Linking pesticide exposure and dementia: What is the evidence?

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ABSTRACT

There has been a steep increase in the prevalence of dementia in recent decades, which has roughly followed an increase in pesticide use some decades earlier, a time when it is probable that current dementia patients could have been exposed to pesticides. This raises the question whether pesticides contribute to dementia pathogenesis. Indeed, many studies have found increased prevalence of cognitive, behavioral and psychomotor dysfunction in individuals chronically exposed to pesticides. Furthermore, evidence from recent studies shows a possible association between chronic pesticide exposure and an increased prevalence of dementia, including Alzheimer's disease (AD) dementia. At the cellular and molecular level, the mechanism of action of many classes of pesticides suggests that these compounds could be, at least partly, accountable for the neurodegeneration accompanying AD and other dementias. For example, organophosphates, which inhibit acetylcholinesterase as do the drugs used in treating AD symptoms, have also been shown to lead to microtubule derangements and tau hyperphosphorylation, a hallmark of AD. This emerging association is of considerable public health importance, given the increasing dementia prevalence and pesticide use. Here we review the epidemiological links between dementia and pesticide exposure and discuss the possible pathophysiological mechanisms and clinical implications of this association.

1. Introduction

Dementia, and in particular its commonest form, Alzheimer's disease (AD), constitutes a major health problem, being associated with significant morbidity and mortality (Ballard et al., 2011). Consequently, the financial and emotional burden of dementia is enormous, both at the level of the individual and his/her caregivers and at the level of the society at large (Jonsson and Wimo, 2009). Furthermore, there has been a worrisome steep increase of dementia prevalence in recent decades and this trend, given the aging population in Western and other countries, such as China and India, is expected to continue in the forthcoming years (Ballard et al., 2011).

This major health impact of dementia has instigated multiple studies on possible etiological factors accounting for the onset and progression of dementing illnesses. The vast majority of dementia cases occur in the elderly, making age the most important, but non-modifiable risk factor. Genetic factors have been estimated to account for up to 70% of the risk associated with AD; other risk factors include obesity, smoking, lack of exercise, mid-life hypertension and diabetes (Ballard et al., 2011). Special interest has focused on environmental factors of rising importance that could parallel the rising prevalence of dementia. Much work has been focused on exposure to toxic metals such as copper, aluminum and lead, the latter receiving special attention because of the possibility that exposures in early development may influence neurodegenerative disease in later life (Cannon and Greenamyre, 2011). In contrast, exposure to pesticides has received comparatively little attention with regard to their possible role in dementia. Pesticides are used in agriculture, farming or other applications for protecting humans from the damaging effects of pests (Sanborn et al., 2007; Hernández et al., in press). Target pests for pesticides include insects, weeds, animals, birds, nematodes and microorganisms, that produce harm to humans either directly or indirectly (e.g. by reducing the production and quality of an agricultural exploitation or by the spread of disease).

The nature of pesticides, that is to control living species, is at the heart of their potential toxicity to humans. Furthermore, the fact that they need to be deliberately spread to the environment to reach their targets leads to inadvertent exposure of most of the

human population. The toxicity of pesticides can often cross species barriers and inflict damage to many species, including humans. Specifically, many pesticides, in particular insecticides, are neurotoxic (Bjørling-Poulsen et al., 2008). Acute toxic effects are well known, but uncertainties still remain regarding chronic and long term effects, including their effect on the pathogenesis of cancer, dementia (including AD dementia), Parkinson's disease (PD) and other devastating disorders (Gilden et al., 2010).

It has been repeatedly reported that acute high-level exposure to certain pesticides has significant neurotoxic effects (Costa et al., 2008). These acute effects of pesticides depend on the nature of the pesticide, the route of exposure, the amount of pesticide absorbed and the time frame within which this exposure took effect. A well-known example of the acute effect of pesticides is the acute inhibition of the enzyme acetylcholinesterase in organophosphate poisoning, which presents with muscle weakness, convulsions, respiratory and circulatory problems, ataxia, tremor, salivation, lacrimation, miosis, sweating, diarrhea and urinary incontinence (Aygun, 2004).

Chronic exposure to pesticides has also been associated with a variety of neurological disorders, the most well-known example being the possible association between PD and pesticide exposure (Brown et al., 2006; Tsatsakis et al., 2008; Moretto and Colosio, 2011; Freire and Koifman, 2012; Tsatsakis et al., 2012a). Other neurological diseases possibly associated with chronic pesticide exposure include amyotrophic lateral sclerosis and peripheral polyneuropathy (Sanborn et al., 2007; Costa et al., 2008; Gilden et al., 2010; Kanavouras et al., 2011; Kamel et al., 2012).

In addition, there is evidence of increased prevalence of cognitive, behavioral and psychomotor dysfunction in individuals chronically exposed to pesticides (Bosma et al., 2000). A possible link of chronic pesticide exposure to increased prevalence of dementia, including its commonest form, AD would raise considerable public health concern, given the ever increasing dementia prevalence and the widespread pesticide use. Here we review the epidemiological links between dementia and pesticide exposure and discuss the possible pathophysiological mechanisms and clinical implications of this association.

2. Information from epidemiological and other clinical studies

2.1. Introduction to the methodology of the studies and their limitations

The key issue in any toxicological epidemiological study is collection of sound and adequate data on the levels of exposure of the individuals under investigation. Epidemiological studies are sometimes retrospective, and retrospective exposure assessment is very often a challenge. This is especially true in the field of pesticides, where intermittent exposure, non-continuous use of variable mixtures of active ingredients and intraseasonal variability of the active ingredients used make the identification of the source of exposure extremely difficult. This means that instead of exposure data, different crude proxies of exposure are used, for example "having been in the past an agricultural worker" or even "having been a rural area dweller". Other proxies of exposure can be "having been a pesticide applicator" or only "having used personal protective devices". Thus, the high risk of recall bias or/and misclassification in exposure subgroups is obvious. In light of these, it is often practically impossible to define the specific active ingredients and the source and magnitude of exposure.

Use of retrospectively recalled symptoms as a marker of exposure is notoriously inaccurate, since symptoms (such as headache or "head tension", sleep disturbances, feeling nauseated or "dizzy",

chest pain and difficulty in breathing, feeling weak, tremor or "shaking", numbness, "burning" or "tingling" sensations, problems with vision, easy fatigability and cognitive symptoms, including confusion and difficulty in concentrating) are non-specific and subject to recall bias. Furthermore, these symptoms are indicators of acute or subacute effects, not necessarily present in chronic or prolonged exposures. Therefore, quantitative estimation of the exact level of pesticide exposure is extremely complex. Thus, in most studies the level of occupational exposure to pesticides is crudely divided to low, moderate or high. Moreover, it is extremely difficult to assess pesticide exposure not related to occupation. Finally, it is debatable whether we should measure peak, average or cumulative exposure to pesticides as an index of the exposure for an individual. Various possible biological and epidemiological markers of chronic exposure to pesticides are currently under intense investigation, given the important health implications of this exposure.

Despite the limitations presented above, there is an increasing number of studies linking exposure to pesticides to cognitive dysfunction and even overt dementia, including AD dementia (Table 1). These studies are presented below, taking into account the fact that dementia, especially AD dementia, is part of a continuum, spanning from mild cognitive and neurobehavioral deficits to mild cognitive impairment and then to overt dementia. In addition, the reader should bear in mind that the boundaries among these three entities are at times arbitrary and hard to accurately define.

2.2. Pesticides and their possible cognitive and neurobehavioral effects

There have been several studies linking pesticide exposure to cognitive and neurobehavioral deficits (Colosio et al., 2003, 2009; London et al., 2012). In these studies, subjects exposed or supposedly exposed to pesticides or related compounds (e.g. industrial compounds or chemical warfare reagents) underwent a series of neuropsychological tests to assess their cognitive and neurobehavioral skills. In some of these studies, researchers were privileged to be able to compare pre- and post- exposure levels of performance. In case this was not feasible, the comparison was with a carefully selected control group.

In the PHYTONER study performed in Bordeaux, France, Baldi et al. (2011) recruited 929 vineyard workers, with a mean age of about 50 years and at least 20 years of agricultural work. The study population was further divided into separate categories of exposure (none, direct and indirect). Reexamination of 614 individuals after four years, using a questionnaire and nine neurobehavioral tests, showed cognitive decline associated with chronic pesticide exposure. Specifically, exposed individuals had a mean two-point MMSE (Mini-Mental State Examination) score decline and faster decrease in performance over time compared to non-exposed subjects. More extensive evaluation showed that impairment in visual working memory (according to the Benton Visual Retention Test) and other cognitive domains was more prominent in individuals exposed to pesticides. In this study, the association between exposure and mental decline was surprisingly most pronounced in women and in subjects with high levels of education and no alcohol consumption. This could be interpreted that either the absence of factors negatively affecting cognitive function (low education level, high alcohol consumption) allows the effect of pesticide exposure to be detectable or, alternatively, the presence of these factors accentuates the effect of pesticide exposure. Unfortunately, in accordance with other studies, most participants could not recall the exact type of pesticide they were exposed to and thus a direct association between specific chemical agents or even combinations of pesticides (Hernández et al., in press) and cognitive impairment could not be established.

Table 1
Evidence relating the role of pesticide exposure to cognitive disorders (selected studies).

Clinical entity	Study	Country	Number of study subjects	Pesticide type	Study type	Outcome
Cognitive and neurobehavioral performance	Baldi et al. (2011) (PHYTONER study)	France	929	All pesticides	Prospective cohort	Increased risk (OR = 1.35–5.60)
Cognitive and neurobehavioral performance	Rohlman et al. (2007)	USA	175	All pesticides	Case-control	Increased risk (NR)
Mild cognitive dysfunction	Bosma et al. (2000)	Netherlands	1069	All pesticides	Prospective cohort	Increased risk (self reported OR = 3.07; job related OR = 2.02)
AD	McDowell et al. (1994)	Canada	793	All pesticides and fertilizers	Case-control	Increased risk (OR = 2.17.)
AD	Tyas et al. (2001)	Canada	694	Defoliants and fumigants, pesticides and fertilizers	Prospective cohort	Increased risk (defoliants, fumigants: aRR = 4.35, 95% CI 1.05–17.90; pesticides/fertilisers: aRR = 1.45 (95% CI 0.57–3.68)
AD	Gauthier et al. (2001)	Canada	1924	All pesticides	Case-control	No evidence of association (OR = 0.97)
AD	Gun et al. (1997)	Australia	340	Organophosphates solvents	Case-control	Weak evidence of association (solvents: RR = 1.31, 95% CI 0.83–2.07; organophosphates: RR = 2.54, 95% CI 0.41–27.06)
AD	Baldi et al. (2003) (PAQUID study)	France	1507	Various pesticides used in vineyards	Prospective cohort	Increased risk in men (RR = 2.4, 95% CI 1.02–5.63)
AD	Parron et al. (2011)	Spain	17,429	All pesticides	Ecological study	Increased risk (OR = 2.10, 95% CI 1.96–2.25)
AD	Hayden et al. (2010) (The Cache County Study)	USA	5092	All pesticides	Prospective cohort	Increased risk (HR 1.42, 95% CI 1.06–1.91)
FTLD	Rosso et al. (2003)	Netherlands	204	All pesticides	Case-control	No evidence of association
Vascular dementia	Lindsay et al. (1997)	Canada	664	All pesticides	Case-control	Increased risk (OR = 2.6, 95% CI 1.30–5.23)
Vascular dementia	Hebert et al. (2000)	Canada	8623	All pesticides	Prospective cohort	Increased risk (OR = 2.05, 95% CI 1.03–3.85)
PD-dementia	Hubble et al. (1998)	USA	94	All pesticides	Case-control	Increased risk (pesticide exposure + ≥ 1 CYP 2D6 29B+ allele: 83% probability of PD-D; p = 0.0491)

NR, not reported; OR, odds ratio; RR, relative risk; HR, hazard ratio; AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; PD, Parkinson's disease.

In another study attempting to assess the neuropsychological effects of pesticides, Rohlman et al. (2007) examined in Oregon (USA) 175 adolescent and adult farmers of Hispanic descent using computerized neurobehavioral tests of attention, response speed, coordination and memory. Analysis of the results showed that adolescents performed better than adults, which suggests either that the young are not as vulnerable as the adults or that cumulative pesticide exposure is more important for cognitive decline than acute exposure. On the other hand, we should note that there is some evidence that a previous episode of severe acute poisoning may affect cognitive functions and behavior (Colosio et al., 2003). In that case, it is unclear whether these effects are the consequence of direct pesticide neurotoxicity or can be attributed to a more generic (e.g. ischemic) brain injury. In a study of similar design, Rothlein et al. (2006) compared the neurobehavioral performance of 92 Hispanic immigrant farmworkers with 45 non-agricultural controls matched by age and educational level. They found that farmworkers performed worse than controls but more importantly there was a positive correlation between urinary organophosphate metabolite levels and poorer performance on some neurobehavioral tests, thus confirming that low level long term occupational exposure to organophosphates could adversely affect cognitive performance.

Although a possible relationship between occupational pesticide exposure and cognitive decline is suggested by several studies, as already mentioned, this is not the case for the effects of long-term non-occupational exposure. The difficulty of assessing non-occupational exposure and the sparse data available on this association preclude any definite conclusions. Well-designed prospective studies are needed to assess this important issue.

There has been an extensive literature and public interest on the Gulf War syndrome, which is characterized by non-specific symptoms, such as general malaise and mild cognitive deficits. This poorly defined nosological entity is thought to result from multiple chronic exposures, including exposure to the antidotes against nerve gases chronically administered to soldiers and to the mixtures of pesticides used to treat sleeping bags and tents during the Gulf War (Anger et al., 1999; Storzbach et al., 2001; Tuite and Haley, 2013; Haley and Tuite, 2013). By analogy, and even though this has not yet been proven, it is conceivable that a similar clinical picture, often observed in farmers using pesticides, could result from chronic pesticide neurotoxicity.

2.3. Pesticides and mild cognitive impairment

Mild cognitive impairment (MCI) is considered a prodromal stage of dementia and specifically of AD, since, per year after the MCI diagnosis, 5–15% of the affected individuals will develop AD (Petersen, 2011). Essentially, amnestic MCI and overt AD are considered part of the same pathophysiological spectrum and thus are expected to share the same etiological factors.

MCI is manifested clinically by cognitive changes that are intermediate between those observed in AD and those seen in normal aging. Patients with MCI do not display the functional impairment seen in AD; however, they show objective and subjective evidence

of cognitive impairment beyond the changes associated with normal aging (Petersen, 2011).

There have been only a few reports linking pesticide exposure to MCI. For example, Bosma et al. (2000) used cross-sectional and prospective data from the Maastricht Aging Study to link occupational pesticide exposure of arable crop farmers and gardeners with increased risk of mild cognitive dysfunction.

The relatively recent appearance of MCI as a diagnostic entity has not allowed the time for well-designed studies to investigate the effect of pesticides on MCI onset. The lack of specific and well-defined criteria for MCI was another factor hindering studies directed at assessing the association of MCI with pesticide exposure. The recent introduction of criteria for MCI due to AD by the National Institute of Aging/AD Association is a step toward resolving this problem (Albert et al., 2011). Thus, it is expected that well-designed epidemiological studies will address this issue, given also that deciphering the etiology of MCI, a prodromal stage of AD, will allow more promising preventive and therapeutic interventions compared to those targeting AD itself, which is a stage when non-reversible neurodegeneration has already occurred.

2.4. Pesticides and Alzheimer's disease

There have been an increasing number of studies in recent years on the association between pesticide exposure and AD. Although AD etiology is multifactorial with a strong genetic component and AD has existed long before the introduction of pesticides in common use, the increasing incidence of the disease, especially in rural areas, has focused interest on a possible role of pesticides in AD pathogenesis.

Occupational exposure to pesticides and fertilizers was associated, among other factors, with risk of AD (odds ratio 2.17) in a large case-control study by McDowell et al. (1994) involving 258 AD patients and 535 controls (Canadian Study of Health and Aging). However, the association was no longer significant when stratified by level of education. In another Canadian study, Tyas et al. (2001) reported adjusted relative risk of 4.35 for AD after exposure to defoliants and fumigants. In this study, cognitively intact subjects completed a risk factor questionnaire and then were reassessed five years later for the development of AD (Tyas et al., 2001). However, there was only a weak and non-significant association with exposure to pesticides and fertilizers. In a third Canadian case-control study, Gauthier et al. (2001) studied 1924 individuals (>70 years old) randomly selected in a rural area of Quebec, Canada. Structured questionnaires were used to obtain medical, occupational and demographic data. This study failed to show a significant risk of AD related to exposure to pesticides. However, this study's outcome was compromised by the fact that the main measure of environmental exposure was indirectly assessed based on dwelling and the Agriculture Statistics of Canada for herbicide and insecticide spraying in these areas at the specified time period. On the other hand, a questionnaire on occupational exposures in the same study also failed to show pesticides as a risk factor. Another study from Australia (Gun et al., 1997) reported an almost two-fold unadjusted relative risk (RR) for AD after organophosphate use, albeit with a wide confidence interval (95% CI 0.41–27.06). Limitations of the latter study were its retrospective nature and the small number of cases and controls.

One of the largest prospective studies on the possible association between occupational pesticide exposure and AD and PD was performed by Baldi et al. (2003) and included 1507 French adults of diverse occupations (PAQUID Study). On the basis of new cases diagnosed in a 5-year follow-up period, there was an increased, adjusted for confounding factors, relative risk for exposed men, but not women, for both PD and AD (5.6 and 2.4, respectively). Furthermore, lower performance in MMSE was associated with exposure

even in individuals without a formal diagnosis of PD or AD. The lack of increased risk in women could be due to the fact that pesticide handling is traditionally performed by men. The main pesticides used by vineyard workers in this study were dithiocarbamates and folpet (fungicides) and organophosphates and carbamates (insecticides). However, no causal relationship between specific chemicals and PD or AD could be established, due to lack of sufficient information on the use of specific pesticides.

The study by Parron et al. (2011) in Andalusia, Spain, involved a total of 17,429 subjects, for which data were collected during the period between 1998 and 2005 using hospital records. The authors categorized patients according to their living status in areas of high or low pesticide use, based on the extent of intensive agriculture and pesticide sales. The risk of AD, PD, multiple sclerosis and suicide attempts was higher in areas with high pesticide use. However, in the multivariate analysis, only the risk for AD and suicide attempts remained significant (Parron et al., 2011). The analysis did not take into account any other possible sources of environmental toxins polluting the area, although there was no evidence of neurotoxins other than pesticides in the areas studied.

The Cache County study (Hayden et al., 2010; Jones, 2010) was one of the largest and best designed studies investigating the possible association between occupational exposure to pesticides and dementia or AD. In this study, 5092 participants, aged more than 65 years and living in the agricultural Cache County in Utah, USA, were screened for dementia at baseline (with a modified MMSE test and the Dementia Questionnaire) and completed detailed questionnaires, aiming, among others, to classify them by pesticide exposure to exposed and non-exposed and to identify occupational exposure to various types of pesticides. Cognitive functions were reassessed after three, seven and ten years, with 60.5% (3084 patients) of the 5092 initial patients completing the study. Results showed that, after adjustment for various factors, such as APOE status, the exposed group had a modestly increased risk for all-cause dementia (HR = 1.38, 95% CI 1.09–1.76) and for AD (HR = 1.42, 95% CI 1.06–1.91). Exposure to organophosphates showed a slightly higher association with AD than organochlorines. However, there was no additional risk for those individuals exposed to both organophosphates and organochlorines. One of the few limitations of this study was the lack of accurate assessment of safety equipment use and intensity of exposure. However, the study had great epidemiological validity, due to the use of a large sample size that was homogeneous as to socio-demographic variables. In addition, due to their religious background, more than 90% of the study subjects reported low or no alcohol and tobacco use, and this could have allowed the pesticide effect to be better evaluated.

2.5. Pesticides and frontotemporal dementia

Frontotemporal lobar degeneration or frontotemporal dementia (FTD) is characterized by progressive onset of behavioral changes and deficits in executive function and language (Seelaar et al., 2011). There are three main types of FTD: behavioral variant of FTD (bvFTD), semantic dementia and progressive non-fluent aphasia. Depending on the type of FTD there is selective progressive atrophy of frontal and/or temporal lobes, with relative preservation of parietal and occipital lobes (Premi et al., 2012). It is the second most common cause of young-onset dementia after AD and is associated with significant burden given that affected individuals are of highly productive age.

There is a strong genetic component in FTD, with 30–50% of cases being familial due to mutations, in most cases, in the microtubule associated protein tau (MAPT) and progranulin (GRN) genes. However, there is also evidence for a role of exogenous factors, such as head trauma (Rosso et al., 2003).

Due to the relative rarity of the disease at the population level, pesticide exposure has been studied as a contributing factor to FTD onset in relatively few studies and no association was found (Rosso et al., 2003). However, given that overlap in clinical and neuropathological features has recently favored the idea of a continuum between FTD and motor neuron disease (MND), and MND has already been associated with pesticide exposure (Kanavouras et al., 2011; Pamphlett, 2012), further studies are warranted to clarify this issue.

2.6. Pesticides and Lewy body dementia or other types of parkinsonian dementia

In most epidemiological studies, dementia with Lewy bodies (DLB) is the second most common subtype of dementia following AD (Hanson and Lippa, 2009). The patients present with fluctuating cognitive difficulties, visual hallucinations and parkinsonism. Given the common pathophysiological mechanism between PD and Lewy body dementia (LBD), as well as the clinical overlap between these two entities, it is possible that pesticides could be involved in the pathogenesis of LBD, as they have been associated with the development of PD. Furthermore, pesticide exposure could be associated with PD dementia (Hubble et al., 1998). Finally, there have been several isolated cases of pesticide exposure with consequent mixed syndromes of dementia and parkinsonism (Laske et al., 2004). A detailed account of the relation of Parkinsonian disorders with pesticide exposure is beyond the scope of this article and can be found in another paper in the current issue.

2.7. Pesticides and vascular dementia

Vascular dementia is a common form of dementia in aged adults, and is typically characterized by abrupt onset and stepwise deterioration of cognitive deficits, in association with the extent and progression of the underlying vascular (usually ischemic) brain pathology (Kirshner, 2009). Information from the literature is scant; however, occupational exposure to pesticides or fertilizers conferred a two-fold increased risk of developing vascular dementia in the Canadian Study of Health and Aging (Lindsay et al., 1997; Hebert et al., 2000). Interestingly, there is also a common mixed type of dementia, showing features of both AD and vascular dementia. In this case, the mixed type of the disorder makes the assessment of the effects of pesticides even more challenging.

3. Possible mechanisms of pathogenesis

As discussed above, there is some epidemiological evidence on the possible association of neurodegenerative dementing diseases and pesticide exposure. However, it is currently unclear what the mechanism of pathogenesis of these effects might be, even though many of the pesticides are known to adversely affect the nervous system either acutely or chronically (Kamel and Hoppin, 2004). Also, it is known that the effect of some of the pesticides can be direct, as in the case of several insecticides, or indirect, by interfering with basic metabolic pathways that ultimately fail to support the high energy requirements of the nervous system.

Thus, there is an increasing interest in the possible neurotoxic mechanisms of the most important pesticides, in relation to their main mode of action in human cells, including neurons. Although many studies on pesticide-induced neurotoxicity have focused on PD pathophysiology, some of the molecular mechanisms involved in the progression of neurodegeneration could equally, or even preferentially, apply to dementia (and specifically AD) pathogenesis.

As already discussed, pesticides include a wide and heterogeneous array of compounds targeting insects (insecticides), fungi (fungicides), insects, fungi and bacteria (fumigants), and undesired plants (herbicides). A major constraint of most epidemiological studies is that they have not clearly dissected out the possible contribution of individual pesticides, or even category of pesticides. In this section we will examine putative mechanisms of neurotoxicity of common classes of pesticides with regard to their possible contribution to dementia pathogenesis.

3.1. Fumigants

Fumigants are various heterogeneous compounds used against insects, rodents, fungi and bacteria in the soil or in buildings, such as hospitals (Colosio et al., 2003; Byrns and Fuller, 2011). Once widely used, many of these chemicals were banned due to their toxicity, such as the adverse effect of dibromochloropropane (DBCP) on male fertility.

However, there are many fumigants still in use, including phosphide, methyl bromide, ethylene oxide, sulfuryl fluoride and chlorine dioxide (Keifer and Firestone, 2007; Byrns and Fuller, 2011). Acute toxicity of phosphide includes a gastrointestinal and pulmonary syndrome, and could even lead to neurological manifestations such as central nervous system depression, ataxia, tremor and convulsions (Bjørling-Poulsen et al., 2008). There is limited evidence that chronic exposure to zinc phosphide elicits neuropsychological problems and other neurological deficits (Bjørling-Poulsen et al., 2008). Phosphides liberate phosphine gas, which in turn disrupts the function of the mitochondrial electron transport chain. On the other hand, methyl bromide induces both pulmonary and nervous system toxicity (including seizures), probably due to its alkylating capacity (Byrns and Fuller, 2011).

3.2. Fungicides

Fungicides are a wide variety of substances directed against fungi and include hexachlorobenzene, pentachlorophenol, pthalamides, dithiocarbamates, such as maneb, zineb and mancozeb (Hatcher et al., 2008), and conazoles. Most of these compounds contain sulphur or metals, such as manganese and zinc (and in the past mercury). Non-specific effects of poisoning in humans include generalized central nervous system depression, paresthesias and tremor. Since manganese is associated with parkinsonian symptoms and dithiocarbamates with disruption of the proteasome system, it is possible that chronic exposure to these compounds could lead to neurodegeneration, although no specific studies in this direction have so far been performed. In this respect, there have been several studies indicating possible association of PD pathogenesis with exposure to fungicides such as maneb and ziram (Moretto and Colosio, 2011; Freire and Koifman, 2012).

3.3. Herbicides

Herbicides are substances used against undesirable plants and include bipyridines (such as paraquat), phosphomethyl amino acids (such as glyphosate), chloroacetanilides (such as alachlor and metolachlor) and chlorophenoxy compounds (Hatcher et al., 2008).

Paraquat has been extensively studied in relation to the development of PD (Franco et al., 2010; Moretto and Colosio, 2011; Freire and Koifman, 2012) and some studies have demonstrated neuronal cell loss (in particular of dopaminergic neurons), probably through inducing oxidative stress and triggering cell death (Brown et al., 2006; Franco et al., 2010). There have also been studies showing that paraquat toxicity is augmented by other pesticides, such as maneb (Moretto and Colosio, 2011). However, the question of neurodegeneration and associated dementia has not been formally addressed yet.

3.4. Insecticides

There are several categories of insecticides, namely anticholinesterases (organophosphates and carbamates), avermectins (ivermectin, abamectin and emamectin), botanicals (nicotine, rotenone and pyrethrins), organochlorines (cyclodienes, DDT, cyclohexanes, etc.) and pyrethroids (permethrin, deltamethrin etc.). Many of these compounds are active against insects through direct neurotoxicity, and relative homology of some neural functions in humans and insects make these insecticides toxic also to humans. Among the most known neurotoxic insecticides are organophosphates, rotenoids (rotenone), organochlorines and pyrethroids.

3.4.1. Organophosphates

Organophosphates and carbamates, which have been in the past among the most widely used insecticides, are known inhibitors of acetylcholinesterase (Kavvalakis and Tsatsakis, 2012). This inhibition could lead to accumulation of acetylcholine in the neuromuscular and other synapses and continuous neurotransmission which ultimately leads to synaptic dysfunction. There is also ample evidence that organophosphates and carbamates affect lipid, carbohydrate and protein metabolism, including a profound effect on insulin secretion by the pancreatic beta-cells (Karami-Mohajeri and Abdollahi, 2011; Androutsopoulos et al., in press). Also, it is possible that these compounds contribute to increased oxidative stress (Karami-Mohajeri and Abdollahi, 2011).

Since acetylcholine is present in all animal species, the toxic effects of organophosphates do not occur only in insects, but also in vertebrates, including humans, and there is evidence that toxicity to humans is related also to genetic factors (Povey, 2010).

Although there are only scarce data on the association of organophosphates to PD, their mechanism of action and some epidemiological data, raise the possibility of association to AD. For example, it has been observed that individuals exposed to organophosphates display memory and learning impairment, especially after acute poisoning (Srivastava et al., 2000; Colosio et al., 2003). However, current biomarkers of organophosphate exposure (such as blood cholinesterase activity and urinary levels of organophosphate metabolites) do not seem to correlate consistently with neurobehavioral performance (Rohlman et al., 2011). Here the main caveat is that in subjects with a previous episode of severe acute poisoning the changes can be consequent to a nonspecific brain injury (anoxia); interestingly, however, it seems that in heavily exposed subjects without a previous acute poisoning (for example, sheep dippers) some changes can be pointed out. These data support the possibility of a direct neurotoxicity of organophosphate pesticides.

Another hint to the possible association of organophosphates to AD comes from a number of studies reporting that certain polymorphisms on the PON1 gene for Paraoxonase 1 (an arylesterase involved in the hydrolysis of organophosphates), in accordance with similar results obtained in PD studies (Manthripragada et al., 2010), correlated to increased risk for AD (Erlich et al., 2006; Chapuis et al., 2009; Erlich et al., 2012; Androutsopoulos et al., 2011) or even to altered AD pathology (Leduc and Poirier, 2008; Leduc et al., 2009). Yet, there were also studies in which this association was not replicated (Cellini et al., 2006; Klimkowicz-Mrowiec et al., 2011). Furthermore, paraoxonases serve, apart from their role in organophosphate detoxification, in preventing oxidation of low-density lipoproteins (antioxidant function).

It was recently shown that organophosphates can dysregulate dopaminergic signaling, enhance glutamatergic (and possibly excitotoxic) neurotransmission and, more importantly, lead to hyperactivity of the Cdk5 kinase and tau hyperphosphorylation (Torres-Altoro et al., 2011). In this respect, tau hyperphosphorylation is the hallmark of AD, as hyperphosphorylated tau is the main component of neurofibrillary tangles (Torres-Altoro et al., 2011). Hyperphosphorylation of tau disrupts the structure and function of microtubules in AD patients, impairing axonal transport. As shown in both in vitro and in vivo experiments, chronic low exposure to organophosphates leads to structural changes of microtubules (Grigoryan and Lockridge, 2009; Jiang et al., 2010).

Since the major class of drugs used to treat AD (donepezil, rivastigmine and galantamine) are also acetylcholinesterase inhibitors (Pohanka, 2011), one could expect that organophosphates would be beneficial for AD. On the other hand, treatment of AD with acetylcholinesterase inhibitors is symptomatic and not disease-modifying. It is therefore possible to speculate that chronic inhibition of brain acetylcholinesterase by organophosphates could lead to excess synaptic acetylcholine, chronic excitation of post-synaptic neurons, downregulation of post-synaptic acetylcholine receptors, excitotoxic damage and degeneration of these cholinergic systems and ultimately to the cholinergic deficit observed in AD.

3.4.2. Botanicals (rotenone)

Rotenone and similar compounds are used extensively in farming and other applications. Because of its ability to inhibit the mitochondrial complex I, it can be argued that rotenone could contribute to the pathogenesis of PD (Franco et al., 2010; Moretto and Colosio, 2011) and possibly AD. In addition, it has been shown in organotypic brain-slice cultures that rotenone decreased significantly the number of cholinergic neurons in the basal nucleus of Meynert (Ullrich and Humpel, 2009), a finding that could be relevant to the pathogenesis of AD.

3.4.3. Organochlorines

Organochlorines (e.g. DDT) include dichlorodiphenylethanes, cyclodienes, and other related compounds. Their mechanism of action involves disruption of the sodium/potassium currents of the nerve fibers by several mechanisms, including persistent opening of the sodium channels and interaction with GABA receptors (Keifer and Firestone, 2007). There is also evidence that organochlorines affect energy metabolism, including glucose homeostasis (Karami-Mohajeri and Abdollahi, 2011). Due to their persistence in the environment, most of the organochlorine pesticides have been banned in North America and Europe. However, there are still concerns about their health effects, due to their potential to bioaccumulate and their use in other countries (Tsatsakis et al., 2009, 2012b).

Several epidemiological studies and results from experiments indicate that organochlorines, and especially cyclodienes, are linked to the pathogenesis of PD (Dick, 2006). By analogy, it is possible that these compounds contribute to the neurodegeneration associated with AD and other dementias. However, there is so far only limited and indirect evidence. For example, in one small pathologic study by Fleming et al. (1994), pp-DDT was significantly more likely to be found in brains of AD patients than in normal controls or brains of patients with PD.

3.4.4. Pyrethrins

Pyrethrins are a class of natural compounds (derived from the chrysanthemum flower) with insecticidal properties that are widely used even in households. Pyrethroids are semisynthetic analogs that have higher environmental stability (Keifer and Firestone, 2007). This class of compounds is further subdivided in two groups, depending on the neurological effects in high doses administered to experimental animals: C–S group (salivation, choreoathetosis and seizures) and T group (tremor). Extremely high doses lead to coma and death.

Pyrethrins have been shown to interact with sodium and chlorine channels, to affect dopamine recycling and to increase neurotransmitter release (Brown et al., 2006; Costa et al., 2008). However, there are currently no specific studies which have pointed to a possible role for pyrethrins or pyrethroids in dementia.

4. Discussion-clinical implications

To this date several studies have provided evidence for an increasingly important epidemiological link between cognitive decline and pesticide exposure, even though it is not yet clear whether single acute exposure is more important than chronic exposure. This epidemiological link is most evident on tests of neuropsychological performance, whereas the evidence for an association of pesticide exposure with an increased risk for AD and other forms of dementia is still limited and conflicting.

Since the primary mechanism responsible for the acute toxicity of organophosphates is acetylcholinesterase inhibition, which is also a legitimate therapeutic target in AD, a pathogenic (or even beneficial) role of pesticides in dementia would appear most likely for this group of insecticides. Clarification of this issue deserves more emphasis in future studies.

Another issue of concern is the possible neurodevelopmental effects of pesticides, either in utero or during childhood (London et al., 2012). It is known that the developing central nervous system is more vulnerable to many environmental toxins. Whether exposure of the immature brain to pesticides translates to increased propensity to develop dementia in later life remains to be elucidated. This is of special interest since it has been shown that the neurodegenerative process starts several decades before the onset of clinically overt dementia.

An equally interesting field of research is the possible interaction of pesticides with the genotype of the exposed individual. Thus, some individuals, due to their genetic composition, may be more vulnerable to the toxic effects of pesticides compared to other individuals with different genetic background (Manthripragada et al., 2010). This would help to explain the occurrence of dementia in some individuals but not in others, even though both groups may have been exposed to the same pesticides. For example, it has been shown experimentally that different strains of mice show a differential susceptibility to the neurotoxic action of paraquat (Yin et al., 2011).

The public health impact of the possible association between dementia and environmental factors including pesticides is potentially enormous, given the rising dementia prevalence in Western societies and the continuous use of pesticides. This is an issue of concern for many countries, especially in view of the current financial difficulties straining health-care resources (Wimo and Prince, 2010; Schwarzkopf et al., 2012). Furthermore, it is expected that a decrease in dementia prevalence would lead to a significant financial benefit (Wimo et al., 2007; Mesterton et al., 2010).

In conclusion, more targeted prospective studies are needed to decipher the link between exposure to pesticides and dementia, especially dementia of the AD type, given that many of the current studies are inconclusive with regard to a possible association with specific compounds. Thus, on the basis of the available data, it is not possible to come to firm conclusions, but there are several leads calling for further investigation, with a particular attention to exposure of the most vulnerable groups, such as children and pregnant women. Meanwhile, clinicians should include pesticide exposure in their questioning of patients and, in appropriate cases, they should include in their differential diagnosis and their diagnostic work-up the possibility of pesticide neurotoxicity, either acute or chronic (Darvesh et al., 2004; Passov et al., 2011). Minimizing pesticide exposure is a sensible precaution in any case, regardless of a possible link to development of dementia.

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