Do pesticides and manganese affect human health?

Recent extensive neurotoxicological research could not document combinatorial effects of maneb, chlorpyrifos and manganese related to Parkinson’s disease.

One Danish and several international epidemiological studies have demonstrated an increased incidence for developing Parkinson’s disease (PD) in persons occupationally exposed to pesticides and persons living in areas with frequent use of pesticides. However, it was not possible to specify any causative pesticide but two pesticides, chlorpyrifos and maneb (manganese containing fungicide) are both suspected of inducing effects that might contribute to PD.

Manganese is a widely used coformulant to many commercial pesticide products and is often sprayed because it is essential for normal plant growth. Manganese is a known neurotoxic compound. When inhalation exposed it can induce parkinsonism-like symptoms, manganism.

Therefore, there is potential for combinatorial effects, even for potentiation, when coexposed to pesticides and manganese, but knowledge is sparse. Consequently, to add knowledge the Danish Environmental Protection Agency, via its Pesticide Research Programme funded an extensive 3-year research project at The Danish Institute for Food and Veterinary Research. The aim was to investigate the neurotoxic effect of chlorpyrifos, maneb and manganese in rats when single exposed to each compound and when coexposed for a period of 12 weeks. Focus was placed on two specific brain regions, corpus striatum and substantia nigra that both are highly relevant to PD and on the neurotransmitter dopamine (DA) that is also central to PD. Up-to-date neurochemical and immunohistochemical methods were applied as biomarkers for adverse effects on the brain.

Three studies were carried out to illuminate the neurotoxic effects of maneb, chlorpyrifos and maneb when single exposed.

Maneb induced a dose-dependent increased manganese concentration in corpus striatum (Figure 1) and a dose-dependent decreased concentration of the neurotransmitter 5-hydroxytryptamine (5HT) in corpus striatum and in the rest of the brain. Immunohistochemical investigations did not reveal any effect in corpus striatum or substantia nigra.

Chlorpyrifos did not affect the concentration of any neurotransmitter whereas a dose-dependent reduced enzyme activity of acetylcholinesterase (AChE) was disclosed in corpus striatum (Figure 2), the rest of the brain and in plasma. AChE is an important parameter for adverse effects in the brain. Immunohistochemical investigations did not reveal any effect.

Dosing with manganese chloride documented a dose-dependent increased manganese concentration in corpus striatum, rest of the brain and in plasma. Manganese decreased the concentration of the neurotransmitters DA, 5HT, glutamate, taurine and γ-aminobutyric acid (GABA) and the activity of AChE. However, these effects could not be reproduced in the combinatory study. Immunohistochemical investigations did not reveal any effect.

In eight extensive combinatory studies maneb, chlorpyrifos and manganese chloride were dosed...
alone or in all binary and the ternary combination.

Co exposure to maneb and chlorpyrifos reduced the striatal concentrations of DA and 5HT. This is regarded as an early sign of neurotoxicity.

All dosing-regimens involving chlorpyrifos reduced the striatal activity of AChE, that was also disclosed after single exposure to maneb and coexposure to maneb and manganese. Maneb and manganese coexposure reduced the concentration of glutamate, taurine and GABA in corpus striatum. Immunohistochemical investigations did not reveal any combinatory effects.

Manganese reduced the brain weight. Immunohistochemical investigations could not confirm neurodegeneration, either necrotic or apoptotic, in corpus striatum or substantia nigra.

Dosing with manganese or maneb alone increased the manganese concentration in corpus striatum and in the rest of the brain. Coexposure to manganese and maneb increased the manganese concentration in an additive manner.

In summary, dosing with maneb, chlorpyrifos and manganese chloride induced several effects of relevance for development of neurotoxicity and dosing might increase the risk of development of PD. However, no consistent pattern of combinatory effects of maneb, chlorpyrifos and manganese emerged except for the additivity of maneb and manganese in relation to the brain manganese concentration. However, this does not exclude that application of another study design might have disclosed combinatory effects. A potential for combinatory effects still persists that must be investigated in near future.

**Literature**


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**Figure 1.** Manganese concentration in corpus striatum from rats dosed intraperitoneally once a week during 12 weeks with vehicle (control, 0.9% NaCl) or maneb (MB). Data are presented as mean ± standard deviation. There were 12 rats in each group.

* P < 0.05 between values from control and exposed rats.

**Figure 2.** Activity of acetylcholinesterase (AChE) in corpus striatum from rats dosed subcutaneously once a week during 12 weeks with vehicle (control, peanut oil) or chlorpyrifos (CH). Data are presented as mean ± standard deviation. There were 12 rats in each group.

* P < 0.05 between values from control and exposed rats.