NOAEL was identified in this study. This LOAEL serves as the basis of the chronic oral MRL for PCBs of 0.02 µg/kg/day (4).

Neurological Effects-PCBs., ATSDR (4) derived the intermediate oral MRL of 0.03 µg/kg/day for PCB mixtures based on a LOAEL of 0.0075 mg/kg/day (no NOAEL was identified) for neurobehavioral changes in infant monkeys that were orally exposed from birth to 20 weeks of age to a synthetic mixture of PCBs representing 80% of the PCB congeners found in samples of human breast milk and an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolating from monkeys to humans, and 10 for human variability). The intermediate-duration oral MRL is expected to provide protection against possible neurological and neurodevelopmental effects from chronic exposure.

Reproductive Effects-PCBs Application of an uncertainty factor of 30 (3 for extrapolation from monkeys to humans and 10 for human variability) to the NOAEL of 0.005 mg/kg/day for reduced conception rate in monkeys (12) yields a TTD_{REPROD} of 0.2 µg/kg/day.

Developmental Effects-PCBs The development of the neurological system appears to be a target of critical public health concern associated with pre- and/or post-natal exposure to PCB mixtures (4) and these findings serve as the basis of the intermediate oral MRL of 0.03 µg/kg/day and is expected to be protective of neurological neurodevelopmental effects from chronic oral exposure to PCBs.

HI is calculated as sum of hazard quotients (concentration divided by TTD). Since WOE evaluation predicted PCBs antagonism of TCDD immunotoxicity and TCDD developmental toxicity, the HI would overestimate the risk for these endponts.

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