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Metabolism of Pesticides by Human Cytochrome P450 Enzymes *In Vitro* – A Survey

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1. Introduction

Cytochrome P450 enzymes (CYPs) are active in the metabolism of wide variety of xenobiotics. The investigation of the contributions of human CYPs in pesticides metabolism, especially insecticides, is still growing. One of the background tools to facilitate this task is by sorting the contribution of each human CYP isoform in the metabolism of pesticides. This paper attempts to provide a comprehensive literature survey on the role of human hepatic CYPs such as human CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 and CYP3A7 in pesticides biotransformation in vitro as well as to sort the reactions mediated. Based on relevant publications identified by searching databases from 1995 through 2011, more than 400 metabolic reactions were reported to be mediated at least in part by human CYPs in vitro. Some information on older papers was obtained from previous literature surveys compiled by Hodgson 2001 & 2003. Finally, we give brief insight into potential modulations and consequences of human CYP genes – pesticides interactions.

2. Xenobiotic biotransformation

Xenobiotic biotransformation is the process by which lipophilic foreign compounds are metabolized through enzymatic catalysis to hydrophilic metabolites that are eliminated directly or after conjugation with endogenous cofactors via renal or biliary excretion. These metabolic enzymes are divided into two groups, Phase I and Phase II enzymes (Rendic and Di Carlo, 1997; Oesch et al. 2000). Phase I reactions are mediated primarily by cytochrome P450 family of enzymes, but other enzymes (e.g. flavin monooxygenases, peroxidases, amine oxidases, dehydrogenases, xanthine oxidases) also catalyze oxidation of certain functional groups. In addition to the oxidative reactions there are different types of

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hydrolytic reactions catalysed by enzymes like carboxylesterases and epoxide hydrolases (Low, 1998; Hodgson and Goldstein, 2001; Parkinson, 2001).

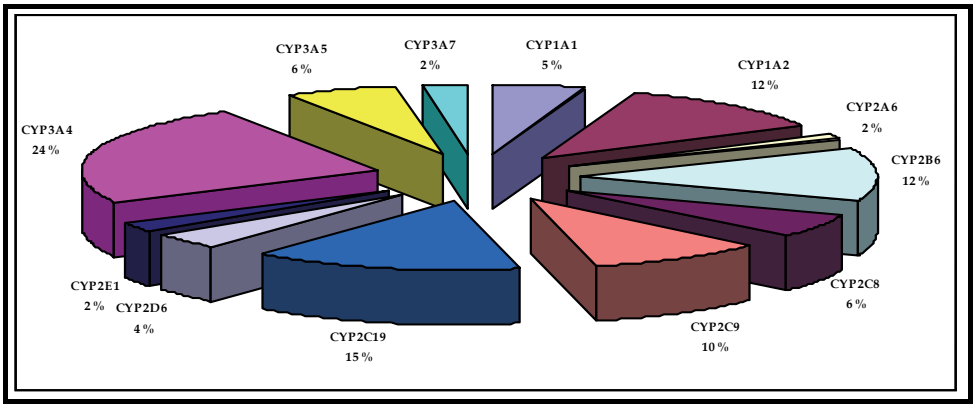

Fig. 1. The percentage of human recombinant cytochrome P450 isoforms involved in pesticides metabolism. 63 compounds (36 insecticides; 14 fungicides; 10 herbicides; 2 plant growth regulators and a biocide agent) were metabolized at least in part by one or more human enzymes yielded 495 metabolic reactions.

Phase I products are not usually eliminated rapidly, but undergo a subsequent reaction in which an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid combines with the existing or newly added or exposed functional group to form a highly polar conjugate to make them more easily excreted (LeBlanc and Dauterman, 2001; Rose and Hodgson, 2004; Zamek-Gliszczynski et al. 2006).

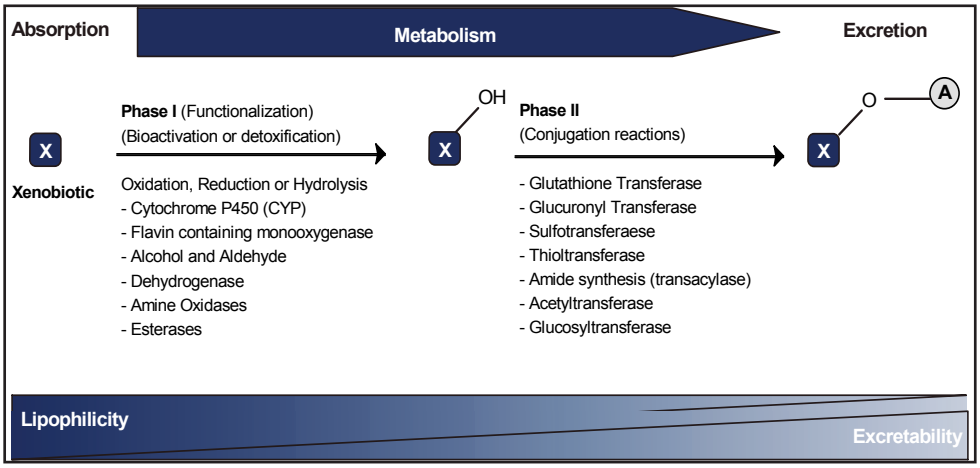

Fig. 2. Schematic description of the two main phases of drug metabolism. In general, a parent compound is converted into an intermediate metabolite which is then conjugated, but metabolism may involve only one of these reactions. Some metabolites are more toxic than the parent compound (Ahokas and Pelkonen, 2007; Liska et al. 2006).

3. Cytochrome P450 enzyme system

3.1 Nomenclature, location and microsomal preparation

P450 enzymes are categorized into families and subfamilies by their sequence similarities. The human genomes comprise 57 CYP genes and about the same numbers of pseudogenes, which are grouped according to their sequence similarity into 18 families and 44 subfamilies. The web site, http://drnelson.utmem.edu/CytochromeP450.html, contains more detailed classification related to the cytochrome P450 metabolizing enzymes. The CYP enzymes in the families 1-3 are active in the metabolism of a wide variety of xenobiotics including drugs (Rendic and Di Carlo, 1997; Pelkonen et al. 2005; Zanger et al. 2008). CYPs are found in high concentration in the liver, but are present in a variety of other tissues, including lung, kidney, the gastrointestinal tract, nasal mucosa, skin and brain (Lawton et al. 1990; Hjelle et al. 1986; Tremaine et al. 1985; Dutcher and Boyd, 1979; Peters and Kremers, 1989; Adams et al. 1991; Eriksson and Brittebo, 1991; Khan et al. 1989; Dhawan et al. 1990; Bergh and Strobel, 1992) and located primarily in the endoplasmic reticulum.

Microsomes can be prepared easily from frozen liver tissue, and enzymatic activities are stable during prolonged storage (Beaune et al. 1986; Pearce et al. 1996; Yamazaki et al. 1997). Microsomes consist of vesicles of the hepatocyte endoplasmic reticulum and are prepared by standard differential ultracentrifugation (Pelkonen et al. 1974). Microsomes are derived from the endoplasmic reticulum as a result of tissue homogenization and are isolated by two centrifugation steps. The tissues are typically homogenized in buffer and centrifuged at 10.000g for 20 minutes, the resulting supernatant, referred to as S9 fraction, can be used in studies where both microsomal and cytosolic enzymes are needed. S9 fraction is centrifuged at 100.000g for 60 minutes to yield the microsomal pellets and a cytosolic supernatant. The pellet is typically re-suspended in a volume of buffer and stored at -70º C (Figure 3) (Testa and Krämer, 2005).

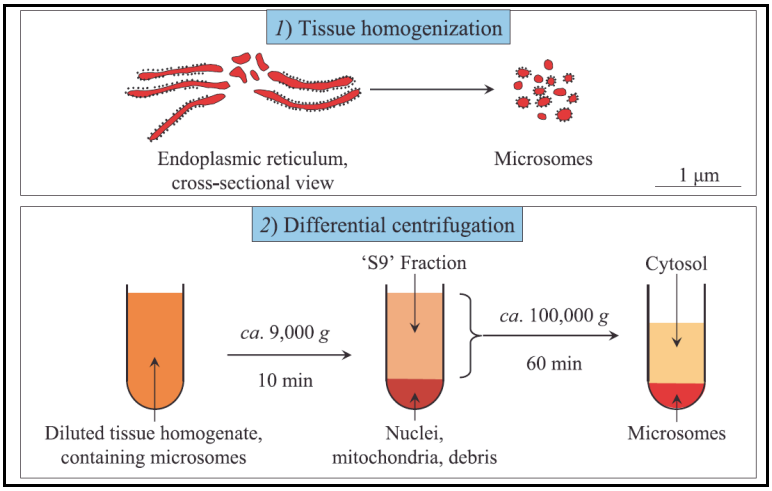

Fig. 3. A simplified scheme of the preparation of microsomes (Testa and Krämer, 2006).
Testa and Krämer: The biochemistry of drug metabolism - an introduction part 1. Principals and overview. Chemistry & Biodiversity. 2005, 3, 1053-1101; © Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Microsomes have many advantages including easy adaptation to higher throughput assays, easy preparation and use, good stability during storage, high CYP concentration and high rate of metabolite turnover. (Pelkonen et al. 2005; Brandon et al. 2003; Ekins et al. 1999; Ekins et al. 2000; Pelkonen and Raunio, 2005).

3.2 Function

CYP oxidation reactions involve a complex series of steps. The initial step involves the binding of a substrate to oxidized CYP, followed by a one-electron reduction catalyzed by NADPH cytochrome P450 reductase to form a reduced cytochrome-substrate complex. The next several steps involve interaction with molecular oxygen, the acceptance of the second electron from NADPH cytochrome b5 reductase, followed by subsequent release of water and the oxygenated product of the reaction. This reaction sequence results in the addition of one oxygen atom to the substrate, while the other atom is reduced to water (Parkinson, 2001; Rose and Hodgson, 2004; Guengerich, 2001) (figure 3).

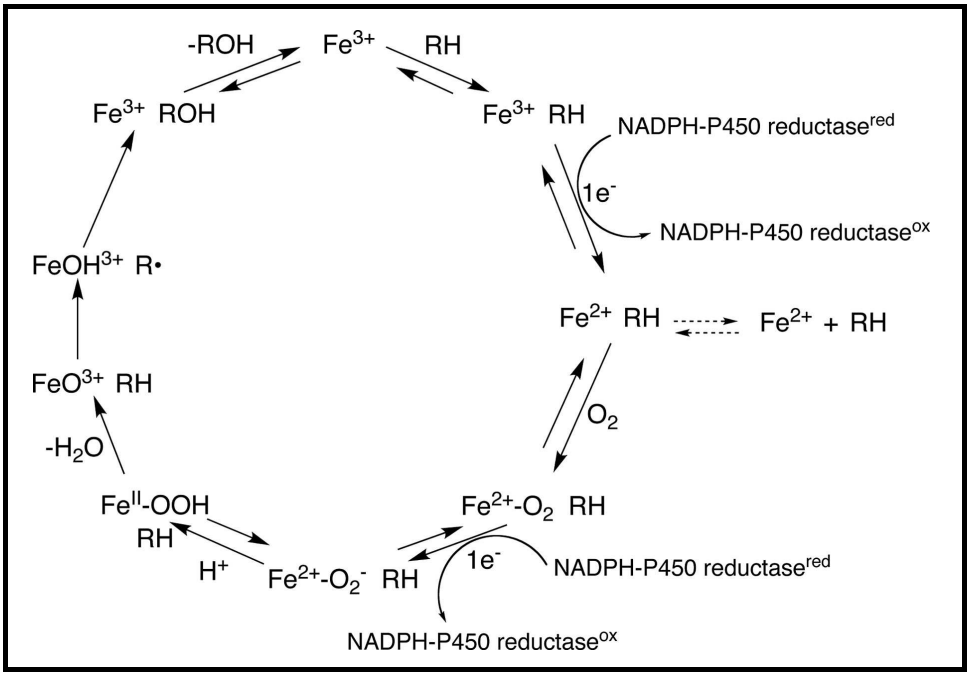

Fig. 4. Generalized P450 catalytic cycle (Sohl et al. 2008) (Sohl et al. J. Biol. Chem. 2008).

4. *In vitro* approaches

In vitro approaches to characterize metabolic fate for human clearance predication have become more frequent with the increase in the availability of human-derived materials. All

models have certain advantages and disadvantages, but the common advantage to these approaches is the reduction of the complexity of the study system. In vitro model range from simple to more complex systems: individual enzymes, subcellular fractions, cellular systems, liver slices and whole organ, respectively. However, the use of in vitro models is always a compromise between convenience and relevance. Different in vitro models and their advantages and disadvantages have been described previously (Pelkonen et al. 2005; Brandon et al. 2003; Pelkonen and Raunio, 2005; Pelkonen and Turpeinen, 2007).

5. Identification of the individual CYP enzyme(s) involved in the metabolism of a xenobiotic

To understand some of the factors related to xenobiotic metabolism that can influence the achievement of these aims, there are several important points to consider such as determination of the metabolic stability of the compound, identification of reactive metabolites, evaluation of the variation between species, identification of human CYPs and their isoforms involved in the activation or detoxification, evaluation of the variation between individuals, identification of individuals and subpopulations at increased risk and finally overall improvement of the process of human risk assessment.

Basically the identification of the individual CYP enzyme(s) involved in the metabolism of a xenobiotic is necessary for in vitro – in vivo extrapolation and prediction if the results of the metabolic stability and metabolic routes in human in vitro systems indicate that CYP enzymes contribute significantly to the metabolism of a xenobiotic. Due to the broad substrate specificity of CYP enzymes, it is possible for more than one enzyme to be involved in the metabolism of a single compound.

In vitro methods have been established to determine which CYP isoform(s) is (are) involved in the metabolism of a xenobiotic (Pelkonen et al. 2005; Pelkonen and Raunio, 2005). The identification could be achieved by different approaches such as *cDNA*-expressed enzymes, correlation studies, inhibition studies with CYP-selective chemical inhibitors and specific antibodies and inhibition of CYP enzymes.

5.1 *cDNA*-expressed enzymes

The availability of a full panel of recombinant enzymes covering the major human liver CYPs allows a direct approach for assaying the metabolism of a compound by incubation with the isolated isoforms. This can be done by following substrate consumption or product formation by each isoform using the same analytical methods as for human liver microsomes-based assays (Reponen et al. 2010). The biotransformation of a xenobiotic by a single CYP does not necessarily mean its participation in the reaction in vivo. The relative roles of individual CYPs cannot be quantitatively estimated using this approach due to the interindividual variation in the levels of individual active CYPs in the liver (Guengerich, 1999; Guengerich, 1995). However, cDNA-expressed CYPs are well suited for isozyme identification in a high-throughput screening format (White, 2000). The relative importance of individual isoform to in vivo clearance is dependent upon the relative abundance of each isoform. When taking into account the average composition of human hepatic CYPs, an approximate prediction of the participation of any CYP enzyme in the whole liver activity can be achieved (Rodrigues, 1999; Rostami-Hodjegan and Tucker, 2007).

5.2 Correlation studies

Using a bank of "phenotyped" liver microsomes, correlation analysis could be performed. Correlation analysis involves measuring the rate of xenobiotic metabolism by several liver samples from individual humans and correlating reaction rates with the level of activity of the individual CYP enzymes in the same microsomal samples. If there are a sufficient number of individual samples (at least ten), the correlation plot would give the information needed for the evaluation of the participating CYPs. The higher the correlation between the activities, the larger the probability that the respective CYP enzyme is responsible for the metabolism of the xenobiotic. Another approach is to correlate the levels of an individual CYP determined by Western blot analysis against the metabolic activity (Beaune et al. 1986; Brandon et al. 2003; Berthou et al. 1994; Guengerich, 1995; Jacolot et al. 1991; Wolkers et al. 1998).

5.3 Inhibition studies with CYP-selective chemical inhibitors and specific antibodies

Pooled human liver microsomes or individual liver microsomal samples should be used to examine the effect of CYP-selective chemical inhibitors or selective inhibitory antibodies. Antibody inhibition involves an evaluation of the effects of inhibitory antibodies against selective CYP enzymes on the metabolism of a xenobiotic in human liver microsomes. Chemical inhibition involves an evaluation of the effects of known CYP enzyme inhibitors on the metabolism of a xenobiotic. Several compounds have been characterized for their inhibitory potency against different CYPs; for example, furafylline is perhaps the most potent and selective inhibitor of CYP1A2, tranylcypromine of CYP2A6, thiotepa and ticlopidine of CYP2B6, trimethoprim and sulfaphenazole are selective inhibitors of CYP2C8 and CYP2C9, respectively, fluconazole may be used for CYP2C19, quinidine is a commonly used in vitro diagnostic inhibitor of CYP2D6 activity, pyridine and disulfiram of CYP2E1, and ketoconazole and itraconazole are among many potent and relatively selective inhibitors of CYP3A4 often used in vitro and in vivo as diagnostic inhibitors (Rendic and Di Carlo, 1997; Pelkonen et al. 2005; Pelkonen and Raunio, 2005; Bourrie et al. 1996; Clarke et al. 1994; Nebert and Russell, 2002; Pelkonen et al. 2008; Schmider et al. 1995; Sesardic et al. 1990).

5.4 Inhibition of CYP enzymes

Testing the inhibitory interactions of a xenobiotic on CYP-specific model activity in human liver microsomes in vitro provides information about the affinity of the compound for CYP enzymes (Pelkonen and Raunio, 2005). The type of CYP inhibition can be either irreversible (mechanism-based inhibition) or reversible. Irreversible inhibition requires biotransformation of the inhibitor, while reversible inhibition can take place directly, without metabolism. Reversible inhibition is the most common type of enzyme inhibition and can be further divided into competitive, noncompetitive, uncompetitive, and mixed-type inhibition (Pelkonen et al. 2008). The inhibitory interactions of a xenobiotic on CYP enzymes can be tested by co-incubating a series of dilutions of a xenobiotic with a reaction mixture containing single or multiple substrates. In the single substrate assay, traditionally CYP interaction studies are performed using specific assays for each CYP isoform. A decrease in probe metabolite formation produced by inhibition is usually analyzed by LC-UV, LC-MS or fluorometry. In the cocktail assay, several CYP-selective probes are incubated with human liver microsomes and analyzed by LC-MS-MS (Tolonen et al. 2007; Turpeinen et al. 2006; Turpeinen et al. 2005; Tolonen et al. 2005).

6. Pesticides reported to be metabolized at least in part by certain human cytochrome P450

During the recent years, a large number of papers have been published on the activities of human CYPs involved in the metabolism of pesticides. Human CYPs involved in metabolism of pesticides and related compounds were listed and updated previously several years ago by Hodgson 2001 & 2003 (Hodgson, 2001; 2003). Abbreviations used in the coming tables are listed in table 1. The updated human CYPs and their isoforms catalyzing pesticides biotransformation in addition to reactions detection methods are listed below in tables containing the primary CYP-specific information (Tables 2 to 13). Additional summary table contains information classified according to individual metabolic reactions and chemical classes of pesticides (Table 14).

Chemical class	Abb.	Pesticide type	Abb.	Detection method	Abb.
Acylalanine	AcA	Algicide	A.	Acetylcholine esterase inhibition	AChE inh.
Carbamates	CA	Biocide agent	B. A.	Electron capture detector	ECD
Chloroacetamide	ChAc	Biocide	B.	Gas chromatography	GC
Chlorinated cyclodiene	CCD	Fungicide	F.	Liquid chromatography	LC
Conazole	CZ	Herbicide	H.	Mass spectrometry	MS
Neonicotinoid	NC	Insect repellent	I. R.	Nuclear magnetic resonance	NMR
Organochlorine	OC	Insecticide	I.	Photo Diode Array Detector	PDA
Organophosphorus	OP	Molluscicide	M.	Thin layer chromatography	TLC
Organotin	OT	Plant growth regulator	PGR.	Ultraviolet detector	UV
Oxathiin	OX				
Phenyl pyrazole	PP				
pyrethroid	PY				
phenyl urea	PU				
Triazine	TA				
Triazole	TriA				

Table 1. Abbreviations

6.1 CYP1A1

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Ametryne	TA	H.	N-Deethylation N-Deisopropylation Sulfoxidation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deethylation N-Deisopropylation	LC-UV	Lang et al. 1997
				LC/PDA & LC-MS	Joo et al. 2010
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS	Abass et al. 2010
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

DEET		I. R.	Aromatic methyl oxidation	LC-UV	Usmani et al. 2002
Dimethoate	OP	I.	Desulfuration	AChE inhibition	Buratti and Testai, 2007
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Fenthion	OP	I.	Sulfoxidation	LC-UV	Leoni et al. 2008
Furametpyr	OX	F.	N-Demethylation	TLC, NMR, MS	Nagahori et al. 2000
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Terbuthylazine	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
Terbutryne	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
Terbutryne	TA	H.	Sulfoxidation	LC-UV	Lang et al. 1997
τ-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 2. Pesticides reported to be metabolized at least in part by human CYP1A1.

6.2 CYP1A2

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Ametryne	TA	H.	N-Deethylation N-Deisopropylation Sulfoxidation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deethylation N-Deisopropylation	LC-UV	Lang et al. 1997
				LC/PDA & LC-MS	Joo et al. 2010
Azinophos methyl	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbofuran	CA	I.	Ring oxidation	LC-UV	Usmani et al. 2004a
Carbosulfan	CA	I.	N-S cleavage	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration	AChE Inh., LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Tang et al. 2001; Foxenberg et al. 2007; Mutch and Williams, 2006
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Cypermethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Diazinon	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Mutch and Williams, 2006; Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai, 2007
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c

Fenthion	OP	I.	Desulfuration Sulfoxidation	LC-UV	Leoni et al. 2008
Furametpyr	OX	F.	N-Demethylation	TLC, NMR & MS	Nagahori et al. 2000
Imidacloprid	NC	I.	Nitroimine reduction	TLC	Schulz-Jander and Casida, 2002
Malathion	OP	I.	Desulfuration	AChE Inh.	Buratti et al. 2005
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Methoxychlor	OC	I.	O-Demethylation	TLC	Stresser and Kupfer, 1998
Parathion	OP	I.	Desulfuration	AChE Inh., LC-UV	Buratti et al. 2002
Parathion	OP	I.	Desulfuration	AChE Inh.	Sams et al. 2000
			Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Mutch and Williams, 2006; Mutch et al. 2003; Mutch et al. 1999; Butler and Murray, 1997
Phorate	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Terbuthylazine	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
Terbutryne	TA	H.	N-Deethylation Sulfoxidation	LC-UV	Lang et al. 1997
τ-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 3. Pesticides reported to be metabolized at least in part by human CYP1A2.

6.3 CYP2A6

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Carbaryl	CA	I.	Aromatic hydroxyl-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbosulfan	CA	I.	N-S cleavage	LC-MS	Abass et al. 2010
DEET		I. R.	N-Deethylation	LC-UV	Usmani et al. 2002
Diazinon	OP	I.	Desulfuration Dearylation	LC-UV	Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai, 2007
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Imidacloprid	NC	I.	Imidazolidine oxidation	TLC	Schulz-Jander and Casida, 2002

Table 4. Pesticides reported to be metabolized at least in part by human CYP2A6.

6.4 CYP2B6

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Acetachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Alachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Ametryne	TA	H.	Sulfoxidation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deisopropylation	LC-UV	Lang et al. 1997
				LC/PDA & LC-MS	Joo et al. 2010
Azinophos methyl	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Butachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Tang et al. 2001; Foxenberg et al. 2007; Mutch and Williams 2006; Croom et al. 2010
DEET		I. R.	Aromatic methyloxidation	LC-UV	Usmani et al. 2002
Diazinon	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai 2007
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Endosulfan-α	CCD	I.	Sulfoxidation	LC-UV	Casabar et al. 2006
				GC-ECD	Lee et al. 2006
Imidacloprid	NC	I.	Nitroimine reduction	TLC	Schulz-Jander and Casida 2002
Fenthion	OP	I.	Desulfuration Sulfoxidation	LC-UV	Leoni et al. 2008
Malathion	OP	I.	Desulfuration	AChE Inh.	Buratti et al. 2005
Metachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Metalaxyl	AcA	F.	O-Demethylation Lactone formation	LC-MS	Abass et al. 2007b
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Methoxychlor	OC	I.	O-Demethylation	TLC	Stresser and Kupfer

					1998
Parathion	OP	I.	Desulfuration	AChE Inh. LC-UV	Buratti et al. 2002
				AChE Inh.	Sams et al. 2000
			Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2003; Mutch et al. 1999; Butler and Murray 1997
Phorate	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Profenofos	OP	I.	Hydroxypropylation Desthiopropylation	LC-MS	Abass et al. 2007a
Terbutryne	TA	H.	Sulfoxidation	LC-UV	Lang et al. 1997
triadimefon	TriA	F.	t-butyl group metabolism	LC-UV	Barton et al. 2006
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 5. Pesticides reported to be metabolized at least in part by human CYP2B6.

6.5 CYP2C8

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Ametryne	TA	H.	N-Deisopropylation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deisopropylation	LC/PDA & LC-MS	Joo et al. 2010
Bifenthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbosulfan	CA	I.	N-S cleavage	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Cypermethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Deltamethrin	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Diazinon	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai 2007
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Esfenvalerate	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Mutch et al. 2003
Resmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

S-Bioallethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
τ-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 6. Pesticides reported to be metabolized at least in part by human CYP2C8.

6.6 CYP2C9

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Ametryne	TA	H.	N-Deisopropylation Sulfoxidation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deisopropylation	LC/PDA & LC-MS	Joo et al. 2010
Bifenthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Chlorpyrifos	OP	I.	Desulfuration Dearylation	LC-UV	Tang et al. 2001; Croom et al. 2010
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Cypermethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Diazinon	OP	I.	Desulfuration Dearylation	LC-UV	Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai 2007
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Endosulfan-α	CCD	I.	Sulfoxidation	LC-UV	Casabar et al. 2006
Esfenvalerate	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Fenthion	OP	I.	Desulfuration Sulfoxidation	LC-UV	Leoni et al. 2008
Imidacloprid	NC	I.	Imidazolidine oxidation	TLC	Schulz-Jander and Casida 2002
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Methoxychlor	OC	I.	O-Demethylation	TLC	Stresser and Kupfer 1998
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007
Phorate	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Resmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
S-Bioallethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
τ-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Tributyltin	OT	B. A.	Dealkylation	GC	Ohhira et al. 2006
Triphenyltin	OT	F.; A.; M.	Dearylation	GC	Ohhira et al. 2006
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 7. Pesticides reported to be metabolized at least in part by human CYP2C9.

6.7 CYP2C19

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Ametryne	TA	H.	N-Deethylation N-Deisopropylation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deisopropylation N-Deethylation	LC-UV LC-UV	Lang et al. 1997
				LC/PDA & LC-MS	Joo et al. 2010
Azinophos methyl	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002
Bifenthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbofuran	CA	I.	Ring oxidation	LC-UV	Usmani et al. 2004a
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Tang et al. 2001; Foxenberg et al. 2007; Mutch and Williams 2006; Croom et al. 2010
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Cypermethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
DEET		I. R.	N-Deethylation	LC-UV	Usmani et al. 2002
Deltamethrin	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Diazinon	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002
			Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai 2007
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c

Endosulfan-α	CCD	I.	Sulfoxidation	LC-UV	Casabar et al. 2006
Esfenvalerate	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Fenthion	OP	I.	Desulfuration Sulfoxidation	LC-UV	Leoni et al. 2008
Fipronil	PP	I.	Sulfoxidation	LC-UV	Tang et al. 2004
Furametpyr	OX	F.	N-Demethylation	TLC NMR & MS	Nagahori et al. 2000
Imidacloprid	NC	I.	oxidation	TLC	Schulz-Jander and Casida 2002
Malathion	OP	I.	Desulfuration	AChE Inh.	Buratti et al. 2005
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Methoxychlor	OC	I.	O-Demethylation bis-O-Demethylation	TLC	Stresser and Kupfer 1998
Myclobutanil	TriA	F.	n-butyl metabolism	LC-UV	Barton et al. 2006
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2003
Parathion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002
Phorate	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Profenofos	OP	I.	Hydroxypropylation Desthiopropylation	LC-MS	Abass et al. 2007a
Resmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
S-Bioallethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Terbuthylazine	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
τ Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
triadimefon	TA	F.	t-butyl metabolism	LC-UV	Barton et al. 2006
Tributyltin	OT	B. A.	Dealkylation	GC	Ohhira et al. 2006
Triphenyltin	OT	F.; A.; M.	Dearylation	GC	Ohhira et al. 2006
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 8. Pesticides reported to be metabolized at least in part by human CYP2C19.

6.8 CYP2D6

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Atrazine	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Chlorpyrifos	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006

			Desulfuration	AChE Inh.	Sams et al. 2000
DEET		I. R.	Aromatic methyl oxidation	LC-UV	Usmani et al. 2002
Diazinon	OP	I.	Desulfuration	AChE Inh.	Sams et al. 2000
			Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Kappers et al. 2001
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Imidacloprid	NC	I.	Nitroimine reduction	TLC	Schulz-Jander and Casida 2002
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Parathion	OP	I.	Desulfuration	LC-UV	Mutch and Williams 2006; Mutch et al. 2003
				AChE Inh.	Sams et al. 2000
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b

Table 9. Pesticides reported to be metabolized at least in part by human CYP2D6.

6.9 CYP2E1

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Atrazine	TA	H.	N-Deethylation N-Deisopropylation	LC-UV	Lang et al. 1997
			N-Deisopropylation	LC/PDA & LC-MS	Joo et al. 2010
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
DEET		I. R.	Aromatic methyl oxidation	LC-UV	Usmani et al. 2002
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Imidacloprid	NC	I.	Nitroimine reduction	TLC	Schulz-Jander and Casida 2002
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Mutch et al. 2003

Table 10. Pesticides reported to be metabolized at least in part by human CYP2E1.

6.10 CYP3A4

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Acetachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Alachlor	ChAc	H.	N-Dealkoxylation Aliphatic hydroxy-lation	LC-UV	Coleman et al. 2000; Coleman et al. 1999
Ametryne	TA	H.	N-Deethylation N-Deisopropylation Sulfoxidation	LC-UV	Lang et al. 1997
Atrazine	TA	H.	N-Deethylation N-Deisopropylation	LC-UV	Lang et al. 1997
				LC/PDA & LC-MS	Joo et al. 2010
Azinophos methyl	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002
Bioresmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Butachlor	ChAc	H.	N-Dealkoxylation	LC-UV	Coleman et al. 2000
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbofuran	CA	I.	Ring oxidation	LC-UV	Usmani et al. 2004a
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration	AchE Inh. & LC-UV	Buratti et al. 2002; Sams et al. 2000; Buratti et al. 2006
			Desulfuration Dearylation	LC-UV	Tang et al. 2001; Foxenberg et al. 2007; Mutch and Williams 2006; Croom et al. 2010; Dai et al. 2001
cis-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Cypermethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
DEET		I. R.	N-Deethylation	LC-UV	Usmani et al. 2002
Diazinon	OP	I.	Desulfuration	AchE Inh. & LC-UV	Buratti et al. 2002
				AChE Inh.	Sams et al. 2000
			Desulfuration Dearylation	LC-UV	Mutch and Williams 2006; Kappers et al. 2001
Dimethoate	OP	I.	Desulfuration	AChE Inh.	Buratti and Testai 2007
Diniconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Disulfoton	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Endosulfan-α	CCD	I.	Sulfoxidation	LC-UV	Casabar et al. 2006
				GC-ECD	Lee et al. 2006
Endosulfan-β	CCD	I.	Sulfoxidation	GC-ECD	Lee et al. 2006
Epoxiconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Fenbuconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Fenthion	OP	I.	Desulfuration Sulfoxidation	LC-UV	Leoni et al. 2008
			Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Fipronil	PP	I.	Sulfoxidation	LC-UV	Tang et al. 2004

Furametpyr	OX	F.	N-Demethylation	TLC NMR & MS	Nagahori et al. 2000
Hexachlorobenzene	OC	I.	Aromatic hydroxylation	TLC NMR & MS	Mehmood et al. 1996
Hexaconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Imidacloprid	NC	I.	Imidazolidine oxidation Nitroimine reduction	TLC	Schulz-Jander and Casida 2002
Ipconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Malathion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2005; Buratti et al. 2006
Metalaxyl	AcA	F.	Ring hydroxylation Methyl hydroxylation O-Demethylation Lactone formation	LC-MS	Abass et al. 2007b
Metconazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Methiocarb	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Myclobutanil	TA	F.	n-butyl metabolism	LC-UV	Barton et al. 2006
Myclobutanil	TA	F.	Aliphatic hydroxylation	LC-MS	Mazur and Kenneke 2008
Paclobutrazole	TA	PGR	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Parathion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2002; Buratti et al. 2006
			Desulfuration	AChE Inh.	Sams et al. 2000
			Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2003; Mutch et al. 1999; Butler and Murray 1997
Pentachlorobenzene	OC	I.	Aromatic hydroxylation	TLC NMR & MS	Mehmood et al. 1996
Phorate	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Profenofos	OP	I.	Hydroxypropylation Desthiopropylation	LC-MS	Abass et al. 2007a
Propiconazole	CZ	F.	Aliphatic hydroxylation	LC-MS	Mazur and Kenneke 2008
Resmethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
S-Bioallethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b
Terbuthylazine	TA	H.	N-Deethylation	LC-UV	Lang et al. 1997
Terbutryne	TA	H.	N-Deethylation Sulfoxidation	LC-UV	Lang et al. 1997
t-Bromuconazole	CZ	F.	Aromatic hydroxylation	LC-MS	Mazur and Kenneke 2008
τ-Permethrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
triadimefon	TA	F.	t-butyl group metabolism	LC-UV	Barton et al. 2006
Tributyltin	OT	BA.	Dealkylation	GC	Ohhira et al. 2006
Triphenyltin	OT	F. A. M.	Dearylation	GC	Ohhira et al. 2006
Triticonazole	CZ	F.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
Uniconazole	CZ	PGR.	Hydroxylation	LC-MS	Mazur and Kenneke 2008
β-Cyfluthrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009
λ-Cyhalothrin	PY	I.	Oxidative metabolism	LC-MS	Scollon et al. 2009

Table 11. Pesticides reported to be metabolized at least in part by human CYP3A4.

6.11 CYP3A5

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Carbaryl	CA	I.	Aromatic hydroxy-lation Methyl Oxidation	LC-UV	Tang et al. 2002
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration Dearylation	LC-UV LC-UV	Foxenberg et al. 2007; Mutch and Williams 2006; Croom et al. 2010
			Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
DEET		I. R.	N-Deethylation	LC-UV	Usmani et al. 2002
Deltamethrin	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Diazinon	OP	I.	Desulfuration Dearylation	LC-UV	Mutch and Williams 2006
Diuron	PU	H.	N-Demethylation	LC-MS	Abass et al. 2007c
Endosulfan-α	CCD	I.	Sulfoxidation	GC-ECD	Lee et al. 2006
Endosulfan-β	CCD	I.	Sulfoxidation	GC-ECD	Lee et al. 2006
Esfenvalerate	PY	I.	Oxidative metabolism	LC-MS	Godin et al. 2007
Fenthion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Malathion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Myclobutanil	TriA	F.	n-butyl metabolism	LC-UV	Barton et al. 2006
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2003; Mutch et al. 1999
			Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Sulprofos	OP	I.	Sulfoxidation	LC-UV	Usmani et al. 2004b

Table 12. Pesticides reported to be metabolized at least in part by human CYP3A5.

6.12 CYP3A7

Pesticide	Chemical class	Type	Metabolic pathway	Detection method	Reference
Atrazine	TA	H.	N-Deisopropylation	LC/PDA & LC-MS	Joo et al. 2010
Carbosulfan	CA	I.	N-S cleavage Sulfoxidation	LC-MS	Abass et al. 2010
Chlorpyrifos	OP	I.	Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007; Croom et al. 2010
			Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Endosulfan-α	CCD	I.	Sulfoxidation	LC-UV	Casabar et al. 2006
Fenthion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Malathion	OP	I.	Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006
Parathion	OP	I.	Desulfuration Dearylation	LC-UV	Foxenberg et al. 2007
			Desulfuration	AChE Inh. & LC-UV	Buratti et al. 2006

Table 13. Pesticides reported to be metabolized at least in part by human CYP3A7.

6.13 Metabolic reactions

Table 14 contains information classified according to individual metabolic reactions and the corresponding pesticides.

Reactions	Pesticides	CYP enzymes involved at least in part
Aliphatic hydroxylation	Alachlor; myclobutanil; propiconazole	CYP3A4
	Carbaryl	CYP1A1; CYP1A2; CYP3A4
	Hexachlorobenzene; pentachlorobenzene; τ-bromuconazole	CYP3A4
Aromatic methyl oxidation	DEET	CYP2B6
bis-O-Demethylation	Methoxychlor	CYP2C18
Dealkylation	Tributyltin	CYP2C9; CYP2C18; CYP2C19; CYP3A4
Dearylation	Chlorpyrifos; diazinon	CYP1A2; CYP2A6; CYP2B6;CYP2C9; CYP2C19; CYP2D6; CYP3A4; CYP3A5
	Parathion	CYP2C19; CYP3A4; CYP2B6; CYP2C8; CYP3A5; CYP1A2;
	Triphenyltin	CYP2C9; CYP2C18; CYP2C19; CYP3A4

Desthiopropylation	Profenofos	CYP3A4; CYP2B6
Desulfuration	Azinophos methyl	CYP2C19; CYP3A4
	Chlorpyrifos	CYP2C19; CYP3A4; CYP2B6; CYP3A5; CYP2D6; CYP3A7
	Diazinon	CYP1A2; CYP2A6; CYP2B6;CYP2C9; CYP2C19; CYP2D6; CYP3A4; CYP3A5
	Dimethoate	CYP1A2; CYP3A4
	Fenthion; malathion	CYP1A2; CYP2B6; CYP3A4; CYP3A5; CYP3A7
	Parathion	CYP2C19; CYP3A4; CYP2B6; CYP2C8; CYP3A5; CYP2C8; CYP2D6
Hydroxylation	Diniconazole; epoxiconazole; fenbuconazole; hexaconazole; ipconazole; metconazole; paclobutrazole; triticonazole; uniconazole	CYP3A4
Hydroxypropylation	Profenofos	CYP2B6; CYP2C19
Imidazolidine oxidation	Imidacloprid	CYP3A4
Lactone formation	Metalaxyl	CYP2B6
Methyl Oxidation	Carbaryl	CYP1A2; CYP2B6
n-butyl side-chain metabolism	Myclobutanil	CYP2C19
N-Dealkoxylation	Acetachlor; alachlor; butachlor	CYP3A4; CYP2B6
	Metachlor	CYP2B6
N-Deethylation	Ametryn; atrazine; terbuthylazine; terbutryne	CYP1A1 CYP1A2 CYP2C19 CYP3A4
	DEET	CYP2C19
N-Deisopropylation	Ametryne; atrazine	CYP1A1; CYP1A2CYP2B6 CYP2E1 CYP2C8 CYP2C9 CYP2C19 CYP3A4, CYP3A7
N-Demethylation	Diuron	CYP1A1; CYP1A2; CYP2C19; CYP3A4
	Furametpyr	CYP1A2; CYP2C19
Nitroimine reduction	Imidacloprid	CYP3A4
N-S cleavage	Carbosulfan	CYP3A4; CYP3A5
O-Demethylation	Metalaxyl	CYP2B6
	Methoxychlor	CYP1A2; CYP2C19
Oxidative metabolism	Bifenthrin; s-bioallethrin; λ-cyhalothrin	CYP2C19
	Bioresmethrin; cypermethrin; τ -permethrin	CYP1A2; CYP2C19
	cis-permethrin; resmethrin	CYP2C9; CYP2C19
	Deltamethrin	CYP2C8; CYP2C19; CYP3A5
	Esfenvalerate	CYP2C8; CYP2C19; CYP3A5; CYP2C9
	τ-cyfluthrin	CYP2C8; CYP2C19
Ring hydroxylation	Metalaxyl	CYP3A4

Ring oxidation	Carbofuran	CYP3A4
Sulfoxidation	Ametryn	CYP1A2
	Carbosulfan	CYP1A1; CYP2B6; CYP3A5
	Disulfoton; phorate; sulprofos	CYP2C9; CYP2C18; CYP2C19
	Endosulfan-α	CYP2B6; CYP3A4
	Endosulfan-β	CYP3A4; CYP3A5
	Fenthion; methiocarb	CYP2C9; CYP2C19
	Fipronil	CYP3A4
	Terbutryne	CYP1A2; CYP3A4
t-butyl group metabolism	Triadimefon	CYP2C19

Table 14. Type of reactions catalyzed at least in part by CYPs in one or more corresponding pesticide biotransformation.

7. Induction of CYP enzymes

Induction is defined as an increase in enzyme activity associated with an increase in intracellular enzyme concentration. CYP-pesticides interactions involve either induction or inhibition of metabolizing enzymes. Many induction studies have been conducted in vitro using primary human hepatocytes, human hepatoma cell lines or cell lines derived from other human tissues (Dierickx, 1999; Delescluse et al. 2001; Coumoul et al. 2002; Sanderson et al. 2002; Wyde et al. 2003; Lemaire et al. 2004). Primary culture of hepatocyte maintain whole cell metabolism since transporters and both phase I and phase II enzymes are present. Likewise, HepaRG cells express a large panel of liver-specific genes including several CYP enzymes, which is in contrast to HepG2 cell lines. In addition to P450 enzymes, HepaRG cells have a stable expression of phase II enzymes, transporters and nuclear transcription factors over a time period of six weeks in culture (Aninat et al. 2006; Anthérieu et al. 2010; Kanebratt and Andersson, 2008; Turpeinen et al. 2009).

Both immunoblotting and reverse transcription polymerase chain reaction (RT-PCR) techniques have been applied to examine the pesticide-CYP induction (Wyde et al. 2003; Lemaire et al. 2004; Das et al. 2006; Sun et al. 2005; Johri et al. 2007; Barber et al. 2007). However, problems in tissue availability, interindividual differences, reproducibility and ethical issues preclude the efficient large-scale use of human primary hepatocytes for induction screening.

One important factor regulating the expression of drug metabolising enzymes is induction by a diverse group of endogenous and exogenous substances that bind to the nuclear receptors pregnane X receptor (PXR) or constitutive androstane receptor (CAR), thereby causing significant up-regulation of gene transcription (Pelkonen et al. 2008; Handschin and Meyer, 2003). Therefore, the development of mechanism-based test systems for induction screening, based for example on in vitro pregnane X receptor/constitutive androstane receptor activation, is currently very active, and some test systems are in use as a first step for the identification of potential inducers (Pelkonen et al. 2005; Pelkonen and Raunio, 2005).

Whereas the acute effects of exposure to high doses of pesticides are well known, the long-term effects of lower exposure levels remain controversial. The ability of chemicals to induce metabolic enzymes, including cytochrome P450 (CYP), has long been considered as one of

the most sensitive biochemical cellular responses to toxic insult (Gonzalez et al. 1993; Denison and Whitlock Jr., 1995), since it often occurs at much lower doses of the chemical than those known to cause lethal or overtly toxic effects. Assessment of inducibility of xenobiotic-metabolising enzymes by pesticides is vital for health risk assessment. Numerous pesticides are capable of inducing their own metabolism and by enzyme induction can also lead to enhanced biotransformation of other xenobiotics. Several articles on CYP gene inducibility by pesticides and other chemicals used in agriculture and public health have been published (Abass et al. 2009) and a review article dealing with CYP gene modulation by pesticides is needed.

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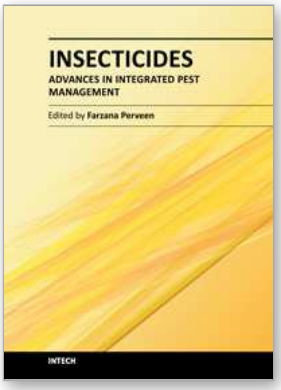

Insecticides - Advances in Integrated Pest Management

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This book contains 30 Chapters divided into 5 Sections. Section A covers integrated pest management, alternative insect control strategies, ecological impact of insecticides as well as pesticides and drugs of forensic interest. Section B is dedicated to chemical control and health risks, applications for insecticides, metabolism of pesticides by human cytochrome p450, etc. Section C provides biochemical analyses of action of chlorfluazuron, pest control effects on seed yield, chemical ecology, quality control, development of ideal insecticide, insecticide resistance, etc. Section D reviews current analytical methods, electroanalysis of insecticides, insecticide activity and secondary metabolites. Section E provides data contributing to better understanding of biological control through Bacillus sphaericus and B. thuringiensis, entomopathogenic nematodes insecticides, vector-borne disease, etc. The subject matter in this book should attract the reader's concern to support rational decisions regarding the use of pesticides.

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