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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 -70°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 I. 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 isoform 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, thiopeta 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  | Aldicarb       | A.   | Acetylcholine esterase inhibition | AChE inh. |
| Carbamates     | CA   | Carbaryl       | B.   | Electron capture detector | ECD |
| Chloroacetamide| ChAc | Herbacide      | B.   | Gas chromatography | GC |
| Chlorinated cyclohexane | CCD | Herbicide | 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.   | Ultraviolet detector | UV |
| Organotin      | OT   | Plant growth regulator | PGR. | Thin layer chromatography | TLC |
| Oxaathiin      | OX   | Neonicotinoid  | I.   | Thin layer chromatography | TLC |
| Phenyl pyrazole| PP   | Carbosulfan    | I.   | Thin layer chromatography | TLC |
| Oxathiin       | OX   | Triazine       | TA   | Thin layer chromatography | TLC |
| Phenyl pyrazole| PP   | Triazine       | TA   | Thin layer chromatography | TLC |
| Phenyl urea    | PU   | Triazine       | TA   | Thin layer chromatography | TLC |
| Phenyl pyrazole| PP   | Triazine       | TA   | Thin layer chromatography | TLC |

Table 1. Abbreviations

6.1 CYP1A1

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

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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    | LC-UV            | Lang et al. 1997 |
| Atrazine      | TA             | H.   | N-Deethylation    | LC-UV            | Lang et al. 1997 |
| Azinophos methyl | OP            | I.   | Desulfuration     | AChE Inh.       | Buratti et al. 2002 |
| Bioresmethrin | PY             | I.   | Oxidative metabolism | LC-MS          | Scollon et al. 2009 |
| Carbaryl      | CA             | I.   | Aromatic hydroxylation | LC-UV       | Tang et al. 2002 |
| Carbofuran    | CA             | I.   | N-S cleavage      | 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 |
| 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.       | Buratti et al. 2002 |
| 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 |
### Table 3. Pesticides reported to be metabolized at least in part by human CYP1A2.

| Pesticide          | Chemical class | Type | Metabolic pathway                | Detection method | Reference                      |
|-------------------|----------------|------|----------------------------------|------------------|--------------------------------|
| 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            |
| Phorate           | OP             | I.   | Sulfoxidation                    | LC-UV            | Usmani et al. 2004b            |
| Sulprofos         | OP             | I.   | Sulfoxidation                    | LC-UV            | Usmani et al. 2004b            |
| Terbutylazine     | 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 4. Pesticides reported to be metabolized at least in part by human CYP2A6.

| Pesticide          | Chemical class | Type | Metabolic pathway                | Detection method | Reference                      |
|-------------------|----------------|------|----------------------------------|------------------|--------------------------------|
| Carbaryl          | CA             | I.   | Aromatic hydroxylation 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 |
### 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               |
| Atrazine               | TA             | H.   | Sulfoxidation                    | LC-UV                 | Lang et al. 1997                  |
| Atrazine               | TA             | H.   | N-Deisopropylation               | LC-UV, LC/PDA & LC-MS | Lang et al. 1997, Joo et al. 2010 |
| Azinophos methyl       | OP             | I.   | Desulfuration                    | AChE Inh. LC-UV       | Buratti et al. 2002               |
| Bioresemethrin         | 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 hydroxylation           | LC-UV, LC/PDA & LC-MS | Lang et al. 1997, Joo et al. 2010 |
| 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; Kappens 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               |
| MCP2A                  | AcA            | 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               |
| Pesticide       | Chemical class | Type | Metabolic pathway                        | Detection method | Reference                                      |
|-----------------|----------------|------|------------------------------------------|------------------|------------------------------------------------|
| Parathion       | OP I.          |      | Desulfuration                            | AChE Inh. LC-UV  | Buratti et al. 2002                            |
|                 |                |      | Desulfuration Dearylation                | AChE Inh. LC-UV  | Sams et al. 2000                               |
| Phorate         | OP I.          |      | Desulfuration                            | LC-UV            | Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2003; Mutch et al. 1999; Butler and Murray 1997 |
| Profenofos      | OP I.          |      | Hydroxypropylation Desthiopropylation    | LC-UV            | Abass et al. 2007b                             |
| Terbutryne      | TA H.          |      | Sulfoxidation                            | LC-UV            | Lang et al. 1997a                              |
| triadimefon     | TriA F.        |      | t-butyl group metabolism Oxidative       | 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                                      |
|-----------------|----------------|------|------------------------------------------|------------------|------------------------------------------------|
| Amitrazine      | 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 hydroxylation 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                        |
| Dicuron         | 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                            |
| Pesticide            | Chemical class | Type | Metabolic pathway                  | Detection method | Reference                        |
|----------------------|----------------|------|-----------------------------------|------------------|----------------------------------|
| 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 hydroxylation Methyl Oxidation | LC-UV            | Tang et al. 2002                 |
| Chlorthalon          | OP             | I.   | Desulfuration Dearylation         | LC-UV            | Tang et al. 2001; Croom et al. 2010 |
| Chlordifen           | OP             | I.   | Desulfuration Dearylation         | LC-UV            | Kappers et al. 2001              |
| Chlorpyrifos         | OP             | I.   | Desulfuration Dearylation         | LC-UV            | Usmani et al. 2004b              |
| Cypermethrin         | 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.          | AChE Inh.        | Buratti and Testai 2007          |
| Dieldrin             | PU             | H.   | N-Demethylation                  | LC-MS            | Abass et al. 2007c               |
| Endosulfan-α         | CCD            | I.   | Sulfoxidation                     | LC-UV            | Casab 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              |
| 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           |
| 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 hydroxylation 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        |
| 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        |
| Dimethoate | OP             | I.   | Desulfuration Dearylation          | LC-UV                             | Mutch and Williams 2006; Kappers et al. 2001 |
| Disulfoton | OP             | I.   | Sulfoxidation                      | AChE Inh.                         | Buratti and Testai 2007    |
| Diuron     | PU             | H.   | N-Demethylation                    | LC-MS                             | Usmani et al. 2004b        |

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

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

| Pesticide | Chemical class | Type | Metabolic pathway | Detection method | Reference |
|-----------|----------------|------|-------------------|------------------|-----------|
| Atrazine  | TA             | H.   | N-Deethylation    | LC-UV            | Lang et al. 1997 |
| Carbaryl  | CA             | I.   | Aromatic hydroxylation Methyl Oxidation | LC-UV | Tang et al. 2002 |
| Chlorpyrifos | OP           | I.   | Desulfuration Dearylation | LC-UV | Mutch and Williams 2006 |
### Table 9. Pesticides reported to be metabolized at least in part by human CYP2D6.

| Pesticide | Chemical class | Type | Metabolic pathway | Detection method | Reference |
|-----------|----------------|------|-------------------|------------------|-----------|
| Atrazine  | TA H.          |      | N-Deethylation    | LC-UV            | Lang et al. 1997 |
|           |                |      | N-Deisopropylation|                  |           |
| Carbaryl  | CA I.          |      | Aromatic hydroxylation | LC-UV           | Tang et al. 2002 |
|           |                |      | Methyl Oxidation   |                  |           |
| 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 |
| Methiocarb | OP I.          |      | Sulfoxidation     | LC-UV            | Usmani et al. 2004b |
| Parathion | OP I.          |      | Desulfuration     |                  |           |
|           |                |      | Dearylation       |                  |           |
| Sulprofos | OP I.          |      | Sulfoxidation     | LC-UV            | Usmani et al. 2004b |

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

| Pesticide | Chemical class | Type | Metabolic pathway | Detection method | Reference |
|-----------|----------------|------|-------------------|------------------|-----------|
| Atrazine  | TA H.          |      | N-Deethylation    | LC-UV            | Lang et al. 1997 |
|           |                |      | N-Deisopropylation|                  |           |
| Carbaryl  | CA I.          |      | Aromatic hydroxylation | LC-UV           | Tang et al. 2002 |
|           |                |      | Methyl Oxidation   |                  |           |
| 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       |                  |           |
### 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            | LC-UV                             | Coleman et al. 2000; Coleman et al. 1999 |
| Ametryne          | TA             | H.   | N-Deethylolation           | LC-UV                             | Lang et al. 1997              |
| Atrazine          | TA             | H.   | N-Deethylation,            | LC-UV                             | Lang et al. 1997              |
| Azinophos methyl | OP             | I.   | Desulfuration              | AChE Inh. & LC-UV                 | Buratti et al. 2002           |
| Bioremethrin      | PY             | I.   | Oxidative metabolism      | LC-MS                             | Scollon et al. 2009           |
| Butachlor         | ChAc           | H.   | N-Dealkoxylation           | LC-UV                             | Coleman et al. 2000           |
| Carbarly          | CA             | I.   | Aromatic hydroxylation,    | LC-UV                             | Tang et al. 2002              |
| Carbosulfan       | CA             | I.   | N-S cleavage,              | 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 |
| 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-Deethylolation           | LC-UV                             | Usmani et al. 2002            |
| Diazinon          | OP             | I.   | Desulfuration              | AChE Inh. & LC-UV                 | Buratti et al. 2002           |
| Dimethoate        | OP             | I.   | Desulfuration              | AChE Inh.                         | Sams et al. 2000              |
| Diniconazole      | CZ             | F.   | Hydroxylation              | LC-MS                             | Buratti and Testai 2007       |
| Disulfoton        | PU             | H.   | N-Demethylation            | LC-MS                             | Usmani et al. 2004b           |
| Endosulfan-α      | CCD            | I.   | Sulfoxidation              | LC-UV                             | Casabar et al. 2006           |
| Endosulfan-β      | CCD            | I.   | Sulfoxidation              | GC-ECD                            | Lee et al. 2006               |
| Epoxiconazole     | CZ             | F.   | Hydroxylation              | GC-ECD                            | Lee et al. 2006               |
| Fenbuconazole     | CZ             | F.   | Hydroxylation              | LC-MS                             | Mazur and Kenneke 2008        |
| Fenthion          | OP             | I.   | Desulfuration,             | LC-UV                             | Leoni et al. 2008             |
| Fipronil          | PP             | I.   | Sulfoxidation              | AChE Inh. & LC-UV                 | Buratti et al. 2006           |
| Pesticide                | Metabolite                          | Enzyme | Method                        | Reference                          |
|-------------------------|-------------------------------------|--------|-------------------------------|-----------------------------------|
| 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       | 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, Dearylation    | AChE Inh. & LC-UV | Buratti et al. 2002; Buratti et al. 2006 |
| 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, Deshiopropylation | 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           |
| Terbutylazine           | TA H. N-Deethylation                | LC-UV  | Lang et al. 1997              |
| Terbutryn              | TA H. N-Deethylation Sulfoxidation  | LC-UV  | Lang et al. 1997              |
| t-Bromuconazole         | CZ F. Aromatic hydroxylation        | LC-MS  | Mazur and Kenneke 2008        |
| t-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 Oxidative metabolism         | LC-MS  | Mazur and Kenneke 2008        |
| β-Cyfluthrin            | PY I. Oxidative metabolism          | LC-MS  | Scollon et al. 2009           |
| α-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.
### Table 12. Pesticides reported to be metabolized at least in part by human CYP3A5.

| Pesticide       | Chemical class | Type | Metabolic pathway                        | Detection method | Reference                      |
|-----------------|----------------|------|------------------------------------------|------------------|-------------------------------|
| Carbaryl        | CA             | I.   | Aromatic hydroxylation 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         |
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 |
|                 |                |      |                         | 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    |
|                 |                |      |                         | 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; r-bromacronazol                       | CYP3A4                                 |
| Aromatic methyl oxidation| DEET                                                                      | CYP2B6                                 |
| β-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       |
| Metabolism Pathway | Insecticide | CYP Enzymes |
|--------------------|-------------|-------------|
| 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; terbutylazine; terbutryn | CYP1A1 CYP1A2 CYP2C19 CYP3A4 DEET CYP2C19 |
| N-Deisopropylation | Ametryne; atrazine | CYP1A1; CYP1A2 CYP2B6 CYP2E1 CYP2C8 CYP2C9 CYP2C19 CYP3A4 CYP3A7 |
| N-Demethylation | Diuron | CYP1A1; CYP1A2; CYP2C19; CYP3A4 |
| | Furametpyr | CYP1A2; CYP2C19 |
| Nitroimine reduction | Imidacloprid | CYP3A4 |
| N-S cleavage | Carbasulfan | CYP3A4; CYP3A5 |
| O-Demethylation | Metalaxyl | CYP2B6 |
| | Methoxychlor | CYP1A2; CYP2C19 |
| Oxidative metabolism | Bifenthrin; s-bisallethrin; λ-cyhalothrin | CYP2C19 |
| | Bioresmethrin; cypermethrin; τ-permethrin | CYP1A2; CYP2C19 |
| | cis-permethrin; resmethrin | CYP2C9; CYP2C19 |
| | Deltamethrin | CYP2C8; CYP2C19; CYP3A5 |
| | Esfenvalerate | CYP2C8; CYP2C19; CYP3A5; CYP2C9 |
| | t-cyfluthrin | CYP2C8; CYP2C19 |
| Ring hydroxylation | Metalaxyl | CYP3A4 |
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| 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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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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