POLLUTANTS BIOTRANSFORMATION

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Abstract. All living organisms are exposed to large amounts of xenobiotics, many of which may be toxics. The presence of xenobiotics in a living organism can unbalance the living body by inhibiting its growth or interfering with one or more components or chemical reaction on which it is dependent. The sum of the processes by which a xenobiotic (pesticide) is subject to chemical changes in living organisms is named biotransformation. Biotransformation reactions (phase I or phase II) are important in understanding the metabolism of endogenous molecules (endobiotics), or of the exogenous ones (xenobiotics) and their purpose is to increase the protective mechanisms developed in relation to cells or biological fluids. The equilibrium among the concentration of parent pesticides, biotransformation intermediates and conjugates, is responsible for the cellular, tissue or organism toxicity.

Keywords: pesticide, biotransformation, toxicity, xenobiotic, health

1. Introduction

The living organisms are dynamic systems which function as entities, being the result of interdependent chemical reactions and processes that take place continuously and are maintained in a steady state (Coman et al., 2006): lipid peroxidation, oxidative stress, inflammation, genotoxicity, cytotoxicity.

All living organisms are exposed to large amounts of xenobiotics, many of which may be toxics. The penetration of some xenobiotics in the human body

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may alter cell function and may induce various pathologic states (Vulimiri et al., 2010).

The presence of xenobiotics in a living organism can unbalance the body by inhibition of its growth or interaction with one or more components or chemical reactions.

Among xenobiotics, pesticides have a great potential to induce biological changes in target organisms (pests) as well as in non-target organisms, thanks to their small specificity (Malekinejad et al., 2006).

Pesticides (xenobiotics), in human (mammalian) organisms, suffer metabolic alterations in various organs and tissues (Coman and Draghici, 2004; Beard, 2006) such as liver, skin, kidney, plasma, intestine, brain and placenta (Figure 1).

The sum of the processes by which a xenobiotic (pesticide) is subject to chemical changes in living organisms is named biotransformation.

2. Phase I Biotransformation

Biotransformation reactions (phase I or phase II) are important in understanding the metabolism of the endogenous molecules (endobiotics) or of the exogenous ones (xenobiotics). Their purpose is to increase protective mechanisms developed in relation to cells or biological fluids.

The parent pesticides or the pesticide metabolites resulted from phase I biotransformation, may act on functional compounds and induce pathologic states, or may be eliminated after the transport through body fluids, via bile or urine (Coman et al., 2006).

In a number of cases, the products of pesticide phase I biotransformation (metabolites) are more toxic than the parent pesticides, thanks to the hydrophilic compounds resulted from enzymatic biotransformation of initial hydrophobic compounds (Ferrari et al., 2007). In this situation the term bioactivation is used (Denisov et al., 2009; Dufol and Guillen, 2009) because hydrophilic metabolites may easily interact especially with endogenous functional molecules (proteins, enzymes, nucleic acids) leading to an increase in toxicity.

Phase I biotransformation has not achieved spectacular results in terms of molecular mass and solubility changes in relation to the xenobiotic metabolite, but the new functional groups introduced by oxidation reactions will facilitate phase II biotransformation (conjugation) in the presence of phase II enzymes. Increases in molecular mass and solubility of xenobiotic metabolites are achieved through the process of conjugation (Strazielle et al., 2004; Carozza et al., 2009).

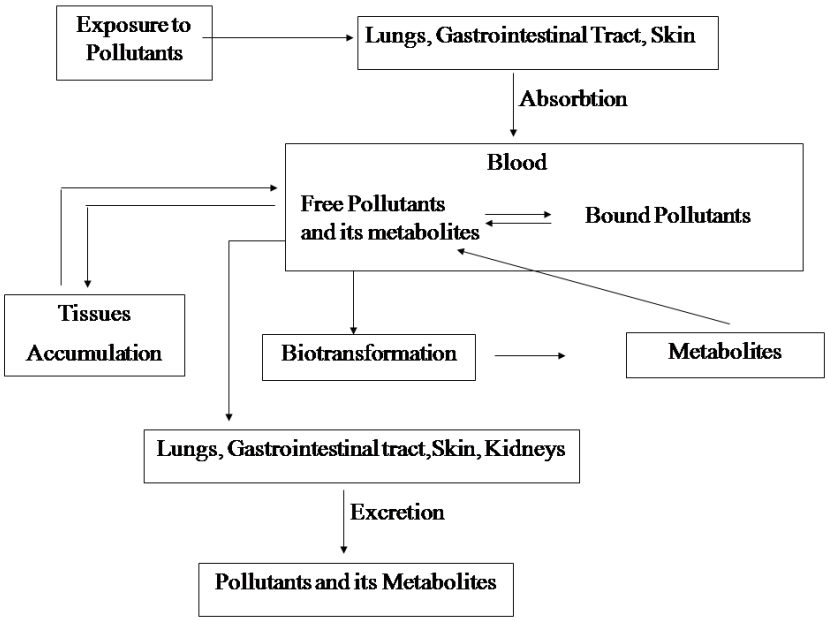

Figure 1. The circuit of xenobiotics (pesticides) in human body.

Many pesticides or their reactive more hydrophilic metabolites, formed in phase I biotransformation mostly by cytochrome P-450 enzymes, are detoxified by phase II biotransformation (Zhang et al., 2009) in the presence of conjugating enzymes (glutathione S-transferases, UDP-glucuronosyltransferases, N-acetyltransferases, sulfotransferases (Figure 2).

Cytochromes P-450 (CYP) are the major phase I biotransformation enzymes, which consist of a family of enzymes that catalyze several reductive or oxidative reactions of xenobiotics or endobiotics to form the intermediates which can be substrates for phase II biotransformation enzymes (Kohle and Bock, 2007; Gonzales et al., 2009).

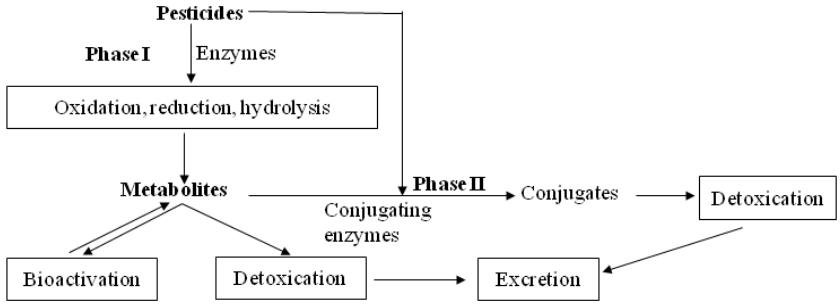

Figure 2. General scheme of biotransformation.

Other enzymes also act in Phase I biotransformation alongside of CYP, and these are: monooxigenases, peroxidases, hidrolases, dehidrogenases, aminooxidases, xantinoxidase (Figure 3).

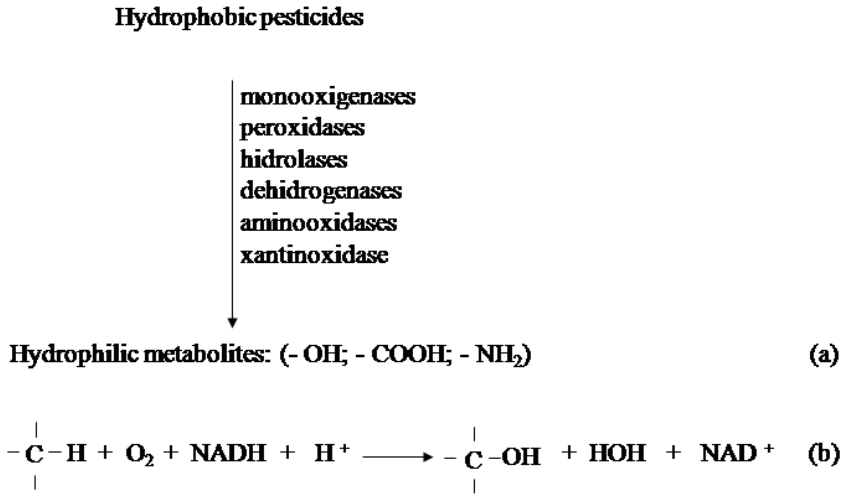

Figure 3. Phase I Biotransformation, (a) general scheme; (b) scheme of monooxigenase action

The basic reactions from phase I biotransformation, which introduce an oxygen atom on the substrate molecule are catalyzed by cytochromes P450, (monooxygenase activity).

The Phase I biotransformation of chlorpyrifos (an organophosphate pesticide), in the presence of CYP, leads to the corresponding oxon analog by desulfurization (Figure 4). The metabolic desulfurization process of organophosphate pesticides is considered bioactivation (Badea et al., 2009; Sanchez et al., 2012), because oxon compounds are up to 1000 times stronger inhibitors of acetylcholinesterase, than the parent compounds.

The CYP family of enzymes can lead to either the activation or detoxification of pesticides in living organisms. The relative rates at which pesticides are activated or detoxified can be essential for toxicology. For CYP activation of pesticides, the phase II biotransformation is essential in the detoxification process.

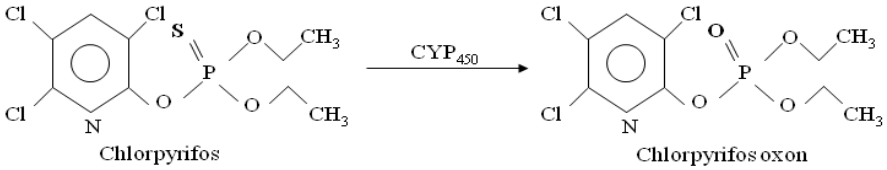

Figure 4. Enzymatic transformation of chlorpyrifos in chlorpyrifos oxon in living organisms.

3. Phase II Biotransformation

Phase II biotransformation enzymes, engaged in catalyzing conjugation, have been less studied than the phase I biotransformation enzymes, engaged in catalyzing global biotransformation processes (Hernandez et al., 2012).

These species can be considered cellular incinerator enzymes, because they have the ability to catalyze the conversion of many xenobiotic substances (drugs, pesticides, organic compounds, carcinogens) or of their metabolites into compounds that can be excreted or degraded for excretion (M.J.Zamec et al., 2006).

The Phase II biotransformation is generally seen as a way for detoxifying the living body, and the inhibition of the enzymes that catalyze these chemical changes may lead to increased toxicity of xenobiotics or of their metabolites (Frova, 2006).

A family of phase II enzymes, which includes (UDP-glucuronosyltransferases (UGTs), sulfotransferases (ST), Glutathione-S-transferases (GSTs), N-acetyltransferases) catalyzes the chemical conjugation reactions (Figure 5).

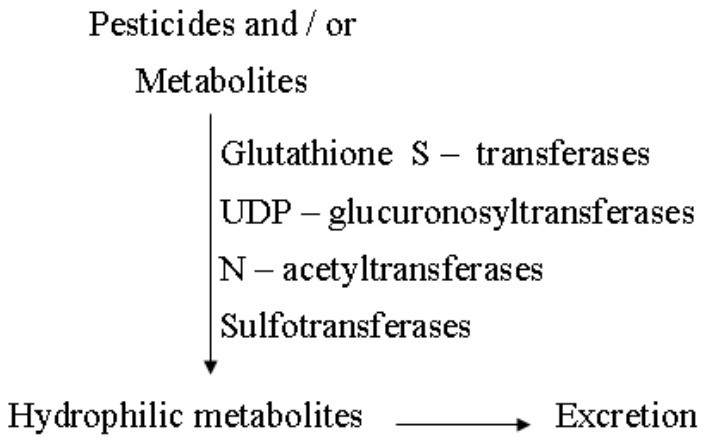

Figure 5. General scheme of phase II biotransformation processes

Phase II biotransformation enzymes catalyze reactions that add hydrophilic inner cosubstrates (glutathione, UDP-glucuronic acid, 3'-phosphoadenozin-5'-phosphosulphate) to pesticides (Figure 6) or their phase I biotransformation metabolites (Prade et al., 1998; Meijerman et al., 2008).

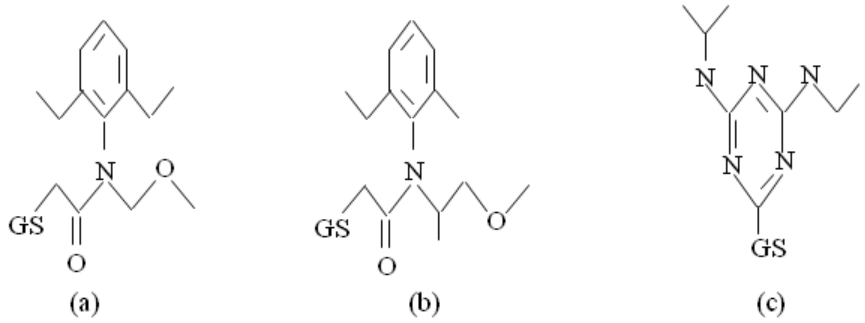

Figure 6. Conjugate structures of some herbicides with glutathione (GS), (a) alachlor; (b) metalachlor; (c) atrazine.

Glucuronidation is a major detoxification pathway in all vertebrates, and the reaction is catalyzed by a multigene family of isoenzymes, the UDP-glucuronosyltransferases (E.C. 2.4.1.17).

UDP-glucuronosyltransferases catalyse the transfer of a glucuronic acid residue, from UDP-glucuronic acid to compounds possessing carboxyl-, hydroxyl-, amino-, or sulfhydryl groups (Kohle and Bock, 2007; Coman et al.,

2009). Mammalian UGTs used UDP-glucuronic acid as glycosyl donor and the reaction products are water soluble β-D-glucuronides, which circulate in biological fluids and are excreted in urine (Figure 7).

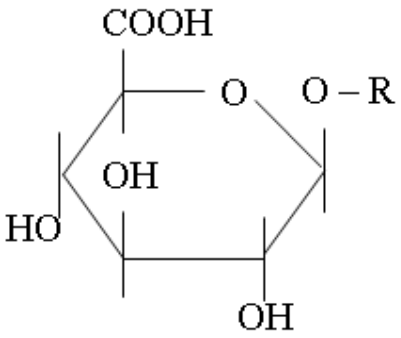

Figure 7. General structures of β-D-glucuronides

The detoxifying reaction catalyzed by UDP-glucuronosyltransferases can be inhibited by a large variety of compounds, other than environmental pollutants (pesticides):

- natural or synthetic toxic substances (food ingredients);
- endogenous compounds (bile acids, long chain acyl-CoAs);
- drugs.

The disturbance of the glucuronidation reactions, leads to an increase in the human pathologic potential and to the development of pesticide toxicities or death (Tolson and Wang, 2010).

Glutathione S-transferases (E.C. 2.5.1.18) act as detoxifying enzymes, and catalyze conjugation of inner glutathione with electrophilic compounds (Prade et al., 1998; Meijerman et al., 2008).

As UGTs, ST, GSTs are found in all aerobic organisms and also in plants, GSTs are responsible for their tolerance to the triazine pesticides metalachlor and alachlor (Fig.6).

GSTs are able to interact with several classes of herbicides (triazines, diphenylethers, thiocarbamates, chloroacetamides) or their phase I metabolites, to detoxify the mammalian body (Prade et al., 1998).

The level of GSTs can be considered an important protective factor against xenobiotics (pesticides) and oxidative stress.

The sulfotransferases are a family of enzymes that catalyze the conjugation by transfer of a sulfonyl group, from a sulfate donor to amino or hydroxyl groups of pesticides or pesticide metabolites.

ST form a group of cytosolic enzymes, that have a higher affinity for substrates (xenobiotics) but lower reaction capacity than UGTs (Gonzales et al., 2009).

4. Conclusion

The sum of the processes by which a xenobiotic (pesticide) is subject to chemical changes in living organisms is named biotransformation.

The biotransformation processes in mammalian bodies are running in the presence of some specific or non-specific enzymes. At molecular level these enzymes transform the xenobiotics into metabolites that have electrophilic functional groups which can increase their solubility in biological fluids in order facilitate their elimination from the body, or can increase their reactivity compared to the parent pesticide, leading to a increase in toxicity.

Pesticides pose a public health risk for humans and induce numerous problems for the environment that are hard to solve.

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