

## Parkinson's disease among diphenyl-exposed paper mill workers

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## Background

- 3 index cases of Parkinson's disease among paper mill workers
- Production of wrapping paper for preservation of citrus fruits between 1954-1970 at the paper mill
- Exposure to diphenyl, a fungicide
- A common cause?

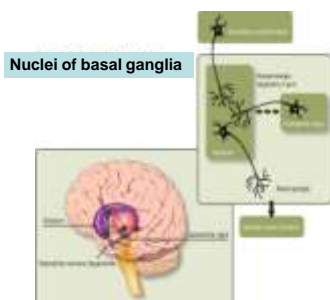
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## Parkinson's Disease

### Symptoms

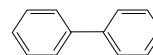
Tremor  
Rigidity  
Bradykinesia

Progressive loss of dopaminergic neurons in the substantia nigra pars compacta



## Diphenyl

- An aromatic hydrocarbon
- Fungistatic properties
- Neurotoxic effects reported

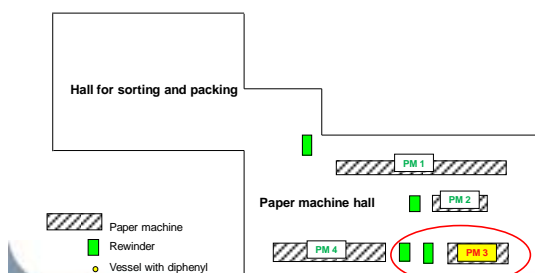


Diphenyl  
 $C_{12}H_{10}$

- Exposure levels estimated to be more than twice the TLV of 1.3 mg/m<sup>3</sup> for diphenyl in air in some areas

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## The production hall in the paper mill



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## Methods

### Identification of a cohort of exposed workers

Company files, trade union cards, pay-sheets

- 506 exposed workers
- 284 still alive in August 2002 (Table)
- 222 deceased

Age	50-55	55-59	60-64	65-69	70-74	75-79	80-84	85-89	>90	Total
Males	10	48	74	59	29	20	14	6	4	264
Females	0	2	3	4	2	4	1	2	2	20

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## Methods

### Case-finding

- Cases reported from the industrial health service
- National Hospital Discharge Register

### Case definition

- Cases of Parkinson's disease with levodopa treatment < 80 years
- Second examination by a neurologist at the University Hospital

## Results

- 5 cases of Parkinson's disease in the exposed group,  $n = 255$
  - Estimation of expected number of cases from age- and sex-standardized prevalence rates in the Swedish population (Fall et al., 1996)  $n = 0.9$
- RR 5.6 (95% CI 1.8-13)**
- 9 cases of Parkinson's among the deceased workers ( $n=222$ )
  - Estimation of expected number of cases from data on lifetime risk of developing Parkinson's disease (Elbaz et al., 2002) = 4.3 cases

**RR 2.1 (95% CI 0.96-4.0)**

## Results – the PD cases

- All had worked in the zone with the highest exposure
- Latency from start of exposure to onset of symptom 31 (27-34) years
- Mean age at onset of symptoms 51 years

Case	Age	Years of exposure	Age at start of exposure	Age at onset of symptoms	Rest tremor	Rigidity	Bradykinesia	Levodopa response
1	63	12	19	52	+	+	+	+
2	63	4	26	55	+	+	+	+
3	58	9	17	44	+	+	+	+
4	54	4	18	51	+	-	+	+
5	63	2	21	55	+	+	-	+

## Discussion

- Relative risk for PD higher in the group of exposed workers; same tendency among deceased workers
- All cases worked in the zone with the highest exposure (more than twice the TLV of 1.3mg/m<sup>3</sup> for diphenyl in air)
- Mean age at onset of symptoms 51 years (66 years in Sweden; Fall et al., 1996)
- Latency from start of exposure to onset of symptoms was similar among our cases = 31(27-34) years

Wastennson et al., *Parkinsonism Relat Disord* 2006

**First cluster of PD linking to the pesticide diphenyl – could it be due to chance?**

**And then – new PD cases**

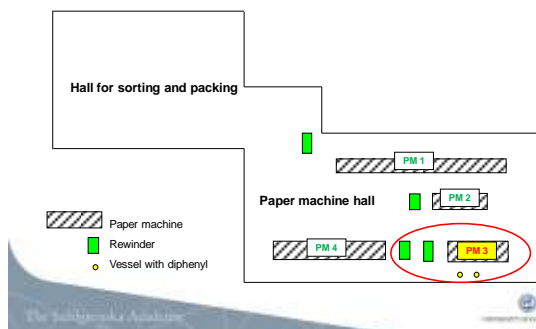


## New PD cases

- Two cases of PD (one male and one female) were admitted to our clinic after the primary investigation
- Exposure levels at their work-place estimated to be >TLV of 1.3 mg/m<sup>3</sup> for diphenyl in air
- Additional exposure by dermal contact
- Association with diphenyl exposure or sporadic cases?

Case	Age	Years of exposure	Age at start of exposure	Age at onset of symptoms	Rest tremor	Rigidity	Bradykinesia	Levodopa response
6	82	6	43	83	+	+	+	+
7	74	5	28	73	+	-	+	+

## The production hall in the paper mill

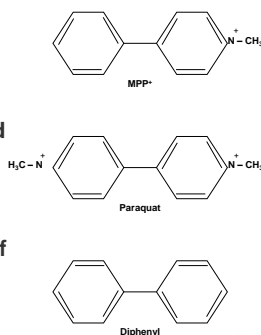


## Discussion

- The cause of Parkinson's disease unknown
- Possible etiology: a combination of genetic predisposition, aging and exposure to environmental agents
- Two-fold increased risk for Parkinson's disease after exposure to pesticides
- Animal model studies (paraquat, rotenon)

## Diphenyl is a pesticide (fungicide)

The neurotoxin MPTP causes a parkinsonian syndrome in humans and is similar to some pesticides (paraquat)



The chemical structure of diphenyl has similarities to MPTP and paraquat

## Conclusions

- First cluster of PD linking to the pesticide diphenyl
- Hypothesis: exposure to diphenyl may start a process of progressive neuron loss in susceptible individuals?
- An update of the cohort of exposed workers is needed, as well as studies on animals, and other groups of diphenyl-exposed workers



## The research team

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