# The comparative toxicokinetics of dioxin-like chemicals and the role of CYP1A2 in their disposition.

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Dioxins and PCBs are ubiquitous environmental pollutants. A variety of sources release these chemicals into the environment as components of complex mixtures. The chemicals present in these mixtures have varying degrees of lipid solubility, volatility, and persistence. These and other properties of the chemicals result in chemical specific fate and transport throughout the environment. The differences in their fate and transport properties produce a weathering of these mixtures in which the congener patterns alter from one matrix to another. Thus, human exposure is different from the mixture originally released into the environment. Similarly, in humans and wildlife, these chemicals also undergo a variety of processes such as, absorption, metabolism and elimination which result in internal exposures different from the administered exposures. These pharmacokinetic properties play significant roles in the qualitative and quantitative toxicity of each chemical.

The relative potency of dioxin-like chemicals is an integration of their Ah receptor binding affinity and their pharmacokinetic properties. While for many chemicals, Ah receptor binding affinity are also important in their relative potency, for some chemicals, pharmacokinetic properties play the predominate role. For example, OCDD is practically insoluble in aqueous environments and its absorption through the gastrointestinal tract is poor. Short-term studies indicate that this chemical does not have dioxin-like activity, due to is limited absorption. However low dose repeated exposure to this chemical enables OCDD to accumulate to toxic concentrations and induce dioxin-like effects[1].

The chemicals included in the TEF methodology have several common properties. They are structurally related, bind to the Ah receptor, persistent and bioaccumulate. Many of the chemicals also share similar disposition properties. Except for hepatic tissue, dioxins distribute in animals and humans based on the lipid content of the tissue. If lipid content was the sole basis for the tissue distribution of dioxins, then adipose tissue should always have more dioxins than hepatic or other tissues. In addition, liver/fat ratios should be less than one since adipose tissue contains approximately 20 times more lipid than hepatic tissue. However, many of the dioxin-like chemicals included in the TEF scheme are sequestered in hepatic tissue. The exceptions appear to be the mono-ortho substituted PCBs, which do not appear to concentrate in rodent livers[2]. Hepatic sequestration is dose dependent and results in a greater accumulation of these chemicals in hepatic tissue compared to adipose tissue. The sequestration of these chemicals is typically quantified by the ratio of the concentration of the chemicals in hepatic tissue compared to adipose

tissue. Typically, these ratios are much greater than one and have attained values of 40 or higher depending on the congener, species and dose [2]

There are several lines of evidence that indicate an inducible binding protein is responsible for the hepatic sequestration. The hepatic accumulation of these chemicals is dose-dependent [3] [4]. Accumulation in hepatic tissue is supralinear with dose and in extra-hepatic tissue, accumulation is sublinear with dose. This dose-dependency is best described by the relationship between the % of the administered dose retained/gram tissue vs. administered dose or by comparisons of liver/fat concentrations ratios vs. administered dose. Within the liver, TCDD accumulates in the microsomes in a dose-dependent manner similar to the accumulation in the liver as a whole tissue [5]. Earlier studies demonstrated that TCDD and related chemicals can inhibit the enzymatic activity of CYP1A2 [6, 7]and that dioxin-like chemicals bind to CYP1A2[8, 9]. These data led to the hypothesis that CYP1A2 is the hepatic dioxin-binding protein responsible for the dose-dependent sequestration. The role of CYP1A2 was recently confirmed using CYP1A2 knockout mice[10]. In wild-type mice, TCDD and 2,3,4,7,8-pentachlorodibenzofuran (4-PeCDF) were sequestered in hepatic tissue, while in CYP1A2 knockout mice, liver/fat concentrations of these chemicals were approximately 0.2-0.4, demonstrating a lack of sequestration[10].

The comparison of the hepatic sequestration of different congeners is often difficult. The hepatic sequestration of a particular congener is dependent upon its binding affinity to CYP1A2 and the concentration of CYP1A2 in the liver. Frequently, the data available is limited to liver and adipose tissue concentrations. Because the sequestration is dose-dependent, comparison of the relative sequestration of different congeners must include information on the induction of CYP1A2. In mice this data is available for a series of PHDDs, PCDFs, and PCBs [2]. These data indicate that the structure activity relationship for sequestration is different from the SAR for dioxin-like biochemical and toxicological effects [2]. In general, higher chlorinated congeners are sequestered to a greater extent than lower chlorinated congeners. 4-PeCDF is the most highly sequestered congener in mice[2]. When comparing the sequestration across species, these comparisons are often more difficult. For example, little information is available on the concentrations of CYP1A2 in liver samples from the various species in studies examining the disposition of these chemicals. Hence comparisons of the sequestration between different species is limited to qualitative descriptions. Sequestration has been observed in hamsters, guinea pigs and marmoset monkeys[11] .

In humans there is data demonstrating sequestration in hepatic tissue. One of the difficulties in interpreting these data is that there is no information on CYP1A2 concentrations in these samples. In the human data, there appears to be similar structure activity relationships for sequestration. (i.e. greater sequestration of the higher chlorinated congeners). Once again, direct quantitative comparisons are difficult. Most of the data in humans are from populations with background exposure [12] . These subjects should be considered low dose exposure and most likely do not have significant CYP1A2 induction. Because hepatic sequestration is dose-dependent, caution should be excercised when comparing the disposition of these chemicals between humans and experimental animals. Most of the animal data examining hepatic sequestration is in the high dose range. The human data is predominately low dose exposures. Once again, because of the dose-dependency in hepatic sequestration direct quantitative comparisons are difficult to make.

Species differences in the disposition of these chemicals can impact the dose response relationships for dioxin-like chemicals. For example, in the CYP1A2 knockout mice, significantly less of the dose of dioxins goes to the liver compared to the wild-type mice. Therefore, non-hepatic tissues receive greater concentrations of dioxins compared to the wild-type [10]. If human liver poorly sequesters these chemicals compared to experimental animals, then a greater percentage of the body burden in a human will be in extra-hepatic tissue compared to equivalent exposures in experimental animals. These potential differences in disposition could result in increased sensitivity of the human to the non-hepatic toxicities of dioxins, particularly low dose developmental effects. Future studies should examine the relationship between CYP1A2 induction and sequestration in humans to better understand these species differences.

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