Metabolism of Drugs and Other Xenobiotics

Pavel Anzenbacher,Ulrich M. Zange (Editors), John Wiley & Sons, 2012

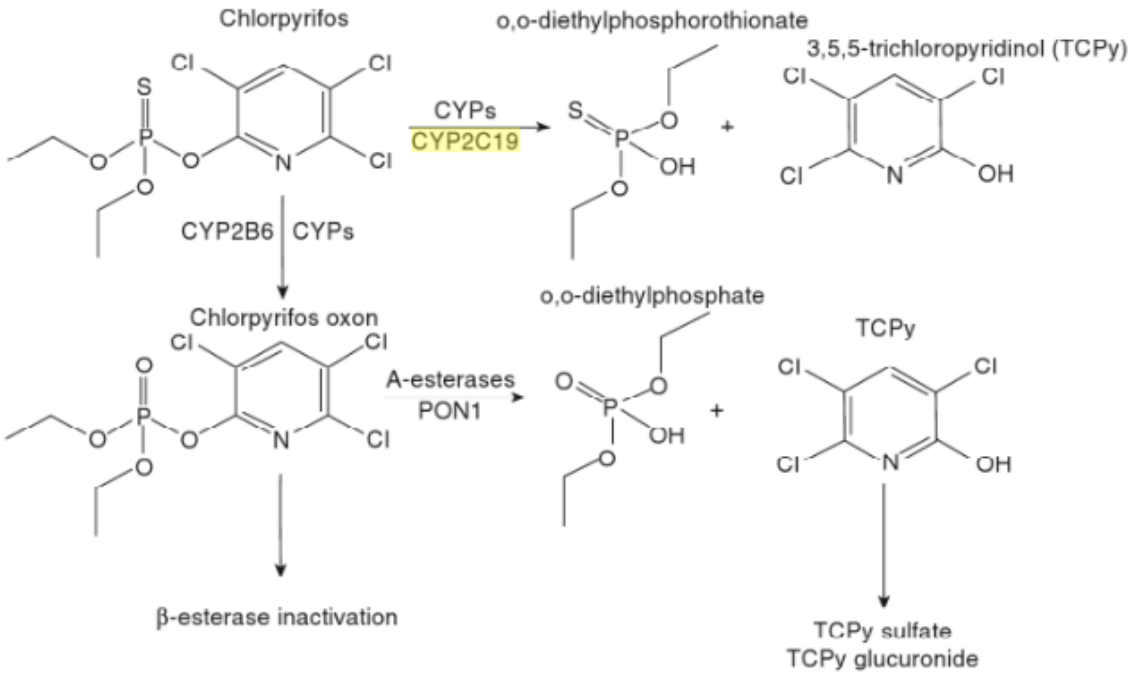

Figure 25.2 Primary human enzymes contributing to the metabolism of the organophosphate insecticide chlorpyrifos, as reported by Foxenberg *et al.* [13].

of an insecticide. For carbamate metabolism, CYP1A1, CYP1A2, CYP2B6, CYP2C19, and CYP3A4 have been identified as the primary human CYPs involved in metabolism for a variety of compounds [27–29]. Table 25.2 summarizes kinetic parameters for the metabolism of several organophosphate and carbamate insecticides from recombinant human CYP2B6, CYP2C19, and CYP3A4. For pyre-

CYP2B6, CYP2C19, and CYP3A4 are all actively involved in the metabolism of several different insecticides, but the kinetic values vary among the different CYPs (see Table 25.2). For the compounds shown in Table 25.2, CYP2B6 and CYP2C19 consistently have a lower K_m value for metabolite formation compared to CYP3A4, indicating that both CYP2B6 and CYP2C19 have a higher affinity for the different insecticide compounds. The low K_m value of CYP2B6 and CYP2C19 suggests that these CYPs play a predominate role in insecticide metabolism at low-level real-world exposures. CYP3A4 has the largest V_{max} value for metabolite formation for

Paraoxonase 1 (PON1) is a high-density lipoprotein-associated enzyme that is synthesized in the liver and secreted into the plasma where it hydrolyzes lipid peroxides. In addition to hydrolyzing lipid peroxides, PON1 has received a great deal of attention for its ability to detoxify the oxon metabolite of organophosphate insecticides [44–46]. The *in vitro* catalytic efficacy of PON1 is substrate-dependent, with activity being relatively high towards diazinon oxon, moderate towards chlorpyrifos oxon, and low towards paraoxon [47]. PON1 knockout mice are extremely sensitive to diazinon oxon and chlorpyrifos oxon, but do not show increased sensitivity to paraoxon. Intraperitoneal injection of purified PON1 into PON1 knockout mice provides protection against the toxicity of diazinon oxon and chlorpyrifos oxon, but not against paraoxon [48–50]. These *in vivo* observations support the *in vitro* observations that PON1 activity is substrate-dependent and suggest that the *in vitro* catalytic efficiency of PON1 determines the *in vivo* efficacy for detoxifying organophosphate insecticides [48].

shown to be inhibitors of certain CYPs [74]. Organophosphates, in addition to being able to inhibit CYPs, have also been shown to induce a number of CYP isoforms [75, 76]. For example, chlorpyrifos has been shown to induce CYP1A1, CYP1A2, CYP3A4, CYP1B1, and CYP2B6 mRNA *in vitro*, and also increased the enzymatic activity of CYP1A1, CYP2B6, and CYP3A4 [76]. Uniquely, the carbamate carbaryl has been shown to induce the CYP1A family via interaction with the aryl hydrocarbon receptor [77]. Other toxins in addition to insecticides can also influence CYP levels. For example, alcohol and nicotine have been shown to induce CYP2B6—one of the most important CYPs in chlorpyrifos bioactivation—in the liver and the brain [78].

Toxicology of Organophosphate & Carbamate Compounds

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et al., 2001). The ratio of desulfuration versus dearylation of chlorpyrifos is 3.38 for CYP2B6 but only 0.14 for CYP2C19, suggesting that the former isoform favors desulfuration, whereas the latter is more likely to generate the dearylation product of chlorpyrifos. CYP3A4 has similar activity toward both pathways. People with a higher activity of CYP2C19 and lower activities of CYP2B6 and -3A4 may be less sensitive to the acute toxicity of chlorpyrifos because of less chlorpyrifos-oxon generated. This selectivity of the reaction pathway suggests that CYP not only involves the addition of oxygen to form the phosphooxythiiran intermediate (Chambers, 1992) but also influences the rearrangement of the oxidized molecule. It is possible that the selectivity of CYP2C19 may be specific for each individual OP. Although several studies have reported that CYP2C19 is more active in dearylation than desulfuration of several phosphorothionates (Buratti *et al.*, 2003; Tang *et al.*, 2001; Vittozzi *et al.*, 2001), it has been reported that CYP2C19 is also highly active in the desulfuration of diazinon (Kappers *et al.*, 2001).

In humans, many CYP isoforms are involved in three major pathways of carbaryl metabolism—4-, 5-, and methyl hydroxylation—that do not share a common intermediate (Tang *et al.*, 2002). Different isoforms show different activities toward these pathways. Among active CYP isoforms, CYP1A1 and -1A2 have the greatest ability to form 5-hydroxycarbaryl, CYP3A4 and -1A1 are the most active in generation of 4-hydroxycarbaryl, and CYP2B6 is the primary isoform for methyl hydroxylation of carbaryl. Fewer CYP isoforms are involved in carbofuran metabolism, which has only one major metabolic pathway (Usmani *et al.*, 2004a). CYP3A4 is the predominant isoform responsible for carbofuran oxidation. The metabolic activity toward carbofuran in human liver microsomes correlates very well with CYP3A4 activity and can be significantly inhibited by ketoconazole, a CYP3A4-specific inhibitor. A study of *in vitro* metabolism of thioether containing OP and CM pesticides indicated that the CYP2C family is highly responsible for sulfoxidation (Usmani *et al.*, 2004b).

Polymorphisms of several human CYP isoforms have been observed, including CYP2C19 and -3A4 (Demorais *et al.*, 1994; Dai *et al.*, 2001). These genetic defects affect

metabolism of chlorpyrifos (Tang *et al.*, 2001; Dai *et al.*, 2001). The activity of chlorpyrifos metabolism in polymorphic isoforms of CYP2C19 is significantly lower than that in wild-type isoforms. Polymorphisms of CYP3A4 have various effects on chlorpyrifos metabolism; some alleles display lower activity than the wild type, some display higher activity, and others display the same activity as the wild type. Similarly, changes in XME activity due to exposure to alcohol, tobacco, drugs, and some occupational chemicals may also alter the metabolism of pesticides catalyzed by these enzymes, increasing blood concentrations of pesticides or their active metabolites and prolonging the clearance process. Therefore, certain human subpopulations may be more vulnerable to pesticide toxicity due to high frequency of defective CYP alleles or repeated exposure to XME inducers or inhibitors.