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9.22 Pesticides and Hepatotoxicity

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Abbreviations

ALDH	aldehyde dehydrogenase
ANTU	α-naphthylthiourea
ARE	antioxidant response element
CAR	constitutive androstane receptor
CYP	cytochrome P450
DNOC	4,6-dinitro-*o*-cresol
EDB	ethylene dibromide
FMO	flavin-containing monooxygenase
GST	glutathione *S*-transferase
HCB	hexachlorobenzene
MDP	methylenedioxyphenyl
PCP	pentachlorophenol
PPAR	peroxisome proliferator-activated receptor
PXR	pregnane X receptor
siRNA	small interfering RNA
UDP	uridine diphosphate
UGT	UDP-glucuronyl transferase
UROD	uroporphyrinogen decarboxylase
USEPA	U.S. Environmental Protection Agency

9.22.1 Introduction

The intended use of pesticides, namely, deliberate application to an infested environment ensures that humans are exposed to numerous pesticides of many different chemical and use classes. Although by design pesticide target species are most susceptible by a wide margin, specificity issues analogous to those for chemotherapeutics cannot guarantee tolerance in nontarget species. The value of pesticides in increasing crop yields necessary for provision of food, fiber, and, more recently, biofuels, plus their vital contributions to public health requires a thorough, rational understanding of their toxicity to enable safe use.

Pesticide absorption occurs through skin and the respiratory and gastrointestinal tracts with eventual disposition to the liver from all routes of exposure. As with other xenobiotics, the liver is the primary site of pesticide biotransformation for the purpose of facilitating clearance through excretion of water-soluble products. However, the liver's role as the immediate recipient of orally absorbed chemicals, plus its abundance of oxidative metabolism, makes it a common target for more toxic metabolic products when detoxifying and protective mechanisms are overwhelmed. Consequently, the ability of the liver to function as a center of intermediary metabolism may be impaired and related systemic effects become clinically apparent. Both acute pesticide poisonings

with liver involvement and epidemiological evidence of liver toxicity and cancer associated with chronic pesticide exposures have been reported.

The wide array of structural features identified as alerts for hepatotoxicity is present among the diverse chemical structures comprising the pesticides. Pesticides chemically range from the persistent, highly lipophilic organochlorines with generally low acute toxicity to the organophosphate insecticides, which are one of the more frequent causes of poisonings reported to Poison Control Centers (Blondell 2007). Examples of liver toxicity exist among members of the various use classes including acaricides, algicides, fungicides, herbicides, insecticides, molluscicides, nematocides, and rodenticides. Commonly used pesticides, as indicated by their common and chemical names, within each of these use classes are categorized in **Table 1** (Cope *et al.* 2004). Acute effects, as observed with high dose, occupational or accidental exposures to pesticides, typically involve neurotoxicity, although a few case reports with liver damage exist. Prior description of hepatotoxicity in testing on research animals for these same chemicals suggests similar mechanisms may operate in susceptible individuals in high exposure scenarios. Pesticide toxicity with liver involvement is more typical of subchronic or chronic exposures in test and experimental animals, and some epidemiology supports similar effects in humans, including carcinogenicity.

The most well-studied bioconversions of pesticides in liver result from metabolism catalyzed by the cytochrome P450 (CYP)-dependent monooxygenases. The substantial number of known CYP-catalyzed reactions with pesticide substrates is primarily a function of the extensive knowledge base for this large group of enzymes (Hodgson and Levi 2001). Metabolism by flavin-containing monooxygenase (FMO) isoforms is the next most frequent with some substrates common with the CYPs (Hodgson and Levi 1992). Equally important for specific pesticides is metabolism by other enzymes, including phase I reactions catalyzed by prostaglandin H synthetase/cyclooxygenase (COX1/2), molybdenum hydroxylases/aldehyde (AOX) and xanthine oxidases, alcohol and aldehyde dehydrogenases (ALDHs), and esterases. Phase II conjugations important for pesticide metabolism include those typical of products of other xenobiotic oxidations, especially those catalyzed by the *N*-acetyl-, sulfo-, uridine diphosphate (UDP)-glucuronyl-, methyl-, and amino acid (taurine, glycine) transferases (Cerrara and Periquet 1991). Glutathione *S*-transferases (GSTs) are important catalysts in primary reactions of nucleophilic substitution of the many chlorinated pesticides as evidenced by the frequent detection of mercapturates as human urinary metabolites. Depending upon the substrate, examples of both activation and detoxication can be found with any of these enzymes, although metabolic activation by CYP isoforms to damaging electrophiles reactive with critical nucleophilic sites of proteins and DNA has been best characterized. Human polymorphisms have been found for several of the metabolic enzymes important for pesticide metabolism, and epidemiological associations with susceptibilities to various pesticide health effects have provided information about functional consequences of metabolism by affected enzymes.

Over 2500 animal CYP isoforms have been characterized and genomic and protein sequences are known. A system of nomenclature based upon derived amino acid sequences was proposed in 1987 and entries are continuously updated with the most recent version as of 29 February 2008 Cytochrome P450 Webpage. Degree of similarity in sequence is used in grouping members to CYP numeric gene family, then letter subfamily (Nelson 2006) such that individual isozymes have unique CYP number–letter–number annotations, for example, CYP1A1. Whereas some CYP isoforms are substrate specific, those involved in xenobiotic metabolism tend to be relatively nonspecific, although substrate preferences are usually evident. FMOs, like CYPs, are located in the endoplasmic reticulum of hepatocytes and other vertebrate cells and catalyze NADPH-dependent monooxygenation of pesticides, especially those with N, S, or P heteroatoms (Ziegler 2002).

Pesticides are not only substrates for hepatic metabolic enzymes, but may also act as inhibitors or inducers, often with selectivity for specific isoforms. Inhibition of CYPs occurs with metabolites that are highly reactive at the enzyme active site, such as those formed upon oxidative desulfuration (Levi *et al.* 1988), or from competing substrates. Similar metabolism-dependent AOX inhibition of neonicotinoid nitroreduction has been reported (Dick *et al.* 2007). Nonsubstrate pesticides and metabolites also are inhibitors of metabolic enzymes, such as the inhibition of carboxylases by organophosphate pesticides (Ross and Crow 2007) and mitochondrial low K_m ALDH2 with S-oxidized metabolites of thiocarbamate herbicides (Zimmerman *et al.* 2004). Pesticide

Table 1 Examples of pesticides with use and chemical classes

Class	*Principal chemical type*	*Example: common name (chemical name)*
Algicide	Organotin	Brestan (triphenyltin acetate)
Fungicide	Dicarboximide	Captan (*N*-trichloromethylthio-4-cyclohexene-1,2-dicarboximide)
	Chlorinated aromatic	Pentachlorophenol
	Dithiocarbamate	Maneb (manganese ethylenebisdithiocarbamate)
	Mercurial	Phenylmercuric acetate
Herbicide	Amides, acetamides	Propanil (*N*-(3,4-dichlorophenyl) propionamide)
	Bipyridyl	Paraquat (1,1′-dimethyl-4,4′-bipyridinium)
	Carbamates, thiocarbamates	Barban (4-chloro-2-butynyl-*m*-chlorocarbanilate)
	Phenoxy	2,4-D (2,4-dichlorophenoxyacetic acid)
	Dinitrophenol	DNOC (4,6-dinitro-*o*-cresol)
	Dinitroaniline	Triflualin (2,6-dinitro-*N*,*N*-dipropyl-4-trifluoromethylaniline)
	Substituted urea	Monuron (3-(*p*-chlorophenyl)-1,1-dimethylurea)
	Triazine	Atrazine (2-chloro-4-ethylamino-6-isopropylamino-*S*-triazine)
Nematocide	Halogenated alkane	Ethylene dibromide (EDB) (1,2-dibromoethane)
Molluscicide	Chlorinated hydrocarbon	Bayluscide (2,5-dichloro-4′-nitrosalicylanilide)
Insecticide synergists	Methylenedioxyphenyl	Piperonyl butoxide (5-((2-(2-butoxyethyl)ethoxy)methyl)-6-propyl-1,3-benzodioxole)
	Dicarboximide	MGK-264 (*N*-(2-ethylhexyl)-5-norbornene-2,3-dicarboximide)
Insecticides	Chlorinated hydrocarbons	
	DDT analogues	DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl) ethane)
	Chlorinated alicyclic	BHC (hexachlorocyclohexane)
	Cyclodiene	Aldrin (1,2,3,4,10,10a-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene)
	Chlorinated terpenes	Toxaphene (mixture of chlorinated terpenes)
	Organothiophosphate	Parathion (*O*,*O*-diethyl-*O*-*p*-nitrophenylphosphorothioate)
	Carbamate	Carbaryl (1-naphthyl-*N*-methylcarbamate)
	Thiocyanate	Lethane (2-thiocyanatoethyl laurate)
	Dinitrophenols	DNOC
	Fluoroacetates	Nissol (2-fluoro-*N*-methyl-*N*-(1-naphthyl)acetamide)
	Botanicals	
	Nicotinoids	Nicotine (3-(1-methyl-2-pyridyl)pyridine)
	Rotenoids	Rotenone (1,2,12,12a-tetrahydro-8,9-dimethoxy-2-(1-methylethenyl)-(1)-benzopyreno(3,4-b)furol-(2,3-h)furo(2,3-h)-(1)-benzopyran-6-(6aH)-one)

(*Continued*)

Table 1 (Continued)

Class	*Principal chemical type*	*Example: common name (chemical name)*
	Pyrethrins	Pyrethrin I (2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid 2-methyl-4-oxo-3-(2,4-pentadienyl)-2-cyclopenten-1-yl ester)
	Synthetic pyrethroids	Fenvalerate (cyano(3-phenoxyphenyl)methyl-4-chloro-α-(1-methylethyl)benzeneacetate)
	Juvenile hormone analogues	Methoprene (isopropyl(2E-4E)-11-methoxy-3,7,11-trimethyl-2,4-dodeca-dienoate)
	Growth regulators	Diflubenzuron (1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea)
	Phenyl pyrazoles	Fipronyl (5-amino-1-(2,5-dichloro-4-(trifluoro)phenyl)-1H-pyrazole-3-carbonitrile)
	Inorganics	
	Arsenicals	Lead arsenate
	Fluorides	Sodium fluoride
	Microbials	Thuricide (protein from *Bacillus thuringiensis*)
		Avermectin
Acaricides	Organosulfur compounds	Ovex (*p*-chlorophenyl *p*-chlorobenzenesulfonate)
	Formamidine	Chlordimeform (*N′*-(4-chloro-2-methylphenyl)-*N*,*N*-dimethylmethanimidamide)
	Dinitrophenols	Dinex (2-cyclohexyl-4,6-dinitrophenol)
	DDT analogues	Chlorobenzilate (ethyl-4,4′-dichlorobenzilate)
Rodenticides	Anticoagulants	Warfarin (3-(α-acetonylbenzyl)-4-hydroxycoumarin)
	Botanicals	
	Alkaloids	Strychnine sulfate
	Glycosides	Scillaren A and B
	Fluorides	Fluoroacetate
	Inorganics	Thallium sulfate
	Thioureas	ANTU (α-naphthylthiourea)

induction of liver metabolism, studied for decades at the enzymatic level, has more recently been described in molecular terms. From their relative reactivity in recombinant expression systems numerous pesticides have now been determined to be ligands of nuclear receptors that regulate gene expression of various metabolic enzymes. Panels of pesticides have been ranked for efficacy in activation of the aryl hydrocarbon receptor (AhR) (Long *et al.* 2003), pregnane X receptor (PXR) (Lemaire *et al.* 2006; Matsubara *et al.* 2007), and peroxisome proliferator-activated receptors (PPARα and γ) (Takeuchi *et al.* 2006). Alternately, pesticide regulation of constitutive androstane receptor (CAR) occurs indirectly through derepression as has also been detected with an expression system engineered into a reporter cell line (Sueyoshi *et al.* 1999). Complementary information has been derived from toxicogenomic profiles of expression arrays for pesticides relative to that of prototype nuclear receptor activators (Goetz *et al.* 2006; Tully *et al.* 2006). Signature response elements for specific nuclear receptors, as activated by prototype ligands or similarly active pesticides, are embedded in gene promoters of individual CYP isozymes (Rose and Hodgson 2001); likewise, expression of some GSTs and UDP-glucuronyl transferases (UGTs) are regulated by the same activator–nuclear receptor interaction with response elements upstream of their genes (Shelby and Klaassen 2006). Also, transcriptional regulation of some GST and UGT isoforms are mediated by antioxidant response element (ARE) in their promoters, which enables their induction indirectly by pesticides associated with oxidative stress.

Many studies have demonstrated that oxidation of xenobiotics can be affected by both endogenous and exogenous factors. Endogenous factors include species, strain, age, gender and gestational, developmental, and hormonal status (Ronis and Cunny 2001). Growth hormone, thyroid, adrenal, and pancreatic hormones are important physiological regulators of hepatic xenobiotic-metabolizing enzymes. Although not as well studied as with pharmaceutical substrates, pesticide metabolism-dependent hepatotoxicity can be expected to vary with these endogenous factors. Exogenous factors that modulate xenobiotic metabolism include stress, disease state, and diet. Pesticides, being regulated as potential food residues, have been more extensively studied in this context as nonnutritional dietary components. Although the relative importance of CYP and FMO isoforms for the metabolism of the same substrate may have important toxicological implications, much less is known about the role of exogenous or endogenous factors on the hepatic metabolism of pesticides by FMOs. For mice, the greater FMO enzymatic activity detected in the livers of females of several strains could be attributed to differential expression of FMO1 and FMO3 isoforms between males and females (Falls *et al.* 1995). Hepatic FMO5, the other major mouse liver isoform, and the major isoforms of adult human liver, FMO3 and FMO5, do not exhibit gender-dependent differences in expression (Ripp *et al.* 1999). The observation that human FMO1, whose expression is negligible in adult liver (Cashman and Zhang 2006), exhibits greater rates of catalysis of sulfoxidation of certain phosphorothioate and carbamate thioether pesticides than FMO3 (Furnes and Schlenk 2005) suggests a greater role for CYPs in this reaction in human liver.

Determination of pesticide products of metabolism by individual oxidative and conjugative liver enzymes has been facilitated by the availability of *in vitro* preparations engineered to overexpress specific isozymes. However, prediction of the functional consequences of such products to hepatocyte toxicity is a greater challenge. Pharmacological approaches in animals and hepatocyte cell culture have been used historically to approach this issue, but suffer from lack of specificity of responses to prototype inducers and inhibitors. More recently, development of molecular tools better targeted at ablating specific gene products, such as knockout mice (Gonzalez 2003) or cells transfected with small interfering RNAs (siRNAs), offers systems with greater promise for discerning toxic effects of reactive products of pesticide metabolism. Health effects of xenobiotics independent of metabolism are being better appreciated as parent molecule effects on hepatocyte lipid and carbohydrate metabolism become more evident. A broader role for nuclear receptors characterized primarily as mediators of xenobiotic-induced metabolism has recently been appreciated upon discovery of their cross talk with traditional hormonal regulators of energy metabolism (Konno *et al.* 2008). These new developments will have major implications for future mechanistic understandings of pesticide hepatotoxicity based upon metabolism and nuclear receptor activation.

Limitations of time and space militate against a comparative approach to the relationship between pesticides and the liver and this chapter is devoted, with only a few exceptions, to this relationship

relative to the liver of humans and the surrogate mammals used in research and risk analysis. However, effects on fish liver are of increasing importance to environmental toxicologists and have been the subject of many recent reports. The diversity of these reports is illustrated by the following examples: *Carassius auratus* and alachlor (Yi *et al.* 2007); *Gasterosteus aculeatus* and prochloraz (Sanchez *et al.* 2008); *Ictalurus punctatus* and methoxychlor (James *et al.* 2008); *Micropterus salmoides* and p,p′-DDE (Barber *et al.* 2007); *Oncorhyncus mykiss* and dieldrin (Barnhill *et al.* 2003); *Oreochromis mossambicus* and monocrotophos (Rao 2006); *Oreochromis niloticus* and paraquat (Figueiredo-Fernandes *et al.* 2006); *Rhamdia quelen* and glyphosate (Glusczak *et al.* 2007); *Salmo salar* and *p,p′*-DDE (Mortensen and Arukwe 2006). There is a much smaller body of literature on birds (Cortright and Craigmill 2006), reptiles (Gunderson *et al.* 2006), and various food and feral mammals (Dupuy *et al.* 2001).

9.22.2 Enzymes

9.22.2.1 Pesticides as Substrates for Liver Enzymes

As illustrated in **Table 2**, CYP carries out many different monooxygenations of pesticide substrates, such as epoxidation (aldrin), N-dealkylation (atrazine), O-dealkylation (chlorfenvinphos), sulfoxidation (phorate), and oxidative desulfuration (parathion) (Kulkarni and Hodgson 1980, 1984a,b). Substrates for the FMO are similarly diverse but all are soft nucleophiles, a category that includes many organic chemicals with sulfur, nitrogen, phosphorus, or selenium heteroatoms. Although CYP isoforms appear to prefer hard nucleophiles as substrates there is considerable overlap and most, if not all, substrates for FMO are also CYP substrates. The reverse, however, is not true, since oxidations at carbon atoms are readily catalyzed by CYP but rarely, if at all, by FMO. However, even when the same substrate is oxidized by both CYP and FMO there may be differences in the rate of oxidation, in the products, or in the stereochemistry of the same product. While isoforms of both CYP and FMO are expressed in the liver, they are broadly expressed in other organs, the proportions of different isoforms varying from organ to organ. Pesticide substrates for FMO include organophosphates such as phorate and disulfoton, which yield sulfoxides; the phosphonate, fonofos, which yields fonofos oxon; carbamates such as aldicarb and methiocarb; dithiocarbamate herbicides such as sodium metham; botanical insecticides such as nicotine; and cotton defoliants such as the trivalent organophosphorus defoliant, folex (Levi and Hodgson 1988; Smyser and Hodgson 1985; Smyser *et al.* 1985, 1986; Tynes and Hodgson 1985b; Venkatesh *et al.* 1992).

Early studies on the contribution of individual CYP isoforms using partially purified CYP preparations from mouse liver showed considerable variation between fractions in oxidation of pesticide substrates, in spectral binding, and in inhibition by piperonyl butoxide (Beumel *et al.* 1985; Levi and Hodgson 1985). Subsequently, the use of highly purified CYPs from the livers of phenobarbital- and β-naphthoflavone-treated mice showed that these fractions have much higher activity toward the organophosphorus insecticides fenitrothion, parathion, and methyl parathion than did similar fractions from the livers of untreated mice, suggesting the importance of the CYP1A and CYP2B families in these oxidations. The isoforms also produced different amounts of detoxication products as compared to the more toxic oxons with CYP2Bs forming more of the oxon (Levi *et al.* 1988). Similar studies showed the importance of the CYP2B family in the hepatic metabolism of phorate to phorate sulfoxide (Kinsler *et al.* 1988, 1990).

The hepatic metabolism of organophosphorus insecticides continues to be investigated in both humans and rodents. In general they are either activated to their oxons, potent inhibitors of acetylcholinesterase and other esterases, or detoxified through a common intermediate containing a phosphooxythirane ring. This intermediate is generated by CYP isoforms, particularly CYP1A2, CYP2B6, and CYP3A4 (see **Tables 2** and **3**).

The role of both carboxylesterases, CYPs and alcohol and ALDHs in the hepatic metabolism of pyrethroids has recently been studied in both rodents (Anand *et al.* 2006a,b; Choi *et al.* 2002; Crow *et al.* 2007; Godin *et al.* 2006, 2007a,b; Huang *et al.* 2005; Price *et al.* 2008; Ross *et al.* 2006) and humans (Crow *et al.* 2007; Godin *et al.* 2006, 2007a,b; Huang *et al.* 2005; Price *et al.* 2008; Ross *et al.* 2006). The role of carboxylases in the human hepatic metabolism of malathion has also been evaluated (Buratti and Testai 2005) (see **Tables 2** and **3**).

The metabolism of methoxychlor, because of its importance as an environmental endocrine disruptor, has received considerable attention, particularly in

Table 2 Metabolism of pesticides catalyzed by liver microsomal enzymes

Reaction	*Example*	*References*
CYP-dependent oxidations		
N-Dealkylation	4-Nitrophenyl *N*,*N*-dimethyl carbamate → 4-nitrophenyl *N*-methyl carbamate	Hodgson and Casida (1961); Strother (1972)
	Dimethoate → des *N*-methyl derivatives	Lucier and Menzer (1970)
	Dicrotophos → des *N*-methyl derivatives	Tseng and Menzer (1974)
	Atrazine, simazine, terbutryn → *N*-dealkylated derivatives	Adams *et al*. (1990); Rodriguez and Harkin (1995)
	Diuron → desmethyldiuron	Abass *et al*. (2007)
O-Dealkylation		
Ether cleavage	Methoxychlor → mono- and dihydroxy derivatives	Kapoor *et al*. (1970); Kishimoto *et al*. (1995); Kurihari and Oku (1991)
	Propoxur → 2-hydroxyphenyl *N*-methyl carbamate	Oonthan and Casida (1966, 1968)
	Alachlor → RCH_2OH → HCHO	Jacobsen *et al*. (1991)
Ester cleavage	Chlorfenvinphos → desethyl derivatives	Donninger *et al*. (1967, 1972); Hutson (1981)
	EPN oxon → desmethyl EPN oxon	Nomeir and Dauterman (1979)
Epoxidation (to stable epoxides)	Heptachlor → heptachlor epoxide	Khan (1969)
	Aldrin → dieldrin	Kulkarni and Hodgson (1984a)
Ring hydroxylation (via arene oxide)	Carbaryl → 4- and 5-hydroxycarbaryl	Dorough and Casida (1964); Hutson (1981)
	Naphthalene → naphthalene epoxide	Jerina *et al*. (1968, 1970)
	Dieldrin → 12-hydroxydieldrin	Baldwin *et al*. (1972); Hutson (1976)
	Terbutol	Suzuki *et al*. (2001)
Side-chain hydroxylation	Carbaryl → *N*-hydroxymethyl carbaryl	Dorough and Casida (1964); Hutson (1981) Tang *et al*. (2002)
	Butacarb → hydroxybutyl derivatives	Douch and Smith (1971a,b)
	TOCP → hydroxmethyl TOCP cyclic phosphate	Eto *et al*. (1962)
	Pyrethrins → hydroxymethyl derivatives	Casida *et al*. (1975–1976); Class *et al*. (1991)
	S,*S*,*S*-tributyl phosphorotrithioate (DEF) oxidation at C adjacent to S leading to dealkylation	Hur *et al*. (1992)
Heterocyclic ring hydroxylation	Nicotine → hydroxynicotine	Hucker *et al*. (1960)
Desulfuration/ dearylation	Parathion → paraoxon	Buratti *et al*. (2003); Davison (1995); Foxenberg *et al*. (2007); Kamataki and Neal (1976); Kim *et al*. (2005)
	Diazinon → diazoxon	Buratti *et al*. (2003); Poet *et al*. (2003); Yang *et al*. (1969, 1971)
	Azinophos-methyl	Buratti *et al*. (2003)
	Chlorpyrifos	Buratti *et al*. (2003); Poet *et al*. (2003); Tang *et al*. (2001)
	Other OPs → oxons	Buratti and Testai (2007); Kulkarni and Hodgson (1984a)
Dehydrogenation	β- and γ-Chlordane → dichlorochlordene	Chadwick *et al*. (1975); Street and Blau (1972)

(*Continued*)

Table 2 (Continued)

Reaction	*Example*	*References*
Sulfoxidation	Phorate → phorate sulfoxide → phorate sulfone	Levi and Hodgson (1988)
	Vamidothion → vamidothion sulfoxide	Mehmood *et al*. (1996)
	Thiazopyr → thiazopyr sulfoxide → thiazopyr sulfone	Feng *et al*. (1994)
	Metam-sodium	Kim *et al*. (1994); Smyser and Hodgson (1985); Smyser *et al*. (1985, 1986)
	DEF – oxidation of S adjacent to P	Hur *et al*. (1992)
	Diallate, triallate, and sulfallate	Hackett *et al*. (1993); Mair and Casida (1991)
	S-oxidation of dithianes	
	S-oxidation of 7-*N*,*N*-dimethylamino-1,2,3,4,5-pentathiocyclooctane	Xia *et al*. (1995)
FMO-dependent oxidations		
N-oxidation	Nicotine → nicotine *N*-oxide	Tynes and Hodgson (1985a,b)
	Tetram → tetram *N*-oxide	Hajjar and Hodgson (1980, 1982)
Sulfoxidation	Phorate → phorate sulfoxide	Hajjar and Hodgson (1980, 1982); Levi and Hodgson (1988)
	Methiocarb → methiocarb sulfoxide	Tynes and Hodgson (1985a,b)
	Metam-sodium	Kim *et al*. (1994); Smyser and Hodgson (1985); Smyser *et al*. (1985, 1986)
Oxidative desulfuration	Fonofos → fonofos oxon	Hajjar and Hodgson (1980, 1982); Smyser and Hodgson (1985); Smyser *et al*. (1985, 1986)
Reduction		
Nitro reduction	Parathion → aminoparathion	Hitchcock and Murphy (1967)
Dechlorination	DDT → TDE	Esaac and Matsumura (1984)
Hydrolysis	DDVP → desmethyl DDVP	Hodgson and Casida (1962)
	Deltamethrin → 3-(2,2-dibromovinyl)-2,2-cyclopropane carboxylic acid and 3-phenoxybenzaldehyde	Akhtar (1984); Anand *et al.* (2006a,b); Godin *et al*. (2006, 2007a,b); Ross *et al*. (2006)
	Bioresmethrin	Ross *et al*. (2006)
	Esfenvalerate	Godin *et al*. (2007)
	Permethrin	Crow *et al*. (2007); Ghiasudden and Soderlund (1984)
	Pyrethroid-like model substrates	Huang *et al*. (2005)
	Malathion → desethyl malathion	Buratti and Testai (2005)
Conjugation		
Glucuronidation	Dieldrin → dieldrin glucuronide	Baldwin *et al*. (1972); Hutson (1976); Matthews and Matsumura (1969)
	Methoxychlor	Hazai *et al*. (2004)
	Carbaryl → naphthyl glucuronide	Chin *et al*. (1979a,b,c)
Sulfation	Carbaryl → naphthyl sulfate	Chin *et al*. (1979a,b,c)
Acetylation	Fluoroacetamide → fluoroacetyl CoA	
Glutathione conjugation	Methyl parathion → GSH desmethyl methyl parathion + methyl GSH	Abel *et al*. (2004a,b); Choi *et al*. (2006); Hollingworth (1969)
Epoxide hydrolysis	Tridiphane	Magdalou and Hammock (1987)

Table 3 Human hepatic phase I xenobiotic-metabolizing enzymes active in pesticide studies

Phase I isoform	*Substrate*
Alcohol dehydrogenase α	Permethrin metabolite: phenoxybenzyl alcohol (Choi *et al*. 2002)
Alcohol dehydrogenase β-I	Permethrin metabolite: phenoxybenzyl alcohol (Choi *et al*. 2002)
Alcohol dehydrogenase β-II	Permethrin metabolite: phenoxybenzyl alcohol (Choi *et al*. 2002)
Alcohol dehydrogenase γ	Permethrin metabolite: phenoxybenzyl alcohol (Choi *et al*. 2002)
Aldehyde dehydrogenase ALDH3A1	Permethrin metabolite: phenoxybenzyl aldehyde (Choi *et al*. 2002)
CYP1A1	Insecticides: carbaryl (Tang *et al*. 2002); carbofuran; sulprofos (Usmani *et al*. 2004b) Herbicides: ametryne; atrazine; terbuthylazine; terbutryne (Lang *et al*. 1996, 1997); diuron (Abass *et al*. 2007) Insect repellent: DEET (Foxenberg *et al*. 2007; Usmani *et al*. 2002)
CYP1A2	Insecticides: azinphos-methyl (Buratti *et al*. 2002, 2003); carbaryl (Tang *et al*. 2002); carbofuran (Usmani *et al*. 2004a); chlorpyrifos (Buratti *et al*. 2002, 2003; Foxenberg *et al*. 2007; Tang *et al*. 2001); diazinon (Buratti *et al*. 2002, 2003); disulfoton (Usmani *et al*. 2004b); imidacloprid (Schultz-Jander and Casida 2002); methiocarb (Usmani *et al*. 2004b); parathion (Buratti *et al*. 2003; Butler and Murray 1997; Foxenberg *et al*. 2007; Mutch *et al*. 1999, 2003; Sams *et al*. 2000); phorate (Hodgson *et al*. 1998); sulprofos (Usmani *et al*. 2004b); methoxychlor (Hu and Kupfer 2002) Herbicides: ametryne; atrazine; terbuthylazine; terbutryne (Lang *et al*. 1996, 1997); diuron (Abass *et al*. 2007)
CYP2A6	Insecticides: carbaryl (Tang *et al*. 2002); imidacloprid (Schultz-Jander and Casida 2002); methoxychlor (Hu and Kupfer 2002) Insect repellent: DEET (Usmani *et al*. 2002)
CYP2B6	Insecticides: azinophos-methyl (Buratti *et al*. 2002, 2003); carbaryl (Tang *et al*. 2002); chlorpyrifos (Buratti *et al*. 2002, 2003; Foxenberg *et al*. 2007; Tang *et al*. 2001); diazinon (Buratti *et al*. 2002, 2003); disulfoton (Usmani *et al*. 2004b); imidacloprid (Schultz-Jander and Casida 2002); methiocarb (Usmani *et al*. 2004b); parathion (Buratti *et al*. 2003; Butler and Murray 1997; Foxenberg *et al*. 2007; Mutch *et al*. 1999, 2003; Sams *et al*. 2000); phorate (Usmani *et al*. 2004b) Insect repellent: DEET (Usmani *et al*. 2002) Herbicides: acetachlor; alachlor (Coleman *et al*. 2000); ametryne; atrazine; butachlor; metolachlor; terbutryne (Lang *et al*. 1996, 1997)
CYP2C8	Insecticides: carbaryl (Tang *et al*. 2002); carbofuran (Usmani *et al*. 2004a); parathion (Mutch *et al*. 2003); phorate (Hodgson *et al*. 1998); deltamethrin, esfenvalerate (Godin *et al*. 2007a,b); methoxychlor (Hu and Kupfer 2002) Herbicide: ametryne (Lang *et al*. 1997)
CYP2C9	Insecticide: chlorpyrifos (Foxenberg *et al*. 2007; Tang *et al*. 2001); imidacloprid (Schultz-Jander and Casida 2002); parathion (Foxenberg *et al*. 2007); phorate (Hodgson *et al*. 1998) Herbicide: ametryne (Lang *et al*. 1997)
CYP2C9*1	Insecticide: carbaryl (Tang *et al*. 2002); disulfoton; methiocarb; phorate; sulprofos (Usmani *et al*. 2004b); methoxychlor (Hu and Kupfer 2002)
CYP2C9*2	Insecticide: carbaryl (Tang *et al*. 2002); disulfoton; sulprofos (Usmani *et al*. 2004b)
CYP2C9*3	Insecticide: carbaryl (Tang *et al*. 2002); sulprofos (Usmani *et al*. 2004b)
CYP2C18	Insecticides: carbaryl (Tang *et al*. 2002); disulfoton; phorate; sulprofos (Hodgson *et al*. 1998; Usmani *et al*. 2004b)
CYP2C19	Insecticides: azinphos-methyl (Buratti *et al*. 2002); carbaryl (Tang *et al*. 2002); carbofuran (Usmani *et al*. 2004a); chlorpyrifos (Buratti *et al*. 2002; Foxenberg *et al*. 2007; Tang *et al*. 2001); deltamethrin, esfenvalerate (Godin *et al*. 2007); diazinon (Buratti *et al*. 2002; Kappers *et al*. 2001); disulfoton (Usmani *et al*. 2004b); fipronil (Tang *et al*. 2004); imidacloprid (Schultz-Jander and Casida 2002); methiocarb (Usmani *et al*. 2004b); parathion (Buratti *et al*. 2002; Foxenberg *et al*. 2007; Mutch *et al*. 2003); phorate (Hodgson *et al*. 1998); sulprofos (Usmani *et al*. 2004b); deltamethrin, esfenvalerate (Godin *et al*. 2007); methoxychlor (Hu and Kupfer 2002) Insect repellent: DEET (Usmani *et al*. 2002)

(*Continued*)

Table 3 (Continued)

Phase I isoform	*Substrate*
	Herbicides: ametryne; atrazine; terbuthylazine (Lang *et al*. 1996, 1997); diuron (Abass *et al*. 2007)
CYP2C19*1B	Insecticide; chlorpyrifos (Tang *et al*. 2001)
CYP2C19*8	Insecticide: chlorpyrifos (Tang *et al*. 2001)
CYP2C19*6	Insecticide: chlorpyrifos (Tang *et al*. 2001)
CYP2C19*5	Insecticide: chlorpyrifos (Tang *et al*. 2001)
CYP2D6*1	Insecticide: carbaryl (Tang *et al*. 2002); carbofuran; disulfoton; sulprofos (Usmani *et al*. 2004b); methoxychlor (Hu and Kupfer 2002) Insect repellent: DEET (Usmani *et al*. 2002)
CYP2D6	Insecticides: diazinon (Sams *et al*. 2000); imidacloprid (Schultz-Jander and Casida 2002); methiocarb (Usmani *et al*. 2004b); parathion (Mutch *et al*. 2003) Herbicide: atrazine (Lang *et al*. 1997)
CYP2E1	Insecticides: carbaryl (Tang *et al*. 2002); imidacloprid (Schultz-Jander and Casida 2002); parathion (Mutch *et al*. 2003); phorate (Hodgson *et al*. 1998; Usmani *et al*. 2004b) Insect repellent: DEET (Usmani *et al*. 2002) Herbicide: atrazine (Lang *et al*. 1997)
CYP3A4	Insecticide: azinphos-methyl (Buratti *et al*. 2002, 2003); carbaryl (Tang *et al*. 2002); carbofuran (Usmani *et al*. 2004a); chlorpyrifos (Buratti *et al*. 2002, 2003; Dai *et al*. 2001; Foxenberg *et al*. 2007; Tang *et al*. 2001); diazinon (Buratti *et al*. 2003; Kappers *et al*. 2001; Sams *et al*. 2000); dimethoate (Buratti and Testai 2007); disulfoton (Usmani *et al*. 2004b); fipronil (Tang *et al*. 2004); imidacloprid (Schultz-Jander and Casida 2002); methiocarb (Usmani *et al*. 2004b); parathion (Buratti *et al*. 2003; Butler and Murray 1997; Foxenberg *et al*. 2007; Kappers *et al*. 2001; Mutch *et al*. 1999, 2003; Sams *et al*. 2000); phorate (Hodgson *et al*. 1998; Usmani *et al*. 2004b); sulprofos (Usmani *et al*. 2004b); vamidothion (Mehmood *et al*. 1996); methoxychlor (Hu and Kupfer 2002) Insect repellent: DEET (Usmani *et al*. 2002) Herbicide: acetachlor; alachlor (Coleman *et al*. 1999, 2000; Hodgson *et al*. 1998); ametryne; atrazine; butachlor; terbuthylazine; terbutryne (Lang *et al*. 1996, 1997); diuron (Abass *et al*. 2007)
CYP3A4-F189S	Insecticide: chlorpyrifos (Dai *et al*. 2001)
CYP3A4-L293P	Insecticide: chlorpyrifos (Dai *et al*. 2001)
CYP3A4-M445T	Insecticide: chlorpyrifos (Dai *et al*. 2001)
CYP3A4-P467S	Insecticide: chlorpyrifos (Dai *et al*. 2001)
CYP3A5	Insecticide: carbaryl (Tang *et al*. 2002); carbofuran (Usmani *et al*. 2004a); chlorpyrifos (Foxenberg *et al*. 2007); deltamethrin, esfenvalerate (Godin 2007); parathion (Foxenberg *et al*. 2007; Mutch *et al*. 2003); phorate (Mutch *et al*. 2003; Usmani *et al*. 2004b); sulprofos (Usmani *et al*. 2004b); deltamethrin, esfenvalerate (Godin *et al*. 2007); methoxychlor (Hu and Kupfer 2002) Insect repellent: DEET (Usmani *et al*. 2002)
CYP3A7	Insecticide: carbofuran (Usmani *et al*. 2004a); chlorpyrifos (Foxenberg *et al*. 2007); parathion (Foxenberg *et al*. 2007)
FMO1	Insecticide: aldicarb (Schlenk *et al*. 2002); disulfoton; methocarb; sulprofos (Usmani *et al*. 2004b); phorate (Hodgson *et al*. 1998; Usmani *et al*. 2004b)
FMO3	Insecticide: aldicarb (Schlenk *et al*. 2002)
Carboxylase	Insecticide: bioresmethrin (Ross *et al*. 2006); permethrin (Crow *et al*. 2007; Ross *et al*. 2006) Pyrethroid-like model substrates (Huang *et al*. 2005) Malathion (Buratti and Testai 2005)

Adapted from Hodgson, E. *J. Biochem. Mol. Toxicol*. **2003**, *17*, 201–206.

the laboratory of the late David Kupfer (e.g., Hazai *et al.* 2004; Hu and Kupfer 2002a,b).

Other recent studies of hepatic pesticide metabolism include those on azole fungicides (Barton *et al.* 2006; Mazur *et al.* 2007), the carbamate insecticide terbutol (Suzuki *et al.* 2001), and the herbicide diuron (Abass *et al.* 2007) (see **Tables 2** and **3**).

Studies of *in vitro* metabolism of pesticides by liver enzymes were, until recently, carried out using tissues from surrogate animals. During the last decade, however, due to the availability of human liver enzymes and recombinant human xenobiotic-metabolizing enzymes, there has been an increasing number of studies of human metabolism of pesticides and, in some instances, the effects of polymorphisms. A summary of pesticide substrates for human hepatic xenobiotic-metabolizing enzymes is presented in **Table 3**. It is apparent that essentially all of the human xenobiotic-metabolizing CYPs, as well as some other phase I enzymes have one or more pesticide substrates. A number of studies have shown the importance of both the relative amounts of different CYP isoforms present (Buratti and Testai 2005; Buratti *et al.* 2002, 2003, 2007; Mutch *et al.* 2003; Tang *et al.* 2001, 2002; Usmani *et al.* 2002, 2004a) as well as the effect of polymorphisms on the extent of metabolism and the distribution of metabolites (Dai *et al.* 2001; Tang *et al.* 2001) (additional references can be found in Hodgson 2003).

The extensive role of GSTs in the metabolism of methyl parathion has been studied using human liver cytosol and recombinant human enzymes (Abel *et al.* 2004a,b). The role of GSTs in the metabolism of chlorpyrifos has also been evaluated in human hepatocytes (Choi *et al.* 2006).

Epoxide hydrolase is another phase I enzyme known to metabolize pesticides, a well-known example being the metabolism of the herbicide, tridiphane, by the epoxide hydrolase of mouse liver (Magdalou and Hammock 1987).

Conjugation reactions of pesticides are less well known although some aspects have been reviewed (Dorough 1984; Matsumura 1985; Motoyama and Dauterman 1980) and several types of conjugation are known to involve pesticides as substrates. Glucuronides are important metabolites of carbamates, including banol, carbaryl, and carbofuran (Mehendale and Dorough 1972), as well as some organophosphorus and other pesticides (Hutson 1981). Ethereal sulfates, although not important in pesticide metabolism, may be formed from the oxidative metabolites of carbaryl and carbofuran (Dorough 1968). GST is important in the metabolism of organophosphorus pesticides (Abel *et al.* 2004a,b; Choi *et al.* 2006; Motoyama and Dauterman 1980) and halogenated herbicides such as the chloroacetanilides and chloro-*S*-triazines (Abel *et al.* 2004a,b; Cho and Kong 2007). The conjugation products are typically further metabolized and, in humans, excreted as urinary mercapturic acids. Interestingly, the addition of GSH (molecular weight 307) to these 200–300 molecular weight xenobiotics creates a product that exhibits a species-dependent disposition due to differences in size thresholds for biliary transport in this range.

Although not strictly speaking a detoxication reaction, hepatic aliesterase, by forming a stable phosphorylated enzyme with organophosphates (oxons), may serve as an inert storage protein (Chambers *et al.* 1990).

9.22.2.2 Pesticides as Inducers of Liver Enzymes

Several early studies (Guzelian *et al.* 1980; Kolmodin-Hedman 1973; Kolmodin *et al.* 1969; Kreiss *et al.* 1981; Poland *et al.* 1970), based on the half-life of aminopyrene or excretion of 6β-hydroxycortisol, provided evidence for induction of hepatic CYP in humans exposed to pesticides. Early experiments (Hodgson *et al.* 1991) in surrogate animals confirmed hepatic enzyme induction but methods for identification of individual isoforms were not yet available and reliance was placed on assessment of enzyme activities. Accordingly the pesticide was often classified as a phenobarbital, 3-methylcholanthrene or mixed-type inducer. The measurement of zoxazolamine paralysis time, hexabarbital sleeping time, and aniline hydroxylase activity made possible the demonstration that DDT and its principal metabolite, DDE, were CYP inducers in mice (Abernathy *et al.* 1971a,b). Induction by pesticides is summarized in **Table 4**.

Due to their importance as endocrine disruptors many of the recent studies of induction of liver enzymes by organochlorine pesticides have involved either methoxychlor or *o,p*-DDE. Methoxychlor was shown to induce CYPs 1A, 2B, 2C, 2E, and 3A in both male and female rats (Oropeza-Hernandez *et al.* 2003) and EROD and PROD activity in HepG2 cells (Dehn *et al.* 2005; Medina-Diaz and Elizondo 2005). *o,p*-DDT or its metabolite *o,p*-DDE has been shown to induce CYP3A4. Of considerable mechanistic importance is the finding that the nuclear receptors PXR and

Table 4 Induction of liver microsomal enzyme activity following treatment *in vivo*, and involving pesticides as either inducers or substrates

Inducer and/or substrate	*Species*	*Effect*
Synergists		
Sesoxane	Mouse	Hexobarbital sleeping time increased (Fine and Molloy 1964)
Piperonyl butoxide	Mouse	Hexobarbital sleeping time increased (Fine and Molloy 1964). Hexobarbital sleeping time increased up to 12 h, decreased after 24–72 h (Kamienski and Murphy 1971). Parathion toxicity increased after 1 h, decreased after 48 h (Kamienski and Murphy 1971). Microsomal CYP content decreased after 2–12 h, increased after 12–36 h (Philpot and Hodgson 1972). Induction of CYP 2B10, 1A1, and 1A2; 1A2 by an Ah-independent mechanism (Adams *et al*. 1993a,b, 1995; Lewandowski *et al*. 1990; Philpot and Hodgson 1972; Ryu *et al*. 1996)
Chlorinated hydrocarbon insecticides		
BHC	Rat	*In vitro* metabolism of hexobarbital increased, hexobarbital sleeping time decreased, scillicocide toxicity decreased. All isomers similar (Koransky *et al*. 1964)
Trichloro-237	Rat	Hexobarbital sleeping time decreased (Hart and Fouts 1963)
γ-Chlordane	Rat	Hexobarbital sleeping time decreased (Hart and Fouts 1963)
Endrin	Rat	Hexobarbital sleeping time decreased (Hart and Fouts 1963)
DDT	Rat	No effect on hexobarbital sleeping time (Hart and Fouts 1963)
		Hexobarbital sleeping time decreased. Hexobarbital metabolism *in vitro* increased. Metabolism of aminopyrine increased. Metabolism of *p*-nitrobenzoic acid increased
		No effect on aniline metabolism. Increased detoxication of EPN. Increased O-demethylation of *p*-nitroanisole. Increased N-demethylation of aminopyrine (Hart and Fouts 1963; Kinoshita *et al*. 1966)
	Squirrel monkey	Increased metabolism, *in vitro*, of EPN and *p*-nitroanisole (Cranmer *et al*. 1972)
	Human	Increase in CNS arousal with phenobarbital administration (Rappolt 1973)
DDT and analogues	Mouse	Increased P450 levels, aniline hydroxylase activity, zoxazolamine paralysis time, and hexobarbital sleeping time. QSAR for 28 analogues (Abernathy *et al*. 1971a,b)
Diphenyl hydantoin	Rat	DDT and DDE storage decreased, *in vitro* DDT metabolism increased (Cranmer 1970)
o,*p*-DDD	Guinea pig	Phenobarbital sleeping time decreased, *in vitro* phenobarbital metabolism increased (Straw *et al*. 1965)
p,*p*-DDD	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971)
o,*p*-DDT	Rat	PXR and CAR-dependent increase in CYPs 2B2 and 3A2 (Kiyosawa *et al*. 2008).
	HepG2 cells	Increase in CYP3A4 mRNA (Medina-Diaz *et al*. 2005, 2007)
p,*p*-DDE	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971). Induction of CYP 2b 3A (Wyde *et al*. 2003)
Chlordane	Rat	*In vitro* metabolism of hexobarbital, aminopyrine, and chlorpromazine unchanged after 1 dose, all increased after 3 doses (Hart *et al*. 1963)
		Decreased toxicity of dicoumarol (Welch and Harrison 1966)
	Dog	Increased metabolism *in vitro* of estrone (Welch *et al*. 1971)
Lindane	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971). Increased expression of mRNA for CYP1A1, 1A2, 2B1, 2B2, and 2E1 as well as associated catalytic activities (Johri *et al*. 2003, 2008)

Heptachlor	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971)
Toxaphene	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971)
		Increased detoxication of EPN, O-demethylation of *p*-nitroanisole, and N-demethylation of aminopyrine (Kinoshita *et al*. 1966)
Dieldrin	Rhesus monkey	Increased metabolism *in vitro* of chlorfenvinphos (Wright *et al*. 1972)
	Dog	Increased metabolism *in vitro* of chlorfenvinphos (Wright *et al*. 1972)
	Rat	Increased metabolism *in vitro* of chlorfenvinphos (Wright *et al*. 1972)
	Rat	Increased metabolism *in vitro* of estradiol-17β (Welch *et al*. 1971)
	Mouse	Increased metabolism *in vitro* of chlorfenvinphos (Wright *et al*. 1972)
Mirex	Mouse/rat	Increased O-demethylation *in vitro* of *p*-nitroanisole and CYP content (Baker *et al*. 1972)
Mirex and kepone	Rat	Increased warfarin hydroxylation *in vitro* and increased CYP content (Kaminsky *et al*. 1978)
	Gerbil	Increased benzo(a)pyrene hydroxylase activity *in vitro* and increased CYP content (Crouch and Ebel 1987)
	Mouse	Increased acute *in vivo* hepatotoxicity; mirex had greater effect (Fouse and Hodgson 1987)
		Increased CYP and N- and O-dealkylation *in vitro* (Fabacher and Hodgson 1976)
		Induction of CYP2B10, iA2, and 3A (Lewandowski *et al*. 1989)
Methoxychlor	Rat	Increase in total CYP and gender-dependent increases in CYP 1A1- and 1A2-related activities (Orepeza-Hernandez *et al*. 2003)
Organophosphorus insecticides		
3-Methylcholanthrene	Rat	Increased metabolism *in vitro* of azinphosmethyl to a cholinesterase inhibitor (Murphy and DuBois 1957)
Phenobarbital	Rat/mouse	Decreased *in vivo* toxicity of parathion, methyl parathion, demeton, disulfoton, azinphosmethyl, dioxathion, ethion, carbophenothion, mevinphos, and EPN (DuBois 1969)
Malathion	Rat	Increased CYP (Matthews and Devi 1994)
S,*S*,*S*-Tri-*n*-butyl phosphorotrithioate	Hen	Increased CYP (Lapadula *et al*. 1984)
Carbamate insecticides		
Carbaryl	Chicken	Pentobarbital sleeping time decreased (Puryear and Paulson 1972)
Pyrethroid insecticides		
Deltamethrin	Rat	Increase in mRNA and protein for Cyps 1A and 2E (Johri *et al*. 2006)
Pyrethrins	Rat	Increase in CYP2B1 and CYP2B1/2 mRNA and associated enzymatic activities, and increase in testosterone 6β-hydroxylase activity (Price *et al*. 2008)
	Human	Increase in testosterone 6β-hydroxylase activity, CYP2B6 and CYP3A4 mRNA (Price *et al*. 2008)

(*Continued*)

Table 4 (Continued)

Inducer and/or substrate	*Species*	*Effect*
Rodenticides		
Phenobarbital	Human	Pharmacological activity of warfarin decreased (Robinson and MacDonald 1996)
	Dog	Dicoumarol toxicity *in vivo* decreased (Welch *et al*. 1967)
Acetylsalicylic acid	Rat	Dicoumarol prothrombin time decreased (Coldwell and Zawidzka 1968)
Heptobarbital	Human	Excretion of dicoumarol metabolites increased (Aggeler and O'Reilly 1969)
Herbicides		
Alachlor	Rat	Induction of CYP2B1/2 and 1A1/2 protein and associated activities (Hanioka *et al*. 2002)
Metolachlor	Rat	Induction of CYP2B1/2 and CYP3A1/2 protein (Dalton *et al*. 2003)
Monuron	Rat	Detoxication of EPN, O-demethylation of *p*-nitroanisole, and N-demethylation of aminopyrine increase for 1–3 weeks, then return to normal (Kinoshita and DuBois 1967)
Diuron	Rat	Detoxication of EPN, O-demethylation of *p*-nitroanisole, and N-demethylation of aminopyrine increase for 1–3 weeks, then return to normal (Kinoshita and DuBois 1967)
	Mouse hepatoma cells	AhR-dependent induction of CYP1A1 mRNA (Zhao *et al*. 2006)
Tridiphane	Mouse	Induction of CYP4A (Levi *et al*. 1992) Induction of epoxide hydrolase (Moody and Hammock 1987)
Fungicides		
Griseofulvin	Human	Pharmacological action of warfarin decreased (Cullen and Catalano 1967)
Parnon	Rat	*In vitro* metabolism increased (Hoffman *et al*. 1968)
Azoles	Rat	Increase in liver weight, liver pathology, total CYP, CYPs 2B1 and 3A2, and associated enzyme activities (Barton *et al*. 2006; Martin *et al*. 2007; Sun *et al*. 2006, 2007)
	Mice	Increase in liver weight, liver pathology, total CYP, CYPs 2B1 and 3A2, and associated enzyme activities (Allen *et al*. 2006; Sun *et al*. 2006; Ward *et al*. 2006)
Pesticide adjuvant		
Toximul	Mice	PPAR-dependent increases in peroxisomal acyl-CoA oxidase, thiolase, and Cyp4A10 and 4A14 (Upham *et al*. 2007)

CAR are involved in the induction either in HepG2 cells (Medina-Diaz *et al.* 2007) or in immature, ovariectomized rats (Kiyosawa *et al.* 2008; Wyde *et al.* 2003). Lindane has been shown to induce P450s 1A and 2B in rats, including ontogenic changes (Johri *et al.* 2008; Parmar *et al.* 2003).

The azole fungicides have been shown to be inducers of various xenobiotic-metabolizing enzymes or activities, primarily in rodents (Allen *et al.* 2006; Barton *et al.* 2006; Martin *et al.* 2007; Sun *et al.* 2006, 2007; Ward *et al.* 2006) (see also **Table 4**).

Mirex was shown to be one of the most potent pesticide inducers of liver CYPs, inducing CYP2B10 as well as testosterone metabolism in mouse liver (Baker *et al.* 1972; Fabacher and Hodgson 1976; Lewandowski *et al.* 1989). A related pesticide, kepone, although less potent, was also a CYP inducer in mice (Fabacher and Hodgson 1976).

Methylenedioxyphenyl (MDP) chemicals such as piperonyl butoxide and sesamex have been used as pyrethroid and carbamate pesticide synergists. Other MDP chemicals such as safrole and isosafrole are secondary plant chemicals often found in foods, the former having been shown to be a liver carcinogen in rodents at high doses. MDPs affect multiple enzyme systems (Goldstein *et al.* 1970; Hodgson and Philpot 1974), including CYPs, and their effect is biphasic, an initial inhibition of activity followed by induction (Kamienski and Murphy 1971; Kinsler *et al.* 1990; Philpot and Hodgson 1972). The inhibitory activity has been attributed to the formation of a stable inhibitory metabolite complex formed when a carbene resulting from the removal of water from an MDP compound hydroxylated on the methylene carbon combines with the heme iron of a CYP isoform (Dahl and Hodgson 1979). Induction by MDPs results in increases in several CYP isoforms not found at detectable levels in unexposed animals (Adams *et al.* 1993a,b 1995; Lewandowski *et al.* 1990).

Cook and Hodgson showed that while isosafrole induced the Ah receptor it did not activate this receptor, rather it appeared to induce CYP1A2 by an Ah-independent mechanism (Cook and Hodgson 1986; Marcus *et al.* 1990). A number of other studies, utilizing both Ah+ (C57BL/6) and Ah– (DBA/2) strains of mice and numerous MDP chemicals (Adams *et al.* 1993a,b; 1995; Murray *et al.* 1985; Ryu *et al.* 1995, 1996) all provided QSAR evidence that the methylene carbon and the lipophilicity of the side chains were necessary for induction and supported, indirectly, the hypothesis that CYP1A2 was induced by an Ah receptor-independent mechanism. This was ultimately confirmed by the use of Ah receptor-knockout mice (Ryu *et al.* 1996).

Tridiphane (2-(3,5-dichlorophenyl)-2-(2,2,2-trichloroethyl) oxirane) is a herbicide synergist used in conjunction with atrazine, the synergistic ability being due to its ability to inhibit GST. Tridiphane is also a peroxisome proliferator in rodents (Moody and Hammock 1987) and is an excellent example of a pesticide that can function as both an inhibitor and an inducer, with different specificities for each activity. Induction of CYP4A and associated enzyme activity (Levi *et al.* 1992) has been demonstrated. CYP4As are among the battery of enzymes induced by peroxisome proliferators.

Hepatic enzymes other than those in the microsomes can also be induced by pesticides, sometimes by the same chemicals that induce microsomal enzymes. This includes tridiphane, which induces epoxide hydrolase in mouse liver (Moody and Hammock 1987) and *m*-dichlorobenzene, a pesticide, which induces γ-aminolevulinic acid synthase, a mitochondrial enzyme (Poland *et al.* 1971). GSTs are also induced by a variety of pesticides, although as a general rule the levels of induction are lower than those for CYPs (Fabacher *et al.* 1980; Hodgson *et al.* 1980; Kulkarni *et al.* 1980; Robacker *et al.* 1981).

Several pesticides have been tested for activation of the PXR receptor in engineered expression systems (Lemaire *et al.* 2006; Matsubara *et al.* 2007). Since human 3A4 is transcriptionally regulated, in part, by PXR, induction of this CYP is expected for the pesticides active in the *in vitro* systems. In rats, one of these compounds, the herbicide metolachlor, was shown to induce the rat ortholog CYP3A2, as well as CYPB1/2 at approximately one-fifth the potency of phenobarbital (Dalton *et al.* 2003). Similarly, PXR activation by conazole fungicides is supported by activity in the PXR expression system and from toxicogenomic profile-like signatures of prototype PXR ligands (Goetz *et al.* 2006; Tully *et al.* 2006). Similar approaches have defined transcriptional mechanisms for pesticide induction of other CYPs through their activity as ligands for relevant transcriptional activators.

Although a small number of studies showed induction by pesticides in rat hepatocytes, for example, the induction of CYP2B1 by pyrethroids (Heder *et al.* 2001), the recent availability of human hepatocytes has enabled induction by pesticides in humans to be investigated (Das *et al.* 2006, 2008a,b). These studies reveal that fipronil is an effective inducer of

CYP1A1, CYP2B6, and CYP3A4 in human hepatocytes, at concentration as low as $1.0\,\mu mol\,l^{-1}$. The pyrethroids, deltamethrin, and permethrin, while not as effective as fipronil, induced the same CYP isoforms. The insecticide, chlorpyrifos, and the insect repellent, DEET (*N*,*N*-diethyl-*m*-toluamide), are also capable of inducing xenobiotic-metabolizing CYP isoforms in human hepatocytes. All of these results of studies utilizing human hepatocytes suggest that pesticide–pesticide interactions are possible in the human liver and this possibility should be investigated. It might also be noted that, to a greater or lesser extent, these pesticides are also cytotoxic to human hepatocytes but generally at higher concentrations than those required for CYP isoform induction.

Among recent studies of interest is the demonstration of the induction of Cyp4A10 and Cyp4A14 in mice by the pesticide adjuvant, Toximul, an effect mediated through the PPARα receptor (Upham *et al.* 2007). Diuron and related phenylurea herbicides induced CYP1A1 via the Ah-receptor in several cell lines, including at least one human cell line (Zhao *et al.* 2006). Further studies showed the induction, in rodents, of CYPs 2B and 3A by the herbicide, metolachlor (Dalton *et al.* 2003), CYPs 1A and 2B by deltamethrin (Johri *et al.* 2006), and induction of a number of CYP-related metabolic activities by the herbicide, alachlor (Hanioka *et al.* 2002).

9.22.2.3 Pesticides as Activators of Liver Enzymes

Activation, as distinct from induction, is a stimulatory effect on enzyme activity caused by an interaction at the active site of the enzyme and/or an allosteric effect on enzyme protein conformation. As a consequence, activation tends to be rapid. Induction (Section 9.22.2.2), on the other hand, involves the synthesis of new enzyme and tends to be slower than activation.

Although activation of CYP enzyme activity is less frequently encountered, and less well understood, than inhibition or induction, it has been known for some time. Enhancement, by acetone, of the hepatic microsomal *p*-hydroxylation was first reported in 1968 (Anders 1968). Both flavone and benzoflavone stimulate benzo(a)pyrene metabolism by rabbit liver CYPs, the extent of stimulation depending on the CYP isoform involved (Huang *et al.* 1981). 6β-Hydroxylation of testosterone by the human isoform, CYP3A4, is significantly increased by incubation of the enzyme with pyridostigmine bromide (Usmani *et al.* 2003) and Buratti and Testai (2007) have presented evidence for the autoactivation of CYP3A4 during dimethoate metabolism. More recently (Cho *et al.* 2007), we have shown that chlorpyrifos oxon significantly activates the production of 1-naphthol,2-naphthol, trans-1,2-dihydronaphthalenediol, and 1,4-naphthoquinine from naphthalene by human liver microsomes. Further, it was shown that production of naphthalene metabolites by CYPs 2C8, 2C9, 2C19, 2D6, 3A4, 3A5, and 3A7 was activated by chlorpyrifos oxon while the production of naphthalene metabolites by CYPs 1A1, 1A2, 1B1, and 2B6 was inhibited by chlorpyrifos oxon.

Activation effects on CYP metabolism of the insect repellent DEET were also noted (Cho *et al.* 2007). Chlorpyrifos oxon inhibited the formation of *N*,*N*-diethyl-*m*-hydroxymethylbenzamide from DEET by human liver microsomes while stimulating the formation of *N*-ethyl-*m*-toluamide from DEET. This was reflected by the finding that CYP2B6, the principal isoform for *N*,*N*-diethyl-*m*-hydroxymethylbenzamide production, was inhibited by chlorpyrifos oxon while CYP3A4, the principal isoform for *N*-ethyl-*m*-toluamide production, was activated.

9.22.2.4 Pesticides as Inhibitors of Liver Enzymes

Pesticides can inhibit CYP isoforms by several mechanisms including competitive inhibition in which the pesticide competes for the active site with the substrate, which may or may not be another pesticide. Noncompetitive inhibition involves binding to and modification of the enzyme in such a way as to affect its catalytic activity. Suicide inhibition involves the generation of a reactive metabolite of the substrate that binds to the enzyme inhibiting its activity toward its or other substrates.

It has been known for some time, from studies based on parathion and rabbit liver CYP (Halpert *et al.* 1980; Neal 1980; Neal and Halpert 1982; Neal *et al.* 1983), that organophosphorus insecticides containing the P═S moiety are irreversible inhibitors of CYP. While the focus of research on activation of OPs has centered on oxon formation via CYP-mediated oxidative desulfuration, since the latter are potent inhibitors of acetylcholinesterase, the inhibition of CYP is based on the release of highly reactive atomic sulfur during this reaction and the subsequent interaction of this sulfur with the CYP

involved. The mechanism of this inhibition is complex since it involves reactions at more than one site in the CYP molecule. However, it is known (Neal *et al.* 1983) that at least 50% of the loss of monooxygenase activity during parathion metabolism is due to the loss of heme from the CYP isoform involved. The remaining loss of activity is probably due to interactions of atomic sulfur with cysteine residues in the CYP protein.

More recent studies, in surrogate animals, have included inhibition of 6β-testosterone hydroxylation in the rat (Murray and Butler 2004), the effect of chlorpyrifos in mice (Cometa *et al.* 2007), and the interactive toxicity of organophosphorus insecticides in neonatal (Kacham *et al.* 2006) and adult (Karanth *et al.* 2004) rats.

This knowledge has only recently been applied to the human hepatic metabolism of endogenous metabolites such as steroid hormones, the metabolism of clinical drugs, or the metabolism of other pesticides (see **Table 5** and Hodgson and Rose 2006 for additional references).

MDP compounds, such as the insecticide synergist, piperonyl butoxide, affect multiple enzyme pathways (Goldstein *et al.* 1974; Hodgson and Philpot 1974) and show a complex relationship with CYPs, acting as substrates, inducers (see Section 9.22.2.2 and Kamienski and Murphy 1971; Kinsler *et al.* 1990; Murray 2000; Philpot and Hodgson 1972), and both competitive and noncompetitive inhibitors. The MDP compound serves first as a substrate and competitive inhibitor and then, as it is metabolized, gives rise to a reactive intermediate, almost certainly a carbene (Dahl and Hodgson 1979), that interacts with the heme iron of CYP forming a stable inhibitory complex.

Pesticide interactions based on the inhibition of hepatic enzymes other than CYPs are illustrated, in the case of carboxylesterases, by studies of the inhibition of pyrethroid hydrolysis by carbaryl or chlorpyrifos oxon (Choi *et al.* 2004) and malathion hydrolysis by isomalathion and other pesticides (Buratti and Testai 2005). Tridiphane (2-(3,5-dichlorophenyl)-2-(2,2,2-trichloroethyl) oxirane) an herbicide synergist, acts by inhibiting GSTs in plants (Lamoureux and Rusness 1986). It also inhibits this enzyme in mammalian liver while simultaneously functioning as an inhibitor of CYP2B10 (Magdalou and Hammock 1987; Moreland *et al.* 1989).

9.22.2.5 Pesticides in Complex, Multienzyme Pathways

Although CYP and FMO have many substrates in common, the products may be different and have different toxicities. Moreover, CYPs, but not FMOs, are easily induced. Thus it is important to know the relative contributions of the different monooxygenases toward the same substrate. Methods used for this purpose include extrapolation from results obtained using recombinant enzymes, the use of product-specific and/or enzyme-specific substrates, or manipulation of microsomes in which isoforms of both CYP and FMO are found. This latter technique, using heat treatment to eliminate FMO and an antibody to the NADPH-CYP reductase to eliminate

Table 5 Inhibition of human hepatic phase I metabolism by pesticides

Substrate	*Enzyme*	*Inhibitor(s)*	*Reference*
Xenobiotic substrates			
Carbaryl	Liver microsomes	Chlorpyrifos	Tang *et al*. (2002)
Carbaryl	CYP2B6	Chlorpyrifos	Tang *et al*. (2002)
DEET	Liver microsomes	Chlorpyrifos	Usmani *et al*. (2002)
Fipronil	Liver microsomes	Chlorpyrifos	Joo *et al*. (2007)
Fipronil	CYP3A4	Chlorpyrifos	Joo *et al*. (2007)
Imipramine	Liver microsomes	Chlorpyrifos, azinphosphos methyl, parathion	Di Consiglio (2005)
Imipramine	CYPs 1A2, 3A4, 2C19	Chlorpyrifos, azinphosphos methyl, parathion	Di Consiglio (2005)
Nonane	Liver microsomes	Chlorpyrifos	Joo *et al*. (2007)
Nonane	CYP2B6	Chlorpyrifos	Joo *et al*. (2007)
Endogenous substrates			
Estradiol	Liver microsomes	Chlorpyrifos, fonofos, carbaryl, naphthalene	Usmani *et al*. (2005)
Estradiol	CYP1A2	Chlorpyrifos, fonofos, carbaryl, naphthalene	Usmani *et al*. (2005)
Estradiol	CYP3A4	Chlorpyrifos, fonofos, deltamethrin, permethrin	Usmani *et al*. (2005)
Testosterone	Liver microsomes	Chlorpyrifos, phorate, fonofos	Usmani *et al*. (2003)
Testosterone	CYP3A4	Chlorpyrifos	Usmani *et al*. (2003)

CYP activity, has proven most useful, particularly in the case of liver microsomes (Kinsler *et al.* 1988, 1990; Tynes and Hodgson 1983, 1985a,b).

A good example is the insecticide phorate, which undergoes a complex series of oxidations, the products of which are generally more toxic than the parent compound. FMO forms only one product, the (−)-sulfoxide, from phorate while several CYP isoforms form the (+)-sulfoxide and several additional products. Although both phorate sulfoxide isomers are substrates for further CYP oxidation, the (+)-isomer is always preferred (Levi and Hodgson 1988). The relative contribution of FMO is higher in the liver of female than of male mice. Although total oxidation is higher in the liver than in other tissues, the contribution of FMO is higher in the lung, kidney, and skin, being as high as 90% of total metabolism in kidney microsomes from female mice. By contrast, CYP is responsible for 50–70% of the total metabolism in the liver. Furthermore, the contribution of CYP in the liver is increased by prior *in vivo* treatment with CYP inducers, such as phenobarbital (Kinsler *et al.* 1988, 1990).

The pesticide naphthalene is a good example of a substrate for CYP isoforms only (i.e., it is not metabolized by FMO) that has, nevertheless, a complex phase I metabolism, with both secondary and tertiary metabolites (including 1-naphthol, 2-naphthol, trans-1,2-dihydronaphthalenediol, and 1,4-naphthoquinine) being produced by various CYP isoforms (Cho *et al.* 2007).

9.22.3 Toxicity

9.22.3.1 Pesticides as Hepatotoxicants: Noncarcinogenic Effects

Poisonings from acute exposure to single, high doses of pesticides are usually determined by neurotoxic effects, but case reports with liver damage occasionally appear in the clinical literature. One example is a recently reported case of poisoning of an Iranian rice farmer with clinical and histopathological evidence of liver toxicity caused by the chloroacetanilide herbicide butachlor (Daryani *et al.* 2007), which is consistent with known acute hepatotoxicity of alachlor and acetochlor in rats (Ashby *et al.* 1996; Heydens *et al.* 1999). The highly toxic bipyridyl herbicide paraquat, which is reduced by mitochondrial complex I to generate a radical cation (Cocheme and Murphy 2008), primarily targets lung, but also affects liver. Livers from patients and rodents after lethality from metal phosphide rodenticides exhibit hepatocellular necrosis.

Noncarcinogenic hepatotoxicity is more typically detected as a finding during histopathological assessment after subchronic or chronic exposures required for pesticide registration. In some cases, clues to mechanism of toxicity are evident from type of microscopic lesion; however, follow-up biochemical studies have been pursued infrequently. Incentive for sponsorship of mechanistic studies has increased with application of the new EPA cancer guidelines (Cohen *et al.* 2003) and, as a result, a greater understanding of effects on the hepatocyte function is occasionally available for newer pesticides. For example, vesicular fat accumulation within hepatocytes is a frequent moderate toxicity observed with xenobiotics and is attributed to suboptimal hepatic processing of lipoproteins. The pyrimidine fungicide mepanipyrim has been found to cause dysfunction of intracellular trafficking of VLDL lipoprotein (Terada *et al.* 1999).

Two other liver pathologies observed upon longer-term exposure with a sizable number of pesticides are peroxisome proliferation and porphyria. Peroxisome proliferators are a diverse group of chemicals including fibrate hypolipidemic drugs, phthalate plasticizers, perfluorinated fatty acids, and various chemical classes of herbicides. Typically, peroxisome proliferators, upon activation of nuclear receptor PPARα, cause hepatomegaly through hypertrophy, hyperplasia, and suppression of apoptosis and induce hepatic metabolic enzymes, including CYP4A isozymes active in long-chain fatty acid ω-oxidation. Although they are nonmutagens, they are rodent hepatocarcinogens. It has not been determined which of the biochemical and cellular effects are causal to rodent liver carcinogenesis or whether noncancerous effects on cholesterol metabolism are adverse (Le Jossic-Corcos *et al.* 2004). It is increasingly clear that peroxisome proliferation as a mode of action of hepatocarcinogenesis does not occur in humans and a mechanistic basis for this species specificity has recently been described (Gonzalez and Shah 2008). Herbicides found to be rodent peroxisome proliferators include dicamba, lactofen, tridiphane, and the phenoxy acetic and propanoic acids, 2,4-D, diclofop, and fluazifop (Kostka *et al.* 2002).

Liver porphyria is a symptom of the human disease porphyria cutanea tarda, an inherited deficiency in uroporphyrinogen decarboxylase (UROD)

of the heme biosynthesis pathway. A similar condition results experimentally in rodents upon treatment with polyhalogenated aromatic hydrocarbons, including the discontinued fungicide hexachlorobenzene (HCB). Contemporary interest in health effects of ecological HCB residues exists for this persistent organic pollutant. HCB has been shown to modify UROD from treated rat liver such that production of coproporphyrinogen is reduced by half (Chaufan *et al.* 2005). That similar effects occur in humans is suggested by higher mean urinary excretion of coproporphyrins observed for workers employed in the manufacture of the wood preservative pentachlorophenol (PCP) (Hryhorczuk *et al.* 1998). The herbicides oxadiazinon and the nitrodiphenyl ether fomesafen inhibit the more distal protoporphyrinogen oxidase of the heme synthesis pathway to cause a similar outcome (Krijt *et al.* 2003).

Biochemically, numerous pesticides act by producing oxidative stress in the liver causing damage to accrue with continuous challenge until various pathological lesions are evident. Some redox reactions couple directly with endogenous partners within the hepatocyte, like the bipyridyl and nitrophenol herbicides, while others may act indirectly by chronic induction of oxidative enzymes whose reaction cycles allow some leakage of reactive oxygen species. Pesticides with this mode of action can be recognized from their induction of a signature panel of adaptive gene products. Expression of these genes is often mediated by transcriptional activation of their upstream ARE upon binding to Nrf2, whose translocation to the nucleus is enabled by oxidant inactivation of the cytoplasmic docker Keap. Inability of PCP to induce the protective enzyme NAD(P):quinone oxidoreductase 1 in livers of *nrf*2-deficient mice (Umemura *et al.* 2006) results from such a mechanism.

The availability of human hepatocytes has enabled studies to be made of the hepatocytotoxicity of pesticides (Das *et al.* 2006, 2008a,b). Using adenylate kinase, caspase-3/7, and the trypan blue exclusion assay as measures of apoptosis and/or necrosis, fipronil, the pyrethroids deltamethrin and permethrin, chlorpyrifos, and DEET have all been shown to be hepatocytotoxic with fipronil as the most active. Cytotoxicity in cryopreserved human hepatocytes is seen with chloroacetanilide herbicides (Kale *et al.* 2008) and in HepG2 cells (Miranda and Meyer 2007) so it is clear that these cells will be of greater utility in the future.

9.22.3.2 Pesticides as Hepatocarcinogens

Epidemiological studies have implicated pesticides as one class of environmental agents contributing to human cancer, although usually at a marginal level of significance (Alavanja *et al.* 2005). In contrast, a relatively large number of chemicals test positive in the 2-year rodent bioassay, with liver being the most frequently affected (Gold *et al.* 2001). However, recent emphasis on mode of action of carcinogenicity has refined interpretation of the bioassay results to augment simple incidence data in rodents with feasibility estimates in humans. This is illustrated by the organochlorine pesticide dieldrin for which carcinogenicity in mouse liver is now understood to require disposition of the chemical in amounts able to cause an accumulation of oxidant-mediated faults. Further, modeling of dieldrin disposition in human liver from worst-case exposure scenarios does not predict comparable levels (Stevenson *et al.* 1999). This parallels the lack of elevated liver cancer incidence decades after occupational exposure to dieldrin during production, as actually quantitated using blood levels collected during exposure (van Amelsvoort *et al.* 2009).

Similar information on the human cancer effects of a variety of pesticides can be anticipated from the Agricultural Health Study. Incidence data for about 20 cancer sites are now available for comparison to historical cancer rates derived from registries maintained by enrollees' state of residence. Specific pesticide use and length of time used were classified as exposure metrics from self-reporting at time of enrollment and ~50 000 nonurban pesticide applicators have enrolled. After the ~6–8 years that have passed since enrollment, incidence rates for all cancers collectively are comparable for pesticide applicators and their reference group (Alavanja *et al.* 2005). Rates for individual sites have been reported for specific pesticides, the herbicides alachlor (Lee *et al.* 2004b), atrazine (Rusiecki *et al.* 2004), cyanazine (Lynch *et al.* 2006), dicamba (Samanic *et al.* 2006), glyphosate (De Roos *et al.* 2005), metolachlor (Rusiecki *et al.* 2006), pendimethalin (Hou *et al.* 2006), and trifluralin (Kang *et al.* 2008) and the insecticides carbaryl (Mahajan *et al.* 2007), chlorpyrofos (Lee *et al.* 2004a), diazanon (Beane Freeman *et al.* 2005), dichlorvos (Koutros *et al.* 2008), fonofos (Mahajan *et al.* 2006a), malathion (Bonner *et al.* 2007), and phorate (Mahajan *et al.* 2006b). These evaluations have suggested associations of cancers of the lymphohematopoietic system with alachlor

and fonofos, lung with diazinon, and of melanoma with carbaryl. Independent analysis of the alachlor study data concludes that this association may be overstated (Lash 2007). No significant elevations of liver cancer were determined in pesticide applicators; however, this conclusion is statistically weakened by the low incidence of cancer at this site.

Rodent liver is one of the most well-studied models of multistage, chemically induced carcinogenesis (Ito *et al.* 2000; Pitot *et al.* 1996). Chemicals have been identified that act as either the so-called initiators or promoters, as well as complete carcinogens that effect both stages. In fact, one of the first identified rat liver tumor promoters was the organochlorine pesticide DDT (Peraino *et al.* 1975). Chemical initiation involves genotoxicity to yield rare cells with latent, heritable aberrations in growth control. Promotion results from chronic, differential stimulation of growth and survival of clones of initiated cells relative to normal surrounding cells. An understanding of stage-specific mechanistic aspects has allowed development of short-term *in vitro* screening assays, such as those for *Salmonella* mutagenesis by initiators and inhibition of gap junctional communication by promoters. Another feature of rodent liver is the presence of chemically induced microscopic multicellular aggregates, the altered hepatocyte foci that are believed to be early preneoplasias (Groos *et al.* 2007). These are the end points for medium-term *in vivo* assays involving sequential application of a pulse of initiator, then extended treatment with promoter and/or hepatotoxicant (diethylnitrosoamine-partial hepatectomy model (DEN-PH)) (Ito *et al.* 2000; Laconi *et al.* 2000).

The organochlorine insecticides have frequently been shown to be hepatocarcinogens in the rodent bioassay (Smith 1991). These nonmutagenic compounds cause pleiotropic effects in liver consistent with their activity as tumor promoters. They are generally positive in the medium-term *in vivo* assays and inhibit cell–cell communication accompanied by decreased function of gap junctions (Cowles *et al.* 2007). In many cases, evidence points to metabolism-based oxidant stress from relatively high levels of liver chemical as the proximate determinant of the carcinogenic cascade. Whether it is feasible that such amounts of organochlorine pesticides could accumulate in human liver is questionable, as discussed above for dieldrin (Stevenson *et al.* 1999; van Amelsvoort *et al.* 2009).

Evidence for rodent hepatocarcinogenicity for pesticides of other use or chemical classes is less frequent than that for the organochlorine pesticides. Rodent oncology test results can be found by reviewing fact sheets for currently used active ingredients or the IRIS database for historical information. Both are available from the U.S. Environmental Protection Agency (USEPA). In general, members of the organophosphate, carbamate, and pyrethroid insecticide classes have given negative results, with the exception of tetrachlorvinphos in mice (Woo and Arcos 1989). There is some evidence for tumor-promoting activity of some older pyrethroids from the medium-term *in vivo* assay (Hemming *et al.* 1993). Fenvalerate registrations in the United States have been recently canceled (USEPA 2008) and its use has been replaced with the noncarcinogen esfenvalerate. Cypermethrin has tested negative in the rodent bioassays conducted for its registration. Of the ~70 entries on the EPA list of new active ingredients with actions from 2000 to date, health effect summaries for nine include descriptions of malignant cancers in livers of either male or female rats or mice. These are the herbicide fluthiacet-methyl; fungicides benthiavalicarb-isopropyl, epoxiconazole, fluazinam, metconazole, metrafenone, and tetraconazole; and insecticides, metofluthrin and pymetrozine. Of importance is the lack of rodent hepatocarcinogenicity for the newer phenyl and benzoylurea herbicides in this list in contrast to previously described tumor promoter activity of older members of this group in the medium-term *in vivo* assay.

9.22.3.3 Pesticides as Modifiers of Hepatotoxicity

Xenobiotics in general can have profound effects on the hepatotoxicity of other chemicals both at the acute and at the chronic level. The simplest interaction would result from additive effects of pesticide hepatotoxicants. Theoretically, this could be the basis for the cumulative risk assessment provision of the Food Quality Protection Act; however, hepatotoxicity data has yet to define a common mechanism group for this purpose. As reviewed above, interactive effects of pesticides are more frequently related to their ability to act as inducers or inhibitors of xenobiotic-metabolizing enzymes (Levi and Hodgson 2001; Rose and Hodgson 2001). As such, they can be predicted to participate in interactions analogous to drug–drug interactions, some of which lead to acute liver damage. The ability of grapefruit juice consumed at dietary levels to effect adverse

responses of therapeutic levels of CYP3A4-metabolized drugs (Kane and Lipsky 2000) demonstrates that the pharmacokinetics of drugs can be altered by nondrugs encountered in much lower amounts.

For the toxic effects of chemicals that are known clinically to involve the liver, it is not clear whether pesticide exposures have a significant impact. Despite these uncertainties there are several examples of pesticides having an effect on the potency of other hepatotoxicants in experimental animals. One of the most dramatic has been the 70-fold sensitization to lethality from carbon tetrachloride hepatotoxicity induced by the cyclodiene insecticide chlordecone. This phenomenon is structurally specific and unrelated to CYP induction since the congener mirex, a strong inducer, is ineffective. Rather, a chlordecone impairment of the ability of liver to promptly regenerate after CCl_4-induced hepatocellular necrosis appears to account for this interaction (Dalu and Mehendale 1996). Further studies have extended this relationship to other chemical pairs affecting liver, and also to other tissues (Soni and Mehendale 1998).

Alterations in hepatic intermediary metabolism of carbohydrates and lipids would also be predicted from pesticide inhibition of catabolic and anabolic enzymes. For example, cholinergic innervation of liver (Xue *et al.* 2000) and neuronal-type acetylcholinesterase activity (Perelman *et al.* 1990) are possibly relevant to variations in liver glycogen content in animals treated with organophosphate insecticides (Goel *et al.* 2006; Rezg *et al.* 2006). Further, cross talk of pesticide-activated nuclear receptors with transcriptional regulators of intermediary metabolism would be expected to mediate interactive effects. These types of issues have recently been explored with prototype chemicals (Konno *et al.* 2008), but relevance to pesticide effects have yet to be systematically addressed.

9.22.4 Conclusions

Knowledge of the interactions of pesticides and liver xenobiotic-metabolizing enzymes, as well as the mechanisms of carcinogenic and noncarcinogenic pesticide hepatotoxicity, have advanced considerably since the previous edition. In large part, due to the ready availability of recombinant enzymes, information is now available on isoform specificity, not only in pesticide metabolism, but also in induction and inhibition by pesticides although much more needs to be done to obtain the complete picture needed to advance toxicokinetics and risk assessment, and to contribute to systems biology. Human studies, although still too few in the area of pesticide toxicity, are now possible through the availability of recombinant enzymes, human hepatocytes, and human cell fractions.

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