Chapter 8 — Neurological and Mental Health Impacts of Pesticides

Neurotoxic symptoms and signs have long been known to be important in acute poisonings with several chemical classes of pesticides, starting from the initial development of organophosphorus compounds as "nerve gases" for military use. Chronic effects have been less accepted, although over the past decade a number of studies have investigated them.

Study Types

We uncovered four relevant reviews: two included considerable animal and pathological data (2, 3), one gave a very useful overview of human case reports and epidemiological studies (1), and one was a systematic review on Parkinson's disease (PD) and pesticide exposure, which included a meta-analysis (4). We built on the meta-analysis by searching for omitted and more recent studies, and used the first three reviews as background.

We found 61 relevant reports of primary studies in the peer-reviewed literature in the four languages, from all continents of the world. Among these we judged 42 to be of sufficient quality to meet our review objectives (see Reference & Study column in the Tables 1–3, on health impacts; the table are organized by design, date of publication, and alphabetical order). In terms of epidemiological design and health impacts, one was an *ecological* study looking at rates of PD across counties in California. As found in the review of Colosio et al. (1), the majority, 28, were *cross-sectional* studies looking at function via symptoms including mental health, sensory capacities, neurobehavioural tests, and/or nerve conduction measures. However, eight were *case-control* studies, two focusing on mental health-related mortality and six on neurodegenerative disorders. Four *cohort* studies came from wealthier countries with adequate information systems for the long-term tracking of neurodegenerative disorders. Unfortunately, no intervention evaluations involving reduction of pesticide use and potential reversibility or improvement of neurotoxic effects were found. This is consistent with Keifer's (65) systematic review which primarily uncovered studies on exposure reduction with only a few of adequate quality documenting impacts on acute poisonings, and none on reductions in pesticide-related sub-acute or chronic effects.

Exposures Included

The majority of studies documented mixed human exposure to pesticides, both by use (insecticide, fungicide, herbicide, etc.) and chemical type (organophosphorus, carbamate, pyrethroids, dithiocarbamate-metal, etc.) (see Pesticides Type column in tables). Organophosphorus and carbamate compounds were most commonly studied in cross-sectional studies in keeping with their known neurotoxic effects. Cross-sectional studies were often able to include biological markers either of absorbed dose, such as herbicide or alkyl-phosphates in urine, or acute and sub-acute pathophysiological effects, such as acetylcholinesterase levels in blood (see Exposure Assessment notations in same column). Some studies did an exceptionally good job of documenting exposures to specific substances, e.g., exposure to fumigants by Calvert et al. (17). Surprisingly few studies of pyrethroids were found, consistent with Colosio et al. (1) who found only case series for their review.

Health Impacts

Mental & emotional impacts – Table 1

The four cross-sectional studies primarily focused on the mental and emotional impacts of pesticides are presented in Table 1a. One followed up on the subsequent effects of an acute spill in the community (5) which may have involved some generalized stress effects as well as chemical specific effects. Two found associations between an earlier pesticide poisoning and current minor psychiatric morbidity (6) or depression (9), in keeping with earlier case series involving follow-up of those experiencing a pesticide poisoning (67). Unsettlingly, Keifer et al. (7) found that substantially higher proportions of residents — including adolescents — who were often subject to drift from aerial spraying, had mental and emotional symptoms compared with those who were not subject to such drift, consistent with other studies of broader nervous system function listed in Table 2. Further, the two case-control studies (Table 1b.) found some evidence of an association between pesticide use and suicide among Canadian farmers (8) and death from mental disorders (particularly neurotic disorders of women) among the US population with occupations involving pesticide exposure (10).

Functional nervous system impacts – Table 2

Very wide ranges of remarkably sophisticated physiological, sensory, motor, cognitive, and emotional tests have been applied in cross-sectional studies (Table 2) to determine associations between pesticide exposures and functional impacts in a wide range of populations globally. Analytically, most of the acceptable studies measured and controlled for covariates that might also affect nervous system function.

Associations between previous pesticide poisonings, particularly from organophosphates and carbamates, and decrements in current function are most consistently positive. A number of newer studies tried to separate effects associated with past pesticide-related illness from current exposure, often successfully (e.g., Wesseling et al., 46). Yet distinctions between the effects of chronic or cumulative exposure and current intensity of exposure were harder to make, except when organophosphorus compounds were of primary interest and cholinesterase levels could be used as a surrogate for current and sub-acute exposures. Associations between exposure and both cholinesterase levels and neurological decrements, see e.g., Ernest et al. (23), are indicative of current exposure effects; however, depressed cholinesterase levels, accompanied by significant deficits among the exposed, is indicative of chronic effects, see e.g., Srivastava et al. (40). Unfortunately for many exposed populations, such as Ecuadorian farm families (18, 19), mixed past poisoning, cumulative exposure, and current work and home exposures are overlaid. Further, maternal, in-utero, and early childhood exposures are likely all involved in producing neuro-developmental effects in pre-schoool children in such pervasive exposure situations as Mexican valley agriculture (28).

Those with greater exposures, including the occupationally exposed such as termiticide applicators (20) or farmers who frequently handle concentrates (36), also more consistently show decrements in function. Neurobehavioural and neuropsychological testing that is more integrative more consistently detects differences between pesticide exposed and non-exposed groups. Together, these studies provide important evidence of subclinical effects of pesticides on the nervous system that may become manifest in a smaller proportion of clinical cases.

Neuro-degenerative impacts - Table 3

The studies on neurodegenerative outcomes included one ecological study (Table 3.a), two case-control studies (Table 3.b), and four cohort studies (Table 3.c) where Parkinson's disease (PD) was the outcome. In terms of exposure, some studies focused on herbicides but most examined mixtures of occupational exposures. Health outcomes ranged from PD on clinical examination, through adjusted PD hospitalization incidence, to deaths from PD. Nevertheless, all found positive associations between exposure and PD measures. Combined with the earlier review (4), overall 8 + 7 = 15 of the published 19 + 7 = 26 studies of pesticide–PD associations have been significantly positive. Given that some of the newer studies reported here had measures of effect that were higher, e.g. RR 5.6 in Baldi et al. (14), and some lower, e.g. SHR for PD = 130 in Tuchsen et al. (45), than the combined odds ratios in Priyadarshi et al. (4), the range of 1.8 to 2.5 in different parts of the world would likely be little changed. These data provide remarkably consistent evidence for a relationship between PD and past occupational pesticide exposure.

One case-control study among PD patients found that a genetic marker–pesticide interaction was positively associated with the dementia subtype of PD (29). One case-control (26) and one cohort study (14) focused on Alzheimer's disease (AD). Although the former did not find associations with any pesticide exposure measures, the latter did among men. The one case-control study on amyotrophic lateral sclerosis (ALS) (33) found consistently elevated adjusted odds ratios for pesticide exposure among both genders. Hence, evidence of other neurodegenerative effects of pesticides is also accumulating.

Relevance and Implications

We uncovered a remarkable consistency of findings of nervous system effects of pesticide exposures from pathophysiological and functional tests, through clinical examinations, to health care use and mortality data. Further, the time course varied from current exposures through past poisonings to lifetime occupational exposure. Strikingly, only two studies including effects on children were found (7, 28), despite the considerable concern about pesticide effects on sensitive populations such as inner-city children (66). Nevertheless, the findings in children were consistent with those found in working age adults and seniors.

Taken together, the research provides sufficient evidence supporting the reduction of exposure by known methods in occupational settings (65). It also supports reductions in use in other settings, though fewer studies exist of non-occupational exposure. The extent to which particular pesticides should be prioritized for reduction in use is difficult to ascertain, given that mixed exposures were by far and away the most common types found in epidemiological studies. Linkage with animal studies, clinical case literature, and other sources of information on particular pesticide use and toxicity would be required to initiate such work.

Chapter 8 — Neurological and Mental Health

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Note: Some of the following may appear in the Nervous System Disorders list.

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Chapter 8 — Neurological and Mental Health

Tables

Table 1 Adequate Quality Studies of Mental & Emotional Health Impacts

1. a. Cross-sectional Studies (n=4)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Bowler R et al (1994)	Residents of a community exposed to chemical spill in Northern California; controls from nearby community upstream from spill; N=334	Metam sodium; self-reported exposure	Cases and controls matched by age, education, gender, race, number of children; odour perception, litigation status	Structured clinical interview, self-administered questionnaire, impact of event scale, mood scale, env worry scale, perceived social support scale, perceived control scale, Minnesota Multiphasic Personality Inventory 2, profile of mood states-revised. Salivary cortisol, BP, pulse 30 min after initial clinical interview (high stress) and then after final exit interview, 2-3 hr later (low stress)	paired t-test, McNemar chi square	Greater levels of depression, anxiety, somatic symptoms in spill residents, greater environmental worry and lower perceived social support. Also higher systolic BP. Cortisol levels unchanged between high and low stress measurements in spill residents. Significant differences for those who perceived the odour on a number of scores and scales. Litigants differed from non-litigants on mood scale, IES scale, intrusion subscale of IES, social support (higher for all).	5.5
Keifer M et al., *(*1996)	100 residents 10 yrs and over, majority female each from an exposed rural community and a control urban community	Organo-phosphorus and pyrethroid compounds, Aerial spraying in last 15 days via questionnaire: sighting spray planes, 24% daily and 85% 3 or more in exposed community vs. 0 drifted upon by a spray plane 44% in exposed vs. 0% , crossed recently sprayed fields 57% vs 2%,	Age, sex, current smoking & drinking	Acute symptoms, modified Q-16 neurotoxic symptom questionnaire includes considerable mental & emotional symptoms, red blood cell cholinesterase level	ANOVA for differences in mean cholinestera se, chi-square for univariate proportions, Polychotomo us logistic regression for symptom category	prevalence odds ratios significantly elevated for myriad of nervous system, mental and emotional symptoms. Adjusted prevalence odds ratios for residence in exposed community, by symptom categories: non-specific 1.6 (0.8-3.2), possible 4.1 (1.7-10.2), probable 9.9 (2.9-34.4)symptoms	4
Faria-Neice et	1282 farm workers from	Questionnaire identifying:	Sex, age, municipality,	Medicine use and psychiatric hospitalization record.	Kappa for concordance	Prevalence of MPM: 38% of the farm workers (34.9 – 40.2)	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
al., (1999)	446 farms	– Hectares cultivated – Level of industrialization. – Equipment use.	marital status, ethnic group, years schooling	– Alcoholic (CAGE). – Work injuries. – and Minor psychiatric mordibity (MPM) based on SRQ-20 (self-report questionnaire of 20 items), cutoffs for women 8/20 abnormal, men 6/20	among interviewers. Adjusted rates. Conditional logistic regression for crude and adjusted OR.	"Pesticide poisoning (previous)" was strongly associated with MPM: OR 2.65 (1.83-3.86). For MPM in > 25 Ha, OR = 1.46 ($CI_{95\%}$1.07 – 8.98)	
Stal-Iones et al (2002)	Farm residents from 8 counties in Colorado; N=761	Organo-phosphates, other pesticides; self-reported illness from pesticide exposure in past 12 months	Gender, age, race, education, marital status, social support, negative life events, involvement in farm work, self-reported health status, ETOH use	Symptoms of pesticide poisoning; depression as assessed using Center for Epidemiologic Studes-Depression (CES-D) scale (16+ = clinical depression)	OR, conditional logistic regression	Depression associated with pesticide-related illness OR=5.87 (CI 2.56–13.44)	4

1.b. Case-control studies (n=2)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Pickett W et al., (1998)	Canadian Farm Operators Cohort. N=13089 Cases committed suicide between 1971-87; controls matched for age and province.	Insecticides and herbicides; responses to 1971 Census of Agriculture; main variables were: 1) # of acres sprayed for control of insects; 2) # of acres sprayed for control of weeds; 3) $ spent on agricultural chemicals	21 variables from 1971 Census of Agriculture, including size of farm, type of agricultural practices carried out, financial characteristics of farm operation, also socioeconomic status, ratio of income to expenditures, single marital status, no reported agricultural sales, weeks of paid labour	Suicides reported in Canadian Mortality Database of individuals in the CFOC	OR, stepwise logistic regression	OR 1.71 CI (1.08-2.71) for 1-48 vs 0 acres sprayed of herbicides amongst those who had no hired help. No association for main analyses.	4.5
van Wijn-gaarden et al., (2003)	U.S. mortality detail files 1988-92; N=338,208	Usual occupation and industry as listed on death certificate; classified as exposed/unexposed based on occupational code (listed in paper).	Marital status, race, age, gender, geographic location	Death from mental disorder - cause of death from death certificate	OR, logistic regression	OR=1.46 (CI 1.33-1.60) for employment in jobs potentially involving pesticide exposure. Stronger among women, OR=2.65 (CI 1.89-3.71), especially for deaths from neurotic disorders, OR=4.3 (CI 2.4-7.6)	4.5

Table 2. Adequate Quality Studies of Functional Nervous System Impacts (all cross-sectional studies, n=24)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Sack et al., (1993)	37 male volunteers from 102 pesticide applicators with 9 or more years of work in lawn care company, 35 volunteers nonexposed from U of Cincinnati community	Organo-phosphates, carbamates, organochlorine insecticides Chlorphenoxy herbicides	age, ethanol cigarette consumption, height, weight	– Detailed physical exam including neurological – postural sway testing with fixed, strain-gauge platform	bivariate correlation, multiple regression, stepwise regression analysis	– Sway length values significantly higher among exposed (p=.0001) – Exposure to pesticides (p=.0215) and recent Organophosphates exposure (p=.0391) associated with higher sway.	4
Ruijten et al., 1994	Exposed were flower bulb farmers in the Netherlands, controls were from general population; N=198	Zineb and maneb fungicides; exposure assessed by self-report, generating a personal exposure index	Age, alcohol consumption, education, physical work activity, socioeconomic status, growing flowers (in addition to bulbs)	Health symptoms questionnaire, autonomic nerve function (cardiotachogram - resting arrhythmia, forced respiratory sinus arrhythmia, muscle-heart reflex), peripheral nerve function (motor nerve conduction velocity, motor response amplitudes, distal latency of median and ulnar nerves, antidromic sensory nerve conduction velocity)	Z-scores, t-tests, ANCOVA, multiple linear regression	Decreased conduction velocities in motor fibers of median (-1.1m/s) and peroneal (fast fibers: -1.2m/s, slow fibers: -1.3m/s) nerves and in sensory fibers of median (-1.4m/s) and sural (-0.9m/s) nerves. Refractory period increased in sural and peroneal nerves. Decrease found in resting sinus arrhythmia (-10%)	5
Ames et al., 1995	Agricultural pesticide applicators in California with prior hx. of documented cholinesterase inhibition; controls were friends who did not work with pesticides brought by case subjects; N=135	Organophosphates and carbamates; used medical-supervision records to determine exposure	Age, ethnicity, BMI, education, test language	Nerve-conduction amplitude & velocity, vibrotactile thresholds, 8 tests from neurobehavioural evaluation system, Santa Ana dexterity test, pursuit aiming test, postural sway test	Multiple linear regression	No association found between exposure and impaired performance on tests	4
Mc-Connell et al (1994)	36 previously poisoned cases and	Poisoning by methamidophos and other	age, height, history of	Vibrotactile thresholds measured using Vibratron	Univariate & multi-variate	Vibration thresholds significantly increased in all tested areas, and	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	36 age, sex & SE background matched controls	organo-phosphates via questionnaire	working with pesticides, recent alcohol consumption, history of solvent exposure, history of working with vibrating machinery, extent of callus formation	2	analysis Jonck-heere test for ordered categories comparing metha-midophos cases vs other OP cases vs controls	markedly more increased between methamidophos poisoned and other OP poisoning. (p<0.007)	
Misra et al., (1994)	32 pesticide workers engaged in spraying fenthion, 25 hospital employees matched for age, sex, education and SE status	fenthion, questionnaire on practices, AChE levels	age, sex, education, socio- economic status, nutritional deficiencies, drugs, alcohol, other previously diagnosed neurological disorders	– Med history and exam, – Neuropsychological tests, Benton Visual Retention Test, Weschler memory scale, Alexander Passalong test and the finger dexterity test	Student's T, linear correlation coefficient for relationship between AChe and others	Significantly poorer performance among exposed for: – Benton Visual Retention test (p<0.01), Weschler memory scale (p<0.05) and Alexzander Passalong test(p<0.01). – Serum AChE significantly reduced in exposed (p<0.01) – ERP: P3 latency of only 1 exposed was prolonged, however the group difference was significant (p<0.01)	4.5
Steen-land et al., (1994)	128 poisoned men and 90 non poisoned, non exposed, volunteers and their friends as controls	California surveillance data on pesticide poisoning, various organo-phosphates,	age, race, BMI, education, preferred language, hours of sleep, alcohol consumption the evening prior to the test, smoking habits, use of prescription RX, medical history, current exposure to	– Nerve conduction studies – Vibrotactile thresholds – 8 computerized neurobehavioral tests from the Neurobehavioral Evaluation System, version 4.22, – 2 non-computerized neurobehavioral tests of psychomotor function – computerized measurement of postural sway	Multi-variate linear regression	For all poisoned subjects: only significant for test of sustained visual attention (p=0.05). – For those with definite poisoning, vibrotactile sensitivity was ALSO significantly worse(p<0.05) – For those hospitalized, the symbol digit test (p=0.04) was ALSO significantly altered – Chlorpyridos and phosalone poisoned subjects showed some decrement in peripheral nerve function.(p<.05) – Signif. worse performance on 6	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			solvents or peseticides, coffee consumption the morning of the test.	– Standard neurological examination		tests by those who took > 1 day off from work (p<.05)	
Ernest et al., (1995)	34 all possible males in the subject group working in insecticide manufacturing plant, and 34 in the control	Organo-phosphorus compounds, questionnaire, length of exposure to pesticides, pseudo-cholinesterase activity,	age, noise levels in plant, past exposure in controls	Assessment of hearing impairment and pseudo-cholinesterase levels, liver functions, brain stem pathology and peripheral neuropathy, questionnaire and liver function tests, audiometry, EMG, brain stem auditory evoked responses and full neurological exam.	Student's T Test , Chi square analysis with Yates correction and Fisher's exact probility test	Correlations between exposure and: pseudo-cholinesterase (p<0.001), peripheral neuropathy (p<0.001) – No statistically significant difference by exposure group for EMG recordings & evoked brain stem auditory potentials	4
Ste-phens et al., (1995)	Exposed - 146 sheep farmers, every 10th farmer on the wool marketing board list Controls – 143 quarry workers	Organo-phosphates, questionnaire and urine test to rule out recent pesticide exposure	age, educactional level, laterality, lifetime ROH consumption, smoking habits, other substance abuse, recent viral infection, caffeine consumption, computer familiarity, first language, time of day of testing	neuropsychological functions- digit span for short term memory, Simple reaction time for sustained attention, symbol-digit substitution test for information processing speed, and category search for long term memory function.	ANCOVA	After adjusting for covariates, farmers significantly slower in performance of 3 tests: simple reaction time(p<0.0001), symbol digit substitution(p=0.04) and syntactic reasoning(p=0.04) – Significant effect of dose-response for syntactic reasoning test (p<0.0001)	6
Beach et al., (1996)	146 exposed sheep farmers and 143 unexposed quarry workers, selection based on symtomatology after	Organo-phosphates, questionnaire to calculate: avearage number of sheep in flock x number of dips a year x number of years using organo-	current or previous illnesses, medcns, family history of neuro disease,	acute toxicity symptoms, neurological symtoms, assessment by self report/ questionnaire and clincal neuro exam	Chi Square for categorical data or Kruskal Wallis test	Significant difference in 2 point discrimination of dorsum of hand(p=.011) and foot(p<.001) between symptomatic sheep farmers, asymptomatic sheep farmers and controls	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	dipping(10 most sx, 10 least and 10 controls	phosphates	alcohol, exposure to other neurotoxins..		for non-parametric data		
Amado et al., (1997)	154 flower + 139 textile = 293 workers	Questionnaire. Pesticide exposure (re-entry times, hygiene practices, safety practices. – sun exposure). Industry type, job type and job duration in flower production. Categories of exposure (only flowers vs. combined)	Age, Sex, Ultraviolet radiation.	Chromatic confusion index (CIC) for each eye. Obteined as average of the measurements of both eyes, resulting from the addition of the values from the corresponding table of Lonthony method.	Differences of prevalence (X2); OR crude and adjusted. Stratified analysis, OR_{MH}, weighted by age and sex.	Prevalence of dichromatopsy exposed: 59.1 Controls 50.4 p=0.07 (marginal) High exposure: 60.3% low exposure or no exposure : 50.0 p= 0.04 OR: Crude = 1.5 ORadj: 1.7 (1.04 –2.7)	4
Fiedler et al., (1997)	Exposed: tree fruit farmers; controls: blueberry/cranberry growers and hardware store owners; New Jersey; N=99	Organophosphates; exposure determined by occupation and self-report to generate exposure metric	Age, education, intellectual ability (as measured by Wide Range Achievement Test-Reading), years of farming	Neuropsych: Tests of concentration (simple reaction time for dominant and non-dominant hand, continuous performance, Stroop colour-word task), visuomotor coordination (hand-eye coordination - grooved pegboard, Trails A & B, digit symbol), verbal memory (California verbal learning test - List A total, digit span), visual memory (visual reproduction I & II, continuous visual memory), verbal ability (information), expressive and receptive language (animal naming, revised token test). Psych: MMPI-2	Student's t-test, covariate analyses, stepwise regression	Exposed TFF vs controls: increased simple reaction time, dominant hand F=6.83, p=0.01; non-dominant hand F=6.41, p=0.01. High exposed vs low exposed: increased simple reaction time, dominant hand F=5.61, p=0.02.	4.5
Cole et al.,	Pesticide applicators	Organophosphate &	Concomitant	Neurobehavioural Core	Univariate	Farm group performed worse on	5.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
(1997)	in Ecuador, other farm workers, consumers, non-farm workers as controls; N=246	carbamate insecticides, dithiocarbamate fungicides; exposure determined by self-report and by farm records of pesticide usage	medical problems, EtOH, age, education, solvent exposure	Test Battery (Digit span, Benton visual retention, digit symbol, simple reaction time, Santa Ana, pursuit aiming test, profile of mood states), digit vigilance, Trails A & B, block design, Weschler Adult Intelligence Scale (information, similarities, vocabulary); grouped into attention, visuo-spatial, psychomotor, motor, affective	regression, linear regression	most tests	
Guillette, et al., (1998)	4 & 5 year old Yaqui children in two communities of Sonora, Mexico. Foothill (n=17) and valley (n=33)	Interviews with residents and farmers. Foothill annual DDT spraying, valley mixed organochlorine, organophosphorus, & pyrethroid compounds, 2 crops/year up to 45 applications/crop, daily household bug sprays	Diet, education, socioeconomic status broadly described for two communities. Maternal reproductive history individually	Rapid assessment tool for pre-school children included anthropometry, stamina and Developmental Scales (Bayley & McCarthy)	ANOVA valley vs. foothill, Scheffe's F tests	Among valley children, significantly lower stamina, ability to catching balls, fine eye-hand coordination, 30 minute recall, and ability to draw a person	4
Calvert et al., (1998)	123 exposed recruited from 40 fumigation companies (volunteer), 120 controls were recruited by fumigation workers: friends within 5 years of age and never exposed to pesticides	Fumigants, Sulfuryl Fluoride and Methyl Bromide principally	age, race, BMI, limb surface temperature, education , language in which test is taken, alcohol consumption, smoking	Questionnaire – Nerve conduction test – Vibration testing – 7 computer administered neurobehaviora tests from NES(Hand-eye coordination, Simple Reaction time, continuous performance test, Symbol digit test, Pattern Memory, Serial Digit Learning, Mood Scales) – NES vocabulary test	Student's t for continuous demo-graphic character-istics , Chi square to compare categorical demo-graphic charac-teristics and	No diff between groups for chronic bronchitis, urinary protein concentrations, color vision test or postural sway test – Significant deficits on smell test particluarly among those exposed to sulfuryl fluoride (p=0.03) – Significantly lower performance of exposed in Santa Ana test of perferred hand (p=0.03) – Significantly reduced nerve conduction velocity of the median motor nerve in the forearm (p=0.02)	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
				– Santa Ana Dexterity – Postural sway testing, – Contrast sensitvity via Pelli-Robson chart, – Color visitin with Farnsworth D-15 panel, - Olfactory function with U of Pennsylvania Smell Identification Test. – Spot unine – Chronic bronchitis evaluation with questions by ATS – Neuro exam by MD for gross neuro abnormalities not related.	outcomes, Fisher exact when expected table frequencies <5, multiple linear regression.	– Pattern Memory the only computer neurobehavioral test which exposed did significantly worse that control (p=0.05)	
Cole et al., (1998)	Pesticide applicators in Ecuador, other farm workers, consumers, non-farm workers as controls; N=246	Organophosphate and carbamate insecticides, dithiocarbamate fungicides; exposure determined by self-report and by farm records of pesticide usage	Age, concomitant medical conditions, past pesticide poisonings, EtOH use, height, years using solvents, callus, air temperature, potato intake, BMI	Symptom questionnaire, neuro exam (standard protocol - finger-nose, heel-ankle, Romberg, Mingazini, gait, deep tendon reflexes, power, deep sensation, vibration sensation)	Polytomous logistic regression, multiple linear regression	Applicators had more current PNS symptoms (OR=3.1), signs of poor coordination (OR4.3), abnormal deep tendon reflexes (OR=2.9), reduced power (OR=2.1), higher toe vibration thresholds (beta=0.035)	5.5
Engel et al., (1998)	67 Hispanic farm workers and 68 age, gender, ethnicity and education matched controls, volunteer sample	Thinners were exposed primarily to azinphosmethyl and possibly to phosmet or methyl parathion, questionnaire and serum erythrocyte cholinesterase activity. Timing of thinning relative to testing, use of	age, gender, height, other (non-thinning)farm work performed in current season, history of farm work, history of	Mean cholinesterase activity: mean diff of -1.4(95%CI = -2.5, -0.3, p=.01) Sensory and motor nerve functions as well as neuromuscular junction testing, assessment via electrodes	Conti-nuous outcomes using Student's T test and multiple regression. Dicho-tomous	dose-response relationship between thinning hours and any neuro-physiological measure (p=.20)	6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		protective clothes and practices, number of days work clothes were worn between washing, and frequency of bathing.	working with pesticides, proximity of the home to nearby farms, use of pesticides in or around the home, alcohol and tobacco use.		outcomes – prevalence ratios via stratified analysis		
London et al., 1998	Fruit farms belonging to 3 large cooperatives; exposed were applicators, controls were other workers; South Africa; N=247	Job-exposure matrix to take into account lifetime direct and indirect exposures; plasma cholinesterase as biological marker of recent exposure; also considered potential exposure to pesticides at home	Age, height, education, numeracy, visual acuity, alcohol intake, past pesticide poisoning, recent OP exposure, nonoccupational residential exposure, long-term occupational OP exposure	14 symptoms, vibration sense (Vibatron II), static motor steadiness, dynamic steadiness, motor tremor, neurobehavioural test battery	Chi-square, OR; Linear and logistic regression	OR for high score for neurological symptoms: past pesticide poisoning 4.08 (1.48–11.22), current applicator 2.25 (1.15–4.39)	5.5
Bazylewicz-Walc-zak et al., (1999)	Garden enterprise employees in Poland; cases worked in greenhouse, controls worked in other jobs; N=51	Organophosphates (Dichlorvos, Methamidophos, Methidathion, Pirimiphos-Methyl), carbamates, synthetic pyrethroids, dithiocarbamates; pesticide exposure determined by air sampling, measuring pesticide concentrations on clothing, skin washes	Age, education, smoking, alcohol, drugs	Polish adaptation of The Neurobehavioral Core Test Battery: 6 tests of cognitive and psychomotor functions (Simple Reaction Time, Digit Symbol, Digit Span, Benton Visual Retention, Santa Ana, Aiming) and 2 symptom questionnaires (Profile of Mood States, Finnish Subjective Symptoms Questionnaire)	ANOVA	Fatigue: F=2.71, p=0.10 for increase in fatigue for exposed compared to controls, over time; GI Sx: F=5.63, p=0.02 for increase in GI Sx for exposed compared to controls, over time	4.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Steen-land et al., (2000)	Current and former termiticide applicators in North Carolina; controls were friends and blue-collar state employees; N=380	Chlorpyrifos; exposure assessed by self-report, urine TCP	Age, race, education, smoking, BMI, prior night's hours of sleep, prior night's alcohol consumption, current exposure to solvents, coffee consumption day of tests, history of diabetes, carpal tunnel syndrome, nerve disorder, nerve injury, back disorder.	Neurobehavioural evaluation system, vibrotactile test, arm/hand tremor, postural sway, manual dexterity, eye-hand coordination (Trails A and B), vision (acuity, contrast sensitivity, colour vision), olfaction, nerve conduction velocity, clinical neurologic examination, 24-item questionnaire; also did subgroup analyses (workers currently applying, workers formerly applying, workers with self-reported poisonings)	Linear regression, logistic regression	Poisoned group significantly worse on sustained attention & mood. Hospitalized cases had significantly lower vibrotactile sensitivity.	5.5
Srivas-tava et al., (2000)	59 exposed workers in pesticide manufacturing plant, and 17 controls not engaged in production or handling.	Quinalphos and various other chemical compounds used in it's prodution, questionnaire and AChE levels	age, work history, physical activity at work, gender, social charac-teristics, use of cigarettes, alcohol	– Detailed clinical history – Detailed neurological examination – Lab work – Neurobehavioral tests: Digit span, Digit symbol test, Bourdon Weirsma vigilance test.	Student's t test, chi-square and Fisher's exact test	– AChE values in exposed (24.27 +/-11.21) vs non exposed (24.21=/-12.60) – Significantly ($p<0.05$) more complaints of weakness, abnormal plantar and Ankle reflexes, and poorer performance on memory, learning & vigilance testing.	4
Baldi I et al (2001)	Vineyard workers in Gironde, France; convenience sample; N=917	Mainly fungicides; exposure measurement by work records	Demographics, education, smoking, EtOH, environmental pesticide exposure (e.g. drinking well water), depression, use of psychotropic	Battery of 9 neuro-psychological tests	chi-square, multivariate logistic regressions	Adjusted risks of low performance for directly exposed vs. non-exposed: OR=3.5 for BVRT; OR=3.1 for TMT-B; other tests, OR=1.4-3.0	6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			drugs, current exposure				
Dick et al., (2001)	Current termiticide workers who reported using chlorpyrifos-containing products within past 3 weeks; controls were same-gender friends of cases; North Carolina; N=158	Chlorpyrifos (OP) – e.g. Dursban TC, Equity, Cyren TC; exposure determined by urinary TCP concentration	Age, wt, ht, BMI, gender, ethnicity, education, tobacco use, EtOH, diabetes, high BP, depression, neck/back disorder, neurologic problems, serious injury to nervous system, carpal tunnel syndrome	Sensory tests: cross-cultural smell identification test, visual acuity and functional acuity contrast sensitivity test, Farnsworth D-15 and Lanthony D-15d color vision tests, vibrotactile threshold. Motor tests: arm-hand tremor test, grooved peg board (manual dexterity), trail-making test (eye-hand coordination), sway (postural stability)	Linear regression model with Bonferroni correction	Color vision (Lanthony) increased for L (p=0.001) and R (0.041) in relation to TCP; Postural sway increased for HEC-Length (p=0.000), SEO-Length (p=0.032), SEC-Length (p=0.000), SEC-Area (p=0.000) in relation to TCP	4.5
Pilking-ton et al., (2001)	Expose: English and Scottish sheep dippers; controls: non-sheep dipping farmers, ceramic workers; N=772	Organophosphates; exposure assessed by self-report of practices, including handling of concentrate	Age, sex, alcohol, country,	Symptom questionnaire (motor, sensory, autonomic), quantitative sensory tests (heat, cold, vibration)	OR, Linear logistic regression, multiple linear regression, generalized additive models	Elevated adjusted odds ratios for concentrate handling and symptoms (p=0.005), with majority of effect among small group of highly exposed concentrate handlers	4
Wesse-ling et al., (2002)	Poisoned identified by compulsory occupational accident reports to the Nat'l Insurance Institute.Of the 162, 94 were identified.-81 of 82 eligible participated (mean # months since poisoning =27, range 12-43)	Poisonings from organo-phosphates and carbamates. Controls via questionnaire ; some with varying exposures to pesticides, others without any exposure.	age, education, ROH, smoking, other solvents exposure, visual acuity, history of loss of consciousness, history of convulsions, other neuro or psychiatric	Neurobehavioral functionning among those with past mild poisoning vs non history of poisoning, via: Memory testing(Visual via Benton visual retention; Verbal via Rey verbasl learning), Attention(Visual via Digit Vigilance; Verbal via Dibit Span), Psychomotor	multiple linear regression analysis	-Poisoned group performed less well in 13 of 14 tests. -Significant difference for Digit symbol (p<0.05), Questionnaire 16 and Brief symptom inventory (P<0.01) -Significant differences in Questionnaire 16 and BSI among those poisonned with OP, but not with those poisoned with Carbamates	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	Random selection of control subjects = 130 (10 refusals) from banana plantations		conditions, malaria, chronic metabolic or infectious diseases, current use of Rx, hours of sleep night before testing, sense of well-being and liquor, caffeine intake on the day of testing.	(Coordination via Santana dexterity; Steadiness via Pursuit aiming 2, Speed via Finger tapping, Reaction via Simple reaction time), Visuomotor (Coding via Digit-symbol, Planning via Trails-A, Problem solving via Block design), Language via Vocabulary and Neuropsych. symptoms via Questionnaire-16, affect via Brief symptom inventory (BSI)		-Worse performance among those exposed recently to pesticides, although not significant.	
Farahat et al., (2003)	52 exposed matched by age, SE class and years of education (>=12) to controls.	OP pesticides, questionnaire assessment	age, smoking, BMI, education, coffee consumption	Clinical examination incl. neurological testing of cranial nerves, motor system, reflexes sensory system. Neurobehavioral tests: Similarities, Digit Symbol and Trailmaking part A and B, Block Design, Paced Auditory Serial Addition Test, Letter Cancellation, Digit Span, Benton Visual RetentionTest, Story Recall parts A and B, Eysenck Personality Questionnaire – serum AChE	multiple regression analysis, Holm's modifi-cation of the Bonferroni correction for multiple compa-risons.	AChE significantly lower in the exposed (p=.0001), -Significantly lower performance among exposed on Similarities (P=0.003), Digit Symbol (p=0.001), Trailmaking A(p=.03) and B (p=.015), Letter Cancel (p=0.037), Digit Span Forward (p=0.037) and Backward (0.003), Benton (p=0.003) -Significant trend towards lower performance as duration of exposure rose for many tests -Neuro symptoms of dizziness and numbness were significantly higher in exposed (<0.008)	4
Sta-llones et al., (2002)	Farmers in 8 counties in NE Colorado; N=761	OP pesticides, herbicides; work activities (rel. to pesticide exp.), exposure was episode of pesticide poisoning	Neurological symptoms, types of pesticides, years of	24 neurological symptoms	OR, condi-tional logistic regression	OR of having had a pesticide-related illness: (female?) gender 0.27 (0.14-0.52), depressed 2.39 (1.36-4.20), sleep too much 3.09 (1.62-5.89), use OP 2.34 (1.17-	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			schooling, alcohol, farm income, age, sex			4.66)	

Table 3 Neurodegenerative Impacts

3.a. Ecological study

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Ritz et al., (2000)	Deaths in California counties from 1984-1993 or 4	Agricultural census data of %age of land treated with pesticides used to classify counties of residence as none, low, medium & high, exposure, with duration of living in county of residence prior to death.	age, race, gender, place of birth, education	Proportion of deaths by county comparing cause of death (underlying or associated) for PD vs IHD	Logistic regression	Proportional odds of PD significantly higher in pesticide use areas using continuous and ordinal exposure classification. OR from 1.44 to 1.52, all CI not including 1	6

3.b. Case-control studies (n= 5)

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
John-son et al., (1997)	144 PD patients and 464 control subjects matched for age, race and sex	various herbicides, insecticides and fungicides via questionnaire	age, sex, race, smoking	Clinically diagnosed Parkinson's disease	ANOVA	Farming significantly associated with PD (adjusted for age, sex, race p=0.043), also significant after adjusting for 3 pesticides) *herbicide (p=0.012) /insecticide (p=0.001) contact at work (association greater with those having >=10 years of exposure)	5
Liou et al., (1997)	120 patients with Parkinson's (PD) and 240 hospital control subjects matched on age and sex	paraquat, other pesticides and herbicides un specified, Open ended questionnaire	drugs, infection, tumor, previous stroke, know toxins, age, sex	Neurologist evaluation for dx of parkinson's (based on 2 or more cardinal signs of PD)	Matched analysis, Chi square calculatedusing the extended Mantel-Haenszel method	Significantly increased risk for PD with occupational or residential exposure to pesticides /herbicides OR= 2.9 (2.3, 3.7) -strong association between paraquat & PD OR 3.2 (2.4, 4.3).	5
Mc-Guire et al., (1997)	Cases: Dx of ALS in 4 yr period; matched controls randomly selected from population; Washington State; N=522	Job Hx from age 15 to date of Dx, exposure to chemicals, PPE, home activities /hobbies (unblinded); panel assessment of occupational exposures (blinded) for exposure index	Age, sex, respondent type (self or proxy), education, exposure to metals /solvents /agricul-tural chemicals	Dx of Amyotrophic Lateral Sclerosis	Condi-tional logistic regression	OR for exposure to agricultural chemicals: both sexes: self-report 1.6 (1.0-2.7), panel 2.0 (1.1-3.5); men: self-report 2.1 (1.1-3.8), panel 2.4 (1.2-4.8); insecticides, both sexes, panel 2.1 (1.1-4.1); self-report and panel 2.5 (1.1-5.7); dose-response for insecticides for men, panel: low exposure 2.0 (0.5-7.7), high exposure 2.8 (1.1-6.8); home and workplace exposure to pesticides, men, panel 2.8 (1.2-6.7)	6
Hubble et al., (1998)	246 screened, 43 met dx criteria for PD with Dementia and 51 met the criteria for PD without dementia	Interview re occupation, farm living, lifelong residence hx, water source, pesticide exposure	Age, head trauma, alcohol, family history of AD or PD, smoking,	Unified Parkinson's Disease Rating Scale, neuro examination, Neuropsy evaluation included Mattis Dementia Rating Scale(DRS).	Chi square, t-test, multiple logistic regression	pesticide exposure in combination with a genetic trait (CYP 2D6 29B+ allele) was significantly associated with PD+D (p=0.032) Pesticide alone was not significantly associated with PD+D	4.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			Genetic Markers			(p=0.584).	
Gaut-hier et al., (2001)	68 cases of Altzheimer'sDisease and 68 age and sex matched controlsx	multiple types of exposure and types of pesticides used, questionnaire and regional pesticide data	age, occupational exposure, education level, presence of family cases, ApoE allele	3 steps to Dx of AD: 1. 3MS test-score of <=78 2. cognitive function via (CERAD battery, Benton's test of verbal fluency). Dx in accordance with DSM4 3. NINCDS-ADRDA criteria – Blood samples for genotyping of ApoE	Logistic regression	No significant relationship with exposure to neurotox substances and AD (p=1) – No signifcant relationship with long term expoure to pesticides (OR 1, CI 0.45-2.21)as well as herbicide (1.08, CI 0.49-2.37) and insecticide (1.73 CI 0.79-3.78) and AD even after adjusting for education, family history and ApoE presence.	5.5

3.c. Cohort studies (n=4)

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Tuch-sen et al., (2000)	2273872 participants, of which 90430 men 38505 women where expected to be occupationally exposed	Occupational codes of farming, horticulture and related groups	Age, gender	Hospitalization due to Parkinson's assessed via National Inpatient Register	Age standardized hospitalization ratio by gender	Among male self employed farmers SHR for PD= 130 (95%CI 103-163), consistent but not significant pattern of high risk in other likely exposed work groups	5
Engel et al, (2001)	Cohort of mostly orchardists who participated in earlier cohort study; controls from various occupations; Washington State; N=310	All types of pesticides; exposure determined by self-report questionnaire	Age, race, EtOH, smoking, use of well water, farm employment, size of farm, Hx of stroke, neck/back disorders, neurological disorders, arthritis	20-minute structured neurological exam administered by nurse - unified Parkinson's disease rating scale for presence & severity of motor signs; Parkinsonism if 2+ of: rest tremor, rigidity, brady-kinesia, impaired postural reflexes; or 1 sign plus on anti-parkinsonian meds	Prevalence ratio; Generalized linear model	PR=2.0 (1.0-4.2) for PD among subjects in highest tertile of years of exposure to pesticides; no increased risks associated with specific pesticides/classes	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Petro-vitch et al., (2002)	Follow up of 7986 japanese american men born between 1900 and 1919 who were enrolled in the longitudinal Honolulu Heart Program	Work on pineapple or sugarcane plantations, pesticide exposure at home or work for at least one year	age, sex, cigarette smoking, coffee and caffeine intake	Developpment of PD, via questionnaire, clincal diagnosis and records (hospitalization records, death certificates, medical records from local neurologists).	Proportional hazards regression models , Relative risks estimated	After age adjustment, significant association with PD and length of time working on a plantation (p=0.01). Incidence of PD tended to increase with reported years of exposure to pesticides, but not significant (p=0.10) -After adjustment for age, cigarettes and caffeine, a significant association for work on a plantation vs none (p=.006 for those working >20 yrs))	6
Baldi et al., (2003)	Population of the PAQUID study 1507 French elderly living in Gironde, France in their home or institution	Assessed by self-report questionnaire, used to construct job-exposure matrix	history of smoking, age, sex, education level, rural living or living in proximity to vineyards.	Cognitive impairment, depression, Parkinson's and dementia, evaluated by questionnaire and clinical examination (Mini Mental State Exam – MMSE)	Prevalence odds ratios for cross-sectional comparison of baseline MMSE Age based Cox proportional hazards model for incident cases	OR = 1.45 (95% CI 1.04-2.02) for occupational exposure and reduced MMSE score In men, RR parkinsons for occupationally exposed= RR 5.6 (95% CI 1.5-21.6) & for Alzheimers RR= 2.9 (95CI% 1.0-5.6)	5