REVIEW

Factors Affecting the Storage and Excretion of Toxic Lipophilic Xenobiotics

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ABSTRACT: Lipophilic toxins have been introduced into the environment both as functional compounds, such as pesticides, and as industrial waste from incineration or the manufacture of electrical transformer components. Among these substances are compounds that are carcinogenic and that affect the endocrine system. Accidental high exposures of humans to some lipophilic toxins have produced overt disease symptoms including chloracne and altered liver function. These toxic materials have been the recent focus of international effort to reduce or eliminate classes of halogenated hydrocarbons from the environment. Evidence of the widespread distribution of lipophilic toxins in the biosphere has been obtained by analyses of human tissues and human milk. The principal route of entry of lipophilic toxins into humans is through the food chain, and most of them are stored in adipose tissue. A common route of excretion is in bile, but there is also evidence of nonbiliary excretion into the intestine. Enterohepatic circulation of many of these compounds slows their removal from the body. Substances that interrupt the enterohepatic circulation of compounds that enter the intestine by the biliary and nonbiliary routes increase the rate of their removal from the body and reduce their storage half-lives. Reduction in body fat, along with these dietary substances that interrupt enterohepatic circulation, further enhances the excretion rate. Areas for further research include optimizing regimens for body burden reductions, understanding the nature of nonbiliary excretion, and following the effects of tissue redistribution during loss of body fat.

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BACKGROUND

Many lipophilic xenobiotic compounds enter the body and are deposited in adipose depots and other tissues. Several classes of these chemicals that are known to contribute to the risk of cancer and death enter the environment intentionally as pesticides or unintentionally as industrial by-products. Accidental exposure to high levels of some lipophilic toxins results in chronic disease affecting the liver and skin. An enormous amount of research has focused on the toxicity, carcinogenicity, developmental effects, endocrine effects, and other metabolic alterations by these compounds. For most of these compounds, a "no-effect" level has not been established. These substances have been detected in the tissues of essentially all humans and animals and may contribute to the risk of disease or altered development. The chemical stability of many of these xenobiotics has resulted in environmental accumulation and increasing concentrations in people and animals through dietary and respiratory intakes.

The presence of lipophilic toxins in the environment has received a high level international attention, scientific study, and governmental action. The awareness of the ubiquitous nature of toxic lipophiles has resulted in efforts to minimize their introduction into the environment. There also have been sporadic efforts to intervene at the level of the individual to reduce toxicity.

This paper reviews these interventions to help determine their potential utility as a complementary or alternative approach to environmental efforts to manage lipophilic toxins. The sections that follow first give a brief overview of the types of materials and the current environmental concerns. In addition, brief views of the absorption, tissue distribution, metabolism, and excretion of some representative compounds are presented to give a picture of the paths that lipophiles follow as they enter, move within, and ultimately leave an organism. Although the behavior of the compounds varies among classes and individual molecular species, it is possible to make some generalizations that help establish a basis for consideration of methods of intervention.

Recent Efforts to Change the Environment

The United Nations (U.N.) sponsored a study of the presence and sources of lipophililic toxins in the environment and concluded that global production of 12 of these materials should be reduced or eliminated. The study led to a multinational treaty imposing reductions in the use and production of these persistent organic pollutants (POP). In May 2001, representatives of 127 countries including the United States agreed to this treaty. The treaty specifies the control of eight pesticides [aldrin, chlordane, DDT (dichlorodiphenyl-trichloroethane), dieldrin, endrin, heptachlor, mirex, and toxaphene], two industrial chemicals [polychlorinated biphenyls (PCBs), once used in electrical transformers; and hexachlorobenzene, formerly used in the manufacture of synthetic rubber and also as a fungicide], and two by-products of combustion and industrial processes (dioxins and furans). Structures illustrating the 12 POP that are the subject of the treaty are given in Figure 1. All of these substances are characterized by carbon-chlorine

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Abbreviations: Ah, arylhydrocarbon; DDE, 1,1-dichloro-2,2-bis(chlorophenyl)ethylene; DDT, dichlorodiphenyl-trichloroethane; PBB, polybrominated biphenyl; PCB, polychlorinated biphenyl; POP, persistent organic pollutant; SPE, sucrose polyester; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

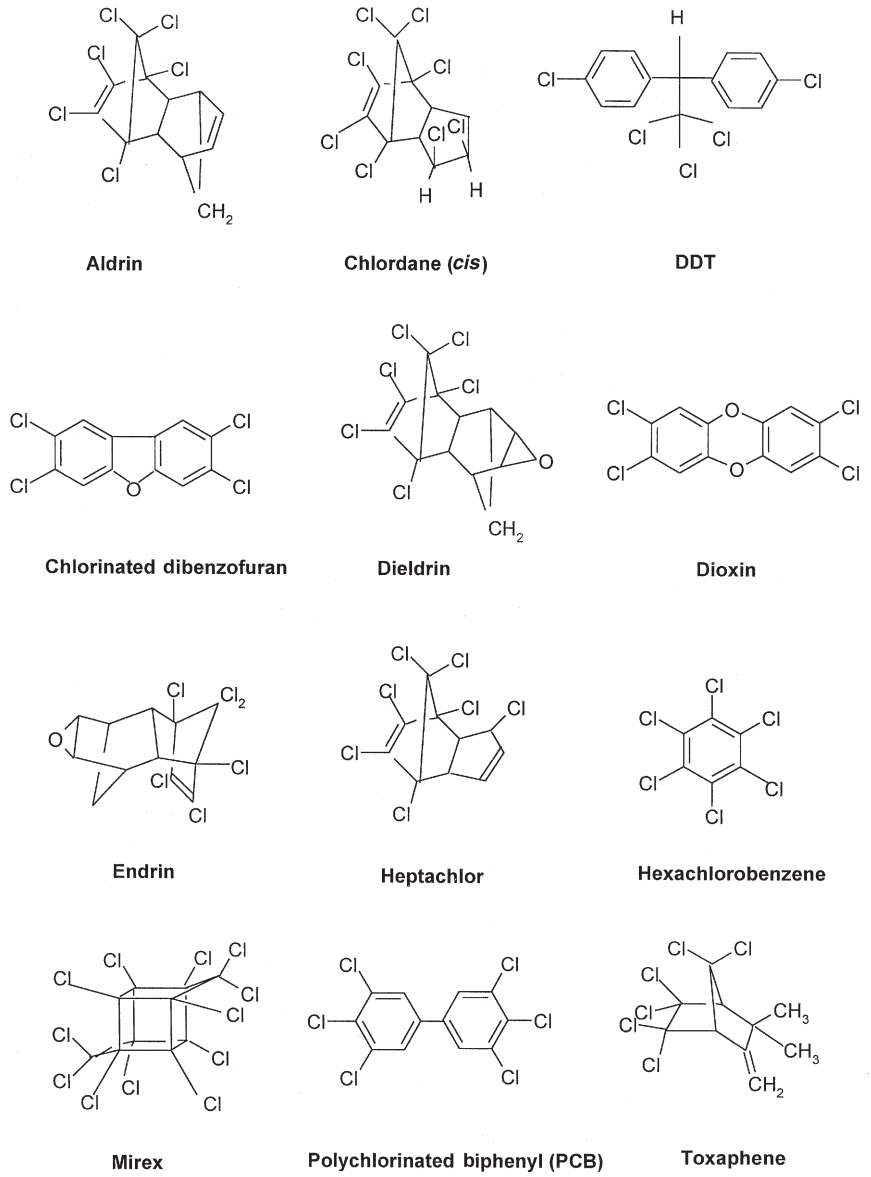


FIG. 1. Persistent organic pollutants included in the United Nations treaty.

bonds with stabilities that result in very long half-lives in the environment. Because of their stability and lipophilic character, these materials ascend the food chain from plants to deposition in fat depots and other tissues of higher organisms.

The principal focus for the international management of these materials in the environment has thus become that of elimination and reduction at the sources rather than intervention in individuals or populations with high levels of the materials. This approach does not affect the levels of toxic lipophiles that have already been deposited in the environment. An additional strategy is to find ways to hasten elimination of these substances from the body; to that end, studies have addressed the metabolism and excretion of many of these substances.

This interventional approach is key. The environment and the tissues of virtually all people in all countries already have a considerable burden of these persistent compounds, and it would be desirable to intervene to favorably alter their metabolic course. Finding the best ways to reduce body burdens of these materials is important since there is no consensus about the concentrations in tissues that might result in long-term detrimental health effects. For many of these compounds, a no-effect concentration has not been determined, and the possibility remains that any tissue concentration could increase the risk of disease. In addition to dealing with low-level, long-term exposure, there is a need for optimal treatment of the effects of acute exposure, such as that resulting from accidental ingestion or environmental accidents.

We review here interventions that could affect the absorption, distribution, metabolism, and/or excretion of lipophilic xenobiotic substances. These substances include the chlorinated compounds (POP) cited in the U.N. treaty as well as other lipophilic substances of known or putative toxicity.

Lipophilic Toxins in the Environment

Numerous studies have determined the presence of various lipophilic materials in the environment and in humans. Since it is beyond the scope of this review to consider studies of lipophilic toxins in the environment, several studies are cited to illustrate the widespread distribution.

One of the most important and most studied substances that provide evidence for the widespread distribution of lipophilic toxins is human milk. A review by Jensen (1) documented the levels of organochlorine compounds including DDT and other contaminants in milk in samples from many countries. Levels in human milk are markedly higher than those in dairy milk as would be predicted from the human position at the top of the food chain. Substances other than DDT also appear in human milk. Hofvander *et al.* (2) reported measurable levels of DDT, DDE (the principal metabolite of DDT), PCBs, dieldrin, and hexachlorobenzene in human milk in Sweden. The primary concern about these toxins in human milk is their potential effect on children's health and development (3,4).

PCBs were used extensively as coolants and lubricants in electric transformers prior to 1977. Although their use was banned that year in the United States, they remain in the environment because of their resistance to chemical decomposition. Evidence for slow disappearance from the body was reported by Wolff and coworkers (5), who longitudinally followed PCB concentrations in capacitor manufacturing workers after PCB use at their manufacturing facility was discontinued. The levels of organochlorine pesticides and PCBs in butter from 23 countries were studied by Kalantzi and coworkers (6). They found a wide range of concentrations, with levels of DDT and its metabolites being highest in countries where this pesticide is still in use. Current levels of PCBs in chicken and pork in Belgium were found to be remarkably high—12% of samples contained more than 50 ng of PCBs/g of fat (7). These levels were unrelated to the contamination of animal feed cited below and were attributed to recycling of fat into animal feed.

The ubiquitous nature of POP is also seen in the very high levels of organochlorines from autopsy samples from Greenland Inuits who consumed high levels of sea mammal fat containing these substances (8). This finding is consistent with an environmental path that begins with an industrial source and ends with humans at the top of the food chain. Another view of the food chain was provided by a study of Kelly and Gobas (9). Organic pollutants in Arctic terrestial animals were traced from lichen to caribou and finally to wolf. They reported evidence for the biomagnification of hexachlorocyclohexane and tetrachlorobenzene *via* this food chain.

Environmental accidents have occurred that have contaminated geographical areas or groups of people. Polybrominated biphenyl (PBB) fire retardants were accidentally introduced into cattle feed that resulted in the contamination of Michigan dairy products and essentially all of the population of Michigan (10). Animal feed was contaminated by PCBs, dioxins, and furans in Belgium in 1999 (11). These exposures resulted in continuing surveillance programs to assess the effects of the toxins on health. In Japan in 1968, cooking oil contaminated with dioxins produced symptoms of chloracne, malaise, and joint pain that were designated as Yusho disease (12). A similar example was the tragic contamination of cooking oil with PCBs in Taiwan in 1979 (13).

Polynuclear aromatic compounds (polycyclic aromatic compounds) are another class of lipophilic toxins/carcinogens. Substances such as benzo(α)pyrene are produced in fossil fuel emissions and are carcinogenic in animals and humans (14,15). Compounds in this class are also found in meats cooked over coals or open flames. Two examples of this class of lipophilic toxins, benzo(α)pyrene and 7,12-dimethylanthracene are shown in Figure 2.

Phthalate esters are plasticizers that are present in numerous plastic/polymeric products around the globe. Phthalate esters are hepatocarcinogens in rats, presumably acting through peroxisome proliferation (16). The relevance of this effect to cancer in humans remains uncertain (17,18). Given the ubiquitous nature of this class of lipophilic compounds, the potential risks of phthalates remain a subject of concern and study (19). A commonly used phthalate ester plasticizer is presented in Figure 2.

These examples represent numerous studies of the widespread distribution of lipophilic toxins. They point out not only the global nature of the problem but also the extent of penetration into the biosphere.

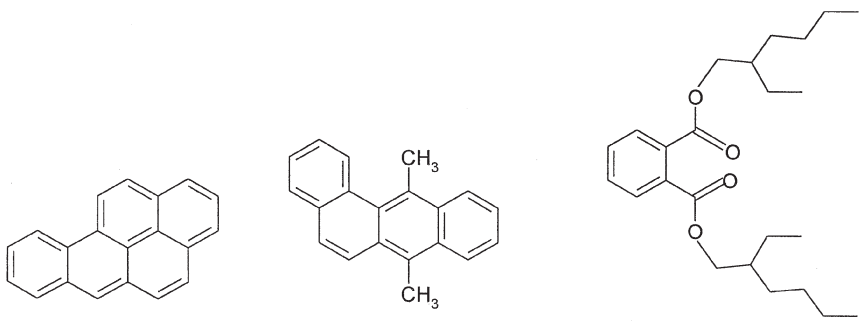


FIG. 2. Examples of polycyclic aromatic hydrocarbons and a commonly used phthalate ester plasticizer.

Toxicity and Carcinogenicity

The results of studies sponsored by the United Nations and the subsequent treaty based on these studies are evidence of consensus about the risk to health of POP in the environment. Chlorinated hydrocarbon pesticides, PBBs, and the class of polycyclic aromatic hydrocarbons are included in the list of substances "reasonably anticipated to be human carcinogens" in the U.S. Department of Health and Human Services *9th Report on Carcinogens* (20). That report upgraded dioxins to the category of "known human carcinogens." Some examples of the many studies that have addressed the toxicity and carcinogenicity of lipophilic compounds are given below.

Among the first reports was that of Fitzhugh and Nelson (21), who studied the oral toxicity of DDT in rats. Mukerjee (22) reviewed the effects of dioxins, which are among the most toxic of the lipophiles, and noted the chloracne, changes in liver function, and associations of increased risk of cancer. Hexachlorobenzene promotes hepatocarcinogenesis in rats (23). Polycyclic aromatic hydrocarbons have been studied extensively and have been shown to cause DNA damage (see, e.g., 24) and to be associated with increased cancer risk (see, e.g., 14,25,26). Estrogenic effects of organochlorine compounds have been suggested to increase the risk of breast cancer, although recent studies have not supported this hypothesis (27). There are indications that other endocrine effects of these compounds may adversely affect health (28).

Absorption, Distribution, Metabolism, and Excretion

Absorption

Oral ingestion is generally the principal route of entry for lipophiles that ascend the food chain. Absorption by inhalation or through the skin is therefore of less importance when considering methods for intervening in the absorption process.

Studies of oral absorption of toxic lipophiles have utilized techniques and mechanisms associated with the absorption of dietary triacylglycerols, fat-soluble vitamins, and cholesterol. Dietary lipids enter the small intestine, are emulsified to small droplets in the presence of detergent bile salts, are hydrolyzed into more polar products (fatty acid and 2-monoacylglycerol) by pancreatic lipase, and are incorporated into mixed micelles with bile salts. Dietary fat increases the absorption of some lipophilic compounds through the formation of these mixed micelles that can effectively solubilize such compounds as cholesterol and vitamin E. Micelles transport not only the lipid digestion products but also lipophilic solutes to the enterocyte. In the enterocyte triacylglycerols are synthesized and incorporated into lipid-based particles that are stabilized with protein (chylomicrons). These chylomicrons are transported in lymph, which can be studied in thoracic duct-cannulated animals. Chylomicrons carry most lipophilic compounds that are absorbed from the intestine. They enter the blood circulation and are partially degraded to remnant particles by the action of lipoprotein lipase. Some of the components of the chylomicrons and their remnants are delivered to peripheral tissues prior to their uptake by the liver.

The nonpolar character of toxic lipophiles suggests a pathway of absorption and transport similar to that of the dietary fats and fat-soluble vitamins. Studies of the absorption of halogenated hydrocarbons are consistent with this pathway. Some studies of toxic lipophile absorption are summarized in Table 1.

Distribution

Understanding the distribution of lipophilic toxins among tissues is an important area of research and has been the subject

TABLE 1
Studies of the Absorption of Toxic Lipophiles[a]

Study design	Results	Reference
Lymph was collected from rats dosed with [^{3}H]2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	30% of dose appeared in lymph chylomicrons in 24 h.	29
[^{14}C]DDT in sunflower oil was dosed to thoracic duct-cannulated rats.	63% of dose was in 72-h lymph collection, and 9% in feces. DDT was transferred to other lipoproteins from chylomicrons.	30
DDT was administered to rats in corn oil or in ethanol and the appearance in lymph was measured.	DDT absorption from corn oil was twice the absorption from ethanol as the vehicle.	31
[^{14}C]DDT, benzo(α)pyrene, octadecane, and hexadecane were administered to rats with thoracic duct cannulae. Chylomicrons were assayed and injected into recipient rats.	The compounds appeared in the triacylglycerol phase of chylomicrons. The labeled compounds in injected chylomicrons were taken up by high density lipoprotein in recipient animals.	32
Lymphatic absorption of a moderately lipophilic PCB congener was studied in sheep.	There was little lymphatic absorption.	33
Pregnant rats were fed hexachlorobenzene with high-fat and low-fat diets. Adipose tissue was assayed.	The amount of hexachlorobenzene found in the high-fat group fat was twice that of the low-fat group.	34
[^{3}H]Benzo(α)pyrene absorption was studied in rats with cannulated bile ducts and mesenteric lymph ducts.	Low concentration in lymph relative to bile was explained by metabolism of the benzo(α)pyrene to polar metabolites in the enterocyte and absorption *via* the portal vein.	35

[a]Abbreviations: DDT, dichlorodiphenyl-trichloroethane; PCB, polychlorinated biphenyl.

TABLE 2
Studies of the Tissue Distribution of Toxic Lipophiles[a]

Study design	Results	Reference
Autopsy samples from Greenlanders who consumed sea mammals were analyzed.	Chlorinated pesticides and PCBs accumulated in the liver, brain, and fat.	8
Rats were injected intravenously with [^{14}C]-2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	Radioactivity was found in liver, white and brown adipose tissue, thyroid, and adrenals.	42
Octachlorodibenzo-*p*-dioxin was dosed orally to rats.	There was little conversion of the parent compound to metabolites. Most deposition was in adipose tissue, liver, and skin.	43
Mice lacking inducible hepatic binding protein, CYP1A2, were dosed orally with dioxin, dibenzofuran, and PCB.	Dioxin and dibenzofuran uptake by the liver was reduced in the knockout animals.	44

[a]For abbreviation see Table 1.

of numerous studies. Although the distribution varies greatly among the compounds of interest, some generalizations can be made. Lipophilic toxins are transported in lipoproteins (36) but may be associated with albumin (37). Uptake and retention of lipophiles and their lipophilic metabolites depends on the lipid content of the tissue or compartment (38). The amount of uptake by the liver can be determined by the induction of systems such as the arylhydrocarbon (Ah) receptor and binding to the cytochrome P450 complex as in the case of dioxins (39). As seen in a study of dioxin pharmacokinetics, the determinants of the compound's disposition include lipophilicity, liver binding elements, diffusion-limited tissue distribution, and metabolic elimination (40). Presumably these determinants apply in varying degrees to most of the lipophilic toxins. The most lipophilic substances are absorbed *via* the lymph, are carried in lipoproteins, accumulate in adipose tissue, and are taken up by the liver and other tissues. Evidence that retention in adipose tissue influences the distribution to other tissues was seen in a study by Rozman *et al*. (41). In rats, hexachlorobenzene excretion decreased with increasing body weight and fat. Studies that illustrate the uptake by fat and liver are listed in Table 2.

Metabolism

The persistence of many lipophilic compounds in the body reflects resistance to metabolism and provides reason for consideration of interventions to increase their rate of elimination. The metabolism of lipophilic toxins varies among the classes and individual compounds. Individual congeners within classes have a wide range of elimination rates (45). People who ingested cooking oil contaminated with PCBs were studied to determine rates of elimination (46). There was a wide range of rates among the individual PCB congeners. In general the hexa- and heptachlorinated congeners were eliminated much more slowly than the tetra- and pentachlorinated compounds. The study was consistent with slower elimination of slowly metabolized congeners. Half-lives for pentachlorinated congeners ranged from 3 to 24 mon. Other classes of lipophilic toxins also are retained for long periods in the body. Dioxins and dibenzofurans have been estimated to have half-lives that range from 4 to 12 yr (47). Half-lives of 12.9 to 28.7 yr have been estimated for PBBs in women (48).

The conversion of lipophilic compounds to more polar species is a common metabolic path for many substances. Aryl hydroxylase catalyzes the hydroxylation of polycyclic aromatic hydrocarbons to produce species that are mobilized for transport in the blood, bile, and urine (49). PCBs and other halogenated hydrocarbons are metabolized by cytochrome P450-dependent monooxygenases to form more hydrophilic species (e.g., 50). The transformation of lipophilic xenobiotics by cytochrome P450 and other systems includes both activation and detoxification, and there have been extensive reviews of these metabolic pathways (51–54).

Hexachlorobenzene and pentachlorobenzene metabolism was studied in the rat after 13 wk of dietary exposure (55). In this study of the more polar derivatives in urine, pentachlorophenol and tetrachlorohydroquinone were formed in addition to sulfur and glucuronide derivatives.

A review of dibenzodioxins discussed the difference in metabolism of the congeners and concluded that the 2,3,7,8-chlorinated species has high toxicity due in part to affinity for the cytosolic Ah receptor protein (39). Another tetrachloro dioxin congener (1,2,7,8-tetrachlorodibenzo-*p*-dioxin) was shown to be converted to polar species in the rat (56). Glucuronides and diglucuronides of the hydroxy derivatives of the congener were identified.

Of relevance to this review are the lipophilic substances that are slowly metabolized to more hydrophilic metabolites and/or those with principal metabolites that are highly lipophilic and slowly excreted. The persistence of organic pollutants in the environment is the result of their stability and is reflected in resistance to chemical alteration by reactions including those that are enymatically catalyzed in the intact organism.

Excretion

Biliary and nonbiliary. Lipophilic xenobiotics are excreted in feces and urine. Fecal excretion is the principal route for unchanged lipophilic compounds and their lipophilic metabolites, whereas urinary excretion is the path of more polar metabolites. Biliary excretion can account for a large portion

of the fecal elimination of many compounds; however, there is evidence that some lipophilic substances follow a nonbiliary route.

The excretion of hexachlorobenzene was studied by Ingebrigtsen and coworkers (57). In bile duct-cannulated rats dosed intragastrically with [^{14}C]hexachlorobenzene, only small fractions of the dose appeared in bile as the parent compound and as pentachlorobenzene (2.0 and 1.8%, respectively). The data indicated that the major part of biliary excretion of radioactivity was contained in other metabolites. Urinary excretion accounted for 2.1% of the dose during the 4 d after its administration. Urinary metabolites of hexachlorobenzene include pentachlorophenol, sulfur-containing derivatives, and glucuronides (55).

Octachlorodibenzo-*p*-dioxin was studied in rats by Birnbaum and Couture (43). The fecal route was the major pathway for elimination with minimal urinary excretion for both intravenous and oral administration of the ^{14}C-labeled compound.

Evidence of a nonbiliary route of excretion of lipophilic toxins resulted from studies of the organochlorine pesticide, chlordecone. Excretion data obtained from humans exposed to chlordecone and rats that were administered the compound are consistent with this route as a significant excretory pathway (58,59). The authors observed that fecal excretion of chlordecone was maintained or increased when bile flow was diverted relative to that seen while bile flow was intact.

More evidence for nonbiliary intestinal excretion was reported by Rozman *et al.* (60). A study in the rhesus monkey showed that bile diversion did not alter fecal excretion of hexachlorobenzene. The presence of unchanged hexachlorobenzene in feces when the bile mainly contained metabolites was seen as evidence that nonbiliary excretion *via* exfoliation of the epithelium or exudation across the mucosa was a significant excretory route (61).

Toxic lipophiles in the lumen of the intestine from biliary and nonbiliary excretion routes are a principal target for intervention to accelerate elimination rates. Nonbiliary transport of lipophilic compounds into the lumen of the intestine is poorly understood in terms of their cellular or molecular associations, but as discussed in a later section, there is evidence of enterohepatic circulation of compounds that enter the intestinal lumen *via* a nonbiliary route. Lipophilic compounds that enter the intestine in bile also take part in enterohepatic circulation. Most of the past and current efforts to hasten the egress of toxic lipophiles from the body have focused on interruption of enterohepatic circulation to direct the compounds into fecal excretion instead of reabsorption from the intestine.

Lactation. Lipophilic compounds repeatedly have been observed in milk from humans and other species. An important path for the elimination of lipophilic substances from the body is through the lactation process. As discussed below, the mobilization of fat that provides a source of energy for neonates results in the accompanying transport of stored lipophiles into milk.

Patton (62) reviewed ideas about the movement of lipophilic xenobiotics from adipose tissue to the mammary gland. Fatty acid is released by hormone-sensitive lipase in the adipocyte, is transported to the mammary gland bound to albumin, and is re-esterified into triacylglycerol. It is not clear whether lipophilic xenobiotics stored in adipose tissue follow this same path to the mammary gland.

A study of the distribution of PCBs in female mice illustrates the importance of milk as an excretory route (63). The animals were treated with [^{14}C]PCB (2,4,5,2′,4′,5′-hexachlorobiphenyl) by intraperitoneal injection in corn oil 2 wk prior to mating. At 20 d postpartum, 98% of the dose was eliminated, and the level in the offspring was consistent with transfer of the mother's entire body burden of PCB to the pups. The level of PCB in virgin mice matched with the mothers maintained through the same time period remained essentially constant.

An example of the removal of lipophilic toxic materials from humans was reported by Schechter and coworkers (64). They followed the levels of lipophilic materials in the blood and milk of a mother who nursed twins for a period of 38 mon. Dioxin and dibenzofuran concentrations in milk decreased from 309 to 173 and from 21 to 9 ng/kg, respectively, during 30 mon. Hexachlorobenzene concentration decreased from 10.7 to 1.8 ng/g. These observations reflect the mobilization of the mother's adipose tissue to provide energy in milk, and the mobilization of stored dioxin, dibenzofuran, and hexachlorobenzene accompanying the fat.

Clearly, milk can be a major excretory route for lipophilic toxins, but the obvious consequence of this route is the introduction of the toxin into the neonate. There have been few studies that have addressed ways to affect the rate or amount of excretion of lipophilic toxins in milk.

EFFECTS OF DIETARY ADDITIVES

The foregoing discussion is intended to give an overview as a background for the review of methods that alter the residence time and elimination rate of toxic lipophiles in an organism. These interventions include specific dietary additives, changes in energy intake, and variations in dietary fat.

Nonabsorbable Lipids

Effect on Absorption from the Diet

Since most toxic lipophiles enter the body orally *via* food and water, the first approach for potential intervention is reduction of absorption from the intestine. As discussed by Jandacek (65) and Patton (62), a large fraction of dietary lipophiles enter the mouth and stomach dissolved in or associated with dietary triacylglycerol. Lipophiles that are adsorbed to other dietary constituents presumably associate with the dietary fat during mastication and mixing in the stomach.

In the small intestine, triacylglycerol is split into fatty acids and 2-monoacylglycerol, which form mixed micelles with bile salts and phospholipid from bile. During this

digestion process, a triacylglycerol oil phase remains mixed with an aqueous micellar phase until its digestion is complete. There is also evidence of liquid crystalline phases in the intestinal lumen during this process (66). Lipophiles are distributed among these phases but are presumably transported to the enterocyte membrane in the bile salt mixed micelles. Entry into the enterocyte and incorporation into chylomicrons presumably occur for many lipophiles. A strong affinity for an oil phase, as is the case for lipophiles with octanol–water partition coefficients of $>10^5$, results in retention of a large portion of the lipophile in the oil.

The triacylglycerol oil phase in the intestinal lumen is relatively transient. Digestion and absorption of dietary fat are efficient and fast, so that the oil phase disappears quickly. It is possible, however, to maintain an oil phase that competes with the micellar phase for lipophile solubilization. Sucrose esterified with long-chain fatty acids is not hydrolyzed by pancreatic lipase, and thereby maintains an intestinal oil phase throughout gastrointestinal transit (67). Sucrose esterified with six or more long-chain fatty acids has been termed "sucrose polyester" (SPE) and is a component of olestra (brand name, Olean®) (68).

DDT in rats. (i) Olestra. The effect of olestra (SPE) on the absorption of dietary [^{14}C]DDT was studied in the rat by Volpenhein and coworkers (69). When [^{14}C]DDT dissolved in soybean oil was intragastrically intubated into rats fitted with thoracic duct cannulas, 67% of the dose was recovered in a 48-h lymph collection. When the dosing oil comprised 50% soybean oil and 50% SPE, 21% of the dose was in the lymph. Data from rats that did not undergo surgery were consistent with the lymph recoveries. After dosing with the same oils used in the thoracic duct experiments, the animals received *ad libitum* semipurified diets without DDT, but which contained 20% by weight soybean oil or the same blend of 50% soybean oil and 50% SPE used in the lymphatic measurements. Animals dosed with soybean oil excreted less than 10% of the radioactivity in 72 h after its ingestion, whereas those dosed with 50% soybean oil and 50% SPE excreted more than 55% of the dose. The recovery of radioactivity from extracted tissues was consistent with the reduction in absorption by SPE. Approximately 60% of the dose appeared in total carcass fat of the soybean oil group compared with 20% in the soybean oil-SPE group. Similar results were obtained from the liver and epididymal fat pads, with recovery from the soybean oil-SPE group equal to one-third that of the soybean oil group.

These data are consistent with the nonabsorbable oil interfering with the absorption of the lipophile from the diet. The apparent mechanism is that of retention of or transport to the nonabsorbable oil, thereby diminishing the concentration of the lipophile in the micellar phase. Since micellar solubilization is obligate for the absorption of lipophiles, absorption was decreased in the presence of a nonabsorbable oil.

(ii) Mineral oil. A study of the effect of another nonabsorbable lipophilic material, mineral oil, on absorption from the diet did not provide clear answers. Keller and Yeary (70) tested the effects of mineral oil and sodium sulfate on the intestinal absorption of DDT in rats. Rats were intragastrically gavaged with [^{14}C]DDT in either soybean oil, mineral oil, 15% sodium sulfate with acacia, or water with acacia. After an hour the same formulations were intubated without DDT. This procedure was repeated 24 h later. The animals were sacrificed 48 h after the first dosing regimen, and tissues were taken for measurement. Adipose concentration of DDT was used as the principal assay. The authors concluded that the most important observation was the higher absorption observed when soybean oil was ingested. There was minimal difference among the other groups. The data may indicate the facilitation of the absorption of the pesticide by the presence of hydrolyzable dietary fat.

In contrast with the results of Keller and Yeary, another study found that mineral oil reduced markedly the appearance of DDT in lymph collected for 4 h after oral dosing (71). The peak lymphatic concentration after dosing in mineral oil was approximately one-fourth of that seen after dosing in arachis oil. DDT absorption was also determined from plasma areas under the curve in rats that did not undergo surgery. The decrease in absorption seen in the rats fed mineral oil relative to those fed arachis oil was consistent with the measurements of DDT in lymph.

Lindane in pigs. Morgan and coworkers (72) studied the effects of dietary additives on the absorption of the lipophilic pesticide lindane (the γ isomer of hexachlorocyclohexane). Anesthetized pigs were gavaged with lindane and various test formulations, and plasma lindane concentrations were followed for 150 min. The formulations that were compared included water (control), activated charcoal, mineral oil, and castor oil. The authors concluded that none of the treatments reliably altered the gastrointestinal absorption of the pesticide.

Effects on Stored Lipophiles

Olestra. (i) Animal studies. The effects of three dietary lipids that are either poorly absorbed or not absorbed were studied in rats. Hexachlorobenzene elimination was measured during consumption of diets containing either olestra (SPE), squalane (30-C saturated hydrocarbon; 2,6,10,15,19,23-hexamethyltetracosane, obtained by hydrogenation of squalene), or paraffin (73). [^{14}C]Hexachlorobenzene was added to the diet for 4 d, and after 10 additional days the rat diets were supplemented with 8% olestra, paraffin, or squalane. After 3 wk of treatment, measurements of radioactivity in feces were made, and the excretion in each of the treatment groups was found to be three times higher than that of the control groups. Significant reductions in the tissue levels of radioactivity in the treatment groups were consistent with the excretion data. The authors suggested that in light of the absence of biliary excretion of hexachlorobenzene, nonabsorbable oils reduced the effective concentration gradient between blood and the gut lumen.

The effect of olestra on the elimination of [^{14}C]DDT (and/or its principal metabolite, DDE) was studied in gerbils

(74). Gerbils were given [^{14}C]DDT orally and maintained on chow until a log-linear fecal excretion rate was established. Excreted radioactivity increased more than twofold when 2.5 wt% olestra was added to the diet. Similar increases were seen with 5 and 10% olestra. Animals were changed to diets that provided 50–75% of normal caloric intake, and fecal excretion of radioactivity increased approximately 50% above that of control animals. When olestra was included in the reduced energy diet at a level of 10%, the average increase in fecal excretion was eightfold that of the control animals.

These studies of olestra in animals indicated that olestra could be used to interrupt enterohepatic circulation of lipophilic toxins that had been stored in the body after oral ingestion. Studies in humans discussed below have supported its potential use in removing lipophilic toxins from the body.

(ii) Human trials. Olestra has been studied in detoxification of dioxin in human trials. Gesau *et al.* (75) fed olestra to two subjects who had elevated levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Five different dosing regimens were used, and olestra ingestion ranged from 15 to 66 g/d. Fecal excretion of TCDD was markedly increased with olestra consumption. In one patient the increase ranged from 3- to 10-fold above that prior to olestra consumption. In the other patient the increase ranged from three- to eightfold, depending on the specific regimen.

Moser and McLachlan (76) studied olestra in three healthy volunteers with normal exposure to lipophilic pollutants. Fecal excretion of dioxins, dibenzofurans, PCBs, and hexachlorobenzene was measured after 8 d of ingestion of 25 g/d of olestra. The excretion was compared with that of an initial 3-d control phase without olestra consumption. The excretion during the olestra period was 1.5 to 11 times higher than that during the control period, depending on the specific compound. Excretion enhancement (the increase in a compound's excretion relative to its ingestion) increased for all compounds during olestra ingestion. The authors also reported the interesting observation that the excretion enhancement decreased as the octanol/water partition coefficient of the lipophile of interest increased.

Mineral oil/hexadecane/squalane. Mineral oil is a cut of petroleum distillates that is dominated by but not limited to long-chain hydrocarbons, including hexadecane. Paraffin/paraffin oil also includes long-chain hydrocarbon compounds. Squalane is defined in an earlier section. These materials are poorly absorbed from the intestine and maintain an intestinal lipid phase during gastrointestinal transit; however, partial absorption may occur and has been implicated in histological lesions in the liver and spleen (77,78). The absorption of trace amounts of mineral oil and its components has not prevented its use as a model lipid sink in elimination studies, but it raises issues relative to its use in long-term human therapy.

Richter (79) reviewed studies that intervened to change the rate of fecal excretion of hexachlorobenzene and cited 12 studies that utilized mineral oil in changing the excretion of hexachlorobenzene, hexachlorocyclohexane, pentachlorobiphenyl, hexabromobiphenyl, chlordecone, mirex, and DDT. Significant enhancement of the rate of excretion was seen with mineral oil in all but one of the cited studies. Five studies with squalane and four with hexadecane were also cited in Richter's review. Both compounds effected increases in the excretion of hexachlorobenzene in the studies reviewed. The review noted that hexadecane is partially absorbed and therefore is not suitable for consideration as a nonabsorbable lipid for therapeutic purposes; there is also evidence for the accumulation of dietary squalane in the liver of rodents (73,80).

Much of the work that was carried out with these poorly absorbed oils was directed by K. Rozman and T. Rozman. Table 3 summarizes the design and results from their studies and from those of other investigators.

Mineral oil (paraffin oil) has been the subject of most studies of intervention in the metabolism of lipophilic toxins. The data are clearly supportive of its interference with the reabsorption of lipophiles that enter the intestinal lumen *via* bile or a nonbiliary mechanism. Although the possibility of absorption of mineral oil limits its applicability in humans, the experiments with animals have demonstrated the validity of an intervention that is based on interruption of enterohepatic circulation of lipophiles.

Resins

Pharmaceutical cationic ion exchange resins have been used to treat hypercholesterolemia by binding bile salts in the intestine and enhancing their excretion. Since these polymeric resins are not absorbed, bind bile salts, and have lipophilic backbones, they were considered as candidates for intervention in the enterohepatic excretion of some lipophilic toxins. The use of cholestyramine in people contaminated with chlordecone in the study discussed below was the first effective detoxification of a lipophilic toxin that was stored in the body (95).

Cholestyramine binds the pesticide chlordecone *in vitro* and enhances its excretion in rats (96). Rats were given ^{14}C-chlordecone by stomach tube and after 7 d assigned to diets containing cholestyramine or silica gel/cellulose (control). Measurements of fecal excretion and tissue concentrations ensued. The concentration in the liver was reduced by 39% in the cholestyramine group relative to controls, in fat, by 30%, and in the brain, by 50%. Significant increases in fecal excretion and decreases in body burden were seen in the cholestyramine group relative to the control group.

The reduction of chlordecone from human subjects with a high body burden was reported by Cohn and colleagues (95). Workers in a factory that manufactured chlordecone exhibited symptoms of toxicity attributed to the pesticide. A double-blinded trial of subjects who received either placebo or 24 g/d of cholestyramine was carried out. Cholestyramine increased the fecal excretion by 3- to 18-fold. A significant reduction in the half-life of chlordecone (calculated from longitudinal measurements of blood levels) was seen with cholestyramine. Chlordecone excretion in the bile of a patient fitted with a T-tube was 19 times faster than that in feces,

TABLE 3
Studies with Mineral Oil, Squalane, or Hexadecane[a]

Study design	Results	Reference
Mineral oil and hexadecane were fed to rats and rhesus monkeys that had been dosed with [^{14}C]hexachlorobenzene (HCB). Fecal excretion and tissue levels of ^{14}C were measured.	Hexadecane at a level of 5% in the diet increased ^{14}C-HCB fecal excretion 4- to 13-fold; mineral oil caused a six- to ninefold enhancement. Blood and adipose tissue levels of ^{14}C decreased with increased excretion.	60
Rats were dosed orally with [^{14}C]HCB and fed diets containing 8% squalane, paraffin oil, or sucrose polyester. Fecal excretion was monitored.	The half-life, calculated 35–38 d after discontinuation of the HCB diet, was reduced to approximately one-third of that of the control group by all oils.	73
[^{14}C]HCB was dosed to rats in the diet. After 35 and 53 d, animals were sacrificed for analysis. Feces were analyzed.	The fast and slow half-lives of elimination were reduced by 48 and 77% by paraffin oil. There were reductions of HCB in all analyzed tissues; fat concentration was reduced more than 80% by paraffin oil.	81
[^{14}C]PCB (2,4,6,2′,4′-pentachlorobiphenyl) was dosed orally to rats. A control diet was compared with a diet with 8% light paraffin oil. Feces were assayed.	The paraffin oil group excreted 54% of the dose, and the control animals, 43%, during the 4 wk after discontinuation of the PCB-containing diet.	82
Rhesus monkeys were given mirex and then received a diet containing 5% mineral oil.	Fecal excretion was increased 50% 1 mon after dosing; the increase was 400% 6 mon after dosing. The long-term effect was attributed to "deep" storage in fatty tissue.	83
Rhesus monkeys were given 5% mineral oil after a dose of 2,4,5,2′,4′,5′-hexabromobiphenyl.	Fecal excretion increased 175% with the addition of mineral oil to the diet.	84
Rats dosed with [^{14}C]HCB were given hexadecane. The effect of bile duct ligation was tested.	Bile duct ligation, dietary hexadecane, and the combination of all treatments increased fecal excretion. The combination of treatments was more effective than each alone.	85
Orally dosed [^{14}C]HCB in intestinal segments was measured; the effect of hexadecane on HCB intestinal excretion in the segments was determined.	The data indicated that hexadecane increased excretion of HCB in the colon.	86
Rhesus monkeys were dosed orally with [^{14}C]HCB with varying doses. Bile flow was diverted, and excretion was measured in animals given diets with and without mineral oil.	Fecal excretion of HCB was raised fivefold by mineral oil. Urinary excretion was not altered by mineral oil.	87
Rhesus monkeys were dosed orally with [^{14}C]DDT and given a diet with 5% mineral oil. Fecal excretion and adipose tissue levels were assayed.	Mineral oil doubled the excretion rate and halved the amount of radioactivity in the adipose tissue.	88
Hexadecane was injected into ligated intestinal segments of rats previously dosed with [^{14}C]HCB; the effect on intestinal excretion was determined.	Intestinal excretion increased in the order jejunum > ileum > cecum and colon. The authors noted that high residency time makes the colon an important site for interaction with hexadecane.	89
Sheep were fed [^{14}C]HCB and then given diets containing 5% mineral oil or 5% hexadecane. Fecal excretion and adipose stores were measured.	Treatment with hexadecane and mineral oil increased fecal excretion threefold. Reductions in adipose tissue corresponded to increases in excretion.	90
Lactating goats dosed with mirex were given 5% light mineral oil. Fecal excretion, blood, and milk concentrations of mirex were measured. Mineral oil as 3% of the diet was fed to cattle that produced butterfat contaminated with DDT.	Fecal excretion of mirex from goats was increased by dietary mineral oil. There were no changes in concentrations in milk or blood during the period of mineral oil consumption. Fecal DDE excretion from cows increased with mineral oil consumption; milk concentrations did not change with mineral oil treatment.	91
Rabbits and rats were dosed with [^{14}C]HCB and given a diet containing 5% hexadecane.	Half-lives were of HCB in the rat (24 d) and rabbit (32 d) were similar. Hexadecane increased fecal excretion of HCB four- to fivefold.	92
Chickens with HCB or pentachlorophenol body burdens were given mineral oil, colestipol, and/or reduced caloric intake.	5 wt% mineral oil in the diet reduced body burden to 36% of dose, compared with 63% of dose with no treatment.	93
Heptachlor epoxide was given to mink. The effect of diet restriction with a diet containing 10% mineral oil was observed.	Rapid reduction of body burden occurred with control (*ad lib* diet) animals; mineral oil and restricted diet did not accelerate the reduction relative to the control.	94

[a]DDE, 1,1-dichloro-2,2-bis(chlorophenyl)ethylene. For other abbreviations see Table 1.

Table 4
The Use of Resins to Intervene in Toxic Lipophile Excretion[a]

Study design	Results	Reference
Rhesus monkeys were orally dosed with [^{14}C]HCB, and 4% cholestyramine was added to the diet. Fecal excretion of ^{14}C was measured.	Cholestyramine did not increase the rate of fecal excretion above that seen during a period without dietary cholestyramine.	60
[^{14}C]DDT was given to gerbils, and the excretion was followed after diets with and without 4% cholestyramine.	A modest increase in excretion of radioactivity was observed with added cholestyramine.	74
Rhesus monkeys dosed with 2,4,5,2′,4′,5′-hexabromobiphenyl (PBB) were given 4% cholestyramine in the diet.	Fecal excretion of the PBB increased 50% with the addition of the resin.	84
Chickens were fed HCB or pentachlorophenol and given colestipol with or without food restriction.	Marked reductions in body burdens were seen for both compounds with colestipol; greater reductions were seen when colestipol was combined with food restriction.	93
Turkeys and chickens were orally administered [^{14}C]dieldrin and fed resins.	Based on carcass analyses, the resins were generally ineffective in reducing the dieldrin levels.	97,98
Rhesus monkeys dosed with [^{14}C]-pentachlorophenol were given a diet containing 4% cholestyramine; fecal excretion was monitored.	Fecal excretion of radioactivity increased 9- to 14-fold with cholestyramine in the diet.	99
Rhesus monkeys were orally dosed with [^{14}C]pentachlorophenol and fed cholestyramine.	Fecal excretion of pentachlorophenol increased by as much as 40%.	100
PBBs were fed to chickens. Colestipol was fed alone or in combination with a starvation regimen.	Colestipol alone had minimal effect but reduced body burden by 70% in 21 d in combination with starvation.	101
Patients exposed to PCBs and dibenzofurans were given 8–12 g/d cholestyramine for 24 wk.	In 4 of 6 patients there was no effect of cholestyramine. Fecal excretion of PCBs increased by 36–46% in the other two.	102,103
Rats fed rice oil contaminated with PCBs and dioxins were given 5% cholestyramine alone or in combination with squalane and rice bran.	Cholestyramine alone enhanced excretion of some congeners by factors of 1.3–3.3. Combinations with rice bran and squalane somewhat enhanced the excretion. Excretion of a heptachlorodibenzodioxin congener was not affected by the resin.	104
Rats received PBB for 6 mon followed by normal diets for 4 mon. Cholestyramine was included in the diet for 6 mon.	Cholestyramine did not reduce the levels of bromine in the tissues.	105

[a]For abbreviations see Tables 1 and 3.

thereby indicating the existence of an enterohepatic circulation of chlordecone.

Other trials that have studied cholestyramine and colestipol (also a bile salt-binding cationic resin) are summarized in Table 4.

Activated Carbon

Activated carbon, which is used as an adsorbent in treatment of patients with acute poisoning, has also been studied as a treatment for stored lipophilic toxins. The rationale for its use is that of interference with enterohepatic circulation of compounds that enter the intestine *via* biliary and nonbiliary routes. The use of activated carbon in studies of lipophilic toxin metabolism is summarized in Table 5.

Protoporphyrin

One study was carried out with dietary protoporphyrin and hemin (108). The rationale for the use of these materials was apparently based on expected low intestinal absorption of protoporphyrin and hemin and predicted high adsorption of lipophilic substances to these substances. Animals that were given the oil that contained polychlorinated dioxin and polychlorinated dibenzofuran were subsequently provided a diet that contained either 0.5% disodiumprotoporphyrin or 0.5% hemin. The protoporphyrin group excreted 2.1 times the amount of the toxins in feces relative to the control group. The group that received hemin was not different from the control group.

Dietary Fibers/Indigestible Polysaccharides

As noted in Table 4, rice bran fiber in combination with cholestyramine slightly increased the excretion of polychlorinated dibenzofuran congeners relative to cholestyramine alone in rats with body burdens of these compounds (104). The same study included comparisons of rice bran and other fibers (burdock, corn, soybean) that were included in the diet at a concentration of 10% by weight. All of the fibers significantly increased the excretion of all measured dibenzofuran and dioxin congeners except the 1,2,3,4,6,7,8-heptachlorodibenzodioxin relative to the control group. The effect of the rice bran fiber was the greatest, with rates of excretion ranging from 1.9 to 3.3 times that of the control group.

A comparison of the effects of some indigestible polysac-

TABLE 5
The Use of Activated Carbon in Detoxification of Lipophiles

Study design	Results	Reference
3 patients with body burdens of chlordecone were given 40 g/d of activated charcoal.	Excretion rate was increased by less than twofold by the carbon.	95
Turkeys and chickens were administered ^{14}C-dieldrin orally and fed activated carbon.	Activated carbon had no effect on the rate of elimination.	96,98
Rats received PBB for 6 mon followed by normal diet for 4 mon. Activated charcoal was included in the diet for 6 mon.	Activated charcoal did not reduce the concentration of bromine in tissues.	105
Activated carbon was fed as 5% of the diet with or after DDT exposure to rats and cows.	Activated carbon decreased DDT absorption but had no effect on rate of elimination.	106
Mice, rats, and guinea pigs were injected intraperitoneally or subcutaneously with 2,3,7,8-tetrachloro-*p*-dioxin and given chow or chow plus charcoal.	Mortality was reduced from 93 to 53% in mice; 80 to 50% in rats; 64 to 29% in guinea pigs.	107

charides on the accumulation of pentachlorobenzene was performed in rats (109). Rats were fed either cellulose (control), sodium alginate, guar gum, or γ-carrageenan at a level of 5 wt% of the diet. After 2 wk they were dosed orally with 20 mg of pentachlorobenzene, maintained with the experimental diets for seven more days, and then sacrificed to assay tissues. Body weight and adipose tissue mass (as percentage of body weight) were significantly lower in each of the polysaccharide groups relative to the control. The level of pentachlorobenzene was lower in the livers, kidneys, and adipose tissue of the animals that ate the polysaccharides relative to the control group. Fecal excretion of pentachlorobenzene was higher than that from control animals in the groups fed sodium alginate and guar gum. The authors suggested that lower adipose tissue mass seen in the polysaccharide groups was in part responsible for the enhanced excretion of pentachlorobenzene.

Amount and Type of Absorbable Dietary Fat

Contrasted with the studies of energy deprivation, Nakashima *et al.* (34) studied the effect of a high-fat diet on the elimination of hexachlorobenzene in lactating rats. Pregnant rats fed a high-fat diet transferred hexachlorobenzene more slowly in milk to pups than those fed a low-fat diet. This observation may reflect a reduced rate of mobilization of the adipose stores in the high-fat fed mothers so that the stored hexachlorobenzene also was transported more slowly.

In addition to the effects of nonabsorbable dietary fats, there is evidence that the fatty acid composition of typical dietary fats may influence the metabolism of organochlorine compounds. Umegaki reported that fish oil enhanced the metabolism of pentachlorobenzene in rats relative to the effects of lard or soybean oil (110). Fish oil not only enhanced the levels of the principal metabolite of pentachlorobenzene, pentachlorophenol but also reduced the concentration of pentachlorobenzene in fat. The authors suggest that reduced accumulation of adipose tissue in the animals fed fish oil contributed to its reduced accumulation.

Umegaki and Ikegami (111) studied the influence of dietary fatty acid on hexachlorobenzene metabolism. They reported that relative to soybean oil, fish oil and lard in the diet resulted in a lower total fat mass and higher concentrations of hexachlorobenzene in the blood, liver, and brain. The animals that received fish oil had higher urinary levels of pentachlorophenol, a principal metabolite of hexachlorobenzene. The authors concluded that fish oil increased cytochrome P450 and accelerated hexachlorobenzene metabolism, thereby increasing oxidation to more polar compounds (51).

The absorption of [^{3}H]benzo(α)pyrene was measured in rats that were fitted with bile and lymph duct cannulae and fed 50 or 500 μmol of olive oil (35). There was no effect of the level of dietary fat on the recovery of radioactivity in bile and lymph. The results were consistent with rapid conversion of benzo(α)pyrene to polar compounds in the enterocytes and absorption *via* the portal vein rather than lymph.

CHANGES IN BODY FAT

Adipose tissue is the principal depot for accumulation of many lipophilic toxins. Therefore, reduction in adipose tissue stores (e.g., from weight loss) can release stored lipophilic toxins into the circulation and expose other sites to them. The following outcomes of this release are possible: storage in tissues that are more affected than adipose tissue by the compounds; increased metabolism resulting from increased uptake by the liver; decrease in body burden; and combinations of these events. Some studies of adipose tissue and weight reduction have examined excretion rates and tissue distribution. There also have been studies in which weight reduction was combined with use of nonabsorbable dietary lipids.

A suggestion of adipose tissue "protecting" more sensitive targets from lipophilic toxins was presented by Geyer *et al.* (112), who suggested that the toxicity of dioxin is inversely related to the amount of body fat in an animal. Based on the relationship between toxicity and body fat among and within species, the authors concluded that body fat is a reservoir that limits the exposure of target organs to toxic lipophiles. This kind of relationship underscores the importance that changes in adipose tissue mass might have on lipophilic toxin metabolism.

Effects of Weight Loss on Elimination of Lipophiles in Experimental Animals

The study by Davison and Sell (98) of dieldrin in chickens cited in Table 4 included a regimen of severe starvation. The authors observed significant increases in excretion and complementary reductions in carcass levels of dieldrin with reduction in energy intake.

Mitjavila *et al*. (113) studied the effect of restricted food intake on DDT metabolism in the rat. Animals received DDT daily *via* intragastric gavage. They were then subjected to 3 d of starvation followed by 14 d of a fat mobilization period with a diet limited to 2.5 g food/d/rat. Tissue compositions of DDT and DDE were assayed. The half-life of DDT was calculated to be 5 d under these conditions, markedly less than estimates of 2 mon from studies of *ad libitum* feeding. Observation of the animals led the authors to conclude that the rat liver is capable of metabolizing large quantities of DDT that are mobilized by reduction of adipose stores of the pesticide.

In the study by Polin *et al.* (93) (cited in Table 4) of chickens with body burdens of hexachlorobenzene and pentachlorophenol, the effect of reduction of food intake was studied. Treatment with food restriction at 50% of *ad libitum* intake reduced the body burden to 37% of the initial dose of hexachlorophene, compared with a value of 63% for the *ad libitum* diet control group. The analogous figures for pentachlorophenol reduction were 25 and 70% of the dose, respectively. Chickens that were fed 10 wt% colestipol or 10 wt% mineral oil showed a further reduction to 19% of the original dose for each treatment.

As already noted in the summary of the study by Mutter *et al*. (74), caloric deprivation with and without dietary olestra in gerbils increased the rate of excretion of DDT/DDE. This increase was approximately 50% above that from control animals that received an *ad libitum* diet when no other treatment was included. The combination of dietary olestra with caloric deprivation markedly increased the excretion rate to approximately eight times that of the excretion from fed control animals.

A combination of mineral oil and food restriction was studied in the elimination of PBBs from chickens in the study by Polin *et al.* cited in Table 4 (101). Both mineral oil and food restriction treatments resulted in reductions in body burdens greater than those seen in control animals at relatively low doses of the PBBs (0.1 and 1.0 ppb in the diet). At higher dose levels of PBBs, there were minimal effects in terms of percent reduction.

Restricted caloric intake was ineffective in a study of rats with a body burden of PBBs (105). The animals were fed a mixture of PBBs for 6 mon followed by a diet free of PBBs for 4 mon. Reduction in energy intake did not reduce the level of PBBs in adipose tissue.

The study of an interesting lactation process was reported by Polischuk and coworkers (114), who measured the concentration of chlorinated organic compounds in polar bears undergoing an extensive fast and lactating. They found that the concentration of PCBs, chlordanes, and chlorobenzenes in milk lipids increased markedly during the fasting period. The concentrations of DDT and hexachlorocyclohexane did not have a consistent pattern.

Effect of Weight Loss on Elimination in Humans

Two subjects who were part of the Biosphere 2 project near Tucson, Arizona, participated in measurements of blood levels of PCBs and DDE (115). In the conditions of a closed ecological space and self-sufficient food supply, men and women lost 18 and 10% of body weight during 2 yr, respectively, with most of the loss in the first 6–9 mon. The blood concentrations of the toxicants were reported to increase during the first 12–18 mon and then decrease. The initial increase is consistent with the mobilization of adipose tissue, and the subsequent decrease may reflect reduced body stores.

The effect of modest weight loss on the concentration of hexachlorobenzene and DDT in the breast milk of women with relatively low levels of the contaminants was reported (116). There was no change in the milk concentration of these compounds with a mean weight loss of 4.1 kg.

Effect of Weight Loss on Tissue Distribution in Experimental Animals

Dale *et al.* (117) studied the effect of caloric restriction in rats that received 200 ppm DDT added to chow for the duration of the study. One group was sacrificed after 90 d of *ad libitum* feeding. A second group was sacrificed after a sequence of 90 d of *ad libitum* followed by 10 d of 50% reduction in normal energy intake. A third group followed the regimen of 90 d of *ad libitum* feeding, 10 d of 50% caloric deprivation, and 40 d of *ad libitum* feeding. A fourth group followed a regimen of *ad libitum* feeding for 140 d before sacrifice. The levels of DDT and its metabolite DDE in tissues were measured. The concentration of DDT and DDE increased in the tissue and the lipid fractions of fat, brains, plasma, livers, and kidneys of animals that were energy-deprived at 100 d relative to those sacrificed at 90 d. Although excretion of DDT and metabolites increased during energy deprivation, the excretion rate did not prevent the increase in concentration of DDT and its metabolites in the examined tissues.

Findlay and deFreitas (118) studied the effect of lipid utilization on the mobilization of DDT in pigeons. Homing pigeons were dosed with [^{14}C]DDT in corn oil for 16 d. Some of the birds were maintained at 6°C without food until they had lost 18–20% of their body weight and then sacrificed. The distribution of radioactivity among tissues was measured in the birds and compared with that from a group that was not stressed by the weight loss regimen. The total amount of DDT in the fat in the stressed birds was reduced relative to the unstressed birds at all doses of DDT that were administered. The concentration of DDT in the fat lipids was two- to threefold higher in the stressed birds. The total DDT in breast muscle

increased 172 to 262% in the stressed birds, and the concentration increased 174 to 235%.

Weight loss in female rats that were dosed orally with hexachlorobenzene and restricted to 30% of normal intake for 7 d resulted in a marked increase in hexachlorobenzene in all tissues (119). The levels in the brain and liver were elevated 367 and 496%, respectively.

The effects of restricted feeding on pentachlorobenzene in rats was reported by Umegaki *et al.* (120). The animals that were eating *ad libitum* or with intake restriction received a single dose of pentachlorobenzene in soybean oil. Fecal excretion of dietary pentachlorobenzene was decreased by restriction of feed intake to 50 and 25% of *ad libitum* consumption. Its accumulation in liver, brain, and fat was also reduced by dietary restriction. The authors concluded that the reduced level in these tissues was the result of increased metabolism by the liver resulting from a decrease in adipose tissue mass and mobilization of the compound.

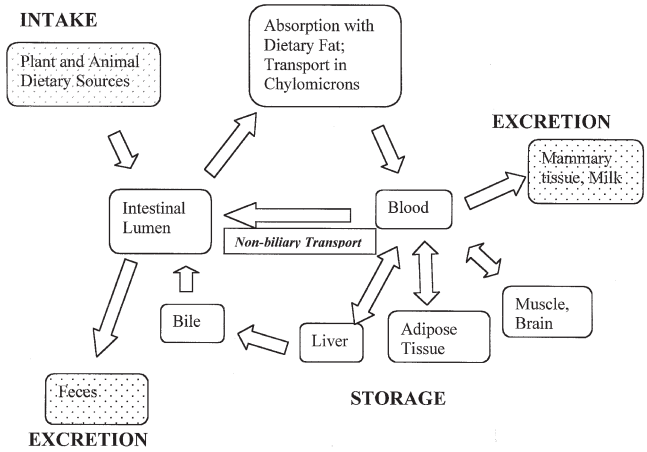
A study of the effect of fasting on the estrogenic effect of DDT and β-hexachlorocyclohexane was studied in mice (121). The animals were injected with the the halogenated compounds and then fasted for 2 d. Uterine weights of fasted and fed animals were compared with those from animals injected with vehicle (control animals). The uterine weights of the animals injected with β-hexachlorocyclohexane were greater than those from fed animals or from fasted control animals. Fasting did not alter the estrogenic effect of DDT. The authors concluded that lipolysis accompanying fasting releases β-hexachlorocyclohexane with subsequent stimulation of estrogen target tissues. The data indicated that DDT was mobilized in a different manner.

There is evidence that energy restriction may make an animal more vulnerable to the toxic effects of lipopohiles. In rats fed hexachlorobenzene, the restriction of energy intake to 50% of a control diet resulted in an increase in liver hypertrophy and hepatocyte foci (23).

DISCUSSION

Summary of Lipophilic Toxin Metabolism

The research discussed in the previous sections provides a general view of the metabolism of toxic lipophiles. This view is summarized in the diagram in Scheme 1. Oral ingestion is the principal entry route for most of these compounds. Dietary fat, which facilitates the absorporption of lipophilic xenobiotics, may act as a carrier for the compounds. They are incorporated into chylomicrons, transported to peripheral tissues and the liver, and may exchange with circulating lipoproteins. They are carried in the blood by lipoproteins. The way that they are metabolized varies among the classes of compounds and among the individual congeners within the classes. Metabolism of very lipophilic compounds converts them into more hydrophilic molecules such as glucuronides or hydroxylated derivatives. Molecules that are very hydrophilic are excreted in urine whereas more lipophilic compounds are transported in bile. In addition, there is evidence that lipophilic compounds that are excreted in feces may be of nonbiliary origin. The nature of this excretory route is unclear, but presumably it results from the sloughing of intestinal cells that accumulate lipophilic substances and/or from a hypothetical secretion directly out of the cells. It is clear from several studies that reabsorption of lipophilic compounds from the intestine occurs with subsequent enterohepatic circulation. It is also evident that enterohepatic circulation occurs for compounds both of biliary origin and of nonbiliary origin.



SCHEME 1

There is convincing evidence that many lipophilic xenobiotics and their more lipophilic metabolites are stored in adipose tissue. Uptake by other tissues and organs also occurs, in some cases resulting from induction of and affinity for enzyme systems such as aryldehydrogenase, and in other cases from the lipid content of the tissue.

Lipophilic xenobiotics are mobilized from adipose tissue when the adipose stores are depleted through reduction in energy intake. The fate of these mobilized molecules varies with the compound and with other conditions, including interventions. Some are taken up by other tissues and organs, including muscle and brain. There is some evidence that toxic effects increase with the transport of compounds from adipose tissue to more sensitive organs. Mobilization generally increases biliary and nonbiliary transport into the intestine, which in turn enhances fecal excretion and enterohepatic circulation.

Mobilization of lipophiles from adipose stores accompanies the transport of triacylglycerol from adipose tissue into milk during lactation. Milk fat formed during lactation can remove a large fraction of a body burden of many lipophilic xenobiotics. There are obvious implications of this process for the health of infants ingesting breast milk.

Summary of Interventions That Alter Storage and Elimination of Lipophilic Toxins

Interventions that can potentially alter the storage and rates of elimination of lipophilic toxins have generally been

directed toward interruption of their enterohepatic circulation. Poorly absorbed materials that adsorb or dissolve lipophilic compounds in the intestinal lumen can reduce absorption that returns them into the circulation and tissues. Nonabsorbable substances that bind lipophiles, such as lipids (olestra, mineral oil), fiber, resins, and activated carbon increase elimination rates in a number of studies, and these results are consistent with interruption of enterohepatic circulation. Nonabsorbable lipids and activated carbon also reduce the initial absorption of dietary lipophilic xenobiotics by the same mechanism of adsorption/dissolution and fecal excretion.

Another approach has been the combination of substances that reduce enterohepatic circulation with a reduction in body fat stores. This combination has been more effective than separate regimens of weight loss or nonabsorbable binders of lipophilic compounds. In addition, there is some evidence that weight loss alone may cause redistribution of toxic compounds to tissues that are more sensitive than adipose tissue. Interruption of the enterohepatic circulation combined with weight loss may reduce this undesirable effect of weight loss alone.

To date there have been no studies of the effects of a high-energy or high-fat diet in combination with substances that interfere with enterohepatic circulation. This regimen could potentially provide a safe method for reducing the body burden of lipophilic xenobiotics by minimizing concentrations in sensitive tissues. The observation by Nakashima *et al.* (34) of a high-fat diet reducing excretion of hexachlorobenzene in milk lends support to this approach.

Conclusions and Direction for Further Work

There have been numerous attempts to alter the storage and elimination of lipophilic xenobiotics both in animal models and in humans. It is clear that clinically significant changes in elimination rates can be achieved by regimens that reduce the enterohepatic circulation of toxic lipophiles and their metabolites. There have not, however, been systematic approaches that address the combination of regimens to optimize the conditions for the safe and rapid elimination of stored toxic lipophiles.

Many lipophilic substances are known to be toxic and/or carcinogenic, have poorly understood or unknown "no-effect" levels in humans, and are distributed widely in the environment and the biosphere. This scenario warrants continued efforts to develop safe and achievable regimens for reducing body burdens of toxic lipophiles.

In spite of the large amount of work on the elimination of toxic lipophiles, there remain unaddressed areas that warrant further research. An optimal regimen for toxic lipophile removal from the body has not been systematically developed to provide guidance for removal of toxins in situations of acute and of chronic exposure. A better understanding of the nature of nonbiliary excretion in the intestine may provide new ways to control the rate of elimination of toxic lipophiles. There have only been a few studies that have been directed to understand the effect of dietary regimens on the important area of the transport of toxic lipophiles in milk. Since toxic lipophiles are suspected to influence early childhood development, there is a clear need to understand the relationships of lactation, fat mobilization, and toxin transport. Given the known detrimental effects of persistent toxic lipophiles and their widespread distribution in the environment, there is a need to gain better understanding of influences on their elimination from the human body, the top of the food chain for lipophile accumulation.

REFERENCES

1. Jensen, A.A. (1983) Chemical Contaminants in Human Milk, *Residue Rev. 89*, 1–128.
2. Hofvander, Y., Hagman, U., Linder, C.E., Vaz, R., and Slorach, S.A. (1981) WHO Collaborative Breast Feeding Study. I. Organochlorine Contaminants in Individual Samples of Swedish Human Milk, 1978–1979, *Acta Paediatr. Scand. 70,* 3–8.
3. Tryphonas, H. (1998) The Impact of PCBs and Dioxins on Children's Health: Immunological Considerations, *Can. J. Public Health 89* (Suppl. 1), S49–S52; S54–S57.
4. Weisenberg, E. (1986) Hexachlorobenzene in Human Milk: A Polyhalogenated Risk*, IARC Sci. Publ. 77*, 193–200.
5. Wolff, M.S., Fischbein, A., and Selikoff, I.J. (1992) Changes in PCB Serum Concentrations Among Capacitor Manufacturing Workers, *Environ. Res. 59*, 202–216.
6. Kalantzi, O.I., Alcock, R.E., Johnston, P.A., Santillo, D., Stringer, R.L., Thomas, G.O., and Jones, K.C. (2001) The Global Distribution of PCBs and Organochlorine Pesticides in Butter, *Environ. Sci. Technol. 35*, 1013–1018.
7. Schepens, P.J., Covaci, A., Jorens, P.G., Hens, L., Scharpe, S., and Van Larebeke, N. (2001) Surprising Findings Following a Belgian Food Contamination with Polychlorobiphenyls and Dioxins, *Environ. Health Perspect. 109*, 101–103.
8. Dewailly, E., Mulvad, G., Pedersen, H.S., Ayotte, P.L.J., Demers, A., Weber, J.P., and Hansen, J.C. (1999) Concentration of Organochlorines in Human Brain, Liver, and Adipose Tissue Samples from Greenland, *Environ. Health Perspect. 107*, 823–828.
9. Kelly, B.C., and Gobas, F.A. (2001) Bioaccumulation of Persistent Organic Pollutants in Lichen-Caribou-Wolf Food Chains of Canada's Central and Western Arctic. *Environ. Sci. Technol. 35*, 325–334.
10. Wolff, M.S., Anderson, H.A., and Selikoff, I.J. (1982) Human Tissue Burdens of Halogenated Aromatic Chemicals in Michigan, *JAMA 16,* 2112–2116.
11. Bernard, A. (2000) Food Contamination by PCBs/Dioxins in Belgium: Analysis of an Accident with Improbable Health Consequences, *Bull. Mem. Acad. R. Med. Belg. 155*, 195–201.
12. Masuda, Y., Kuroki, H., Haraguchi, K., and Nagayama, J. (1985) PCB and PCDF Congeners in the Blood and Tissues of Yusho and Yu-Cheng Patients, *Environ. Health Perspect. 59*, 53–58.
13. Chen, P.H., Luo, M.L., Wong, C.K., and Chen, C.J. (1982) Comparative Rates of Elimination of Some Individual Polychlorinated Biphenyls from the Blood of PCB-Poisoned Patients in Taiwan, *Food Chem. Toxicol. 20*, 417–425.
14. Perera, F. (1981) Carcinogenicity of Airborne Fine Particulate Benzo(a)Pyrene: An Appraisal of the Evidence and the Need for Control, *Environ. Health Perspect. 42*, 163–185.
15. Ernst, P., and Theriault, G. (1984) Known Occupational Carcinogens and Their Significance, *Can. Med. Assoc. J. 130*, 868–867.

16. Conway, J.G., Tomaszewski, K.E., Olson, M.J., Cattley, R.C., Marsman, D.S., and Popp, J.A. (1989) Relationship of Oxidative Damage to Hepatocarcinogenicity of the Peroxisome Proliferators Di(2-ethylhexyl)phthalate and Wy14,643, *Carcinogenesis 10*, 513–519.
17. Doull, J., Cattley, R., Elcombe, C., Lake, B.G., Swenberg, J., Wilkinson, C., Williams, G., and Van Gemert, M. (1999) A Cancer Risk Assessment of Di(2-ethylhexyl)phthalate: Application of the New U.S. EPA Risk Assessment Guidelines, *Regul. Toxicol. Pharmacol. 29*, 327–357.
18. Huber, W.W., Grasl-Kraupp, B., and Schulte-Hermann, R. (1996) Hepatocarcinogenic Potential of Di(2-ethylhexyl)-phthalate in Rodents and Its Implications on Human Risk, *Crit. Rev. Toxicol. 26*, 365–481.
19. Latini, G. (2000) Potential Hazards of Exposure to Di-(2-ethylhexyl)phthalate in Babies, a Review, *Biol. Neonate 78*, 269–276.
20. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *9th Report on Carcinogens,* Revised January 2001, Environmental Health Information Service.
21. Fitzhugh, O.G., and Nelson, A.A. (1946) The Chronic Oral Toxicity of DDT (2,2-bis *p*-chlorophenyl-1,1,1-trichloroethane), *J. Pharmacol. Exp. Ther. 89*, 18–30.
22. Mukerjee, D. (1998) Health Impacts of Polychlorinated Dibenzo-*p*-dioxins: A Critical Review, *J. Air Waste Manag. Assoc. 48*, 157–165.
23. Kishima, M.O., Barbisan, L.F., Estevao, D., Rodrigues, M.A., and Vianna De Camargo, J.L. (2000) Promotion of Hepatocarcinogenesis by Hexachlorobenzene in Energy-Restricted Rats, *Cancer Lett. 152*, 37–44.
24. Shoket, B. (1999) DNA Damage in Humans Exposed to Environmental and Dietary Polycyclic Aromatic Hydrocarbons, *Mutat. Res. 424*, 143–153.
25. Ernst, P., and Theriault, G. (1984) Known Occupational Carcinogens and Their Significance, *Can. Med. Assoc. J. 130*, 868–867.
26. Boffetta, P., Jourenkova, N., and Gustavsson, P. (1997) Cancer Risk from Occupational and Environmental Exposure to Polycyclic Aromatic Hydrocarbons, *Cancer Causes Control 8*, 444–472.
27. Snedeker, S.M. (2001) Pesticides and Breast Cancer Risk: A Review of DDT, DDE, and Dieldrin, *Environ. Health Perspect. 109* (Suppl. 1), 35–47.
28. Safe, S.H. (2000) Endocrine Disruptors and Human Health—Is There a Problem? An Update, *Environ. Health Perspect. 108*, 487–493.
29. Lakshmanan, M.R., Campbell, B.S., Chirtel, S.J., Ekarohita, N., and Ezekiel, M. (1986) Studies on the Mechanism of Absorption and Distribution of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Rat, *J. Pharmacol. Exp. Ther. 239*, 673–677.
30. Pocock, D.E., and Vost, A. (1974) DDT Absorption and Chylomicron Transport in Rat, *Lipids 9*, 374–381.
31. Sieber, S.M. (1976) The Lymphocytic Absorption of *p,p′*-DDT and Some Structurally Related Compounds in the Rat, *Pharmacology 14*, 443–454.
32. Vost, A., and Maclean, N. (1984) Hydrocarbon Transport in Chylomicrons and High-Density Lipoproteins in Rat, *Lipids 19*, 423–435.
33. Busbee, D.L., Yoo, J.S., Norman, J.O., and Joe, C.O. (1985) Polychlorinated Biphenyl Uptake and Transport by Lymph and Plasma Components, *Proc. Soc. Exp. Biol. Med. 179*, 116–122.
34. Nakashima, Y., Ohsawa, S., and Ikegami, S. (1999) High-Fat Diet Enhances Accumulation of Hexachlorobenzene in Rat Dams and Delays Its Transfer from Rat Dams to Suckling Pups Through Milk, *J. Agric. Food Chem. 47*, 1587–1592.
35. Laher, J.M., Rigler, M.W., Vetter, R.D., Barrowman, J.A., and Patton, J.S. (1984) Similar Bioavailability and Lymphatic Transport of Benzo(α)pyrene When Administered to Rats in Different Amounts of Dietary Fat, *J. Lipid Res. 25*, 1337–1342.
36. Spindler-Vomachka, M., Vodicnik, M.J., and Lech, J.J. (1984) Transport of 2,4,5,2′,4′,5′-Hexachlorobiphenyl by Lipoproteins *in vivo, Toxicol. Appl. Pharmacol. 74*, 70–77.
37. Busbee, D.L., and Ziprin, R.L. (1994) Gastrointestinal Uptake and Vascular Transport of 2,4′-Dichlorobiphenyl, *Arch. Toxicol. 68*, 96–102.
38. Van Der Molen, G.W., Kooijman, S.A., and Slob, W. (1996) A Generic Toxicokinetic Model for Persistent Lipophilic Compounds in Humans: An Application to TCDD, *Fundam. Appl. Toxicol. 31*, 83–94.
39. Van Den Berg, M., De Jongh, J., Poiger, H., and Olson, J.R. (1994) The Toxicokinetics and Metabolism of Polychlorinated Dibenzodioxins (PCDDs) and Dibenzofurans (PCDFs) and Their Relevance for Toxicity, *Crit. Rev. Toxicol. 24*, 1–74.
40. Buckley, L.A. (1995) Biologically-Based Models of Dioxin Pharmacokinetics. *Toxicology 102*, 125–131.
41. Rozman, T., Rozman, K., and Smith, G.S. (1983) Relationship of Body Weight to Disposition of Hexachlorobenzene in Rats, *Toxicol. Lett. 18*, 171–175.
42. Weber, L.W., Ernst, S.W., Stahl, B.U., and Rozman, K. (1993) Tissue Distribution and Toxicokinetics of 2,3,7,8-Tetrachlorobenzo-*p*-dioxin in Rats After Intravenous Injection, *Fundam. Appl. Toxicol. 21*, 523–534.
43. Birnbaum, L.S., and Couture, L.A. (1988) Disposition of Octachlorodibenzo-*p*-dioxin (OCDD) in Male Rats, *Toxicol. Appl. Pharmacol. 93*, 22–30.
44. Diliberto, J.J., Burgin, D.E., and Birnbaum, L.S. (1999) Effects of CYP1A2 on Disposition of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 2,3,4,7,8-Pentachlorodibenzofuran, and 2,2′,4,4′,5,5′-Hexachlorobiphenyl in CYP1A2 Knockout and Parental (C57BL/6N and 129/Sv) Strains of Mice, *Toxicol. Appl. Pharmacol. 159*, 52–64.
45. Mes, J., Arnold, D.L., and Bryce, F. (1995) The Elimination and Estimated Half-Lives of Specific Polychlorinated Biphenyl Congeners from the Blood of Female Monkeys After Discontinuation of Daily Dosing with Aroclor 125, *Chemosphere 30*, 789–800.
46. Chen, P.H., Luo, M.L., Wong, C.K., and Chen, C.J. (1982) Comparative Rates of Elimination of Some Individual Polychlorinated Biphenyls from the Blood of PCB-Poisoned Patients in Taiwan, *Food Chem. Toxicol. 20*, 417–425.
47. Flesch-Janys, D., Becher, H., Gurn, P., Jung, D., Konietzko, J., Manz, A., and Papke, O. (1996) Elimination of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in Occupationally Exposed Persons, *J. Toxicol. Environ. Health 47*, 363–378.
48. Blanck, H.M., Marcus, M., Hertzberg, V., Tolbert, P.E., Rubin, C., Henderson, A.K., and Zhang, R.H. (2000) Determinants of Polybrominated Biphenyl Serum Decay Among Women in the Michigan PBB Cohort, *Environ. Health Perspect. 108*, 147–152.
49. Ramesh, A., Inyang, F., Hood, D.B., and Knuckles, M.E. (2000) Aryl Hydrocarbon Hydroxylase Activity in F-344 Rats Subchronically Exposed to Benzo(α)pyrene and Fluoranthene Through Diet, *J. Biochem. Mol. Toxicol. 14*, 155–161.
50. Borlakoglu, J.T., Wilkins, J.P., and Dils, R.R. (1991) Distribution and Elimination *in vivo* of Polychlorinated Biphenyl (PCB) Isomers and Congeners in the Pigeon, *Xenobiotica 21*, 433–445.
51. Rietjens, I.M.C.M., den Besten, C., Hanzlik, R.P., and van Bladeren, P.J. (1997) Cytochrome P450-Catalyzed Oxidation of Halobenzene Derivatives, *Chem. Res. Toxicol. 10*, 629–635.

52. Williams, D.E., Lech, J.J., and Buhler, D.R. (1998). Xenobiotics and Xenoestrogens in Fish: Modulation of Cytochrome P450 and Carcinogenesis, *Mutat. Res. 399*, 179–192.
53. Hodgson, E., Rose, R.L., Ryu, D.-Y., Falls, G., Blake, B.L., and Levi, P.E. (1995) Pesticide-Metabolizing Enzymes, *Toxicol. Lett. 82–83*, 73–81.
54. Hodgson, E., and Levi, P.E. (1996) Pesticides: An Important but Underused Model for Environmental Health Sciences*, Environ. Health Perspect. 104* (Suppl. 1), 97–106.
55. Den Besten, C., Bennik, M.M., Van Iersel, M., Peters, M.A., Tennis, C., and Van Bladeren, P.J. (1994) Comparison of the Urinary Metabolite Profiles of Hexachlorobenzene and Pentachlorobenzene in the Rat, *Chem. Biol. Interact. 90*, 121–137.
56. Hakk, H., Larsen, G., and Feil, V. (2001) Tissue Distribution, Excretion, and Metabolism of 1,2,7,8-Tetrachlorodibenzo-*p*-dioxin in the Rat, *Chemosphere 42*, 975–983.
57. Ingebrigtsen, K., Skaare, J.U., Nafstad, I., and Forde, M. (1981) Studies on the Biliary Excretion and Metabolites of Hexachlorobenzene in the Rat, *Xenobiotica 11*, 795–800.
58. Boylan, J.J., Cohn, W.J., Egle, J.L., Blanke, R.V., and Guzelian, P.S. (1979) Excretion of Chlordecone by the Gastrointestinal Tract: Evidence for a Nonbiliary Mechanism, *Clin. Pharmacol. Ther. 25*, 579–585.
59. Guzelian, P.S. (1981) Therapeutic Approaches for Chlordecone Poisoning in Humans*, J. Toxicol. Environ. Health 8*, 757–766.
60. Rozman, K., Rozman, T., and Greim, H. (1981) Enhanced Fecal Elimination of Stored Hexachlorobenzene from Rats and Rhesus Monkeys by Hexadecane or Mineral Oil, *Toxicology 22*, 33–44.
61. Rozman, K. (1985) Intestinal Excretion of Toxic Substances, *Arch. Toxicol.* (Suppl. 8), 87–93.
62. Patton, J.S. (1986) Cellular Pathways in the Movement of Lipophilic Xenobiotics from GI Tract to Breast Milk, in *Human Lactation 2* (Hamosh, M., and Goldman, A.S., eds.), pp. 475–497, Plenum, New York.
63. Gallenberg, L.A., and Vodicnik, M.J. (1987) Potential Mechanisms for Redistribution of Polychlorinated Biphenyls During Pregnancy and Lactation, *Xenobiotica 17*, 299–310.
64. Schechter, A., Ryan, J.J., and Papke, O. (1998) Decrease in Levels and Body Burden of Dioxins, Dibenzofurans, PCBs, DDE, and HCB in Blood and Milk in a Mother Nursing Twins over a Thirty-Eight Month Period, *Chemosphere 37*, 1807–1816.
65. Jandacek, R.J. (1982) The Effect of Nonabsorbable Lipids on the Intestinal Absorption of Lipophiles, *Drug Metab. Rev. 13*, 695–714.
66. Hernell, O., Staggers, J.E., and Carey, M.C. (1990) Physical-Chemical Behavior of Dietary and Biliary Lipids During Intestinal Digestion and Absorption. 2. Phase Analysis and Aggregation States of Luminal Lipids During Duodenal Fat Digestion in Healthy Adult Human Beings, *Biochemistry 29*, 2041–2056.
67. Mattson, F.H., and Volpenhein, R.A. (1972) Hydrolysis of Fully Esterified Alcohols Containing from One to Eight Hydroxyl Groups by the Lipolytic Enzymes of Rat Pancreatic Juice, *J. Lipid Res. 13*, 325–328.
68. *Federal Register,* Part III, U.S. Department of Health and Human Services, Food and Drug Administration, 21 CFR Part 172, Food Additives Permitted for Direct Addition to Food for Human Consumption: Olestra: Final Rule *62*, 3118–3173. January 30, 1996.
69. Volpenhein, R.A., Webb, D.R., and Jandacek, R.J. (1980) Effect of a Nonabsorbable Lipid, Sucrose Polyester, on the Absorption of DDT by the Rat, *J. Toxicol. Environ. Health 6*, 679–683.
70. Keller, W.C., and Yeary, R.A. (1980) A Comparison of the Effects of Mineral Oil, Vegetable Oil, and Sodium Sulfate on the Intestinal Absorption of DDT in Rodents, *Clin. Toxicol. 16*, 223–231.
71. Palin, K.J., Wilson, C.G., Davis, S.S., and Phillips, A.J. (1982) The Effect of Oils on the Lymphatic Absorption of DDT, *J. Pharm. Pharmacol. 34*, 707–710.
72. Morgan, D.P., Dotson, T.B., and Lin, L.I. (1977) Effectiveness of Activated Charcoal, Mineral Oil, and Castor Oil in Limiting Gastrointestinal Absorption of Chlorinated Hydrocarbon Pesticide*, Clin. Toxicol. 11*, 61–70.
73. Richter, E., Fichtl, B., and Schafer, S.G. (1982) Effects of Dietary Paraffin, Squalane and Sucrose Polyester on Residue Disposition and Elimination of Hexachlorobenzene in Rat, *Chem. Biol. Interact. 40*, 335–344.
74. Mutter, L.C., Blanke, R.V., Jandacek, R.J., and Guzelian, P.S. (1988) Reduction in the Body Content of DDE in the Mongolian Gerbil Treated with Sucrose Polyester and Caloric Restriction, *Toxicol. Appl. Pharmacol. 92*, 428–435.
75. Geusau, A., Tschachler, E., Meixner, M., Sandermann, S., Papke, O., Wolf, C., Valic, E., Stingl, G., and McLachlan, M. (1999) Olestra Increases Faecal Excretion of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, *Lancet 354,* 1266–1267.
76. Moser, G.A., and McLachlan, M.S. (1999) A Non-Absorbable Dietary Fat Substitute Enhances Elimination of Persistent Lipophilic Contaminants in Humans, *Chemosphere 39*, 1513–1521.
77. Boitnott, J.K., and Margolis, S. (1970) Saturated Hydrocarbons in Human Tissues. 3. Oil Droplets in the Liver and Spleen, *Johns Hopkins Med. J. 127*, 65–78.
78. Kamimura, H., Koga, N., Oguri, K., Yoshimura, H., Inoue, H., Sato, K., and Ohku, M. (1989) Studies on Distribution, Excretion and Subacute Toxicity of Squalane in Dogs, *Fukuoka Igaku Zasshi 80*, 269–280.
79. Richter, E. (1986) Stimulation of Faecal Excretion of Hexachlorobenzene: A Review, *IARC Sci. Publ. 77*, 605–610.
80. Richter, E., Schafer, S.G., and Fichtl, B. (1983) Stimulation of the Faecal Excretion of 2,4,5,2′,4′,5′-Hexachlorobiphenyl in Rats by Squalane, *Xenobiotica 13*, 337–343.
81. Richter, E., Lay, J.P., Klein, W., and Korte, F. (1977) Enhanced Elimination of Hexachlorobenzene in Rats by Light Liquid Paraffin, *Chemosphere 6*, 357–369.
82. Richter, E., Lay, J.P., Klein, W., and Korte, F. (1979). Paraffin-Stimulated Excretion of 1,4,6,2′,4′-Pentachlorobi[^{14}C]-phenyl by Rats, *Toxicol. Appl. Pharmacol. 50*, 17–23.
83. Rozman, T., Rozman K., Williams, J., and Greim, H. (1981) Enhanced Fecal Excretion of Mirex in Rhesus Monkeys by 5% Mineral Oil in the Diet, *Drug Chem. Toxicol. 4*, 251–262.
84. Rozman, K., Rozman, T., Williams, J., and Greim, H. (1982) Effect of Mineral Oil and/or Cholestyramine in the Diet on Biliary and Intestinal Elimination of 2,4,5,2′,4′,5′-Hexabromobiphenyl in the Rhesus Monkey, *J. Toxicol. Environ. Health 9*, 611–618.
85. Rozman, K., Rozman, T., Ballhorn, L., and Greim, H. (1982) Hexadecane Enhances Non-Biliary, Intestinal Excretion of Stored Hexachlorobenzene by Rats, *Toxicology 24*, 107–113.
86. Rozman, T., and Rozman, K. (1983) Intraluminal Hexadecane Enhances Large Intestinal Excretion of Tissue Hexachlorobenzene in Rats, *Toxicol. Lett. 16*, 253–257.
87. Rozman, K., Rozman, T., and Greim, H. (1983) Stimulation of Nonbiliary, Intestinal Excretion of Hexachlorobenzene in Rhesus Monkeys by Mineral Oil, *Toxicol. Appl. Pharmacol. 70*, 255–261.
88. Rozman, K., Ballhorn, L., and Rozman, T. (1983) Mineral Oil in the Diet Enhances Fecal Excretion of DDT in the Monkey, *Drug Chem. Toxicol. 6*, 311–316.
89. Rozman, K., Rozman, T., and Greim, H. (1983) Enhanced Intestinal Excretion of ^{14}C-Hexachlorobenzene in Rats by

Intraluminal Injection of Hexadecane, *J. Appl. Toxicol. 3*, 48–50.
90. Rozman, K., Rozman, T., Greim, H., Nieman, I.J., and Smith, G.G. (1983) Use of Aliphatic Hydrocarbons in Feed to Decrease Body Burdens of Lipophilic Toxicants in Livestock, *J. Agric. Food Chem. 30*, 98–100.
91. Rozman, K., Rozman, T., and Smith, G.S. (1984) Liquid Paraffins in Feed Enhance Fecal Excretion of Mirex and DDE from Body Stores of Lactating Goats and Cows, *Bull. Environ. Contam. Toxicol. 32*, 27–36.
92. Scheufler, E., and Rozman, K. (1984) Comparative Decontamination of Hexachlorobenzene-Exposed Rats and Rabbits by Hexadecane, *J. Toxicol. Environ. Health 14*, 353–362.
93. Polin, D., Olson, B., Bursian, S., and Lehning, E. (1986) Enhanced Withdrawal from Chickens of Hexachlorobenzene (HCB) and Pentachlorophenol (PCP) by Colestipol, Mineral Oil, and/or Restricted Feeding, *J. Toxicol. Environ. Health 19*, 359–368.
94. Crum, J.A., Aulerich, R.J., Polin, D., Braselton, W.E., and Bursian, S.J. (1994) The Efficacy of Mineral Oil Combined with Feed Restriction in Enhancing the Elimination of Heptachlor Epoxide from Mink *(Mustela vison), Arch. Environ. Contam. Toxicol. 26*, 374–380.
95. Cohn, W.J., Boylan, J.J., Blanke, R.V., Farris, M.W., Howell, J.R., and Guzelian, P.S. (1978) Treatment of Chlordecone (Kepone) Toxicity with Cholestyramine, *N. Engl. J. Med. 298*, 243–248.
96. Boylan, J.J., Egle, J.L., and Guzelian, P.S. (1978) Cholestyramine: Use as a New Therapeutic Approach for Chlordecone (Kepone) Poisoning*, Science 199*, 893–895.
97. Davison, K.L., and Sell, J.L. (1978) Dieldrin-^{14}C Elimination from Turkeys, *Arch. Environ. Contam. Toxicol. 7*, 245–255.
98. Davison, K.L., and Sell, J.L. (1978) Dieldrin-^{14}C Elimination from Chickens, *Arch. Environ. Contam. Toxicol. 7*, 369–377.
99. Ballhorn, L., Rozman, T., Rozman, K., Korte, F., and Greim, H. (1981) Cholestyramine Enhances Fecal Elimination of Pentachlorophenol in Rhesus Monkeys, *Chemosphere 10*, 877–888.
100. Rozman, T., Ballhorn, L., Rozman, K., Klaasen, C., and Greim, H. (1982) Effect of Cholestyramine on the Disposition of Pentachlorophenol in Rhesus Monkeys, *J. Toxicol. Environ. Health 10*, 277–283.
101. Polin, D., Lehning, E., Pullen, D., Bursian, S., and Leavitt, R. (1985) Procedures to Enhance Withdrawal of Xenobiotics from Chickens, *J. Toxicol. Environ. Health 16*, 243–254.
102. Iida, T., Hirakawa, H., Matsueda, T., Nakagawa, R., Takenaka, S., Morita, K., Narazaki, Y., Fukamachi, K., Tokiwa, H., Takahashi, K., and Yoshimura, H. (1991) Therapeutic Trial for Promotion of Fecal Excretion by PCDFs and PCBs by the Administration of Cholestyramine in Yusho Patients, *Fukuoka Igaku Zasshi 82*, 317–325.
103. Murai, K., Tsuji, H., and Fujishima, M. (1991) Treatment of Yusho Patients with Cholestyramine, *Fukuoka Igaku Zasshi 82*, 326–329.
104. Morita, K., Hironori, H., Matsueda, T., Iida, T., and Tokiwa, H. (1993) Stimulating Effect of Dietary Fiber on Fecal Excretion of Polychlorinated Dibenzofurans (PCDF) and Polychlorinated Dibenzo-*p*-dioxins (PCDD) in Rats, *Fukuoka Igaku Zasshi 84*, 273–281.
105. McConnell, E.E., Harris, M.W., and Moore, J.A. (1980) Studies on the Use of Activated Charcoal and Cholestyramine for Reducing the Body Burden of Polybrominated Biphenyls, *Drug Chem. Toxicol. 3*, 277–292.
106. Fries, G.F., Marrow, G.S., Gordon, C.H., Dryden, L.P., and Hartman, A.M. (1970) Effect of Activated Carbon on Elimination of Organochlorine Pesticides from Rats and Cows, *J. Dairy Sci. 53*, 1632–1637.
107. Manara, L., Coccia, P., and Croci, T. (1984). Prevention of TCDD Toxicity in Laboratory Rodents by Addition of Charcoal or Cholic Acids to Chow, *Food Chem. Toxicol. 22*, 815–818.
108. Morita, K., Matsueda, T., and Iida, T. (1999) Effect of Protoporphyrin on Digestive Tract Absorption of Dioxins in Rats, *Fukuoka Igaku Zasshi 90*, 162–170.
109. Ikegami, S., Umegaki, K., Kawashima, Y.L., and Ichikawa, T. (1994) Viscous Indigestible Polysaccharides Reduce Accumulation of Pentachlorobenzene in Rats, *J. Nutr. 124*, 754–760.
110. Umegaki, K., Ikegami, S., and Ichikawa, T. (1995) Fish Oil Enhances Pentachlorobenzene Metabolism and Reduces Its Accumuation in Rats, *J. Nutr. 125*, 147–153.
111. Umegaki, K., and Ikegami, S. (1998) Feeding Fish Oil to Rats Accelerates the Metabolism of Hexachlorobenzene, *J. Nutr. Sci. Vitaminol. 44*, 301–311.
112. Geyer, H.J., Scheunert, I., Rapp, K., Gebefugi, I., Steinberg, C., and Kettrup, A. (1993) The Relevance of Fat Content in Toxicity of Lipophilic Chemicals to Terrestial Animals with Special Reference to Dieldrin and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), *Ecotoxicol. Environ. Saf. 26*, 45–60.
113. Mitjavila, S., Carrera, G., and Fernandez, Y. (1981) Evaluation of the Toxic Risk of Accumulated DDT in the Rat: During Fat Mobilization, *Arch. Environ. Contam. Toxicol. 10*, 471–481.
114. Polischuk, S.C., Letcher, R.J., Norstrom, R.J., and Ramsay, M.A. (1995) Preliminary Results of Fasting on the Kinetics of Organochlorines in Polar Bears *(Ursus maritimus), Sci. Total Environ. 15*, 160–161, 465–472.
115. Walford, R.L., Mock, D., MacCallum, T., and Laseter, J.L. (1999) Physiologic Changes in Humans Subjected to Severe, Selective Calorie Restriction for Two Years in Biosphere 2: Health, Aging, and Toxicological Perspectives, *Toxicol. Sci. 52* (Suppl. 2), 61–65.
116. Lovelady, C.A., Whitehead, R.A., McCrory, M.A., Nommsen-Rivers, L.A., Mabury, S., and Dewey, K.G. (1999) Weight Change During Lactation Does Not Alter the Concentrations of Chlorinated Organic Contaminants in Breast Milk of Women with Low Exposure, *J. Hum. Lact. 15*, 307–315.
117. Dale, W.E., Gaines, T.B., and Hayes, W.J. (1962) Storage and Excretion of DDT in Starved Rats, *Toxicol. Appl. Pharmacol. 4*, 89–106.
118. Findlay, G.M., and DeFreitas, A.S.W. (1971) DDT Movement from Adipocyte to Muscle Cell During Lipid Utilization, *Nature 229*, 63–65.
119. Corbella, J., To-Figueras, J., Rodamilans, M., and Gomez, J. (1986) Mobilization, Redistribution and Excretion of Hexachlorobenzene Following Food Restriction in Rats, *IARC Sci. Publ. 77*, 289–295.
120. Umegaki, K., Ikegami, S., and Ichikawa, T. (1993) Effects of Restricted Feeding on the Absorption, Metabolism, and Accumulation of Pentachlorobenzene in Rats, *J. Nutr. Sci. Vitaminol. 39,* 11–22.
121. Bigsby, R.M., Caperell-Grant, A., and Madhukar, B.V. (1997) Xenobiotics Released from Fat During Fasting Produce Estrogenic Effects in Ovariectomized Mice*, Cancer Res. 57*, 865–869.

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