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Mini-Review

Pesticides, depression and suicide: A systematic review of the epidemiological evidence

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ABSTRACT

It has been suggested that high exposure to pesticides, including poisoning, experienced by agriculture workers and rural residents may result in an elevated risk of psychiatric disorders and suicidal behavior. Epidemiological data supporting this hypothesis are very limited. An updated systematic review was conducted in epidemiologic literature on the relationship of pesticide exposure with depression and suicide published over the last 15 years by using MEDLINE database. A total of 11 studies on depression and 14 studies on suicide met inclusion criteria. Depression or other psychiatric disorders have shown increased risks associated with previous pesticide poisoning in 5 studies, with statistically significant odds ratios (OR) ranging from 2.08 to 5.95. Lower risk estimates have been found for chronic pesticide exposure. Among studies on suicide, 4 reports found increased suicide rates in areas with intensive pesticide use (OR between 1.60 and 2.61) compared to areas with lower pesticide use. Occupation in agriculture has shown a significant association with higher suicide risk than other occupational groups in 4 studies (OR between 1.30 and 4.13), but not in one recent report. Regarding specific pesticides, lifetime use of chlorpyrifos was related with increased suicide mortality (OR = 2.37) in one study. Scientific evidence of association between pesticide exposure and either depression or suicide has been shown in some populations, in studies using varying epidemiological approaches, but is still very limited and inconclusive. Review of the literature warrants further research to explore such relationships, in particular prospective studies among large samples of high- and low-dose-exposed workers, using detailed exposure assessments, and evaluating other potential sources of psychological stress.

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Introduction

Depression is one of the most common mental disorders in general medical care and can be seen as a state of mood, a symptom, a syndrome or as a clinical diagnosis (http://www.who.int/mental_health/management/depression). Epidemiological studies have shown that depression prevalence is higher in industrialized countries than in non-developed ones and negatively correlates with social status (Jaga and Dharmani, 2007; WHO, 2002). Up to 4% of men and 8% of women suffer from a clinically significant depressive disorder, while depressive symptoms are much more common (WHO, 2002).

Suicide is one of the three main causes of death worldwide among individuals from 15 to 35 years of age (WHO, 2000a), and has increased in 60% in the last 45 years. In general, the incidence of suicide is higher in developing countries and, where it is a major public health problem, mainly affecting females and rural communities (London, 2009). Conversely, suicides in industrialized countries affect more males and urban population (Jaga and Dharmani, 2007). Suicidal behavior is a serious mental health problem and often associated with many psychiatric diseases (Kim et al., 2011). Among them, depressive disorder accounts for about 20–35% of all suicide deaths (Baldessarini et al., 2003; Wilson et al., 2003).

It has been suggested that exposure to high levels of pesticides, including poisoning, experienced by agriculture workers and rural residents may result in an elevated risk of neuropsychiatric sequelae (mood disorders, depression and anxiety) and suicide attempts and mortality (London et al., 2005, 2012; Meyer et al., 2010; Pearce et al., 2007). In fact, the relation between farming, pesticide exposure or poisoning, depression, injury and suicide is an area of increasing concern (London et al., 2012).

Organophosphorus (OP) pesticides and other cholinesterase-inhibiting agents such as carbamates have been particularly involved in the risk for these psychiatric disorders (Wesseling et al., 2010). The immediate effects of high-level exposure to OP

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pesticides have been well documented, causing changes in peripheral, autonomic, and central nervous system (CNS) function (i.e. cholinergic crisis). In fact, OP pesticides are one of the most common causes of poisoning worldwide and epidemiologic studies have reported that the annual incidence of OP pesticide poisonings among agricultural workers in developing countries varies from 3 to 10% (Koh and Jeyaratnam, 1996). Further, suicide in developing countries often involves the use of pesticides as the causative agent (London, 2009). In this regard, several studies in the past addressed the use of pesticides for acts of self-poisoning into suicide (London et al., 2005; Trojanowska et al., 1978).

Epidemiological data

To our knowledge, the first study on involuntary exposure to pesticides in relation to suicide was published in the early 90s, which observed an increased mortality risk of suicide (Standardized mortality ratio, SMR = 210) in a cohort of forestry workers exposed to phenoxy acid herbicides (Green, 1991). Other studies published in the 90s decade reported increased suicide rates among farmers (Boxer et al., 1995; Malmberg et al., 1999). In 1997, however, an expert panel concluded that long-term exposure to OP compounds did not cause problems in the peripheral or central nervous system, nor neurobehavioral effects, unless acute or severe poisoning occurred (Clegg and van Gemert, 1999).

Besides increased risk for suicide, OP exposure has also been linked to neuropsychological disorders, such as depression and anxiety (Amr et al., 1997; Fiedler et al., 1997; Stephens et al., 1995; Van Wijngaarden, 2003). Roberts and Lee (1993) found farming, fishing and forestry occupations to have the highest lifetime risk for major depression. In 2000, Rehner et al. investigated an ecological disaster with the OP insecticide methyl parathion in Mississippi, USA. Authors found that, regardless of the residential level of methyl parathion contamination, more than half of the victims reported depressive symptoms, being people who had been exposed to the insecticide for the longest period of time those at highest risk for depression (Rehner et al., 2000). According to Roberts and Lee (1993), a large population-based study found that male agricultural workers had the highest level of depression of all occupational groups (Sanne et al., 2004). Also, the level of anxiety in male farmers was significantly higher than the average level among all working male participants (Sanne et al., 2004).

In 2005, a literature review was published addressing mortality and morbidity studies related to suicide among pesticide-exposed populations, and of human and animal studies of CNS toxicity related to OP pesticides (London et al., 2005). Authors of the review identified higher suicide rates in farming populations and epidemiological evidence of association between acute and chronic OP exposure and affective disorders, concluding that OP pesticides may be part of the causal pathway leading to suicide. However, such a review work was mainly focused on suicide and pesticide poisoning in non-developed countries. To our knowledge, no other reviews on the field have been published to date.

Overall, evidence of an association between high pesticide exposure or poisoning and risk of psychiatric disorders, including and suicidal behavior, is increasing (Mackenzie Ross et al., 2010; MacFarlane et al., 2011; Wesseling et al., 2010; Zhang et al., 2009). Among recent findings are those by Beseler and Stallones (2010), who confirmed that specific depressive symptoms occurred more often in farmers with a pesticide poisoning and these symptoms may lead to an increased risk of farm injuries. However, epidemiological data are still very inconsistent and do not allow to identify any relevant causal pathway. Scientific evidence on effects of chronic low-dose exposure to pesticides is particularly lacking.

Experimental data: biological plausibility

While the peripheral and central nervous system consequences of acute high-level pesticide exposure are well established, particularly for OC insecticides, evidence for long-term nervous system sequelae of cumulative low-dose exposures is less clear (Colosio et al., 2003; Kamel and Hoppin, 2004).

Regarding depression and suicide, literature on their relation with high pesticide exposure has also focused on OP insecticides and, to lesser extent, carbamates as candidates for causing psychiatric disorders (Wesseling et al., 2010); among them, depression and anxiety are the disorders most frequently associated with acute OP poisoning (London et al., 2005). Both OP and carbamate insecticides are known cholinesterase-reducing agents (Kamanyire and Karalliedde, 2004). The inhibition of acetylcholinesterase (AChE) results in decreased degradation of acetylcholine, leading to the over-stimulation of cholinergic receptors of both muscarinic and nicotinic type and, consequently, stimulating central and peripheral nervous system persistently.

Although their classic toxic effects are caused by AChE inhibition, it is increasingly clear that OP pesticides can act through multiple mechanisms, not necessarily related to AChE inhibition, that culminate in biochemical deficiencies and/or behavioral impairment. Regarding the neurotransmitter serotonin system, there is evidence that the effects are highly dependent on OP, and that the direction and the magnitude of the effect may vary among distinct OP compounds (Levin et al., 2010; Slotkin and Seidler, 2008; Slotkin et al., 2009). Thus, the effects of long-term exposure to the OP insecticide chlorpyrifos have been involved in the serotonergic system (Aldridge et al., 2004; Andrade et al., 2003; Moreno et al., 2008; Pung et al., 2006; Raines et al., 2001; Slotkin, 2004; Slotkin et al., 2002), showing long-term changes in serotonin-related emotional behaviors (Chen et al., 2011). Deficiencies of the serotonergic system are frequently associated with emotional disorders, such as depression, anxiety, and post-traumatic stress disorder (Toth, 2007), which are known to be linked to suicidal behavior in humans (London, 2009).

Animal studies have also shown that exposure to other OP pesticides such as diazinon, parathion and dichlorvos during prenatal or neonatal periods also provoke widespread abnormalities in cholinergic, dopaminergic and serotonergic synaptic functions (Aldridge et al., 2005; Levin et al., 2010; Slotkin and Seidler, 2008; Slotkin et al., 2006, 2008, 2009). For instance, diazinon and parathion evoked alterations serotonin receptors in the brain of neonatal rats exposed to doses below those required for cholinesterase inhibition (Slotkin et al., 2006). In adults, several important changes in glutamatergic, noradrenergic, dopaminergic and serotonergic systems have been observed, such as reductions of norepinephrine levels in rats exposed to dichlorvos (Ali et al., 1980) and increases in glutamate and GABA uptake in rats exposed to the highly toxic OP methamidophos (Gubert et al., 2011). Interestingly, alterations in synaptic transmission promoting decreases of specific serotonergic biomarkers have been recently observed in adult mice sub-chronically exposed to methamidophos at doses below the threshold for cholinergic hyperstimulation (Lima et al., 2011), as well as depressive-like behavior have been identified (Lima et al., 2009).

Although biological mechanisms linking pesticide exposure and psychiatric disorders need to be elucidated yet, recent experimental findings suggest that exposure to OP pesticides affecting non-cholinergic systems may contribute to depression, impulsivity or some combination of these disturbances in mood that could also explain the association of OP exposure with suicide (Beseler et al., 2008; London et al., 2005, 2012; Mackenzie Ross et al., 2010).

In this paper, a systematic review was carried out on the epidemiological association between pesticide exposure and depression and suicide, updating the available scientific literature exploring this issue.

Methods

The scientific literature on pesticide exposure and either depression or suicide published between 1995 and 2011 was searched. This period was chosen because epidemiological studies linking occupational or environmental exposure to pesticides and those outcomes have basically emerged in the last 15 years. Studies were identified by using MEDLINE and SCIELO databanks. Systematic searches of the scientific literature were conducted using the following key words: pesticides, pesticide exposure, organophosphates, occupational pesticide exposure, agricultural workers, farm workers, and farmers, in combination with any of the following words: depression, psychiatric disorders, mood disorders, affective disorders, and suicide. Articles were limited to studies in humans and to reports published in English, Spanish and Portuguese. Case reports and reviews were not included.

Only original research articles meeting the following eligibility criteria were included in the final search results: epidemiological studies investigating the association of exposure to any type of pesticide or pesticide-exposure related factors (e.g. occupation in agriculture, area devoted to agriculture) on depression (or related symptoms of affective disorders) or suicide–related outcomes (ideation, attempts or mortality). Studies directly addressing voluntary pesticide intake to commit suicide were excluded aiming to focus the scope of this review.

Results

A total of 221 original studies published after 1995 were identified that pertained to the relation between pesticides and depression or suicide in humans. Following the eligibility criteria described previously, a great number of studies were excluded concerning self-poisoning ($N = 124$) and case reports ($N = 75$). Finally, 22 reports concerning original epidemiological studies of pesticide exposure and depression or suicide were included in this review. The studies were divided into two categories and corresponding tables according to the assessed outcomes: depression and psychiatric disorders (11 studies) presented in Table 1, and suicide (14 studies) presented in Table 2. Three studies evaluated both suicide and depression in relation to pesticide exposure (Meyer et al., 2010; Parrón et al., 2011; Wesseling et al., 2010) and were included either in Tables 1 and 2.

Among investigations in the present review, 5 studies have a ecologic design (Faria et al., 2006; Meyer et al., 2010; Parrón et al., 1996, 2011; Pires et al., 2005); 9 are cross-sectional surveys (Amr et al., 1997; Bazylewicz-Walczak et al., 1999; Gallagher et al., 2008; Mackenzie Ross et al., 2010; Sanne et al., 2004; Stallones, 2006; Stallones and Beseler, 2002; Wesseling et al., 2010; Zhang et al., 2009); 5 used a case–control design (Beseler et al., 2006, 2008; MacFarlane et al., 2011; Pickett et al., 1998; Van Wijngaarden, 2003); and 3 are prospective studies (Beard et al., 2011; Beseler and Stallones, 2008; Lee et al., 2007).

Individual-level studies reviewed providing risk estimates [odds ratio (OR), relative risk (RR) or hazard ratio (HR)] and their corresponding 95% confidence intervals (CI) are displayed in forest plots in Fig. 1 (depression) and 2 (suicide).

Pesticide exposure and depression

Among epidemiological studies exploring the association between pesticide exposure and depression or other psychiatric disorders (e.g. anxiety), case definition have been conducted through clinical evaluation in most of the studies, although cases for depression have been self-reported (Beseler et al., 2006, 2008) or derived from official registries (Meyer et al., 2010; Parrón et al., 2011) in two studies each. Validated scales used to assess depression include the widely used Center for Epidemiologic Studies-Depression scale, CES-D (Beseler and Stallones, 2008; Stallones and Beseler, 2002), the Hospital Anxiety and Depression Scale, HADS (Mackenzie Ross et al., 2010; Sanne et al., 2004), the Brief Symptom Inventory, BSI (Wesseling et al., 2010), and the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, DSM-III (Amr et al., 1997).

Ecological studies

Among the reviewed literature, only one large study out of two ecological studies is suggestive of an association between pesticide exposure and affective disorders (Meyer et al., 2010) (Table 1). That study recorded hospitalizations of 3517 agricultural workers from the state of Rio de Janeiro, Brazil, and reported that farmers living in areas with higher rates of pesticide expenditure were at greater risk for hospitalization due to mood disorders (International Classification of Diseases ICD-10: F30–F39 disorders, including depression), when compared to two reference populations (RR ranging from 2.0 and 4.0) (Meyer et al., 2010). Conversely, a recent study showed that people living in Southern Spanish areas with higher pesticide use did not present higher risk for affective disorders compared to low-exposure areas, with OR around the unity (Parrón et al., 2011).

Cross-sectional studies

Seven cross-sectional studies were identified on pesticides and depression. Even tough they present methodological disparities, i.e. different sample sizes, varying exposure definitions and outcome assessment tools, and different statistical methods of analysis, however, all of them found positive results regarding association between exposure and outcome.

In a study taking part of the Colorado Farm Family Health and Hazard Surveillance (CFFHHS) project, farmers with history of pesticide poisoning had a statistically significant 6-fold increased risk for depressive symptoms (OR = 5.95, 95% CI = 2.56–13.84) (Stallones and Beseler, 2002). More recently, a study in Costa Rica gave some support to the hypothesis of association between high-dose exposure to cholinesterase-inhibiting pesticides and neuropsychiatric sequelae (Wesseling et al., 2010). Authors reported a statistically significant association between past poisoning with OP pesticides, but not carbamates, and an excess of psychological distress symptoms assessed with the BSI scale among 78 banana workers (OR ranging from 1.90 to 3.56, and an OR of 2.42 for depressive symptoms), compared with 130 unexposed workers. In addition, symptom scores among such banana workers revealed a statistically significant increase with the number of past poisonings in five dimensions of the BSI (OR = 2.88 for depression among workers with $\geq$2 poisonings vs. none), showing evidence of a dose–response effect (Wesseling et al., 2010).

In a Norwegian cohort of 17,295 workers, risk for depression were two times higher among farmers compared to non-agricultural workers, particularly among males working full time (OR = 2.30, 95% CI = 1.61–3.28) (Sanne et al., 2004). A group of 127 sheep farmers from the UK with a history of exposure to low levels of OP pesticides presented a statistically significant higher frequency of symptoms of depression ($p < 0.001$) and anxiety ($p < 0.01$) compared to 78 unexposed rural workers (Mackenzie Ross et al., 2010). In addition, sheep farmers performed significantly worse than non-exposed workers on several cognitive tasks after controlling for mood state. A very small study in Poland observed increased risk for clinical depression and cognitive dysfunctions among female farmers (Bazylewicz-Walczak et al., 1999). Finally, higher prevalence of several affective disorders including

Table 1
Summary of studies on pesticide exposure/farming activities and depression or other affective disorders.

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
Meyer et al. (2010)	Brazil (Rio de Janeiro state)	3517 agricultural workers, 20–59 yrs	Ecological	Per capita use of pesticides (1996) (quartiles) "Exposure area": Serrana rural region in Rio de Janeiro (RJ) Reference areas: city and state of RJ	Hospitalizations due to mood disorders in 1998–2007	Unconditional logistic regression Stratified analysis: age (20–39, 40–59 yrs), gender, and time interval.	RR ~2.0–4.0 for all subjects, compared with the state and city of RJ
Parrón et al. (2011)	Spain (Andalusia)	2674 subjects from the general population with neurological disorders	Ecological	High vs. low pesticide exposure based on amounts of pesticides used (kg/person or tons per health district)	Affective psychosis in 1998–2005 (manic, depressive, mixed type or bipolar disorders)	Unconditional logistic regression Adjusted by age, gender, and interaction gender*exposure	High vs. low exposure areas: Crude analysis: OR = 1.02 (0.94–1.10) for total population OR = 1.03 (0.92–1.15) for men OR = 1.01 (0.90–1.12) for women Fully adjusted analysis: OR = 0.71 (0.63–0.80) for total population OR = 1.18 (0.99–1.41) for men
Amr et al. (1997)	Egypt	208 pesticide formulators and 72 controls (urban unexposed workers) 172 pesticide applicators and 151 controls (rural unexposed workers) Matched by age, socioeconomic and educational level	Cross-sectional	Formulators and applicators of mixture of pesticides (carbamates, pyrethroids, OPs, OCs)	DSM-III-R disorders: depressive neurosis, situational/reactive depression, others. DSM-III-R symptoms: irritability, depressed mood, insomnia, erectile dysfunction, loss of interest, headache. GHQ: somatic symptoms, anxiety, insomnia, social dysfunction, and severe depression.	Crude comparison of frequencies between exposed and controls	Formulators vs. controls: PR = 1.56 for total psychiatric disorders, depressive neurosis, depression, irritability and erectile dysfunction. PR = 1.99 for symptoms in those working ≥20 years Applicators vs. controls: PR = 1.78 for total psychiatric disorders and dysthymic disorder. ↑ Prevalence of GHQ cases (total score and all dimensions)
Bazylewicz-Walczak et al. (1999)	Poland	26 female greenhouse workers and 25 unexposed control women	Cross-sectional	Questionnaire: Air pollution Contamination of skin and clothes Work timing	Cognitive and psychomotor functions (Neurobehavioral Core Test Battery) Symptom questionnaires Assessment before and after the spraying season	Analysis of variance	Exposed vs. controls: ↑ tension-anxiety ↑ anger-hostility ↑ fatigue-inertia ↑ depression-dejection ↑ neurological symptoms-central ↑ simple reaction time ↑ aiming errors ↓ motor steadiness No significant effects of exposure after a single spraying season

Table 1 (*Continued*)

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
Stallones and Beseler (2002)	US (Colorado, CFFHHS Project, 1992–1997)	761 farmers and spouses	Cross-sectional	Questionnaire: Farm residence and operation, pesticides used, health status, medical care access, health protection. Type of pesticide used when reporting specific symptoms	Depressive symptoms: CES-D scale	Conditional logistic regression Adjusted by age, gender, having fair or poor health, experiencing a reduction in income, being unmarried, not having graduated from high school, see relatives, and number drinks. County-stratified analysis	CES-D score > 15: OR = 5.95 (2.56–13.84) for acute-pesticide illness (chest-discomfort, difficulty breathing and irritation of eyes and skin) OR = 4.50 (1.20–16.65) for using OP when reporting eye irritation OR = 5.40 (1.05–27.43) for using OP when reporting chest discomfort
Sanne et al. (2004)	Norway (Hordaland Health Study – HUSK, 1997–1999)	Cohort of 17,295 workers, 40–49 yrs 917 farmers	Cross-sectional	Occupations: farmers vs. non farmers (full-time vs. part-time)	Depression and anxiety: Hospital Anxiety and Depression Scale (HADS-A and HADS-D)	Unadjusted logistic regression Gender-stratified analysis	HADS-D ≥ 8, ORs for farmers compared to non farmers: OR = 2.03 (1.61–2.55) for all men OR = 1.68 (1.19–2.35) for all women OR = 2.30 (1.61–3.28) for full-time men OR = 2.12 (1.28–3.52) for full-time women OR = 1.89 (1.42–2.51) for part-time men OR = 1.43 (0.91–2.24) for pat-time women Animal producers: OR = 3.13 (1.88–5.22) for all men OR = 1.27 (0.39–4.18) for all women
Wesseling et al. (2010)	Costa Rica	78 banana workers (54 OP poisoned and 24 carbamate poisoned), 15–55 yrs. 130 unexposed control workers (60% working in plantations and 40% working in a multinational company)	Cross-sectional	Previous poisoning with a cholinesterase inhibiting pesticide (OP or carbamates)	Psychological distress: Brief Symptom Inventory (BSI) (10 dimensions[a])	Unconditional logistic regression Adjusted for age, education, recent and cumulative exposure, alcohol, head injury, time of day of examination and examiner.	BSI score ≥63 (abnormal): Somatization, OR = 2.92 (1.64–5.22) for all poisoned; OR = 3.10 (1.61–6.00) for OP poisoned; OR = 2.56 (1.05–6.21) for carbamates poisoned. Depression, OR = 2.08 (1.16–3.72) for all poisoned; OR = 2.42 (1.26–4.66) for OP poisoned; OR = 1.45 (0.59–3.60) for carbamate poisoned. General severity index, OR = 2.57 (1.44–4.59) for all poisoned; OR = 3.56 (1.84–6.92) for OP poisoned; OR = 1.26 (0.51–3.11) for carbamates poisoned. Somatization, OR = 2.10 (1.04–4.22) for 1 poisoning event; OR = 4.57 (2.02–10.33) for ≥2 poisoning events (p-trend < 0.001). Depression, OR = 1.58 (0.77–3.25) for 1 poisoning event; OR = 2.88 (1.34–6.18) for ≥2 poisoning events (p-trend = 0.019) General severity index, OR = 2.41 (1.19–4.87) for 1 poisoning event; OR = 2.79 (1.30–6.00) for ≥2 poisoning events (p-trend = 0.005)

Table 1 (*Continued*)

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
Mackenzie Ross et al. (2010)	UK	127 sheep farmers (working or retired) 78 unexposed controls (rural workers or retired) 18–70 yrs	Cross-sectional	Low-level exposure to OP (no history of undiagnosed or diagnosed acute intoxication)	Depression and anxiety: Hospital Anxiety and Depression Scale (HADS-A and HADS-D) Cognitive functioning (test battery, e.g. WAIS-III)	Multivariate ANOVA	Depression (HADS-D ≥ 8): higher proportion of farmers ($\chi^2 = 33.97$, $p < 0.001$) compared to unexposed workers Anxiety (HADS-A ≥ 8): higher proportion of farmers ($\chi^2 = 7.25$, $p < 0.01$) compared to unexposed workers Cognitive tests: Sheep farmers performed significantly worse than non exposed workers on memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for mood.
Beseler et al. (2006)	US (Iowa and North Carolina, Agricultural Health Study – AHS cohort, 1993–1997)	2051 cases 27,023 controls of women spouses of pesticide applicators	Nested case–control Population based	Lifetime pesticide use: never; low (≤225 days); high (>225 days) Diagnosed pesticide poisoning Ever use of classes of pesticides: insecticides, herbicides, fumigants and fungicides	Self-reported physician diagnosed depression (requiring medication, yes/no)	Unconditional logistic regression Adjusted for state, age, race, off-farm work, alcohol, cigarette smoking, physician visits and solvent exposure. Factor analysis (PCA): groups of related-use pesticides	OR = 3.26 (1.72–6.19) for history of pesticide poisoning. OR = 1.09 (0.91–1.31) for cumulative pesticide poisoning. OR = 1.08 (0.95–1.23) for > 50% time applying pesticide. OR = 1.06 (0.91–1.24) for > 50% time for mixing pesticide. OR = 1.09 (0.99–1.20) for insecticides use OR = 1.07 (0.97–1.18) for herbicides use OR = 1.25 (0.91–1.72) for fumigants use OR = 1.12 (0.91–1.38) for fungicides use.
Beseler et al. (2008)	US (Iowa and North Carolina, Agricultural Health Study – AHS cohort, 1993–1997)	534 cases 17,051 controls of pesticide applicators	Nested case–control Population based	Cumulative pesticide exposure: low (<226 days); intermediate (226–752 days); high (>752) Unusually high pesticide exposure event (HPEE) Diagnosed pesticide poisoning	Self-reported physician-diagnosed depression (requiring medication, yes/no)	Unconditional logistic regression Adjusted for state, age, education, marital status, doctor visits, alcohol use, smoking, solvent exposure, not currently having crops or animals, and ever working a job off the farm, number of years lived or worked on a farm, and use of personal protective equipment	OR = 2.57 (1.74–3.79) for diagnosed pesticide poisoning OR = 1.07 (0.87–1.31) for intermediate vs. low exposure OR = 1.11 (0.87–1.42) for high vs. low exposure OR = 1.65 (1.33–2.05) for HPEE Sub-group without history of acute poisoning: OR = 1.54 (1.16–2.04) for high cumulative pesticide exposure
Beseler and Stallones (2008)	US (Colorado, CFFHHS Project, 1993–1996)	653 farm residents and spouses	Prospective	Pesticide poisoning at baseline (ever/never) (1993)	Depressive symptoms: CES-D scale	Generalized estimating equations (weighted least-squares regression) Adjusted model: gender, age, marital status Fully adjusted model: health status, odds income, and increased debt	CES-D score > 15 Adjusted model: OR = 2.59 (1.20–5.58) Fully adjusted model: OR = 2.00 (0.91–4.39); OR = 3.29 (1.95–5.55) for "being bothered by things"; OR = 1.93 (1.14–3.27) for "feeling everything as an effort"

OP: organophosphate; OC: organochlorine; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised; GHQ: General Health Questionnaire; CES-D: Center for Epidemiologic Studies-Depression; WAIS: Wechsler Adult Intelligence Scale; PR: prevalence ratio; OR: odds ratio; RR: relative risk; IFFHHS and CFFHHS: Iowa and Colorado Farm Family Health and Hazard Surveillance.

[a] BSI consists of subscales of the following dimensions (somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoid ideation, psychoticism and general severity index) and a general severity index.

Table 2
Summary of studies on pesticide exposure/farming activities and suicide.

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
Parrón et al. (1996)	Spain (Andalusia)	251 cases of suicides	Ecological	Exposure area and 2 reference areas Occupation: farmers vs. non farmers	Suicides deaths 1976–1987 (standardized rates 100,000 habitants)	Simple bivariate analysis (Comparison among areas and occupations)	↑ Rates in the exposure area compared with referent areas ($p < 0.05$) OR = 2.30 for the exposure area vs. reference area 1 and OR = 1.60 vs. reference area 2 ↑ Rates among farmers OR = 1.97 (0.96–4.05) for all suicides and those in the exposure area ↑ Rates of suicides using pesticides.
Pires et al. (2005)	Brazil (Mato Grosso do Sul state)	501 suicide attempts and 139 suicide deaths	Ecological	Insecticide and herbicide demand per type pf crop, micro-region and habitant (kg/hab) in 2000 (11 microregions)	1992–2002: Suicide attempts (100,000 hab, rural population) Suicide deaths (100,000 hab, total population)	Pearson coefficients	↑ Prevalence of suicide attempts and deaths in areas of higher insecticide use compared with areas with lower use. Pearson: $r = 0.61$ ($p = 0.05$) between cotton production and suicide attempts. No statistical significance with suicide deaths.
Faria et al. (2006)	Brazil (Rio Grande do Sul state)	4766 suicides, >15 yrs	Ecological	Main farm crops in 35 microregions	Suicide deaths in 1994–1998 (age-adjusted rates in each micro-region, 100,000 persons-year)	Hierarchical analysis Model level 1: socioeconomic and cultural, agricultural, and geographical factors*. *Upper income, schooling, human development index, divorce rate, religion, urbanization rate, large land-holdings, and single-residents households, among others. Model level 2: main crop, adjusted for the 1st level variables.	No associations between increased suicide rates and any of the agricultural variables.
Meyer et al. (2010)	Brazil (Rio de Janeiro state)	3517 agricultural workers, 20–59 yrs	Ecological	Per capita use of pesticides (1996) (quartiles) "Exposure area": Serrana rural region in Rio de Janeiro (RJ) Reference areas: city and state of RJ	Suicide deaths in 1981–2005 (Time periods: 1980–1989, 1990–97, 1998–2005) Hospitalizations due to suicide attempts in 1998–2007	Unconditional logistic regression: Mortality OR (MOR) according to quartiles of pesticide use Stratified analysis: age (20–39, 40–59 yrs), gender, and time interval.	Suicide: MOR = 2.61 (2.03–3.35) for areas in the upper quartile of pesticide use, compared with the 1st quartile. MOR = 4.13 (1.60–8.93) for farmers vs. non farmers in Serrana region MOR = 7.92 (3.13–16.77) for females in Serrana region vs. females in RJ city and state Hospitalizations: RR = 11.17 (10.00–12.49) for Serrana region vs. RJ city. RR = 2.92 (2.70–3.16) for Serrana region vs. RJ state.
Parrón et al. (2011)	Spain (Andalusia)	1349 subjects from the general population	Ecological	High vs. low pesticide exposure based on amounts of pesticides used (kg/person or tons per health district)	Suicide attempts in 1998–2005	Unconditional logistic regression Adjusted by age, gender and interaction gender*exposure	High vs. low exposure areas: Unadjusted analysis: OR = 1.87 (1.67–2.08) for total population OR = 2.00 (1.69–2.37) for men OR = 1.77 (1.53–2.05) for women Adjusted analysis: OR = 1.76 (1.49–2.08)

Table 2 (*Continued*)

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
Stallones (2006)	US (Colorado)	4991 suicide deaths 107,692 deaths from other causes	Cross-sectional	Occupations related to pesticide exposure (exposed) vs. others (non exposed)	Suicide deaths in 1990–1999	Unconditional logistic regression Adjusted for age, race, Hispanic ethnicity, years of education, marital status Gender stratified analysis	Men: OR = 1.14 (0.97–1.34) for occupationally exposed vs. non exposed Women: OR = 1.98 (1.01–3.88) for occupationally exposed vs. non exposed
Gallagher et al. (2008)	New Zealand	2024 suicide deaths	Cross-sectional	Occupations	Suicide deaths in 2001–2005	Comparison of suicide death rates among occupations Adjusted for age and sex	People working in farming, fisheries, or forestry and trades had higher suicide rates than people in other occupations.
Zhang et al. (2009)	China	9811 rural residents, ≥15 yrs	Cross-sectional	Storage of pesticides at home (yes/no)	Suicide ideation within 2 years before 2001 Mental disorder: General Health Questionnaire (GHQ)	Unconditional logistic regression Adjusted for gender, age, education, socioeconomic status, marital status, physical health, family history of suicidal behavior, GHQ and study design effects.	Unadjusted analysis: OR = 2.12 (1.54–2.93) Adjusted analysis: OR = 1.63 (1.13–2.35) OR = 3.38 (1.49–7.66) in plane regions
Wesseling et al. (2010)	Costa Rica	78 banana workers (54 OP poisoned and 24 carbamate poisoned), 15–55 yrs. 130 unexposed control workers (60% working in plantations and 40% working in a multinational company)	Cross-sectional	Previous poisoning with a cholinesterase inhibiting pesticide (OP or carbamates)	Suicide ideation	Unconditional logistic regression Adjusted for age, education, recent and cumulative exposure, alcohol, head injury, time of day of examination and examiner.	OR = 3.58 (1.45–8.84) for all poisoned OR = 3.72 (1.41–9.81) for OP poisoned OR = 2.57 (0.73–9.81) for carbamate poisoned OR = 2.65 and 4.98, respectively, for 1 and ≥2 poisonings vs. none (p-trend = 0.01)
Pickett et al. (1998)	Canada (Canadian Farm Operator Cohort-CFOC)	1457 cases 11,656 controls	Nested case–control Population based	Acres of herbicide and insecticide use	Suicide deaths in 1971–1987	Unconditional logistic regression Adjusted for age, province, marital status, number of machines, total sales, oat sold, capital value of holding, and weeks of paid labor.	OR = 1.71 (1.08–2.71) for 1–48 vs. no acres sprayed with herbicides and insecticides (in a subset of farmers with no hired help for spraying task) OR = 1.68 (1.15–2.46) for seasonal vs. year-round farm work. OR = 1.61 (1.24–2.10) for 13 vs. no weeks/year of paid labor on the farm.
Van Wijngaarden (2003)	US	11,707 cases 132,771 controls (other causes of death), 20–64 yrs	Case–control Population based	Exposure vs. non exposure to pesticides based on job title	Suicide deaths in 1991–1992	Unconditional logistic regression Adjusted for marital status, education, geographic area and race. Age and gender stratified analysis	OR = 1.3 (1.2–1.4) for all subjects (exposed vs. non exposed). OR = 1.5 (1.3–1.8) for subjects 35–49 yrs. OR = 1.6 (1.0–2.7) for all women OR = 1.2 (1.1–1.4) for all men

Table 2 (*Continued*)

Study	Country	Population	Design	Exposure	Outcome	Analysis	Results
MacFarlane et al. (2011)	Australia	Male workers: 90 suicide deaths 270 controls Matched by age, state of residence and live status	Nested case–control Population based	Interview 1960–1980: Exposure to 4 pesticide classes Overexposure (blood-tested cholinesterase inhibition) Occupation	Suicide deaths in 1983–2004	Conditional logistic regression Adjusted for reported pesticide exposure, overexposure to OP/carbamate pesticides and occupation	OR = 1.07 (0.59–1.95) for exposure to OP/carbamate insecticides OR = 0.95 (0.55–1.63) for OC insecticides OR = 0.65 (0.40–1.10) for herbicides/fungicides OR = 0.84 (0.40–1.76) for organometal pesticides OR = 1.90 (0.73–4.93) for overexposure to OP/carbamates OR = 1.16 (0.64–2.12) for occupation in agriculture OR = 0.93 (0.49–1.78) for occupation in horticulture, gardening or nursery
Lee et al. (2007)	US (Agricultural Health Study – AHS cohort, 1993–1997)	55,071 pesticide applicators	Prospective	Lifetime chlorpyrifos exposure: non-exposed; low (≤20 days); intermediate (20.1–56.0); high exposed (≥56.1)	Suicide deaths in 1993–2001	Poisson regression Adjusted for age, gender, education, smoking, alcohol consumption, and state of residence	RR = 2.37 (1.03–5.48) in the highest chlorpyrifos exposure group (≥56.1 days)
Beard et al. (2011)	US (Agricultural Health Study – AHS cohort, 1993–1997)	81,998 pesticide applicators and their spouses	Prospective	Ever use of any pesticide Cumulative lifetime days of use Ever use of 50 specific pesticides Cumulative lifetime days of use of 22 pesticides Ever use of 10 classes of pesticides[a]	Suicide deaths in 1993–2009	Cox proportional hazards regression Adjusted for age, gender, number of children in family, smoking, and alcohol consumption	HR = 0.83 (0.33–2.08) for >5 years mixed or applied pesticides, compared to none HR = 0.89 (0.36–2.20) for >20 days/year mixed or applied pesticides, compared to none HR = 0.61 (0.33–1.13) for >370 cumulative lifetime days of mixed or applied pesticides, compared to ≤9 days No statistically significant increased HR for ever use of specific pesticides or functional/chemical classes, nor cumulative lifetime days of use of specific pesticides

OP: organophosphate; OC: organochlorine; OR: odds ratio; RR: relative risk; HR: hazard ratio.

[a] Functional pesticide classes: fumigants, fungicides, herbicides, insecticides; Chemical pesticide classes: phenoxy herbicides, triazine herbicides, carbamates, OC insecticides, OP insecticides, pyrethroids insecticides.

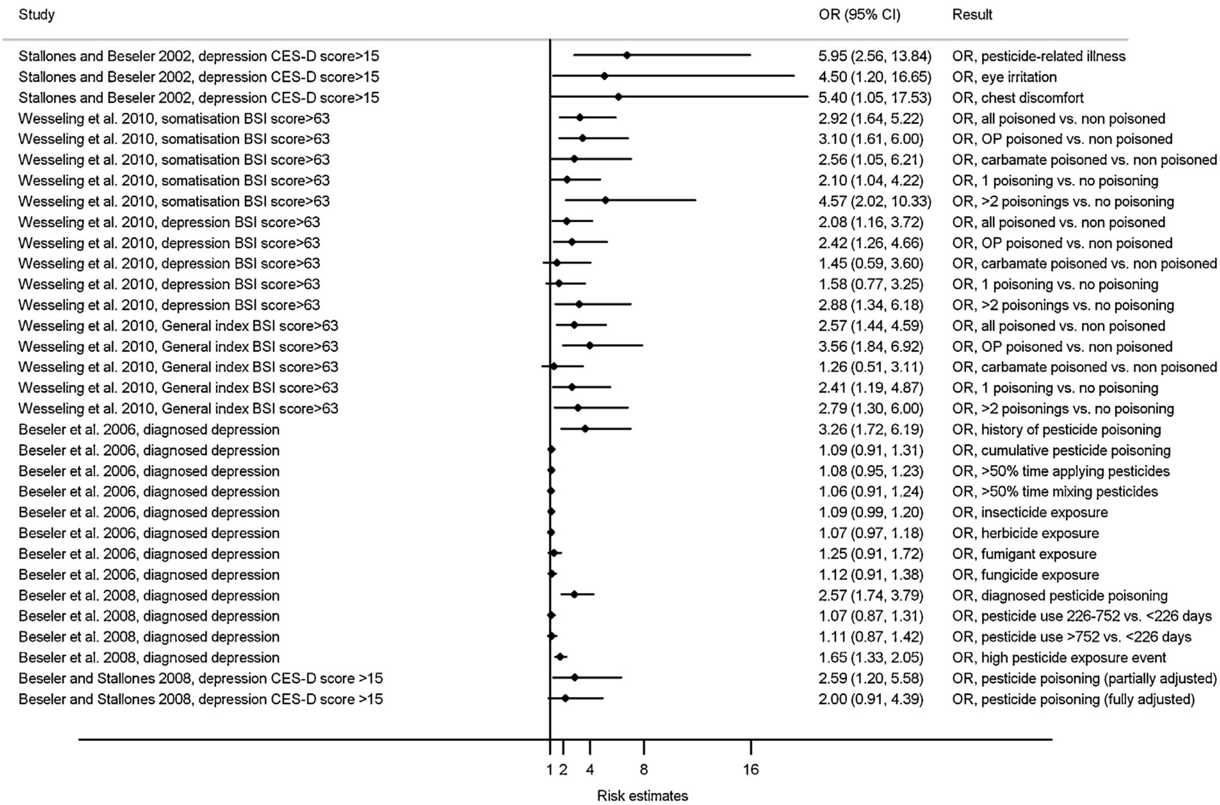

Fig. 1. Forest plot of epidemiologic studies examining pesticide exposure and risk of depression.

depression was found in pesticide formulators and applicators in Egypt compared to unexposed workers (prevalence ratios, PR of 1.56 and 1.78, respectively), as well as in formulators working for a longer period (PR = 1.99) (Amr et al., 1997). Although reporting positive associations with pesticide exposure, these four cross-sectional studies did not control for any risk factor for depression, such as age, alcohol use, or education.

Case–control studies

Two large nested case–control studies have been published among pesticide applicators and spouses enrolled in the Agricultural Health Study (AHS) cohort, both finding positive associations between pesticide exposure and depression (Beseler et al., 2006, 2008). After adjusting for a number of confounders (i.e. state of residence, age, race, off-farm work, alcohol, cigarette smoking, physician visits and solvent exposure), 3-fold increased risk for self-reported diagnosed depression was observed in female spouses of pesticide applicators with a history of pesticide poisoning (OR = 3.26, 95% CI = 1.72–6.19), but no statistically significant association was found for cumulative pesticide exposure (Beseler et al., 2006). Likewise, adjusted risk estimate for self-reported depression was significantly higher (OR = 2.57, 95% CI = 1.74–3.79) among male and female applicators previous diagnosed of pesticide poisoning (Beseler et al., 2008). When using more detailed exposure variables, a significantly higher risk of depression was observed in farmers having experienced an unusually high-pesticide exposure event (OR = 1.65, 95% CI = 1.33–2.05) and among those with no history of acute poisoning but with a high lifetime pesticide exposure (OR = 1.54, 95% CI = 1.16–2.04). No association was found when exposure to specific pesticide groups (i.e. insecticides, herbicides, fumigants, fungicides, OP, organochlorines) was examined (Beseler et al., 2006).

Prospective studies

Only one prospective study on pesticide exposure and depression has been identified in the literature, which was drawn from the CFFHHS project on farmers and their spouses in Colorado (Beseler and Stallones, 2008). In this study, individuals with previous pesticide poisoning had a higher risk of having clinical depressive symptoms in adjusted models (OR = 2.59, 95% CI = 1.20–5.58), but not in models additionally adjusted for health status, debt, and income (OR = 2.00, 95% CI = 0.91–4.39) (Beseler and Stallones, 2008).

Pesticide exposure and suicide

When reviewing the literature on pesticides and suicide, it is observed that different outcomes have been studied, i.e. suicide ideation, suicide attempts, and mortality due to suicide (Table 2). Data on deaths or attempts in 10 studies were obtained through official registries, while two studies used a questionnaire to obtain self-reported information on suicide ideation (Wesseling et al., 2010; Zhang et al., 2009).

Ecological studies

Five ecological studies investigated suicide mortality and other suicide-related outcomes, four of them suggesting a positive association with pesticide exposure. A study in Southern Spain showed that the suicide rate in a farming area was significantly higher than rates in other geographic areas with lower agricultural activity (ORs of 1.60 and 2.30), as well as farmers presented a borderline significant increase in the risk of suicide (OR = 1.97, 95% CI = 0.96–4.05) compared with non farmers (Parrón et al., 1996) (Table 2). More recently, the latter research group showed that people living in areas with higher pesticide use had increased prevalence and risk for suicide attempts compared to those living in low-exposure areas (OR = 1.87, 95% CI = 1.67–2.08) (Parrón et al., 2011).

In the aforementioned study in the countryside of Rio de Janeiro, Brazil, agricultural workers who lived in areas with higher rates of pesticide expenditure had increased risk for suicide mortality (OR = 2.61, 95% CI = 2.03–3.35), as well as increased risk for hospitalization by suicide attempts (ORs ranging from 2.92 to 11.17) (Meyer et al., 2010). In addition, farmers showed a higher mortality odds ratio (MOR) for suicide than did non farmers (MOR = 4.13, 95% CI = 1.60–8.93). Another ecological study in the South-west of Brazil found higher prevalence of suicide attempts and deaths in areas of higher insecticide use in agriculture (vegetable and fruit crops) compared with areas with lower use (Pires et al., 2005). However, these studies did not control for important socioeconomic confounders such as marital status, education, income, or alcoholism. Additionally, no association was found between farming activity and suicide rates in a study that analyzed suicide mortality according to socioeconomic variables and agriculture crops in the South of Brazil (Faria et al., 2006).

Cross-sectional studies

Among the four cross-sectional investigations on pesticides and suicide, two studies reported significant increases in risk of suicidal thoughts associated with pesticide exposure (Wesseling et al., 2010; Zhang et al., 2009). Psychological distress symptoms were found to be associated with past OP poisoning in banana workers from Costa Rica (Wesseling et al., 2010), including suicide ideation (OR = 3.72, 95% CI = 1.41–9.81). Also, score for suicidal thoughts showed a statistically significant increase according to the number of past poisonings (OR = 4.98 for among workers with $\geq$2 poisonings vs. none). For their part, Zhang et al. (2009) found that Chinese rural residents reporting pesticide storage at home had a higher suicidal ideation compared to subjects with no residential pesticides exposure (OR = 1.63, 95% CI = 1.13–2.35)

The other two cross-sectional studies used death certificates to describe suicide among individuals with different occupations (Gallagher et al., 2008; Stallones, 2006). In Colorado, potential exposure to pesticides through occupation was associated with significantly increased risk of mortality from suicide either in men (OR = 1.47, 95% CI = 0.97–1.34) or women (OR = 1.98, 95% CI = 1.01–3.88) (Stallones, 2006). In accordance with these findings, a study in New Zealand reported that people working in farming, fisheries, or forestry and trades had higher suicide rates than people in other occupations (Gallagher et al., 2008).

Case–control studies

Two population-based case–control studies observed an association between pesticide-related exposure and higher suicide risk. One of them, nested in a Canadian cohort of farmers, showed a statistically significant increase of suicide deaths among herbicide and insecticide applicators compared to non-sprayer farmers (OR = 1.71, 95% CI = 1.08–2.71) (Pickett et al., 1998). The second study found higher suicide risk among 35–49 year-old workers with occupations with a high probability of pesticide exposure (OR = 1.3, 95% CI = 1.2–1.4), which was particularly higher among female workers (OR = 1.6, 95% CI = 1.0–2.7) (Van Wijngaarden, 2003). Conversely, a recent nested case–control study (MacFarlane et al., 2011) could not find a statistically significant increase in suicide mortality risk among Australian male workers in relation to history of overexposure to OP or carbamate insecticides as measured by blood cholinesterase inhibition. This study evaluated 90 deaths by suicide during 1960–1980, and an OR of 1.90 (95% CI = 0.73–4.93) was observed for overexposure to OP/carbamates. No association was either found with reported exposure to organochlorine insecticides, fungicides or herbicides, organometal pesticides, or with occupations with pesticide exposure (MacFarlane et al., 2011).

Prospective studies

As observed for depression, very few prospective studies have been published in relation to suicide. One study found a 2-fold increased risk (RR = 2.37, 95% CI = 1.03–5.48) of suicide mortality among pesticide applicators enrolled in the AHS cohort (US) having experienced a longer lifetime of exposure to chlorpyrifos (Lee et al., 2007) (Table 2). However, a recent study among workers from the same cohort reported no increased suicide risk in relation to prior pesticide use (Beard et al., 2011).

Discussion

Epidemiological evidence of association

Pesticide exposure and depression

Reviewed scientific literature on the association between pesticide exposure and depression or other affective-related psychiatric disorders provides limited evidence of a causal relationship (Table 1). Cross sectional is the study design that most epidemiologic studies on pesticides and depression have used (6 out of 11 reports) and, even though significant associations were found in those transversal studies, some results were obtained using small sample sizes (Bazylewicz-Walczak et al., 1999; Mackenzie Ross et al., 2010; Wesseling et al., 2010) or univariate analysis (Amr et al., 1997; Mackenzie Ross et al., 2010; Sanne et al., 2004).

The strongest evidence of association between exposure to pesticides and depression were those derived from the AHS and CFFHHS cohort studies in the US, which found increased risk of depression (ranging from 2.6 to 6.0) associated with past pesticide poisoning among large samples of farmers (Beseler et al., 2006, 2008; Beseler and Stallones, 2008; Stallones and Beseler, 2002). The largest of these studies, exploring 2051 females with self-reported depression and 27,051 controls, found risk estimates close to the unity for continuous exposure to different pesticide groups assessed in several working conditions (Beseler et al., 2006). However, a statistically significant 3-fold increase in the risk of depression was reported among women with previous episodes of pesticides poisoning (Beseler et al., 2006), which was subsequently confirmed (Beseler et al., 2008; Beseler and Stallones, 2008). These results suggest that a history of pesticide intoxications may lead to neuropsychiatric disorders such as depression. According to this hypothesis, statistically significant increases in risks for symptoms of psychological somatization (OR = 4.57) and depression (OR = 2.88) were reported in individuals with more than 2 previous events of pesticide poisoning (Wesseling et al., 2010). In contrast, clinical manifestation of psychiatric disorders following chronic exposure to low levels of pesticides may be influenced by individual susceptibility determined by genetic polymorphisms of enzymes involved in pesticide metabolism (Nioi and Hayes, 2004; Singh et al., 2011), as well as by epigenetic mechanisms involved in neuropsychiatric disorders development (Ai et al., 2012; Murgatroyd and Spengler, 2012).

Pesticide exposure and suicide

Evidence of a link between pesticide exposure and risk of suicide is also limited and findings are derived from studies that have used various methodologies and different epidemiological designs. Nonetheless, they have generally reported increased suicide rates related to pesticide use or occupation in agriculture. In addition, when compared with data on depression, findings for suicide show risk estimates of higher magnitude, including those from population-based studies (Fig. 2).

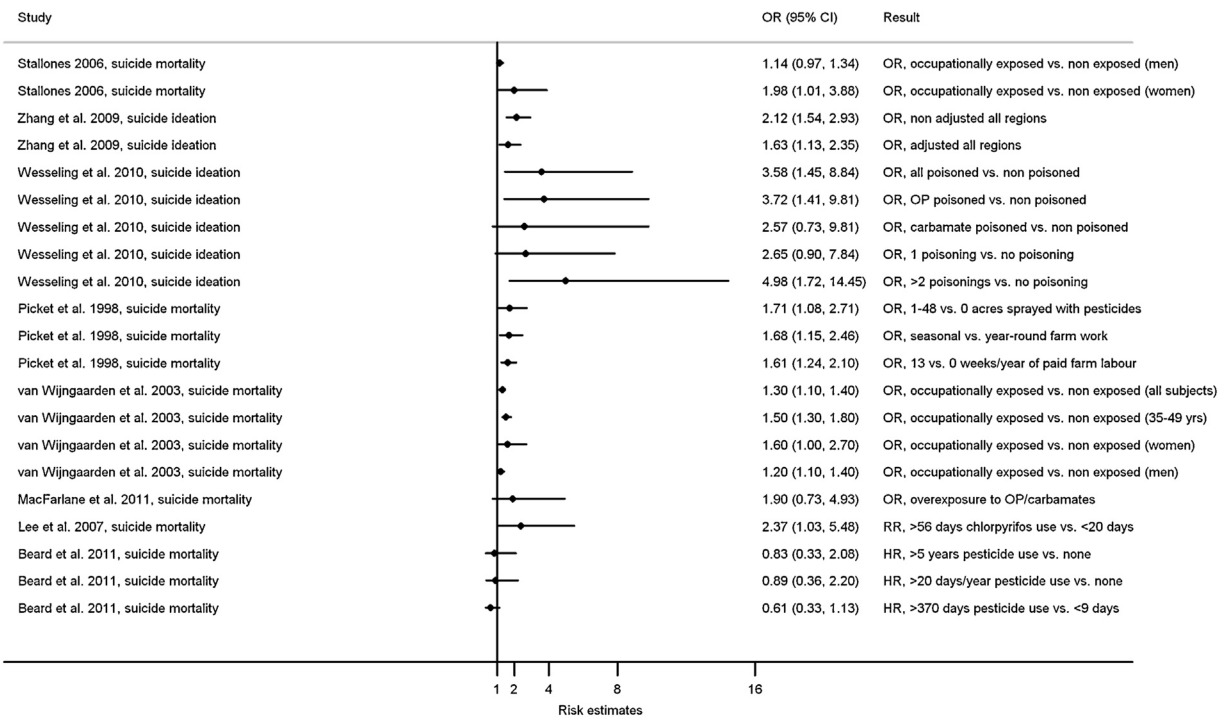

Fig. 2. Forest plot of epidemiologic studies examining pesticide exposure and risk of suicide.

Availability of both suicide and pesticide data from public registries makes ecological design suitable to investigate the potential relation between exposure pesticide usage and this outcome. In this regard, relevant findings have been obtained in ecological studies in Brazil (Meyer et al., 2010) and Spain (Parrón et al., 1996, 2011). It is noteworthy to highlight the differences in risk estimates of suicide mortality observed in Brazil and those reported in other countries. In the former, agriculture workers 20–39 years old from a large area with intensive use of pesticides in fruit and vegetable crops presented statistically significant mortality OR for suicide, ranging from 4.5 to 9.4, compared to the general population (Meyer et al., 2010). Other researchers could not observe results of similar magnitude elsewhere. This is the case of the two ecological studies that reported increased population-based suicide risks, but lower in magnitude, in Spanish areas with high pesticide use compared to low exposure areas (Parrón et al., 1996, 2011). Among individual-level studies, risk estimates between 1.2 and 3.7 have been reported in seven studies with miscellaneous designs, exposure measures, studied outcome and statistical analysis (Table 2). Finally, the most recent findings do not support the hypothesis of such an association between pesticide exposure and suicide in a large cohort study of about 82,000 pesticide applicators and their spouses (Beard et al., 2011).

Suicide is a complex event needing the consideration of multiple aspects involved in the process leading to suicidal behavior. In the context of the present review, several studies have suggested that agricultural working is a risk factor for suicide, but conditions other than pesticide exposure must to be considered. Farmers are likely to be exposed to several hazards at their workplace, such as access to toxic substances (i.e. pesticides), working instruments or weapons and machines, animals, heavy manual labor or physical activity, that may lead to a higher risk of substance abuse, injury and suicide in this occupational group (Beseler and Stallones, 2010). Additionally, uncertainty related with agricultural activity is a constant for farmers due to uncontrolled natural hazards (e.g. excess/lack of sun light, rain, low temperature, winds, and plagues) and due to worldwide up and down balance of the agricultural market, which can mainly affect small-scale farmers. Moreover, agricultural workers very often depend on banking loans to carry out their activity (i.e. buying seeds, machines, fertilizers or pesticides), leading to a permanent stressful scenario if crops are unsuccessful. Farmers in developing countries may be thus particularly vulnerable to workplace hazards due to a combination of factors such as agriculture-related uncertainties, low education, low household income, high alcohol consumption, isolation, and poor use of personal protective equipments, among others. For instance, differently to farmers from developed countries, Brazilian population of agriculture workers studied by Meyer et al. (2010) is characterized by low income, low education, and low political level of organization and participation. These conditions make this population a social group with a restricted ability to have a comprehensive understanding of the multiple adversities of life, and probably, to face them. Hence, it is feasible that the neurotoxic effects triggered by pesticide exposure may lead to suicide more rapidly in rural populations of developing countries compared to rural workers from developed areas, which enjoy a higher education, higher income, better legal protection, a better understanding of citizenship rights, and which live in societies with active social welfare institutions to support them.

Study limitations

Drawing clear conclusions on the association between pesticide exposure, depression and suicide is hampered by several methodological flaws in the reviewed studies. These limitations are summarized in the following topics.

Exposure measure

One of the main difficulties when trying to draw conclusions after reviewing studies on the field is the miscellaneous scenario on exposure metrics. There is a wide variation in pesticide exposure definition, which is mainly based on crude and broad measures such as urban vs. rural living or pesticide expenditure in ecological analysis (Meyer et al., 2010; Parrón et al., 1996, 2011), self-reported exposure based on job title (Van Wijngaarden, 2003), self-reported pesticide poisoning (Beseler and Stallones, 2008), or pesticide possession (Zhang et al., 2009). In fact, most studies have focused on occupational use as a proxy for chronic pesticide exposure and have compared high-exposed workers with low- or non exposed workers (Amr et al., 1997; Mackenzie Ross et al., 2010; Sanne et al., 2004; Wesseling et al., 2010). Broad measures of pesticide exposure may not appropriately represented the real magnitude of exposure, as it has been reported for living with an applicator or living in a farm (Acquavella et al., 2005; Alexander et al., 2006; Arbuckle and Ritter, 2005). Hence, such a lack of detailed and validated exposure measures could lead to potential exposure misclassification, compromising the epidemiological validity of study findings.

More detailed exposure information, such as cumulative lifetime exposure and gradation of exposure levels, have been used to a lesser extent (Beard et al., 2011; Beseler et al., 2006, 2008; Lee et al., 2007; Mackenzie Ross et al., 2010). It is important to emphasize that, differently to poisoning, there is no consensus yet regarding the effects on the CNS of low-dose and continuous pesticide exposure, and further research requires to make use of more accurate markers of exposure. Therefore, the distinction between low-dose exposure, acute high-dose exposure, and poisoning events is very important when attempting to establish a link between pesticides and psychiatric disorders. However, very few studies have made such a distinction (Beseler et al., 2006, 2008; MacFarlane et al., 2011). As suggested by Beseler et al. (2008), psychiatric disorders may be also associated with chronic pesticide exposure in the absence of past poisoning.

On the other hand, very few studies have collected detailed information on use of specific chemical or functional classes of pesticides other than OPs, such as OC, pyrethroids, carbamates, herbicides, fungicides or fumigants (Beard et al., 2011; Beseler et al., 2006; MacFarlane et al., 2011). In fact, epidemiological research has been mainly focused on workers generally exposed to OP pesticides, since biological plausibility is lacking for non-cholinesterase depressants. Thus, elevated risk of depression (Beseler et al., 2006) and suicide (Beard et al., 2011; MacFarlane et al., 2011) did not show statistically significant association with self-reported exposure to any particular class of pesticides. Only specific lifetime exposure to chlorpyrifos, history of cholinesterase inhibition, and previous poisoning events involving OP/carbamate pesticides have shown a positive and statistically significant association with depression (Wesseling et al., 2010) and suicide risks (Lee et al., 2007; MacFarlane et al., 2011; Wesseling et al., 2010). Because pesticides from different chemical classes may interact with the CNS through different mechanisms (Jett, 2011), the association with psychiatric disorders should be further investigated according to the potential modes of action of substances.

Case definition

A potential source of further inconsistency in the reviewed literature is the varying outcome definition within the categories of depression and suicide. Definition of cases by self-report methods could affect sensitivity and specificity in the measurement of outcome, which could lead to outcome misclassification and biased results. The use of validated scales for clinical diagnosis of depression and other psychiatric disorders is necessary to strengthen quality of future studies.

Similarly, different outcomes have been used for suicide, i.e. mortality due to suicide, suicide attempt (obtained from hospitalization records), and self-reported suicide ideation. Suicide from death certificates is a relatively valid outcome, despite it is commonly underreported for cultural reasons in some countries, being artificially replaced by other causes of death. Suicidal thoughts based on a single question might be a potential source of outcome misclassification (Wesseling et al., 2010).

Methodological aspects concerning case definition should be of particular concern in investigations conducted in rural communities and developing countries, where access to mental health care and training of physicians to ask about depressive symptoms are limited, as well as quality of medical and mortality registries are lower compared to developed areas. As a consequence, regional differences in diagnosis of depression status and ascertainment of suicide cases are prone to hamper inter-study and country to country comparisons.

Study design and methodology

Epidemiological validity of reports may in part depend on aspects regarding the design of the study. Most information on pesticide exposure and diagnosed depression was collected cross-sectionally, while ecological design has been most widely used in suicide studies. Both ecological and cross-sectional designs prevent researchers from establishing a causal relationship between the exposure and the outcome. This is a particularly relevant aspect when studying suicide and pesticide exposure, since the direction of the association is not always evident (London et al., 2005). On the other hand, retrospective self-reporting of exposures is the most commonly used method for estimation of pesticide exposure cross-sectional and case–control studies, which present the limitation of potential for recall bias. Prospective self-report of the exposure and the use of more objective methods, such as job exposure matrices, may reduce such a potential recall bias.

The selection of a good referent group obtained from a well defined study-base is important to reduce the likelihood of bias for confounding. Controls should be drawn from the same population as cases, being representative of the total population. In this regard, referent groups provided by nested case–control studies and population-based cohort studies on depression (Beseler et al., 2006, 2008; Sanne et al., 2004) and suicide (MacFarlane et al., 2011; Van Wijngaarden, 2003) may be better than those provided by some cross-sectional reports in which a group of exposed workers was compared with an unexposed control group with potentially different demographic and lifestyle characteristics (Amr et al., 1997; Mackenzie Ross et al., 2010).

Sample size

Interpretations of study findings could be also limited by small sample sizes. When exposure strata contain few subjects even slight misclassification of diagnosis or exposure may substantially alter observed associations. In general, small samples are likely to lead to unstable risk estimates (MacFarlane et al., 2011).

Co-stressors and confounders

Psychiatric disorders in people working in agriculture is a public health problem that may result from a complex interaction of risk factors, including age, gender, ethnicity, geographic region, social, cultural and economical factors, medical conditions, and hereditary factors (WHO, 2000b). As mentioned above, agricultural populations from developing countries are particularly vulnerable to workplace hazards due to agriculture-related uncertainties and several social factors, such as poverty, low education, frequent alcohol consumption, frequent smoking, substance abuse, unmarried status, social isolation, poorer social support, and poorer access to health care. These adverse conditions would predispose farmers to mental disorders and, consequently, to suicidal behaviors.

The use of personal protective equipments or clothing is another important covariate that should be considered to examine the association between pesticides use and health outcomes. Use of protective equipments may be directly related to pesticide exposure, but also there may be a relationship between emotional status and low safety knowledge or poor safe behavior, which would lead to a higher risk of injury (Beseler and Stallones, 2010). In the present review there are included several reports from developing countries (i.e. Costa Rica, Brazil, China), where availability or use of personal protection equipments in agricultural practices is very limited. Only one study in this review considered this information in the adjustment of the association with depression risk (Beseler et al., 2008). The lack of control for the use of protective equipments, a potential confounder of the association between pesticide exposure and suicide or depression, may have also accounted for inconsistency of results among studies. Besides access to pesticides, possession or access to lethal means, such as weapons and other working instruments (e.g. sickles, machetes, ropes, pesticides, among others) and use of machines would also contribute to elevate the risk for suicide among agricultural workers.

Hence, to address the question of whether pesticide exposure plays a role in elevating the risk for depression or suicide, social stressors, use of protective equipments and other potential confounders (e.g. medical and psychiatric history) should be measured into avoid introducing a bias. Up to now, several studies did not control for a number of these potential confounders (MacFarlane et al., 2011; Mackenzie Ross et al., 2010; Meyer et al., 2010; Parrón et al., 1996, 2011; Sanne et al., 2004).

In general, the main limits of existing studies are the scarce knowledge of exposure levels, the lack of control for important confounders (i.e. social stressors and use of protective equipments), and the variability of the testing methods used to define cases. Conducting prospective longitudinal or cohort studies, where exposure assessment can be more easily controlled, or the evaluation of cohorts of workers a priori selected for the availability more detailed and accurate exposure measures (preferably exposure biomarkers) may be a challenging and promising approach.

Relation between pesticides, depression and suicide

Although depression and suicide are different outcomes and should be analyzed separately, they are not independent, since depression is the most common psychiatric disorder among suicide attempters. The linkage between depression and suicide is possibly mediated through the impact of depression on impulsivity and lack of self control (London, 2009; Oquendo and Mann, 2000). In fact, it has been suggested that addressing depression may reduce risk of injuries among farm workers (Beseler and Stallones, 2010; Sprince et al., 2002; Tiesman et al., 2006). Nonetheless, depression could also be a self-limited outcome not yielding to suicide (Prasko et al., 2010), which may be influenced by risk factors other than depression, such as alcohol/substance use, mood and personality disorders (e.g. impulsivity, aggressiveness, hopelessness, high emotional reactivity) (Goldney et al., 2002; Hawton and van Heeringen, 2009; Nock et al., 2008).

It is important to stress that the hypothesis raised by the literature reviewed here is concerning the idea that the use and availability of pesticides may be risk factors for mental health problems. Such statement does not derive from the fact that these chemicals are used in suicide attempts, but because their use could be causally and directly associated with psychiatric disorders, such as depression, suicidal thoughts or suicidal behaviors.

Besides depression and suicide, both chronic and acute exposure to pesticides (not only OP insecticides) have been associated with a range of symptoms and disorders related to the peripheral and central nervous system, i.e. neurobehavioral disorders, cognitive impairments, alterations in peripheral nerve function, sensory neuropathy and neurodegenerative illnesses, such as Parkinson's and Alzheimer diseases (Brown et al., 2006; Cole et al., 1998; Moretto and Colosio, 2011; Rohlman et al., 2007). Several mechanisms of action has been proposed for these outcomes, i.e. disturbances of neuroendocrine function in the brain, changes in neurotransmitter system (e.g. inhibition of AChE), altered intracellular signaling (e.g. sodium channels), oxidative stress processes, alteration of serotonergic system, and alteration of the nigrostratial dopaminergic homeostasis (Corrigan et al., 2000; Franco et al., 2010; Moretto and Colosio, 2011). The neurotoxic response triggered by pesticide exposure might be characterized by complex neurophysiologic and neurochemical processes which might be interrelated and depend, among other factors, on exposure conditions and variability in xenobiotic metabolism possibly generated by genetic polymorphisms. The understanding of these underlying mechanisms of action in the CNS is crucial to generate and confirm this and other hypotheses on neurological features related to pesticide exposure.

Final remarks

The few epidemiological studies conducted to date have shown increased risks of psychiatric disorders and suicide associated with pesticide exposure; however, studies present several methodological weaknesses and results are inconsistent. Findings from the present review suggest that, whether an association between pesticide exposure and either depression or suicide exists, the risk estimates might not be greater than 3.0 (Figs. 1 and 2). Moreover, affective disorders and suicide do not seem to be the result of a cumulative process of pesticide exposure dependent of the dose and the duration of the exposure. Thus, excepting for findings by Meyer et al. (2010), a clear monotonic dose–response pattern has not been reported in the literature. An alternative explanation for the lack of a dose–response effect would be that the association between pesticide exposure and depression and suicide may become apparent when a certain threshold of exposure is reached among genetically susceptible individuals, as it has been observed for cumulative exposures to other chemicals (Attias et al., 2005). In other words, the risk of psychiatric disorders in individuals with long-term pesticide exposure might be influenced by genetic vulnerability to the neurotoxic effects of pesticides due to genetic variants in enzymes involved in pesticide detoxification, such as paraoxonase (Brown et al., 2006; Cherry et al., 2002; Costa et al., 2003).

Conclusions

Depression and suicide have multiple risk factors and may greatly depend on their epidemiology and socio-demographic characteristics. It is increasingly suggested that pesticide exposure is a risk factor for depression and suicide. However, epidemiological evidence is still very limited, particularly in relation to the effects of chronic and low-dose exposures, as well as a causal relationship has not been established yet. Interpretation of the reviewed findings is complex and should be made with caution since studies have been conducted in diverse populations, have used varying epidemiological approaches, and they lack of detailed and reliable exposure assessment. We highlight the need of prospective epidemiological studies with larger samples of both high (or poisoned) and low-dose exposed workers, with detailed quantifications of exposure, validated case definitions, controlling for potential confounders, and investigating the role of genetic susceptibilities. Finally, despite inconsistency of findings and study limitations, measures must be adopted to restrict pesticides access and commercialization and to reduce the exposure to highly toxic pesticides among agricultural workers to prevent psychiatric disorders and suicidal behaviors, particularly in developing countries in which pesticides are still extensively used.

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