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Assessing the connection between organophosphate pesticide poisoning and mental health: A comparison of neuropsychological symptoms from clinical observations, animal models and epidemiological studies

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ABSTRACT

Psychiatry and psychology are beginning to recognize the importance of lead, mercury and heavy metals as causal partners in the development of mental disorders. Further, mental health researchers and clinicians are embracing the idea that the combined effects of genetics and environmental exposures can result in perturbations in brain neurochemistry leading to psychiatric disorders. The purpose of this review is to examine the biological foundations for the epidemiological observations previously identified by reviewing the toxicology literature and relating it to epidemiological studies addressing the role of poisoning with organophosphate pesticides (OPs) in neurobehavioral and neuropsychological disorders. The goal of this review is to raise awareness in the mental health community about the possibility that affective disorders might be the result of contributions from environmental and occupational pesticide poisoning.

1. Introduction

Psychiatry and psychology are beginning to recognize the importance of lead, mercury and heavy metals as causal partners in the development of mental disorders (Genuis, 2008a). Further, mental health researchers and clinicians are embracing the idea that the combined effects of genetics and environmental exposures can result in perturbations in brain neurochemistry leading to psychiatric disorders (Genuis, 2008b). Some clinicians are unaware that environmental toxins may play a role in initiating mental disorders because of the segregation of the neurotoxicological and psychiatric literature. Recent reviews have recounted the growing number of studies showing that exposure to high levels of organophosphate pesticides (OPs) have been associated with depression and high suicide rates in agricultural and other pesticide exposed workers (Freire & Koifman, 2013; Jaga &

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Dharmani 2007) and in suicidal ideation among highly exposed workers (Wesseling et al., 2010). These observations are telling because, aside from mood and affective disorders, farmers generally have lower frequencies of psychiatric disorders than other occupational groups (Thelin, Holmberg, Nettelbladt, & Thelin, 2009; Thomas et al., 2003). However, British farmers reported thinking that "life was not worth living" and this depressive symptom might be indicative of increased suicidal ideation and increase the risk of suicide (Thomas et al., 2003). This highlights the importance of addressing why the suicide rate in some farming communities is so high given the fact that farmers generally have better mental health than their urban counterparts and also than workers in other occupations (Boxer, Burnett, & Swanson, 1992; Charlton, 1995; Fragar & Henderson, 2005; Gregoire, 2002; Gunderson et al., 1990; Hawton, Fagg, Simkin, Harriss, & Malmberg, 1998; Kposowa, 1999; Stallones, 1990; Stallones, Doenges, Dik, Valley, 2013). A link between a history of organophosphate exposure and suicide has been suggested in several epidemiological studies (Meyer et al., 2010; Parron, Hernandez, & Villanueva, 1996; Stallones, 1990; Stallones, 2006; van Wijngaarden, 2003).

The purpose of this review is to examine the biological foundations for the epidemiological observations previously identified by reviewing the toxicology literature and relating it to epidemiological studies addressing the role of poisoning with OPs in neurobehavioral and neuropsychological disorders. There have been a number of excellent reviews of both toxicology (Colovic, Krstic, Lazarevic-Pasti, Bondzic, & Vasic, 2013; Karalliedde, Edwards, & Marrs, 2003; Kwong, 2002) and epidemiology (Freire & Koifman, 2013; Jaga & Dharmani 2007; Jokanovic & Kosanovic, 2010; London et al., 2012) on this topic, but the reviews from these disciplines have not been integrated using a neuroscience framework. The goal of this review is to raise awareness in the mental health community about the possibility that affective disorders might be the result of contributions from environmental and occupational pesticide poisoning.

2. Brief history of organophosphate compounds: relevance to mental health

OPs are some of the most common pesticides in use today and are similar to some of the chemical warfare agents developed during World War II, Although not as toxic as nerve gases, the approximately 200 OP chemicals act by inhibiting cholinesterases, including the nervous system enzyme acetylcholinesterase (AChE) (Kwong, 2002). OPs are quickly absorbed through the skin, mucous membranes, gastrointestinal tract and respiratory tract, but it is inhalation exposure, which causes the most rapid onset of symptoms (Vale, 1998). Short-term acute toxic effects are caused by an inhibition of AChE, an enzyme that inactivates the neurotransmitter, acetylcholine, causing acetylcholine to accumulate at the cholinergic synapses (Vale, 1998). The result is cholinergic syndrome defined as an overstimulation of muscarinic and nicotinic acetylcholine receptors in the central and peripheral nervous systems.

3. Biological basis for depression

Depression is an illness with a basis in environmental stress and alterations in neurotransmitter systems including the noradrenergic, cholinergic, serotonergic, and dopaminergic pathways (Janowsky & Risch, 1987; Stone, Lin, Rosengarten, Kramer, & Quartermain, 2003). One of the earliest observations was that monoamine depletion, which reduces the available serotonin or norepinephrine neurotransmitters, results in depressive symptoms (Bunney & Davis, 1965; Schildkraut, 1965). This observation was supported by the efficacy of the monoamine oxidase inhibitors and tricyclic antidepressants used to treat depression and by the determination that these drugs increase monoamine receptor sensitivity (Charney, Menkes, & Heninger, 1981). Recent research suggests that epinephrine acting at alpha-1 adrenoceptors may also play a role due to its stress-mediating effects (Stone et al., 2003), and is consistent with a previous finding that epinephrine effects are reduced in response to physostigmine in depressed patients (Janowsky, Risch, Ziegler, Huey, & Rausch, 1986). The most accepted hypothesis is that no single neurotransmitter is responsible for depression, but that many alterations in interacting pathways cause the dysregulation that leads to depression (Siever & Davis, 1985). The understanding of the biological mechanisms and neurotransmitters systems underlying depression can be credited to the study of drug effects in animal models and psychiatric patients (Janowsky, el-Yousef, Davis, & Sekerke, 1972).

Several models suggest that alterations in the cholinergic system play a pivotal role in the development of depression (Janowsky & Risch, 1987). The first is the monoamine–acetylcholine interaction model based on evidence showing that psychostimulants, which increase catecholaminergic activity, show reciprocal effects with cholinomimetics, which increase cholinergic activity. The second model is that the cholinergic system acts alone or with other neurotransmitter systems to directly regulate mood. The third model (The Balance Hypothesis) states that a pharmacologically-induced change in acetylcholine level causes changes in systems other than the cholinergic system, such as GABA, serotonin, dopamine and norepinephrine, but does not directly cause depression. The fourth model asserts that acetylcholine acts as a regulator of stress, and depression is one possible response to stress (Dagyte, Den Boer, & Trentani, 2011; Janowsky & Risch, 1987). In support of the fourth hypothesis, acetylcholine turnover increases with increases in stress in animals, and exaggerated responses are seen in rats that are bred to be cholinergically supersensitive.

There is a body of evidence in both human populations and animal studies demonstrating that drugs which mimic the effects of OPs, or have the same mode of action as OPs, affect mood. These studies show that the cholinergic effects of OP intoxication can be reproduced in either of two ways: (1) administration of cholinergic agonists, primarily muscarinic agonists such as arecoline, oxotremorine, pilocarpine, scopolamine and RS-86 or (2) administration of cholinesterase inhibitors [diisopropylfluorophosphate (DFP), physostigmine] that have been used clinically (Janowsky & Risch, 1987; Overstreet, Miller, Janowsky, & Russell, 1996). Cholinergic

agonists, the first group, act by increasing activity of muscarinic acetylcholine receptors resulting in the same effect as inhibiting AChE. Both approaches result in increased acetylcholine activity which mimics the effects of OP exposure.

Researchers over the past 30 years have proposed that mood disorders stem from an imbalance between adrenergic and cholinergic factors (Fig. 1). This model has since been modified based on the strength of evidence that the dopaminergic, in addition to the adrenergic pathway, is strongly implicated in mania (van Enkhuizen et al., 2014). Janowsky and colleagues published the cholinergic-adrenergic hypothesis of depression and mania in 1972 (Janowsky et al. 1972) and provided evidence for the hypothesis using individuals exposed to physostigmine and methylphenidate (Janowsky, El-Yousef, & Davis, 1973). The central premise of the hypothesis is that depression is a consequence of central cholinergic predominance and mania is a consequence of adrenergic predominance. Anticholinergic drugs have been shown to induce depression and reduce mania in bipolar patients (Janowsky & Risch, 1987). The most studied anticholinesterases used to induce depression or reduce mania are DFP and physostigmine (Janowsky et al. 1973). Research participants who were given OPs in the 1970s produced a short-term response that included retarded depression, fatigue, irritability, impaired concentration, confusion and anxiety (Janowsky et al., 1972, 1973).

In addition to the observations that cholinergic agonists and cholinesterase inhibitors reduce mania in bipolar patients, rat studies show that increased activity in the cholinergic system results in a later compensatory antagonistic activation of the adrenergic system (Janowsky & Risch, 1987). The observed withdrawal effects from antidepressants resulting in a depressed mood, anxiety, withdrawal, agitation and insomnia, are believed to be associated with muscarinic receptor hypersensitivity or what has been termed "cholinergic overdrive" (Dilsaver and Greden, 1984). Additionally, reciprocal interactions have been observed between agents that increase catecholaminergic activity and those that increase cholinergic activity (Janowsky & Risch, 1987). Methylphenidate reverses psychomotor retardation, which occurs after anticholinesterase agents (Janowsky, Overstreet, & Nurnberger, 1994). Psychomotor retardation in humans is associated with feelings of fatigue, lack of thoughts, and

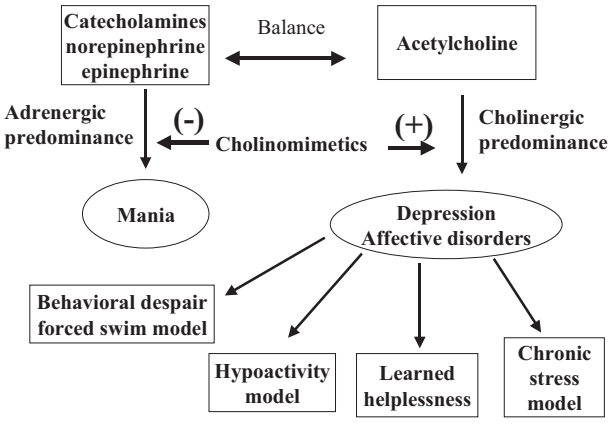

Fig. 1 – The Janowsky et al. (1972) Balance Hypothesis.

anergy with decreased activity (Janowsky et al. 1994). Methylphenidate antagonized by physostigmine and amphetamine is antagonized by arecoline (Janowsky & Risch, 1987).

Evidence specifically implicating acetylcholine in depression can be found in the literature. Abnormal levels of cortical choline have been reported in several brain imaging studies of depressed individuals (Charles et al., 1994; Steingard et al., 2000). After treatment with antidepressants, these increased levels reverted to normal levels (Charles et al, 1994). The acetylcholine precursors choline and lecithin can induce depression (Casey, 1979; Davis, Hollister, & Berger, 1979; Tamminga, Smith, Change, Haraszti, & Davis, 1976).

Patients with affective disorders are more sensitive to the negative affect and inhibitory effects of cholinomimetics than are control groups (Janowsky, Risch, Parker, Huey, & Judd, 1980; Janowsky, Risch, Judd, Huey, & Parker, 1981). Using the Profile of Mood States Scales, self-reported anxiety, depression, hostility, confusion and decreases in elation were significantly greater in affective disorder patients than in other psychiatric patient groups or normal controls after physostigmine infusion (Janowsky et al. 1980, 1981).

Physostigmine and other cholinomimetic drugs cause increases in HPA axis activity and result in increased cortisol secretion and elevated ACTH levels, characteristic of depression in humans (Risch et al., 1981). Increased beta endorphin, released following stimulation by ACTH and corticotropin-releasing hormone (CRF), is also observed in depressed patients, as well as those administered physostigmine and arecoline (Risch et al. 1981).

Some of the most interesting effects of cholinomimetics are on the sleep parameters (Janowsky & Risch, 1987; Poland et al., 1997). Sleep abnormalities are related to dysregulation of the muscarinic cholinergic system (Gillin, Sitaram, & Mendelson, 1982; Sitaram, Nurnberger, Gershon, & Gillin, 1982). Sleep EEG abnormalities in depression in humans is well studied and is associated with decreased rapid eye movement (REM) latency where the first REM sleep cycle occurs earlier in the depressed (65 min) than in non-depressed (90 min) and increased REM density where there are more REM sleep events (Shaffery, Hoffmann, & Armitage, 2003). In addition, REM sleep time is increased in depressed compared to non-depressed individuals and wave patterns are altered indicating different types of brain activity during the sleep cycle (Shaffery et al. 2003). Cholinergic agonists administered to non-depressed individuals cause the same effects as those seen in depressed individuals (Janowsky & Risch, 1987; Poland et al., 1997). Arecoline, a cholinergic agonist, was shown to significantly shorten REM latency when infused into patients with an affective disorder or with a family history of affective disorder compared to normal controls (Janowsky & Risch, 1987). Berger, Lund, Bronisch, and von Zerssen (1983) found that physostigmine induced arousal and awakening from sleep more frequently in patients with affective disorders than in normal controls (Berger et al., 1983) (and later showed supershortening of REM latency in depressives orally administered the muscarinic agonist, RS-86) (Berger, Hochli, Zulley, Lauer, & von Zerssen, 1985).

Janowsky's adrenergic-cholinergic imbalance model fits the physiological, behavioral and neurobiological data better than other hypotheses in humans or animals (Shaffery et al.,

2003) and is most relevant to OP-induced depression. All of the models reduce to two current theories: (1) that acetylcholine alters other neurotransmission systems (GABA, serotonin, dopamine or norepinephrine) but does not directly cause depression, and/or (2) that acetylcholine regulates the effects of stress and depression may be just one possible outcome. Recent developments in the field suggests that acetylcholine disruption may bridge these two models where cognitive symptoms are a direct result of both acetylcholine alterations and chronic stress; mood may be a result of disruptions in connected neurotransmitter pathways (Dagyte et al., 2011).

Chronic stressful life events (allostatic overload) can result in HPA-axis dysregulation (Anisman, Merali, & Hayley, 2008; Stone, Lin, & Quartermain, 2008). Alterations in the HPA axis are associated with the changes in the positive reward pathways resulting in anhedonia and the characteristic lack of interest or pleasure in activities characteristic of depression (Stone, Quartermain, Lin, & Lehmann, 2007; Stone et al., 2008). Stress alters the levels of 5-HT and NE receptor subtypes, as well as altering their turnover rates and localization (Lau, Heimann, Bartsch, Schloss, & Weber, 2013; Nestler et al., 2002; Nutt, 2002; Wong et al., 2000). These changes in the 5-HT and NE neurotransmitter systems in the hypothalamus can result in altered secretion of CRH (Mitchell, 1998; Nemeroff, 1996; Reul & Holsboer, 2002), decreases in growth factors such as Brain-Derived Neurotrophic Factor (BDNF) (Duman, Malberg, & Nakagawa, 2001) and increases in inflammatory cytokines (Hayley, Poulter, Merali, & Anisman, 2005; Maes, 1999). In the HPA dysregulation model of depression, overwhelming evidence shows that stress is a key element in altering the HPA-axis in animals and humans. However, chronic stress has been shown to increase the release of acetylcholine and sensitize cholinergic neurons in the rat hippocampus (Mark, Rada, & Shors, 1996; Mizoguchi, Yuzurihara, Ishige, Sasaki, & Tabira, 2001). Acetylcholine appears to play a role in responding to stress, and may have a role in memory deficits associated with depression (Mizoguchi et al., 2001). However, acetylcholine release is a response to the stress-initiating events (Paul, Jeon, Bizon, & Han, 2015).

All models and theories to date include the importance of the cholinergic system, but knowing what role it plays in relation to other neurotransmission systems will be difficult to tease out. The Flinders Sensitive Line (FSL) rat model has proven beneficial to our present understanding of depression and changes in neurotransmission systems.

Developed at the University of Flinders in Australia, the FSL rat represents the genetic predisposition for supersensitivity to cholinergic agonists and is the model used for understanding human genetic predisposition to depression (Overstreet & Russell, 1982). These rats are supersensitive to cholinergic and serotonergic (5-HT1A) agonists and show characteristic symptoms of depression found in humans (Overstreet, Daws, Schiller, Orbach, & Janowsky, 1998). They have increased rapid-eye movement (REM) sleep, appetite and weight changes and reduced activity, and increased anhedonia, all of which can be reversed with tricyclic antidepressants and serotonin reuptake inhibitors (Overstreet & Russell, 1982). The biochemical similarities with humans are an HPA axis dysfunction, abnormalities in slow-wave and REM sleep, and immune system dysfunction (Yadid et al., 2000). The FSL rats exhibit exaggerated immobility in the forced swim test compared to the Flinders Resistant Line (FRL) control rat (Overstreet et al. 1998). FSL rats also have increased hippocampal and striatal muscarinic acetylcholine receptors, indicating an upregulation of the muscarinic noradrenergic pathway. This observation supports the Janowsky balance hypothesis that increases in cholinergic activity may lead to increases in the adrenergic pathways, which involve the catecholamine neurotransmitters.

4. Epidemiological studies on mood disorders and organophosphates

Deaths from agricultural exposures to OP compounds were reported as early as 1949 (West, 1968). Several early studies were reported which would likely not be approved by an ethical review board today. Sustained low-level administration using daily injections of DFP produced insomnia, excessive dreaming, emotional lability, increased libido, paresthesias, visual hallucinations, and tremor in healthy volunteers (Grob, Lilienthal, Harvey, & Jones, 1947). In 1950, a paper was published linking the phosphate ester compound DFP to psychiatric symptoms (Rowntree, Nevin, & Wilson, 1950). The investigators administered the compound to 17 schizophrenics, 9 manic-depressives and 10 normal controls. In 6 of the schizophrenics, psychosis was activated with symptoms continuing for months after exposures were stopped; among the manic depressives mania was lessened, insomnia and depression were increased, and increased dreaming was induced. Among the normal volunteers altered emotional affect was induced including depression, irritability, lassitude, apathy, dejection and unhappiness (Rowntree et al., 1950).

Table 1 summarizes results from case series reports described below. Acute poisonings from inhibition of cholinesterase due to these compounds were reported beginning in the 1940s (Gershon & Shaw, 1961). Early central nervous system symptoms of organophosphorous compound exposures included giddiness, uneasiness, restlessness, anxiety and tremulousness (Grob, Garlick, & Harvey, 1950). In moderately poisoned cases, the symptoms were followed by headache and by insomnia with excessive dreaming and nightmares (Durham, Wolfe, & Quinby, 1965; Grob et al., 1950). In extremely severe poisoning cases the symptoms were followed by ataxia, tremor, drowsiness, difficulty concentrating, mental confusion, disorientation, and changes in speech characterized by slurring, difficulty informing words and in self-expression and multiple repetition (Grob et al., 1950). Apathy, withdrawal and depression were also reported to occur (Durham et al., 1965). In a case series, two forms of psychiatric illness were reported following episodes of OP poisoning: depression and schizophrenia (Gershon & Shaw, 1961). Durham et al. (1965) studied lapses of attention among pesticide applicators and controls during and after the spraying season. Poisoned individuals were also included in the study (Durham et al., 1965). Results were consistent with the hypothesis that poisoning with OPs resulted in reduction of mental alertness and increased mental confusion (Durham et al., 1965).

Table 1 – Literature based on case series reports assessing neuropsychological symptoms associated with history of acute pesticide poisoning.

Neuropsychological symptom	Author and year
Cognitive effects	
Mental alertness	Durham et al., 1965; Grob et al. 1950
Memory	Dille & Smith, 1964; Gershon & Shaw, 1961
Concentration/vigilance	Dille & Smith, 1964; Durham et al., 1965; Gershon & Shaw, 1961; Grob et al., 1950
Mood and personality	
Anxiety, irritability, giddiness, tension, restlessness, nervousness	Dille & Smith, 1964; Grob et al., 1950; Gershon & Shaw, 1961; Tabershaw & Cooper, 1966
Depression	Durham et al., 1965; Gershon & Shaw, 1961
Sleep disorders	Durham et al., 1965; Grob et al. 1950;Tabershaw & Cooper, 1996

By 1975, there was general consensus that several behavioral sequelae were associated with OP poisoning including: 1) impaired vigilance and reduced concentration; 2) slowing of information processing and psychomotor speed; 3) memory deficit; 4) linguistic disturbance; 5) depression and 6) anxiety. Studies of asymptomatic workers at risk for repeated exposures had produced equivocal results concerning these behavioral abnormalities, meaning that in studies where exposed but not poisoned workers were included in the surveys, the results were mixed with regard to behavioral effects (Levin, Rodnitzky, & Mick, 1976). Further, how long the effects reported would last was addressed in few of the early studies (Metcalf & Holmes, 1969; Tabershaw & Cooper, 1966). In California, organophosphate poisoned individuals were followed for at least three years after the acute event to assess how long the adverse consequences of the poisoning would persist (Tabershaw & Cooper, 1966). Of the 114 individuals, symptoms lasted for six months or longer among 43 [37.7%]. The persistent symptoms included blurred vision, gastrointestinal problems, headaches, chest pain, nervousness, weakness and weight loss. Many of the workers were intolerant to further pesticide exposures.

In Colorado, follow-up of a cohort of workers poisoned by organophosphate compounds was conducted (Metcalf & Holmes, 1969). Workers were enrolled in 1952 and subjected to a battery of psychological tests to search for classic evidence of brain damage. Testing conducted within 72 h of pesticide exposure showed no organic brain damage but always showed erratic and slowed functioning among those with a symptomatic exposure. Generalized weakness and confusion was observed after exposure and changes in EEG were found and described as indicative of drowsiness. Psychiatric evaluation comparing the exposed to a control group found chronic complaints including forgetfulness, difficulty thinking, visual difficulty, and persistent aches and pains. Drowsiness, fatigability and loss of interest in work were found in 45% of exposed and only 5% in the control group. In the follow-up study, a number of tests to evaluate cognition were conducted including the Wechsler Adult Intelligence Scale (WAIS), Benton Visual Retention Test, and a Story Recall Task. Dysfunctions most clearly seen in the exposed group were disturbed memory, difficulty in maintaining alertness and difficulty focusing attention. In sleep studies the investigators found that excessive drowsiness reported by exposed workers related to a demonstrable underlying disturbed physiology. The deficits reported were believed to be consistent with the hypothesis that deep midbrain effects of OP compounds were of major importance in the production of the CNS changes described.

A number of studies comparing pesticide poisoned workers to a control group have been conducted. Table 2 contains a summary of studies which included controls which are described in detail in the following section. Levin et al. (1976) reported that exposed farmers and pesticide applicators scored significantly higher on the Taylor Manifest Anxiety Scale compared to non-exposed farmers. Reidy, Bowler, Rauch, and Pedrozza (1992) reported that twice poisoned migrant farm workers scored lower than controls on measures of motor speed and visuospatial memory and higher on anxiety and depression symptom checklists one to two years after the poisoning episode. Savage et al. (1988) studied individuals who had experienced an acute organophosphate poisoning many years prior to the study. Matched controls were compared to poisoned cases and given a medical examination, the Halstead–Reitan test battery, the WAIS, the Peabody Individual Achievement Test and the Minnesota Multiphasic Personality Inventory (MMPI). Neurological tests showed memory deficits and six cases were classified as depressed compared with none of the controls. Exposed cases scored significantly worse on 18 of 34 subtests on the Halstead–Reitan test and twice as many cases as controls had Average Impairment Scores in the range characteristic of cerebral lesion. On the WAIS the poisoned cases had an average Full-Scale IQ 5 points lower than the control group and did significantly worse on six verbal tests. On the MMPII, cases scored higher on validity scales and on the paranoia and social introversion scales. Rosenstock, Keifer, Daniell, McConnell, and Claypole (1991) assessed individuals in Nicaragua who had been poisoned two years prior to testing and compared them to an age-matched control group. The poisoned group performed much worse on five of six WHO recommended neuropsychological tests (Rosenstock et al., 1991). Steenland, Jenkins, Ames, O'Malley, Crislip et al. (1994) studied organophosphate poisoned workers in California compared to controls and reported evidence of neuropsychological damage and disturbed peripheral nerve damage among the poisoned group. Eight neurobehavioral tests from the Neurobehavioral Evaluation System were used including mood scales, finger

Table 2 – Literature with comparison groups assessing neuropsychological symptoms associated with history of acute pesticide poisoning.

Neuropsychological symptom	Author and year
Cognitive effects	
Had difficulty concentrating	Metcalf & Holmes, 1969; Savage et al., 1988; Stallones & Beseler, 2002b
Been confused/disoriented	Metcalf & Holmes, 1969; Rosenstock et al., 1991; Stallones & Beseler, 2002b
Memory	Levin et al., 1976; McConnell, Keifer, & Rosenstock, 1994; Metcalf & Holmes, 1969; Reidy et al., 1992; Savage et al., 1988; Stallones & Beseler, 2002b
Difficulty understanding books, newspapers, magazines	Metcalf & Holmes, 1969; Steenland et al., 1994; Stallones & Beseler, 2002b
Mood and personality	
Irritability	Stallones & Beseler, 2002b; Steenland et al., 1994
Depression/depressive symptoms	Ahmed & Davies, 1997; Amr et al., 1997; Beard et al., 2013; Beseler et al., 2006; Beseler et al., 2008; Beseler & Stallones, 2008; Kim et al., 2013; Levin et al., 1976; Reidy et al., 1992; Savage et al., 1988; Stallones & Beseler, 2002a; Stallones & Beseler, 2002b; Steenland et al., 1994
Sleep disturbances	London et al., 1998; Metcalf & Holmes, 1969; Stallones & Beseler, 2002b; Wesseling et al. 2001
Anxiety	Levin et al. 1976; Reidy et al., 1992; Wesseling et al., 2001
Aggression/Anger	Wesseling et al., 2010
Impulsivity	Wesseling et al. 2010

tapping, sustained attention, hand-eye coordination, simple reaction time, symbol digit, pattern memory, and serial digit learning (Steenland et al., 1994). London, Nell, Thompson, and Myers (1998) studied pesticide applicators on South African fruit farms using a neuropsychological battery, neurological symptoms, vibration sense, and motor tremor and found the neurological symptoms were more prevalent among workers with a prior organophosphate pesticide poisoning compared with controls. Wesseling, van Wendel de Joode, and Monge (2001) studied banana workers in Costa Rica who had documented organophosphate poisoning and found that scores on somatization, obsessive-compulsiveness, anxiety, phobic anxiety, and hostility were significantly higher among poisoned workers compared with a control group. In summary, studies assessing pesticide poisoned workers find a large number of deficits related to mood, memory, reaction times and coordination that are consistent with the animal studies that have been reported.

Keifer, Rivas, Moon, and Checkoway (1996) studied community residents living near cotton fields in Nicaragua. Acute pesticide poisoning symptoms, a modified version of the Q-16 to assess psychiatric symptoms (Lundberg, Hogberg, Michelsen, Nise, & Hogstedt, 1997), and red blood cell cholinesterase levels were assessed in relation to aerial spraying with OPs. Compared with urban residents, the poisoned group had significantly elevated prevalence odds ratios (OR) as follows: non-specific symptom category 1.6 (95% confidence interval – CI .8, 3.2); possible symptom category 4.1 (95% CI 1.7, 10.2); and probable symptom category 9.9 (95% CI 2.9, 34.4). These findings indicate there may be a relationship between severity of poisoning and adverse outcomes. This finding was supported by a more recent study conducted among male farmers in South Korea that also assessed the relationship between self-reported depression and severity of pesticide poisoning symptoms (Kim, Ko, & Lee, 2013). Using information on source of treatment and number of reported poisoning episodes, they reported the following: cases with moderate to severe symptoms OR 2.81, 95% CI 1.71, 4.63; cases treated in outpatient clinics or hospitals OR 2.52, 95% CI 1.15, 5.53; and those with multiple poisoning episodes OR 1.82, 1.19, 2.76 (Kim et al., 2013). The authors concluded that severity of poisoning was associated with an increased likelihood of depression (Kim et al., 2013).

Delgado et al. (2004) followed 53 patients who had been hospitalized for acute OP poisoning for two years after the episode and compared them with 23 non-poisoned individuals. The Q-16 was used to assess psychiatric symptoms. Symptom scores increased over the two year follow-up for all groups with a smaller change among the unexposed group. The difference between the poisoned and control groups was not significantly different after controlling for age, education, and alcohol consumption (Delgado et al., 2004).

In the Agricultural Health Study, female spouses of pesticide applicators were diagnosed with depression more often in the presence of a history of a pesticide poisoning than spouses who had not been poisoned (OR 3.26, 95% CI 1.72, 6.19) and in applicators (OR 2 .57, 95% CI 1.74, 3.79) after controlling for state of residence, age, race, off-farm work, alcohol consumption, cigarette smoking, physician visits, and solvent exposure (Beseler et al., 2006; Beseler et al., 2008). In a more recent analysis of the same cohort, wives of applicators who reported a pesticide poisoning had a slightly higher incidence (new cases) of physician diagnosed depression (OR 1.78, 95% CI .76, 4.14) compared with wives who did not report a pesticide poisoning (Beard et al., 2013).

Results from a number of laboratory, clinical, and epidemiological studies led several investigators to propose a long-term neuropsychiatric syndrome resulting from organophosphate exposure which separated those effects occurring as a result of poisoning from those associated with chronic long term, low dose exposure. Ahmed and Davies (1997) described the syndrome they called chronic organophosphate–induced neuropsychiatric disorder (COPIND) as characterized by the following symptoms: one or more episodes of severe flu-like

symptoms lasting more than three days following exposure (and sometimes hypersalivation, abdominal cramps and diarrhea); mood destabilization; suicidal thinking; cognitive impairment; language disorder including word finding and expressive disorders; alcohol intolerance including marked increase in inebriating effects of alcohol, severe hang-over and quasi-allergic effects; heightened sense of smell; handwriting deterioration; sensitivity to exposure to low concentrations of organophosphates; and decreased exercise tolerance reflected in initial normal muscle power but inability to maintain it and no evidence of generalized weakness. Jamal (1997) conducted an extensive review of neurologic effects of chronic organophosphate pesticide exposure and designated two types of COPIND. The first (COPIND1) represented cases of acute poisoning resulting from long-term effects and the second (COPIND2) occurring from long-term exposures to subclincal doses (Ahmed & Davies, 1997; Jamal, 1997). This syndrome is consistent with the animal evidence that exposure to chlorpyrifos leads to adverse neurodevelopmental effects and neurobehavioral effects associated with disruption of serotonin (Aldridge, Levins, Seidler, & Slotkin, 2005; Aldridge, Seidler, & Slotkin, 2004; Alridge, Seidler, Meyer, Thillai, & Slotkin, 2003, Dam, Garcia, Seidler, & Slotkin, 1999; Raines, Seidler, & Slotkin, 2001; Slotkin, 1999; Slotkin, 2004; Slotkin, Tate, Cousins, & Seidler, 2002; Slotkin, Tate, Ryde, Levin, & Seidler, 2006).

Mood swings associated with exposure to organophosphates tend to be brief in duration and can involve swings from depression or to irritability and anger (Davies et al., 2000). Instability of mood rather than pervasive mood states and the absence of elevation of mood distinguish these cases from functional affective disorders and cyclothymia (Davies, et al., 2000). The change in personality observed has been reported to be an abrupt personality change confirmed by partners' or other family members (Davies, et al., 2000; Savage et al., 1988). Davies et al. (2000) report that impulsive suicidal thoughts come out of the blue and may result in serious action using tractors, shotguns and nooses for hanging. Cognitive impairments often described by patients include difficulty in retaining recent information and concentration reflected in filling out forms. Names of familiar people may be forgotten temporarily and in serious cases the ability to perform

Table 3 – Summary of symptoms comparing clinical and case studies of organophosphate exposure to symptoms reported in epidemiological studies of occupationally-exposed workers.

Symptoms reported from pharmacological, clinical and case series of exposure to OP compounds in humans	Symptoms reported in epidemiological studies of moderate to high exposures and acute poisoning
Chronic, low dose administration of cholinesterase inhibitors (DFP, physostigmine) to psychiatric patients:	**Epidemiological literature of moderate to high exposure to OPs:**
Cognitive effects	*Cognitive effects*
• Impaired concentration	• Impaired concentration
• Confusion	• Confusion
Mood disorders	• Memory problems
• Retarded depression	• Drowsiness/impaired vigilance
• Fatigue	*Mood disorders*
• Irritability	• Retarded depression
• Sleep dysregulation (insomnia, excessive dreaming)	• Fatigue
• Emotional lability	• Irritability
• Lassitude	• Sleep dysregulation (insomnia, excessive dreaming)
• Apathy	• Emotional lability
• Dejection	• Lassitude
• Unhappiness	• Apathy
• Anxiety	• Withdrawal
Neurological disorders	• Unhappiness
• Paresthesias	• Anxiety
• Visual hallucinations	*Neurological disorders*
	• Visual difficulty
	• Headache
Symptoms in early case studies of OP poisoning in humans	**Symptoms in acute poisoning from OP exposure (in addition to above):**
Cognitive effects	*Cognitive effects*
• Difficulty concentrating	• Reduced motor speed
• Disorientation	• Reduced visuospatial memory
• Mental confusion	• General memory deficits
• Changes in speech	*Mood and other psychiatric disorders*
Mood and other psychiatric disorders	• Somatization
• Emotional lability, giddiness	• Obsessive-compulsiveness
• Restlessness	• Anxiety
• Anxiety	• Phobic anxiety
• Drowsiness	• Paranoia
• Insomnia	• Social Introversion
• Apathy, withdrawal	• Hostility
• Depression	• Impulsivity
• Hostility, anger	
• Schizophrenia	

sequential tasks is lost because previous steps are forgotten and memory problems are reported. . Fundamental impairment of central information processing and an IQ loss involving dominant hemispheric functions were found in a small number of neuropsychological assessments conducted.

Two studies conducted in Colorado have been analyzed in an attempt to isolate OP pesticide poisoning specific symptoms of depression (Beseler et al., 2008; Stallones & Beseler, 2002a, 2002b). One survey was conducted in an eight county area of northeastern Colorado that included 47% of the agriculturally employed population (Stallones & Beseler, 2002a). Farms were sampled and farm operators and spouses of the operators were included in the study population. A total of 761 individuals representing 479 farms were enrolled in the study (Stallones & Beseler, 2002a). In the first study, self-reported OP pesticide poisoning symptoms were significantly associated with high depressive symptoms included headache/dizziness; eye irritation; nausea/vomiting; chest discomfort; difficulty breathing; and skin irritation (Stallones & Beseler, 2002a). These symptoms are indicative of a severe OP pesticide poisoning episode among those who reported depressive symptoms. In a subsequent analysis of the same study population, neurological symptoms significantly correlated with a self-reported poisoning were difficulty concentrating, problems with memory, depression, irritability, heart palpitations with exertion, excessive sleep, difficulty moving fingers, and headaches at least once a week (Stallones & Beseler, 2002b). After controlling for other factors, depression and sleeping too much remained significant (Stallones & Beseler, 2002b). In another study conducted in Colorado, a sample of rural farms was selected and enrolled farm operators and spouses were followed over three years (Beseler & Stallones, 2008). Farm residents reported personally mixing or applying organophosphate pesticides and reported symptoms associated with having experienced an organophosphate pesticide exposure. After adjusting for gender, age, marital status, income, debt and overall health status, the two predictors of pesticide poisoning related depressive symptoms were being bothered by things and restless sleep, both being somatic symptoms of depression (Beseler & Stallones, 2008). Of note is that those who reported a pesticide poisoning at baseline were more likely to be depressed in the subsequent years of the study relative to those who had not been poisoned (Beseler & Stallones, 2008). Earlier cross-sectional studies of individuals who had been pesticide poisoned also suggested that somatic symptoms of depression persisted after the acute poisoning episode (Ahmed & Davies, 1997; Amr, Halim, & Moussa, 1997).

Table 3 contains a summary of symptoms which have been reported in studies of OP poisoned workers and psychiatric populations. Despite use of a wide range of different assessment instruments, study designs, and target populations, a number of symptoms are consistently being reported which are related to affective and somatic components of dysfunction. These include depression, anxiety, irritability, hostility, confusion, impaired memory and concentration, and fatigue. The importance of linking these symptoms to environmental exposures is highlighted through the studies of suicidal ideation and high suicide rates in pesticide exposed populations.

5. Conclusions

The epidemiological concept of "The Healthy Worker Effect" (McMichael, 1976) strongly applies to farming because those with serious mood disorders would be unable to maintain the intensity of work required in farming and therefore would be likely to leave the farm workforce. In addition, farmers often own farms that have been in their families for generations and families with a history of psychiatric disorders, including vulnerabilities to stress-mediated depression, would not have the resilience to remain in farming. It is not likely that farmers are susceptible to the stresses and increased allosteric loads that would result in alterations in their HPA-axis. They have learned to deal with the uncertainties in weather, crop prices and all of the other uncontrollable events that they and their families have long endured. It is far more likely that the initiating event resulting in depression and an increased risk of suicide in farmers is having had a high OP pesticide exposure or OP poisoning.

The most likely explanation for depression in OP-poisoned farmers is alterations in the cholinergic system; which then alters the balance between the cholinergic and catecholaminergic systems, resulting in depression. An examination of the symptoms reported by pharmacological, clinical, toxicological and epidemiological studies all indicate a strong increase in negative affect and somatic complaints, with only a minimal impact on the positive affect dimension of depression. Certainly, retarded activity and anhedonia are seen in farmers occupationally exposed to high levels of OPs, but these are not the primary complaints or most prevalent symptoms. The most frequently reported symptoms are depressed mood, irritability and changes in sleep patterns, which are different from the symptoms associated with alterations in the HPA axis. Studies of depression related to the stress pathway show a strong loss of positive affect, as measured by behavior inactivity, anhedonia, and loss of reward-seeking behavior. The symptoms observed in OP-poisoned farmers are not suggestive of a stress-mediated pathway in the development of depression.

Certainly there are other mechanisms by which OPs could cause depression aside from the inhibition of AChE. In susceptible individuals, these other targets may have a role in depression where inhibition of AChE activity is not observed. OPs have been associated with increasing inflammation and resulting in the release of cytokines in the brain (Banks & Lein, 2012). Neuroimmunological factors have been implicated in depression (Jo, Zhang, Emrich, & Dietrick, 2015). Inflammation and cytokine release could certainly exacerbate the initial insult on the cholinergic system and prolong the depressive state. Additionally, there are targets in the brain that are not associated with AChE inhibition, such as neuropathy target esterase. The FSL rat was shown to have increased levels of arachidonic acid-containing phosphatidylcholine. The elevated arachidonic acid could directly inhibit nicotinic acetylcholine receptors and alter serotonin signaling pathways (Green, Anyakoha, Yadid, Gispan-Herman, & Nicolaou, 2009). These changes in the fatty acid composition of the cellular membrane is characteristic of inhibition of neuropathy target esterase, long known to be a

target of OP pesticides and implicated in the development of COPIND (Jamal, 1997).

The severity and duration of depression in OP-poisoned farmers could be a combination of all of these effects. It might be that the initial inhibition of AChE or neuropathy target esterase begins a cascade of events that leads to increased cytokine release by the immune system; increased inflammation and involvement of glia cells; and disruption of the HPA axis, glutamatergic and monoaminergic systems, in addition to the cholinergic and catecholaminergic systems, If the totality of the attack is sufficient, COPIND may ensue.

OPs are a large and diverse group of compounds with varying degrees of specificity, activity, and toxicity. Dose cannot easily be predicted from exposure due to formulation differences in the compound, the mixing and application methods used, personal protective equipment worn, and individual biological differences in detoxification, metabolism and excretion. Although acute poisoning effects are well-defined, chronic health effects after poisoning can be vague, for example, sheep-dippers that report having ill health from OP pesticide exposure (Rees, 1996). Beginning with the studies of Grob et al. (1947, 1950) and Dille and Smith (1964), depression was reported as an acute effect of OP poisoning. This is most likely due to stimulation of cholinergic pathways, and, possibly a compensatory mechanism of upregulation of muscarinic pathways, as shown by Janowsky and others (1972, 1973, 1980, 1981, 1986, 1987, 1994).

Since chemical contaminants are endemic in our environment and resources to study them are limited, research will continue to be lacking. Efforts should be targeted at reducing exposures, increasing education, and developing treatments that go beyond pharmaceutical interventions, which may alleviate symptoms but fail to address the underlying causes. Given the continued problem of stigmatization in underserved communities, acknowledging environmental factors as causal influences in psychiatric disorders might motivate treatment-seeking behavior.

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