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The Toxicokinetics and Metabolism of Polychlorinated Dibenzo-*p*-Dioxins (PCDDs) and Dibenzofurans (PCDFs) and Their Relevance for Toxicity

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ABSTRACT: This article reviews the present state of the art regarding the toxicokinetics and metabolism of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs). The absorption, body distribution, and metabolism can vary greatly between species and also may depend on the congener and dose. In biota, the 2,3,7,8-substituted PCDDs and PCDFs are almost exclusively retained in all tissue types, preferably liver and fat. This selective tissue retention and bioaccumulation are caused by a reduced rate of biotransformation and subsequent elimination of congeners with chlorine substitution at the 2,3,7, and 8 positions. 2,3,7,8-Substituted PCDDs and PCDFs also have the greatest toxic and biological activity and affinity for the cytosolic arylhydrocarbon (Ah)-receptor protein. The parent compound is the causal agent for Ah-receptor-mediated toxic and biological effects, with metabolism and subsequent elimination of 2,3,7,8- substituted congeners representing a detoxification process. Congener-specific affinity of PCDDs and PCDFs for the Ah-receptor, the genetic events following receptor binding, and toxicokinetics are factors that contribute to the relative *in vivo* potency of an individual PCDD or PCDF in a given species. Limited human data indicate that marked species differences exist in the toxicokinetics of these compounds. Thus, human risk assessment for PCDDs and PCDFs needs to consider species-, congener-, and dose-specific toxicokinetic data. In addition, exposure to complex mixtures, including PCBs, has the potential to alter the toxicokinetics of individual compounds. These alterations in toxicokinetics may be involved in some of the nonadditive toxic or biological effects that are observed after exposure to mixtures of PCDDs or PCDFs with PCBs.

KEY WORDS: halogenated dibenzo-*p*-dioxins, dibenzofurans, toxicokinetics, metabolism, enzyme induction, toxicity.

I. INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) represent groups of halogenated polycyclic aromatics, comprising 210 different congeners (Figure 1; Table 1). These compounds are formed as unwanted byproducts in a variety of chemical and thermal processes and, except for scientific research, they are of no economical importance. It has been well established that PCDDs and PCDFs are formed during the synthesis of a wide array of commercial chemical products, especially those based on chlorinated aromatics, precursors, and intermediates. These products have a broad range of applications, ranging from herbicides and fungicides for chlorinated phenoxybenzenes and phenols, to heat-transfer fluids and fire retardants for chlorinated and brominated biphenyls (PCBs and PBBs).[128,288] In addition, a variety of combustion processes, e.g., burning of solid waste from municipal incinerators, lead to continuous formation and partial release of PCDDs and PCDFs into the environment.[61,65,129,214,237]

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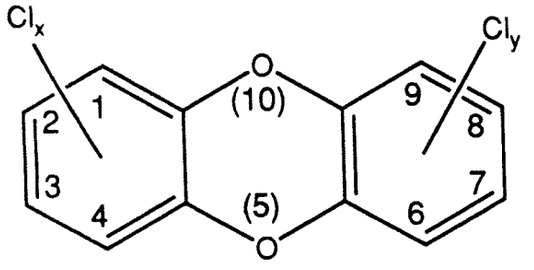
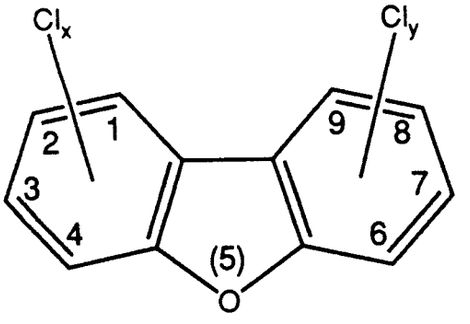


PCDD



PCDF

FIGURE 1. General molecular structure and numbering of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs).

TABLE 1
Number of Possible Congeners of PCDDs and PCDFs/

Number of chlorine atoms	Number of possible isomers	
	PCDD	PCDF
1	2	4
2	10	16
3	14	28
4	22	38
5	14	28
6	10	16
7	2	4
8	1	1
Total	75	135

The congener pattern produced depends largely on the precursors and chemical reactions. Surprisingly, it appears that upon combustion of chemically not well-defined and variable matrices, similar congeneric patterns result.[278–289] PCDDs and PCDFs have become widely disseminated into the global environment and, due to long range transport, can be found in even the most remote areas.[232,233,244] Although formation of these compounds also occurs during natural combustion processes, e.g., forest fires, it has been firmly established that the main environmental contamination is related to the industrial production and use of chlorinated hydrocarbons.[70,71]

Once released into the environment, these compounds are extremely stable as they are resistant toward chemical oxidations and hydrolysis. Moreover, the 2,3,7,8-substituted congeners withstand biodegradation and persist in the environment. These proteins, in combination with the lipophilic nature of these compounds, lead to an effective transport into the foodchain, with pronounced accumulation of these congeners at higher trophic levels, including humans (see References 26–28, 46, 82, 87, 90, 92–94, 100, 111, 118, 119, 133, 178, 179, 229, 233, 236, 244, 248–251, 289, 299, 300, 310, 330, 331, 334, 339, 353, 354). This occurrence in the biotic environment has raised public concern during the last few decades about possible adverse effects on the ecosystem and human health (see References 62, 64, 68, 102, 123, 132, 134, 140, 143, 163, 167, 235, 291, 293, 393, 402).

PCDDs and PCDFs elicit a broad spectrum of biological and toxicological effects that are dose-dependent and species- and tissue-specific. A marked structure-activity relationship exists whereby lateral substituents are extremely active and exhibit "dioxin-like" activity (see References 17, 83, 107, 115, 124, 186, 187, 223, 305, 306, 385). A broad spectrum of toxic responses, including teratogenic, reproductive, behavioral, neuroendocrine, immunotoxic, hepatotoxic effects, have been observed in laboratory animals as well as wildlife species exposed to these compounds.[102,116,122,157,191,204,207,224,337] The tumorigenic actions of some congeners in rodents most likely are not the result of genotoxicity, but rather via a promotional, and possibly hormonal, mechanism.[125,149,150] For humans, there is evidence for adverse health effects following accidental and occupational exposure or after food consumption involving contaminated fish (see References 64, 88, 123, 132, 134, 138, 143, 163, 215, 235, 291, 293, 301, 303).

These compounds also elicit a wide spectrum of biochemical effects, including induction of phase I and II enzymes, most noticeably CYP1A1 and CYP1A2.[85,86,135,136,222,223] Indirect effects, such as alterations of hormonal metabolism leading to lowered thyroid hormone levels, for example, may have an influence on growth and development of the living organism.[172] Most of the toxic and biological responses are thought to be initiated through the binding of these compounds to a soluble intracellular protein, the arylhydrocarbon (Ah) receptor. There is evidence that binding to the Ah receptor is an essential initial event, followed by other processes, such as translocation of the transformed ligand-receptor complex and binding to the dioxin-responsive enhancer (DRE) elements on DNA for the expression of many of the species- and tissue-specific, toxicological and biological responses (see References 79, 85, 98, 109, 189, 276, 277, 279, 280, 306, 387–390). However, there also is growing evidence that some effects, e.g., alterations in vitamin A, thyroid hormone metabolism, and acute lethality,[51,265–267,296,297] do not necessarily have to be Ah-receptor-mediated.[194–196]

Undoubtedly, the toxicity of PCDDs and PCDFs is produced by the parent compound and not the metabolites.[188,378,379] Thus, metabolism and excretion of these compounds mainly represent a detoxification process. In this respect, toxicokinetics as well as metabolism plays a significant role in determining the overall toxicity of these compounds.

This paper reviews the present scientific knowledge on the toxicokinetics of PCDDs and PCDFs in different species, including humans, with special emphasis on the relationship between toxicokinetics and toxicity.

II. UPTAKE

A. Absorption from the Gastrointestinal (GI) Tract

The absorption of PCDDs and PCDFs from the GI tract has been studied for a number of individual congeners, mostly in radiolabeled form. Although numerous studies with mixtures of these compounds have been done, only limited information can be derived from these experiments about uptake from the GI tract because complete mass balances were not determined. Absorption of 2,3,7,8-TCDD or related isostereomers is variable, incomplete, vehicle-dependent, and congener-specific. Based on the available data, it is suggested that there are no interspecies differences in the GI absorption of these compounds. In addition, there are indications that passage across the intestinal wall is predominantly limited by molecular size and solubility. The influence of molecular size and solubility appears to be most significant for hepta- and octachlorinated congeners, which exhibit decreased absorption in mammals as well as in fish. Information about the mechanism(s) for the GI absorption of these compounds is very limited. In rats, chylomicrons were found to be the major carriers responsible for transport of 2,3,7,8-TCDD following oral exposure. This transport occurs essentially via the lymphatic route.[170] Limited data also suggest that aging of the intestinal tract does not significantly influence the absorption of 2,3,7,8-TCDD. A study using rats between 13 weeks and 26 months of age showed no influence of aging on the absorption of 2,3,7,8-TCDD.[117] Coadministration of other halogenated aromatics, like 2,2′,4,4′,5,5′-HxCB, did not influence the intestinal uptake of 2,3,7,8-TCDD in the rat, but in contrast the absorption of this PCB was enhanced.[117]

1. Rat

When 2,3,7,8-TCDD is orally administered in an oily vehicle to rats, this compound is efficiently absorbed from the GI tract. Several studies reported 70 to 85% absorption following a single exposure to a dose from 1 to 50 µg/kg.[11,258,295] A 42-day semichronic study using a daily dose of 0.5 or 1.4 µg kg/day 2,3,7,8-TCDD in the diet reported that 50 to 60% of the consumed dose was absorbed.[91] The lower absorption observed in this study may be attributed to the lower bioavailability of these compounds from the diet when compared with other studies using oily vehicles. For 2,3,7,8-TCDF, an absorption efficiency of approximately 90% was observed after oral administration of 0.1 and 1.0 µmol/kg b.w. using a 1:1 vegetable oil-to-ethanol mixture.[31] Incomplete and variable absorption of

1,2,3,7,8-PnCDD (19 to 71%) was reported 2 days after a single oral dose of 0.03 μmol/kg.[372] The absorption efficiency of 2,3,4,7,8-PnCDF was reported in three different studies. Within 24 to 72 h, 70 to 85% of this compound at the doses 0.1 or 1.0 μmol/kg was absorbed from the GI tract.[47,139,399] In general, these findings indicate that 2,3,7,8-substituted tetra- and pentachlorinated congeners are well absorbed from the GI tract. In contrast with the former compounds, OCDD was very poorly absorbed from the intestinal tract. Dose-dependent absorption of OCDD was observed, with 2 to 15% of the dose absorbed following a single oral exposure at doses from 50 to 5000 μg/kg. Most effective absorption was found at the lower dose range when administered in a *o*-dichlorobenzene-to-corn oil (1:1) mixture.[37]

2. Mice

As in the rat, 2,3,7,8-TCDD is effectively absorbed by the GI tract of the female C57BL/6J mouse. Only 15 to 20% of a single oral dose of 20 μg/kg was excreted in the feces within 1 day after exposure, representing the percentage of the dose not absorbed. Pretreatment with 2,3,7,8-TCDD reduced the initial excretion of this compound by feces, indicating enhanced absorption from the GI tract.[69] These results are in contrast with another study using male ICR/Ha Swiss mice, in which the intestinal absorption of 2,3,7,8-TCDD was considerably lower, with only 24 to 33% absorption of a single dose of 135 μg/kg.[153] It is, however, unclear whether these differences are due to differences in strain or experimental designs.

3. Hamster

Like the two preceding species, hamsters can effectively absorb 2,3,7,8-TCDD from the GI tract. After a single oral dose of 650 μg/kg, 74% was absorbed within the first 24 h.[239] No information is available about intestinal absorption for other individual congeners in this species. However, a mixture study using tetra- to octachlorinated PCDDs and PCDFs showed that the higher molecular weight congeners were less absorbed.[352]

4. Guinea Pig

In the guinea pig, data about GI absorption have been reported only for 2,3,7,8-TCDD and 2,3,7,8-TCDF. Single doses of 0.005 μmol/kg 2,3,7,8-TCDD and 0.02 μmol/kg 2,3,7,8,-TCDF b.w. were taken up to an extent of approximately 50 to 90% from the intestines, respectively.[74,230] The higher absorption observed for 2,3,7,8-TCDF compared to 2,3,7,8-TCDD may be a result of the better relative solubility of the former compound.

5. Monkey

The few studies done with monkeys and these compounds provide very little information about the absorption efficiency from the GI tract.[32,48,165] Results from a single dose experiment with 2,3,4,7,8-PnCDF using one Rhesus monkey indicate that approximately 80% of the compound was still residing in the stomach and small intestine 6 h after administration.[48] When evaluating this result, it should be considered that this time may have been too short for optimal absorption.

6. Human

Although extensive information is available about residue levels in human tissues and milk, information on GI absorption is known only from one individual. After a self-administered dose of 1.14 ng/kg b.w. 2,3,7,8-TCDD, an intestinal uptake of >86% was determined from fecal excretion during the first week after ingestion.[273] These results give some indication that, at least in adult humans, GI tract absorption of 2,3,7,8-TCDD seems to be comparable to most rodent species used in laboratory studies.

7. Birds

To our knowledge, no toxicokinetic studies with individual PCDDs and PCDFs have been done with bird species. However, a 9-week study with chickens provides evidence that, as with mammals, even the higher chlorinated congeners,

like 1,2,3,4,6,7,8-HpCDD and OCDD, can be readily absorbed from the GI tract.[227]

8. Fish

In fish, the absorption of PCDDs and PCDFs from the intestinal tract was found to be species dependent[212] and is probably influenced more by molecular size than hydrophobicity.[246] This suggestion is based on the absence of bioaccumulation of the higher chlorinated congeners, e.g., OCDD and OCDF, in laboratory studies. Studies with rainbow trout and fathead minnow using 1,2,3,7-TCDD, 1,2,3,4,7-PnCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD exhibited a 1.5- to 2-fold higher uptake efficiency in the former species.[212] After oral dosage with an oily vehicle, the absorption efficiencies in the rainbow trout for nontoxic di-, tri-, tetra-, and octachlorinated congeners were between 2 to 16% of the administered dose.[228] A dietary accumulation study with rainbow trout indicated that 2,3,4,7,8-PnCDF is effectively absorbed from the intestinal tract, with an uptake efficiency of about 40%.[213] In the same species, approximately 37% of a dose of 1,2,3,4,7,8-HxCDD, was absorbed following dietary exposure, whereas only 13% of the 1,2,3,4,6,7,8-HpCDD dose was absorbed.[212] Oral as well as aqueous exposures studies with OCDD and rainbow trout or fathead minnow indicate an apparently rapid clearance of this compound from the body that was unexpected. These observations were explained by the authors as predominant adsorption of this compound on the gill surfaces and GI epithelia. Therefore, the rapid clearance may then be caused by natural cell turnover.[211] Another bioaccumulation study involving OCDF using the guppy (*Poecilia recticulata*) showed that accumulation through dietary uptake was insignificant.[105]

B. Influence of Molecular Size, the Vehicle, and Enterohepatic Circulation

Several studies using either mixtures or individual congeners showed that the molecular size of PCDDs and PCDFs becomes a limiting factor for hepta- and octachlorinated congeners since absorption decreased following oral exposure.[37,197,356] Besides information about rodents, data from a cow study indicated that GI absorption was related to molecular size. Absorption from the intestinal tract decreased with increasing molecular size, ranging from 80% for 2,3,7,8-TCDD/TCDF to 20 to 40% for OCDD/OCDF.[197] Most oral exposure studies have used either vegetable oil or organic solvents, e.g., ethanol, as vehicles. In the rat, differences in GI uptake, using liver deposition as an index of bioavailability, were studied with two different lipophilic carriers, arachidis oil and Miglyol 812. Both vehicles yielded similar uptake for the tetra- to hexachlorinated dioxins and dibenzofurans.[355] In contrast to mammals, oral administration of PCDDs and PCDFs in an oily vehicle can result in very low absorption rates in fish.[228] For the metabolites of 2,3,7,8-substituted congeners, enterohepatic circulation can be considered to be of no significance. In rats, a comparison of biliary and fecal excretion of 2,3,7,8-TCDD metabolites showed that it does not play an important role in intestinal uptake.[283] Similar results were reported for metabolites of 1,2,3,7,8-PnCDF, a compound that is rapidly metabolized in the rat.[49]

C. Other Routes of Administration

When comparing other exposure studies with those using other modes of administration, e.g., intraperitoneal (i.p.) or subcutaneous (s.c.) dosage, some significant differences have been observed regarding body distribution. These differences should be taken into consideration when data from these experiments are used for risk assessment after environmental exposure.

1. Intraperitoneal

When a single i.p. treatment of rats with 2,3,7,8-TCDD was compared with a similar oral administration, no differences in uptake were observed based on deposition in the liver and adipose tissue.[170] A comparative study with rats using a complex mixture of PCDDs and PCDFs, administered either intraperitoneally or subcutaneously, showed that liver retention was independent of the route of

administration for most of the congeners. Differences were observed for deposition in the adipose tissue, which was distinctly higher following i.p. administration. The adipose/liver concentration ratio between i.p. and s.c. application also was congener specific and increased with the number chlorine atoms. Within one group of isomers, this ratio was found to be lowest for the 2,3,7,8-substituted isomer(s).[54] The latter observation may be attributed to the higher liver affinities found for 2,3,7,8-substituted PCDDs and PCDFs.

2. Intramuscular (i.m.)

The i.m. route is not an efficient or recommended way to administer 2,3,7,8-TCDD to experimental animals. Three days after an i.m. dose of 0.42 μg/kg TCDD in toluene, 20 to 35% of the dose was still present at the application site. Moreover, toluene as a vehicle caused significant cell necrosis at the site of application, thus being obsolete from an ethical standpoint.[4]

3. Intravenous (i.v.)

Body distribution of the lower chlorinated PCDDs and PCDFs did not differ significantly between oral and i.v. administration. Comparative studies using single doses of 0.1 to 1.0 μmol/kg b.w. 2,3,7,8-TCDF or 2,3,4,7,8-PnCDF did not reveal any differences in distribution to liver and skin in the rat following oral or i.v. exposure.[31,49] Similar results have been obtained for the guinea pig after a single i.v. or oral dose of 0.02 μmol/kg 2,3,7,8-TCDF.[74] For the higher chlorinated congeners, there are indications that liver deposition may be higher after i.v. administration. After i.v. administration of a complex mixture of PCDDs and PCDFs, the liver deposition of 2,3,7,8-substituted hexachlorinated congeners were about twice as high compared with oral administration in oily vehicles.[355]

4. Subcutaneous

When using the s.c. route of exposure, the composition of the vehicle largely influences the uptake rate from the application site. This uptake is reduced by two factors: (1) the presence of an oily substance and (2) tissue irritation from the organic solvent. After testing a number of combinations between DMSO and toluene, a ratio of toluene-to-DMSO of 1:2 0.2 ml/kg b.w. was found to be the most suitable vehicle for 2,3,7,8-TCDD if the experimental design requires this route of application.[4,54] This route of administration was found to be an effective method for dosing rats with 2,3,7,8-TCDD, producing reproducible and complete absorption for pharmacokinetic studies. Three days after exposure, >90% was absorbed and distributed in the rat. At day 5, only 2% remained at the application site.[2] After s.c. administration of a defined mixture of PCDDs and PCDDs in a similar solvent to rats, the absorption from the application site appeared to be less efficient with increasing molecular size of the compounds. Seven days after application, only 5% of the 2,3,7,8-TCDD was still present at the site; in contrast, 16% of the OCDD remained.[6] These results differ from those of another study using 2,3,7,8-TCDD. After s.c. application, the uptake and distribution in rats was three to seven times slower when compared with the oral or i.p. route of administration.[170] The use of an extremely lipophilic vehicle (corn-to-oil acetone = 24:1 v/v) can explain the decreased uptake in this study. In Marmoset monkeys, uptake rate from the injection site is comparable with the rat. As in the rat, a decrease in uptake was observed with increasing molecular size. Retention at the injection site increased from 2.7 to 8.3% for tetra- to heptachlorinated congeners during a 7-day experiment.[5]

5. Percutaneous

Dermal permeation of PCDDs and PCDFs is very limited and at least in the rat was found to be dose and age related. Percutaneous application of 2,3,7,8-TCDD and 2,3,4,7,8-PnCDF showed clearly that transport through the skin was more effective in 10-week-old Fisher 344 rats than in rats of 36 or 96 weeks of age. Percutaneous uptake of both compounds was at least 50% less effective in the rats aged 36 weeks when compared with those of 10-week-old animals. No differences in skin absorption were found between

weeks 36 and 120. A decrease in blood flow through the skin between 3 and 4 months of age was suggested as a possible explanation for these age-related changes in skin absorption.[18] The dermal absorption of 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 1,2,3,7,8- and 2,3,4,7,8-PnCDF studied in Fischer F344 rats was found to be structure and dose dependent. The highest dermal absorption was observed for 2,3,7,8-TCDF, in which approximately 48% of the applied dose was absorbed. For each compound, the relative absorption (percentage of administered dose) declined with increasing dose, whereas the absolute amount entering the body (microgram per kilogram) increased nonlinearly with dose. In addition, at 3 days following exposure, >80% of the 2,3,7,8-TCDD could be removed from the application site using acetone-soaked cotton swabs. This indicates that the majority of the parent compound is associated with the epidermis and had not penetrated to the dermis.[50] In an additional study with rats, approximately 41% of a low dose of 200 pmol 2,3,7,8-TCDD was absorbed 120 h after dermal application.[19] In the Rhesus monkey, penetration through the skin also was found to be very ineffective; 6 h after dermal application of a single dose of 1,2,3,7,8-PnCDF, >99% was still present at the application site.[48] The degree of dermal absorption also is dependent on the physicochemical properties of the vehicle. This was observed after cutaneous administration of 2,3,7,8-TCDD to hairless rats using different vehicles. Application in vaseline reduced the dermal penetration by about 90%. In contrast, dermal uptake from a polyethylene glycol 1500 formulation was not different from that of a 50% ethanol solution.[269]

6. Gills

Uptake through the gills is considered strongly congener specific and was found to decrease with molecular size. In bioaccumulation studies using PCDDs having different numbers of chlorine substituents, a significant decrease in uptake rate constant was observed for rainbow trout and fathead minnow when comparing hexa- to octachlorinated PCDDs. For these compounds, it also was noted that uptake of different congeners is species specific.[210] The influence of molecular size on uptake and bioaccumulation in fish was recently reviewed.[246] It is proposed that an effective cross diameter >0.95 nm will impair permeation across the gill. Compounds that exceed this size include 1 and 4 substituted PCDDs and PCDFs, e.g., OCDD and OCDF. Uptake from the fish GI tract could depend less strongly on this critical size. With this hypothesis, the authors tried to explain the inconsistent results observed between fish experiments using exposure via food or water.

D. Role of (Environmental) Matrices

In general, PCDDs and PCDFs absorbed on sediment or combustion particles are less bioavailabe, depending on the composition of the matrix, in which its carbon content plays a major role. Extreme caution should be taken when enzyme-induction is used as the sole parameter for monitoring the bioavailability of PCDDs and PCDFs in soil. The presence of other compounds in contaminated soil also may contribute to elevated levels of CYP1A1-related activities, such as arylhydrocarbon hydroxylation (AHH) or 7-ethoxyresorufin-O-deethylation (EROD). Furthermore, AHH activity is not exclusively induced by CYP1A1 inducers. In addition, sufficient knowledge should be present about the dose-response curve in the species used. Target organ concentration will probably provide the most useful means for determining bioavailability.[342]

1. Soil

Exposure through contaminated sediment and soil is considered to be one of the more important environmental pathways through which these compounds enter the foodchain. Extensive field studies in contaminated areas have clearly illustrated that a positive correlation exists between PCDD and PCDF levels in animals and their soil contact.[40,118,119,179,402] Information about the bioavailability of PCDDs and PCDFs from contaminated sediment is virtually lacking. A study about CYP1A1 induction in carp combined with residue analysis indicates that sediment-bound

PCDDs and PCDFs are indeed bioavailable for fish.[363] The absorption in rats of 2,3,7,8-TCDD artificially added to soil has been estimated to be approximately 50% as efficient as the absorption of this compound from ethanol. The absorption efficiency decreased as the time of the 2,3,7,8-TCDD-soil contact increased. Similarly, the acnegenic stage in the rabbit ear test was significantly reduced when using soil-bound 2,3,7,8-TCDD.[269] Oral exposure of guinea pigs to two types of 2,3,7,8-TCDD-contaminated soil resulted in liver retention, which was about 10 to 15 times lower than that measured after an equivalent dose in corn oil. However, in rats, hepatic microsomal AHH induction was independent of whether equivalent doses of 2,3,7,8-TCDD were administered bound in soil or dissolved in corn oil.[190] Oral administration of three different 2,3,7,8-TCDD-contaminated soils from Missouri to rats indicated an average bioavailability of 43%. This bioavailability did not change significantly within a 500-fold dose range for soils contaminated with 2, 30, or 600 µg/kg 2,3,7,8-TCDD, respectively.[317] The authors suggest that an oral bioavailability of 25 to 50% would be a realistic value for use in risk assessments. However, bioavailability of 2,3,7,8-TCDD strongly depends on the type of soil, as indicated by studies with rats and guinea pigs. From New Jersey soil, the bioavailability of 2,3,7,8-TCDD was <2%, whereas TCDD from soil sprayed with 2,4,5-T was found to be approximately 30% bioavailable.[342,344] Such differences in bioavailability among soil types contaminated with 2,3,7,8-TCDD can be explained by a number of factors, which can be related to binding forces of the molecules to the soil constituents. These include composition of the soil, duration of the contact, and method of application. It was found that a correlation exists between bioavailability and solvent extractibility of 2,3,7,8-TCDD from soils.[318] Furthermore, there is evidence for a decreased extractibility with increasing contact time between soil and 2,3,7,8-TCDD, reflecting an increased binding strength caused by "aging" of the contaminated soil.[127,255]

Used as a marker, AHH induction activity in the rat liver indicated that 2,3,7,8-TCDD was "highly" bioavailable from soil, but exact values for the bioavailability were not established.[190] Based on this test principle, the bioavailability of TCDD from contaminated Missouri soil was estimated to be approximately 50% of that observed following administration in an oily vehicle.[181] Upon dermal exposure, the soil matrix influences (decreases) TCDD bioavailability to a significantly greater extent than after oral ingestion. The degree of transdermal uptake by rats of 2,3,7,8-TCDD from contaminated soil, determined 24 h after contact with the skin, was approximately 1% of the dose. A shorter contact time (6 h) resulted in a dermal penetration of about 0.6% of the dose. The concentration of TCDD in the soil (10 or 100 µg/kg) as well as the presence of engine oil as a co-contaminant did not affect the degree of uptake.[318] A study with guinea pigs suggested that increasing chlorination of PCDDs and PCDFs decreases their relative oral bioavailability from soil. However, these observations may depend on a number of parameters, such as different adsorption to particles, increase in molecular size, and decrease in solubility, eventually leading to less effective intestinal absorption. In addition, these studies were based on liver concentrations and did not take into account congener-specific differences in body distribution.[383] Toxicity studies with invertebrates, like two species of earthworms (*Allolobophora caliginosa* and *Lumbricus rubellus*) indicated that 2,3,7,8-TCDD also is readily bioavailable for these species.[292]

In summary, it is difficult to generalize results from laboratory studies with rodents about the bioavailability of these compounds when adsorbed on soil. A 25 to 50% oral bioavailability has been suggested for the tetra- to hexachlorinated congeners. However, this may include an overestimation of some types of soil, which have a high organic carbon content. Taking into account the role of molecular size, a 10% bioavailability for hepta- and octachlorinated congeners is appropriate. The bioavailability after dermal exposure is most likely around or below 1% for all congeners, which is a conservative estimate, especially for the higher chlorinated congeners.

2. Combustion Particles

For a number of rodent species (i.e., rat, hamster, and guinea pig), 3-month oral exposure studies with HCl-pretreated flyash from a municipal

incinerator indicated a significant but reduced bioavailability. Among the three species, no significant differences were observed for the bioavailability of PCDDs and PCDFs.[350,351] In a similar experiment with rats, using a single dosage of 2.5 g/kg flyash b.w., the tetra- to hexachlorinated congeners were approximately ten times less bioavailable (hepatic retention) than if administered in an oily vehicle. Pretreatment of the flyash to minimize alkaline influence did not change the bioavailability. For the congeners studied, an oral bioavailability of <5% was observed.[355] In a comparative study with rats using flue ash or flue ash extract from a municipal incinerator, it was found that the flue ash matrix reduced the oral bioavailability (hepatic retention) for all 2,3,7,8-substituted congeners by approximately a factor three. Hepatic retention decreased from 21% (2,3,4,7,8-PnCDF) to 1% (OCDD/OCDF) of the dose, depending on the degree of chlorine substitution and rate of metabolic conversion.[333] PCDDs and PCDFs adsorbed on flyash from municipal incinerators also are bioavailable for fish after oral uptake. This was shown in two studies using carp and flyash.[158–161] Although a reduction in bioavailability was observed, exact quantitative data could not be established as the relative contribution of both routes of exposure, gills and intestinal uptake, could not be discerned.[158] Based on the experimental conditions used, it was suggested that GI uptake might be the most important route of exposure in fish.[160] One study with goldfish reported the lack of uptake of PCDDs and PCDFs from flyash.[234] A possible explanation for these negative results may have been the high carbon content of the flyash and/or higher detection limits in the latter study.

Apart from oral uptake of particle-bound PCDDs and PCDFs present in the environment, transpulmonary uptake also was studied using gallium oxide particles contaminated with 2,3,7,8-TCDD. Hepatic cytochrome P450 content and AHH activity were only slightly less induced than after a similar oral dose of TCDD in corn oil. These results indicate that TCDD is taken up rather efficiently through inhalation. Unfortunately 2,3,7,8-TCDD tissue levels were not determined in this study, making quantification of the extent of transpulmonary absorption impossible.[225]

Summarizing the results of bioavailability studies with flyash and flue ash from municipal incinerators, it can be concluded that uptake from the GI tract is lower than that reported for contaminated soils. We suggest that a bioavailability of 5 to 20% for PCDDs and PCDFs on flyash or flue ash would be a realistic estimate, being conservative for the higher chlorinated congeners.

3. Carbon

The presence of carbon in environmental matrices is one of the major factors determining the bioavailability of these compounds. This has been clearly illustrated in studies using rodents or fish.[158,269] In rat, no significant uptake of 2,3,7,8-TCDD bound to activated carbon occurred after a single oral dose.[269] A study with carp showed an inverse relationship between the carbon content of flyash from a municipal incinerator and uptake of 2,3,7,8-TCDD.[158] Furthermore, addition of 1 to 5% activated charcoal to the diet resulted in a substantial decrease in the toxic effects of 2,3,7,8-TCDD or 2,3,4,7,8-PnCDF in rats, mice, and guinea pigs.[183,399] Two studies using 2,3,4,7,8-PnCDF and rats reported a two- to fourfold enhanced excretion of the parent compound in the presence of activated carbon.[139,399] This enhanced fecal excretion coincided with a faster elimination of this congener from the liver.[139] Although the mechanism behind this detoxification process has not been fully elucidated, activated carbon appears to stimulate the direct intestinal excretion of the parent compound, perhaps with involvement of enterohepatic circulation.[399]

III. TISSUE DISTRIBUTION

The tissue distribution in biota has been extensively studied in laboratory experiments using rodents and nonhuman primates. The liver and adipose tissue are the major storage sites of PCDDs and PCDFs for most mammalian species, whereas, depending on the species, the skin and adrenals also can act as primary sites for deposition. Table 2 summarizes the species- and congener-specific distribution of PCDDs and PCDFs in liver and adipose tissue following a single dose of a given radiolabeled congener. In Figures 2 and 3, the

TABLE 2
Liver and Adipose Tissue Distribution of 2,3,7,8-Substituted PCDDs and PCDFs in Several Laboratory Species

	Dose/timepoint	% Liver	Liver/adipose ratio	Ref.
Rat				
TCDD	50 μg/kg; p.o.; 1 day	55.6	10.5	11
TCDD	1 ng/kg; p.o.; 26 weeks	3.9	2.6	386
TCDD[a]	5 μg/kg; i.p.; 1 day	9.4	1.0	267
TCDD[b]	5 μg/kg; i.p.; 1 day	10.8	2.0	267
TCDF	0.1 μmol/kg; i.v.; 1 day	18.1	3.4	31
PnCDD	9 μg/kg; p.o.; 30 days	28.2	3.7	372
1-PnCDF	0.1 μmol/kg; i.v.; 3 days	9.5	2.8	49
4-PnCDF	1 mg/kg; p.o.; 1 day	38.6	3.3	398
4-PnCDF	0.1–1 μmol/kg; i.v.; 3 days	55.0	19.0	47
OCDD	50 μg/kg; p.o.; 3 days	8.4	36.6	37
OCDD	80 ng/kg; p.o.; 26 weeks	2.3	19.0	386
OCDF	80 ng/kg; p.o.; 26 weeks	2.6	39.0	386
C57BL/6J mice				
TCDD	10 μg/kg; i.p.; 3 days	14.1	2.5	97
TCDD	0.5 μg/kg; p.o.; 1 day	28.2	1.4	34
TCDF	0.1 μmol/kg; i.v.; 1 day	35.8	2.3	75
DBA/2J mice				
TCDD	10 μg/kg; i.p.; 3 days	7.2	0.9	97
TCDF	0.1 μmol/kg; i.v.; 1 day	26.1	1.0	75
TCDD	0.5 μg/kg; p.o.; 1 day	20.6	1.0	34
B6D2F1/J mice				
TCDD	10 μg/kg; i.p.; 3 days	24.5	4.4	97
Syrian Golden hamster				
TCDD	650 μg/kg; p.o.; 1 day	12.7	1.4	239
Guinea pig				
TCDD	0.56 μg/kg; i.p.; 45 days	7.1	0.2	241
TCDD	2.0 μg/kg; i.p.; 1 day	11.4	0.2	96
TCDF	0.02 μmol/kg; i.v.; 1 day	15.4	0.7	74
TCDF	7 × 0.003 nmol/kg; p.o.; 49 days	39.7	1.4	74
Rhesus monkey				
TCDF	0.1 μmol/kg; i.v.; 21 days	1.0	1.0	32
4-PnCDF	0.1 μmol/kg; i.v.; 40 days	29.5	NA	48
Rainbow trout				
TCDD	0.5 μg/kg; in diet; 13 weeks	5.0	21.8	146
4-PnCDF	9 μg/kg; p.o.; 31 days	4.8	NA	213
Yellow Perch				
TCDD	0.5 μg/kg; in diet; 13 weeks	9.0	0.2	147
Carp				
4-PnCDF	7 × 0.26 μg/kg; p.o.; 7 days	2.1	NA	363
123678-HxCDF	7 × 0.15 μg/kg; p.o.; 7 days	3.8	NA	363

Note: NA = not available.

[a] Long-Evans strain.
[b] Han/Wistar strain.

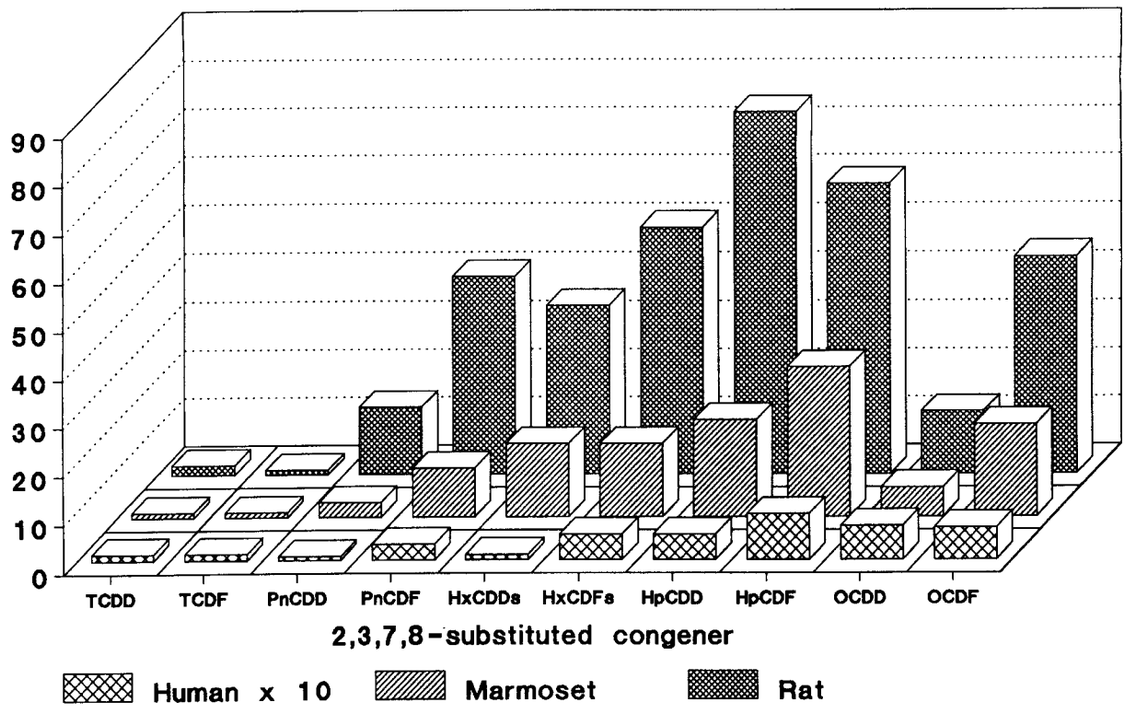


FIGURE 2. The liver-to-adipose tissue ratios for 2,3,7,8-substituted PCDDs and PCDFs in humans, Marmoset monkeys, and rats.[6,226,335]

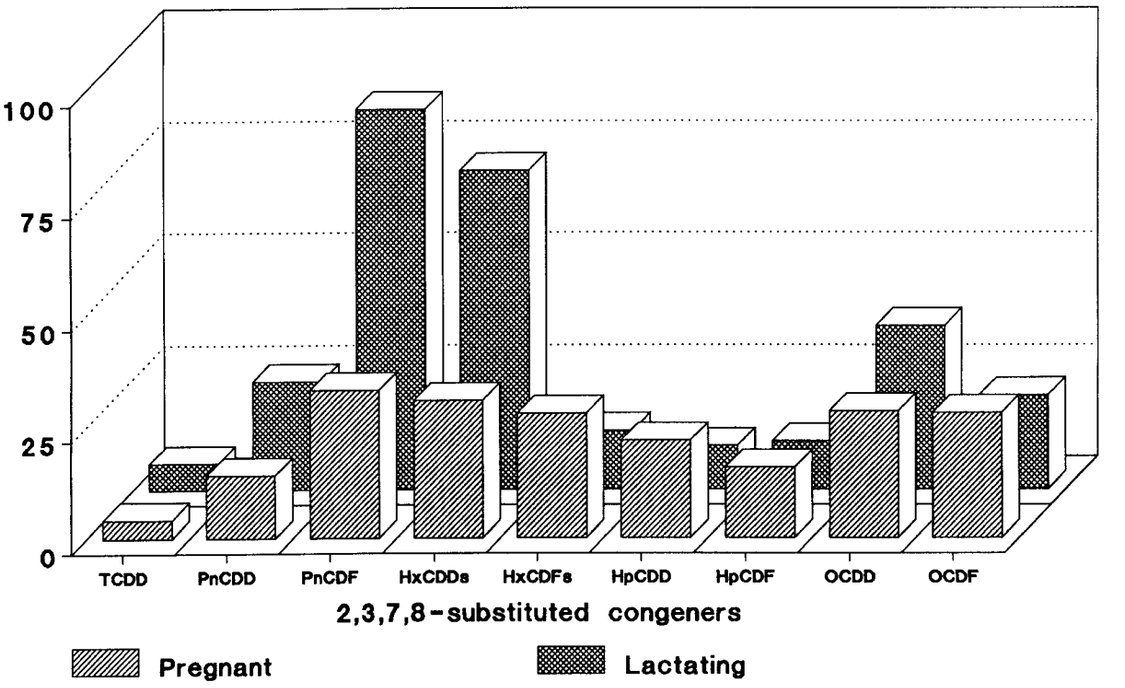


FIGURE 3. Influence of pregnancy and lactation on the liver-to-adipose tissue ratios of 2,3,7,8- substituted PCDDs and PCDFs in rat.[356]

liver-to-adipose tissue ratios for PCDDs and PCDFs are shown for rats, Marmoset monkeys, and humans. The most toxic tetra- and pentachlorinated congeners have now been studied quite extensively in at least two mammalian species, but information is limited for most of the higher chlorinated 2,3,7,8-substituted PCDDs and PCDFs. The limited information about the tissue distribution of PCDDs and PCDFs in fish indicates that the distribution of these compounds in fish differs significantly from that in mammals. Although extensive information is available on the levels of PCDDs and PCDFs in environmental biota, including humans, these data are only of limited use for describing the tissue distribution in a given species. However, these data show that the liver and adipose tissue are major storage sites for mammalian and avian species. In fish, these compounds are associated predominantly with muscle and adipose tissue.

A. Mammals

1. General

Several studies with rats, mice, hamsters, guinea pigs, and monkeys reported that the 2,3,7,8-substituted PCDDs and PCDFs are the predominant congeners retained in tissue and body fluids.[6,9,165,348] This preferential tissue retention already is evident within 24 h after administration of a complex mixture of congeners.[352,357] Minor tissue retention of some non-2,3,7,8-substituted congeners also has been reported.[6] However, in view of the very low toxicity of the non-2,3,7,8-substituted congeners, this should be considered as not toxicologically significant. In addition, these non-2,3,7,8-substituted congeners have seldom been reported to be present in environmental biotic samples, again indicating their low potential for tissue retention and accumulation.[82,233,248,286–288,299] The tissue deposition of PCDFs in the guinea pig is different from that in the rat, mouse, and hamster because some non-2,3,7,8-substituted congeners are retained in this species.[9,351] In all other rodents, substantial tissue retention of the non-2,3,7,8-substituted PCDFs, like 2,3,4,6,7-PnCDF, is rarely reported.[6,226,352,357] Apart from these differences between species, the tissue deposition of these compounds is congener specific and depends on the dose as well as the route of administration.[2,50,54,318,352]

2. Distribution in Blood and Lymph

Once a compound is absorbed from the GI tract, its body distribution is initially determined by its binding capacities to blood components and its ability to permeate across tissue membranes. Studies using thoracic duct cannulated rats indicated that transport of 2,3,7,8-TCDD was primarily via the lymphatic route and was predominantly associated with chylomicrons.[170] A number of studies have focused on the distribution of PCDDs and PCDFs between blood and adipose tissue.[120,252,253,312] Related to lipid content, the serum-to-adipose tissue ratio for 2,3,7,8-TCDD was approximately 1:1. This correlation was observed over a concentration range of almost three orders of magnitude.[252] In blood, <10% of 2,3,7,8-TCDD was associated with red blood cells, indicating that most of this compound is bound to serum lipids and lipoproteins.[252] However, the distribution ratio between plasma lipid and adipose tissue for PCDDs and PCDFs increased with chlorine substitution, indicating an increased binding affinity to plasma proteins for the higher chlorinated congeners (see Figure 4).[252,312] Congener-specific differences also have been observed for *in vivo* binding of the 2,3,7,8-substituted PCDDs and PCDFs to different serum fractions in the blood. Binding to the lipoproteins gradually decreased with increasing chlorine content, with about 75% of 2,3,7,8-TCDD bound to lipoproteins, whereas approximately 45% of OCDD was bound to this fraction. In contrast, binding to other proteins increased with chlorine content, from approximately 20% for 2,3,7,8-TCDD to 50% for OCDD. Considerably fewer PCDDs and PCDFs were bound to the chylomicrons in serum, with <10% bound to this serum fraction.[252] This change in the distribution ratio of PCDDs and PCDFs among blood proteins, lipoproteins, and chylomicrons is illustrated in Figure 5. In general, these *in vivo* results indicate that in serum, the higher chlorinated congeners do not partition according to the lipid content of the fractions. The strong association of PCDDs and PCDFs with

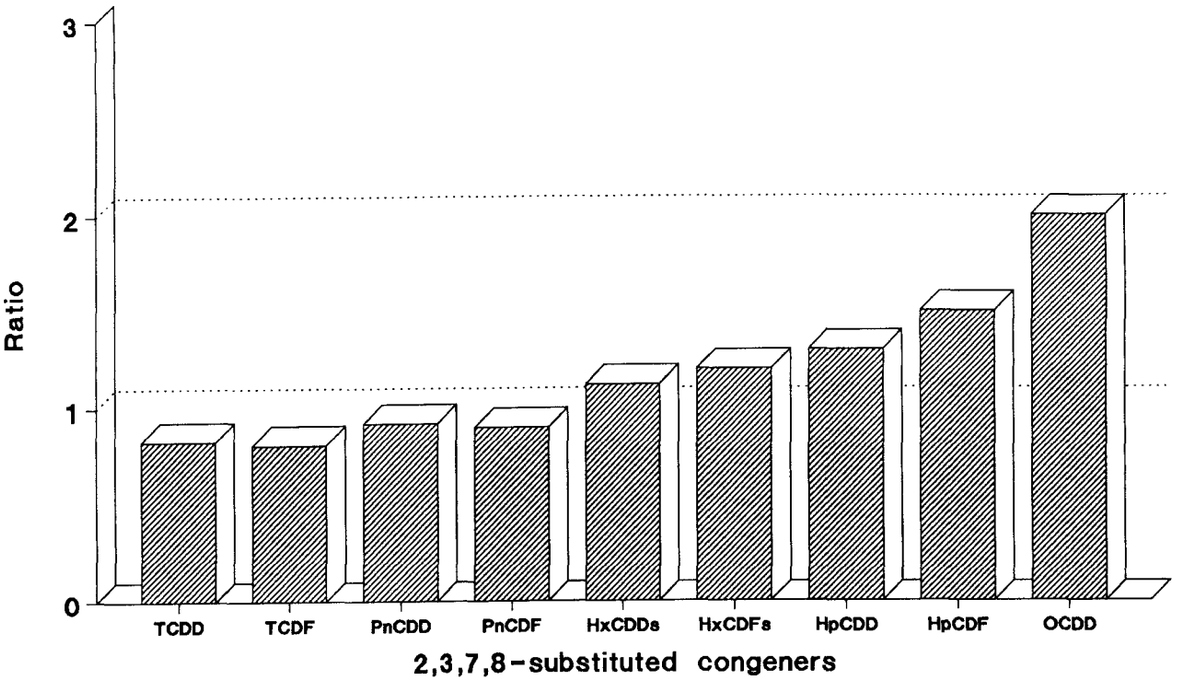


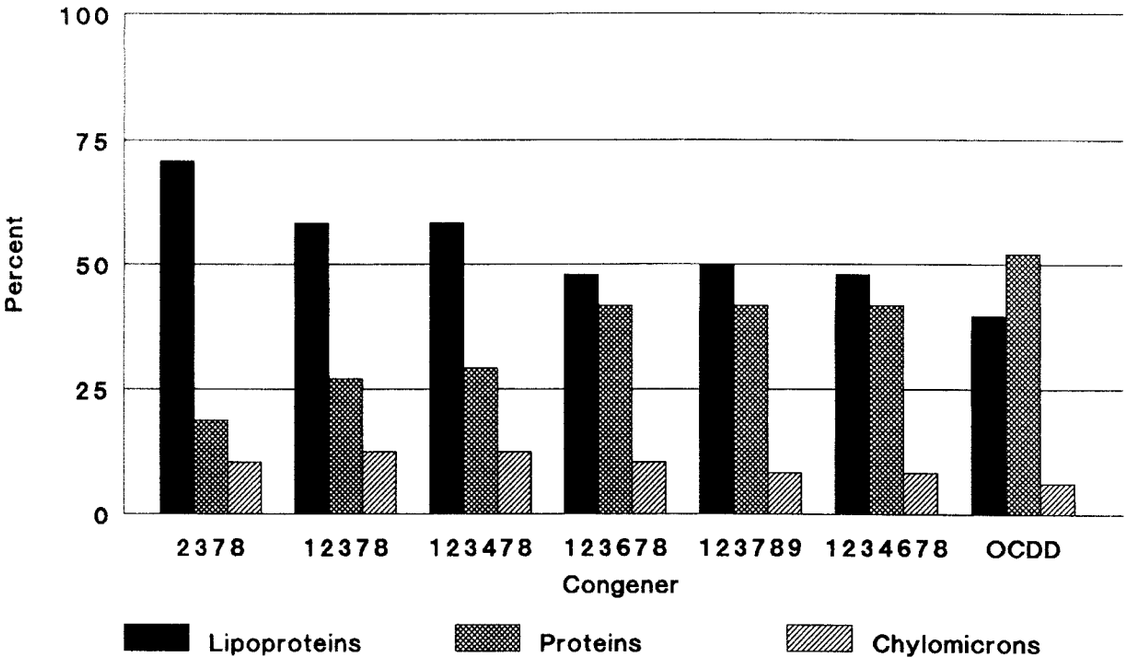
FIGURE 4. Ratio between human plasma lipids and adipose tissue for 2,3,7,8- substituted PCDDs and PCDFs.[312]

lipoproteins and proteins in blood also has been observed using *in vitro* studies with human whole blood. It was observed that 80% of the applied amount of 2,3,7,8-TCDD was associated with lipoproteins, 15% with proteins (primarily serum albumin), and 5% with cellular components.[120] In addition, there are some (limited) theoretical and experimental indications that 2,3,7,8-TCDD and related isostereomers may be associated with plasma prealbumin.[193,254] Binding studies suggest that, within the lipoprotein fraction, 2,3,7,8-TCDD exerts the highest binding affinity per mole of lipoprotein for VLDL, followed by LDL and HDL.[184] This association of 2,3,7,8-TCDD with (V)LDL also was confirmed in a study using cultured human fibroblasts. In this study, some evidence was provided that specific binding to LDL and the LDL receptor pathway may account for some of the rapid early uptake of 2,3,7,8-TCDD with LDL entry.[316] Thus, upon absorption, 2,3,7,8-substituted PCDDs and PCDFs are bound to chylomicrons, lipoproteins, and other serum proteins, followed by vascular transport. Besides passive diffusion, cellular uptake may partly be facilitated through the cell membrane LDL receptor, the hepatic receptor for albumin, and/or other systems.[382]

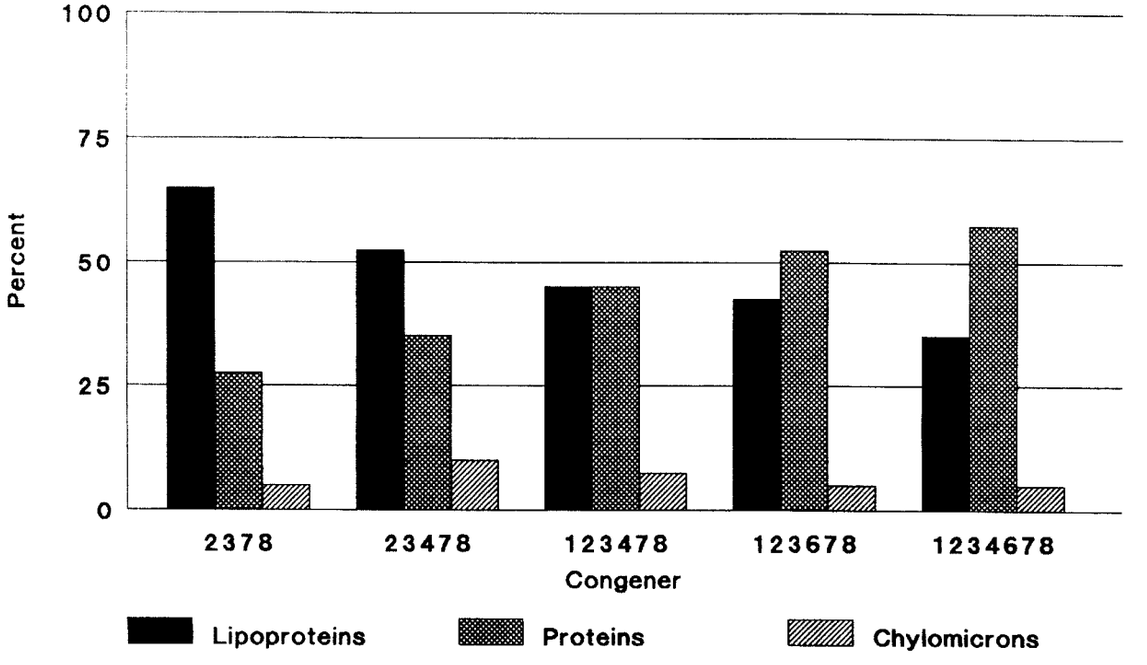
3. Major Storage Sites

a. Rat

Tissue distribution within the first 24 h after exposure to PCDD and PCDF is directly dependent on physiological parameters, such as blood perfusion rate of a given tissue and relative tissue size. As a result, high initial concentrations have been observed in the adrenal glands and muscle tissue.[31,49,239,267] After the initial distribution following single or repeated oral administration of 2 ng to 50 μg/kg 2,3,7,8-TCDD, all investigations reported that the liver and adipose tissue were the major storage depots in the rat. One day after exposure, 40 to 70% of a 2,3,7,8-TCDD dose is usually retained in the liver.[11,170,295,318] Tissues with the second highest 2,3,7,8-TCDD concentration include the skin (<10% of the dose), the intestines (<10%), and the adrenals (<1%).[11] In the rat liver, retention of 2,3,7,8-TCDD was found to be dose dependent. Seven days after a single s.c. dose, ranging from 1 ng to 3 μg/kg 2,3,7,8-TCDD, an up to fivefold increase in hepatic retention could be observed with increasing dose (see Figure 6).[2] A similar dose dependency was observed after



A



B

FIGURE 5. The *in vivo* distribution of 2,3,7,8 substituted PCDDs and PCDFs in human serum fractions:[252] (A) dioxins (CDC method); (B) furans (CDC method).

oral administration of 2 ng to 1.1 μg/kg 2,3,7,8-TCDD, resulting in a maximal increase of liver retention of about 100% after 24 h.[318]

The relative body distribution of 2,3,7,8-TCDF was not significantly different from that of 2,3,7,8-TCDD. One day after a single i.v. or p.o. dose of 0.1 μmol/kg 2,3,7,8-TCDF, deposition to liver and adipose tissue was found to be comparable, with 18 and 14% of the dose, respectively, distributed to these tissues. Muscle and skin contained approximately 2.5% of the dose at this time, whereas blood and other tissues each contained not more than 0.5% of the dose.[31] For most of the 2,3,7,8-substituted penta- to octachlorinated congeners, the relative liver retention tended to be higher than that observed for 2,3,7,8-TCDD and TCDF. For these congeners, e.g., 2,3,4,7,8-PnCDF and 1,2,3,6,7,8-HxCDD, liver retention ranged from 40 to over 90% of the dose several days after administration (see Table 2).[6,47,151,358,372,385,398,399] Studies using complex mixtures of PCDDs and PCDFs also reported high hepatic retention of 2,3,7,8-substituted penta- and hexachlorinated congeners, similar to that found in single compound studies.[6,352,356,367] Less than 10% of a single dose of 0.1 to 1 μmol/kg 2,3,4,7,8-PnCDF was stored in the adipose tissue of rats, whereas skin and muscle contained even less than 1% 3 days after administration.[47] Due to this increasing liver deposition, the distribution ratio between liver and adipose tissue progressively increased with increasing degree of chlorination (see Table 2 and Figure 2). Although its molecular size and limited solubility reduced the uptake of OCDD from the GI tract, its relative tissue distribution was not significantly different from that of other PCDDs and PCDFs. Three days after an i.v. dose of 50 μg/kg OCDD, the relative tissue distribution expressed as percentage of the dose was as follows: liver (74.7%) > adipose (6.0%) > skin (4.5%). A dose-dependent decrease in liver retention from 8.4 to 0.4% of the total dose was observed for oral doses ranging from 50 to 5000 μg/kg OCDD, which is in contrast with the results obtained for

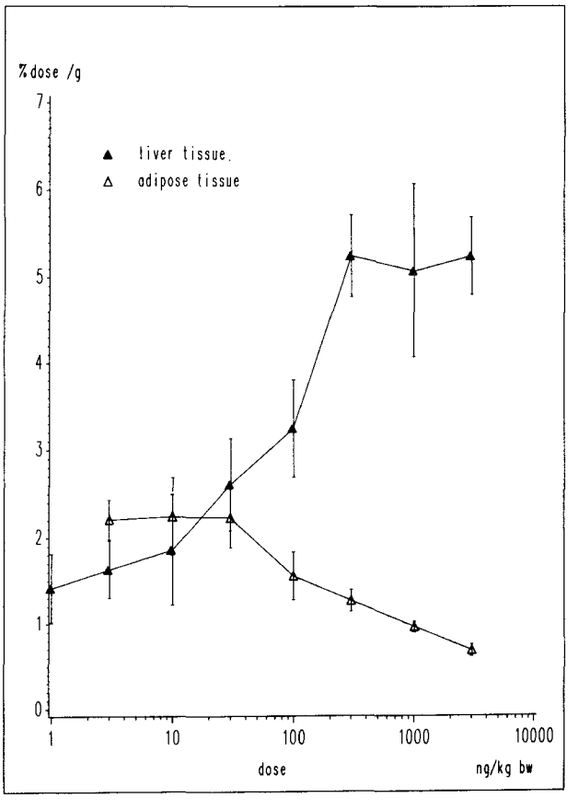


FIGURE 6. Dose-dependent distribution of 2,3,7,8- TCDD in rat liver and adipose tissue.[2]

2,3,7,8-TCDD after s.c. doses.[2,37] This phenomenon may be explained by a decreasing intestinal uptake of OCDD with increasing oral dose due to its molecular size and limited solubility, whereas 2,3,7,8-TCDD uptake after s.c. administration is, of course, not dose dependent. The distribution of heptachlorinated congeners and OCDF were reported to be similar to that of OCDD.[352,356] Although the liver-to-adipose tissue distribution ratio can be used to describe some of the toxicokinetics of these compounds in a given species (see Table 2 and Figures 2 and 3), it should be realized that this ratio is dependent not only on the congener, but also on the dose, the metabolic conversion rate, route of administration, and the observed timepoint after administration. For example, increasing a single s.c. dose from 3 to 3000 ng/kg 2,3,7,8-TCDD changed this ratio from 0.7 to 7.7.[2] It is unclear whether this dose dependency of the liver-to-adipose tissue distribution ratio also may be found for other modes of exposure. Both 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF are rapidly metabolized in the rat liver, but the elimination from the adipose tissue is not as fast as that from the liver.[31,49,357,358] As a result, the liver-to-adipose tissue distribution ratio changed from 14 to 1 within 3 days after an i.v. dose of 0.1 μmol/kg 1,2,3,7,8-PnCDF.[49] The influence of the route of administration on the liver-to-adipose tissue ratio was shown in comparative experiments using i.p. and s.c. methods. Intraperitoneal administration resulted in a much higher distribution to adipose tissue, which increased with degree of chlorination.[54] On the other hand, experiments using percutaneous, i.v., or oral application did not show a significantly altered tissue distribution of 2,3,7,8-TCDD, 2,3,7,8-TCDF, or 2,3,4,7,8-PnCDF.[19,31]

b. Mouse

As in the rat, the major storage sites for 2,3,7,8-substituted PCDDs and PCDFs in mice are the liver and adipose tissue, with other types of tissue usually having concentrations one order of magnitude lower.[34,75,97,205] Liver and adipose tissue distributions of 2,3,7,8-TCDD and 2,3,7,8-TCDF, including strain-related differences, are given in Table 2. In addition to the selective deposition in liver and adipose tissue, whole body autoradiography showed that the nasal olfactory mucosa also was a major site of localization of 2,3,7,8-TCDD in mice.[12,103] In accordance with studies in the rat, the penta- and hexachlorinated congeners exhibit a higher liver deposition than 2,3,7,8-TCDD and TCDF (see Figure 7). Apart from the preferential retention of the 2,3,7,8-substituted congeners, liver deposition of some pseudo-lateral PCDFs, 2,3,6,7- and 2,3,4,6,7-PnCDF, has been reported in C57BL/6J and DBA/2J mice.[360] In hairless mice, the skin is not a major storage site for 2,3,7,8-TCDD, with only 2.5% of an i.p. dose stored in the epidermis and dermis 1 day after dosage. Most of this compound was retained in the dermis, but epidermal levels were considerably higher in the newborn mouse.[282] Several studies have focused on the possible role of the Ah-receptor in the toxicokinetics of PCDDs and PCDFs in mice. The influence of this receptor protein was studied by using mice strains that were either Ah^+ or Ah-receptor responsive.[34,75,97] For the adipose tissue, skin, kidney, and total body concentration, it can be concluded that the Ah-locus and receptor protein do not play a significant role in body distribution.[34] Regarding the role of the Ah-receptor in liver retention, most studies have concluded that it plays some role.[34,97,276] In general, in the livers of the Ah-responsive strain C57BL/6J, 25 to 50% more 2,3,7,8-TCDD or 2,3,7,8-TCDF was retained than in the Ah-nonresponsive DBA/2J strain.[34,75,97,276] In contrast to these studies, liver retention was not found to be different for both strains of mice, using high doses of complex mixtures of these compounds (see Figure 7).[360] It can be postulated that the differences between Ah^+ and Ah^- mice strains are in part dependent on the inducibility of cytochrome P450,[175] rather than on differences in relative adipose tissue content.[97] In view of this suggestion, it should be noted that especially CYP1A2 has strong binding affinitites for 2,3,7,8-substituted congeners.[166,371,398] Because the DBA strain requires a 10 times higher dose for this type of enzyme induction,[276] the Ah-receptor may play an indirect role in liver deposition by facilitating the synthesis of CYP1A2 in the more highly induced C57BL/6J strain at lower dose levels.[224] This hypothesis is supported by results from a study using 2,3,7,8-TCDD pretreatment in C57BL/6J

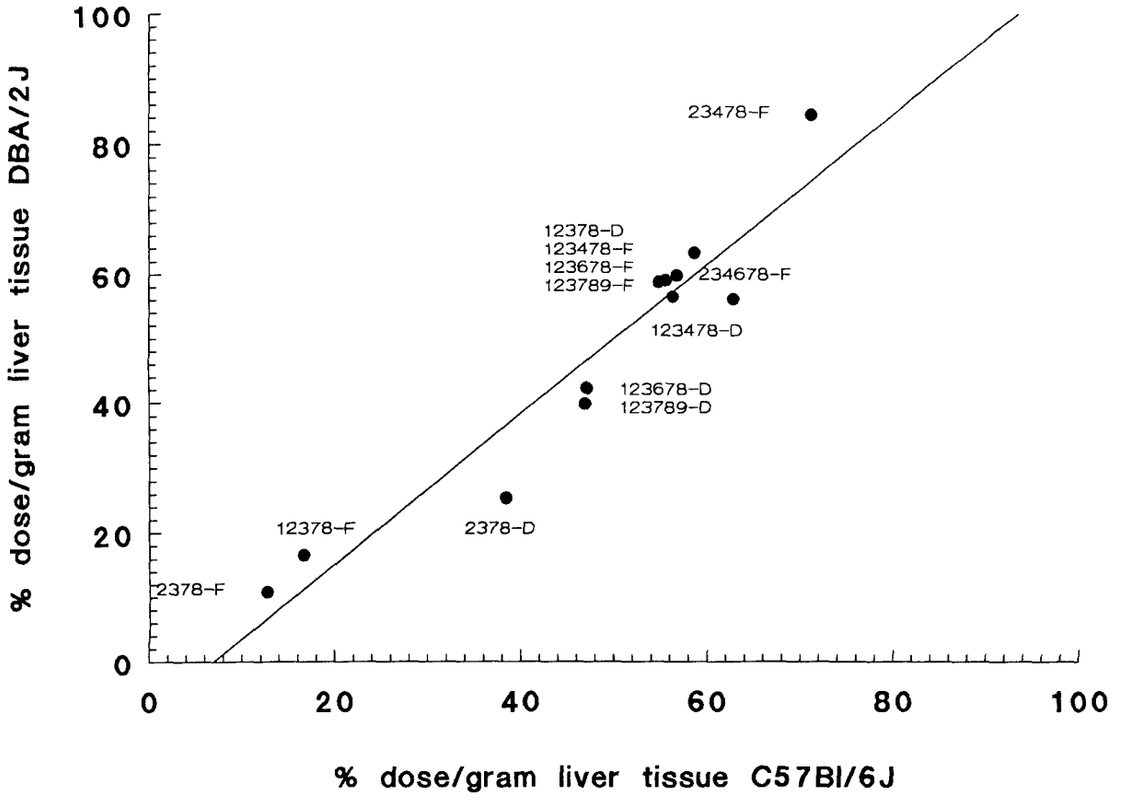


FIGURE 7. Ratio in hepatic retention between C57BL/6J (Ah-responsive) and DBA/2J (Ah-nonresponsive) mice for a number of PCDDs and PCDFs.[360]

mice, which increased by 50% liver deposition of a subsequent dose of radiolabeled 2,3,7,8-TCDD. This observed increase in hepatic retention could not be explained by alterations in absorption, hepatic lipid content, or change in metabolism.[69]

4. Hamster

Body distribution of 2,3,7,8-TCDD in the hamster does not differ significantly from that of rats and mice. However, the adrenals also appear to be a major storage site. After a single p.o. dose of 650 μg/kg 2,3,7,8-TCDD, the relative concentration in different tissues was as follows: liver > adipose tissue > adrenals.[239] The liver deposition of the higher chlorinated 2,3,7,8-substituted PCDDs and PCDFs is congener specific, with the highest retentions again being found for the penta- and hexachlorinated congeners, ranging up to 70% for 2,3,4,7,8-PnCDF at 2 days following exposure.[352]

d. Guinea Pig

With respect to the tissue distribution of 2,3,7,8-TCDD, the guinea pig appears to be similar to the rodent species discussed earlier. Major storage sites are the liver and adipose tissues (data are shown in Table 2).[96,241] Compared to rats, mice, and hamsters, the elimination from guinea pig liver and adipose tissue proceeds more slowly. As a result, >40% of a single dose was still present in the body after 45 days. In addition, high concentrations also were found in the skin and skeletal muscle tissues, each containing 7% of the dose.[241] The body distribution of 2,3,7,8-TCDF in the guinea pig was studied in a single as well as in a multiple-dose experiment. The major tissue depots were comparable with those for 2,3,7,8-TCDD, irrespective of the dose regime. One day after exposure, the hepatic deposition of 2,3,7,8-TCDF was comparable with that of 2,3,7,8-TCDD.[74] This is in contrast with other rodent species (e.g., the rat), which metabolize and elimi-

nate 2,3,7,8-TCDF more rapidly.[31] In contrast to other rodent species, guinea pigs retain some of the PCDFs that are not exclusively 2,3,7,8-substituted. These PCDFs lack two unsubstituted carbon atoms or have adjacent chlorine atoms on the 3 and 4 (6 and 7) positions.[9,351]

e. Monkey

As in rodent species, adipose tissue, skin, and liver are the primary storage sites for the deposition of 2,3,7,8-substituted PCDDs and PCDFs in monkeys. Correspondingly, lower concentrations have been detected in kidney, brain, lung, heart, thymus, and testes. For non-human primates, the liver appears to be a less significant storage site than for rodents. As a result, the liver-to-adipose tissue ratio is significantly lower than observed for the rat. These differences are illustrated in Figure 2. Seven days after a single i.p. dose of 400 μg/kg 2,3,7,8-TCDD to adult and infant Rhesus monkeys, only 10% of this compound was retained in the liver, whereas under similar experimental conditions, 40% was retained in the liver of the rat. In the Rhesus monkey, relatively higher levels were retained in adipose, skin, and muscle tissue than in the rat.[365]

An i.v. dose of 31 μg/kg 2,3,7,8-TCDF exhibited a comparable body distribution in the Rhesus monkey as 2,3,7,8-TCDD did, with skin and adipose tissue remaining major storage sites at 21 days after exposure.[32] Studies in Rhesus monkeys with PCDFs indicate that these compounds, including 2,3,4,7,8-PnCDF, do not exhibit a higher affinity for the liver than 2,3,7,8-TCDD.[48,165] This is in contrast with results from studies with rats.[47,352] At 32 days after a single dose of a complex mixture of PCDFs, only 1 to 5% of the administered 2,3,4,7,8-PnCDF was retained in the liver. Other toxic congeners, like 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF, showed even lower retention in the liver (i.e., <0.2% of the dose).[165] These differences are most likely caused by congener-specific differences in elimination.[32,365] Similar results were obtained after a single i.v. dose of 34 μg/kg 2,3,4,7,8-PnCDF to Rhesus monkeys, in which approximately 10% of the dose was retained in the liver after 40 days.[48] The Marmoset monkey is another non-human primate that has been the subject of some toxicokinetic studies. One week after s.c. administration of a mixture of PCDDs and PCDFs, it was found that liver deposition ranged from 25 to 74% for tetra- to hexachlorinated congeners but again decreased with further increasing molecular size for the hepta- and octachlorinated congeners.[226] In terms of absolute liver retention, the Marmoset monkey was found to be quite similar to the rat for a large number of congeners.[6] The liver-to-adipose tissue distribution ratio, ranging from 1 to more than 10, increased with degree of chlorination (see Figure 2), thus indicating a preferential liver deposition for the higher chlorinated congeners. Apart from the preferential tissue retention of 2,3,7,8-substituted congeners, minor amounts (<5% of the dose) of other congeners also were detected in the adipose tissue.[226] The differences in the liver-to-adipose tissue ratio between this primate species and the rat were suggested to be caused by the low adipose content in the marmoset strain used, combined with a greater genetic variation among primates in general.[5]

f. Human

During the last decade, numerous studies have been done on the distribution and levels of PCDDs and PCDFs in human liver, adipose tissue, milk, and blood. Some of these studies were related to the exposures that occurred after industrial accidents, e.g., the Seveso incident, or after ingestion of contaminated food.[163,167,291,293] Other studies were directed to the background levels of these compounds in humans, particularly in human milk.[26,27,92–94,133,299,330,334,335,353,391,392] Although levels and trends have now been fairly well established for most industrialized countries, most of these data are of limited use for the elevation of toxicokinetics in man. However, these data do give quite reliable information about the background levels of PCDDs and PCDFs in humans. These human data have recently been evaluated for global background levels and risk assessment for the breastfed infant, but these subjects are beyond the scope of this review and the reader is referred to the appropriate literature.[143,391,392] This review gives only a brief outline of the qualitative and quantitative aspects of PCDD and PCDF levels in humans.

Humans exclusively retain the 2,3,7,8-substituted PCDDs and PCDFs in liver. This is based on adipose tissue, milk, and blood analysis.[93,164,167,287,353] Although non-2,3,7,8-substituted PCDFs have been reported in human tissues, e.g., Yusho patients, it has been shown that these compounds were artifacts originating from the alkaline treatment.[302] Quantitatively large variations can be found among individuals, depending on the congener. One study evaluated 2,3,7,8-TCDD concentrations in adipose tissue from U.S. citizens and concluded that levels are log-normally distributed and positively correlated with age.[319] The congeners found in human milk, adipose tissue, and blood, including an approximate range of global averages with maximum and minimum concentrations, are given in Table 3. Qualitatively and quantitatively there are striking similarities between PCDD and PCDF levels in adipose tissue and milk, when expressed on a lipid content basis. Based on the recent studies from the World Health Organization, the global data from human milk will be used to describe the worldwide congener-specific distribution of these compounds in humans.[391,392] Although local sources of contamination might influence the typical congener profile,[310] the background pattern is remarkably similar in most areas of the world. Figure 8 shows the congeneric patterns in human milk from Europe, North America, Asia, and the Pacific.[391,392] For reasons of clarity, OCDD and OCDF have been omitted from these figures. However, OCDD is a major congener present in human tissues and body fluids with levels up to 3000 pg/g. From the HpCDDs, only the 1,2,3,4,6,7,8 isomer is present in a range of 10 to 120 pg/g fat. From the lower chlorinated PCDD congeners, only 1,2,3,6,7,8-HxCDD is present at levels above 100 pg/g, and concentrations of the other two toxic HxCDDs are much lower. Concentrations of 1,2,3,7,8-PnCDD are generally far below 30 pg/g, whereas background levels of 2,3,7,8-TCDD do not exceed 7 pg/g.[133,391,392] An exception was found for the levels of 2,3,7,8-TCDD in South Vietnam, which were well above 10 pg/g, and approximately 5 to 10 times higher than in neighboring countries.[310]

The congener-specific distribution pattern of PCDFs is slightly more complex but, as with PCDDs, a general global pattern can be recognized (see Figure 8). Compared to OCDD, OCDF is only a minor component with levels not exceeding 8 pg/g. Only one HpCDF isomer, 1,2,3,4,6,7,8-HpCDF, is found at slightly higher concentrations than OCDF,

TABLE 3
Maximum and Minimum Average Concentration (ng/kg Lipid) Reported for Human Milk, Adipose Tissue, and Blood[133,250]

	Milk		Adipose tissue		Blood	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
2,3,7,8-TCDD	1	10	<2	28	<2	9
2,3,7,8-TCDF	<0.5	8	<2	9	—	—
1,2,3,7,8-PnCDD	1	18	4	32	6	39
1,2,3,7,8-PnCDF	<0.5	4	—	—		
2,3,4,7,8-PnCDF	2	36	—	—		
Sum 2,3,7,8-PnCDFs	—	—	10	54	18	82
1,2,3,4,7,8-HxCDD	1	13	—	—		
1,2,3,6,7,8-HxCDD	3	8	—	—		
1,2,3,7,8,9-HxCDD	1	12	—	—		
Sum 2,3,7,8-HxCDDs	—	—	11	111	52	100
1,2,3,4,7,8-HxCDF	1	35	—	—		
1,2,3,6,7,8-HxCDF	1	29	—	—		
1,2,3,7,8,9-HxCDF	1	3	—	—		
2,3,4,6,7,8-HxCDF	<0.5	7	—	—		
Sum 2,3,7,8-HxCDFs	—	—	13	68	16	69
1,2,3,4,6,7,8-HpCDD	28	121	29	264	30	142
1,2,3,4,6,7,8-HpCDF	2	35	7	42	16	35
OCDD	28	1300	104	1360	439	889
OCDF	<0.5	18	1	60	—	—

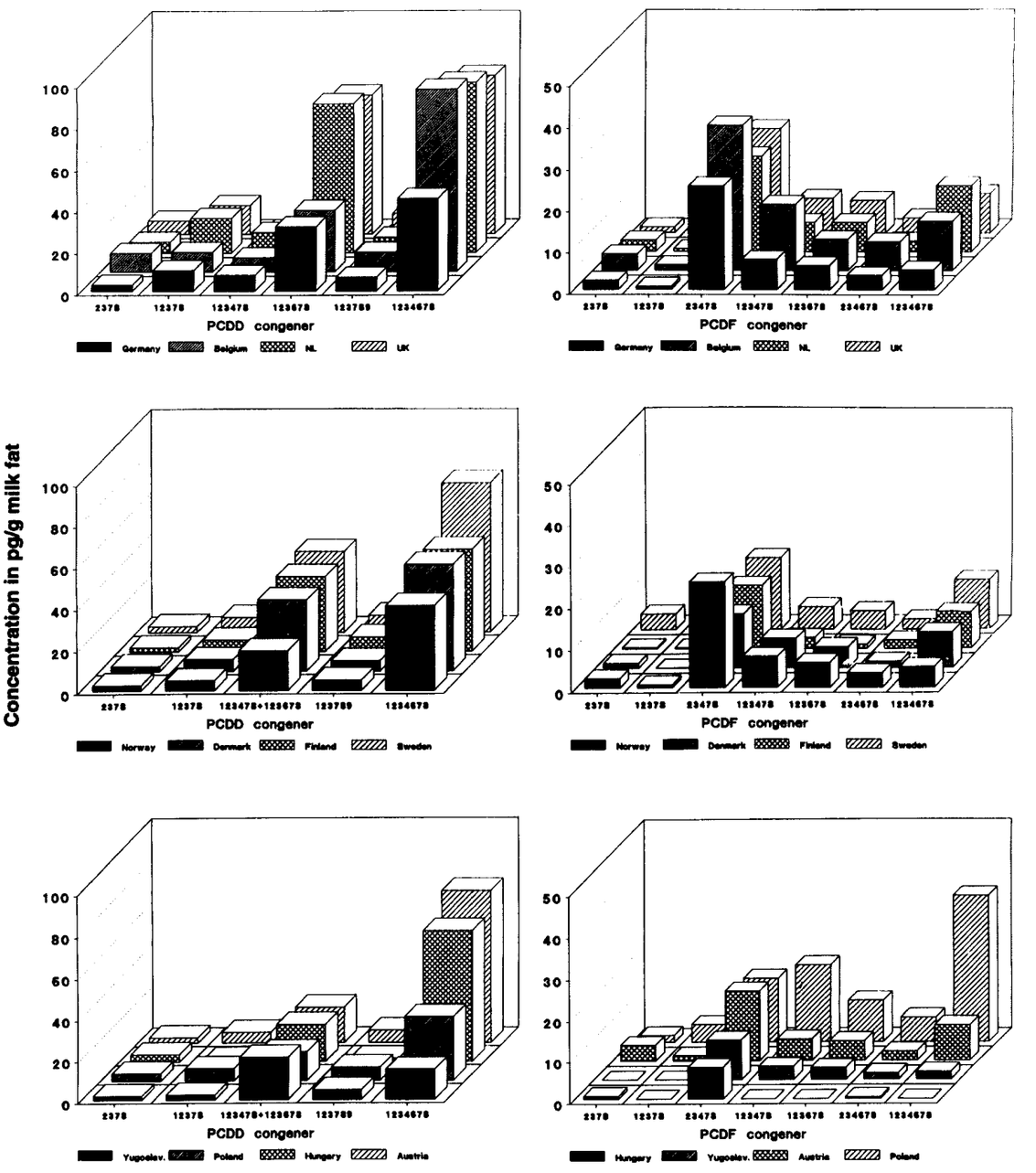


FIGURE 8. Global congener-specific distribution and concentrations of 2,3,7,8-substituted PCDDs and PCDFs in human milk:[392] (A) western Europe (top), northern Europe (middle), central Europe (bottom); (B) North America (top), the Pacific (middle), southeast Asia (bottom).

with maximum levels found between 10 and 20 pg/g. From the lower chlorinated PCDFs, 2,3,4,7,8-PnCDF is by far the congener with the highest concentrations; maxima can be found at around 50 pg/g. Only three toxic HxCDFs have been observed and their relative abundance is 1,2,3,4,7,8-HxCDF > 1,2,3,6,7,8-HxCDF >> 2,3,4,6,7,8-HxCDF, with total concentrations not exceeding 50 pg/g. Two PCDF congeners, 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF, have been observed at low levels ranging from 1 to 5 pg/g. In view of the quantitatively high levels of 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF in commercial PCB formulations,[349] these low levels in human tissues and body fluids may be attributed to

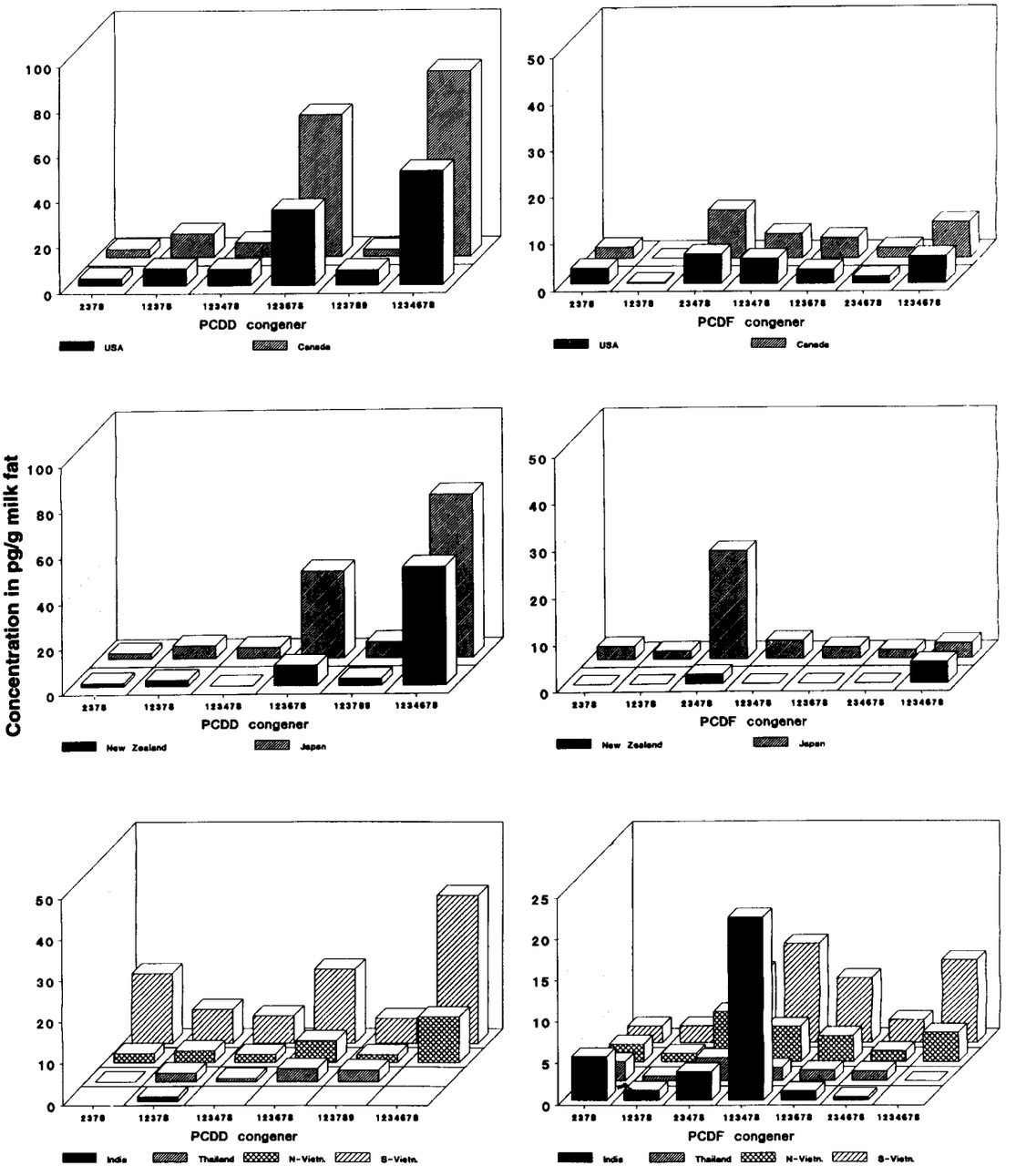


FIGURE 8B.

a rapid metabolism and elimination of both congeners similar to that found in experimental animal studies.[31,49,75,357,358] Two other 2,3,7,8-substituted PCDFs, 1,2,3,7,8,9-HxCDF and 1,2,3,4,7,8,9-HpCDF, are usually not reported, or are detected only at extremely low levels (<0.5 pg/g) in human milk. Their absence also is observed in other environmental biotic samples.[288] It is possible that the absence of these two PCDF congeners has a toxicokinetic basis. Studies with rodents have reported that 1,2,3,7,8,9-HxCDF was eliminated relatively rapidly. However, it may well be a reflection of the fact that both congeners are not readily formed in industrial and combustion processes.[289]

Knowledge about the tissue distribution of PCDDs and PCDFs in humans is limited. At present, only one kinetic study of 2,3,7,8-TCDD has been performed in a human under controlled conditions. After ingestion of a dose of 1.14 ng/kg ^{3}H-2,3,7,8-TCDD by a male volunteer, approximately 90% of the body burden was sequestered in the fat. During the 135-day study, elevated radioactivity was detected in the blood only during the initial 2 days after treatment.[273] These data are consistent with the high bioconcentration potential of 2,3,7,8-TCDD calculated from data on daily intake and adipose levels of humans. In this study, a bioconcentration factor between 104 and 206 was calculated for 2,3,7,8-TCDD in human adipose tissue.[100] Fragmentary information also is available from victims of the Yusho and Yu-Cheng poisonings[163,293] and autopsy material from Germany.[28,334,335] With respect to the liver-to-adipose distribution ratio, the most extensive study so far has been done in Germany. The liver-to-adipose concentration ratio from 28 adults was found to be <5 for congeners having four to six chlorine atoms. For congeners, like OCDD and HpCDF, this ratio increased to >10 (see Figure 2).[334,335] Information derived from the Yusho and Yu-Cheng studies indicate comparable ratios between liver and adipose tissues for 2,3,7,8-PnCDF and 1,2,3,4,7,8-HxCDF.[64,163,293] It has been discussed whether the differences in the liver-to-adipose tissue distribution ratio between humans and rodents can be explained from the differences in the lipid content of both tissues. The above studies showed that PCDD and PCDF concentrations were dissimilar for adipose and liver tissue if calculated on a lipid basis. On a lipid basis, only the concentrations of 2,3,7,8-TCDD and TCDF were indeed within the same range for both tissue types.[178,325] However, for the higher chlorinated congeners, larger deviations were found for concentrations in both tissue types when expressed as lipid content.[335] Infant PCDD and PCDF adipose tissue concentrations from Germany were at least 25 to 50% lower than those measured in adults. An exception was observed for 2,3,7,8-TCDD and TCDF, which had comparable concentrations in infant and adult adipose tissue.[28,335] It has been suggested that these low levels may be attributed to a diluting effect caused by an overproportional increase in body fat of the infant during its first months.[28] If human data on liver and adipose tissue distribution are compared to those from rodents, it can be concluded that human body distribution is quite different from most other species. To illustrate these differences, results from studies with humans, Marmoset monkeys, and rats are compared in Figure 2.[6,226,335] As can be seen, the rat clearly stores considerably more penta-, hexa-, hepta-, and octachlorinated congeners in its liver than humans. The Marmoset monkey, being a non-human primate, takes an intermediate position with respect to liver-to-adipose distribution. Although the ratios show large quantitative differences among the three species, the same qualitative increase in ratio is observed parallel to an increasing chlorine number, except for OCDF.

4. Dose-Dependent Tissue Distribution

Recent findings provide evidence that the tissue distribution of 2,3,7,8-TCDD and related compounds is dose dependent. After an s.c. dose ranging from 1 to 3000 ng/kg 2,3,7,8-TCDD, a clear dose-dependent deposition was observed in the liver and adipose tissue 7 days after administration. This dose-dependent deposition is illustrated in Figure 6. From this, it can be seen that within this short time period the ratio between liver and adipose tissue increases with increasing dose.[2] A 2-year chronic study with rats and 2,3,7,8-TCDD also indicated a dose-related alteration of the liver-to-adipose tissue distribution ratio.[149] Similar dose-dependent increases in liver retention have been reported for other congeners, including 2,3,4,7,8- and 1,2,3,7,8-PnCDF, 1,2,3,6,7,8-HxCDF, and 2,3,7,8-TBDD in rats and mice.[59,69,176,274,281] In addition, an *in vitro* study with isolated primary hepatocytes found an increase in 2,3,7,8-TCDD uptake when cells from 2,3,7,8-TCDD-pretreated mice were used.[315] A number of other studies do not support the dose-dependent tissue distribution of PCDDs and PCDFs described above. No dose-dependent deposition was observed in a semi-chronic study of 2,3,7,8-TCDD in rats receiving 3.5 to 1000 ng/kg/day or in Rhesus monkeys given a single dose of 0.1, 0.5, or 1.0 kg/μmol 2,3,4,7,8-PnCDF.[47,295,340] Although it is not pos-

sible at this time to explain these differences, most available data support a dose-dependent relationship.

5. A Possible Mechanism for Dose-Dependent Liver Tissue Distribution

A few studies have focused on the (intra) cellular distribution of 2,3,7,8-substituted PCDDs or PCDFs in the liver cells of different species.[11,96,114,166,171,176,323,398] The distribution of radiolabeled 2,3,7,8-TCDD in the rat liver was studied in parenchymal and nonparenchymal cell fractions after a single dose of 10 μg/kg. During a period of 147 days, most of the 2,3,7,8-TCDD-derived activity resided in the parenchymal cells (hepatocytes), although nonparenchymal (stellate) cells contained more radioactivity per cell. Based on the elimination rate from both cell types, it was suggested that 2,3,7,8-TCDD is more persistent in nonparenchymal cells.[114] Intracellularly, >90% of the 2,3,7,8-TCDD-derived radioactivity in the rat liver was found to be associated with the microsomal fraction, until several weeks after administration.[11] A similar association of 2,3,7,8-TCDD with the microsomal fraction was observed in the guinea pig liver. After a single dose of 0.3 to 7.0 μg/kg 2,3,7,8-TCDD, 40 to 50% of the 2,3,7,8-TCDD was associated with the microsomal fraction, whereas 20 to 30% was present in the crude nuclear fraction. Six days after administration of the highest dose, levels in the nuclear fraction decreased with increasing levels in the microsomal fraction.[96] The observation that exposure to higher doses of 2,3,7,8-TCDD and related isostereomers results in an overproportionally greater hepatic concentration may be explained in part by a hepatic-binding species induced by 2,3,7,8-TCDD and other Ah-receptor agonists. The close association of 2,3,7,8-substituted PCDDs and PCDFs to the microsomal fraction suggests a high binding affinity to CYP1A2.[166,176,281,370,371,398] In the rat, 2,3,7,8-TCDD was found to be a tight binding inhibitor of CYP1A2 activity, as was shown by inhibition of the CYP1A2-dependent estradiol 2-hydroxylase activity.[370,371] Similar results were obtained with 2,3,4,7,8-PnCDF, which also was strongly associated with the endoplasmatic reticulum fraction in which CYP1A2 is present.[166,398,401] These results are in good agreement with a study in which the tissue deposition of 2,3,7,8-TCDD in the rat was described using a physiologically based pharmacokinetic model. The distribution to the liver was explained to be dependent primarily on the binding of 2,3,7,8-TCDD to microsomal protein. Binding to the Ah-receptor itself was not found to be of quantitative importance for the liver distribution.[176] A recent study by Poland and co-workers using [^{125}I]-iodo,3,7,8-trichlorodibenzo-*p*-dioxin gives the most detailed support to the hypothesis that CYP1A2 plays a significant role as a hepatic binding site for 2,3,7,8-TCDD.[281] This evidence can be summarized as follows: (1) the induced hepatic-binding species was found predominantly in the microsomal fraction and was inactivated by trypsin, mercurials, and heating at 60°C; (2) the induced hepatic-binding site is specific for the liver; (3) the induced microsomal-binding species migrates with the immunochemically stained polyclonal antiserum that binds to CYP1A2. However, preinduction of CYP1A2 did not increase the hepatic uptake of [^{125}]-iodo-3,7,8-trichlorodibenzo-*p*-dioxin in this study, an observation that does not support the above-mentioned hypothesis. The authors suggest that this phenomenon may be attributed to the high affinity binding of isosafrole to CYP1A2, thereby inhibiting the binding of the former compound to the protein. However, this does not explain why 2,3,7,8-TCDD or its isostereomers, which also have high affinity binding to CYP1A2, cannot displace isosafrole and/or its metabolites from the protein. Two recent studies using either 2,3,7,8-TCDD or 2,3,7,8-TBDD in rats could not establish a distinct relationship between increased hepatic uptake and levels of CYP1A2.[59,141,340]

In summary, the available evidence suggests some involvement of CYP1A2 in dose-dependent hepatic retention, but results are by no means conclusive. In relation to specific binding sites in the liver cell, it should be noted that for 3,3′ 4,4′-TCB, an isostereomer of 2,3,7,8-TCDD, autoradiography studies of the liver cell also indicated lipid droplets and mitochondria as other important storage sites.[84] In addition to the binding sites discussed previously, the role of hepatic lipoproteins also has been studied in relation to intracellular transport of 2,3,7,8-TCDD. The reported results indicate that

these lipoproteins may act as carriers in intrahepatic cellular transport.[323]

6. Redistribution

The tissue distribution of 2,3,7,8-substituted PCDDs and PCDFs as observed over a certain time can be largely dependent on the mobilization of the adipose tissue. In most mammalian species, the mobilization of adipose tissue is part of the toxic action of these compounds. Therefore, the body distribution after exposure to high doses is difficult to predict. The liver retention of 2,3,4,7,8-PnCDF in the rat increased from 37 to 68% by 2 weeks after a 1-mg/kg dose, while a simultaneous decrease in adipose tissue concentration was observed.[398] A similar redistribution to the liver was observed in the guinea pig after toxic doses of 2,3,7,8-TCDD or 2,3,7,8-TCDF, resulting in a threefold increase in liver concentrations 9 to 15 days after exposure.[74,96] Although the hamster does not mobilize its adipose tissue as readily as the above species, redistribution of 2,3,7,8-TCDD also has been observed in the hamster at 3 days after i.p. administration of 650 μg/kg.[239]

7. Prenatal Exposure

In the rat, placental transfer of lateral substituted PCDDs and PCDFs was found to be strongly dependent on molecular size, with the highest fetal retention observed for 2,3,7,8-TCDD. Only 2,3,7,8-substituted tetra-, penta-, and hexachlorinated congeners were retained to a measurable extent in the fetus (<0.15% dose per litter) on gestation day 17 after administration of a complex mixture during days 10 to 17 of the pregnancy.[356] In view of the extreme teratogenicity of 2,3,7,8-TCDD and related compounds, its placental transfer has been studied in C57BL/6J and NMRI mice.[220,221,380] When 25 μg/kg 2,3,7,8-TCDD was intraperitoneally administered to female NMRI mouse on gestation days 7 to 13, retention of 2,3,7,8-TCDD between gestation days 11 to 15 ranged from 0.04 to 0.1% of the dose per gram embryonic tissue. Before day 11, higher concentrations were found in the embryos.[220] In a similar type of experiment with C57BL/6J mice, 0.035% of a maternal dose of 30 μg/kg 2,3,7,8-TCDD, administered on day 11 of the pregnancy, was found in the individual embryos on gestation days 12, 13, and 14.[380] As with adult mice, hepatic tissue in the embryo was a major storage site, with levels 2 to 5 times higher than in other fetal tissues.[155,220] The embryonic head also was found to contain significant concentrations of 2,3,7,8-TCDD.[380] Similar experiments with 2,3,7,8-TCDF in pregnant mice showed that placental transfer and embryonic tissue content were much lower than that observed for 2,3,7,8-TCDD.[380] Similar experiments with 2,3,7,8-TCDF in pregnant mice showed that placental transfer and embryonic tissue content were much lower than that observed for 2,3,7,8-TCDD.[380] This is likely due to the higher rate of biotransformation of 2,3,7,8-TCDF in mice, when compared with 2,3,7,8-TCDD.[74] In the Marmoset monkey, placental transport for most congeners leads to lower concentrations in the fetal liver as compared to maternal liver after s.c. maternal exposure. An exception was found for 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF. The low maternal liver concentrations were attributed to rapid metabolism in the maternal liver. In contrast to rodents, substantial placental transfer into fetal adipose tissue was observed for most of the 2,3,7,8-substituted congeners in the Marmoset monkey.[113,156] Information about prenatal transport of PCDDs and PCDFs in humans is extremely limited. Based on liver analysis of four human fetuses, it was concluded that prenatal exposure is quantitatively less important than postnatal exposure.[366]

8. Postnatal Exposure

In rodents and monkeys, the transfer of PCDDs and PCDFs via maternal milk to the neonate is quantitatively much more important than transport to the fetus across the placenta. Excretion via the milk decreases with increasing chlorine content, being most pronounced for the hepta- and octachlorinated congeners.[13,113,152,156,216,221,356] In the rat, transport via the milk can be very effective and results in comparable or slightly lower liver concentrations in the neonates relative to the dams.[152,356] Using a complex mixture of PCDDs and PCDFs, maternal dosing of rats during the first 10 days of lactation resulted in significant

transport via the milk to the sucklings. In general, the livers of the sucklings contained 1 to 8% of the administered dose per litter, depending on the congener. Highest transport was observed for 2,3,7,8-substituted HxCDDs and HxCDFs. For most congeners, liver concentrations in the neonates were only two- to threefold lower than the dams.[356] In these experiments, using pregnant and lactating females, it was observed that lactation results in a decreased deposition of certain congeners in maternal adipose tissue.[356] This is illustrated in Figure 3, where the liver-to-adipose tissue ratio is increased for TCDD, PnCDD, PnCDF, HxCDD, and OCDD in lactating dams relative to pregnant animals. Based on these results, it appears that the PCDDs and PCDFs present in milk seem to be mobilized primarily from the adipose tissue and not from the liver. However, it cannot be excluded that this process occurs via a direct transfer of PCDDs and PCDFs from the blood to the mammalian gland without an intermediate sequestration in adipose tissue. Administration of 25 µg/kg 2,3,7,8-TCDD to mice on gestation day 16 resulted in the efficient transfer of this compound from the lactating mothers to the offspring. The amount of 2,3,7,8-TCDD transferred to the pups during the first 2 postnatal weeks was similar to the dose administered prenatally to the pregnant females when expressed per kilogram bodyweight. Parallel to a decrease in maternal tissue levels, the levels in the nursing pups increased, with the highest concentrations observed in the liver.[221] Rhesus monkeys receiving 0.7 ng/kg/day 2,3,7,8-TCDD for several years excreted approximately 21% of their body burden during the first 4 months of nursing. Thus, mother-to-offspring bioconcentration due to lactation was estimated to be 4.3.[44,45] In the Marmoset monkey, transfer of tetra- to hexachlorinated congeners via the milk leads to hepatic concentrations in the offspring that are equal to or higher than those in the mother. As in the rat, transport via the milk decreased with increasing chlorine content.[156] There also is accumulating evidence that lactation results in a decrease in human body burden of PCDDs and PCDFs. In Germany and Japan, it has been shown that the concentrations of these compounds in milk from multipara women are decreased 25 to 50% compared to that of primipara women. This decrease appears to be congener dependent.[93,94,236]

9. Influence of Mixtures

A number of semichronic laboratory studies have focused on the kinetic behavior of these compounds when administered concomitantly. Exposure to a mixture of PCDDs and PCDFs extracted from flyash showed that the toxicokinetic behavior of the mixture components in the liver of rats, hamsters, and guinea pigs was not substantially different compared with that after administration of the respective components as single compounds.[350,351] These results are in agreement with a study using a mixture of 1,2,3,4,8- and 2,3,4,7,8-PnCDF, in which no influence of the nontoxic isomer was observed on the body deposition of 2,3,4,7,8-PnCDF.[385] The observed consistency in congener patterns seen in biota is most likely a result of the slow metabolic transformation of most of these compounds and of the low level exposure to a more or less stable background level not leading to toxic or biochemical effects that may influence tissue distribution.

B. Birds

Toxicokinetics of PCDDs and PCDFs in birds have not been studied as extensively as they have in mammals. Thus, information about tissue distribution in these species is very limited.[46,206,227,332,354] Toxicokinetics have been described in greatest detail for the herring gull *Larus argentatus*.[46]

1. Major Storage Sites

As in mammals, the liver and body fat tissues in birds appear to be the major sites for storage and accumulation of 2,3,7,8-substituted PCDDs and PCDFs. Preferential accumulation of 2,3,7,8-substituted congeners in birds is similar to that of mammals.[46,206,227,354] While studying the bioaccumulation of a large number of organochlorines, it was observed that the hepatic deposition of lateral-substituted PCDDs and PCDFs increased with the number of chlorine substituents of the respective congener. The mean fraction of PCDDs and PCDFs located in the liver ranged from 5 to 55% of the total body burden of each congener (see Figure 9).[46]

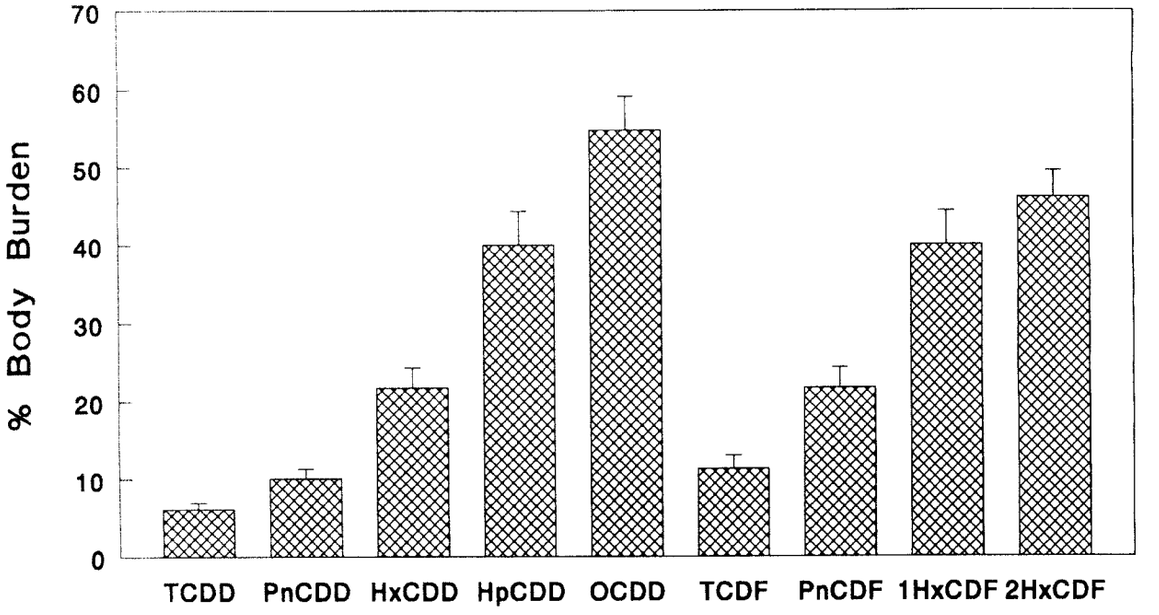


FIGURE 9. Mean percentage of the body burden of 2,3,7,8-substituted PCDDs and PCDFs in the Herring gull liver.[46]

2. Transfer to the Egg

In the herring gull, transport from the body to the egg yolk was found to be influenced by the retention of PCDDs and PCDFs in the liver. The greater hepatic retention of highly chlorinated congeners resulted in a limited transfer of these compounds from the liver to the egg. As a result, the egg-to-liver ratio decreased from the tetra- to the octachlorinated congeners.[46]

C. Fish

In contrast to mammals and birds, the fish liver seems not to be a major storage site for PCDDs and PCDFs. The majority of 2,3,7,8-substituted PCDDs and PCDFs is clearly associated with fatty tissues and carcass.[146,147] Although some tissue retention of non-2,3,7,8-substituted PCDDs has been observed in laboratory experiments, analysis of environmental samples does indicate a preferential retention of the 2,3,7,8-substituted congeners.[211,212,288,321,322,363]

1. Major Storage Sites

In the rainbow trout, >90% of the 2,3,7,8-TCDD body burden was located in organs with a high lipid content, including visceral fat, carcass, skin, and pyloric caeca.[146] These tissues also were the major storage sites for 2,3,7,8-TCDD in the yellow perch.[147] A greater hepatic deposition of 2,3,7,8-TCDD was observed in the yellow perch, where 9% of the body burden was present in the liver, while only about 1% was retained in the rainbow trout liver. In the yellow perch, the gills also accounted for 5% of the body burden.[146,147] The tissue distribution of a limited number of other 2,3,7,8-substituted congeners has been studied in fish. In the rainbow trout, 2,3,7,8-TCDF and 2,3,4,7,8-PnCDF are stored mainly in fat-containing tissues, like muscle and skin.[185,213,322] The liver deposition of both 2,3,4,7,8-PnCDF and 1,2,3,6,7,8-HxCDF accounted for <5% of the body burden in rainbow trout and carp.[213,322,363] At present, the available information does not allow for a conclusion regarding these differences in the congener-specific tissue distribution of 2,3,7,8-substituted PCDDs and PCDFs between fish and mammals. For 2,3,7,8-TCDF, relatively high tissue concentrations have been observed in environmental fish samples, in contrast with samples of mammalian origin.[288] A lower capacity of fish to metabolize this compound can be suggested as the primary cause for these high tissue levels. In support of this hypothesis, a greater persistence of 2,3,7,8-TCDF was observed in rainbow trout when compared with that observed in rats, mice, and guinea pigs.[31,74,75,185]

D. Crustaceans

In contrast with fish, crustaceans also retain PCDDs and PCDFs in their tissues, which do not have the 2,3,7 and 8 chlorine substitution pattern.[67,202,288,290] The reason for the retention of the non-2,3,7,8-substituted compounds in these tissues is unknown, but is consistent with their low drug-metabolizing enzyme activity. PCDDs and PCDFs can accumulate to a great extent in the hepatopancreas of these species.[288]

IV. METABOLISM

With the exception of OCDD, the metabolism of 2,3,7,8-TCDD and related compounds is required for urinary and biliary elimination and therefore plays a major role in regulating the rate of excretion of these compounds. Biotransformation of PCDD and PCDF congeners has been investigated in several species. However, the structures of the metabolites so far have been elucidated only in the rat and dog. Structures of metabolites have been identifed using GC/MS techniques and in part with synthesized standards. In most species, information regarding metabolic pathways is not available. However, several toxicokinetic studies with mammals and fish reported the formation of polar metabolites of radiolabeled congeners by using HPLC techniques. Results of these studies also have been included in this section. In addition, some suggestions are made regarding regioselectivity in oxidative biotransformation of PCDDs and PCDFs.

A. PCDDs

1. Non-2,3,7,8-Substituted PCDDs

In the rat, the biotransformation of a number of nontoxic PCDDs was studied primarily to obtain information on the preferable positions for oxidation and enzymatic hydration. With 2,3-DiCDD, 1,2,4-TrCDD, and 1,2,3,4-TCDD congeners, having one unsubstituted aromatic ring, oxidation on the lateral (2,3,7 or 8) position was observed, yielding either mono- or dihydroxylated compounds. Oxygen bridge cleavage in combination with oxidation was not reported to occur in the non-2,3,7,8-substituted PCDDs.[341] Apart from phenolic products, sulfur-containing metabolites also have been detected in experiments using rats, derived most likely from glutathione conjugation. These compounds appeared to be least important with increasing chlorine content. Such sulfur-containing compounds were seen only from non- and monochlorinated dibenzo-*p*-dioxins.[341]

2. 2,3,7,8-TCDD

a. Rat

Based on the studies with non-2,3,7,8-substituted PCDDs in the rat, it could be expected that those congeners carrying chlorine atoms on all four lateral positions (2,3,7,8) would be slowly metabolized, if at all.[341] Although substituted on these four lateral positions, 2,3,7,8-TCDD was metabolized in the liver of the rat, from which structures were elucidated later.[52,268,270,283] Metabolic transformation included oxidation and reductive dechlorination, involving also an NIH shift from the lateral to the periposition. This was indicated by a minor metabolite, which was identified as 2-hydroxy-1,3,7,8-TCDD. One of the major metabolites, however, was found to be a dihydroxy-TrCDD. Another important metabolic pathway is oxygen bridge cleavage, yielding a dihydroxy-tetrachlorodiphenyl ether. Apparently, oxygen bridge cleavage of the diphenylether can continue as formation of a dichlorocatechol also was observed.[270] Besides the *in vivo* experiments described above, studies with primary rat hepatocyte cultures showed that 2,3,7,8-TCDD also can be metabolized *in vitro*. However, some structural differences in metabolites were found, when compared with the *in vivo* study. Using synthetic standards, major metabolites were identified as 1-hydroxy-2,3,7,8-TCDD and 8-hydroxy-2,3,7-TrCDD.[308] Further investigation is necessary to understand the differences between the *in vivo* and *in vitro* studies. β-Glucuronidase treatment of rat bile and media of hepatocyte cultures suggests that a significant number of 2,3,7,8-TCDD metabolites are present in the form of glucuronide conjugates.[270,283,394] The Long/Evans and Han/Wistar rat strains have large differences in sensitivity, about two orders of a magnitude, toward the acute toxicity of 2,3,7,8-TCDD. The possible role of toxicokinetics and metabolism in these strain differences in toxicity has been inves-

tigated in detail.[267] Based on HPLC elution profiles, some quantitative and qualitative differences were found in metabolic pathways, but structures of metabolites were not elucidated. Although Long-Evans and Han/Wistar rats had one major metabolite in common, at least one metabolite was structurally different from both strains. These differences are not believed to be responsible for the different susceptibilities.[267]

b. Mouse

Several metabolites of 2,3,7,8-TCDD were observed in a toxicokinetic study in C57BL/6J, DBA/2J, and B6D2F/J mice. Qualitatively, the HPLC elution profiles were similar for the three mouse strains, indicating no remarkable strain or Ah-receptor-related differences in metabolic pathways.[97] An *in vitro* study with hepatocytes from C57BL/6J and DBA/2J mice concluded that qualitatively and quantitatively the metabolism of 2,3,7,8-TCDD was similar in the two strains, although there may be some qualitative differences in the metabolites.[315]

c. Hamster

Studies using primary hepatocyte cultures revealed similarities in the HPLC profile of 2,3,7,8-TCDD metabolites formed in the rat and hamster.[395]

d. Guinea Pig

In contrast with the similarities between the above-mentioned species, significant differences were observed in the HPLC profile of 2,3,7,8-TCDD metabolites formed by guinea pig hepatocytes in suspension culture. The rate of 2,3,7,8-TCDD metabolism and the number of metabolites were decreased in the guinea pig, relative to that found in the rat, hamster, and mouse.[394]

e. Dog

Of the six 2,3,7,8-TCDD metabolites observed in the bile of the dog, 2-hydroxy-1,3,7,8-TCDD was found to be the major compound. It was suggested that this metabolite could result from an epoxide formation on the 3,4 position, followed by an NIH-shift. However, this compound was only a minor metabolite in the rat. It is possible that in the rat 2-hydroxy-1,3,7,8-TCDD is converted more easily into (di)hydroxy-TrCDD. In contrast with the rat, glucuronide conjugates were not observed in the dog.[270]

f. Human

No information is presently available about metabolic pathways of 2,3,7,8-TCDD in humans. However, there is some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites.[384]

g. Fish

As in mammals, PCDDs are preferably hydroxylated at the lateral positions in fish. This was shown in experiments using guppies and 2,8-DiCDD, in which 3-hydroxy, 2,8-DiCDD was the major metabolite detected.[320] Information on structural requirements for efficient metabolism of tetrachlorinated dioxins was obtained from a study with guppies using a flyash extract from a municipal incinerator. As in mammals, the presence of two vicinal unsubstituted carbon atoms facilitated metabolism significantly. Non-2,3,7,8-substituted isomers with an alternate chlorine substition pattern, e.g., 1,3,6,8-, 1,3,7,9-, and 1,3,7,8-TCDD, are less easily metabolized, probably due to steric hindrance by chlorine atoms. However, their biotransformation is significantly more efficient than that of 2,3,7,8-TCDD.[321] A study with rainbow trout and 1,3,6,8-TCDD supported the facilitated metabolism of non-2,3,7,8-substituted TCDDs, and a single glucuronide metabolite of this compound was observed in the bile.[211] Strain-specific differences in metabolism of 2,3,7,8-TCDD have been studied in six species of fish: carp, bullhead, rainbow trout, largemouth bass, bluegill, and yellow perch. In all species, at least three TCDD-derived products were formed, with the major metabolite being similar for all species, except the yellow perch. Enzyme hydrolysis using

β-glucuronidase suggests that glucuronide conjugation occurs in most species, but no sulfur-containing metabolites were detected.[146–148]

Based on these studies, it can be concluded that species differences in 2,3,7,8-TCDD metabolism exist in mammals and fish. However, further studies are necessary to identify the specific structures of the metabolites found in various species.

3. Other 2,3,7,8-Substituted PCDDs

Virtually no substantial information about the other 2,3,7,8-substituted PCDDs is available. In the rat, the toxicokinetics of 1,2,3,7,8-PnCDD has been studied and at least three phenolic metabolites were observed, but their structures were not elucidated.[372] In view of the comparable elimination rate with 2,3,7,8-TCDD, similar metabolic pathways on the C3 to C7 positions can be expected, possibly involving oxygen bridge cleavage. Metabolism of OCDD was studied in rats but no metabolites were observed.[37,341] This result could be expected because the OCDD molecule is fully chlorinated and the lack of carbon hydrogen bonds will strongly limit oxygenation by cytochrome P450.

Figure 10 represents a proposed and generalized scheme for the metabolic pathways for PCDDs, based on the information presently available from *in vivo* mammalian studies.

B. PCDFs

1. Non-2,3,7,8-Substituted PCDFs

In analogy to lower chlorinated PCDDs, oxidation of PCDFs, i.e., 2-MCDF and 2,8-DiCDF, preferably occurs on the 2 and 3 positions. The asymmetric structure of the PCDF molecule in combination with the chlorine shift enables a greater number of hydroxylated metabolites, which indeed have been observed.[367] 2,8-DiCDF was partially converted to sulfur-containing metabolites, being quantitatively almost as important as the hydroxylated metabolites. In the feces, 1.1% consisted of sulfur-containing metabolites vs. 3.2% for the hydroxylated compounds. Based on the position of the sulfur atom in the 2,8-DiCDF molecule, an S substitution on the 4 position is favored, which most likely originates from a 3,4 sulfoxide intermediate.[168,169] Of the higher chlorinated PCDF congeners, the metabolism of some tetra- and pentachlorinated congeners has been studied in the rat. Both 1,3,7,8- and 2,3,6,8-TCDF were rapidly metabolized to a number of mono- and dihydroxy TCDFs and TrCDFs. Despite the fact that both TCDFs do not have adjacent unsubstituted carbon atoms, the metabolism rate was relatively high and comparable with 2,3,7,8-TCDF.[275] Metabolism of 1,2,3,4,8-PnCDF in the rat produced mono- and dihydroxy PnCDF as the major metabolites. Based on the structure of 1,2,3,4,8-PnCDF, the metabolites can be expected to be formed via an epoxide intermediate at positions 6 and 7.[260] A noticeable difference between these non-2,3,7,8-substituted PCDFs and 2,3,7,8-substituted PCDFs was that oxygen bridge cleavage was found to be a metabolic pathway only in 2,3,7,8-substituted PCDFs.[275] In addition, sulfur-containing metabolites were found not to be major metabolites for these higher chlorinated congeners, which is in contrast with studies using dichlorinated congeners.[168,169,275]

2. 2,3,7,8-Substituted PCDFs

a. Rat

Metabolism of 2,3,7,8-TCDF yielded a number of metabolites, including mono- and dihydroxy TCDF and TrCDFs. Monohydroxy-TCDF and dihydroxy-TrCDF are the major components present in the bile. In contrast to 2,3,7,8-TCDD, no cleavage of the oxygen bridge was observed.[270] In a recent study, comparison of the mass spectra of 2,3,7,8-TCDF metabolites, isolated from rat bile, with synthesized reference compounds enabled a more substantial structure assigment. The major metabolites identified were 4-hydroxy-2,3,7,8-TCDF and 3-hydroxy-2,3,8-TrCDF. Trace amounts of 2,2′-dihydroxy-4,4′,5,5′-tetrachlorbiphenyl also were detected. Based on the relative abundance of these metabolites, it was suggested that epoxidation on the 4 and 4a C-atoms adjacent to the oxygen bridge prevailed over attack at the 3 and 4 positions.[60] Recent studies with isolated rat hepatocytes in suspension culture also have

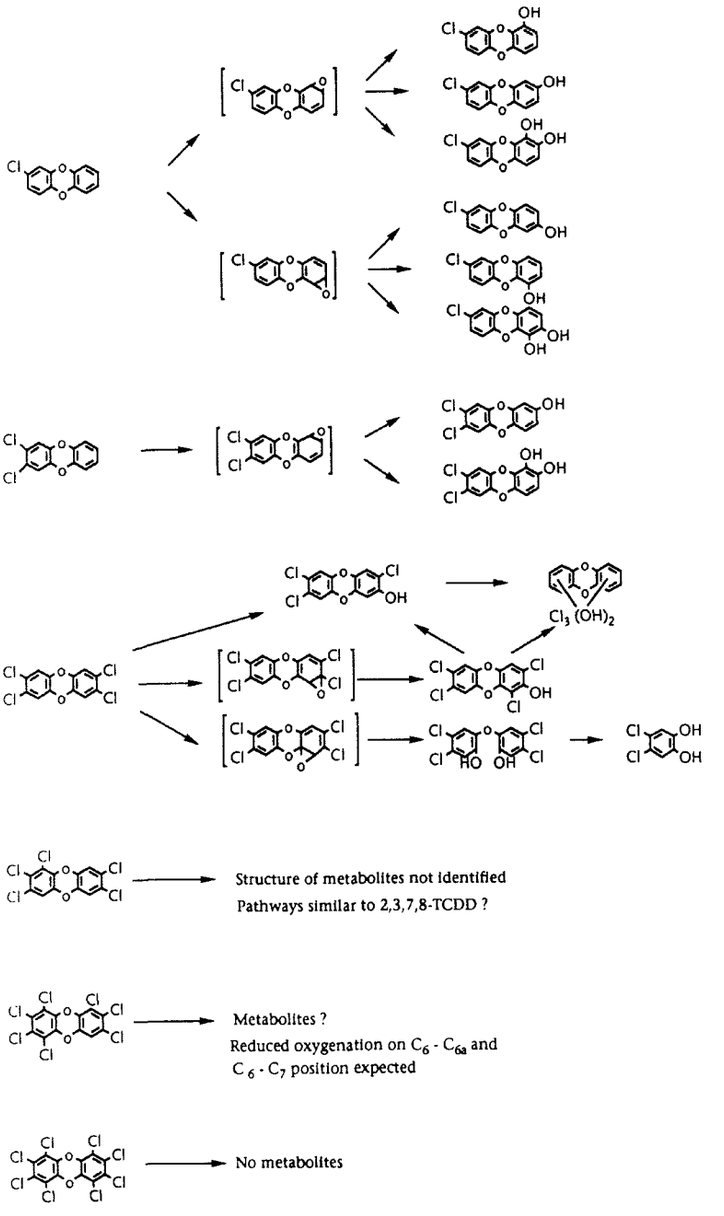


FIGURE 10. A generalized scheme of pathways for the biotransformation of PCDDs based on the information from *in vivo* mammalian studies.

reported that 4-hydroxy-2,3,7,8-TCDF is the major metabolite under *in vitro* conditions.[243] A metabolism study with a mixture of 1,2,7,8-, 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF again confirmed that hydroxylation is the major metabolic reaction, compared with sulfur-containing derivatives. This study confirmed again that oxygen bridge cleavage was only a minor metabolic pathway for PCDFs.[169] In rat bile, the major metabolite of 1,2,3,7,8-PnCDF was identified as a dihydroxy-TCDF. Others, such as hydroxy-TCDFs (2 isomers), hydroxy-PnCDF, dihydroxy-TrCDF, and unknown metabolites, were present in minor amounts. Based on the mass fragmentation of the monohydroxy-PnCDF, it can be assumed that the hydroxy group was not present at the 4 or 6 position,[260] indicating an NIH-shift of a chlorine substituent. Similarly, in the male Fisher F344 rat, only one major metabolite of 1,2,3,7,8-PnCDF was observed in the bile, and one additional metabolite was observed in the urine.[49] The presence of a chlorine atom on the 4 position strongly

decreased the elimination rate of 2,3,4,7,8-PnCDF compared to the preceding isomer.[47,49,358] Nevertheless, rats are capable of slowly metabolizing this biopersistent congener, but there is no distinct predominance of a single metabolite. This may be due to a chlorine substitution pattern that does not favor a specific metabolic pathway. In addition to biotransformation to mono- and dihydroxy-TCDFs and PnCDFs, metabolism through oxygen bridge cleavage to 2,2′-dihydroxy-2,4,4′,5,5′-PnCB also was quantitively important.[260] Further chlorine substitution strongly decreases biotransformation compared with tetra- and pentachlorinated congeners. In the rat, 1,2,3,6,7,8-HxCDF was converted to only one biliary metabolite, a dihdyroxy-PnCDF. In analogous experiments with 1,2,3,4,6,7,8-HpCDF, no metabolites could be detected either;[275] the same was observed with OCDF.[367]

b. Fish

The formation of metabolites of 2,3,7,8-TCDF in rainbow trout was recently reported. It was concluded that this compound was predominantly metabolized to 4-hydroxy-2,3,7,8-TCDF glucuronide and sulfate conjugates and excreted in the bile.[185]

Figure 11 represents a proposed and generalized scheme for the metabolic pathways for PCDFs, based on the information presently available from *in vivo* mammalian studies.

C. Regioselectivity in Oxidative Biotransformation

Several authors have observed the highly selective tissue retention of 2,3,7,8-substituted PCDDs and PCDFs.[5,46,89,159,165,233,348] Although several reasons have been suggested for this selective retention,[359] at present a strong regioselective metabolic attack on either the dibenzo-*p*-dioxin or dibenzofuran molecule can be considered as the most plausible reason. Clearly, the regioselectivity in oxidation by cytochrome P450 must play an important role in this process, but very little information is available on this subject for PCDDs and PCDFs. Therefore, it should be emphasized that in the future a more quantitative approach predicting electron densities in these molecules is needed to elucidate regioselectivity in biotransformation. So far, only one study reported such an approach.[368] However, the theoretically calculated positions for oxygen insertion were not in accordance with the results from laboratory experiments. Based on Hückel molecular orbital calculations, oxygenation in the PCDF molecule should occur at the 1-2 position, but based on actual experiments using 1,2,3,7,8- and 2,3,4,7,8-PnCDF, preferential oxidation occurs at the 3-4 or 4-4a position.[47,49,358]

V. ENZYME INDUCTION

A. Autoinduction of Metabolism

Metabolism plays a major role in determining the elimination from, and thus the persistence of, these compounds in tissues. Although the relative metabolic rates of 2,3,7,8-TCDD and related compounds can be estimated from tissue and excretion half-life data (see Tables 4, 5, and 6), other factors such as growth, relative tissue size, hepatic and extrahepatic binding to proteins, and direct intestinal elimination of the parent compound may have some influence and must be taken into account. Therefore, *in vivo* disposition data provide only a limited approximation of the relative rate of metabolism of a specific congener in a given species. In addition, most of these *in vivo* disposition data were obtained from exposure levels that are associated with a significant induction of CYP1A1 and CYP1A2, which may elicit physiological responses that could influence metabolism and disposition. Therefore, such data may not reflect well the toxicokinetic behavior at low exposure levels. Low dose extrapolations require assessment of the potential for autoinduction of metabolism, which may occur at exposure levels that are associated with enzyme induction.

To assess the ability of 2,3,7,8-TCDD and 2,3,7,8-TBDD to induce their own metabolism in the form of biliary elimination, rats were pretreated with 100 nmol/kg p.o. of each compound 3 days prior to i.v. injection of 1 nmol/kg of the respective ^{3}H-labeled congeners. Biliary excre-

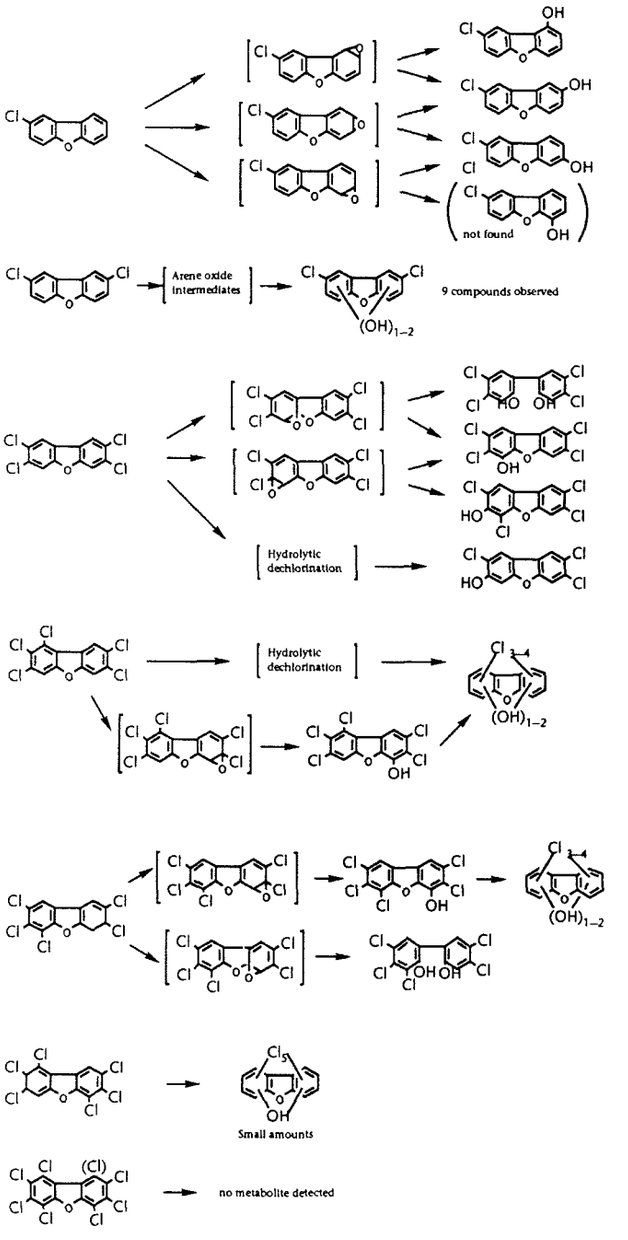


FIGURE 11. A generalized scheme of pathways for the biotransformation of PCDFs based on the information from *in vivo* mammalian studies.

tion of the radiolabeled moiety was not affected by pretreatment, despite a significant induction of CYP1A1 and CYP1A2, resulting in a twofold increase in hepatic levels of the ^{3}H-labeled compounds in the pretreated animals.[58] Under these experimental conditions, autoinduction of 2,3,7,8-TCDD and 2,3,7,8-TBDD metabolism did not occur in the rat *in vivo* at doses that enhanced hepatic uptake and induced cytochrome P450. A comparable study of [^{3}H]-2,3,7,8-TCDD excretion using pretreated or naive female C57BL/6J mice did not report any changes either in GI contents or fecal elimination 24 h after oral administration, although levels of 2,3,7,8-TCDD in the livers of pretreated mice were significantly enhanced.[69] Although these studies suggest that autoinduction of metabolism does not occur for 2,3,7,8-TCDD, other results indicate that its me-

TABLE 4
Metabolism and Excretion of 2,3,7,8-TCDD and Related Compounds

Chemical	Species	Dose	Chemical nature of excretion products (% metabolites)			Ratio of % of dose excreted (feces/urine)	Half-life[a] (days)	Comment	Ref.
			Urine	Bile	Feces				
PCDDs									
2,3,7,8-TCDD	Sprague-Dawley rat (M)	50 µg/kg, p.o.	NA	NA	NA	4.0	17.4 ± 5.6[b]	NC	258
2,3,7,8-TCDD	Sprague-Dawley rat (M)	7 or 72 ppb in diet for 42 days	NA	NA	NA	NA	12	NC	91
2,3,7,8-TCDD	Sprague-Dawley rat (F)	7 or 72 ppb in diet for 42 days	NA	NA	NA	NA	15	NC	91
2,3,7,8-TCDD	Sprague-Dawley rat (M, F)	1.0 µg/kg, p.o.	NA	NA	NA	9.9	31 ± 6[c]	NC	295
2,3,7,8-TCDD	Sprague-Dawley rat (M, F)	0.1 and 1.0 µg/kg/day, 5 days/week for 7 weeks	NA	NA	NA	8.5	23.7	NC	295
2,3,7,8-TCDD	Han/Wistar rat (M)	5 µg/kg, i.p.	>90	NA	70–90	14.1	21.9	NC	267
2,3,7,8-TCDD	Long-Evans rat (M)	5 µg/kg, i.p.	>90	NA	≈20–90	12.0	20.8	NC	267
2,3,7,8-TCDD	Sprague-Dawley (M)	500 µg/kg, i.p.	100	100	NA	NA	NA	NC	222
2,3,7,8-TCDD	C57BL/6J mice (M)	10 µg/kg, i.p.	100	100	85	2.7	11.0 ± 1.2[c]	NC	97
2,3,7,8-TCDD	DBA/2J mice (M)	10 µg/kg, i.p.	100	100	82	1.2	24.4 ± 1.0[c]	NC	97
2,3,7,8-TCDD	B6D2F1J mice (M)	10 µg/kg, i.p.	100	100	86	2.5	12.6 ± 0.8[c]	NC	97
2,3,7,8-TCDD	C57BL/6J mice Ah^b/Ah^d (M)	500 ng/kg, i.p.	NA	NA	NA	3.1	9.42	NC	34
2,3,7,8-TCDD	C57BL/6J mice Ah^d/Ah^d (M)	500 ng/kg, i.p.	NA	NA	NA	2.1	9.74	NC	34
2,3,7,8-TCDD	DBA/2J mice Ah^b/Ah^d (F)	500 ng/kg, i.p.	NA	NA	NA	5.3	10.40	NC	34
2,3,7,8-TCDD	DBA/2J mice Ah^d/Ah^d (F)	500 ng/kg, i.p.	NA	NA	NA	6.8	11.11	NC	34

TABLE 4 (continued)
Metabolism and Excretion of 2,3,7,8-TCDD and Related Compounds

Chemical	Species	Dose	Chemical nature of excretion products (% metabolites) Urine	Bile	Feces	Ratio of % of dose excreted (feces/urine)	Half-life[a] (days)	Comment	Ref.
2-Iodo-3,7,8-TCDD	C57BL/6J mice (F)	[^{125}I] 0.1 nmol/kg, i.p.	NA	NA	NA	NA	14.2	Whole body counting was used to estimate body burden over 30-day period	176
2-Iodo-3,7,8-TCDD	C57BL/6J mice (F)	[^{125}I] 0.1 nmol/kg, i.p., 3 days following pretreatment with 2,3,7,8-TCDD (0.1 µmol/kg, i.p.)	NA	NA	NA	NA	8.0	Whole body counting was used to estimate body burden over 30-day period	176
2,3,7,8-TCDD	Hartley guinea pig (M)	0.5 µg/kg, i.p.	NA	NA	NA	15.7	30.2 ± 5.8[c]	NC	96
2,3,7,8-TCDD	Hartley guinea pig (M)	0.56 µg/kg/i.p.	100	100	19	11.2	93.7 ± 15.5[c]	NC	241
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{3}H] 650 µg/kg, i.p.	NA	NA	NA	1.4	11.95 ± 1.95[c]	NC	222, 239
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{14}C] 650 µg/kg, i.p.	100	100	55–75	NA	10.82 ± 2.35	NC	222, 239
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{3}H] 650 µg/kg, p.o.	NA	NA	NA	NA	14.96 ± 2.53	NC	222, 239
2,3,7,8-TCDD	Human (M)	1.14 ng/kg, p.o.	NA	NA	≈50	>3.1	2120[d]	NC	273, 384
2,3,7,8-TCDD	Rainbow trout	494 ppt in diet for 13 weeks	NA	≈75	NA	NA	105	Elimination followed for 13 weeks following exposure	146
2,3,7,8-TCDD	Yellow perch	494 ppt in diet for 13 weeks	NA	≈90	NA	NA	126	Elimination followed for 13 weeks following exposure	147
1,2,3,7,8-PnCDD	Sprague-Dawley rat (M, F)	8.42–10.06 µg/kg, p.o.	NA	100	NA	12	29.5 ± 2.7	NC	372
1,2,3,4,7,8-HxCDD	Rainbow trout	109 ng/g	NA	NA	NA	NA	46	30 or 31 days in the food	212
1,2,3,4,7,8-HxCDD	Fathead minnow	109 ng/g	NA	NA	NA	NA	106	30 or 31 days in the food	212
1,2,3,4,6,7,8-HpCDD	Rainbow trout	109 ng/g	NA	NA	NA	NA	61	30 or 31 days in the food	212
1,2,3,4,6,7,8-HpCDD	Fathead minnow	109 ng/g	NA	NA	NA	NA	112	30 or 31 days in the food	212

OCDD	Fischer 344 rat (M)	50 µg/kg, i.v.	<33	0	0	>65	≃70	Whole body $t_{1/2}$ estimated from body burden in liver, skin, and adipose tissue over a 56-day period	36
OCDD	Fischer 344 rat (M)	50 µg/kg/day, p.o., for 10 days	NA	NA	NA	NA	≃173	Whole body $t_{1/2}$ estimated from body burden in liver, skin, and adipose tissue over a 112-day period	36
PBDDs									
2,3,7,8-TBDD	Fischer 344 rat (M)	0.001 µmol/kg, i.v.	NA	100	80–90	11.1	 0.7 2.9 17.8	Pool size (% of dose) 11.63 1st component 2.78 2nd component 1.45 3rd component	57
2,3,7,8-TBDD	Fischer 344 rat (M)	0.1 µmol/kg, i.v.	NA	100	80–90	9.2	 0.6 17.8	Pool size (% of dose) 22.47 1st component 2.35 2nd component	57
PCDFs									
2,3,7,8-TCDF	Fischer 344 rat (M)	0.1 µmol/kg, i.v.	100	>96	99	31.4	1.8 0.3	Fecal excretion Urinary excretion	31
2,3,7,8-TCDF	C57BL/6J mice (M)	0.1 µmol/kg, i.v.	100	NA	80	6.5	2.8 1.8 2.0	Urine Feces Urine and feces	75
2,3,7,8-TCDF	DBA/2J mice (M)	0.1 µmol/kg.i.v.	100	NA	80	2.8	4.9 5.4 4.0	Urine Feces Urine and feces	75
2,3,7,8-TCDF	Hartley guinea pig (M)	0.02 µmol/kg, i.v.	>90	NA	<10	1.0	20	Animal exhibited body weight loss	74
2,3,7,8-TCDF	Hartley guinea pig (M)	4 µg/kg, p.o.	NA	NA	NA	NA	40	No observable toxicity	130
2,3,7,8-TCDF	Rhesus monkey (M)	0.1 µmol/kg, i.v.	100	>92	>92	5.4	6.24 10.30 ≃8	Urine Feces Urine and feces	32
2,3,7,8-TCDF	Rainbow trout	1 µg/kg, i.p.	NA	97	NA	NA	15	NC	185

TABLE 5 (continued)
Elimination of 2,3,7,8-TCDD and Related Compounds from Major Tissue Depots

Chemical	Species (sex)	Dose	Tissue	Half-life (days)	Comment	Ref.
2,3,7,8-TCDF	C57BL/6J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	Liver	1.9		75
			Adipose	1.6		
			Skin	0.15	1st component	
				4.0	2nd component	
			Muscle	0.015	1st component	
				1.1	2nd component	
2,3,7,8-TCDF	DBA/2J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	Liver	1.8		75
			Adipose	7.0		
			Muscle	0.02	1st component	
				4.0	2nd component	
1,2,3,7,8-PnCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)			Pool size (% of total dose)	49
			Liver	1.36	42.59 1st component	
				25.72	1.27 2nd component	
			Adipose	12.91	10.19	
			Skin	1.32	7.14 1st component	
				14.53	1.49 2nd component	
			Muscle	0.03	34.81 1st component	
				6.96	7.42 2nd component	
			Adrenal	0.14	0.26 1st component	
				2.36	0.02 2nd component	
			Blood	0.07	5.33 1st component	
				12.42	1.29 2nd component	
1,2,3,7,8-PnCDF	Sprague-Dawley rat (F)	4.0 µg/kg, p.o.	Liver	3.3	69.8% of total dose	358
2,3,4,7,8-PnCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)			Pool size (% of total dose)	47
			Liver	193	67.71	
			Adipose	69	10.53	
			Skin	0.62	3.54 1st component	
				1.23	1.37 2nd component	
			Muscle	0.04	29.40 1st component	
				0.51	2.01 2nd component	
				9.84	0.78 3rd component	
			Blood	0.04	3.18 1st component	
				1.32	0.37 2nd component	
				55	0.008 3rd component	
2,3,4,7,8-PnCDF	Sprague-Dawley rat (F)	5.6 µg/kg, p.o.	Liver	108	78.3% of total dose	358
1,2,3,6,7,8-HxCDF	Sprague-Dawley rat (F)	6.0 µg/kg, p.o.	Liver	73	63.4% of total dose/	358

Note: s.c. = subcutaneous; i.p. = intraperitoneal; i.v. = intravenous; p.o. = *per os.*

hepatic metabolism of 2,3,7,8-TCDF was investigated to assess which enzyme was involved in the metabolism of this compound.[329] Very little metabolism of 2,3,7,8-TCDF was detected in control microsomes (0.3 to 3.0 pmol/mg/h), whereas 2,3,7,8-TCDF metabolism was increased 40- to 200-fold in 2,3,7,8-TCDD-induced rat liver, kidney, and lung microsomes. Because 2,3,7,8-TCDD induces CYP1A1 and CYP1A2 in the rat liver but only CYP1A1 in kidney and lung, these results suggest that CYP1A1 metabolizes TCDF. Studies with selective chemical inhibitors and antibodies to CYP1A1 and CYP1A2 confirmed that CYP1A1 is the primary enzyme responsible for the metabolism of 2,3,7,8-TCDF in rat.[328] 2,3,7,8-TCDF also was metabolized by human liver microsomes and recombinant yeast microsomes expressing human CYP1A1 and reductase. However, this compound was not metabolized by yeast microsomes expressing human CYP1A2 with or without reductase.[328] Based on the EROD activity, a marker of CYP1A1, the relative rate of 2,3,7,8-TCDF metabolism is about 100-fold greater in 2,3,7,8-TCDD-induced rat liver microsomes than in yeast microsomes expressing human CYP1A1 and reductase. Studies in pri-

tabolism may be induced under certain conditions. A small yet significant increase (from 7.0 ± 0.9 to 9.7 ± 1.9% of the administered dose) in biliary excretion of 2,3,7,8-[^{3}H]-TCDD over a 72-h period was observed in TCDD-pretreated rats (10 μg/kg, i.p.) 8 days prior to administration of [^{3}H]-2,3,7,8-TCDD.[270] Studies with female C57BL/6J mice and [^{125}I]-2-Iodo-3,7,8-trichlorodibenzo-*p*-dioxin (ITrCDD) showed a significant modulation of hepatic deposition and elimination if preceded by pretreatment with 2,3,7,8-TCDD. A preadministered dose of 0.1 μmol/kg almost doubled the rate of excretion of ITrCDD, with its half-life decreasing from 14.2 to 8.0 days.[176] In another experiment using a dog, the influence of pretreatment with phenobarbital or 2,3,7,8-TCDD on the biliary excretion of [^{3}H]-2,3,7,8-TCDD metabolites was studied after a single oral dose of 31 or 33.8 ng/kg. Without pretreatment, 24.5% of the absorbed dose was excreted in the bile within 110 h. Phenobarbital did not alter this rate, whereas pretreatment with 2,3,7,8-TCDD (10 μg/kg) 9 days earlier resulted in a doubling of the amount of metabolites excreted in bile.[272] Although this observation is limited to one dog, the results suggest that significant autoinduction of 2,3,7,8-TCDD metabolism and biliary excretion may occur in that species. However, the negative results observed in the rat after pretreatment suggest that autoinduction of 2,3,7,8-TCDD metabolism and subsequent biliary excretion does not occur in rat, at least not to an extent that is biologically relevant.[58,69,270] In contrast to the results with PCDDs and PBDDs, limited data suggest that autoinduction of metabolism and biliary excretion does occur for PCDFs. Pretreatment of rats with 2,3,7,8-TCDF (1.0 μmol/kg, 3 days earlier) significantly increased the biliary excretion of a subsequent dose of [^{14}C]-2,3,7,8-TCDF. Pretreatment resulted in a twofold increase in excretion of compound-derived radioactivity within 8 h after dosing.[192] Similarly, p.o. pretreatment of rats with 500 μg/kg 2,3,4,7,8-PnCDF resulted again in a twofold increase in the biliary elimination of a subsequent dose of [^{14}C]-2,3,4,7,8-PnCDF.[47]

Isolated hepatocytes in suspension culture have been used as an *in vitro* system for studying the autoinduction of the metabolism of 2,3,7,8-TCDD and related compounds.[240,243,396] The metabolism of [^{14}C]-2,3,7,8-TCDD (2.2 μ*M*) was investigated in hepatocytes isolated from untreated, 2,3,7,8-TCDD-, 3-MC-, isosafrole-, or phenobarbital-pretreated rats and hamsters. In both species, 2,3,7,8-TCDD and 3-MC pretreatments elevated the rate of 2,3,7,8-TCDD metabolism five- to sixfold, whereas phenobarbital pretreatment had no effect. Isosafrole produced a 1.8- to 2.5-fold increase in metabolism.[395] These *in vitro* results indicate that 2,3,7,8-TCDD can induce its own rate of metabolism in the rat and hamster at a high substrate concentration (2.2 μ*M*). In contrast, no autoinduction of 2,3,7,8-TCDD metabolism was observed in guinea pig and mouse hepatocytes.[315,394] Together, these results indicate that 2,3,7,8-TCDD is metabolized in the liver by a 2,3,7,8-TCDD-inducible enzyme, which is expressed in the rat and hamster but not in the guinea pig and mouse. More recently, the dose dependency of 2,3,7,8-TCDD metabolism was investigated in rat hepatocytes incubated with [^{3}H]-2,3,7,8-TCDD at concentrations of 0.01, 0.1, and 1.0 μ*M*. No autoinduction was observed at 0.01 μ*M*, which yields hepatocyte concentrations of [^{3}H]-2,3,7,8-TCDD comparable to liver levels attained *in vivo* by a dose of about 10 μg/kg. Similarly, no autoinduction was observed at 0.1 μ*M*, whereas at 1 μ*M* [^{3}H]-2,3,7,8-TCDD metabolism was greater in hepatocytes from TCDD-pretreated rats.[243] These results indicate that TCDD can induce its own rate of metabolism, but this becomes apparent only at doses that could cause overt signs of toxicity *in vivo*. The cause for this dose-dependent autoinduction remains unclear, but probably is the reason for the lack of autoinduction of 2,3,7,8-TCDD metabolism and biliary excretion in the rat, as reported from other studies.[58,69] In a similar experiment, the metabolism of [^{3}H]-2,3,7,8-TCDF also was investigated.[243] At all concentrations, 0.01, 0.1, or 1.0 μ*M*, hepatocytes from 2,3,7,8-TCDD-pretreated rats metabolized 2,3,7,8-TCDF at a rate from 4- to 25-fold higher than that observed in hepatocytes from control rats. The results indicate that 2,3,7,8-TCDF is metabolized in rat liver by a 2,3,7,8-TCDD-inducible enzyme, possibly CYP1A1 or CYP1A2. These *in vitro* results are in accordance with the *in vivo* autoinduction of 2,3,7,8-TCDF metabolism and biliary elimination observed in the rat.[192] The extra-

TABLE 5
Elimination of 2,3,7,8-TCDD and Related Compounds from Major Tissue Depots

Chemical	Species (sex)	Dose	Tissue	Half-life (days)	Comment	Ref.
PCDDs						
2,3,7,8-TCDD	Wistar rat (F)	0.3 μg/kg, s.c.			95% Confidence interval (time period investigated)	2
			Liver	11.5	10.7–12.3 (10–49 days)	
			Liver	16.9	14.0–21.4 (49–91 days)	
			Liver	13.6	12.8–14.4 (10–91 days)	
			Adipose	24.5	22.4–26.8 (14–91 days)	
2,3,7,8-TCDD	Wistar rat (M)	1.0 μg/kg, i.p.	Liver	37.1	Tissue levels were measured for 20 weeks following exposure	170
			Adipose	53.2		
2,3,7,8-TCDD	Sprague-Dawley rat (M)	7 or 20 ppb in diet for 42 days	Liver	11	85% total dose	91
2,3,7,8-TCDD	Sprague-Dawley rat (F)	7 or 20 ppb in diet for 42 days	Liver	13	70% of total dose	91
2,3,7,8-TCDD	C57BL/6J mice (M) Ah^b/Ah^d	0.5 μg/kg, i.p.			Pool size (% of total dose)	34
			Liver	8.5	36.8	
			Adipose	10.3	23.6	
			Skin	16.0	7.6	
2,3,7,8-TCDD	C57BL/6J mice (M) Ah^d/Ah^d	0.5 μg/kg, i.p.			Pool size (% of total dose)	34
			Liver	7.1	20.6	
			Adipose	7.6	31.3	
			Skin	14.9	10.2	
2,3,7,8-TCDD	DBA/2J mice (F) Ah^b/Ah^d	0.5 μg/kg, i.p.			Pool size (% of total dose)	34
			Liver	12.4	29.2	
			Adipose	13.3	30.9	
			Skin	13.2	21.4	
2,3,7,8-TCDD	DBA/2J mice (F) Ah^d/Ah^d	0.5 μg/kg, i.p.			Pool size (% of total dose)	34
			Liver	11.9	20.2	
			Adipose	11.8	42.3	
			Skin	12.8	26.6	
2,3,7,8-TCDD	Rhesus monkey (F)	25 ppt in diet	Adipose	391 ± 88	Mean ± SE (n = 7)	44
OCDD	Fischer 344 rat (M)	50 μg/kg, i.v.			Pool size (% of total dose)	37
			Liver	84	72.7	
			Adipose	38	7.1	
			Skin	3	9.0, 1st component	
				69	0.3, 2nd component	
PBDDs						
2,3,7,8-TBDD	Fischer 344 rat (M)	0.5 μg/kg, i.v. (0.001 μmol/kg)	Liver	4.5	1st component	59
				16.5	2nd component	
			Adipose	57.8		
			Skin	2.5	1st component	
				57.8	2nd component	
			Muscle	1.6	1st component	
				26.7	2nd component	
			Blood	18.2		
PCDFs						
2,3,7,8-TCDF	Fischer 344 rat (M)	30.6 μg/kg, i.v. (0.1 μmol/kg)			Pool size (% of total dose)	31
			Liver	0.10	29.09 1st component	
				1.25	31.39 2nd component	
			Adipose	3.75	17.85	
			Skin	0.45	6.84 1st component	
				11.09	1.22 2nd component	
			Muscle	0.02	24.85 1st component	
				0.72	6.73 2nd component	
			Blood	0.02	1.31 1st component	
				1.14	0.89 2nd component	

TABLE 5 (continued)
Elimination of 2,3,7,8-TCDD and Related Compounds from Major Tissue Depots

Chemical	Species (sex)	Dose	Tissue	Half-life (days)	Comment	Ref.
2,3,7,8-TCDF	C57BL/6J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	Liver	1.9		75
			Adipose	1.6		
			Skin	0.15	1st component	
				4.0	2nd component	
			Muscle	0.015	1st component	
				1.1	2nd component	
2,3,7,8-TCDF	DBA/2J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	Liver	1.8		75
			Adipose	7.0		
			Muscle	0.02	1st component	
				4.0	2nd component	
1,2,3,7,8-PnCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)			Pool size (% of total dose)	49
			Liver	1.36	42.59 1st component	
				25.72	1.27 2nd component	
			Adipose	12.91	10.19	
			Skin	1.32	7.14 1st component	
				14.53	1.49 2nd component	
			Muscle	0.03	34.81 1st component	
				6.96	7.42 2nd component	
			Adrenal	0.14	0.26 1st component	
				2.36	0.02 2nd component	
			Blood	0.07	5.33 1st component	
				12.42	1.29 2nd component	
1,2,3,7,8-PnCDF	Sprague-Dawley rat (F)	4.0 µg/kg, p.o.	Liver	3.3	69.8% of total dose	358
2,3,4,7,8-PnCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)			Pool size (% of total dose)	47
			Liver	193	67.71	
			Adipose	69	10.53	
			Skin	0.62	3.54 1st component	
				1.23	1.37 2nd component	
			Muscle	0.04	29.40 1st component	
				0.51	2.01 2nd component	
				9.84	0.78 3rd component	
			Blood	0.04	3.18 1st component	
				1.32	0.37 2nd component	
				55	0.008 3rd component	
2,3,4,7,8-PnCDF	Sprague-Dawley rat (F)	5.6 µg/kg, p.o.	Liver	108	78.3% of total dose	358
1,2,3,6,7,8-HxCDF	Sprague-Dawley rat (F)	6.0 µg/kg, p.o.	Liver	73	63.4% of total dose/	358

Note: s.c. = subcutaneous; i.p. = intraperitoneal; i.v. = intravenous; p.o. = *per os.*

hepatic metabolism of 2,3,7,8-TCDF was investigated to assess which enzyme was involved in the metabolism of this compound.[329] Very little metabolism of 2,3,7,8-TCDF was detected in control microsomes (0.3 to 3.0 pmol/mg/h), whereas 2,3,7,8-TCDF metabolism was increased 40- to 200-fold in 2,3,7,8-TCDD-induced rat liver, kidney, and lung microsomes. Because 2,3,7,8-TCDD induces CYP1A1 and CYP1A2 in the rat liver but only CYP1A1 in kidney and lung, these results suggest that CYP1A1 metabolizes TCDF. Studies with selective chemical inhibitors and antibodies to CYP1A1 and CYP1A2 confirmed that CYP1A1 is the primary enzyme responsible for the metabolism of 2,3,7,8-TCDF in rat.[328] 2,3,7,8-TCDF also was metabolized by human liver microsomes and recombinant yeast microsomes expressing human CYP1A1 and reductase. However, this compound was not metabolized by yeast microsomes expressing human CYP1A2 with or without reductase.[328] Based on the EROD activity, a marker of CYP1A1, the relative rate of 2,3,7,8-TCDF metabolism is about 100-fold greater in 2,3,7,8-TCDD-induced rat liver microsomes than in yeast microsomes expressing human CYP1A1 and reductase. Studies in pri-

TABLE 6
Half-Life Estimates for 2,3,7,8-TCDD and Related Compound in Humans

Chemical	Exposure incident	Number of individuals	Sample	Time period between first and last analysis	Number of timepoints	Half-life (years)	Ref.
PCDDs							
2,3,7,8-TCDD	Male volunteer	1	Feces	125 days	28	5.8	273
2,3,7,8-TCDD	Ranch Hand Vietnam veterans	36	Serum	5 years	2	7.1[a]	259
1,2,3,6,7,8-HxCDD	Technical pentachlorophenol in wood of home	1	Adipose tissue	28 months	2	3.5	110
1,2,3,4,6,7,8-HpCDD	Technical pentachlorophenol in wood of home	1	Adipose tissue	28 months	2	3.2	110
OCDD	Technical pentachlorophenol in wood of home	1	Adipose tissue	28 months	2	5.7	110
PCDFs							
2,3,4,7,8-PnCDF	Binghamton, NY, state office building	1	Adipose tissue	Initial 43 months	4	4.7	311
			Blood	Final 29 months	4	7.2	
			Combined	Total 6 years	7	4.5	
1,2,3,4,7,8-HxCDF	Binghamton, NY, state office building	1	Adipose tissue	Initial 43 months	4	2.9	311
			Blood	Final 29 months	4	4.4	
			Combined	Total 6 years	7	4.0	
1,2,3,6,7,8-HxCDF	Binghamton, New York, state office building	1	Adipose tissue	Initial 43 months	4	3.5	311
			Blood	Final 29 months	4	4.3	
			Combined	Total 6 years	7	4.9	
1,2,3,4,6,7,8-HpCDF	Binghamton, NY, state office building	1	Adipose tissue	Initial 43 months	4	6.5	311
			Blood	Final 29 months	4	4.1	
			Combined	Total 6 years	7	6.8	
2,3,4,7,8-PnCDF	Yu-Cheng	4	Blood	Initial 2.9 years	2	1.3	303
		3		Final 2.7 years	2	2.9	
		2		Total 5.6 years	3	1.7	
1,2,3,4,7,8-HxCDF	Yu-Cheng	4	Blood	Initial 2.9 years	2	2.1	303
		3		Final 2.7 years	2	5.1	
		2		Total 5.6 years	3	2.4	
1,2,3,4,6,7,8-HpCDF	Yu-Cheng	4	Blood	Initial 2.9 years	2	1.6	303
		3		Final 2.7 years	2	6.1	
		2		Total 5.6 years	3	2.4	
2,3,4,7,8-PnCDF 1,2,3,4,7,8-HxCDF 1,2,3,4,6,7,8-HpCDF	Yu-Cheng	3	Blood	9 years	5–6	2–3	304
2,3,4,7,8-PnCDF 1,2,3,4,7,8-HxCDF	Yusho	9	Blood	7 years	3–5	>5	304
1,2,3,4,6,7,8-HpCDF	Technical pentachlorophenol in wood of home	1	Adipose tissue	28 months	2	<1.7	110
OCDF	Technical pentachlorophenol in wood of home	1	Adipose tissue	28 months	2	1.8	110

[a] 95% confidence interval about the median of 5.8–9.6 years.

mary cultures of rat and human hepatocytes also found that *in vitro* exposure to 2,3,7,8-TCDD (50 n*M*) can markedly induce the rate of 2,3,7,8-TCDF metabolism.[199] In addition, it was observed in this study that 2,3,7,8-TCDF was metabolized in rat hepatocytes at a rate 20- to 50-fold greater than that of human hepatocyte cultures. Thus, although 2,3,7,8-TCDF is metabolized by rat and human CYP1A1, there are marked quantitative differences in metabolism, which suggest that 2,3,7,8-TCDF will be far more persistent in humans.

In summary, *in vivo* and *in vitro* data suggest that autoinduction of 2,3,7,8-TCDD or 2,3,7,8-TBrDD metabolism does not occur in the rat after exposure to sublethal doses of these agents. This is in contrast to 2,3,7,8-TCDF and 2,3,4,7,8-PnCDF, in which *in vivo* and *in vitro* results indicate that autoinduction of metabolism and biliary elimination of these compounds does occur in rat. Recent results also indicate that 2,3,7,8-TCDF is metabolized by rat and human CYP1A1, however, there are marked quantitative differences that suggest that 2,3,7,8-TCDF will be far more persistent in humans.

B. *In Vivo* Induction of Cytochrome P450-Dependent Activities

The induction of CYP1A1 and CYP1A2 enzyme activities by 2,3,7,8-substituted PCDDs and PCDFs has been studied *in vivo* in a variety of species and is one of the most sensitive parameters for biological activity of these compounds. Besides the use of CYP1A1 induction in laboratory experiments, the application in environmental studies with birds and fish also has been illustrated.[29,106,122,327] Most studies have focused on hepatic EROD and AHH activities, which are both CYP1A1-dependent activities.[182] In these studies, the number of doses and/or dose range were usually limited. This factor should be taken into consideration when evaluating the ED_{50} values derived from these experiments.[14,15,83,124,187] Nevertheless, the data from these studies allow some comparison of the CYP1A1-inducing properties of selected 2,3,7,8-substituted PCDDs and PCDFs relative to that of 2,3,7,8-TCDD. In Table 7, the ED_{50} values and relative inducing potencies for CYP1A1-dependent enzyme activities obtained from *in vivo* studies are summarized.[15,83,124,187,217,242] At present, the data from rat studies are most comprehensive, while less information is available for the guinea pig and mouse. Although EROD and AHH activites are both CYP1A1 dependent, it appears from Table 7 that the relative induction potency of a given PCDD or PCDF congener is not always the same for both types of enzyme activities. 2,3,4,7,8-PnCDF, 1,2,3,7,8-PnCDD, and 1,2,3,6,7,8-HxCDD are the next most active inducers after 2,3,7,8-TCDD, with a relative potency ranging from 6 to 23% relative to TCDD. The relative inducing potencies of 2,3,7,8-TCDF, 1,2,3,7,8-PnCDF, and all 2,3,7,8-substituted HxCDFs are much lower, ranging from 1 to 5% relative to 2,3,7,8-TCDD. Although the absolute ED_{50} values for 2,3,7,8-TCDD, 1,2,3,7,8-PnCDF, and 2,3,4,7,8-PnCDF are much lower in guinea pig than in rat, the relative potencies of these congeners show a comparable rank order in both species. These quantitative differences may be related to the relatively greater persistence of these compounds in the guinea pig.

Congener-specific toxicokinetics also may contribute to the relative *in vivo* CYP1A1-inducing potencies of the differnt PCDD and PCDF congeners. CYP1A1 induction studies using rat H-4-II cells showed good linear correlation between the ED_{50} values obtained *in vitro* and short-term *in vivo* studies with immature male rats.[306] These results suggest, at least in rat, that toxicokinetic factors like body distribution and metabolism do not appear to play a major role in determining the congener-specific, CYP1A1-inducing potencies.

C. Hepatic Induction of Phase II Enzyme Activities

Apart from being potent CYP1A1 and CYP1A2 inducers, 2,3,7,8-substituted PCDDs and PCDFs also are able to induce phase II type enzymes, as demonstrated in several laboratory species. The induction of some of the most important phase II enzymes has been investigated. However, there are considerably fewer data available on this subject than on phase I enzyme induction. Discussion is confined to induction in liver only because at present no information is available on

TABLE 7
ED_{50} Values of CYP1A1-Related Enzyme Activities in Several Mammalian Species

Species	Compound	ED_{50} EROD (μmol/kg)	Relative to TCDD	ED_{50} AHH (μmol/kg)	Relative to TCDD	Days after dosing	Remarks	Ref.
Rat,	2,3,7,8-TCDD	0.003	1	0.004	1	14	i.p.	187
Imm. Wistar	1,2,3,7,8-PnCDD	0.056	0.057	0.031	0.13			
	1,2,3,4,7,8-HxCDD	0.130	0.23	0.030	0.13			
	2,3,7,8-TCDF			0.652	0.006	14	i.p.	186
	1,2,3,7,8-PnCDF			1.47	0.003			
	2,3,4,7,8-PnCDF			0.037	0.11			
	1,2,3,6,7,8-HxCDF			0.347	0.012			
	2,3,4,6,7,8-HxCDF			0.265	0.015			
	1,2,3,4,7,8-HxCDF			0.294	0.014			
Guinea pig,	2,3,7,8-TCDD	$0.093*10^{-3}$	1	$0.28*10^{-3}$	1	14	i.p.	124
Imm. Hartley	2,3,4,7,8-PnCDF	$0.71*10^{-3}$	0.13	$1.2*10^{-3}$	0.23			
	1,2,3,7,8-PnCDF	$7.0*10^{-3}$	0.013	$5.9*10^{-3}$	0.047			
Mice,	1,2,3,4,6,7,8-HpCDF	0.314		0.11		12	i.p.	83
C57BL/6J	1,2,3,4,7,8,9-HpCDF	0.200		0.700				
Rat, Imm. Sprague Dawley	2,3,7,8-TCDD	0.0027	1	0.0033	1	2	i.p.	14

extrahepatic induction by PCDDs and PCDFs. The majority of the phase II type enzymes catalyzes conjugation reactions, which facilitate the excretion of the phase I reaction products by the addition of more polar groups to the molecule. DT-diaphorase is an exception to this because it does not introduce new functional groups into the xenobiotic molecule. The localization of most phase II enzymes is less specific than that of the cytochrome P450 isoenzymes. A number of phase II enzymes can be found in the cytosolic and microsomal fractions of the cell, whereas cytochrome P450 isoenzymes are specifically associated with the microsomal fraction. As a consequence, studies on certain phase II enzymes may relate to different forms of the enzyme involved. Thus, a comparison between different experiments may not always be possible. In addition, different substrates, even within one study, have sometimes been used to assay the activities of the Phase II enzymes.[25] Based on the information available from these studies, it was not possible to differentiate all these phase II enzyme forms and substrates. Only sUDPGT, an isoenzyme of UDPGT with a high substrate specificity for steroid hormones, was treated separately.[346] Results from the studies wtih PCDDs and PCDFs covering induction of phase II enzyme activity are compiled in an abridged form in Table 8. As can be seen from these data, UDP-glucuronosyl transferase (UDPGT), DT-diaphorase, and, to a lesser extent, glutathion-S-transferase (GST) are most susceptible toward induction by 2,3,7,8-substituted PCDDs and PCDFs.[297,336,397] Because only UDPGT and DT-diaphorase have been investigated following low and high doses of 2,3,7,8-TCDD, it cannot be excluded that some of the other enzymes also are inducible at higher doses. Sulfo-transferase appears to be the only phase II enzyme to be slightly downregulated by TCDD.[336] None of the studies reported a dose-response relationship or ED_{50} values, but obviously the maximum inducibility seems to be less than that of the CYP1A1- and CYP1A2-dependent enzyme activities, such as EROD or AHH. The maximum reported induction of UDPGT, DT-diaphorase, and GST were 22-, 16-, and 1.4-fold above the control level, respectively.[24,25,297,336] This is significantly less than the 50- to 100-fold induction observed for CYP1A1- and CYP1A2-related activities.[2] As for CYP1A1 and CYP1A2, the mechanism of induction for most forms of phase II enzymes (UDPGT, DT-diaphorase, GST) by PCDDs and PCDFs is regulated via the Ah-receptor.[162,247,257] However, for planar aromatic compounds other than PCDDs or PCDFs, such as β-naphthoflavone, an additional form of GST induction has been elucidated. This mechanism may function independent of the Ah-receptor and requires metabolism of the compound before transcriptional activation of the respective subunit gene (Ya-subunit gene) can take place.[298]

TABLE 8
Induction of Phase II Enzymes in Several Mammalian Species

Species	Enzyme	Location	Compound	Dose (μg/kg)	Induction (fold)	Time (days after dosing)	Ref.
Rat	UDPGT	E.R.	2,3,7,8-TCDD	100	7	10	296
Rat	UDPGT		2,3,7,8-TCDD	150	15–22	4–11	297
Rat	UDPGT	E.R.	2,3,7,8-TCDD	1	1	28	8
Rat	UDPGT		2,3,7,8-TCDD	5	2	28	8
Rat	UDPGT		2,3,7,8-TCDD	10	3	28	8
Rat	UDPGT		2,3,7,8-TCDD	2.5	6	28	8
Rat	UDPGT		1,2,3,7,8-PnCDD	16.2	2	28	8
Rat	UDPGT		2,3,4,7,8-PnCDF	53	2.5	28	8
Rat	UDPGT		OCDD	755	4	28	8
Guinea pig	sUDPGT	E.R.	2,3,7,8-TCDD	2.5	1	5, 10	346
Mouse CD-1	sUDPGT		2,3,7,8-TCDD	40	1.2	—	346
Mouse C57BL	sUDPGT		2,3,7,8-TCDD	40	1.2	—	346
Mouse DBA	sUDPGT		2,3,7,8-TCDD	40	1.2	—	346
Mouse	EH	E.R.	2,3,7,8-TCDD	40	1.5	3–1	95
Rat	EH	E.R.	2,3,7,8-TCDD	10	1.2	10	336
Rat	GST	Cytosol	2,3,7,8-TCDD	10	1.1–1.4	10	336
Rat	ST	Cytosol	2,3,7,8-TCDD	10	0.5–1	10	336
Rat	DT-Diaph.	E.R.	2,3,4,7,8-PnCDF	1,000	7–9	5	397
Rat	DT-Diaph.		2,3,7,8-TCDF	1,000	9	5	397
Rat	DT-Diaph.		1,2,3,7,8-PnCDF	10,000	7	5	397
Rat	DT-Diaph.		1,2,3,4,7,8-HxCDF	10,000	9	5	397
Rat	DT-Diaph.		2,3,4,6,7-PnCDF	1,000	4	5	397
Rat	DT-Diaph.		1,2,3,4,6,7-TCDF	1,000	4	5	397
Chick embryo	DT-Diaph.	Cytosol	2,3,7,8-TCDD	6.4	1.3	7	324
Chick embryo	DT-Diaph.		2,3,7,8-TCDD	32.2	2.8	7	324
Rat	DT-Diaph.		2,3,7,8-TCDD	10	7.1	5–7	324
Guinea pig	DT-Diaph.		2,3,7,8-TCDD	10	1.1	5–7	324
Rat, CD	UDPGT	E.R.	2,3,7,8-TCDD	25	6	4	180
Rat, CD	sUDPGT	E.R.	2,3,7,8-TCDD	25	1	4	180
Rat, Wistar	UDPGT	E.R.	2,3,7,8-TCDD	20	7	7	10
Rat, Wistar	GST	E.R.	2,3,7,8-TCDD	20	1	7	10
Rat, Wistar	EH	E.R.	2,3,7,8-TCDD	20	1.2	7	10
Rat, Wistar	GST	Cytosol	2,3,7,8-TCDD	20	1–1.3	6	16
Rat, S.D.	DT-Diaph.	Cytosol	2,3,7,8-TCDD	45	3	0.5	25
Rat, S.D.	DT-Diaph.	Cytosol	2,3,7,8-TCDD	45	6	1	25
Rat, S.D.	DT-Diaph.	Cytosol	2,3,7,8-TCDD	45	6	1	25
Rat, S.D.	DT-Diaph.	E.R.	2,3,7,8-TCDD	45	2	0.5	25
Rat, S.D.	DT-Diaph.	E.R.	2,3,7,8-TCDD	45	2	1	25
Rat, S.D.	DT-Diaph.	Cytosol	2,3,7,8-TCDD	25–50	14–16	7	25
Rat, S.D.	DT-Diaph.	E.R.	2,3,7,8-TCDD	25–50	8–10	7	25
Rat, S.D.	DT-Diaph.	Mitochondria	2,3,7,8-TCDD	25–50	5	7	25
Rat, S.D.	DT-Diaph.	Cytosol	OCDD	100	1	7	25
Rat, S.D.	DT-Diaph.	Cytosol	OCDD	1,000	1	7	25
Rat, S.D.	DT-Diaph.	E.R.	OCDD	100	1	7	25
Rat, S.D.	DT-Diaph.	E.R.	OCDD	1,000	2	7	25
Rat, S.D.	DT-Diaph.	Mitochondria	OCDD	100	1	7	25
Rat, S.D.	DT-Diaph.	Mitochondria	OCDD	1,000	1.8	7	25
Guinea pig,	DT-Diaph.	Cytosol	2,3,7,8-TCDD	0.6–6	1–1.5	7	25
Hartley	DT-Diaph.	E.R.	2,3,7,8-TCDD	0.6–6	0.7–1	7	25
	DT-Diaph.	Mitochondria	2,3,7,8-TCDD	0.6–6	1	7	25

The significance of enzymatic phase II induction regarding metabolism and elimination of PCDDs and PCDFs is presently not clear. Metabolic breakdown products of PCDDs and PCDFs in the rat are mainly excreted in the form of glucuronidated conjugates. Additionally, minor amounts of sulfur-containing metabolites have been observed, which probably originate from GST or sulfo-transferase-catalyzed conjugations.[168,260,268,341] There is no indication that autoinduction of UDPGT or GST may be rate limiting for the elimination of these compounds, which is in contrast to findings with CYP1A-related activities (see Section V.A).[47,192,247]

VI. ELIMINATION

A. General

In mammalian systems, the liver and adipose tissue represent the major compartments for the disposition of PCDDs and PCDFs. In most experiments, the elimination of these compounds from muscle tissue and blood usually proceeds at a faster rate than from the liver and adipose tissue compartments. The disposition and elimination from the skin are more species dependent and can resemble that of the adipose tissue.[31,47,48,50] In general, the accumulation and elimination of these compounds can adequately be described by a one-compartment open model,[121,295] but for most compounds, a biphasic or even triphasic exponential decay curve could describe the elimination process from different tissues more accurately.[31,47,48,50] Physiologically based pharmacokinetic models also have been used to describe the body distribution and elimination of these compounds in rodents.[144,175–177] The elimination of PCDDs and PCDFs in fish proceeds generally more slowly than in mammals.[146,147] This may be due to a slower rate of metabolism of these compounds in fish and the greater amounts stored in tissues with a high lipid content, when compared with mammalian species. As a result, under laboratory conditions, the uptake and elimination of some lower chlorinated non-2,3,7,8-substituted PCDDs and PCDFs also can be studied in fish. The elimination of the 2,3,7,8-substituted PCDDs and PCDDs occurs predominantly via the bile and the feces as polar metabolites, with much smaller amounts excreted via the urine. In almost all mammalian and fish species studied, the radioactivity in tissues was associated with the parent compound. Apparently, the hydroxylated and/or conjugated metabolites are rapidly eliminated from the body, with the exception of the guinea pig, which appears to retain these polar compounds to a greater extent.[241] Tables 4, 5, and 6 summarize data on the congener, species, and tissue-specific elimination of PCDDs and PCDFs.

B. Mammals

1. Rat

In rat, 2,3,7,8-TCDD is by far the most studied compound. Whole body half-lives ranged from 17 to 31 days, depending on the dose and strain used.[2,3,11,91,258,267,295] One study reported a distinct difference in elimination for 2,3,7,8-TCDD between the liver and adipose tissue, 12 to 17 and 25 days, respectively.[2] However, a multiple-dose study using 0.1 and 1.0 μg/kg/day for 7 weeks did not report significant differences in elimination between liver and adipose tissue.[295] In marked contrast with results from the above experiments, another study reported half-lives for 2,3,7,8-TCDD of 7.6 and 5.3 weeks for the adipose tissue and liver, respectively.[170] The reason for this marked discrepancy with other studies is unknown. Besides excretion of metabolites, the excretion of unchanged PCDDs and PCDFs also was detected in rat feces after s.c. exposure to a defined mixture of congeners.[3] Studies in lactating rats also have found that unchanged 2,3,7,8-TCDD may be excreted in the milk of lactating animals.[180,203,221] In rats, it was shown that lactation can distinctly influence the elimination of these compounds. In a 21-day study in lactating rats, 2,3,7,8-TCDD had a half-life of 7 days in the liver, while under similar conditions nonlactating rats had a half-life of 14 days.[2,152] Therefore lactation, direct intestinal elimination, and perhaps sebum may serve as routes for excretion of 2,3,7,8-TCDD that do not depend on metabolism of the toxin. These data suggest that the *in vivo* half-life for elimination of 2,3,7,8-TCDD and related compounds only provides an approximation of the rate of metabolism

of these compounds in a given animal. In contrast with mice,[97] strain differences in elimination were not observed in rats, with Long Evans and Han Wistar rats having a similar half-life after a single dose of 5 μg/kg 2,3,7,8-TCDD.[267] The elimination of 2,3,7,8-TCDF proceeds much more rapidly than that of 2,3,7,8-TCDD. The whole body half-life for 2,3,7,8-TCDF was found to be approximately 2 days, and in the liver a biphasic elimination was observed with half-lives of 0.1 and 1 day, respectively.[31] The more rapid elimination of 2,3,7,8-TCDF appears to be due to the more rapid metabolism of this compound. *In vitro* studies with TCDD-induced rat hepatocytes in suspension culture support the above hypothesis, with the rate of 2,3,7,8-TCDF metabolism being about 50-fold greater than that of 2,3,7,8-TCDD.[243] Only one study investigated the kinetics of 1,2,3,7,8-PnCDD after administration of a single dose of 10 μg/kg. The whole body half-life of 30 days was comparable to that of 2,3,7,8-TCDD. The addition of one chlorine atom apparently did not influence the elimination when compared with 2,3,7,8-TCDD.[372] 1,2,3,7,8-PnCDF, like 2,3,7,8-TCDF, is one of the few 2,3,7,8-substituted congeners that is relatively rapidly metabolized and eliminated by mammalian systems. The whole body half-life was found to be 6 days,[49] with an even faster elimination $t_{1/2}$ of <5 days from the liver.[9,357,358] Slightly longer half-lives of 12 to 14 days were reported in the adipose tissue and skin.[49] In contrast with the former compound, 2,3,4,7,8-PnCDF, was found to be an extremely persistent compound in the rat, with much slower elimination rates than 2,3,7,8-TCDD.[47,358] The whole body half-life was approximately 64 days, but in contrast with 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF, the elimination from the liver was slower, 108 to 193 days.[47,358] The strong binding of the congener to CYP1A2,[166,398] in combination with the metabolism rate-limiting chlorine atom on the 4 position,[260] could explain this slow liver elimination. 2,3,4,7,8-PnCDF was almost exclusively excreted through the bile in the form of polar metabolites.[47] Two studies reported the liver retention and subsequent elimination of 2,3,4,6,7-PnCDF, a non-2,3,7,8-substituted PCDF. The investigators reported a half-life of <2 days in rat liver.[357,360] With increasing chlorine content, the elimination rate markedly decreases. Whole body, liver, and adipose tissue half-lives ranging from 75 days to 7 years have been estimated for 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDD, and OCDD.[37,358,403] A study using a complex mixture of PCDFs estimated half-lives between 35 and 46 days for 1,2,3,6,7,8-, 1,2,3,4,7,8,-, and 2,3,4,6,7,8-HxCDF, while the half-life of 1,2,3,7,8,9-HxCDF was <10 days.[9] It can be suggested that the observed shorter half-life of 1,2,3,7,8,9-HxCDF may be a direct result of the lack of chlorine substitution on the 4 and 6 position, facilitating metabolism.[49,260,358] From a pharmacokinetic point of view, the exact determination of these long half-lives is questionable, as experimental periods quite often were limited and extrapolations had to be made. In general, an experimental time period of three to five times the half-life is suggested to make an accurate determination. However, this is not possible in many cases because the experiment would exceed the lifetime of the rat.

2. Mice

After a single dose of 10 μg/kg 2,3,7,8-TCDD to C57BL/6J, DBA/2J, and B6D2F1/J mice, significant differences were reported by Gasiewicz and co-workers for the whole body half-lives. The whole body half-life of 2,3,7,8-TCDD was approximately twice as long in the Ah-non-responsive DBA/2J as in the Ah-responsive C57BL/6J strain, 24 and 11 days, respectively.[97] In male ICR/Ha Swiss mice, the whole body half-life of 20 days for 2,3,7,8-TCDD was similar to that reported for DBA mice.[153] Originally, it was suggested that these differences between whole body half-lives could be caused by the greater amount of adipose tissue present in the DBA/2J strain.[97] However, application of a physiologically based pharmacokinetic model showed that differences in body distribution and elimination could be explained not only by the differences in adipose tissue content, but also by the presence of an hepatic microsomal-binding protein.[175] The distribution and excretion of 2,3,7,8-TCDD in congenic male C57BL/6J and female DBA/2J mice, in which the congenic pairs differed only at the Ah-locus (Ah^b/Ah^d or Ah^d/Ah^d), have been examined in detail.[34] The Ah-locus had no effect on the

distribution or excretion, with the exception of elevated hepatic distribution in the Ah^b/Ah^d mice of both strains. However, there were strain differences in the routes and rates of excretion. For example, the elimination rate from liver and adipose tissue was slightly lower for the DBA strain (see Table 5). It was concluded that the distribution and excretion of 2,3,7,8-TCDD were governed primarily by the total genetic background and not by the allele present at the Ah-locus.[34] These findings are consistent with *in vitro* results obtained with hepatocyte suspension cultures of both mouse strains, which showed that the hepatic uptake and metabolism of 2,3,7,8-TCDD was similar in the two strains with genetic differences at the murine Ah-locus.[315] For 2,3,7,8-TCDF, no differences were found in the elimination rate from the liver between C57BL/6J and DBA/2J mice. However, the amount of 2,3,7,8-TCDF deposited in liver was 1.5-fold higher in the C57BL/6J strain. The lower concentration of 2,3,7,8-TCDF in the liver of the DBA mice may account for the slower whole body clearance observed, 4 vs. 2 days for the DBA and C57BL mice, respectively.[75] For mice, lactation is an effective way of eliminating PCDDs and PCDFs from the liver as well as other extrahepatic tissues.[216,220,380] In pregnant female C57BL/6J mice, the elimination of 2,3,7,8-TCDD and 2,3,7,8-TCDF from the liver was found to be more rapid than in adult males.[380]

3. Hamster

Only a few studies have investigated the rate of elimination of 2,3,7,8-TCDD in hamster. Olson and co-workers administered a single dose of 650 µg/kg 2,3,7,8-TCDD either i.p. or p.o. to this species and reported that whole body half-lives were 11 to 12 and 15 days, respectively.[239] Elimination rates of 2,3,7,8-TCDD in liver and adipose tissue were not determined in these *in vivo* experiments, and only the parent compound was observed in these tissues, indicating rapid excretion of the polar metabolites.[239] In another study using primary hepatocyte suspension cultures, comparable metabolism rates of 2,3,7,8-TCDD were observed for hamster and rat, 0.20 and 0.18 pmol/h/mg protein, respectively.[395] Thus, the elimination rate of 2,3,7,8-TCDD *in vivo* was found to be two- to threefold higher in hamster than in rat. However, it is assumed that this difference could not fully explain the remarkable 100-fold difference in sensitivity to the acute toxicity of 2,3,7,8-TCDD between both species.

4. Guinea Pig

From all the rodents studied so far, the guinea pig exhibits the slowest elimination for 2,3,7,8-TCDD and 2,3,7,8-TCDF.[74,130,241] In guinea pig, different half-lives have been reported for 2,3,7,8-TCDD. Animals receiving 2.0 µg/kg 2,3,7,8-TCDD excreted this compound with a half-life of 30 days during a 23-day study.[96] In contrast, a single i.p. dose of 0.56 µg/kg 2,3,7,8-TCDD resulted in a whole body half-life of approximately 94 days during a 45-day study.[241] The discrepancies observed between both studies may be explained by the differences in experimental time period, in which a biphasic elimination may have occurred with distinctly different elimination rate constants. A distinct contrast between guinea pigs and other rodents was the presence of significant amounts of polar metabolites in liver, kidney, skeletal muscle, and adipose tissue ranging from 4 to 28% of the radioactivity present. In addition, 70 to 90% of the radioactivity in the feces was found to be parent 2,3,7,8-TCDD, whereas bile only contained metabolites of 2,3,7,8-TCDD. These results suggest that direct intestinal excretion of the parent compound is the major elimination route in the guinea pig.[241] Elimination rates for 2,3,7,8-TCDD in different types of tissue in the guinea pig have not been reported. A comparative study with primary hepatocyte suspension cultures from guinea pig and rat determined that the elimination rate of 2,3,7,8-TCDD was approximately 3 times faster in rat than in guinea pig.[394] These *in vitro* results are in good agreement with the differences observed for whole body half-life in both species, 94 and 20 to 30 days, respectively (see Table 4). The only other congener studied in any detail in guinea pig is 2,3,7,8-TCDF.[74] As for 2,3,7,8-TCDD, fecal excretion of 2,3,7,8-TCDF included almost exclusively the parent compound, but in urine one or

more polar metabolites were detected. The relatively low levels of metabolites in feces indicate that again excretion by metabolism does not play a major role for 2,3,7,8-TCDF, as was observed for 2,3,7,8-TCDD in this species. A whole body half-life was approximately 20 days,[74] which is significantly less than that of 2,3,7,8-TCDD,[96,241] but still much higher than in rat.[31] Furthermore, the above results indicate that the relatively limited ability of guinea pig to metabolize 2,3,7,8-TCDD and 2,3,7,8-TCDF may contribute to the greater persistence and greater acute toxicity of these congeners in guinea pig.

5. Cow

The elimination of 2,3,7,8-substituted PCDDs and PCDFs in cows has been much less the subject of research than in the preceding species.[89,137,238] After a single dose of 0.05 µg/kg b.w. 1,6[^{3}H]-2,3,7,8-TCDD, administered either on crushed grain or Gerald silt loam soil, the elimination was followed for 14 days. The total elimination via milk was similar for both matrices, ranging between 11 and 16% of the dose during this period. The elimination rate of 2,3,7,8-TCDD in milk closely paralleled that of blood, but levels in blood were approximately 20 times lower.[137] The most recent study examined the elimination of tetra- to heptachlorinated PCDDs and PCDFs in lactating cows. After a single dose of 3.7 or 37.1 ng/kg, mean half-lives ranged from 40 to 50 days for most of the congeners. An exception was found for 2,3,7,8-TCDF, which was attributed to more rapid metabolic clearance. Based on these results, it was suggested that elimination of most PCDDs and PCDFs was governed by passive partitioning over tissues and body fluids, with metabolic clearance playing a minor role.[238]

6. Monkey

Adult female Rhesus monkeys, which had been on a diet containing 25 ppt 2,3,7,8-TCDD for about 4 years, were found to have an average half-life of 391 days in adipose tissue, but the individual variation was large. Passive excretion of 2,3,7,8-TCDD during a 4-month lactation period resulted in excretion of about 21% of the body burden.[44] The half-life of 2,3,7,8-TCDD in the breastfed infants from the above study was approximately 181 days during the first year after birth when corrected for bodyweight gain.[45] These studies indicate that 2,3,7,8-TCDD is exceptionally persistent in the monkey and that elimination of 2,3,7,8-TCDD is faster in the juvenile monkey than in the adult female. In the Rhesus monkey, 2,3,7,8-TCDF was eliminated with a whole body half-life of about 8 days, indicating that this congener also was more persistent in primates than in rodents.[31,32,75] Although the whole body half-life of 2,3,4,7,8-PnCDF was significantly higher than 2,3,7,8-TCDF, 30 to 70 days,[48] it was significantly lower than in rodents.[47,358] However, these data should be considered as minimum values because the animals involved showed overt signs of toxicity during the experimental time period. The elimination rate from the liver, skin, muscle, and adipose tissue was within the range observed for the whole body.[48] The Marmoset monkey is another non-human primate species that has been used to study the kinetics of these compounds. After subcutaneous administration of a complex mixture of PCDDs and PCDFs, the elimination of 2,3,7,8-substituted and otherwise substituted congeners was followed for 28 weeks. Half-lives for the liver and adipose tissue ranged from 8 weeks up to several years for most of the 2,3,7,8-substituted congeners. An exception was found for 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF, with half-lives <7 days.[226] This congener-specific difference is in accordance with studies using rats.[9,31,49,358] Half-lives for several non-2,3,7,8-substituted hexa- and heptachlorinated congeners also were estimated to range from 1 to 5 weeks in the liver and adipose tissue.[226]

7. Human

Table 6 summarizes additional half-life estimates for 2,3,7,8-TCDD and related compounds in humans, based on serum and/or adipose tissue concentrations at two or more timepoints.[259,304,311] After self-ingestion by a 42-year-old man of 105 ng 2,3,7,8-TCDD in corn oil, the half-life for whole body elimination was estimated to be 2120 days.[273] In another study, the half-life of 2,3,7,8-

TCDD in humans was estimated to be approximately 7 years on the basis of 2,3,7,8-TCDD levels in serum samples taken in 1982 and 1987 from 36 of the Ranch Hand personnel who had 2,3,7,8-TCDD levels >10 ppt in 1987.[259] These studies indicate that 2,3,7,8-TCDD is exceedingly persistent in humans. Estimated half-lives for other congeners in Table 6 range from 0.8 to 10 years. These half-life values are rough estimates based on a small number of individuals and based on analysis at as few as two timepoints.[256,319] Estimates also assume a simple, single-compartment, first-order elimination process. In addition, physiologically based pharmacokinetic models also can be used to estimate the elimination of these compounds from humans.[145] The elimination of PCDFs in humans from the Yusho and Yu-Cheng rice oil poisonings also has been the subject of research.[303,304] Yu-Cheng individuals had PCDF blood levels on a lipid basis of 1 to 50 μg/kg, whereas Yusho patients had levels of 0.1 to 5 μg/kg. In the Yu-Cheng individuals, half-lives for three PCDFs were 2 to 3 years, while elimination from Yusho individuals was more variable and slower, with half-lives >5 years (see Table 6) and, in several cases, there was no measurable elimination during the 7 years in which samples were available. The limited results suggest that clearance of these PCDFs in human is at least biphasic, with faster elimination at higher exposures. This suggestion is supported by the longer half-life values also reported for PCDFs in humans at later timepoints after exposure, when concentrations are closer to the background levels of individuals with no unusual exposure.[303,304,311] The bioconcentration factor (BCF) for 2,3,7,8-TCDD was calculated in two different studies that incorporated human data on body distribution and elimination rates. Based on the daily food intake, a BCF value for 2,3,7,8-TCDD was calculated to be between 115 and 400.[100,381]

C. Fish

In contrast to mammals, toxicokinetic studies with PCDDs and PCDFs have been less extensive in fish. The most detailed studies have been with 2,3,7,8-TCDD, where whole body and tissue elimination rates were assessed.[146–148] In addition, the disposition of a number of non-2,3,7,8-substituted congeners has been studied in some fish species. Non-2,3,7,8-substituted congeners are retained in fish to a greater extent than in mammals. However, the 2,3,7,8-substituted PCDDs and PCDFs remain the congeners having the highest degree of bioaccumulation potency.[7,104,105,211,212,228,234,245,320–322] Although uptake and elimination of the non-2,3,7,8-substituted congeners have been measured in laboratory experiments, these compounds have not been measured in fish tissue obtained from the environment.[288] In rainbow trout and yellow perch, 2,3,7,8-TCDD was eliminated from the body more slowly than in mammals, with whole body half-lives of 105 and 126 days, respectively. For most tissues, including liver, the elimination rates were comparable with those from visceral fat and carcass, ranging from 10 to 20 weeks. More than 98% of the 2,3,7,8-TCDD-derived radioactivity was associated with parent compound, whereas in rainbow trout about 2% of the radioactivity in the visceral fat was associated with a polar metabolite. This indicates that both fish species are capable of excreting 2,3,7,8-TCDD metabolites, which is supported by the observation of several polar metabolites in the gallbladder bile.[146–148] Although a relatively small fraction of the 2,3,7,8-TCDD-derived radioactivity was excreted as parent compound in the bile of fish, these studies have mostly detected 2,3,7,8-TCDD metabolites in bile. Two studies have exposed carp to 2,3,7,8-TCDD-contaminated sediment and flyash from a municipal incinerator for several weeks. Results from these experiments indicated that the elimination of 2,3,7,8-TCDD in this species proceeded significantly more slowly than in rainbow trout. The whole body half-life was observed to be >200 days for 2,3,7,8-TCDD in carp.[159] Flyash extract of a municipal incinerator also has been used to study the accumulation and elimination of PCDDs and PCDFs in the guppy and goldfish. Results from these studies indicate that the 2,3,7,8-substituted congeners are more slowly eliminated from the body of the fish.[245,321] Based on these type of experiments, the elimination rates for a number of 2,3,7,8-substituted tetra-, penta-, and hexachlorinated congeners were determined, ranging from 0.210 to 0.046/day.[245] Equivalent half-lives ranged from 3 to 15 days and are extremely short in view of the results

obtained in other aquatic and mammalian species. The elimination of 2,3,7,8-TCDF in rainbow trout after a single dose of 1 μg/kg p.o. followed a biphasic pattern, with a half-life of 14 days during the slow elimination part. Significant amounts of glucuronide and sulfate conjugates of 4-hydroxy, 2,3,7,8-TCDF were detected in bile.[185] These results indicate that fish may be less able to metabolize 2,3,7,8-TCDF than most mammals.[31,32,74] After exposure through food and a depuration period of 180 days, the whole body half-life of 2,3,4,7,8-PnCDF in rainbow trout was 61 to 69 days. In both experiments, 10 to 25% of the 2,3,4,7,8-PncDF-derived radioactivity was unextractable from tissue and could indicate either polar metabolites or unextracted parent compound.[213,322] The elimination of 1,2,3,4,7,8-HxCDD and 1,2,3,4,6,7,8-HpCDD was studied in rainbow trout and fathead minnow after a 30-day exposure through food. The half-lives of both compounds ranged from 46 to 61 and 106 to 112 days for rainbow trout and fathead minnow, respectively.[211] The uptake and elimination of OCDD and OCDF also have been studied by several researchers and they all arrived at the same conclusion: the BCF was significantly lower for these two compounds than for the other 2,3,7,8-substituted congeners. Furthermore, it is generally accepted that this lack of bioaccumulation is caused by very limited uptake due to molecular size rather than by rapid biotransformation. The elimination rates reported in different studies should not be considered reliable as it was sometimes unclear, if indeed, the decrease in internal body burden was measured and not material adsorbed on the outside of the fish.[53,104,105,211,228] These data are summarized in Table 4. In contrast to mammals, the uptake and elimination of several non-2,3,7,8-substituted PCDDs and PCDFs could be more easily studied in fish. In general, the elimination rates observed were faster than those found for the 2,3,7,8-substituted congeners, ranging between 2 and 43 days.[212,228,322] The investigations suggested that these non-2,3,7,8-substituted congeners were rapidly metabolized in fish, as significant amounts of polar and nonextractable radioactivity were observed in bile and tissues.[212,322] In addition, treatment with piperonyl butoxide (PBO), an inhibitor of biotransformation, caused a decrease in elimination rate,[322] thus supporting this hypothesis.

D. Dose-Related Excretion

Although the dose-related tissue distribution of 2,3,7,8-TCDD and related compounds has been described,[2] there is little information available on the dose-related excretion of these compounds. Rose and co-workers investigated the elimination of [^{14}C]-2,3,7,8-TCDD in rats given repeated oral doses of 0.01, 0.1 or 1.0 μg/kg/day, Monday through Friday for 7 weeks or a single dose of 1.0 μg/kg.[295] In the single-dose study, no ^{14}C was excreted in the urine or expired air; in the repeated-dose study, however, 3 to 18% of the cumulative dose was excreted in the urine by 7 weeks. This study indicated that steady-state concentrations will be reached in the bodies of rats in 13 weeks. The rate constant defining the approach to steady-state concentrations was independent of the dose of 2,3,7,8-TCDD over the range studied. Relatively small changes in the excretion of 2,3,7,8-TBDD also were observed after exposures to 1 and 100 nmol/kg.[57,58] These results are consistent with the *in vivo* and *in vitro* evidence suggesting that autoinduction of 2,3,7,8-TCDD and 2,3,7,8-TBDD metabolism does not occur in rat after exposure to sublethal doses of these compounds.[57,58,69,243] In contrast to these compounds, 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF can induce their own rate of metabolism and biliary excretion.[47,192,243] Autoinduction of metabolism would suggest that these compounds may exhibit dose-related excretion, with longer half-lives for elimination at lower doses, which are not associated with enzyme induction. Further data are needed to test this hypothesis.

VII. TOXICOKINETIC MIXTURE INTERACTIONS AND THEIR RELEVANCE FOR TOXICITY

In the environment, exposure, uptake, and elimination of PCDDs, PCDFs, and PCBs are never limited to single congeners. Complex mixtures of the different congeners are usually involved.[26,27,92,134,163,287,293,299,330,334,335,353,391,392] Al-

though most research on the toxicokinetics of these compounds in the labroatory has been carried out with single congeners, a few studies have focused on possible mixture interactions. So far, mixture interactions between PCDDs, PCDFs, and PCBs have been studied mainly in mouse and rat. The three most extensively studied effect parameters are immunological responses, teratogenicity, and enzyme induction, but most studies lack relevant data on toxicokinetics.

A. Interactive Effects on Toxicokinetics

A limited number of studies using mixtures of PCDDs, PCDFs, and PCBs have focused on the interactive effects on the deposition and elimination of these compounds from the rodent liver.[76–78,126,209,218,358,362] A study with binary mixtures of some PCDFs showed that the hepatic elimination of 1,2,3,7,8-PnCDF in Sprague-Dawley rats was not significantly influenced by coadministration with 2,3,4,7,8-PnCDF.[358] In addition, no effects were found on the hepatic elimination rate of 1,2,3,7,8-PnCDD, 1,2,3,6,7,8-HxCDD, or 2,3,4,7,8-PnCDF after mixed administration of these compounds in C57BL/6J mice.[78] In another study, more complex mixtures of PCDFs and PCBs were administered to ICR mice. PCDF coadministration increased the elimination of some PCB congeners from hepatic and adipose tissue approximately twofold.[126]

Interactive effects on PCDD, PCDF, or PCB toxicokinetics also have been observed after coadministration of the di-ortho-substituted 2,2′,4,4′5,5′-HxCB. This PCB has a CYP2B isoenzyme induction pattern that is different from the specific CYP1A isoenzyme induction found for all 2,3,7,8-substituted PCDDs and PCDFs. In a 3-month subchronic feeding study in rats, a modulation of TCDD and 2,2′,4,4′,5,5′-HxCB toxicokinetics was observed after mixed admistration of these two compounds. It was found that rats supplied with food containing 2,2′,4,4′,5,5′-HxCB (10, 30, or 100 mg/kg) and 2,3,7,8-TCDD (5 µg/kg) had a dose-dependent decrease in the TCDD concentration in the liver compared to the group fed 2,3,7,8-TCDD only. Conversely, liver concentrations of HxCB were increased following mixed exposure.[362] Another study found no effects of coadministration of 1, 10, or 100 µmol/kg 2,2′,4,4′,5,5′-HxCB on the cumulative fecal excretion of 3,3′4,4′-TCB in Wistar rats.[209] However, in C57BL/6J mice, coadministration of 300 µmol/kg 2,2′,4,4′,5,5′-HxCB did cause a slight increase in the hepatic elimination rate of 2,3,3′,4,4′,5-HxCB and 3,3′,4,4′,5,5′-HxCB, but not of 2,2′,4,4′,5,5′-HxCB itself.[77] In this last study, deposition to the liver of both 2,3,3′,4,4′,5-HxCB and 2,2′4,4′,5,5′-HxCB also increased 7 days after mixed administration of these compounds. Similarly, 2,2′4,4′5,5′-HxCB cotreatment was found to increase the hepatic deposition of 1,2,3,7,8-PnCDD but not of 1,2,3,6,7,8-HxCDD or 2,3,4,7,8-PnCDF.[78] Such a toxicokinetic modulation also has been reported for liver deposition of 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 2,3,7,8-TBDD after pretreatment with 2,3,7,8-TCDD, both *in vivo* and *in vitro*.[57,69,192,315] However, pretreatment with 350 µg/kg/day OCDD, for 7 days, did not alter the hepatic deposition of a single dose of 100 µg/kg TCDD in rats.[108]

The modulation of hepatic PCDD, PCDF, and/or PCB retention, as reported in the pre- and cotreatment studies quoted earlier, may be explained by the high affinity binding of 2,3,7,8-TCDD and related isostereomers to the CYP1A2 protein.[166,371,398] The role of CYP1A2 as an inducible, but saturable, hepatic-binding site in the deposition and elimination of TCDD and related compounds is supported by physiologically based pharmacokinetic models developed for mice and rats.[175,176] However, the proposed storage function of CYP1A2 in mammalian liver is not unequivocal inasmuch as a recent study could not confirm a direct role of this protein in hepatic retention of TBDD in the rat.[59] An autoradiography study in rats with 3,4,3,4-TCB, a 2,3,7,8-TCDD isostereomer, indicated that, besides the endoplasmatic reticulum, mitochondria and lipid droplets also form important storage sites in rat liver.[84] Consequently, the existence of inducible storage sites in the liver other than CYP1A2 cannot be excluded. In addition, it is likely that the increase in hepatic elimination of PCDDs, PCDFs or PCBs observed in some studies appears when the amount of metabolizing liver enzymes is increased by cotreatment with other compounds. Thus, interactive effects on toxicokinetics are likely to be dependent on the level of hepatic isoenzyme activity and the structure of the congeners involved (see also Section V.A).

B. Induction of Cytochrome P4501A Activity

Several studies have reported on the effect of mixed administration of PCDDs, PCDFs, and PCBs on the induction of CYP1A-dependent enzyme activities, measured as either AHH or EROD, mainly in mice.[20–23] In some cases, the results from these studies appear to contradict each other. Potentiation of EROD induction has been observed in the C57BL/6J mouse after dosing with a mixture of 500 μmol/kg 2,2′4,4′,5,5′-HxCB, a specific CYP2B inducer, and 1 nmol/kg 2,3,7,8-TCDD. Both EROD and AHH activity were three times higher after administration of the mixture than after a dose of 1 nmol/kg 2,3,7,8-TCDD only. Increasing the 2,3,7,8-TCDD dose in the mixture to 100 nmol/kg caused a 20% antagonism of its EROD induction. It is difficult to generalize the results from this study as it also showed that only potentiation was observed in DBA/2J mice. In this mouse strain, cotreatment with 500 μmol/kg 2,2′,4,4′,5,5′-HxCB led to a rather constant potentiation of EROD and AHH activity of approximately 50% throughout a dose range of 10 to 5000 nmol/kg 2,3,7,8-TCDD. Pretreatment with 2,2′4,4′,5,5′-HxCB led to similar results.[20–22] As in mouse, potentiation of CYP1A activity also has been observed in rat. A 25 to 200% elevation of EROD and AHH activity was seen when rats were treated with a mixture of 300 μmol/kg 2,2′4,4′5,5′-HxCB and varying doses of 3,3′4,4′,5-PnCB, 3,3′,4,4′,5,5′-HxCB, or 2,3,3′,4,4′,5-HxCB. The latter three PCB congeners are CYP1A inducers and resemble 2,3,7,8-TCDD in their mechanism of action. 2,2′,4,4′,5,5′-HxCB pretreatment instead of cotreatment caused an even more pronounced potentiation.[174] Such observations also have been made in the C57BL/6J mouse, using similar combinations of these PCB congeners. A 250% increase in EROD activity was observed when 300 μmol/kg 2,2′,4,4′,5,5′-HxCB was coadministered with 60 μmol/kg 2,3,3′,4,4′,5-HxCB. Tissue analysis showed that this increased activity could, at least partly, be explained by an increased deposition of 2,3,3′,4,4′,5-HxCB to the liver.[77] This demonstrates the relevance of toxicokinetic data for at least the explanation of interactive effects on other levels. Two other studies reported antagonism of CYP1A-dependent enzyme induction in C57BL/6J mice. A 25% decrease in the induction of EROD activity was observed after coadministration of 15 nmol/kg TCDD in combination with 25 to 150 μmol/kg Aroclor 1254.[20] Antagonism also was reported after dosing with a mixture of 400 to 1000 μmol/kg 2,2′,4,4′,5,5′-HxCB and 15 nmol/kg 2,3,7,8-TCDD. However, hepatic deposition of 2,3,7,8-TCDD was not lowered by the presence of 2,2′,4,4′,5,5′-HxCB.[30] Antagonistic effects on EROD induction also were observed in rats. A significant antagonism of EROD activity in rat liver was observed after administration of a mixture of 2.5 μg/kg 2,3,7,8-TCDD and 53 μg/kg 2,3,4,7,8-PnCDF. However, this antagonistic effect did not appear until 8 weeks after dosing.[373] The most detailed mechanistic studies regarding the possible antagonism of TCDD-mediated induction of EROD activity have been done with 6-methyl-1,3,8-trichlorodibenzofuran (MCDF). *In vivo* and *in vitro* experiments with mice and rats have shown that MCDF competes with TCDD for the cytosolic Ah-receptor-binding site(s). Subsequently, this MCDF-Ah-receptor complex is translocated to the nucleus. Thus, MCDF inhibits the TCDD-induction response by competing for the Ah-receptor and probably also by partially inactivating genomic-binding sites.[15,23,115,200]

The results from most of the above-summarized studies do not appear to be consistent and seem contradictory as both antagonism and potentiation are observed, sometimes even within a single study. Because the data on interactive effects on enzyme induction are only partially supported by toxicokinetic data, possible explanations often remain speculative. However, a concise examination of the reported results in combination with the available data on modulation of PCDD, PCDF, and PCB deposition to liver, discussed in the previous paragraph, may offer a preliminary explanation. In Figure 12, we have summarized the data of three different studies on interactive effects in either Ah-responsive C57BL/6J mice or rats.[22,30,77,174] The experimental design of these studies was similar using either 2,3,7,8-TCDD or dioxin-like PCB congeners to induce CYP1A-dependent EROD activity. In addition, 300 to 500 μmol/kg 2,2′,4,4′,5,5′-HxCB was coadministered in all studies. Effects were observed 3 to 14 days after administration of the binary mixture. The dotted line in Figure 12 represents the situation of no interaction, and po-

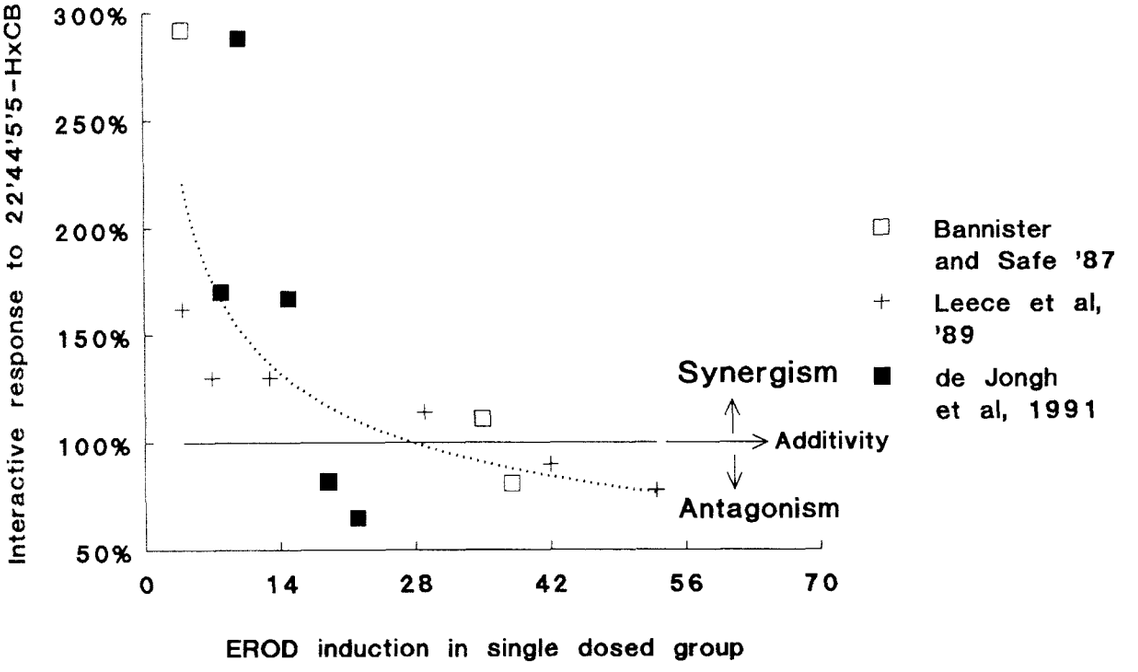


FIGURE 12. The interactive effects of CYP1A-dependent enzyme induction between 2,3,7,8-TCDD and 2,4,5,2′,4′,5′-HxCB as a function of the relative EROD activity.

tentiation or antagonistic effects are located above or below this line, respectively. The observed relationship clearly shows that the occurrence of interactive effects depends on the degree of EROD induction and consequently on the administered dose of the dioxin-like compound. It is apparent from Figure 12 that potentiation predominates as the level of EROD induction decreases. As EROD activity increases, antagonism becomes more prevalent. Based on these observations, it can be postulated that the observed interactive effects are the result of more than one mechanism, some of which are discussed next.

The mechanism behind the antagonism of PCDD- or PCB-induced EROD activity by 2,2′4,4′,5,5′-HxCB may involve active competition on the Ah-receptor-binding site between both ligands. As was illustrated in Figure 12, antagonistic effects commonly appear when EROD activity is induced several-fold by 2,3,7,8-TCDD or one of its isostereomers. The coadministered compound, often 2,2′,4,4′,5,5′-HxCB, has a low but significant affinity for the Ah-receptor. On a molar basis, it is present in high amounts compared to the dioxin-type reference compound. Thus, a competitive effect on the Ah-receptor-binding site by PCBs can occur, resulting in antagonism. This has been observed in studies using 2,2′,4,4′,5,5′-HxCB and the commercial PCB mixture Aroclor 1254.[30] Thus, the mechanism behind this antagonistic effect of 2,2′4,4′,5,5′-HxCB may be similar to that of MCDF discussed previously.[200]

The mechanism behind the potentiation of CYP1A-dependent enzyme activities, observed at low levels of induction, is likely based on the toxicokinetic modulation of liver deposition by 2,2′4,4′,5,5′-HxCB cotreatment. This phenomenon was discussed in the previous paragraph. Because a direct correlation between liver concentrations of the inducing compound and EROD activity has been observed, this mechanism offers a straightforward explanation for the occurrence of potentiating and/or synergistic effects.[2,77,78,314]

There are indications that a second, more indirect mechanism is involved in the potentiating effect of 2,2′,4,4′,5,5′-HxCB cotreatment on the EROD induction mediated by 2,3,7,8-TCDD or related isostereomers. Elevation of hepatic Ah-receptor levels by a nonplanar PCB, like 2,2′,4,4′,5,5′-HxCB, may be the basis for some of

the synergistic responses observed with coadministration of this compound.[21,174,404] Because both CYP1A1 and CYP1A2 expression are mediated by the Ah-receptor,[224,305] this type of mechanism also may account for the potentiation of EROD or AHH activity observed in some of the cited studies.[174]

From the above-discussed studies, it may be concluded that the toxicokinetics of halogenated polycyclic aromatics may be altered when administered in mixtures. As a result, these interactive effects may influence the induction of commonly used biological markers such as EROD and AHH activity. These effects seem to be congener- and dose-dependent and are likely the result of more than one mechanism of action. There is evidence that the CYP1A2 protein plays a key role in these processes, but this requires further investigation.

VIII. ROLE OF TOXICOKINETICS IN DETERMINING TOXICITY

A. Species Differences

When all results from toxicity and toxicokinetic studies with rodents from the last decade are taken into account, it must be concluded that the interspecies differences in toxicity can only partly be explained by differences in toxicokinetics. For different mouse strains, the toxicokinetics of 2,3,7,8-TCDD was governed more by the total genetic background than by the Ah-locus.[34,74,97] In contrast, toxicity depends at least in part on the presence of the Ah-locus and Ah-receptor.[39,276,277,279,280] Large strain differences in the acute toxicity of 2,3,7,8-TCDD have been observed in rats.[263,264,375] However, in contrast with results from mouse studies, these differences, especially between the Han/Wistar and Long-Evans strains, cannot be adequately explained by the presence of the Ah-receptor and its locus.[265] In addition, these strain differences in toxicity could not be explained by strain differences in toxicokinetics.[267] The hamster is clearly the species most resistant to the acute toxicity of 2,3,7,8-TCDD. Although the elimination rate of 2,3,7,8-TCDD is 2- to 3-fold greater in this species than in rats and mice, toxicokinetics alone cannot explain the 10- to 100-fold difference in acute toxicity between hamster and other rodent species.[239] Within one species, e.g., rat or monkey, the large differences in toxicity observed between 2,3,7,8-TCDD and 2,3,4,7,8-PnCDF vs. 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF can be largely attributed to differences in the relative rate of elimination of these congeners.[31,47,49,131,198,219,261,262,295,358] The guinea pig is the rodent species with the slowest metabolism and elimination of 2,3,7,8-TCDD,[96,241] which may be a direct reflection of the lower CYP1A activity and inducibility compared with rat.[394] The slower metabolism and elimination of 2,3,7,8-TCDD and 2,3,7,8-TCDF reduce the rate of detoxification of these compounds in this species. Thus, toxicokinetics in part explains the unique sensitivity of the guinea pig to the acute toxicity of 2,3,7,8-TCDD and 2,3,7,8-TCDF.[74,96,204,241] The relative sensitivity of several fish species to these compounds also is similar to that of guinea pig.[325,326,364] As in guinea pig, the rates for elimination of 2,3,7,8-TCDD in fish are slower than in most rodents and are probably a contributing factor to the relatively high sensitivity of fish to these compounds.[146,147]

B. Molecular Size

For some congeners, e.g., OCDD and OCDF, it has been suggested that molecular size reduces the uptake through the intestinal wall and gills.[231,246] In addition to the reduction in bioavailability, the high degree of chlorination of hepta- and octachlorinated congeners at the same time reduces metabolism and subsequent elimination.[37,275] As a consequence, these congeners, although absorbed in small amounts, can readily accumulate in liver, for which they have a high affinity. The biological and toxicological effect can therefore still be significant at chronic low-level exposures, resulting in potencies ranging from 0.01 to 0.001 of that of 2,3,7,8-TCDD.[37,68,83,386]

C. Tissue Distribution

As can be seen from Figure 2, the tissue distribution of these compounds varies between

different species. Specifically, differences in adipose tissue storage may influence the biological and toxicological effects of these compounds. For most rodents, the distribution between liver and adipose tissue is similar, varying more with the congener than with the species (see References 2, 6, 11, 47, 96, 170, 241, 295, 318, 357, 372, 386, 398, 399). However, primates, including humans, appear to be distinctly different from rodents inasmuch as significantly lower amounts are stored in liver than in adipose tissue.[31,48,165,226,365] At present, there is insufficient information available to make a distinction between the relative contributions of body distribution and genetic background to the overall responses between primates and rodents. Furthermore, species differences in tissue distribution may be related to the magnitude of exposure since a dose-dependent distribution of these compounds has been observed (see Figure 6). In this respect, it also is interesting to note that recently a good correlation was found between fat content and acute toxicity of 2,3,7,8-TCDD among species (see Figure 13). Based on this relationship, an acute LD_{50} value for adult humans of approximately 5 mg/kg was calculated, whereas a higher sensitivity for the newborn was predicted, with an estimated LD_{50} of approximately 0.6 mg/kg.[101]

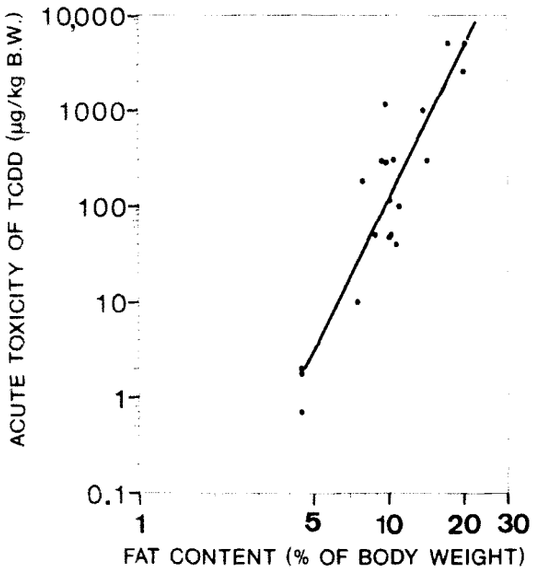


FIGURE 13. Relationship between acute oral toxicity (log LD_{50}) and total fat content (log TBF) in different mammals.[101]

D. Role of Lipoproteins

In addition, there is evidence suggesting that the binding of 2,3,7,8-TCDD to lipoproteins may alter the pharmacokinetics and toxic potency of the compound. Experimentally induced hyperlipidemia in rats delayed the development of overt toxicity (lethality), suggesting that the release of lipoprotein-bound 2,3,7,8-TCDD is related to the metabolic turnover of lipoproteins. In hyperlipidemic rats, the turnover of VLDL and LDL is signficantly delayed compared to normolipidemic animals, and this may contribute to the plasma lipoprotein binding modifying the toxicity of 2,3,7,8-TCDD in hyperlipidemic rats.[184]

E. Toxicity of Metabolites

Structure-activity studies of 2,3,7,8-TCDD and related compounds support the widely accepted principle that the parent compound is the active species. The relative lack of activity of readily excreted monohydroxylated metabolites of 2,3,7,8-TCDD suggests that metabolism is a detoxification process necessary for the biliary and urinary excretion of these compounds. This concept also has been generally applied to related compounds. although data are lacking on the structure and toxicity of metabolites of most PCDD and PCDF congeners. Two studies have addressed the possible *in vivo* toxicity of 2,3,7,8-TCDD metabolites.[188,379] The acute toxic potency of dog metabolites of 2,3,7,8-TCDD was at least 100 times less than the parent compound in guinea pig.[379] The Ah-receptor-mediated toxicity of 2-hydroxy-3,7,8-TriCDD and 2-hydroxy-1,3,7,8-TCDD, both metabolites of 2,3,7,8-TCDD, was assessed in male Wistar rats. The compounds produced no significant effect on body weight gain, thymus, liver, or spleen weights after exposure to a dose as high as 5000 µg/kg b.w. 2-Hydroxy-3,7,8-TriCDD induced CYP1A1-related enzyme activities at dose levels of 1000 and 5000 µg/kg b.w., whereas 2-hydroxy-1,3,7,8-TCDD was inactive as an inducer. Thus, while 2-hydroxy-3,7,8-TriCDD has dioxin-like activity, the potency of the metabolite is more than three orders of magnitude less than that of 2,3,7,8-TCDD.[188] These results are consistent with the

expected rapid conjugation and excretion of these 2,3,7,8-TCDD metabolites.[379] A few studies have addressed the toxicity of metabolites of coplanar PCBs. 5-Hydroxy-3,3′4,4′-TCB and 4-hydroxy-3,3′4′,5-TCB did not produce liver hypertrophy, induction of hepatic AHH or DT-diaphorase activities, or thymus atrophy.[400] In addition, to support metabolism as a detoxification process, there is evidence that Ah-receptor binding and *in vitro* AHH induction do not accurately reflect Ah-receptor-mediated toxicity, presumably because continued occupation of the receptor is required for toxicity.[201]

The structural requirements for the Ah-receptor binding of 7-substituted 2,3-PCDDs, 8-substituted 2,3-, and 2,3,4-PCDFs, including the hydroxylated congeners, have been studied in detail using a QSAR approach.[80,81,294] The binding affinities for these hydroxylated PCDDs and PCDFs to rat Ah-receptor were significantly lower than those of their corresponding chlorine analogs. The results of these studies suggest a rationale for the very low Ah-receptor-mediated toxicity of PCDD and PCDF metabolites. Within one species, the rat, these studies showed that lipophilicity was the major factor regulating ligand binding to the Ah-receptor.[80,81] However, the relationship between the lipophilic character of the substituent and the binding affinity to the Ah-receptor cannot be generalized to other species. An additional study using hepatic cytosol from rat, mouse, hamster, and guinea pig showed that the dominating physicochemical factors for Ah-receptor binding can vary between species. Nevertheless, in all four rodent species the binding affinities of the hydroxylated PCDDs and PCDFs to the Ah-receptor were significantly lower than those of their chlorine analog.[294]

At present, there is evidence that some possibly non-Ah-receptor-mediated processes may be partly governed by metabolites of these compounds. Metabolites of 3,4,3′,4′-TCB have been found to bind to transthyretin, a transport protein of thyroid hormones and vitamin A. As a result, drastic changes can be observed in vitamin A and thyroid hormone levels in rodents exposed to 3,4,3′,4′-TCB.[51] Alterations in vitamin A and thyroid hormone levels also have been observed after administration of PCDDs and PCDFs.[8,172,295,296] Although distinct binding affinities have been observed for metabolites of 2,3,7,8-TCDD to transthyretin *in vitro*,[173] no evidence has been provided so far that metabolites of PCDDs and PCDFs play a significant role in these processes *in vivo*. These results suggest that interaction with transthyretin and metabolites of these compounds is most significant for those congeners that are rapidly metabolized. In this respect, the model compound 3,4,3′,4′-TCB, with a half-life of <2 days in rat, may not have been a good representative for most 2,3,7,8-substituted PCDDs and PCDFs.[1] Nevertheless, drastic alterations in vitamin A and thyroid hormone levels have been observed *in vivo* after administration of 2,3,7,8-substituted congeners, which warrants further investigation of the mechanism of action.[8,172,295,296]

Data on the metabolism of 2,3,7,8-TCDD suggest that reactive epoxide intermediates may be formed. The *in vivo* binding of 2,3,7,8-TCDD-derived radioactivity to rat hepatic macromolecules corresponded to one 2,3,7,8-TCDD-DNA adduct per 35 cells. Based on these investigations, it was suggested that it was unlikely that 2,3,7,8-TCDD-induced oncogenesis acts through a mechanism of covalent binding to DNA and somatic mutation.[298] In addition to these results, two other studies indicated some effects of 2,3,7,8-TCDD and 1,2,3,7,8-PnCDD on hepatic DNA in the rat. Both compounds caused a significant decrease in hepatic I-compounds in female rats, but the mechanism by which these compounds could contribute to carcinogenesis is unknown.[284,285] Further studies of 2,3,7,8-TCDD and related compounds are needed to confirm these results and assess the relationship between covalent binding and the short- and long-term toxicity of these compounds.

F. Enzyme Induction and Some Endocrine or Toxic Effects

In a number of studies, a relationship has been determined between the autoinduction of certain enzyme activities and short-term toxic and endocrine effects of PCDDs and PCDFs. The relationship observed between induction of CYP1A1-related activities and some short-term toxic effects, such as thymic athrophy and reduction in bodyweight gain, has been studied in de-

tail.[305,306] This relationship clearly has a molecular basis, and the mechanism, with its biological and toxicological implications, has been reviewed by several authors.[224,280,305,306] Therefore, this subject is not included in this review, but some less well-known enzyme activities and endocrine effects are discussed in this section.

It has been suggested that sUDPGT, a specific isoenzyme of UDPGT, may play a role in the toxicity of PCDDs and PCDFs. A negative correlation was found between basal sUDPGT activities and LD_{50} values of different species.[95] This observation was explained in relation to the role of estrogen modulation in PCDD/PCDF toxicity since estrogens can be excreted by glucuronidation.[307,343,345] According to the authors, species differences are explained by differences in estrogen sensitivities, estrogen excretion, and estrogen receptors. Therefore, UDPGT may play an indirect role in PCDD and PCDF toxicity.[95]

The induction of the hepatic NAD(P)H: quinone oxidoreductase (DT-diaphorase) by 2,3,7,8-TCDD and some 2,3,7,8-substituted PCDFs also has been the subject of some research.[99,324,397] Simultaneous induction of cytosolic DT-diaphorase and CYP1A-related enzyme activities has been studied in rat, guinea pig, and chick embryo liver. These experiments showed that induction of DT-diaphorase is part of the biological response to these compounds, but the degree of induction is species dependent. These specific differences in inducibility suggest an inverse relationship with toxicity. The authors suggest the possibility of a protective effect toward the toxicity of these compounds,[324] but this should be further substantiated.

Recently, a possible relationship between vitamin K metabolism, a determining factor in blood coagulation, and induction of cytochrome P450 isoenzymes by 2,3,7,8-TCDD and 2,4,5,2′,4′,5′-HxCB has been reported. In rat, different sex-dependent effects were observed on the vitamin K-dependent coagulation factor VII and some of the enzymes modulating the hepatic vitamin K cycle.[42,43] At present, the specific role of induction of either CYP1A or CYP2B, or any other isoenzymes, cannot be assigned yet to the observed effects and should be investigated in more detail.

G. Mixture Interactions

Combinations of PCDDs and PCDFs generally appear to be additive with respect to Ah-receptor-mediated biological and toxicological responses. These additive effects on toxicity can be adequately explained by a single receptor-mediated process in combination with a lack of toxicokinetic modulation in elimination rates between 2,3,7,8-substituted PCDDs and PCDFs.[33,35,36,262,306,309,357,358] For combinations of PCDDs and PCDFs with PCBs, the situation is more complex and nonadditive toxic and biological effects have commonly been described.[20,21,30,72,73,78,126,174,362] In view of the kinetic modulation of 2,3,7,8-substituted PCDDs and PCDFs by PCBs,[78,126,362] it can be concluded that toxicokinetic factors contribute to the observed nonadditive toxicological and biological effects.

H. Human Exposure

The dose-dependent tissue distribution of 2,3,7,8-TCDD and related compounds is a critical factor that must be considered in the future when estimating the concentration of these compounds in human tissues after chronic low-level exposure. This is particularly important because the general human population is exposed to much smaller daily doses than those used in experimental disposition studies. The relevance of differences in human tissue distribution and elimination for risk assessment, when compared with other animal species, has been recently discussed.[313,393] It was recently reported that although 2,3,7,8-TCDF was metabolized by rat and human CYP1A1, the rate of metabolism in the rat was 20- to 100-fold greater than in humans. These results suggest that 2,3,7,8-TCDF will be far more persistent in humans.[199,328] Because of the much longer half-lives observed in humans (see Table 6), higher body burdens will be attained in humans, at an equal daily dose per kilogram body weight, compared with other animal species. Additionally, the differences in body distribution must be taken into account because higher amounts are sequestered in human adipose tissue. For humans, it was estimated that approximately 2.5%

of 2,3,7,8-TCDD is stored in the liver, whereas for rats, approximately 60% is initially retained in this organ. As a result of these specific differences in toxicokinetics, a safety factor of 10 for 2,3,7,8-TCDD was suggested for risk assessment of human exposure.[313] At a recent WHO consultation, these toxicokinetic considerations were taken into account for guidelines concerning an acceptable daily intake (ADI) of 2,3,7,8-TCDD for humans. This resulted in a recommended ADI of 10 pg/kg/day 2,3,7,8-TCDD or its equivalents.[393]

I. Toxic Equivalency Factors (TEFs)

The relative toxicity of PCDDs and PCDFs is estimated by TEFs relative to the most toxic congener, 2,3,7,8-TCDD. At present, this is the only methodology available for the risk assessment when mixtures of these compounds are involved. Additivity, a prerequisite in this concept is supported by numerous *in vivo* and *in vitro* studies with PCDDs and PCDFs.[35,36,274,306,404] In view of the large differences observed in elimination rates and tissue distribution of these compounds between species (see Sections III and VI), it is important to discuss whether or not toxicokinetics are sufficiently considered in the present TEF values. The relative toxic potencies for some Ah-receptor-mediated effects of 1,2,3,7,8-PnCDD, 1,2,3,7,8- and 2,3,4,7,8-PnCDF, and 1,2,3,6,7,8-HxCDF have been studied in semichronic as well as short-term studies with rats.[261,262,306] If the results for each of these compounds are compared, it can be concluded that similar toxic potencies are derived from semichronic and short-term studies for a given compound. Moreover, results of bioassay-derived TEFs from *in vitro* experiments were comparable with those obtained from *in vivo* experiments.[306] Based on these results, it can be suggested that within one species, i.e., rat, toxicokinetics is not a dominant factor governing the Ah-receptor-mediated relative toxic potencies of 2,3,7,8-substituted congeners in studies that lasted as long as 3 months. This fact was substantitated further by a comparison of the relative toxic potencies of 3,3′4,4′-TCB, 2,3′,4,4′,5- and 3,3′,4,4′,5-PncB, 2,3,3′,4,4′- and 2,2′4,4′,5,5′-HxCB between 3-month rat studies and bioassay-derived TEFs, which again were well within each other's range.[66,306,347,369] In spite of the apparent absence of a toxicokinetic factor in short-term or semichronic studies with rats, it is possible that toxicokinetics may become more important in long-term studies, e.g., to determine congener-specific carcinogenic or neurobehavioral effects. Therefore, in comparative long-term toxicity studies, a loading and maintaining dose regime would be a more accurate way to determine relative potencies of individual PCDDs, PCDFs, and PCBs.[63,361] So far, only a few studies have applied such a dosing regime in their experimental design.[154,374] Another point of interest is the influence of the differences in body distribution between species on TEFs. In Section III, it was clearly illustrated that the tissue distribution can vary markedly between species, being most pronounced for fish and birds compared with rodents. These differences in species- and congener-specific tissue distribution could influence the TEF values. Therefore, it is necessary to consider whether TEF values obtained from *in vivo* or *in vitro* experiments with rats can be safely used for other species. A few studies with birds and fish have already indicated that TEF values, especially for dioxin-like PCBs, can vary significantly from those obtained from *in vitro* studies with mammalian tissues.[41,55,56,142,338,376] Therefore, in some cases, TEFs for PCDDs, PCDFs, and PCBs may be species-specific and this should be determined in other than mammalian models. TEFs obtained from fish and bird studies would be more relevant for ecotoxicological risk assessment.

IX. SUMMARY AND CONCLUSIONS

PCDDs and PCDFs are highly lipophilic and, especially the 2,3,7,8-substituted congeners, are extremely stable toward metabolic breakdown. As a result, they accumulate easily in the foodchain, with the greatest tissue concentrations found in species at the higher trophic levels. In this process, toxicokinetics and metabolism play a key role, often determining differences between species.

Absorption from the GI tract of mammals is effective and can exceed 75% of the dose for the

lower chlorinated congeners, but is dependent on the nature of the vehicle. With increasing molecular size, absorption from the intestines is greatly reduced, which is most apparent for the hepta- and octachlorinated congeners. In the environment, these compounds are usually adsorbed on soil, sediment, or combustion particles. As a result, the bioavailability is strongly reduced, depending at least on the carbon content of the matrix. The available data suggest a 25 to 50% bioavailability for soil-bound tetra- to hexachlorinated congeners. For the higher chlorinated congeners, a maximum of 10% bioavailability seems to be more realistic. The oral bioavailability of PCDDs and PCDFs adsorbed on combustion particles is even less, and estimates of 5 to 20% seem to be realistic for flyash or flue ash from municipal incinerators. The permeation through the skin is much less effective than oral uptake. Bioavailability after dermal exposure to soil-bound PCDDs and PCDFs is even much lower and is most likely around or less than 1% for all congeners.

Only the 2,3,7,8-substituted congeners are retained in the body of most species, except the guinea pig and crustaceans, which also retain otherwise substituted congeners. The body distribution is strongly species dependent, with the liver and adipose tissue being the major storage sites. In all mammalian species, postnatal exposure by lactation is quantitatively more important than *in utero* exposure. Differences between liver and adipose tissue distribution are most obvious between rodents and humans. Generally, the ratio between liver and adipose tissue concentration follows the order: rodents >> birds > monkeys > humans > fish. The high liver retention observed for 2,3,7,8-substituted PCDDs and PCDFs in rodents has been attributed to the presence of specific and inducible storage sites in the liver cell. CYP1A2 has been suggested to be one of these storage sites, but results from different studies are equivocal.

The biotransformation of PCDDs and PCDFs depends on the chlorine substitution pattern in the molecule. Metabolic reactions include oxidation and reductive dechlorination, involving arene oxide intermediates and NIH-shifts as well as breakage of the oxygen bounds. Sulfur-containing metabolites also have been identified. Substitution of the 2,3,7, and 8 positions by chlorines strongly reduces the metabolic conversion rate. In the 2,3,7,8-substituted PCDF molecule, the 4 and 6 positions are more susceptible toward metabolic attack than the 1 and 9 positions. As a result, PCDFs with chlorines on the 4 and 6 positions are highly persistent in biota. Metabolic capacities also are species dependent: rats, hamsters, and mice metabolize and eliminate these compounds relatively fast. In contrast, the guinea pig metabolizes these compounds very slowly, which is probably due to a low basal activity and inducibility of certain cytochrome P450 isoenzymes in this species. In general, the urinary and biliary elimination of 2,3,7,8-substituted congeners has been shown to depend on the metabolism of these compounds. Whole body half-lives of the group of 2,3,7,8-substituted congeners in rodents range from a few to more than 100 days. The elimination is slowest in humans, with half-lives being about 7 years for 2,3,7,8-TCDD and probably much longer for some higher chlorinated congeners.

The 2,3,7,8-substituted PCDDs and PCDFs cause strong and prolonged induction of hepatic CYP1A1 and CYP1A2 isoenzymes. This induction is presently the most sensitive bioindicator for these compounds, but its physiological and toxicological significance is unclear. *In vivo* and *in vitro* data suggest that autoinduction of 2,3,7,8-TCDD does not occur after exposure at a sublethal dose. This is in contrast to 2,3,7,8-TCDF and 2,3,4,7,8-PnCDF, where *in vivo* and *in vitro* results support the autoinduction of metabolism and biliary elimination of these compounds in the rat. Consequently, it may not always be appropriate to directly extrapolate high-exposure toxicokinetic animal data to predict kinetics at very low exposures, which may not be associated with significant enzyme induction. Induction of the phase II enzymes UDPGT, DT-diaphorase, and GST by PCDDs and PCDFs occurs simultaneously with CYP1A1 and CYP1A2 induction. Both phase I and II induction are significant for the elimination of these compounds as conjugated metabolites are found in most species.

In vivo studies on the interactive effects of 2,3,7,8-substituted PCDDs and PCDFs have shown no clear interactions on kinetics. Combinations of 2,3,7,8-substituted congeners with PCBs, e.g., 2,2′,4,4′,5,5′-HxCB, can result in a

ratio-dependent antagonism or synergism for some toxic or biochemical effects. Because these PCBs and 2,3,7,8-substituted PCDDs or PCDFs can modulate each other's hepatic retention and disposition, these nonadditive effects may have a toxicokinetic basis.

In the case of PCDDs and PCDFs, it is clearly the parent compound being the causal agent for Ah-receptor-mediated biochemical and toxicological effects. Consequently, kinetics and metabolism play distinct roles as mechanisms for detoxification. These roles are most evident for the congeners with the lowest chronic toxicity, e.g., 2,3,7,8-TCDF and 1,2,3,7,8-PnCDF, which also are rapidly metabolized. In addition, species with a low metabolic capacity for these compounds,like guinea pig and fish, are found to be more sensitive. Based on *in vivo* and *in vitro* experiments, it can be concluded that, at least in rat, congener-specific differences in toxicokinetics are not a dominant factor governing the Ah-receptor-mediated relative toxic potencies in studies that last as long as 3 months. Thus, apart from the influence of toxicokinetics, a genetic factor appears to be predominant in the overall toxic and biochemical effects. This became clear from studies using different rat and mouse strains, but also from differences between species, e.g., rat and hamster.

The body distribution of PCDDs and PCDFs in humans differs considerably from that of most laboratory species inasmuch as most of the body burden is sequestered in the adipose tissue. Elimination of PCDDs and PCDFs in humans is dramatically slower than in any other known mammalian species, resulting in much higher tissue concentrations at a given exposure than would be achieved in rodents. In view of these toxicokinetic differences between humans and other species, it is recommended that toxicokinetic modeling be used to determine safety factors in the future when data from animal experiments are extrapolated to human risk assessment.

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