Neurological disease: the next occupational disease epidemic

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Occupational neurological disease

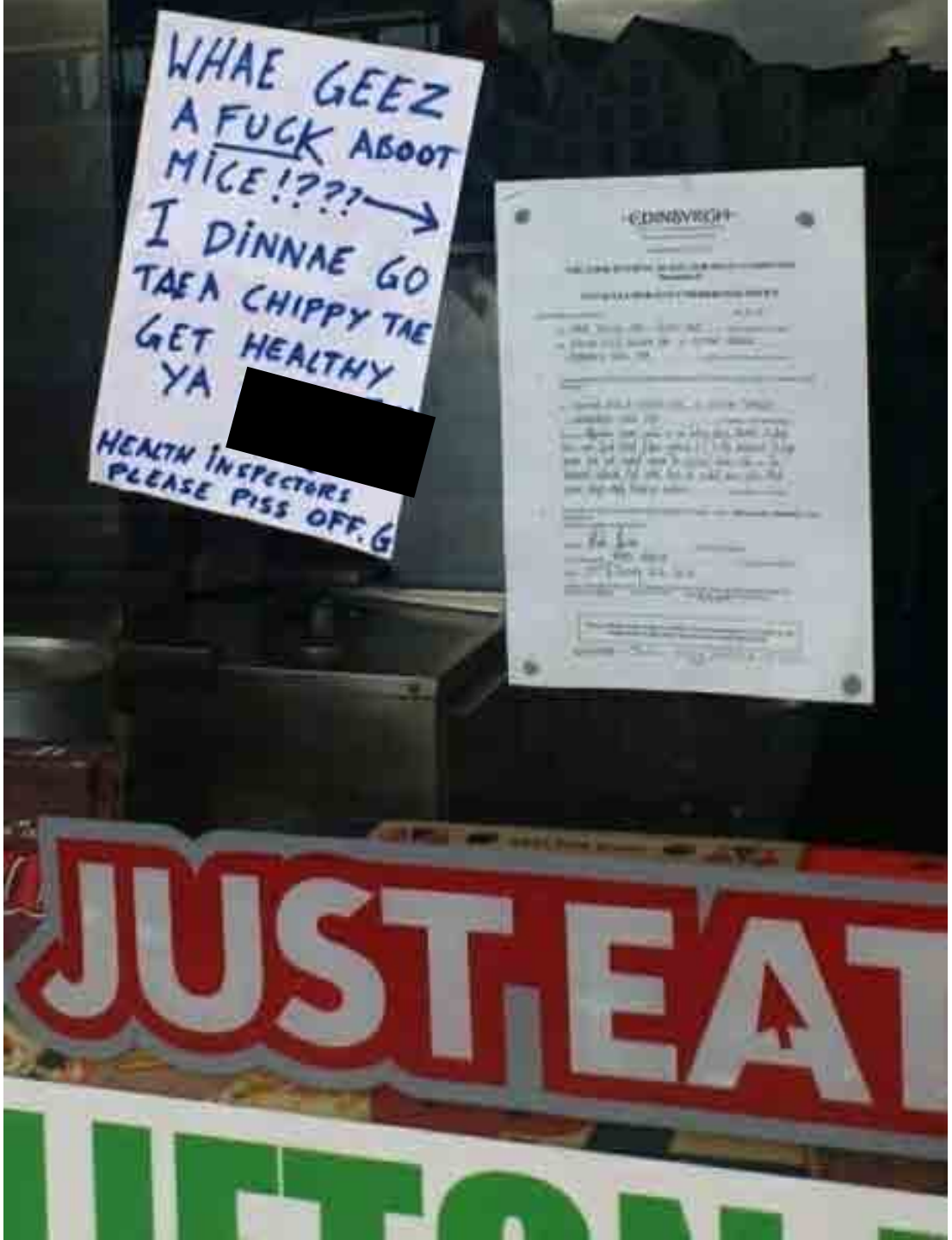
- Public health and occupational health in New Zealand and the United Kingdom
- Neurological disease
- Previous New Zealand research
- Current New Zealand and UK research
- How important is occupational neurological disease?

What I've been doing in the UK

http://www.lshtm.ac.uk/

- Occupational and environmental health
- Neurological disease
- Global Non-Communicable Disease
  - http://www.lshtm.ac.uk/

Food safety in New Zealand



Food safety in the UK

Occupational health in New Zealand and the United Kingdom

- UK occupational health advisory committees
  - Industrial Injuries Advisory Council (UK)
    - http://iiac.independent.gov.uk/
- New Zealand occupational health advisory committees
  - National Occupational Health and Safety Advisory Committee (NOHSAC) (NZ)
  - Gradual Process Committee (ACC) (NZ)
  - Tripartite Committee (NZ)

Occupational neurological disease

- Public health and occupational health in New Zealand and the United Kingdom
- Neurological disease
- Previous New Zealand research
- Current New Zealand and UK research
- How important is occupational neurological disease

Neurological disease

- Neurologic diseases are disorders of the brain, spinal cord and nerves throughout your body. Together they control all the workings of the body. When something goes wrong with a part of your nervous system, you can have trouble moving, speaking, swallowing, breathing or learning. You can also have problems with your memory, senses or mood.
- There are more than 600 types of neurological disease, ranging from headaches through to fatal neurodegenerative diseases

Neurological disease

- Major types of neurological disease include:
  - Genetic: Huntington's Disease, muscular dystrophy
  - Developmental: spina bifida
  - Injuries: spinal cord, traumatic brain injury
  - Infections: meningitis
  - Cancer: brain tumours
  - Diseases of the brain blood vessels: stroke
  - Seizures: epilepsy
  - Neurodegenerative diseases: Parkinson's Disease, motor neurone disease, dementia, multiple sclerosis, peripheral neuropathy, toxic encephalopathy

Neurodegenerative diseases

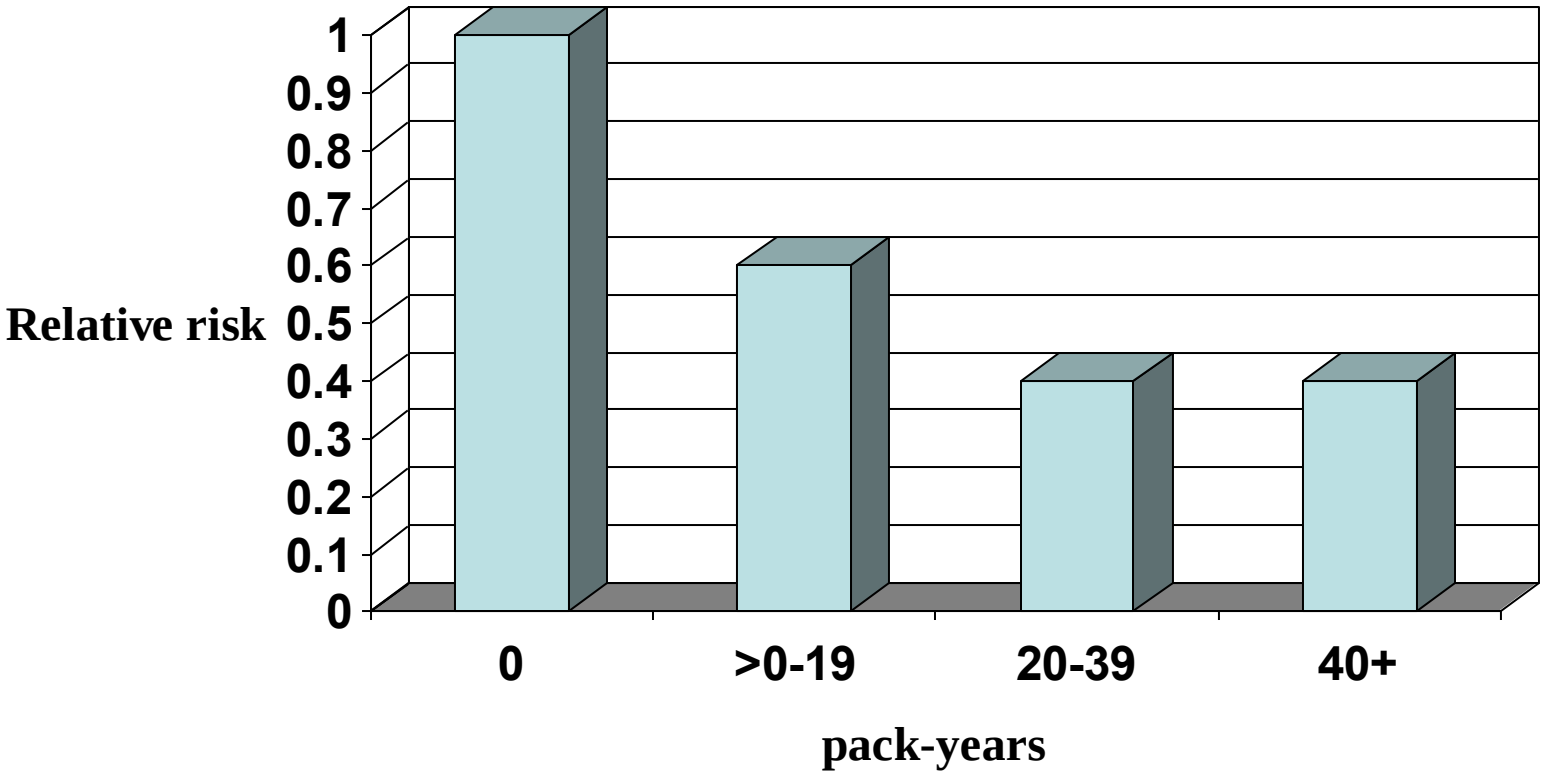
Parkinson's Disease

- Chronic, neurodegenerative disorder due to dopamine deficiency
- Cardinal features: rest tremor; bradykinesia, muscle rigidity (must have 2 out of 3)
- Degenerative disease of the dopaminergic neurons, especially in the substantia nigra
- Mean age of onset 6th decade
- Slowly progressive
- Incidence 19 per 100,000 (MacDonald et al, 2000)
- Slightly increased mortality

Cigarette smoking as a “protective” factor in PD

- **Inverse dose-response seen consistently**
  - **Found in cohort and case-control studies**
  - **Not explained by selective survival of non-smokers**
- **Nicotine may increase (up-regulate) cholinergic “tone”**
- **Monoamine oxidase B (MAO-B) enzyme activity decreased in smokers’ brain**
  - **MAO-B activates MPTP**
  - **MAO-B catabolizes dopamine**

PD relative risk by cumulative cigarette smoking history*



*Checkoway H, et al. *Am J Epidemiol* 2002;155:732-8

Smoking and PD: Nurses Health Cohort Study*

Smoking status (pack-years)	*No. Cases*	*Person-years*	*Relative Risk*[+]
0	87	988,491	1.0
1-9	19	283,100	1.0
10-24	19	366,148	0.8
25-44	12	378,018	0.4
>45	15	250.257	0.4

[+]Age-adjusted RR

*Hernan MA, et al. (2001) *Ann Neurol* 50:780-6

Coffee consumption and PD in Japanese American men: Honolulu Heart Program cohort study, 30-year follow-up*

Coffee intake (oz/day)	*No. cases*	*Age-adjusted rate per 10^4 person-years*	*Relative risk*
0	32	10.4	1.0
4-8	33	5.3	0.6
12-16	24	4.7	0.5
20-24	9	3.7	0.3
≥28	4	1.9	0.2

*Ross CW et al. (2000) *JAMA* 283:2674-9

Joint effects of smoking, coffee, and NSAIDs on PD risk: pooled data from 4 US studies (1186 PD cases, 928 controls)*

Smoking, coffee, NSAIDs risk combination	Odds ratio	95% CI
"High risk": Non-smokers, lowest coffee, lowest NSAID	1.00 [reference]	--
"Middle risk": All other combinations	0.74	0.53 – 1.04
"Low risk": Smokers, highest coffee, highest NSAID	0.13	0.06 – 0.29

*Powers KM, et al. *Mov Disord* 2008;23:88-95

Evidence for occupational causes

Parkinson's Disease

- Head injury
- One known occupational cause is manganese; other metals may be implicated
- Paraquat is an established cause; other pesticides have been strongly implicated
- Also good evidence for organic solvents, and some vidence for wood preservatives, lead and copper
- No New Zealand studies, but all of these occupational exposures occur in New Zealand

Evidence for metals as PD risk factors

- Chronic manganism similar clinical features as PD
- Mn, Fe involved in free radical formation (via Fenton reaction)
- Elevated concentrations of various metals in PD brain (mixed evidence)

Combined occupational metal exposures and PD: Detroit area case-control study*

Metals	*Exposures*	*Relative risk*	*95% CI*
Lead + Copper	Both >20 yr	5.25	1.59-17.2
Lead + Iron	Both >20 yr	2.84	1.07-7.50
Iron + Copper	Both >20 yr	3.69	1.40-9.71

*Gorell JM et al. (1997) *Neurology* 48:650-8

Cohort studies of PD in welding occupations

Study	*Location*	*Cohort size*	*Rel. Risk overall*	*Rel. Risk highest exposed*
Racette (2005)[1]	Alabama	1,423	7.6	10.3 (boilermakers)
Fryzek (2005)[2]	Denmark	6,163	0.9	0.8 (empl. >20 yrs)
Fored (2006)[3]	Sweden	49,488	0.9	Not given
Marsh (2006)[4]	Illinois	12,595	1.0	1.0 (empl. >30 yrs)
Park (2006)[5]	Korea	24,963 (shipbuilders)	4.2	2.0 (welders)
Stampfer (2009)[6]	United States	107,773	0.9	0.8

[1]*Neurology* 2005;64:230-5; [2]*J Occup Environ Med* 2005;47:466-72; [3]*Occup Environ Med* 2006;63:135-40; [4]*J Occup Environ Med* 2006;48:1031-46; [5]*Neurotoxicology* 2006;27:445-9

Parkinsonism prevalence among Alabama welders and boilermakers compared to general population rates*

Occupational group	*Prevalence ratio+*	*95% CI*
Boilermakers	10.3	2.6-40.5
Welders	7.3	3.1-17.1
Welder helpers	9.0	2.8-29.1
Combined	7.6	3.3-17.7

***Racette B, et al. (2005) *Neurology* 64:230-5**

+Compared to prevalence in Copiah County, MS

Pesticides and Parkinson's disease

- Many pesticides neurotoxic
- Structural similarity of MPTP and paraquat
- Animal studies
  - Paraquat + Mn interactions on nigral destruction
  - Rotenone model of PD induction in mice
- Epidemiologic studies
  - Ecological correlation studies
  - Case-control studies (paraquat, OPs, organochlorines)
  - Brain tissue studies (organochlorines)

Residential exposure to paraquat + maneb and PD in the Central Valley, California*

Age group	Cases (%)	Controls (%)	OR (95% CI)
All ages	24	14	1.75 (1.13-2.73)
≤60	27	7	5.07 (1.75-14.7)
>60	23	17	1.36 (0.83-2.23)

*Costello S, et al. *Am J Epidemiol* 2009;169:919-26

Pesticide use and incident Parkinson's disease in US pesticide applicators and spouses*

Exposure	Case % (N=78)	Control % (N=55,931)	OR	95% CI
Personally applied				
No [ref]	12	21	1.0	--
<50% time	17	22	1.2	0.5 - 3.1
≥50% time	71	57	1.9	0.7 – 4.7
Cum. Lifetime days use				
0 - 64 [ref]	28	47	1.0	--
65 - 200	14	16	1.2	0.5 – 2.6
201- 396	23	18	1.7	0.8 – 3.5
>396	35	19	2.3	1.2 – 4.5

***Source: Kamel F, et al., Am J Epidemiol 2007;165:364-74**

+Odds ratio adjusted for age, gender, state

Solvent exposure and Parkinson's Disease

Solvent	OR (95% CI)
Trichloro ethylene	6.1 (1.2-33.0)
Perchlor ethylene	10.5 (1.0-113.0
Carbon tetrachloride	2.3 (0.9-6.1

Goldman et al. Solvent exposure and Parkinson's Disease risk in twins. Ann Neurol. 2011

"Exposure to specific solvents may increase risk of PD. TCE is the most common organic contaminant in groundwater, and PERC and CCl(4) are also ubiquitous in the environment... the potential public health implications are substantial"

Estimated attributable risk fractions for Parkinson's disease

- Genetics: 10%
  - Mendelian (familial PD): 5%
  - Genetic factors in non-familial PD: 5%
- Smoking, caffeine, NSAIDs: 20%*
- Environmental toxicants: 10%
  - Metals
  - Pesticides
  - Solvents
  - Other (e.g., microbes, endotoxin)
- Gene/environment interactions: 20%
- Unknown: 40%

* "protective"

Neurodegenerative diseases

Motor neurone disease

– Spectrum of neurodegenerative disorders characterised by progressive muscular paralysis

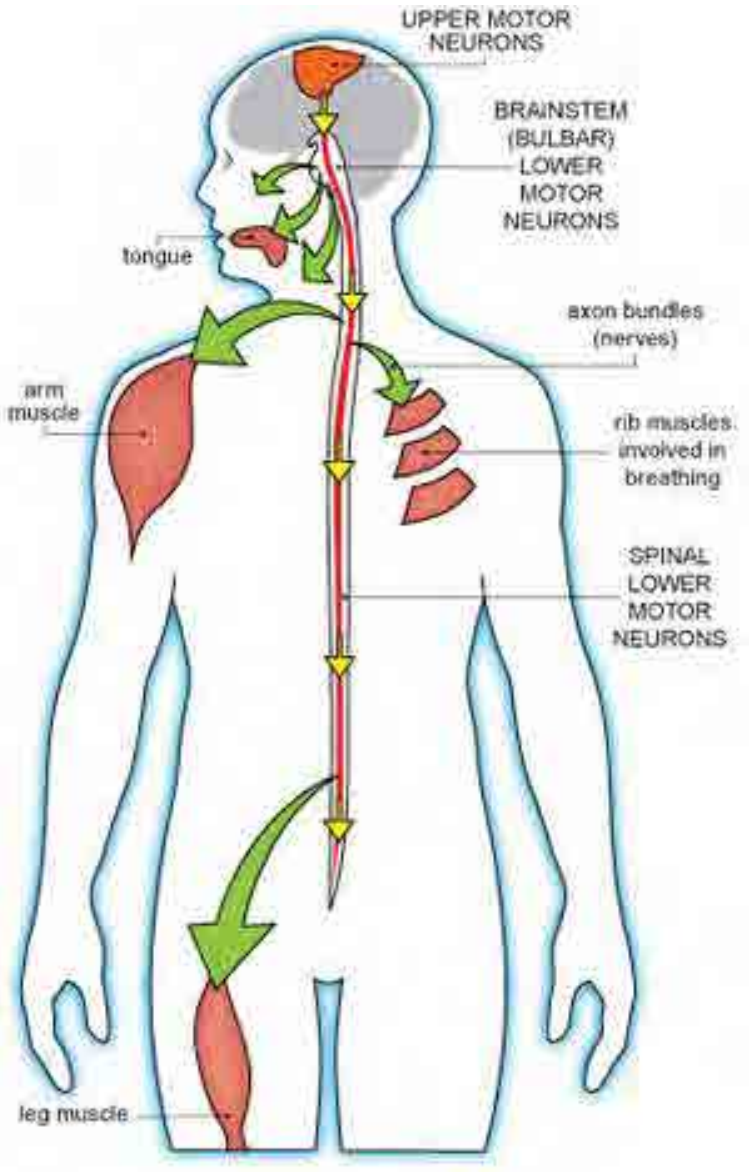
– Amyotrophic Lateral Sclerosis (ALS, 75%), Primary Lateral Sclerosis (PLS), Progressive Bulbar Palsy (PBP), Progressive Muscular Atrophy (PMA)

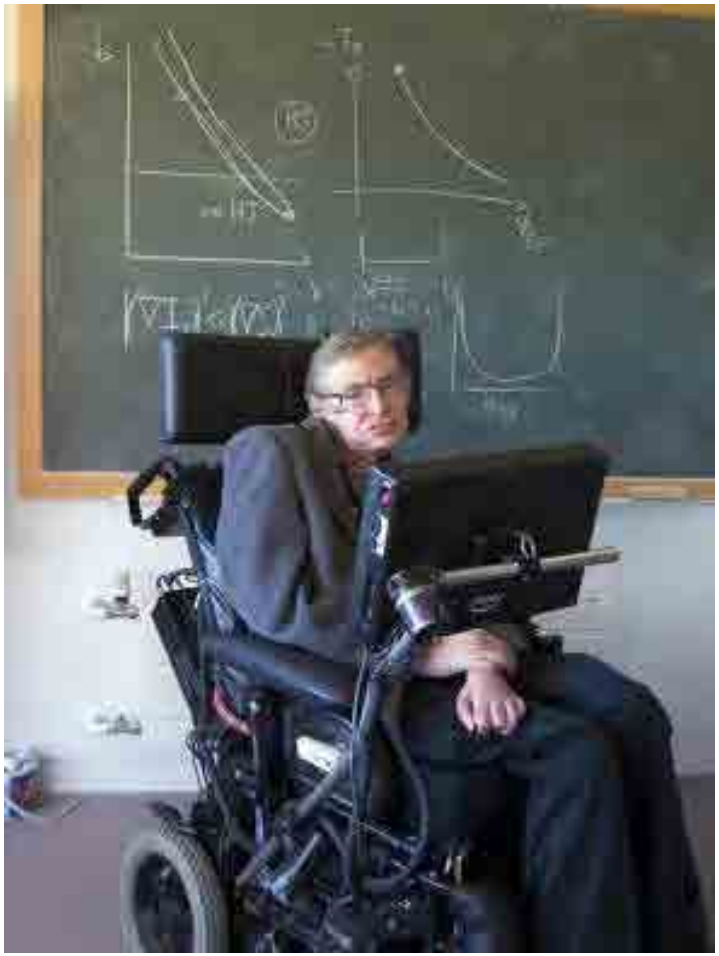
– Incidence is about the same as for multiple sclerosis, but survival is poor (~3 years), so prevalence is low

– Little effective treatment

Motor Neurones

Upper- in red
Lower- in green





Stephen Hawking, Physicist

Lou Gehrig, famous US baseball player, died 1941

Evidence for occupational causes

Motor neurone disease

- Only 5-10% of cases are „familial'; the rest are largely unexplained
- Good evidence of increased risk in professional football players (trauma, exercise, pesticides?)
- Some evidence of associations with agricultural chemicals, electromagnetic fields, welding, electrical occupations, metals, organic solvents
- No New Zealand studies, but all of these occupational exposures occur in New Zealand

Neurodegenerative diseases

Dementia

- Progressive loss of usual and customary cognitive function in several domains
- May have neurodegenerative, vascular, infectious, traumatic causes
- Gradual and insidious symptom onset for Alzheimer's Disease (AD), a continuum starting with mild cognitive impairment
- Less than 5% is „familial'
- Factors associated with cardiovascular disease (hypertension, cholesterol, etc), head trauma, smoking

Evidence for occupational causes

Dementia

- No occupational exposures have been strongly associated with dementia (though few have been studied)
- Some evidence for associations with pesticides, herbicides, liquid plastic, rubber and electrical work
- No New Zealand studies, but all of these occupational exposures occur in New Zealand

Evidence for occupational causes

Peripheral neuropathy

– Group of disorders characterised by temporary or permanent damage to nerves outside the central nervous system

– Peripheral neurotoxins include lead, mercury and arsenic, organic solvents, pesticides, acrylamide

– No New Zealand studies, but all of these occupational exposures occur in New Zealand

Evidence for occupational causes

Chronic solvent-induced toxic encephalopathy

– Disorder of the nervous system arising from exposure to certain organic solvents

– Degreasing agents, paints and glues, manufacture of textiles, plastics, polymers and pharmaceuticals, use of fibreglass

– 100,000 New Zealand workers potentially exposed

– Between 193 and 1997, 193 notified cases, 76 confirmed

Evidence for occupational causes

Subclinical effects have only been extensively studied with solvent exposure, and include:

- Altered mood states
- Irritability
- Euphoria
- Sudden mood changes
- Excessive tiredness
- Feelings of hostility
- Anxiousness
- Slowness

Evidence for occupational causes

Subclinical effects have only been extensively studied with solvent exposure, and include:

- Depression
- Memory problems
- Concentration difficulties
- Headaches
- Blurred vision
- Feelings of drunkenness
- Dizziness
- Slowness
- Loss of libido

Evidence for occupational causes

All of the subclinical effects listed can also be observed in the general population – but they occur more frequently in workers exposed to some occupational risk factors, e.g. solvents

Changes in motor, sensory and cognitive functions can also occur subclinically, and are less prone to problems of recall or symptom recognition

The clinical and subclinical effects of solvent exposure, and other occupational exposures, can have severe effects in terms of morbidity, quality of life, workplace injuries, and lost production

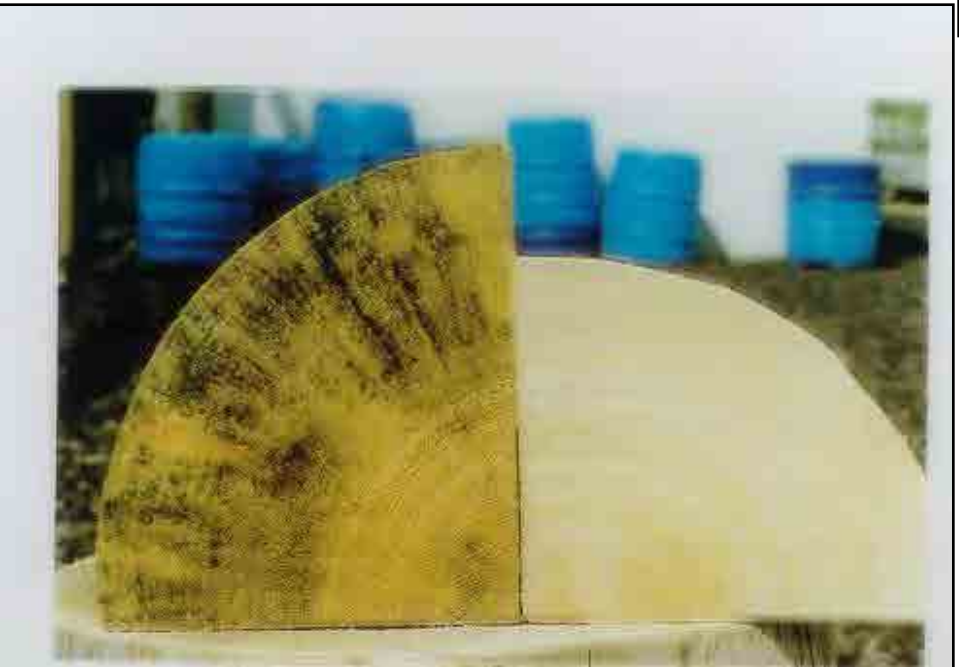
Occupational neurological disease

- Public health and occupational health in New Zealand and the United Kingdom
- Neurological disease
- Previous New Zealand research
  - Timber treatment workers
  - Dioxin-exposed workers
- Current New Zealand and UK research
- How important is occupational neurological disease?

PCP use in New Zealand

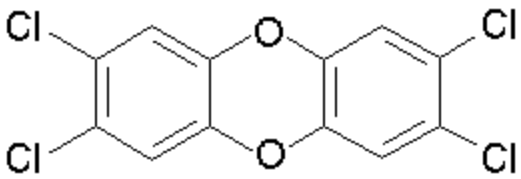
PCP was first registered in 1936 for use as a fungicide to prevent the growth of sap-stain fungi.

From the 1950s to 1988 most freshly sawn timber PCP treated.



Also mixed with oil for use as an alternative to creosote treatment.

P.O.P. - contained PCDD/Fs



Families demand investigation into dioxin contamination

New Zealand Herald

July 15, 2003

Sawmiller fights 11 years for compensation

New Zealand Herald

September 27, 2004

Previous New Zealand research

	Low (n=45)	Medium (n=39)	High (n=43)	*p* - value
Weight loss	16%	15%	33%	0.05
Fever/sweating	29%	36%	47%	<0.01
Excess fatigue	53%	69%	74%	0.04
Q16 positive	62%	74%	81%	0.04
Rash-cleared up eventually	18%	31%	42%	0.01
Hx Emphysema/Bronchitis	4%	5%	16%	0.05
Current chest tightness	13%	13%	35%	0.01
Current or Hx of nausea	16%	41%	40%	0.02

Walls CB, Glass WI, Pearce NE. Health effects of occupational pentachlorophenol exposure in timber sawmill employees: a preliminary study. *NZ Med J* 1998; 111: 362-4.

PCP Study

Historical Cohort Study

Health outcomes

- Mortality
- Cancer Incidence

Exposure assessment

- Quantitative exposure profiles by job title.

Cross-Sectional Morbidity Survey

Health outcomes

- Symptom questionnaire
- Neurological examination
- Blood tests

Exposure assessment

- Job history taken from questionnaire responses
- Serum dioxin samples

Morbidity survey - Results by duration of employment

Health outcome	1-9.9 years worked (n=103)		10+ years worked (n=13)		*p*-value for trend
	OR	95% CI	OR	95% CI	
Eczema	**1.43**	0.84 – 2.43	**2.25**	0.69 – 7.29	0.06
Non-malignant respiratory disease	**3.23**	1.53 – 6.82	**1.73**	0.33 – 9.08	0.30
Thyroid disorder	**1.41**	0.41 – 4.78	**2.36**	0.25 – 22.75	0.04
Persistent fatigue	**1.17**	0.65 – 2.10	**2.31**	0.68 – 7.85	0.13
Recurrent nausea	**2.37**	0.81 – 6.96	**2.73**	0.44 – 16.91	0.07
Recurrent diarrhoea	**2.77**	1.09 – 7.01	**1.88**	0.21 – 17.14	0.49
Often go back and check things	**1.14**	0.69 – 1.88	**1.39**	0.43 – 4.47	0.04
Low libido	**1.17**	0.60 – 2.29	**4.00**	1.19 – 13.43	0.02
Have palpitations of the heart	**1.72**	0.92 – 3.20	**4.17**	1.25 – 13.93	0.02
Sweat with no reason	**2.06**	1.10 – 3.87	**2.43**	0.66 – 8.95	0.12
Frequent mood changes w/out cause	**1.33**	0.73 – 2.40	**4.39**	1.29 – 14.99	<0.01
Straight leg raising	**1.98**	1.07 – 3.66	**3.81**	0.86 – 16.87	0.02

Reference group – non-exposed

Prevalence odds ratios adjusted by age, gender and smoking

Morbidity survey - Results by cumulative exposure score

Health outcome	Cumulative Exposure score 0 - 120 (n=58) OR	95% CI	Cumulative Exposure score 120+ (n=58) OR	95% CI	*p*-value for trend
Asthma	**1.56**	0.53 – 2.53	**1.79**	0.87 – 3.70	0.11
Non-malignant respiratory disease	**3.41**	1.46 – 7.94	**2.68**	1.11 – 6.48	0.42
Thyroid disorder	**1.00**	0.19 – 5.11	**2.03**	0.54 – 7.64	0.10
Recurrent nausea	**1.18**	0.28 – 5.08	**3.71**	1.21 – 11.37	0.24
Often go back and check things	**0.95**	0.51 – 1.75	**1.44**	0.78 – 2.66	0.07
Low libido	**0.89**	0.38 – 2.12	**2.00**	0.96 – 4.16	0.04
Have palpitations of the heart	**1.42**	0.66 – 3.07	**2.49**	1.23 – 5.03	0.07
Frequent mood changes w/out cause	**0.92**	0.43 – 1.97	**2.33**	1.18 – 4.57	0.02
Straight leg raising	**1.46**	0.67 – 3.18	**2.87**	1.41 – 5.82	0.02

Reference group – non-exposed

Prevalence odds ratios adjusted by age, gender and smoking

Morbidity survey - conclusions

- Most participants had low exposure
- No chloracne observed
- Numerous significant associations observed
- Elevated risks of non-malignant chronic respiratory disease consistent with cohort study (and adjusted for smoking)
- Consistent findings of subclinical deficits of a range of neuropsychological and physiological functions
- Similar findings to earlier study (Walls et al,1998) of a self-selected group of ex sawmillers.

New Zealand studies of phenoxy herbicide production workers

Dr Andrea ’t Mannetje - CPHR
Dr Dave McLean - CPHR
Tania Slater – CPHR
Dr Evan Dryson - Department of Labour
Dr Chris Walls - Department of Labour
Professor Manolis Kogevinas - IMIM, Spain
Professor Pier Bertazzi - EPOCA, Italy
Dr Rod Lea - ESR
Dr Barry Borman - MCPHR
Dr Patrick O’Connor - MidCentral Health
Professor Neil Pearce - CPHR

New study: morbidity survey

- **Interview**
  - Lifetime work history & employment at IWD
  - Health, offspring
  - Lifestyle factors
- **Clinical examination**
  - Basic health parameters
  - Skin disease
  - Neurological symptoms
- **Blood taking**
  - Dioxins, Furans levels
  - Blood glucose (diabetes)
  - Effects dioxin at the cellular level

Occupational neurological disease

- Public health and occupational health in New Zealand and the United Kingdom
- Neurological disease
- Previous New Zealand research
- Current New Zealand and UK research
  - Motor neurone disease (MND)
  - Dementia
  - Parkinson's Disease
  - General neurotoxic effects
- How important is occupational neurological disease?

Modifiable risk factors for motor neurone disease:
A New Zealand case-control study

David McLean, Naomi Brewer, Andrea 't Mannetje, Mark Wagstaffe, Jim McGlothlin, Diana Echeverria, Neil Pearce, Jeroen Douwes

Centre for Public Health Research
Massey University
Wellington
New Zealand

The study design

- 550 cases of motor neurone disease (both prevalent and incident) aged 20-69 years
- Identified through the Motor Neurone Disease Association of New Zealand
- Population controls selected from the Electoral Roll (two controls per case)
- telephone or face-to-face interview
    - lifetime occupational history (interpreted with job-exposure-matrix)
    - lifestyle factors

Health effects of exposure to fumigants:
A New Zealand cross-sectional study

Ruth Hinz, Andrea 't Mannetje, David McLean, Mark Wagstaffe, Jim McGlothlin, Diana Echeverria, Neil Pearce, Jeroen Douwes

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The study design

- Cross-sectional study of 400 workers exposed to fumigants (fumigators and dock workers In main ports) and 400 non-exposed workers
- Questionnaire about occupational exposures and neurological, respiratory and skin symptoms
- Nested case-control study of 75 fumigant-exposed workers with symptoms, and 75 fumigant-exposed workers without symptoms
  - More detailed exposure measurements
  - More detailed neurobehavioural testing

Neurotoxic effects of occupational solvent exposure:
A New Zealand cross-sectional study

Sam Keer, Bill Glass, Dave McLean, Bradley Prezant, Diana Echeverria, Wendyl D'Souza, Tania Slater, James McGlothlin, Duncan Babbage, Neil Pearce, Jeroen Douwes

Centre for Public Health Research
Massey University
Wellington
New Zealand

The study design

- Cross-sectional study of 400 workers exposed to solvents as vehicle spray painters, and 200 other blue collar workers with little or no exposure
- Questionnaire about occupational exposures and neurological, respiratory and skin symptoms
- Nested case-control study of 75 fumigant-exposed workers with symptoms, and 75 fumigant-exposed workers without symptoms
  - More detailed exposure measurements
  - More detailed neurobehavioural testing

Motor neurone disease: proposed UK study

- Part of Euro-motor study (European multi-centre study)
- 750 incident cases to be identified through hospitals in South east (London, Brighton – Kings, UCL, QMUL, LSHTM, Imperial) and Northeast (Newcastle, Middlesborough, Sunderland) England
- 750 population controls (chosen through GPs)
- Same questionnaires as Euromotor/NZ studies
- Plus collection of blood samples:
  - Genetics
  - Epigenetics
  - Proteomics
  - Transcriptomics
  - Other biomarkers

Neurological disease studies: proposed UK studies

- Motor neurone disease
  - Case-control study
  - Survival study
- Early onset dementia
  - Case-control study
  - Survival study
- Parkinson's Disease
  - Case-control study
  - Survival study

Occupational neurological disease

- Occupational health in New Zealand and the United Kingdom
- Neurological disease
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- Current New Zealand and UK research
- How important is occupational neurological disease?

Why is neurological disease important?

- An estimated 2 million people in the UK live with a neurological disorder (i.e. more than 100,000 in New Zealand)
- The prevalence will increase as the population ages, both in High Income and Low and Middle Income countries
- Diagnosis of a neurological disease can be devastating, there is no cure, a continuing decline in health, functioning, and quality of life, and major costs to the health system
- Some neurological diseases (e.g. motor neurone disease) are the main reason for euthanasia

[Neurological diseases remain neglected and ignored. Lancet 2012; 379: 287]

Why is occupational neurological disease important?

- Clinical syndromes associated with neurotoxicity comprise one of the ten leading occupational disorders in the United States
- Neurotoxic effects are the basis for the exposure limit criteria for about 40% of the agents considered hazardous by the US National Institute of Occupational Safety and Health (NIOSH)
- The established clinical syndromes represent the severe end of the spectrum, and there are a large number of workers with sub-clinical effects

Estimates of the burden of occupational ill-health in New Zealand

NOHSAC Technical Report

The Burden Of Occupational Disease And Injury In New Zealand

Tim Driscoll
Andrea 't Mannetje
Evan Dryson
Anne-Marie Feyer
Philippa Gander
Selwyn Mccracken
Neil Pearce
Mark Wagstaffe

Scandinavian Journal of Work, Environment & Health

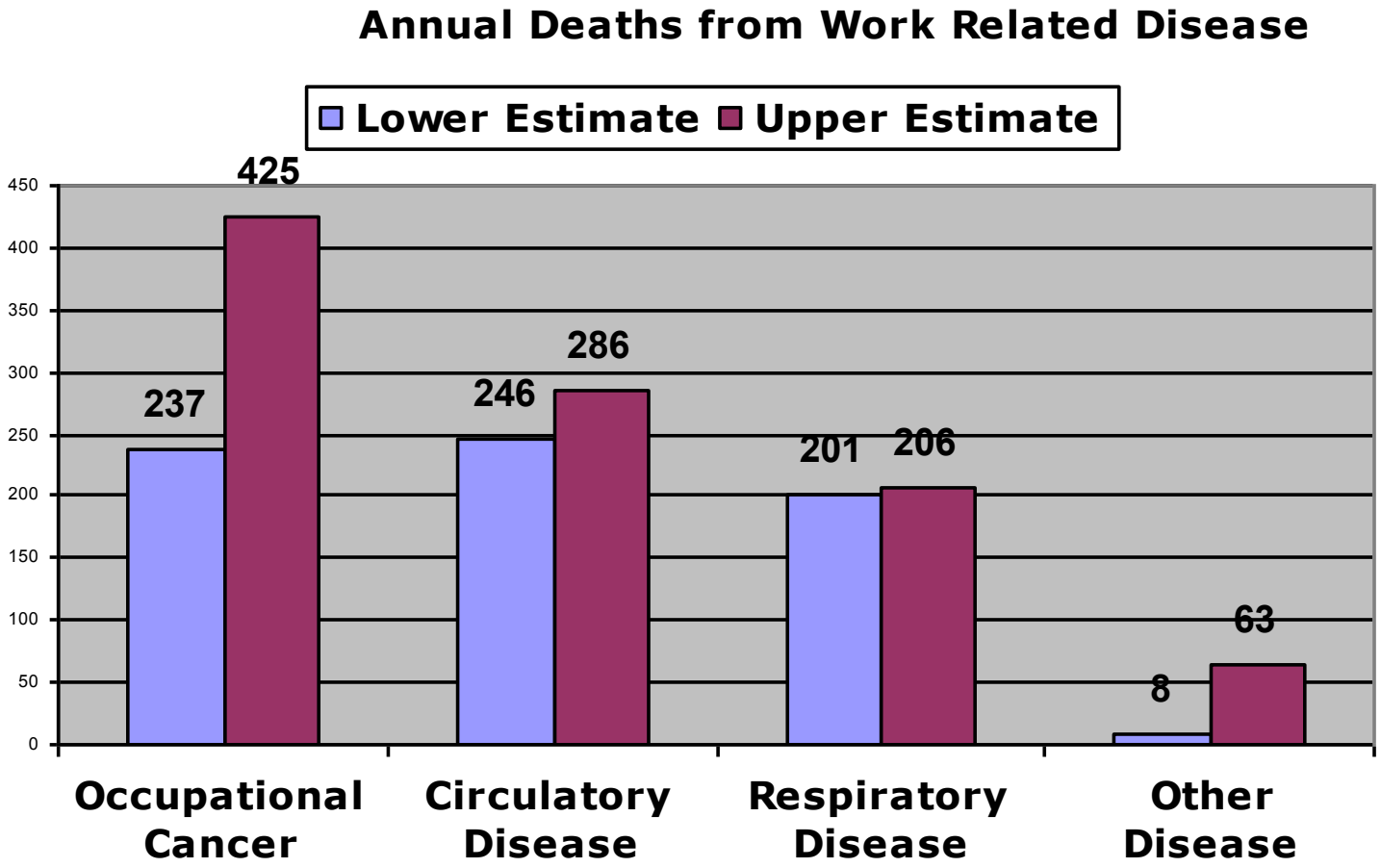
Peer reviewed publication

Quantitative estimates of work-related death, disease and injury in New Zealand

Andrea 't Mannetje
Neil Pearce

published

Summary findings



Why is occupational neurological disease important?

- Recognised occupational neurological disease is just the „tip of the iceberg'
- „Familial' factors play only a minor role
- Most neurological diseases have not been studied in depth with regards to occupational exposures; those that have been (e.g. Parkinson's Disease) have indicated a potentially major role
- If even a small percentage (e.g. 5-10%) of neurological disease is due to occupational causes, this would represent a very large number of cases
- Subclinical neurological disease is probably even more important in terms of the population burden of disease, and effects on productivity and quality of life

Neurological disease: the next occupational disease epidemic

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