Letter to the editor:

METABOLIC DYSHOMEOSTASIS BY ORGANOPHOSPHATE INSECTICIDES: INSIGHTS FROM EXPERIMENTAL AND HUMAN STUDIES

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Dear Editor,

Organophosphate insecticides (OPI), derived from phosphoric, phosphonic or phosphinic acids, find application as agents for controlling insect pest populations. OPIs elicit their characteristic toxicity by phosphorylating and inhibiting the enzyme, acetylcholinesterase (AChE). Cholinergic stress resulting from overstimulation of nicotinic- and muscarinic acetylcholine receptors is the chief mechanism of acute toxicity of OPI (Fukuto, 1990; Sogorb and Vilanova, 2002; Abou-Donia, 2003; Costa, 2006). The ubiquitous nature of AChE and its conserved physiological role in the regulation of neurotransmission means that non-target animals (including humans) are at risk of adverse outcomes in the event of exposure to OPI. Neurotoxicity, characterized by cholinergic and non-cholinergic outcomes, is the most studied aspect of OPI toxicity. However, it is now unequivocally recognized that the toxicity of OPIs goes beyond the realm of neurotoxicity.

A large number of animal studies explicitly demonstrate that OPIs have the propensity to cause hyperglycemia, perturbations in carbohydrate metabolism and endocrine dysregulations. Repeated exposure to OPI precipitates insulin resistance (studies listed in Table 1), a key component of metabolic syndrome. Extrapolating the outcomes of animal experimentation to the human situation is a challenging task. Experimental studies often employ doses much higher than doses of environmental relevance. However, several studies clearly (listed in Table 2) establish that OPI exposure elicits metabolic dyshomeostasis in human subjects. A recent study demonstrates that the incidence of diabetes among Thai farmers positively correlates with OPIs such as chlorpyrifos, dicrotophos, dichlorvos, ethyl-p-nitrophenyl, mevinphos, monocrotophos and methamidophos (Juntarawijit and Juntarawijit, 2018). Thus, it is evident that OPI exposure is a clear risk factor for metabolic dysregulations among those who are occupationally exposed. One has to take cognizance of the fact that levels of exposure to OPI among occupationally exposed people are likely to be higher than the general population. However, a recent study reveals that glycated hemoglobin levels correlate with plasma levels of OPI (due to environmental exposure), but not with AChE activity (Velmurugan et al., 2017). This indicates that low-level OPI exposure may cause metabolic dysregulations.

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Hence, we believe that further studies are needed to evaluate the effects of low-level, chronic non-occupational exposure to OPI on metabolic health.

### Table 1: Experimental studies reporting metabolic dysregulations caused by organophosphate insecticides in rodent models

<table>
<thead>
<tr>
<th>Key findings</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Long term exposure to chlorpyrifos reduces insulin sensitivity and causes fat gain in rats. Chlorpyrifos-treated rats also suffered from disruption of the gut barrier, alteration in gut microflora profile and low-grade inflammation.</td>
<td>Liang et al., 2019</td>
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<td>Diazinon treatment was associated with an increase in blood glucose, insulin and vaspin levels, and glucose intolerance in rats. Increased expression of PTEN and FOXO1 was observed in the livers diazinon treated rats.</td>
<td>Salek-Maghsoudi et al., 2019</td>
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<td>Repeated administration of diazinon for 4 weeks caused increase in blood glucose, creatinine, urea, percentage of lymphocytes, dyslipidemia, increased circulating aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase activities in the adult and aged rats compared to respective controls.</td>
<td>Yousefizadeh et al., 2019</td>
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<td>Methyl-parathion administration to rats causes elevated plasma glucose and creatinine levels along with diminished urinary flow rate and increased urinary excretion of glucose, phosphate, and albumin.</td>
<td>Fuentes-Delgado et al., 2018</td>
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<td>Chronic exposure to monocrotophos causes hyperglycemia and glucose intolerance in mice. Intestinal metatranscriptomic and host metabolomic analyses revealed that short-chain fatty acids such as acetate produced by microbial degradation of organophosphates may induce gluconeogenesis.</td>
<td>Velmurugan et al., 2017</td>
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<tr>
<td>Exposure to acephate during pregnancy and lactation causes glucose intolerance in the offspring in rats.</td>
<td>Ribeiro et al., 2016</td>
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<td>Augmentation of pancreatic beta cell functions precipitate as a way to counter glucose intolerance in rats subjected to chronic exposure to monocrotophos.</td>
<td>Nagaraju and Rajini, 2016</td>
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<tr>
<td>Repeated exposure to malathion caused increase in plasma glucose, insulin and glycated hemoglobin levels along with dyslipidemia in rats.</td>
<td>Lasram et al., 2015</td>
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<td>Chronic exposure to monocrotophos causes elevated fasting glucose, hyperinsulinemia, hypercorticosteronemia, glucose intolerance, insulin resistance and increase in circulating triglyceride levels in rats. Further, tyrosine aminotransferase, glucose-6-phosphatase and glycogen phosphorylase were elevated in livers of treated rats along with loss of glycogen.</td>
<td>Nagaraju et al., 2015</td>
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<td>Repeated exposure (8 weeks) to chlorpyrifos and profenofos causes hyperglycemia in rats.</td>
<td>Hamza et al., 2014</td>
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<td>Repeated exposure to monocrotophos causes increase in blood glucose, dyslipidemia and cardiac toxicity in rats.</td>
<td>Velmurugan et al., 2013</td>
</tr>
<tr>
<td>Repeated exposure to malathion causes fasting hyperglycemia along with increase in phosphoenolpyruvate carboxykinase, glucose 6-phosphatase activity and tumor necrosis factor α levels in the liver.</td>
<td>Mostafalou et al., 2012</td>
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<tr>
<td>Hyperglycemia in rats subjected to a single dose of monocrotophos is attributable to adrenergic mechanisms, while hypercorticosteronemia is responsible for upregulation of liver tyrosine aminotransferase activity.</td>
<td>Joshi et al., 2012</td>
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<tr>
<td>Cholinergic antagonism prevents the hyperglycemic potential of a single dose of monocrotophos.</td>
<td>Joshi and Rajini, 2012</td>
</tr>
<tr>
<td>Acute exposure to chlorpyrifos causes hyperglycemia, hypercorticosteronemia and dyslipidemia in rats.</td>
<td>Acker and Nogueira, 2012</td>
</tr>
<tr>
<td>Acute exposure to malathion causes hyperglycemia and hepatic glycogen depletion in rats.</td>
<td>Lasram et al., 2008</td>
</tr>
<tr>
<td>Repeated exposure to dimethoate causes alteration in glucose homeostasis and oxidative impairments in the pancreas in rats.</td>
<td>Kamath et al., 2008</td>
</tr>
</tbody>
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Key findings | Reference
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A single dose of acephate causes reversible hyperglycemia in rats, with concomitant hypercorticosteronemia and increased activity of hepatic gluconeogenesis enzymes (tyrosine aminotransferase and glucose-6-phosphatase). | Joshi and Rajini, 2009
Sub-chronic exposure to malathion leads to hyperglycemia and up-regulation of hepatic glycogen phosphorylase and phosphoenolpyruvate carboxykinase activity in rats. | Abdollahi et al., 2004

Table 2: Studies that demonstrate the link between exposure to organophosphate insecticides and metabolic dysregulations in human subjects

Key findings | Reference
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A prospective study of cases involving pesticide self-poisoning conducted in parallel in Sri Lanka and Bangladesh showed that OPI poisoning is associated with acute dysregulations in glucose homeostasis that are related to changes in insulin action and secretion. | Gifford et al., 2019
A survey performed in villages of Vadapalanji Panchayat (a southern part of India) revealed that OPI constituted nearly 50 % of used pesticides. A survey of over 3000 participants revealed a prevalence of diabetes (18 %). Plasma organophosphate residues correlated positively with HbA1c. HBA1c values did not correlate with plasma cholinesterase levels. | Velmurugan et al., 2017
A retrospective observational study of 184 non-diabetic patients with organophosphate poisoning suggests that hyperglycemia at presentation is associated with in-hospital mortality rates. | Moon et al., 2016
A study of 50 individuals admitted to Osmania hospital in Hyderabad (India) with OPI poisoning revealed that 38 % of patients had hyperglycemia. Hyperglycemia at admission correlated with suppression of pseudocholinesterase activity. Random blood sugar levels of > 200 mg/dl at admission and pseudocholinesterase levels below 1000 U/L are reported as reliable parameters to predict mortality and ventilator requirement in OPI poisoning. | Rao and Raju, 2016
A study of 71 cases of OPI poisoning revealed that blood glucose levels in subjects were higher (144.7 ± 85.3 mg/dL) than the normal range (70–110 mg/dl). More importantly, a subpopulation of patients exhibiting intermediate syndrome (n=11) exhibited much higher blood glucose levels (186.63 ± 57.31 v/s138.55 ± 71.34 mg/dL) and severe suppression of serum cholinesterase activity (465.11 ± 302.63 v/s 2651.72 ± 1266.68 U/L; normal range – 3,600–12,900 U/L) than the patients without intermediate syndrome (n=56). | Çolak et al., 2014
Transient glycosuria with or without hyperglycemia was reported in a significant number of patients admitted due to OPI poisoning. | Sudhir et al., 2013
A comparative cross-sectional study involving a non-diabetic farmer cohort (n=98) and age-matched control group (n=90) revealed that blood malathion (0.0746 ± 0.01404 v/s 0.0031 ± 0.0006 mg/L), fasting blood glucose (109.1 ± 20.6 v/s 89.8 ± 10.2 mg/dL) and insulin (12.3 ± 4.6 v/s 5.2 ± 1.6 µU/mL) levels were markedly higher in farmer group as compared to the control group. A positive correlation was observed between malathion blood concentration, waist circumference and insulin resistance. | Raafat et al., 2012
91 cases of OPI poisoning were classified into grade 0, 1, 2, and 3. Blood glucose was elevated and serum cholinesterase activity was suppressed in grade 1, 2 and 3 patients. The severity of hyperglycemia was related to cholinesterase suppression. | Amanvermez et al., 2010
A study, involving more than 33000 pesticide applicators, designed to investigate the relationship between lifetime exposure to specific agricultural pesticides and diabetes incidence among the applicators, revealed that | Montgomery et al., 2008
Key findings

chlorpyrifos, coumaphos, diazinon, dichlorvos, phorate, terbufos, and trichlorfon were associated with increased odds of diabetes, with chlorpyrifos, diazinon, and trichlorfon being dose-dependent.

Reference

Hyperglycemia was observed in 982 out of 2708 OPI poisoning cases studied in Pakistan between 2001 and 2007.

Ather et al., 2008

A retrospective study of 220 patients hospitalized in Turkey between the years 1995 and 2004 revealed elevated blood glucose levels in patients (145 ±68 mg/dL) compared to the normal range (70-110 mg/dL).

Yurumez et al., 2007

Elevated levels of glucose, amylase and immunoreactive trypsin levels were observed in children exhibiting acute pancreatitis due to OPI and carbamate poisoning.

Weizman and Sofer, 1992

A case report of 2 fatal OPI poisoning revealed that subjects were associated with severe hyperglycemia, metabolic acidemia and moderate hyperkalemia.

Hui, 1983

A 32 year old male patient with OPI poisoning developed hyperglycemia, glycosuria and ketonuria soon after hospitalization. Intervention with insulin was required to treat hyperglycemia.

Moore and James, 1981

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Conflict of interest

The authors declare no conflict of interest.

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