REVIEW ARTICLE

# *CYP*/*PON* genetic variations as determinant of organophosphate pesticides toxicity

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## Abstract

In the present scenario of increased accumulation of pesticides in the environment, it is important to understand its impact on human health. The focus is on gene–environment interaction, highlighting the consequences and factors that may halt the biotransformation of some pesticides and change their actual dose response curve due to mixed exposure to pesticides. The paraoxonase and cytochrome P450 gene families are involved in the metabolism of oxon derivate (toxic than its parent compound) of organophosphate pesticides, thus, mutations in these genes may impact the metabolic outcome of pesticides and subsequent health hazards. The complex multi gene–environment interaction and one gene – one risk factor are two different aspects to understand the potential health effect related to environmental exposure studies. The genetic polymorphisms are associated with varying levels of risk within the population, as gene products of varied genotype alter the biotransformation of exogenous/endogenous substrates. This paper is aimed to review the impact of endogenous and exogenous factors on a mechanistic pathway of organophosphate pesticide biotransformation and various risk associated with it among the human population. Understanding the genetic polymorphism of genes involved in pesticide metabolism and highlighting the gene isoform dependent interindividual differences to metabolize particular pesticides may help us to unravel the reasons behind differential toxicity for pesticides exposure than expected.

[Kaur G., Jain A. K. and Singh S. 2017 *CYP/PON* genetic variations as determinant of organophosphate pesticides toxicity. *J. Genet.* **96**, xx–xx]

## Introduction

The agrochemicals toxicity could not be determined from exposure to a single chemical in a human system as the pesticide dose response curve may be different in the actual scenario due to multiple pesticide exposures. Its relevance to real world situations is questionable since dose and genetic variations among individuals are actual determinants of agrochemical hazard. The endogenous metabolites, environmental factors, age and a genetic pathway regulates the detoxification process, and provides information about risk and interactions among various agrochemicals. Further to know the toxicokinetics of mixtures of agrochemicals as *CYP*, *PON* and various other factors involved in the determination of toxicity level of a particular pesticide in the human body are discussed in this paper.

Pesticides are liable for acute poisonings, even at small doses (Tsatsakis *et al.* 2009; Farcas *et al.* 2013) and the normal physiology of human gets altered after a repeated pesticide exposure or mixture of pesticides on the same tissue through dose addition or independent action (Reffstrup *et al.* 2010) or interaction, i.e. synergisms and antagonisms (Casida 2010). Further, this long-term pesticides exposure may become the root cause of health-related disorders like cancer (Mostafalou and Abdollahi 2012; Koutros *et al.* 2013), neurodegenerative (Parrón *et al.* 2011; Singh *et al.* 2012), respiratory (Eddleston *et al.* 2006), reproductive and developmental disorders (Saadi and Abdollahi 2012).

### *General overview regarding organophosphate pesticides (OPs)*

Organophosphate chemicals, with the P = S moiety, are known for their less toxicity as compared to other pesticide groups, but are sometime irreversible inhibitors of cytochrome P450. Organophosphate pesticides (OPs), triesters of phosphoric acid were first recognized in 1854 by Clermon (Hazleton 1955), but were not used until 1930s as their toxic potential was not fully established (Obare *et al.* 2010). The fame to utilizing OPs pesticide became trendier due to its relatively short half-life, relatively fast

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**Keywords.** organophosphate pesticides; xenobiotics; cytochrome P450; paraoxonase; genetic polymorphisms.

degradation rates, lower price, lower susceptibility to pest resistance (Ragnarsdottir 2000) and lastly, due to the ban on persistent organochlorine pesticides in the 1970s. The OPs insecticides are potent inhibitors of serine esterases, such as serum cholinesterase, acetylcholinesterase (Mileson *et al.* 1998) and result in accumulation of acetylcholine due to the overstimulation of acetylcholine receptors in synapses of the autonomic nervous system, central nervous system (CNS) and neuromuscular junctions (Pope *et al.* 2005). Thereby, it has numerous health-related chronic harmful effects on human health, e.g. disruption of the endocrine system, neuropsychological disorders, developmental anomaly, hypersensitivity (Mansour 2004), nonHodgkin's lymphoma, lung and prostate cancer (Bonner *et al.* 2010).

### *Metabolism of OPs*

Metabolic pathway of pesticide is an actual determinant of pesticide toxicity inside the human body (Hodgson 2012; Liu *et al.* 2013), as exposure to multiple pesticides may change the toxicokinetics of the individual compounds, hence altering the expected toxicity (Hernández *et al.* 2013b). Xenobiotics biotransformation converts the lipophilic compounds into hydrophilic metabolites directly or after conjugation with endogenous cofactors through biliary or renal excretion (Sevior *et al.* 2012). The biotransformation process comprises of two phases, explained in figure 1. Phase 1 includes functionalization reactions carried by cytochrome P450 enzymes, flavin monooxygenases, monoamine oxidases, carboxylesterases, aldehyde oxidases, aldehyde dehydrogenases, aldo–keto reductases, alcohol dehydrogenases, hydroxysteroid dehydrogenases through various processes such as oxidation, reduction, hydrolysis and conjugation, that produce metabolites with OH, COOH, $NH_2$, SH functional groups (Timbrell and Marrs 2009; Nassar 2010). The OPs, are first converted into active intermediate OPs oxon by metabolic activation of hepatic cytochrome P450s through the removal of sulphur attached to phosphorus and insertion of an oxygen atom (named as oxidative desulphuration step) (Abass *et al.* 2012). The sulphur atom attached to the phosphorus (thiophosphate moiety of insecticides) gets removed and leads to insertion of atomic oxygen by *CYP450s* during organophosphorothionate desulphuration step. The activated sulphur atom is highly reactive

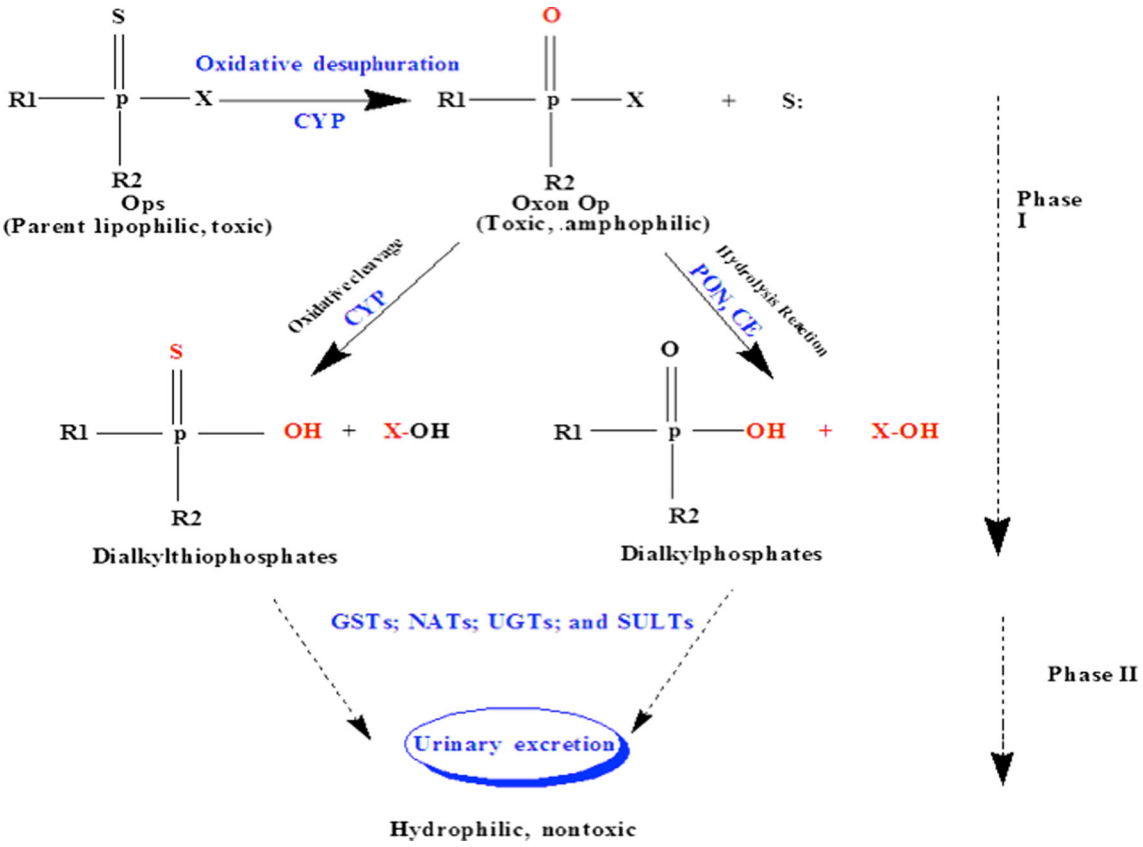


**Figure 1.** General metabolic pathway of organophosphate pesticides. The parent organophosphorothionates bioactivated to highly toxic oxon forms by cytochrome P450 through removal of sulphur attached to phosphorus and insertion of oxygen atom (oxidative desulphuration) using the reactive and electrophilic iron–oxo intermediate, and get detoxified by dearylation to form dialkyl thiophosphates (inactive metabolites) or further gets hydrolyzed to dialkyl phosphates (inactive metabolites) by paraoxonase-1 (*PON1*), and carboxylesterase (CE) in phase I, and further, phase II involves conjugative reactions carried out by glutathione transferases (GSTs); *N*-acetyltransferases (NATs); UDPglucronyltransferase (UGTs); and sulphotransferases (SULTs), UDP-glucuronyltransferases (UGT), sulphotransferases (SULT), *N*-acetyltransferases (NAT), glutathione *S*-transferases (GST) and is excreted out through urine as nontoxic form.

that binds irreversibly to the haem iron of *CYP* at cysteine residues, catalyzing the reaction immediately resulting in a reduction of the enzymatic activity (Butler and Murray 1997; Hodgson and Rose 2006; Rydberg 2012). This event happens when substrate (OPs) binds to the ferric form of the enzyme that results in its reduction to ferrous state. This ferrous form binds to the molecular oxygen followed by addition of another electron and a proton to the iron atom resulting in a reactive and electrophilic iron–oxo intermediate formation. Later, the oxons are hydrolysed by paraoxonase-1 (*PON1*) to form inactive metabolites (Pei *et al.* 1995). It conjugates to various enzymes such as glutathione *S*-transferases enzyme (GSTs), *N*-acetyltransferases (NATs); UDPglucronyltransferase (UGTs); and sulphotransferases (SULTs), UDP-glucuronyltransferases (UGT), sulphotransferases (SULT), *N*-acetyltransferases (NAT), glutathione *S*-transferases (GST) (Fujioka and Casida 2007) and is excreted out of the body through urine (figure 1). Hence, the cytochrome and paraoxonase gene families are the major determinant for biotransformation of the particular pesticides.

#### *Oxon interference for pesticides metabolism*

As described in the previous section that organophosphorothionate pesticides (inactive) first metabolize into the corresponding oxon (active) that results in acetylcholinesterase (AChE) inhibition (Flaskos 2012; Mercey *et al.* 2012). These oxon forms may also inhibit the metabolism of other xenobiotic compounds as the combination of compounds with the same target may cause additive, synergistic or antagonistic effects, thereby the metabolite of one pesticide can halt the metabolism of another as described further.

The oxon, highly toxic form, is mainly catalyzed by *CYP1A2*, *CYP2B6* and *CYP3A4* genes (Buratti *et al.* 2005). It has been investigated that azinphos-methyl, chlorpyrifos and parathion pesticides are bioactivated by *CYP1A2* and *CYP2B6* at low concentrations (Buratti *et al.* 2003) and by *CYP3A4* at higher concentrations in the human liver (Tang *et al.* 2001). The OPs named chlorpyrifos, malathion and diazinon gets converted to more toxic forms through *CYP* metabolism to chlorpyrifos–oxon, malathion–oxon and diazinon–oxon, respectively (Poet *et al.* 2003; Buratti *et al.* 2005). Further, the chlorpyrifos oxon and carbaryl irreversibly inhibit permethrin (pesticide) hydrolysis (Choi *et al.* 2004). Similar results inferred that chlorpyrifos oxon and carbaryl inhibits permethrin metabolism by inhibiting esterase. Hence, the permethrin metabolism halted for the population preexposed with chlorpyrifos and carbaryl. Similarly, the carbaryl is metabolized by various *CYP* isoforms into 5-hydroxycarbaryl (by *CYP1A1* and *1A2*), 4-hydroxycarbaryl (by *CYP3A4* and *CYP1A1*) and carbaryl methylal (by *CYP2B6*). Tang *et al.* (2002) reported that chlorpyrifos oxon form inhibits the *CYP2B6* activity. Thereby, the carbaryl is unable to catalyze into its metabolic product carbaryl methylal by *CYP2B6* in case of chlorpyrifos preexposure. Thus, the carbaryl metabolism halts in the presence of chlorpyrifos. The oxon also inhibits esterase activity during desulphuration of the *CYP450s*, which is responsible for carbaryl hydrolysis to yield naphthol by potentiation effect. It may be possibly due to the difference in the $IC_{50}$ value of the isoforms involved in OP metabolism. Like, the *CYP1A2*, major isoform responsible for oxon formation at low OPT concentrations have lower $IC_{50}$ values, while *CYP3A4* have higher $IC_{50}$ (Buratti *et al.* 2003).

## Gene–pesticide interaction of OPs biotransformation

The varied genetic makeup of an individual may be assumed as a reason that some individuals in the population exhibit a significant susceptibility to OPs exposure to develop a particular disease and others do not (Rose *et al.* 2005). It is complicated by the altered gene expression and mRNA stability due to polymorphism in the regulatory region of a gene to further modify the protein expression (Edwards and Myers 2008; Fire *et al.* 2013).

#### *CYP genes variants and OPs interaction*

The cytochromes P450, haem–thiolate proteins with molecular weight 50,000 Da are responsible for monooxidation of the wide variety of structurally unrelated endogenous as well as exogenous compounds including drugs and pesticides (Zanger *et al.* 2008; Abass *et al.* 2012). These are more sensitive to OPs as compared to other pesticide groups (Abass *et al.* 2007). It has two binding sites, one at the molecule of oxygen (near the centre) and the other, above the haem group. P450 enzymes are classified into 57 *CYP* genes (Košir *et al.* 2013), grouped according to their sequence similarities to 18 families and 44 subfamilies (Samer *et al.* 2013). It was estimated that ~80% of oxidative metabolism and nearly 50% elimination of commonly used drugs completed through three families (*CYP1*, *CYP2* and *CYP3*) of the various P450 enzymes in humans (Wilkinson 2005). The P450s are more abundant in the liver cells as compared to other organs such as kidney, nasal mucosa, lung, gastrointestinal track, brain and skin (Paine *et al.* 2006). Therefore, hepatic P450-mediated metabolism represents the primary means of xenobiotic elimination from the body. The main function of cytochromes P450 is to catalyze monooxygenase reaction by insertion of one oxygen atom into the aliphatic position of an organic substrate, and the other oxygen atom gets reduced to water (Meunier *et al.* 2004). Organophorothionate pesticides are actually weak AChE inhibitors, but bioactivation mediated desulphuration to their phosphate triesters or oxons (by *CYP*), results in a powerful inhibitor of brain and serum AChE (Dzul-Caamal *et al.* 2014). The resultant activated sulphur atoms cause enzyme loss and reduction of the corresponding monooxygenase activity by irreversible binding to the *CYP* catalyzing the reaction (Murray 1999; Buratti *et al.* 2002).

There are numerous reports published to explore the *CYP* variability and expression level in the human population; thereby it becomes primary contributing factor in knowing the variability for any xenobiotic biotransformation. The *CYP3A4*, a major *CYP* expressed protein, accounting for 30% of total *CYP* protein content (Guengerich 1993) is responsible for ~24% in the metabolism of pesticides (Abass *et al.* 2012). The *CYP3A4* has vast and flexible active site responsible for oxidizing either large substrates or multiple smaller ligands (Tang *et al.* 2001). The benfuracarb could inhibit the *CYP3A4* activities (Abass *et al.* 2014), thereby the *CYP3A4* associated metabolism would halt with benfuracarb exposure. The *CYP2B6* is considered as the primary enzyme for xenobiotic bioactivation of azinphos-methyl, parathion and chlorpyrifos (CPS) pesticides (Buratti *et al.* 2003; Foxenberg *et al.* 2007). Further, the *CYP2B6* is inactivated by CPS in a time-dependent and concentration-dependent manner with a $K_{inact}$ of 1.97 $min^{-1}$, a $K_I$ of 0.47 $\mu$M and a partition ratio of 17.7 (D'Agostino *et al.* 2015). Similar $K_{inact}$ and $K_I$ values were observed for other OPs pesticides including chlorpyrifos-methyl, diazinon, parathion-methyl and azinophos-methyl to inactivate *CYP2B6*. The profenofos, chlorpyrifos and fenitrothion were estimated to be most effective in inhibiting *CYP1A1/2* and *CYP2B6* among 18 different pesticide concentrations determined by liquid chromatography–tandem mass spectrometry (LC/MS–MS). Lang *et al.* (2001) reported a total nine point mutations of *CYP2B6* in a Caucasian population with most common genetic variant *CYP2B6.6*. The similar genetic variation of *CYP2B6.4*, *CYP2B6.5* and *CYP2B6.7* genes have been recently examined by Crane *et al.* (2012). In the same study, it has been demonstrated that the individuals with *CYP2B6.6* genotype may be less susceptible to chlorpyrifos toxicity due to its more specific activity and less capacity to bioactivate chlorpyrifos in human liver microsomes compared to wild type. It may be attributable to decreased hepatic protein expression to make the individual with this genotype less susceptible to chlorpyrifos toxicity, indicating that the person with variant isoform behaves differently to pesticides. Recently, a study has been intended to examine Chirostoma jordani fish from three lakes with different levels of OPs contamination in water and sediments. The main isoenzymes involved in bioactivation process were expressed as *CYP2C19* > *CYP2B6* > *CYP3A4* in fish from a lake with high CPF pollution, on the other hand, the fish captured from high concentration of DZN lake, the isoenzymes involved were *CYP3A4* > *CYP2C19* > *CYP2B6* (Dzul-Caamal *et al.* 2014). According to Zhuang *et al.* (2014), *CYP3A4*, *CYP1A2*, *CYP2D6*, *CYP2C9* and *CYP2C19* genes are involved in the secondary metabolic pathway of desulphuration of isocarbophos (ICP). More interestingly, the individual enantiomers of ICP as well as its oxidative desulphuration metabolite isocarbophos oxon (ICPO) has been reported to be inhibitors of acetylcholinesterases at different extents (Zhuang *et al.* 2014).

***PON gene variants and OPs interaction***

*PON* gene family is another proteins family, studied for OP metabolism in human body. Paraoxonase 1 (*PON1*, aryldialkylphosphatase, E.C.3.1.8.1), calcium-dependent enzyme, is a member of a three-gene family i.e. *PON1*, *PON2* and *PON3*, and functions as an esterase and lactonase (Mackness *et al.* 1991). Mazur (1946) first described (Otocka-Kmiecik and Orłowska-Majdak 2013) and located it on the long arm of human chromosome 7 (q21.22; Toptaş *et al.* 2013). The primary function of *PON1* is its lactonase activity common in all *PON* family members. There is about 60–70% identity in amino acid sequences and nucleotide among three *PONs* (Campo *et al.* 2004). The activity of *PON1* genes depends on calcium, and the calcium chelator EDTA binding (figure 2). There are two $Ca^{2+}$ atoms at the active site of *PON1* and perform catalytic and structural functions, respectively. Structurally, the *PON1* has total six-bladed β-propeller enzyme with four strands on each blade. In comparison to other β-propeller enzymes, *PON1* has a closed active site with three α-helices. One of the α-helices contains the *N*-terminal signal peptide that helps to anchor HDL particles. The amino-terminal methionine residue is removed during maturation and secretion of *PON1* (Hassett *et al.* 1991). It has been known for its antioxidant activity to prevent oxidation of lipoproteins by reactive oxygen species formed during oxidative stress (Boshtam *et al.* 2013; Rosenblat *et al.* 2013).

Paraoxonase, an esterase enzyme, is responsible for hydrolysis of particularly oxon metabolite of the OPs pesticide. The triesters of a phosphoric acid act as substrates for paraoxonase enzyme (Costa *et al.* 2003; Mohapatra and Pattanaik 2013). It causes hydroxylation of oxygen analogues of OPs, aromatic esters and carbamate insecticides (Costa *et al.* 2005). Investigation reveals that paraoxonase activity depends on the pattern of anticholinesterase pesticide exposure that could decreases or increases in short-term or long-term pesticide exposure, respectively (Hernández *et al.* 2013a). The expression and function of three *PON*

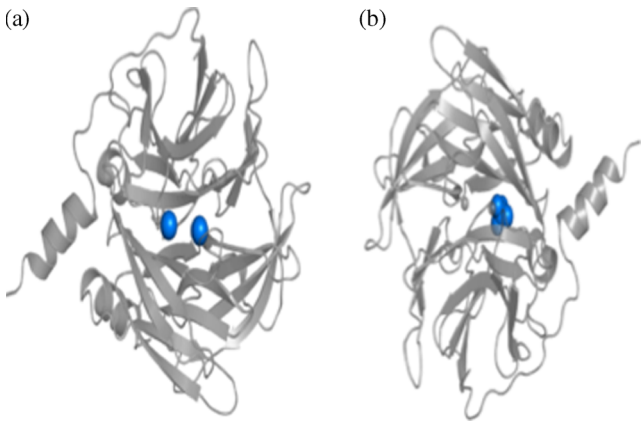


**Figure 2.** Binding of *PON1* with (a) two calcium ions and (b) EDTA.

genes along with its secretion and circulation sites have been explained in table 1.

There are a total of 200 single-nucleotide polymorphisms (SNPs) identified in *PON1* in different regions, while cloning in 1993 (Harel *et al.* 2004). Polymorphisms in the *PON1* gene could influence both quantity as well as quality of *PON1* (Jarvik *et al.* 2000; Li *et al.* 2000). There are two significant polymorphisms in the coding region and five in promoter region of *PON1* gene, i.e. substitution at position 192 (glutamine (Q) by arginine (R)) and at position 55 (leucine (L) by methionine (M) of coding region) (figure 3; Agachan *et al.* 2004) and one in promoter region at position 107 (James *et al.* 2000b). However, the SNPs of the coding region at positions 192 (glutamine (Q) / arginine (R) substitution at codon 192) result in different hydrolytic activities towards various substrates (Humbert *et al.* 1993). The arginine (Arg, R) / glutamine (Gln, Q) substitution has been reported to affect OPase substrate specificity (10-fold decrease in paraoxon hydrolyzing activity). On the other hand, the leucine (Leu, L) / methionine (Met, M) substitution of the L55M SNP has been reported to affect the stability and enzymatic activity of *PON1*. The Q allele has less efficiency

**Table 1.** Expression and function of *PON* genes.

| Gene | Secretion site | Expression and circulation | Function | References |
|---|---|---|---|---|
| *PON1* | Liver | Circulation bound to HDLs in different tissues in the human organism | • Antioxidant<br>• Prevents the oxidation of LDLs<br>• Hydrolyzing nerve gasses and OPs pesticides | Primo-Parmo *et al.* (1996); Costa *et al.* (2005) |
| *PON2* | Liver | Kidney, liver, testis and brain | Protect cells against oxidative damage | Mochizuki *et al.* (1998); Ng *et al.* (2001) |
| *PON3* | Liver | Circulation bound to HDLs, but in human serum | Inhibit the oxidation of LDLs | Blatter *et al.* (1993) |

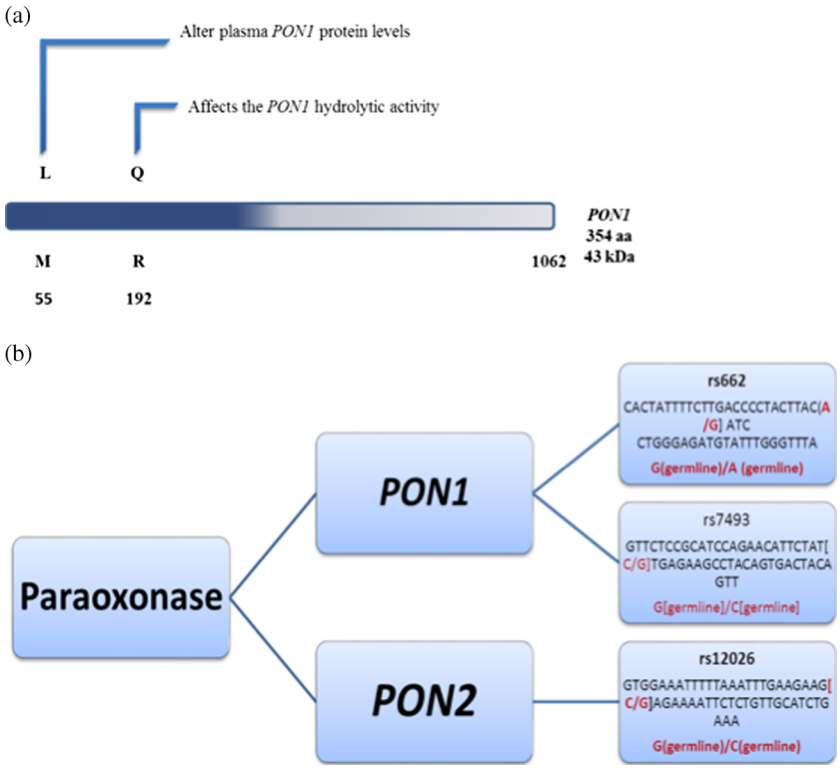


**Figure 3.** (a) *PON1* protein and SNPs with their effect. (b) SNPs of *PON1* and *PON2* genes. The rs662, rs7493, rs12026 SNPs are present on chromosome 7:94937446, 7:95034775 and 7:95041016, respectively. Apart from these, there are more known SNPs (around 22), but have been merged in these three primary mutations.

in hydrolyzing paraoxon, but more efficiency for diazoxon, soman and sarin (Davies *et al.* 1996) and towards oxidized high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs) as compared to the R allele (Ferretti *et al.* 2003). Also, *PON1Q* allele has an association with chronic pesticide poisoning in susceptible farmworkers (Sözmen *et al.* 2007). The genetic polymorphisms of *PON1*, at position 192 and −108, infer different catalytic activities and levels expression (Costa *et al.* 2005). The SNPs mentioned in figure 3b are missense and nonpathogenic in nature.

#### *Signalling receptors for CYP and PON1 expression regulation*

The *CYP* and *PON* genes have essential response to both endogenous and exogenous signals through gene expression or metabolism pathways. Pregnane X receptor (PXR) is the member of the nuclear receptor (NR) superfamily of ligand-activated transcription factors. It plays a significant role in signalling pathways as well as regulation of genes involved in xenobiotic metabolism, especially, *CYP*-mediated biotransformation (Smutny *et al.* 2013). Also, the posttranslational modifications (as phosphorylation) modulate the activity of many nuclear receptors. The retinoids regulate *CYP3A* gene expression through the RXR/CAR-mediated pathway (Chen *et al.* 2010). In keratinocytes, the *CYP1A1* gene expression has been reported to be either downregulated (Wanner *et al.* 1995; Du *et al.* 2006) or upregulated (Vecchini *et al.* 1995) by retinoic acid. The polycyclic hydrocarbons and arylamines get activated to catechol oestrogens through 2-hydroxylation and 4-hydroxylation (carcinogens) by *CYP1A1*, *CYP1A2* and *CYP1B1* (Kim *et al.* 1998). The *CYP1A* and *CYP1B* genes activities induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (polyaromatic hydrocarbons) binds to the aryl-hydrocarbon receptor (AhR), and result in translocation of the ligand-bound AhR into the nucleus and cause dimerization with AhR nuclear translocator (Arnt). This Arnt complex can respond by binding to xenobiotic elements to turn on the *CYP* gene transcription (Hankinson 1995).

The sterol regulatory element (SRE) sequences are reported in *PON1* promoter region. The PPARα is a factor activated by peroxisome proliferators (Gonzalez *et al.* 1998). The uPA reduces hepatic *PON1* gene transcription through its interaction with uPAR on hepatocytes surface by binding to uPAR to stimulate MEK (mitogen-activated protein kinase) interaction with PPARγ in the nucleus that results in export of the nuclear PPARγ to the cytosol. It has been evidenced that the downregulation of *PON1* expression is due to uPA that efficiently decreases the association of PPARγ to *PON1* promoter as PPARγ binds to DNA sequences in the *PON1* promoter region (Fuhrman *et al.* 2007; Khateeb *et al.* 2012). Similarly, the induction of *CYP4A* gene is done by PPARα as the mice lacking PPARα devoid the genes induction for *CYP4A* encoding (Roman *et al.* 1993). Apart from this, several studies have indicated that the steroidogenic (SF-1) has a role in the regulation of *CYP* genes such as *CYP11B1*, *CYP11A*, *CYP17* and *CYP19* through activation of the cAMP pathway (Bakke and Lund 1995; Michael *et al.* 1995; Carlone and Richards 1997).

#### *Endogenous and exogenous inhibition of OPs metabolism*

There are some endogenous and exogenous factors responsible to interfere with the pesticide metabolism. Ageing is also one of the important physiological aspect of individual that widely influences xenobiotic metabolism (Atterberry *et al*. 1997). A report published by Sotaniemi *et al.* (1997) demonstrated an age-related 32% decline in total hepatic cytochrome P450 content from 20 to 80 years of age ($n$ = 226). George *et al.* (1995) reported that the constant content of *CYP1A2* and *CYP2C*, while a decrease in total *CYP2E1*, *CYP3A* and NADPH reductase activities with ageing ($n$ = 71). But, the report published by Schmucker *et al.* (1990) suggests that the microsomal protein content, total P450 and NADPH cytochrome P450 reductase did not alter by ageing (liver samples). The age-related *CYP* decline in content, activity and inducibility was reported in animals as well (Warrington *et al.* 2004; Wauthier *et al.* 2004). Apart from it, the susceptibility to methyl parathion and parathion pesticides decreases with an increase in age in case of rats. Further, the change in susceptibility with age is due to change in enzymatic detoxification rates of oxygen analogues. The carboxylesterase results in hydrolysis of isocarbophos pesticide and then *CYP3A4*, *CYP1A2*, *CYP2D6*, *CYP2C9*, *CYP2C19* involved during desulphuration of isocarbophos as a secondary metabolism pathway. Zhuang *et al.* (2014) reported that the isocarbophos pesticide depletion was faster in the deficiency of carboxylesterase inhibitor (BNPP) as compared to NADPH and BNPP presence, with $t_{1/2}$ of 5.2 and 90 min, respectively, in human liver microsomes. There are some other factors such as deficiency of dietary protein, physical or emotional stress and oxidative stress that also increases the susceptibility towards pesticide toxicity. Quinidine (antiarrhythmic agent) and ketoconazole (an antifungal medication) are reported to inhibit *CYP2D6* and *CYP3A4* for chlorpyrifos and parathion, respectively, by oxidative biotransformation in microsomes (human lymphoblastoid cell line). The *CYP2D6* inhibitors resulted in 50% inhibition of cholinesterase activity for parathion, 38% diazinon and 30% chlorpyrifos as compared to control. Similarly, ketoconazole (*CYP3A4* inhibitor) resulted in 66% inhibition of cholinesterase activity for diazinon, 20% parathion and 5% chlorpyrifos (Sams *et al.* 2000). Similarly, (*O*-(*n*-propyl) *O*-(2-propynyl) phenyl phosphate (PPP) and dietholate (SV1) are reported to be inhibitors of OPs metabolism and also block the metabolism of neonicotinoid insecticide named clothianidin (CLO), imidacloprid (IMI) and thiacloprid in mice (Shi *et al.* 2009). The health status of individuals after exposure to OP pesticides is related to the polymorphism of *PON1* that varies among different ethnic groups (Brophy *et al.* 2001). Hence, the variations in *PON1* activity may also contribute to interindividual variations in susceptibility

**Table 2.** Various dietary, lifestyle, and environmental factors modulating *PON1* activity.

| Factor | *PON1* activity and levels | Observation | References |
|---|---|---|---|
| Smoking | Serum *PON1* levels and activity | Decreased | Nishio and Watanabe (1997); James *et al.* (2000a) |
| Vitamins C and E | Paraoxonase activity | Increased | Jarvik *et al.* (2002) |
| Ethanol and other aliphatic alcohols | Serum *PON1* activity | Decreased | Debord *et al.* (1998) |
| Lactams, and isosteric forms of lactones | *PON1* activity from rat or human liver *in vitro* | Decreased | Gonzalvo *et al.* (1997) |
| Barium, lanthanum, copper, zinc, mercurials | *PON1* activity from rat or human liver *in vitro* | Decreased | Gonzalvo *et al.* (1997) |
| A high-fat diet levels in mice | Serum *PON1* levels in mice | Decreased | Shih *et al.* (1996); Hedrick *et al.* (2000) |
| Triglyceride and triolein | *PON1* activity in rats, dietary | Increased | Kudchodkar *et al.* (2000) |
| Fish oil | Serum *PON1* in rats | Decreased | Kudchodkar *et al.* (2000) |
| Meals rich in thermally stressed olive oil | Postprandial serum *PON1* activity in middle-aged women | Increased | Wallace *et al.* (2001) |
| Phenobarbital | Paraoxonase activity in rodent liver | Increased | Hernández *et al.* (1997); Kaliste-Korhonen *et al.* (1998) |
| 3-Methylcholanthrene | Serum and liver *PON1* activity in rats | Increased | Rodrigo *et al.* (2001) |
| Lipopolysaccharide | Serum and liver *PON1* activity | Decreased | Feingold *et al.* (1998) |
| Valerolactam or E-caprolactam | *PON1* activity | Decreased | Billecke *et al.* (2000) |

to pesticide exposure (Costa *et al.* 2005; Parul *et al.* 2012). Pesticide exposure may disturb the plasma antioxidant activity (Hernández *et al.* 2013a). By this means, it could become a reason for more oxidative stress-induced diseases. Thus, the adverse effects of organophosphate exposure could be more in individuals with unfavourable combinations of gene variants. There are various dietary, lifestyle and various environmental factors which are responsible for altering *PON1* activity and levels complied in table 2.

## Health risk associated with impaired OPs biotransformation

### *CYP associated disorders*

The cytochrome P450 gene family plays various functions in human body apart from xenobiotic biotransformation as depicted in figure 4. Thus, the inhibition of one gene activity could have a deleterious effect on metabolism of others as well as physiological functions of the body. As, the neuronal and glial cell differentiations get inhibited by the oxon up to 1000 times stronger as compared to toxicity by their actual parent phosphorothioates (Flaskos 2012) as the desulphuration of OPs results in more toxic oxon derivatives formation as discussed in previous sections (Leoni *et al.* 2008). As we discussed, the phosphorothioates are also potent inhibitors of *CYP* and thereby effect metabolism of steroid hormones (Ernest and Andrew 2012). The OPs inhibitors of *CYP3A4* and *CYP1A2* irreversibly inhibit testosterone metabolism in human (Butler and Murray 1997; Usmani *et al.* 2006) due to irreversible binding of reactive sulphur from OPs to the *CYP* genes (Hodgson and Rose 2006). Many chemicals including agro as well industrial can serve as substrates, inhibitors and inducers of *CYP2B6* with certain actions often altered by the existence of polymorphic variants (Hodgson and Rose 2007). A similar study is demonstrated by metabolism of pyrethroid pesticides in rat and human hepatic microsomes. Chlorpyrifos can inhibit the metabolism of carbaryl, but also can inhibit the metabolism of steroid hormones (Hodgson and Rose 2005). Various disorders associated with genetic polymorphism of *CYP* gene has been listed in table 3.

### *PON1 associated disorders*

*PON1* has an extensive role in preventing accumulation of lipoporoxides in LDLs (Mackness *et al.* 1991). The polymorphism of *PON1* is associated with variations in cholesterol and lipoprotein levels. *PON1* genetic polymorphisms have been reported to be associated with miscarriage (Blanco-Munoz *et al.* 2013), Parkinson's disease (Kirbas *et al*. 2013), atherosclerosis (Shenhar-Tsarfaty *et al.* 2013), cardiovascular risk (Andersen *et al.* 2012), neurobehavioural and neurodevelopment (Muñoz-Quezada *et al.* 2013; Ross *et al.* 2013). Liu *et al.* (2006) reported that DNA damage

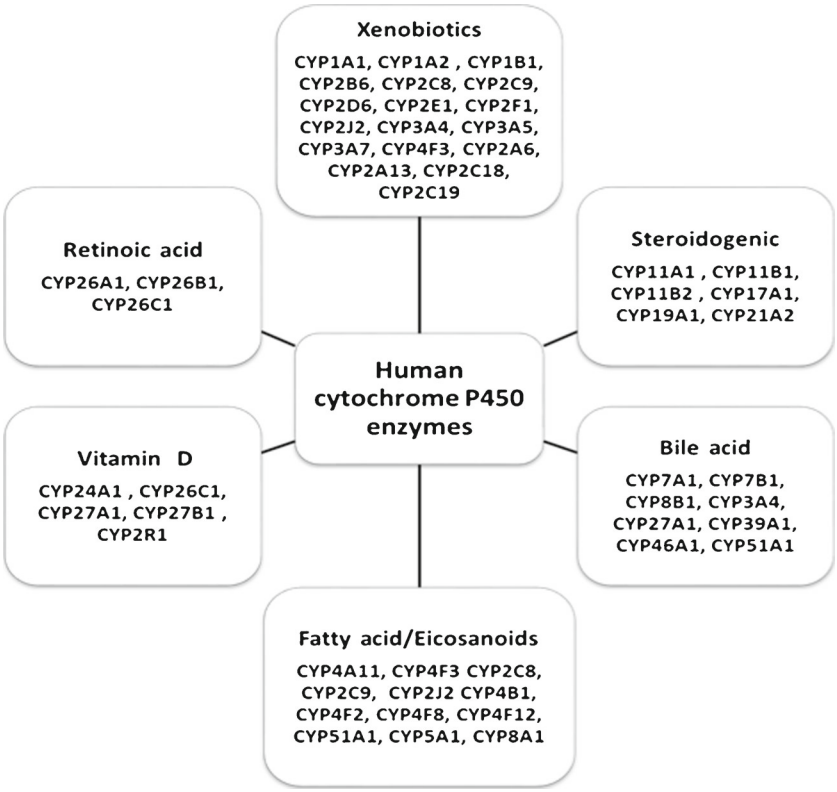


**Figure 4.** Human cytochrome P450 enzyme categorization based on its function.

**Table 3.** Disorders associated with genetic polymorphism of *CYP* gene.

| *PON1* genetic polymorphism | Sample number (*n*) | Disease associated | References |
|---|---|---|---|
| Cytochrome P450IIE1 | ($n = 128$) Japanese, African-Americans, and Caucasians | Lung cancer | Kato *et al.* (1992) |
| *CYP2E1* | Patient ($n = 91$), control ($n = 76$) | Lung cancer | Uematsu *et al.* (1994) |
| *CYP2C8/19* | Patient ($n = 98$) Queensland | Liver pathology | Baker *et al.* (2001) |
| *CYP1A1* (Ile/Val and/or Val/Val) | Patient ($n = 115$), control ($n = 200$) | Prostate cancer | Murata *et al.* (2001) |
| *CYP4A11* | Patient ($n = 37$) Caucasians | Altered blood pressure | Baker *et al.* (2002) |
| *CYP2D6* and *CYP3A5* | Patient ($n = 516$) Central Kentucky | Tardive Dyskinesia | Leon *et al.* (2005) |
| *CYP19* | Patient ($n = 186$), control ($n = 109$) Spain | Hyperandrogenism | Petry *et al.* (2005) |
| *CYP1A1* Ile/Val, *CYP1A2* 1F, *CYP2E1* c1/c2 | Patient ($n = 500$), control ($n = 500$) Hungary | Colorectal cancer | Kiss *et al.* (2007) |
| *CYP2C19*3* AG + AA | Patient ($n = 336$), control ($n = 370$) in a Uighur population | Coronary artery disease | Yang *et al.* (2010) |
| *CYP1A1* Ile/Val and *CYP2E1* I/i and i/i | Patient ($n = 105$), control ($n = 110$) in a Uighur population | Head and neck cancer | Anuradha *et al.* (2016) |
| *CYP2D6*10* | Patient ($n = 194$) | Systemic lupus erythematosus | Lee *et al.* (2016) |

**Table 4.** Disorders associated with genetic polymorphism of *PON1* gene.

| *PON1* genetic polymorphism | Sample number (*n*) | Disease-associated | References |
|---|---|---|---|
| Polymorphism at codon 311 (Cys→Ser; *PON2*) and *PON1* 192Q allele | Patients ($n = 129$) and control ($n = 189$) in Asian Indians | Coronary heart disease | Sanghera *et al.* (1998) |
| Met54Leu of *PON1* and Cys311Ser of *PON2* gene | $n = 372$ | Diabetes microvascular diseases (retinopathy and microalbuminuria) | Kao *et al.* (2002) |
| I102V *PON1* | Patient ($n = 56$), control ($n = 835$) in Finnish Men | Prostate cancer | Marchesani *et al.* (2003) |
| *PON1* 192Q allele, 160R allele, –162A allele and *PON2* 311C allele | Patients ($n = 474$) and control ($n = 475$) in Chinese Han population | Coronary heart disease (CHD) | Wang *et al.* (2003) |
| –161(C/T) SNP of *PON1* | 730 Caucasian and 467 African American participants | Coronary artery disease and carotid artery stenosis, Alzheimer disease | Erlich *et al.* (2006) |
| L55M *PON1* polymorphism | Patient ($n = 502$), control ($n = 502$) | Breast cancer | Victoria *et al.* (2006) |
| rs854560 T>A and rs662 A>G | Patient ($n = 274$), control ($n = 452$) | Epithelial ovarian cancer | Lurie *et al.* (2008) |
| *PON1* 192 R (+) genotype | Patient ($n = 223$), control ($n = 234$) | Lung cancer | Aksoy-Sagirli *et al.* (2011) |
| *PON*-55 M/M genotype | Patient ($n = 109$) and control ($n = 103$) | Systemic lupus erythematosus | Bahrehmand *et al.* (2013) |
| *PON1* –108C>T and p.Q192R polymorphisms | Patients ($n = 104$) and control ($n = 109$) | Dementia | Bednarska-Makaruk *et al.* (2013) |
| SNP (rs662) of the *PON-1* gene | Patients ($n = 94$) and control ($n = 106$) in Chinese Han population | Osteonecrosis of femoral head | Wang *et al.* (2013) |
| *PON1* 192RR and *PON1* 55LL genotypes | Patients ($n = 121$) and control ($n = 79$) in Turkish patients | Bone fragility | Toptaş *et al.* (2013) |
| Q192R genotypes of *PON1* | Patients ($n = 150$) and control ($n = 150$) | Male infertility | Tavilani *et al.* (2014) |
| *PON1 Q192R* polymorphism | Patients ($n = 100$) and control ($n = 205$) | Acute coronary syndrome | Bounafaa *et al.* (2014) |
| Q192R polymorphism of *PON1* | Patients ($n = 100$) and control ($n = 205$) Pregnant women of Saudi population | Gestational diabetes mellitus | Al-Hakeem *et al.* (2014) |
| *PON1*-L55M gene polymorphism | Patients ($n = 50$) and control ($n = 50$) | Behcet's disease | Dursun *et al.* (2014) |
| *PON-1* 192 gene polymorphism | Patients ($n = 120$) and control ($n = 90$) | Rheumatoid arthritis | El-Banna and Jiman-Fatani (2014) |
| p.Q192R of *PON1* | Patients ($n = 76$) and control ($n = 103$) in Turkish women | Uterine leiomyoma (ULM) patients | Attar *et al.* (2015) |
| (192) Q>R polymorphism of *PON1* | Buryat and Russian populations in eastern Siberia | Lipid profile and components of lipid peroxidation and antioxidant protection | Kolesnikova *et al.* (2015) |
| L55M of *PON1* | Patients ($n = 482$), controls ($n = 326$), Indian women | Polycystic ovary syndrome, glucose metabolism, lipid parameters and hyperandrogenemia | Dadachanji *et al.* (2015) |
| –108C/T, 192Q/R, and 55L/M variations of the *PON1* gene | Patients ($n = 455$) and control ($n = 441$) in Chinese women | Lactonase activities and polycystic ovarian syndrome | Zhang *et al.* (2015) |
| Frequency of MM genotype of *PON1* L55M polymorphism | Patients ($n = 199$), first-degree relatives ($n = 280$) and control ($n = 292$) | Bipolar disorder (mental disorder) | Küçükali *et al.* (2015) |
| Paraoxonase1 192 (*PON1* 192) | Patients ($n = 42$) and control ($n = 46$) | Panic disorder (neuropsychiatric disorders) | Atasoy *et al.* (2015) |

was more in heterozygous *PON1* Arg–Gln genotype as compared to homozygous *PON1* Arg–Arg genotype due to pesticide exposure. Also, the damages were higher in *CYP3A5* G_44G genotype than those with *CYP3A5* A_44G/A_44A genotype. There is an association between genetic polymorphism of *PON1* and GSTM1, GSTT1, GSTP1 genotypes with DNA damage in occupational workers exposed to OPs (Singh *et al.* 2011). The analysis showed that the *PON1* 192Q and 55LM polymorphisms can increase the risk of OPs toxicity among the Caucasian populations (You *et al.* 2013). Recently, the study explored the linkage disequilibrium, allelic frequency and haplotype examination of 10 polymorphic variants of genes (named BCHE-A, BCHE-K, *PON1* L55M, *PON1* Q192R, *PON1* –108C/T, *CYP2C19* G681A, *CYP3AP1* –44G/A, *CYP2D6* G1846A, GSTM1∗0 and GSTT1∗0) involved in OPs metabolism. The adverse genotype combination (unusual BCHE variants, *PON1* 55MM/−108TT and null genotype for both *GSTM1* and *GSTT1*) potentially have a greater genetic risk from exposure to OPs in 0.2% of children ($n = 496$) from agriculture area in Spain (Gómez-Martín *et al.* 2015). There is a positive correlation between *PON1* and cholinesterase in the serum of pesticide poisoning individual that suggests patients with higher paraoxonase 1 activity may detoxify the pesticide poisoning more efficiently (Richard *et al.* 2013). Also, the activities of paraoxonase significantly decreased in OPs poisoned patient (Kale 2013). Thus, paraoxonase can act as a potent biochemical marker for the diagnosis and prognosis of OPs poisoning cases. Apart from these anomalies, there are numerous health risks reported by researchers, depicted in table 4.

## Conclusion

The specific cytochrome P450 isoforms have a distinct role in catalyzing the biotransformation of the organophosphorothionate pesticides into specific structures that inhibit cholinesterase in human. The genotoxicity of pesticides is influenced by the individual inheritance of variant polymorphic genes such as *CYP* and *PON* involved in their metabolism. The desulphuration of OPs pesticides gets converted to more toxic metabolites formation as oxon derivatives (by *CYP1A2*, *CYP2B6* and *CYP3A4* genes). Further, the unfavourable metabolizing alleles (*PON1192Q*) are more susceptible to genotoxic effects as compared to favourable alleles. Thus, the oxon interference plays a vital role in OPs metabolism, decision depending on external and internal factors for its metabolism. Apart from it, exogenous inhibitors named bis-para-nitrophenylphosphate (BNPP), (*O*-(*n*-propyl) *O*-(2-propynyl) phenylphosphate (PPP) and dietholate (SV1), quinidine (antiarrhythmic agent) and ketoconazole, etc. are also responsible for impaired function of *CYP–PON* metabolizing pathway. Another interference for OPs metabolism takes place when metabolite of one pesticide halt the metabolism of another pesticide if exposed simultaneously. Thus, the genetic biomonitoring of populations exposed to hazardous pesticides would be warning for any genetic diseases or cancer.

The aetiology of the environment-related disease is important to understand the polymorphism in genes and their response toward the environment. The gene–environment interaction needs to be elaborated by high throughput genotyping of various sequence variants and by using sensitive biomarker for exposure assessment. Thus, there is a need to identify susceptible groups in case of OPs and other pesticide exposure studies in general. The research, particularity in the area of toxicology, to know the mechanism of interaction and its correlation with outcome of a disease should be emphasized. The pharmacogenomic/gene expression profile and signal transduction events (either specific or nonspecific receptors of signal transduction pathways) for pesticide metabolism process need to be understood at the molecular level. It will generate a genetic database to know the integration of expression data with human physiology and know the possible outcome of short-term and prolonged OPs exposure.

**Acknowledgements**

We thank Vice-Chancellor of CUPB for the support. The work was supported by CUPB-RSM and UGC start-up grants. GK is also thankful to UGC for Moalana Azad National Fellowship. We also thank Dr Alpna Saini, Centre for Classical and Modern Languages, Central University of Punjab, for editing and improving the language.

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Received 26 February 2016, in revised form 18 May 2016; accepted 16 June 2016
Unedited version published online: 20 June 2016
Final version published online: 2 February 2017

Corresponding editor: KUNAL RAY