Metabolism of pesticides by human Cytocrome P450 (CYPs)

[1]RAJDEEP KAUR, [2]DR. YOGEETA THAKUR
[1]Research Scholar, [2]Associate Professor
[1,2]School of Agriculture Sciences and Technology
[1,2]RIMT University, Mandi Gobindgarh, Punjab, India-147301

Abstract: As far the today's scenario, organophosphate pesticides (OPs) are widely used pesticides around the world. These are metabolized by cytochrome P450 enzymes by various reactions and pathways. Humans are inexorably exposed to pesticides in a variety of ways. Metabolism is one amongst factors that can affect the overall toxic profile of a pesticide. During metabolism, the pesticide is biotransformed by phase I cytochrome enzyme and then conjugated to more soluble and excretable by phase II. A metabolic enzyme plays a key role in converting the chemicals into inert derivatives which could be easily eliminated from the body. Chronic exposure to low levels of pesticide can cause mutations. As a susceptibility biomarker, the CYP genetic polymorphism can affect the activation and inactivation of pesticide metabolizing genes. In this research work, a metabolism and interactions of pesticides have been investigated by using cytochrome P450 (CYP) technique. Also, a Genotoxicological studies have been carried out in order to get an overall picture of genotoxic exposure. The overall analysis concluded that Genotyping of CYP polymorphisms provides important genetic information that plays role in modulating pesticide metabolism which helps to recognize the effects of pesticides on the human body.

Index Terms **- Organophosphate pesticides, Pesticide metabolism, Cytochrome P450 enzymes, Gene polymorphism.**

I. INTRODUCTION

Exposure to pesticide is a global challenge to risk assessment. Now-a-days a human susceptibility to the carcinogenic effects of pesticides has become a major research goal. Chronic exposure to low levels of pesticide can cause mutations. The traditional toxicity results in finding a link between chemicals in different doses and tissue pathology. The studies are designed to address the potential impact that pesticide exposure may on farm workers and applicators [1]. Furthermore, in agricultural pesticides are used in different formulations depending on the time of growing season. This makes the exposures complex, and the bio-monitoring of exact compounds for exposure evaluation may become difficult. The possible combined toxic effects of such complex exposures are not usually known [2]. The more important aspect in pesticide effect is the ability of an organism to metabolize it. Active ingredients or formulates alone is not sufficient to evaluate the risk of undesirable health effects from pesticide exposure [3]. As far as genotoxicity is concerned, the assessment of cytogenetic alterations in subjects occupationally exposed to pesticides may be used as a marker of early biological effects. Genotoxicological methods can be used to get an overall picture of genotoxic exposure in work with pesticides [4]. Major phase I enzyme is the super family of cytochrome P450-dependent monooxygenases. P450s exist as a large super family of proteins and are the principal enzymes involved in the oxidation of pesticides. The common chemical reactions involved in phase I are aromatic hydroxylations, aliphatic hydroxylations, oxidative N-dealkylations, oxidative O-dealkylations, S-oxidations, reductions, and hydrolysis. UGT's, SULT's, NAT, GST's of phase II enzymes helps in detoxification of pesticides by catalyzing conjugation reactions [5].

The metabolizing enzymes are responsible for protecting the organism by rapidly processing chemicals to inert derivatives that can be easily eliminated from the body through urine or bile [6]. Besides detoxification, it quite often mediates the toxicity of chemicals through metabolic activation of protoxins and pro-carcinogens, so it thought to have a role in individual susceptibility to chemical induced diseases and cancer. The liver is the main organ for pesticide metabolism and transformation reactions. Organophosphate pesticides (OPs) triesters of phosphoric acid are extensively used a group of pesticides in the world. In addition to their use in agriculture, disease control and as remedial agents, OPs are also used in industries as solvents, flame retardants and in defense forces as nerve agents [3]. OPs inhibit acetylcholinesterase resulting in harmful effects on human health. The studies have reported in order to determine the relationship between OP exposure and cancers of different types. Experimental studies (in vitro and in vivo) have shown that a number of OPs exert genotoxic action [7]. OPs are first and foremost metabolized by various hepatic cytochrome P450s turn into an active intermediate organophosphate-oxons (OP-oxons) [8-9]. These active intermediate OP-oxons are hydrolyzed by paraoxonase to 4-nitrophenol and diethyl phosphate [10]. These oxons are recognized to be the mediator of sensitive OP toxicity, due to its capacity to unite and hinder acetylcholinesterase in the nervous system and at neuromuscular junctions [11]. The genotype of an individual can remarkably influence the disposition of a chemical and determine their susceptibility to its toxicity. Exposure to chemicals can result in different gene expression, which in turn can lead to different pharmacodynamic effects. The addition of genomics into toxicological research can provide an improved understanding of how various xenobiotics act in the human body [12].

II. ADVERSE EFFECT OF PESTICIDES

Organophosphates, which were promoted as a more ecnomical substitute to organochlorines. This class also includes malathion, parathion, and dimethoate; are known for adverse effects on the function of cholinesterase enzymes [13], decrease in insulin secretion, disruption of normal cellular metabolism of proteins, carbohydrates and fats [14], and also with genotoxic effects [15] and effects on mitochondrial function, causing cellular oxidative stress and problems to the nervous and endocrine systems [13] Organophosphorus pesticides also cause serious health effects together with cardiovascular diseases [16], negative effects on the male reproductive system [17] and on the nervous system [13, 18-19] and also a possible increased risk for non-Hodgkin's lymphoma [20]. In addition, prenatal to this exposure to organophosphates has been correlated with decreased gestational duration [21] and neurological problems occurring in children [22].

2.1 Dispersion of pesticides into human body

Pesticides can enter the human body by three common ways: through the skin contact, the mouth (ingestion), and the lungs (inhalation) is shown in Fig. 1.

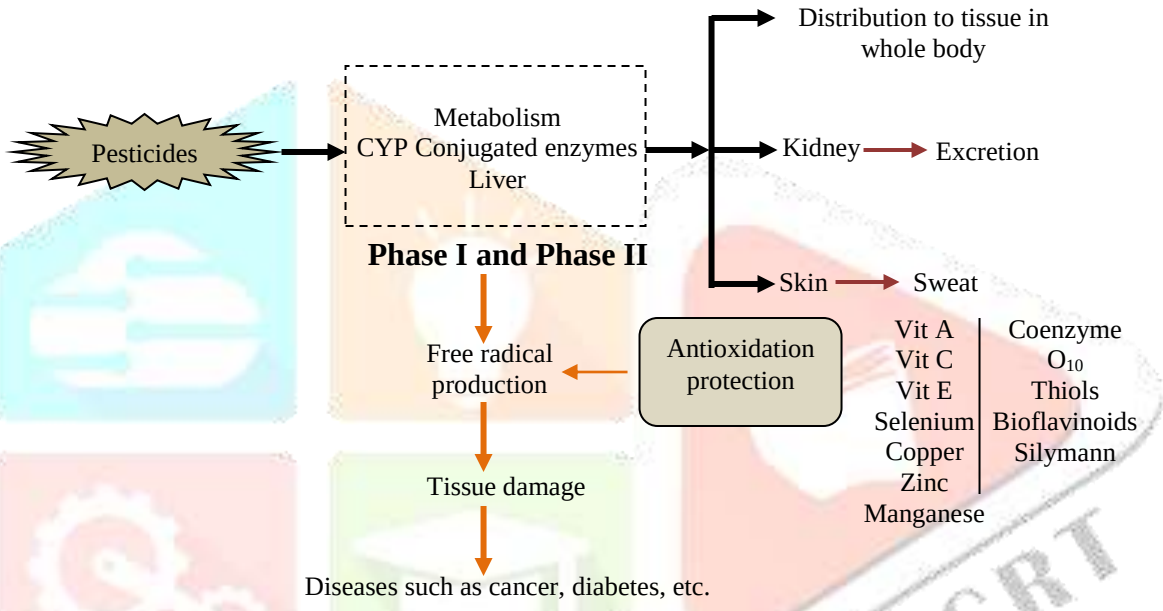

Figure 1 Pesticide Detoxiction pathway [23]

The state of the chemical i.e., solid, liquid, or gas, affects the chances of pesticide penetration into the body [24]. Liquid or gas products can get into the body through all three routes of entry, whereas solids tend to have a lower chance of entry through the lungs. However, if solid particles of the pesticide are small enough or if they remain on the skin long enough, penetration into the body can take place in the same ways as those of liquids or gases. The most common pathway for pesticide poisoning among common users is absorption through the skin [25]. Dermal absorption may occur as a result of splashes and spills when handling (mixing, loading or disposing of) pesticides. To a minor degree, dermal absorption may occur from exposure to great load of residues. The degree of hazard by dermal absorption depends on the toxicity of the pesticide to the skin, the duration of the exposure, the pesticide formulation, and the body part contaminated [26]. Powders, dusts, and granular pesticides are not absorbed so easily through the skin and other body tissues as are the liquid formulations. On the other hand, liquid pesticides containing solvents (e.g., organic solvents) and oil based pesticides usually are absorbed more quickly than dry pesticides. For example, the emulsifiable concentrates, containing a great percentage of the toxic substance in a relatively small amount of solvent, are readily absorbed by the skin. Certain body areas are more prone to absorption of pesticides than other areas.

2.2 Pesticide metabolism

Pesticide biotransformation is the process by which lipophilic foreign compounds are metabolized all through enzymatic catalysis to hydrophilic metabolites [4]. Metabolic enzymes are divided into two groups, Phase I and Phase II enzymes [27]. Phase I reactions are mediated primarily by cytochrome P450 family of enzymes, but other enzymes like flavin monooxygenases, peroxidases, amine oxidases, dehydrogenases, xanthine oxidases also catalyze the oxidation of certain functional groups. In addition to the oxidative reactions, there are different types of hydrolytic reactions catalyzed by enzymes like carboxylesterases and epoxide hydrolases as shown in Fig. 2.

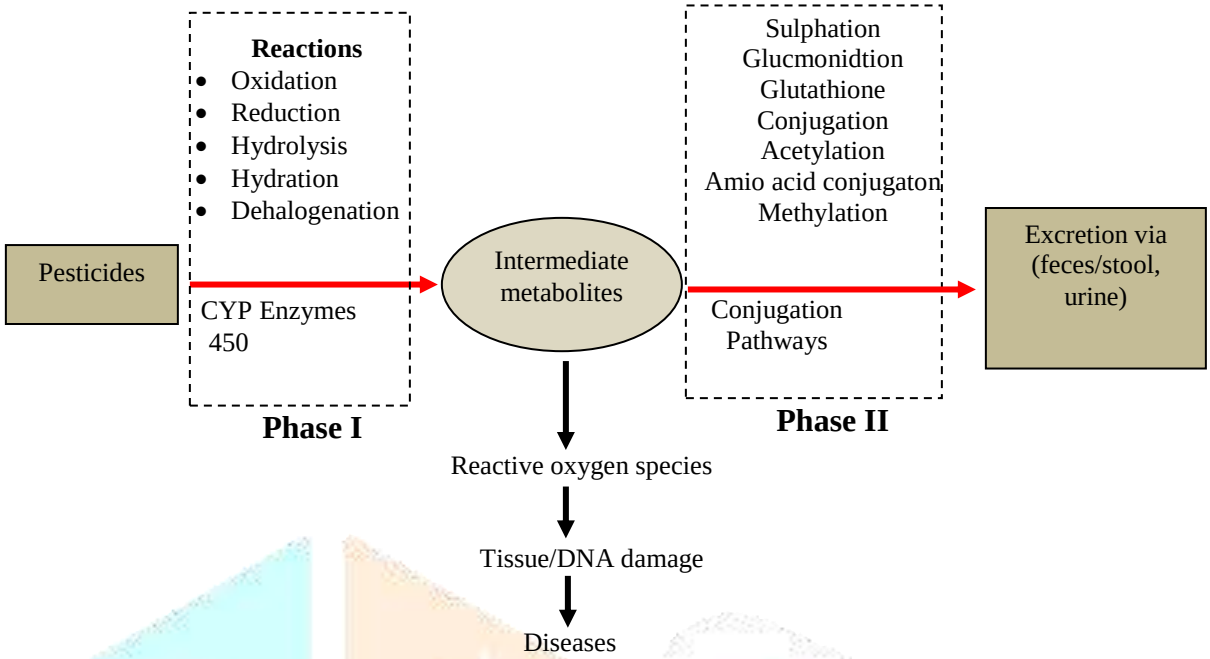

Figure 2 Type of reactions involved [28-31]

Phase I products do not typically eliminate quickly, but undergo a subsequent reaction in which 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 [23, 32]. Proteins involved in pesticide disposition in the body are classified as phase I (oxidative), or phase II (conjugative) metabolizing enzymes, or phase III transporters involved in efflux mechanisms. The main enzymes of phase I metabolism are heme-thiolate proteins of the cytochrome P450 superfamily (CYPs) as already shown in Fig. 1. Phase I enzymes generate functional groups that may consequently serve as a site for conjugation catalyzed by phase II enzymes UDP-glucuronosyltransferases (UGT), Sulfotransferases (SULT), Glutathione S-transferase (GST), and N-acetyltransferase (NAT). These enzymes reactions are necessary for a lipophilic compound to biotransform into a water-soluble product that can be excreted in urine. Phase III transporters like, P-glycoprotein (Pgp), multidrug resistance associated proteins (MRPs), and organic anion transporting polypeptide 2 (OATP2) are expressed in many tissues such as the liver, intestine, kidney, and brain, and play a critical role in pesticide absorption, distribution, and excretion. Along with phase I and phase II enzyme induction/inhibition, pretreatment with different inducers or inhibitors have been shown to vary the expression of phase III transporters, with the ultimate results of altered excretion of pesticides. Exposure to phase I, phase II, and phase III inducers may activate cellular stress response leading to boost in gene expression, which ultimately enhances the abolition and clearance of pesticides. Table 1 shows specific pesticides metabolized by human CYPs, whereas Table 2 shows metabolic reactions carried out by CYP.

Table 1 Specific pesticides metabolized by CYP enzyme

Pesticide	CYP involved	Pathway	Reference
Atrazine	CYP1A1, CYP2C9, CYP1A2, CYP2C19, CYP2D6, CYP2E1,CYP3A4,CYP3A7	N-Deethylation N-Deisopropylation	[33-34]
Carbaryl	CYP1A1, CYP2C9, CYP1A2.CYP2C19, CYP2D6, CYP2E1 CYP3A4, CYP3A7, CYP2C8	Aromatic hydroxylation Methyl Oxidation	[35]
Carbofuran	CYP1A2,CYP2C19, CYP3A4	Ring oxidation	[36]
Carbosulfan	CYP1A1, CYP2C9, CYP1A2.CYP2C19, CYP2D6, CYP2E1 CYP3A4, CYP3A7, CYP2C8	N-S Clevage Sulfoxidation	[37]
Diazion	CYP1A1, CYP2C9, CYP1A2.CYP2C19, YP2D6, CYP2E1 CYP3A4,CYP3A7, CYP2C8, CYP3A5	Desulfuration	[38]
Diuron	CYP1A1, CYP2C9, CYP1A2.CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A7, CYP2C8, CYP3A5	N-Demethylation	[49]

Endosulfan	CYP2B6, CYP2C9, CYP3A4,CYP3A5, CYP3A7	Sulfoxidation	[40-41]
DEET	CYP3A4, CYP2C19, CYP2D6, CYP2E1, CYP3A5	N-Deethylation	[42]
Malathion	CYP1A2, CYP2B6, CYP3A5, CYP3A7	Desulfuration	[43]
Parathion	CYP1A2, CYP2C9, CYP2D6,CYP3A5, CYP3A7	Desulfuration	[9-10;44-45]

Table 2 Metabolic reactions carried out by CYP

Reactions	CYP Enzymes Involved
Desthiopropylation	CYP3A4, CYP2B6, CYP2C19, CYP3A4, CYP2C19, CYP3A4, CYP2B6, CYP3A5, CYP2D6, CYP3A7, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
Desulfuration	CYP1A2, CYP3A4, CYP1A2, CYP2B6, CYP3A4, CYP3A5, CYP3A7, CYP2C19, CYP3A4, CYP2B6, CYP2C8, CYP3A5, CYP2C8, CYP2D6
Hydroxylation	CYP3A4
Hydroxypropylation	CYP2B6, CYP2C19
Imidazolidine	CYP3A4
Lactone formation	CYP2B6
Methyl Oxidation	CYP1A2, CYP2B6
n-butyl side-chain metabolism	CYP2C19
N-Dealkoxylation	CYP3A4, CYP2B6
N-Deethylation	CYP1A1, CYP1A2, CYP2C19, CYP3A4
N-Deisopropylation	CYP1A1, CYP1A2, CYP2B6, CYP2E1, CYP2C8
Nitroimine reduction	CYP3A4
N-S cleavage	CYP3A4, CYP3A5
O-Demethylation	CYP2B6, CYP1A2, CYP2C19
Oxidative metabolism	CYP2C9, CYP2C19, CYP3A5
Ring hydroxylation	CYP3A4
Aliphatic hydroxylation	CYP1A1, CYP1A2, CYP3A4
Dealkylation	CYP2C9, CYP2C18, CYP2C19, CYP3A4, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
Dearylation	CYP2C19, CYP3A4, CYP2B6, CYP2C8, CYP3A5, CYP1A2, CYP2C9, CYP2C18, CYP2C19, CYP3A4

III. CYTOCHROMES P450

Between the enzymes of phase I biotransformation, CYPs show significant catalytic diversity. This enzyme super family, existing in over 50 forms, is the majority important enzyme system involved in the biotransformation of many substances including pesticides. CYPs are erratically distributed in different tissues. Most can be found in almost all tissues and organs. Physiological xenobiotic substrates include drugs, herbal toxins, and pesticides. CYPs mainly catalyze oxidative reactions, insertion of an atom from molecular oxygen into a substrate, i.e. a typical activating (or Phase I) reaction, serving as monooxygenases, oxidases, and peroxidases, although they can act in reduction reactions too. CYPs are separated into three major groups [46]. The first includes CYP families 5 to 51 with an elevated affinity for endogenous substrates, which have remained well conserved all through evolution. The second group includes CYP families 1 to 3, that have a lesser affinity for their substrates and have been less conserved evolutionarily. The third group

includes CYP family 4 which metabolize fatty acids, related substrates, and some xenobiotics. CYP families 1 to 3 are responsible for 70 % to 80 % of all phase I- dependent metabolism number of xenobiotic chemicals [47]. Most of the enzymes in CYP families 1 to 3 show inter-individual variability in catalytic activity. This is also due to genetic polymorphisms or to inconsistency in expression levels. Each CYP isoform has its own set of metabolized substrates. The same xenobiotic is capable of being metabolized by different isoforms into similar or different metabolic products. For enzymes belonging to CYP families, 1 to 4 overlapping substrate specificity is known. The important enzymes for pesticide metabolism are CYP2C9*, CYP2C19, CYP2D6 and CYP3A4, whereas the most important isoforms responsible for the biotransformation of pesticides. In CYP families 2 and 3 HUGO has found new genes like CYP2R1, CYP2S1, CYP2U1 and CYP3A43. There is no obvious relationship between a number of hepatic CYPs and their virtual importance for pesticide metabolism. This might indicate that highly expressed CYPs play an important role in food metabolism and a relatively minor role in pesticide metabolism. Most CYP enzymes are preferentially expressed in the centrilobular area of the liver [48]. Most CYPs involved in the biotransformation of pesticide are inducible [49]. An exception is CYP2D6 in which multiple gene copies are responsible for enlarged detoxifying potential of the enzyme [50]. Induction is a significant adaptive reaction against environmental toxins from the past. CYP expression can be restricted at the transcriptional, mRNA, translational and posttranslational levels. Transcriptional control is extremely important and three crucial cytosolic receptors sense the concentration of environmental xenobiotics, namely the pregnane X-receptor (PXR), constitutive androgen receptor (CAR) and aryl hydrocarbon receptor (AhR). AhR regulates CYP1A1, CYP1A2 and CYP2S1; PXR regulates CYP2C9 and CYP3A4 and CAR regulates CYP2B6, CYP2C9, and CYP3A4. Activation of CYPs as well as phase II and phase III proteins is enthused by increased cellular amounts of pesticides, which may result in superior protein expression and subsequently in lower amounts of pesticides. It is evident that these transcriptional factors are involved in the control of most human pesticide metabolizing CYPs [51]. Table 3 shows the detail of human CYPs gene family.

Table 3 CYP gene families taken from Pubmed

Family	Members	Names
CYP1	3 Subfamilies 3 Gene 1 Pseudogene	CYP1A1, CYP1A2, CYP1B1
CYP 2	13 Subfamilies 16 Gene 16 Pseudogene	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP 2S1, CYP2U1, CYP2W1,
CYP 3	3 Subfamilies 3 Gene 1 Pseudogene	CYP3A4, CYPA5 CYPA7, CYPA43
CYP 4	1 Subfamilies 4 Gene 2 Pseudogene	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2 CYP4X1, CYP4Z1
CYP 5	6 Subfamilies 12 Gene 10 Pseudogene	CYP5A1
CYP 7	1 Subfamilies 1 Gene 0 Pseudogene	CYP7A1, CYP7B1
CYP 8	2 Subfamilies 2 Gene 0 Pseudogene	CYP8A1, CYP8B1
CYP 11	2 Subfamilies 2 Gene 0 Pseudogene	CYP11A1,CYP11B1,CYP11B2
CYP 17	1 Subfamilies 1 Gene 0 Pseudogene	CYP17A1
CYP 19	3 Subfamilies 3 Gene 1 Pseudogene	CYP19A1
CYP 20	1 Subfamilies 1 Gene 0 Pseudogene	CYP20A1
CYP 21	2 Subfamilies	CYP21A2

	1 Gene 1 Pseudogene	
CYP 24	1 Subfamilies 1 Gene 0 Pseudogene	CYP24A1
CYP 26	3 Subfamilies 3 Gene 0 Pseudogene	CYP26A1, CYP26B1, CYP26C1
CYP 27	3 Subfamilies 3Gene 0 Pseudogene	CYP27A1, CYP27B1, CYP27C1
CYP 39 CYP 46	1 Subfamilies 1 Gene 0 Pseudogene 1 Subfamilies 1 Gene 0 Pseudogene	CYP39A1 CYP46A1
CYP 51	1 Subfamilies 1 Gene 3 Pseudogene	CYP51A1

The polymorphic xenobiotic-metabolizing CYP enzymes can be divided into two classes with respect to penetrance for interindividual susceptibility for xenobiotics:

Class I: Composed of CYP1A1, CYP1A2, CYP2E1, and CYP3A4 without important functional polymorphism and active in metabolism of pesticides.

Class II: Composed of CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2D6, which are highly polymorphic and are important for the metabolism of pesticides [52].

IV. CONCLUSION

- Human body is exposed to a number of pesticides, which are metabolized by a variety of enzymes through phase I and phase II reactions. These enzymes mainly contribute in the conversion of pesticides to more polar and water soluble metabolites which are readily excreted from the body.
- During the metabolism of certain pesticides, a variety of reactive and unstable intermediates can be formed, which attack DNA, causing cell toxicity and transformation. Individuals differ in the levels of expression and catalytic activities of metabolic enzymes that activate and/or detoxify pesticides in various organs.
- With existing PCR-based techniques a rapid development of molecular biology approaches the identification of CYP gene polymorphisms and genotyping screening can be done and importance of different polymorphic variant can be discovered.

V. SCOPE OF FUTURE WORK

The goal of the studies *is to* characterize important metabolic profiles of selected pesticides and examine potential interactions to characterize human risks associated with exposure. This study helps to identify those individuals mostly at risk of potential adverse health effects from chronic OP exposure.

VI. ACKNOWLEDGMENT

The author's deeply thankful to RIMT University (Mandi Gobindgarh) for providing a facility to carry out the research work.

REFERENCES

[1] Alavanja, MCR. Hoppin, JA and Kamel, F. 2004. Health effects of chronic pesticide exposure: cancer and neurotoxicity. Annual Review of Public Health, 25(1): 155–197.

[2] Rose, RL. and Hodgson, E. 2005. Metabolism of toxicants. In Hodgson E (ed) Text Book of Modern Toxicology. New York, Wiley: 111–148.

[3] Hayes, WJ. and Laws, ER. 1991. Dosage and other factors influencing toxicity. Handbook of pesticides toxicology, Academic Press, San Diego. 1: 39–105/.

[4] Scarpato, L. Migliore, G. Angotzi, A. Fedi, L. Miligi, N. and Loprieno. 1996. Cytogenetic monitoring of a group of Italian floriculturists: no evidence of DNA damage related to pesticide exposure. Mutation Research,73–82

[5] Rivard, C. Labuda, D. Krajinivic, M. and Sinnett, D. 1999. Risk of childhood leukemia associated with exposure to pesticides with gene polymorphism. Epidemiology, 10: 481-487.
[6] Schenkman, JB. and Cytochrome, P450 dependent monooxygenase: An overview. In Molecular Aspects of Monooxygenases and Bioactivation Toxic Compound 13. Kluwer Academic / Plenum Publishers, New York.1991.
[7] Bolognesi, C. 2003. Genotoxicity of pesticides: a review of human biomonitoring studies. Mutation Research, 543; 251–272.
[8] Tang, J. Cao, Y. Rose, RL. Brimfield, AA. Dai, D. Goldstein, JA and Hodgson, E. 2001. Metabolism of chlorpyrifos by human cytochrome P450 isoforms and human, mouse, and rat liver microsomes. Drug Metabolism and Disposition, 29(9): 1201-1204.
[9] Mutch, E. and Williams, FM. 2006. Diazinon, chlorpyrifos and parathion are metabolised by multiple cytochromes P450 in human liver. Toxicology, 224(2): 22-32.
[10] Mutch, E. Blain, PG. and Williams, FM. 1999. The role of metabolism in determining susceptibility to parathion toxicity in man. Toxicology Letters., 107(1-3): 177-187.
[11] Cascorbi, I. Brockmoller, J. Mrozikiewicz, PM. Muller, A. and Roots, I. 1999. Arylamine *N*-acetyltransferase activity in man. Drug Metabolism Reviews, 33, 489–502.
[12]Sundberg, M. 2004. Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms. Aunyn-Schmiedeberg's Arch Pharmacol, 369: 89-104.
[13] Jaga, K. and Dharmani, C. 2003. Sources of exposure to and public health implications of organophosphate pesticides. Revista Panamericana de Salud Pública 14(3):171-185.
[14] Karami-Mohajeri, S. Abdollahi, M. 2011. Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: a systematic review. Human and Experimental Toxicology, 30(9): 1119–1140.
[15] Li, D. Huang, Q. Lu, M. Zhang, L. Yang, Z. Zong M, and Tao, L. 2015. The organophosphate insecticide chlorpyrifos confers its genotoxic effects by inducing DNA damage and cell apoptosis. Chemosphere, 135: 387-393.
[16] Hung, DZ. Yang, HJ. Li, YF. Lin, CL. Chang, SY. Sung, FC, and Tai, SCW. 2015. The long-term effects of organophosphates poisoning as a risk factor of cvds: a nationwide population-based cohort study. Plos One, 10:e0137632.
[17] Jamal, F. Haque, QS. Singh, S. Rastogi, S. 2015. The influence of organophosphate and carbamate on sperm chromatin and reproductive hormones among pesticide sprayers. Toxicology and Industrial Health,1–10.
[18] Rosenstock, L. Keifer, M. Daniell, WE. Mcconnell, R. and Claypoole, K. 1991. Chronic central nervous system effects of acute organophosphate pesticide intoxica-tion. The Lancet, 338:223-227.
[19] Eskenazi, B. Harley, K. Bradman, A. Fenster, L. Wolff, M. Engel, S. Rauh, V. Wyatt, R. and Pereraet, F. 2006. In utero pesticide exposure and neurodevelopment in three NIEHS/environ-mental agency children's center birth cohorts. Epidemiology, 17: S103.
[20] Waddell, BL. Zahm, SH. Baris, D. Weisenburger, DD. Holmes, F. Burmeister, LF. Cantor, KP. Blair, A. 2001. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes, 12: 509–17.
[21] Eskenazi, B. Harley, K. Bradman, A. Weltzien, E. Jewel, NP. Barr, DB. Furlong, CE. Holland, NT. 2004. Association of in Utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. Environment Health Perspective, 112: 1116–1124.
[22] Rauh, VA. Garcia, WE. Whyatt, RM. Horton, MK. Barr, DB. Louis, ED. 2015. Prenatal exposure to the organophosphate pesticide chlorpyrifos and childhood tremor. Neurotoxicology, 51:80-86.
[23] Rose, RL. and Hodgson, E. 2004. Metabolism of toxicants, In: *Text Book of Modern Toxicology*, Hodgson, E., (Ed.), Wiley, ISBN: 978-0-470-46206-5, 111-148, New York
[24] Berthet, A. Hopf, NB. Miles, A. Spring, P. Charrière, N. Garrigou, A. Baldi, I. Vernez, D. 2014. Human skin in vitro permeation of bentazon and isoproturon formulations with or without protective clothing suit. Archieves of Toxicology, 88: 77-88.
[25] Macfarlane, E. Carey, R. Keegel, T. El-Zaemay, S. Fritschi, L. 2013. Dermal exposure associated with occupational end use of pesticides and the role of protective measures. Safety and Health at Work, 4: 136–141.
[26] Baldi, I. Lebailly, P. Jean, S. Rougetet, L. Dulaurent, S. Marquet, P. 2006. Pesticide contamination of workers in vineyards in France. Journal of Exposure Science and Environmental Epidemiology, 16: 115-124.
[27] Oesch, F. Herrero, ME. Hengstler, JG. Lohmann, M. and Arand, M. 2000. Metabolic Detoxification: Implications for Thresholds. Toxicologic Pathology, 28(3): 382-387.
[28] Parkinson, A. (2001). Biotransformation of xenobiotics, In: Casarett and Doull's toxicology: the basic science of poisons, Klaassen, C.D., (Ed.), Mcgraw-Hill Medical Pub. ISBN: 0071124535, 113–186, New York.
[29] Low, L.K. (1998). Metabolic changes of drugs and related organic compounds, In: Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry, Delgado, J.N. & Remers, W.A., (Ed.), (43–122), Lippincott-Raven, ISBN: 0397515839, Philadelphia
[30] Hodgson, E. and Goldstein, JA. 2001. Metabolism of toxicants: phase I reactions and pharmacogenetics, In: Introduction to Biochemical Toxicology, Hodgson, E. & Smart, R.C., (Ed.), Wiely, 67-113, New York.
[32] Zamek-Gliszczynski, MJ. Hoffmaster, KA. Nezasa, K. Tallman, MN. and Brouwer, KLR. 2006. Integration of hepatic drug transporters and phase II metabolizing enzymes: mechanisms of hepatic excretion of sulfate, glucuronide, and glutathione metabolites. European Journal of Pharmaceutical Sci*ence*, 27: 447-486.
[33] Joo, H. Choi, K. and Hodgson, E. 2010. Human metabolism of atrazine. Pesticide Biochemistry and Physiology, 98: 73-79.

[34] Lang, DH. Rettie, AE. and Bocker, RH. 1997. Identification of enzymes involved in the metabolism of atrazine, terbuthylazine, ametryne, and terbutryne in human liver microsomes. Chemical Research in Toxicology, 10: 1037-1044.
[35] Tang, J. Cao, Y. Rose, RL. and Hodgson, E. 2002. In vitro metabolism of carbaryl by human cytochrome P450 and its inhibition by chlorpyrifos. Chemico-Biological Interactions,141(3): 229-241.
[36] Usmani, KA, Hodgson, E. and Rose, RL. 2004. In vitro metabolism of carbofuran by human, mouse, and rat cytochrome P450 and interactions with chlorpyrifos, testosterone, and estradiol. Chemico-Biological Interactions,150(3): 221-332.
[37] Abass, K. Reponen, P. Mattila, S. and Pelkonen, O. 2010. Metabolism of carbosulfan II. Human interindividual variability in its in vitro hepatic biotransformation and the identification of the cytochrome P450 isoforms involved. Chemico-Biological Interactions, 185(3): 163-173.
[38] Buratti, FM. Volpe, MT. Fabrizi, L. Meneguz, A. Vittozzi, L. and Testai, E. 2002. Kinetic parameters of OPT pesticide desulfuration by c-DNA expressed human CYPs. Environmental Toxicology Pharmacology, 11(3-4): 181-190.
[39] Abass, K. Reponen, P. Turpeinen, M. Jalonen, J. and Pelkonen, O. 2007. Characterization of diuron N-demethylation by mammalian hepatic microsomes and cdna- expressed human cytochrome P450 enzymes. Drug Metabolism and Disposition, 35: 1634-1641.
[40] Clapper, ML. and Szarka, CE. 1998. Glutathione *S*-transferases—biomarkers of cancer risk and chemopreventive response. Chemico-Biological Interactions, 111*:* 377-388.
[41] Lee, H. Moon, J. Chang, C. Choi, H. Park, H. Park, B. Lee, H. Hwang, E. Lee, Y. Liu, K. and Kim, J. 2006. Stereoselective metabolism of endosulfan by human liver microsomes and human cytochrome P450 isoforms. Drug Metabolism and Disposition, 34(7), 1090-1095.
[42] Usmani, KA. Rose, RL. Goldstein, JA. Taylor, WG. Brimfield, AA. and Hodgson, E. 2002. In vitro human metabolism and interactions of repellent N,N-diethyl-mtoluamide. Drug Metabolism and Disposition, 30(3): 289-294.
[43] Buratti, F.M.; D'Aniello, A.; Volpe, M.T.; Meneguz, A. & Testai, E. (2005). Malathion bioactivation in the human liver liver: The contribution of different cytochrome P450 isoform. Drug Metabolism and Disposition, 33(3): 295-302.
[44] Foxenberg, RJ. Mcgarrigle, BP. Knaak, JB. Kostyniak, PJ. and Olson, JR. 2007. Human hepatic cytochrome P450-specific metabolism of parathion and chlorpyrifos. Drug Metabolism and Disposition, 352: 189-193.
[45] Mutch, E. Daly, AK. Leathart, JB. Blain, PG. and Williams, FM. 2003. Do multiple cytochrome P450 isoforms contribute to parathion metabolism in man. Archieves of Toxicology, 2003, 77(6): 313-320.
[46] Krajinovic, M. Sinnett, H. Richer, C. Labuda, D. and Daniel, S. 2002. Role of *NQO1*, *MPO* and *CYP2E1* genetic polymorphisms in thesusceptibility to childhood acute lymphoblastic leukemia. International Journal of Cancer, 97: 230-236.
[47] Autrup H. 2000. Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxicresponse. Mutation Research-Genetic Toxicology and Environment, 464: 65-76.
[48] Zhou M, Maitra SR, Wang P. 2008. The potential role of transcription factor aryl hydrocarbon receptor in downregulation of hepatic cytochrome P-450 during sepsis. International Journal of Molecular Medicine, 21: 423-428.
[49] Xang, X. Solomon, S. Fraser, LR. Trombino, AF. Liu, D. Sonenshein, GE. Hestermann, EV. And Sherr, DH. Constitutive regulation of CYP1B1 by the aryl hydrocarbon receptor (ahr) in pre-malignant and malignant mammary tissue. Journal of Cellular Biochemistry,104: 402-417.
[50] Oinonen, T. and Lindros, KO. 1998. Zonation of hepatic cytochrome P-450 expression and regulation. Biochemical Journal, 329: 17-35.
[51] Lamba, JK. Pharmacogenetics of the constitutive androstane receptor. Pharmacogenomics, 9: 71-83.
[52] Rodriguez-Antona, C. and Ingelman-Sundberg M. 2006. Cytochrome P450 pharmacogenetics and cancer. Oncogene, 25:1679-1691.