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Short Communication

Organophosphate's Serious Adverse Consequences on the Human Population with Specific Biomarkers

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Everyone of us is exposed to a diverse kind of harmful agents and reagents in the environment across the span of a lifetime. And there are several genetic pathways that play a critical role in the development of disease because of these chemical insults [1,2]. However, there are some inherent genetic pathways that are believed to have also evolved for minimizing the adverse effects of these environmental insults. The environmentally responsive genes expressed in these pathways exhibit variable effects; these variations lead to altered effectiveness of these pathways.

Organophosphate (OP) insecticides are commonly used in the US and abroad. Organophosphate used in these commercial insecticides vary in their toxicity and residue levels, and excretion. Organophosphates were endorsed as a more ecological alternative to organochlorines [3], the most common of which is glyphosate. These are mainly used as herbicides and pesticides. In particular, OPs are the esters of phosphoric acid and due to their relatively fast degradation rates are considered safer to use agriculturally. However, both acute or chronic exposure to OPs can produce varying levels of toxicity in mammals, including humans, pets, and farm animals, and other wildlife species, such as many species of birds, insects, etc. and plants.

Some genetic polymorphisms are known to influence the risk of disease or toxicity with certain occupational exposures to these glyphosphates. The genetic susceptibility to occupational exposures has been well stated by Christiani., *et al.* 2008 [4], where it has been documented that because of the high prevalence in the general population, genetic variants that determine susceptibility to environmental exposures may contribute greatly to the development of occupational diseases. Same is true for the farm worker's susceptibility toward herbicides and pesticides.

Organophosphotases are known to inhibit acetylcholinesterase activity, not only in insects but also in aquatic and terrestrial organisms, these lead to respiratory, reproductive, nervous, hepatic, and renal abnormalities. Acetylcholine is a neurohumoral mediator at the cholinergic junctions. Since acetylcholinesterase is the enzyme that degrades acetylcholine following stimulation of a nerve by inhibiting acetylcholinesterase, OPs are responsible for a large number of cases of pesticide poisoning. Other than their inhibition of cholinesterases by these OP's, including acetyl cholinesterase (*AChE*), they also inhibit Butryl cholinesterase (*BChE*) as well. The inhibition of cholinesterases results in the accumulation of acetyl choline leading to muscle overstimulation. Thus, organophosphates allow acetylcholine to accumulate and result in initial excessive stimulation followed by depression.

Organophosphotases, especially the more toxic oxon form, are metabolized by paraoxonase enzyme which is encoded by the *PON1* gene [5]. Previous studies have shown variability in the activity of PON1 gene in humans [6,7], thus indicating a potential genetic based disparity propensity towards OP toxicity. Hoffmann., *et al.* 2010, evaluated genetic variants of cholinesterase and OP-metabolizing enzymes for their association with the risk for OP toxicity. Two common variants are prevalent in the *PON1* gene coding sequence: a Gln192Arg substitution and a Leu55Met [8,9]. The variant Q192R is associated with the decrease in its activity. This low activity variant of *PON1* gene was evaluated as a predictor of sensitivity to OP and is currently an on-going longitudinal study on Washington state agricultural workers. Thus, the Q192R variant of *PON1* that allows the accumulation of acetyl choline on exposed workers contributes to the

increased risk of OP toxicity. However, the Leu55Met does not affect catalytic activity. Furthermore, paraoxonase enzyme data indicate that Q192R variant of the PON1 protein is associated with the decreased ability to metabolize the oxon's form of OP [10]. Two genetic variants, rs2668207 and rs2048493 in the *BChE* gene, were found to be associated with decreased cholinesterase activity in this enzyme and these variants are currently being evaluated further for their contribution to OP toxicity. It is speculated that inherent low activity of *BChE* in agriculture workers may make them more at risk for OP toxicity [11]. In another study PON1 variants L55M, Q192R and I102V are associated with the prostrate cancer [12].

Glyphosate formulations are more toxic than the active substance alone [13]. Glyphosate-based herbicides, such as the well-known "Roundup," can cause DNA damage and act as an endocrine disruptors in human cell lines [12] and leads to cell death [14]. There is documentation for their potential capability to impact cytoskeleton and intracellular transport [15]. Furthermore, besides brain and skeletal muscles, OPs are known to severely affect other vital organs, such as lungs, heart, liver and reproductive, developmental, and bodies defense system.

In some cases, genetic variations may predispose workers to develop disease with workplace exposures. It is also documented that low glyphosate residue may incidentally impact pest and pathogen occurrence in the populations. Another study, based on the analyses using the new bioinformatics tool, have shown that 54% of the human core gut microbial population are sensitive to glyphosate [16]. This study further indicates an actual effect of glyphosate on human and animal microbial population in gut and thus adversely impact health. As a rich and diverse microbial community is living in soil, especially in the plant/soil interface known as the rhizosphere, on plant surfaces, and in animal guts, this insult may have severe implications to both the quality of agricultural produce and to health.

The human exposure to pesticides have been reported by several epidemiological studies [18-22]. The gut microbiome plays a big role in metabolic management, cognitive development, energy creation, homeostasis, and immune system. The results are not only limited in the gut, but also impact many other organs, such as brain due to the microbiome-gut-brain axis. Given that gut microbiota plays a crucial role towards human health and healthy aging. The relevance of the effects of gut microbiota species and pesticides is still not clear, its imperative to have a clear vision on it. Thus, biological significant perturbation on humans should be identified and more efforts are necessary to acquire useful means for a reasonable risk evaluation.

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