Pesticide Metabolism and Potential for Metabolic Interactions

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The Agricultural Health Study is designed primarily to address the potential impact that pesticide exposure may have on farm workers and pesticide applicators. A majority of the health effects being examined in this study are chronic effects that may have some correlations with pesticide exposure. Although pesticide effects are well studied in many animal models, many aspects of pesticide effects remain unexplored in humans. Certainly, one of the more important elements involved in pesticide effects includes the ability of an organism to metabolize the pesticide. In the case of pharmaceuticals, metabolism studies are paramount in the identification of potentially harmful metabolic interactions, and can also be used to determine which individuals might be more sensitive to drug applications as a result of polymorphic enzymes. Yet, until recently, virtually nothing was known about human metabolic pathways, human enzymes involved in those pathways, and due to ignorance in these areas there was virtually no potential to explore the possibility of harmful metabolic interactions between pesticides, pharmaceuticals, and endogenous substrates.

Organophosphate insecticides are one of the predominant pesticide classes that have seen decades of use by farmers and pesticide operators. Most organophosphates are like chlorpyrifos, in that they require metabolic activation for their toxic effects. Similarly, metabolism is responsible for their degradation and subsequent elimination. Comparative studies of chlorpyrifos metabolism using human liver microsomes demonstrated that humans are less efficient than rats and mice in the production of both the active metabolite as well as the primary detoxication product [1]. Assays involving recombinant human CYP isoforms demonstrated that five of twelve CYPs metabolize chlorpyrifos, each producing varying amounts of the two metabolites. The most important isoforms for production of the toxic metabolite were CYP2B6 and 3A4, while the detoxication product was best produced by CYP2C19. A limited study of individuals with widely varying levels of CYP2B6, 3A4, and 2C19 demonstrated that individuals with high levels of 2B6 and 3A4 produced greater concentrations of the toxic metabolite while individuals with higher levels of 2C19 produced more of the detoxication product. Likewise, individuals with polymorphic isoforms CYP3A4 and 2C19 varied greatly with respect to their ability to produce chlorpyrifos metabolites [1].

Phorate is an organophosphate which contains a sulfur in the leaving group that is readily metabolized to phorate sulfoxide. Experiments examining phorate along with two related organophosphates and one carbamate, each possessing thioether substituents in the leaving group, were conducted to determine the extent of sulfoxidation by CYP and FMO isoforms [2]. Although many different CYP isoforms were capable of sulfoxidation, members of the CYP2C family had the greatest capacity, followed by 3A4, 2B6, 2D6*1, and 1A2. FMO1, an isoform which is poorly expressed in adult humans, also had a high capacity for sulfoxidation of these pesticides while the adult FMO isoform, FMO3 had minimal activity [2].

The carbamates, carbaryl, and carbofuran were also examined using human liver microsomes. Carbaryl was metabolized to two predominant metabolites, 4-hydroxy carbaryl and carbaryl methylol, and one minor metabolite, 5-hydroxy carbaryl [3]. Although five different CYP isoforms were capable of producing each metabolite, 4-hydroxy carbaryl was produced primarily by CYP1A1 and 3A4, while carbaryl methylol was the predominant metabolite of CYP2B6. As had been observed for chlorpyrifos, the

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proportion of metabolites produced by individuals of known phenotypes was predictable [3]. In contrast with carbaryl, carbofuran was metabolized by human liver microsomes to one major ring hydroxylated metabolite, 3-hydroxycarbofuran, and two minor metabolites. CYP3A4 was almost exclusively responsible for carbofuran metabolism [4].

Unlike the carbamates and organophosphates studied, permethrin is hydrolyzed by microsomal and soluble esterases to phenoxybenzyl alcohol; which is quickly metabolized by alcohol and aldehyde dehydrogenase to phenoxybenzoic acid [5]. Studies examining the potential of known esterase inhibitors to interfere with permethrin metabolism demonstrated that chlorpyrifos oxon and carbaryl are potent in vitro inhibitors of the first step of this metabolic pathway [6].

Studies of chlorpyrifos and carbaryl indicated that CYP2B6 was involved in the metabolism of both pesticides [1,3]. Metabolism of chlorpyrifos to chlorpyrifos-oxon results in the release of a highly reactive sulfur atom, which binds to the heme iron of CYP, resulting in its inhibition. Coincubation of chlorpyrifos and carbaryl in human liver microsomes resulted in substantial inhibition of carbaryl metabolism; primarily as a result of blocking the production of carbaryl methylol, the primary metabolite produced by CYP2B6 [3].

Because CYP3A4 is the predominant isoform involved in human metabolism of testosterone and was also shown to be important in chlorpyrifos metabolism, the potential for interactions between these two substrates was explored using human liver microsomes and expressed CYP3A4 enzyme. Preincubations of chlorpyrifos with human liver microsomes and CYP3A4 dramatically inhibited testosterone metabolism [7]. The organophosphates phorate and fonofos also inhibited metabolism although several other pesticides did not have such interactions. The power of the chlorpyrifos, phorate, and fonofos to inhibit testosterone metabolism was indicated by their low Ki values (2.0, 5.8, and 34.1 μM, respectively) [7].

Studies in which human hepatocytes are exposed to varying concentrations of pesticides indicate that several pesticides are capable of inducing CYP enzymes. Chlorpyrifos, for example, induces isoforms CYP1A1, 1A2, 2B6, and 3A4 to levels five-fold or greater than controls. Permethrin, which was not metabolized in vitro by CYP isoforms, also induced CYP2A6, 2B6, and 3A4 [8]. The implications of the ability of pesticides to induce CYP isoforms in human hepatocytes will require further study; particularly to determine if concentrations necessary for such induction would occur in vivo.

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