ORGANIC MERCURIALS
USED AS FUNGICIDES

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The results of comparative toxicological investigations of me-
thyl, ethyl and methoxy-ethyl mercury compounds are presented.
The differences in absorption, distribution and elimination of each
group of compounds as well as specificities in the clinical picture
of poisoning are pointed out.

Based on the long-term field experience the author concludes
that occupational exposure to organomercurial fungicides can be
maintained within safe limits. This can be achieved by appropri-
ate technological, protective and medical control measures.

Organic mercurials have been used quite extensively as fungicides in
agriculture, horticulture and forestry. To some extent they have also been
used as fungicides in the paper-pulp industry, the textile and the paint
industry and as bacteriostatic substances in serum preparation. During
the last 10—15 years these substances, and especially methylmercury
compounds, have caused much discussion because of their special toxic
properties.

At the end of 19th century many substances were tested as to their
fungicidal properties. Mercury chloride was thus studied. It was found,
however, that this substances was too toxic to plants in concentrations
giving good protection against fungi. In 1915, Bayer Ltd introduced phe-
nyl mercury compounds, which for many years were the active ingre-
dient of the German preparation Uspulun. In 1923, methyl mercury
compounds were found to be very effective fungicides and their phyto-
toxicity was shown to be relatively low. In 1929, methoxy-ethyl mercury
was claimed to be an effective fungicide.

The organic mercurials used as fungicides in agriculture all have the
general structure.

$$R - Hg = X$$

where R is usually an organic radical with a carbon-mercury bond and
X denotes a more or less dissociable anion, organic or inorganic.

The properties of the organomercury compounds and especially the effects on animal organisms depend mainly on the organic radical. The anion may, to some extent, influence some physical properties, e. g. solubility and volatility, but is of less importance for the biological effect. This influence on volatility is demonstrated in Table 1. The data are collected from different sources. Generally speaking, the methyl mercury compounds have greater volatility than the phenyl and methoxyethyl compounds. However, the anion may modify the volatility considerably.

Table 1

Vapor concentration in air at saturation (20ºC) for different mercury compounds μg Hg/m³

Cation → _____ ↓ Anion	Hg^0	Hg^{2+}	Methyl-Hg^+	Phenyl-Hg^+	Methoxy-ethyl-Hg^+
—	14,00	—	—	—	—
Cl	—	300	94,000	5	2,600
OH	—	—	10,000	—	—
Acetate	—	—	75,000	17	2
Dicyandiamide	—	—	300	—	—

Toxicity. Published data on the toxicity vary, mainly because of differences in technique and animal strains used in the studies. For comparison of the toxicity of different compounds, I used figures from my own laboratory (Table 2). LD_{50} calculated as mg Hg/kg of body weight is lowest for the inorganic mercury salt and higher for the two organic compounds. This is the main difference. The differences between various organic compounds are less consistent.

That the anion may be of importance in practice is demonstrated in Fig. 1, which illustrates an experiment in which animals were kept in

Table 2

Acute toxicity of different mercury compounds mg Hg/kg

Compound → _____ ↓ Animal		Hg^{2+}	Methyl-Hg^+	Phenyl-Hg^+	Methoxy-ethyl-Hg^+
Mouse	ip	5—7	10—16	8—13	—
Rat	po	6—8	17—21	22—23	10—16
Poultry	iv	3	30	20	30

a box. The box was ventilated by air that had to pass through a bottle with a constant amount of a mercury compound mixed with quartz powder. The temperature was kept constant. Air flow was kept constant. It was demonstrated that when the temperature was kept at 28°C, in an experiment with methyl mercury chloride, the animals started to die on the second day and all animals were dead within 4 days. When exposed to ethyl or methyl mercury dicyandiamide, all animals survived 7 days of exposure.
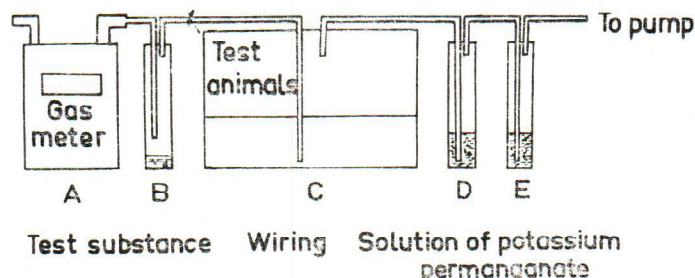

Fig. 1. *Experiment with animals kept in a box*

In an experiment in which the temperature in the bottle was kept at 13—14°C, all the animals survived 5 days of exposure to the chloride and 8 days of exposure to dicyandiamides. At the end of this period the exposure was interrupted and the animals were observed for further 4 weeks without presenting any symptoms of poisoning. In these experiments, chloride was obviously more dangerous than dicyandiamides. No difference was noted between ethyl and methyl compounds.

Absorption, distribution, and excretion. Under practical conditions inhalation appears to be the main route of absorption. Volatility is important. The mode of handling the substance is, of course, also important. When the compound is used as powder, it is difficult to prevent dust formation in handling the treated grain.

It must not be forgotten, however, that cases of poisoning have occurred as a result of consumption of treated grain, and we know from the disasters at Minamata and Niigata that methyl mercury compounds may be absorbed from the gastrointestinal tract.

The skin seems to be a less important route of absorption, though a few Japanese cases of poisoning may have followed upon absorption through the skin.

Organomercurials are rapidly absorbed into the body when they gain entrance to the lungs or the gastrointestinal tract. After absorption, they are transported with the blood to different organs, the distribution being different for different compounds (Table 3). The most important feature is that the phenyl and the methoxy-ethyl compounds give a very high

concentration in the kidney, as does mercury nitrate. The methyl mercury compound, on the other hand, is much more evenly distributed in the body and gives relatively high concentrations in the blood and in the brain. The accumulation in the kidney may, in part, be due to decomposition in the body of the phenyl-mercury and methoxy-ethyl mercury compounds.

The excretion is much slower for the methyl compound than for other compounds (Fig. 2). The excretion rapidly falls to a low level as blood concentration diminishes when the compound is distributed to different organs (Fig. 3). The total amount of mercury excreted within 4 hours (Table 4) is for the methyl mercury compound less than 1/10 of the amount excreted after injection of other compounds. The same difference is demonstrated for rats in Fig. 4. This slow excretion of the methyl mercury compounds has been verified for man in tracer experiments, showing a half-life of the body-burden of about 85 days, and in persons

Table 3

Mercury content ($\mu g/g$) of different organs of rats, which were given subcutaneous injections of mercury compounds (100 $\mu g/kg$) every other day for two weeks. N = 6

Compound	Blood	Liver	Kidney	Brain
Hg $(NO_3)_2$	0.028	0.372	20.1	0.024
Methyl Hg OH	3.04	0.676	2.9	0.155
Phenyl Hg OH	0.313	0.566	26.2	0.008
Methoxyethyl Hg OH	0.033	0.248	26.9	0.009

From Ulfvarson (1962)

Table 4

Urinary excretion of mercury in dogs within 4 hours after intravenous injection of different mercury compounds

Mercury compound	Recovery in per cent of injected dose
Mercury nitrate	2.3
Phenyl Hg nitrate	4.3
Methyl Hg hydroxide	0.20

From Swensson, Lundgren & Lindström (1959)

who have consumed a lot of fish containing methyl mercury. It is of interest to note that about 10% of the body burden in the tracer experiments has been shown to be localized in the head, i. e. in the brain.

In one experiment, *Ulfvarson* fed to rats mercury compounds in drinking water, 100 ng/ml, for 3 weeks. It is clearly demonstrated that after administration of methyl mercury compound mercury is excreted in the
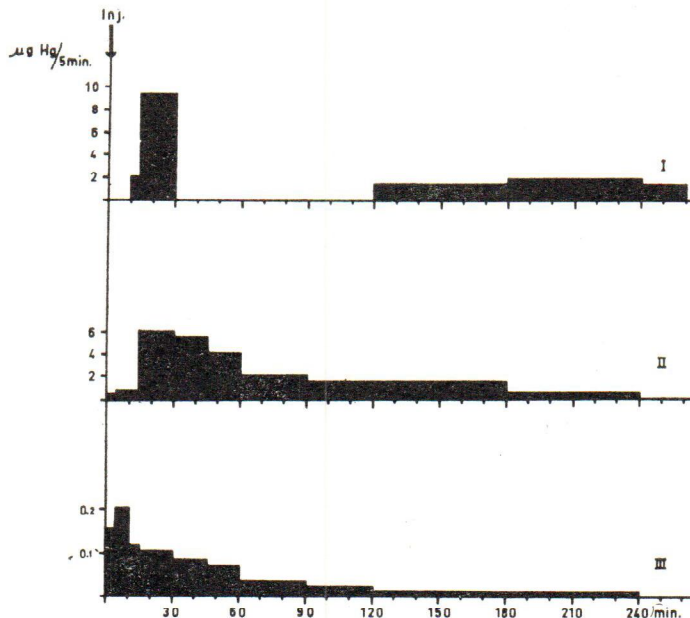

Fig. 2. *Urinary mercury excretion in dogs after a single intravenous injection of different mercury compounds, 0,1 mg Hg/kilogram of body weight. (From Swensson, Lundgren & Lindström 1959)*

faeces, whereas with the other two compounds there is a fairly high urinary excretion. The differences in distribution are also clearly demonstrated. Of course, the slow excretion of methyl mercury makes the cumulation possible and the chronic low-grade exposure is the main type of exposure leading to clinical poisoning.

Poisoning. In man, the *alkyl* mercury compounds produce symptoms mainly from the central nervous system, predominantly ataxic symptoms, such as clumsiness in fine movements, difficulties in speaking, dysphagia (difficulties in swallowing food), and disturbed balance as a consequence of a loss of muscular type is a common finding. Sensory disorders are almost invariably present. Early symptoms are disturbances in superficial sensibility, paresthesia, and numbness of the lips, tongue, and

distal parts of the limbs. Impaired vision due to constricted visual fields may occur, mostly in severe cases of poisoning. Consumption of methyl-mercury-containing food by pregnant women in early pregnancy can cause damage to the foetus and the child may show the clinical picture of cerebral palsy.
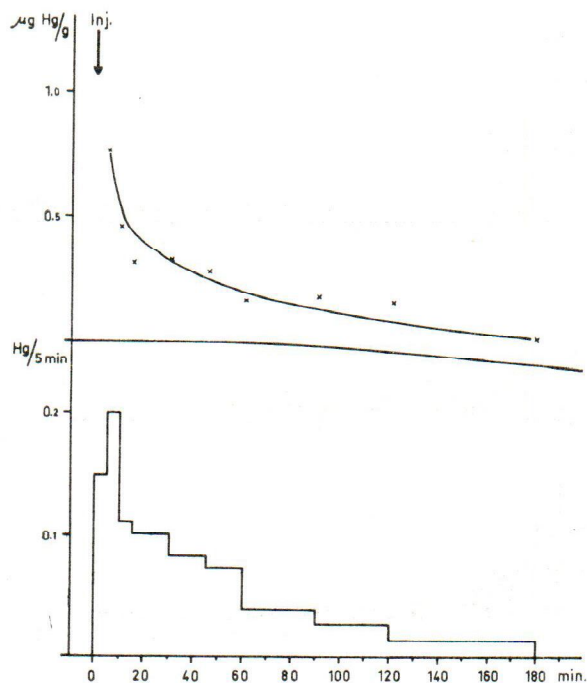

Fig. 3. *Relation between mercury content in blood and urinary excretion of mercury in a dog after a single intravenous injection of methyl mercury hydroxide, 0.1 mg Hg/kilogram of body weight (From Swensson, Lundgren & Lindström 1959)*

Only a few cases of poisoning due to the *methoxy-ethyl* mercury compounds have been reported. The symptoms are similar to those caused by inorganic mercury compounds, i. e. loss of appetite, salivation, stomatitis, diarrhoea, fatigue, headache, proteinuria and renal insufficiency.

Skin contact with the methyl mercury compounds may give rise to reddening and blisters.

Field experiences. In a factory producing the methyl mercury compounds we registered a case of poisoning in the 1940s. Fig. 5 shows that there was a substantial exposure. The factory was rebuilt and the
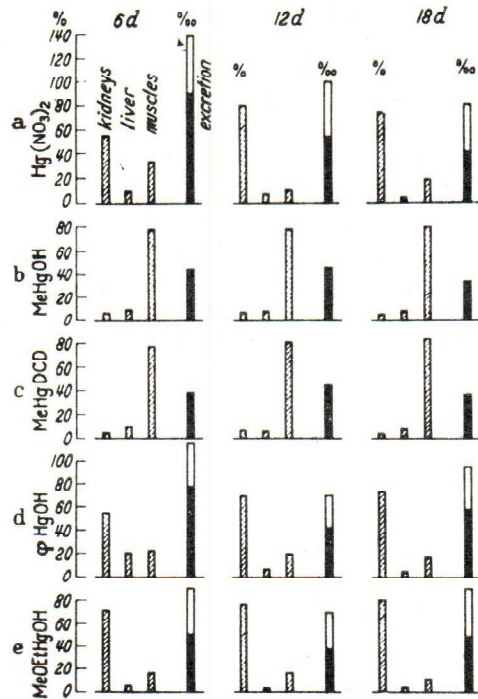
Fig. 4. *Distribution of mercury in different organs after injection of different mercury compounds subcutaneously every other day. Dose 0,1 µg Hg per gram of body weight. Section of groups of rats on 6, 12 and 18 day. Organ content of mercury as percent of the total amount injected. Cumulated excretion of mercury in urine and in feces as percent of amount injected*
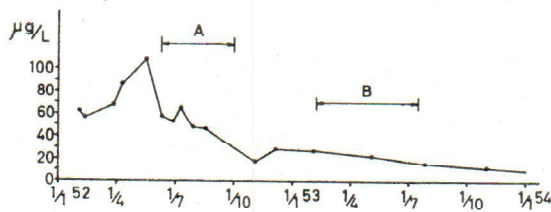*(after Ulfvarson 1962.)*

Fig. 5. *Urinary mercury excretion in employees in a factory producing methyl mercury compounds. During the period A the factory was rebuilt, which resulted in a decreased exposure as measured in mercury excretion. Later on, period B, all working routines were studied and improved, which caused a further decrease in urinary excretion*

exposure diminished. However, it tended to increase again, mainly depending on increased production and lack of supervision. The working routines were investigated, and adequate protective clothing, respirators at certain points, etc. were introduced. These measures have been effective. The workers are supervised all the time and there has been no case of poisoning. In the 1960s, the determinations of mercury in blood showed that the exposure can be kept within safe limits.

In the 1940s we had a few cases of poisoning at a seed-dressing station. Fig. 6 shows the excretion of Hg in the urine before and after reconstruction. It will be seen that exposure seems to have been very high, though the excretion may have been partly due to elementary Hg as an impurity in the preparation. At that time we had no method for the
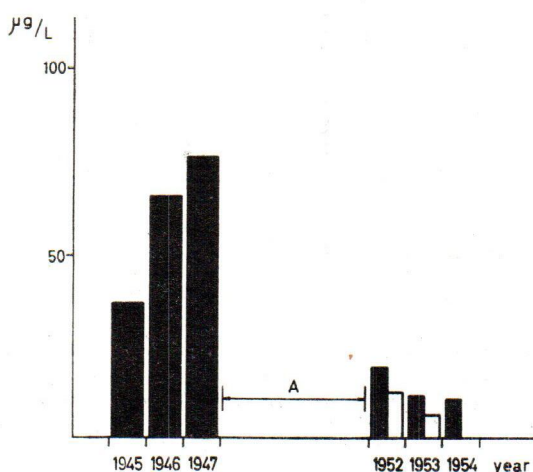

Fig. 6. *Urinary excretion of mercury in workers in a seed dressing plant where a case of poisoning occurred. Between 1948 and 1951 the station was rebuilt, new machinery constructed etc. After that the mercury excretion decreased considerably indicating a decrease in exposure*

determination of mercury in blood. The station was rebuilt with adequate exhaust system and a change from powder to wet dressing, as shown. The exposure, measured in urinary excretion, diminished quite substantially although the amount of grain treated at the same time increased manifold. The workers have been subjected to continuous medical check-ups, but no cases of poisoning have been detected.

Fig. 7 shows the urinary excretion of mercury in employees at seed dressing stations. The stations handling the largest amounts of seed have good equipment and the exposure to the workers is less than at stations with inadequate equipment. Small stations treat seed only for a short period and therefore exposure is less in spite of inferior equipment.
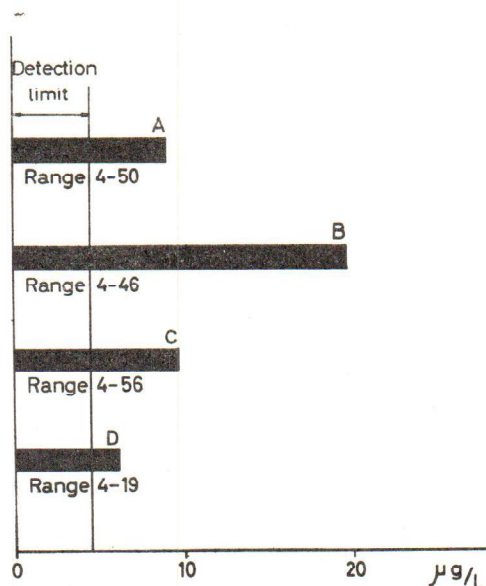
Fig. 7. *Urinary mercury excretion in workers at different types of seed dressing stations. A. Big stations with good equipment; B. Big stations with satisfactory equipment; C. Small stations with satisfactory equipment; D. Farmers using rather primitive equipment*

The methoxy-ethyl mercury compounds have caused no problems in practice. From 1966 they have been used as fungicides in Sweden, since the use of methyl mercury compounds was then prohibited. We have followed the exposure at the stations and determined the mercury content in the blood of workers. As the season is relatively short and this compound is rapidly excreted, we took our blood samples immediately — 2 days after the dressing campaign. In no case did we find an increase of the mercury content in the blood caused by exposure. This may be due to the low vapor pressure and to the fact that the machinery used was the same as that constructed for the much more dangerous and volatile methyl mercury compound.

Treatment. It is generally admitted that we have no effective treatment of methyl mercury poisoning. Recently, however, *Ulfvarson* and I have demonstrated that if penicillamine is given during the latency period, animals may survive a lethal dose of the compound and development of symptoms may be prevented. We think that this may be of practical importance.

Methyl mercury compounds prohibition. When the use of methyl mercury compounds was prohibited in 1966, it was not because of risks in connection with the handling of the substances, which, as had been demonstrated, could be done safely, but for other reasons. It had been found that the use of this substance caused damage to the wildlife

and, furthermore, there was a higher content of mercury in some Swedish types of food than in food from other countries, where methyl mercury compounds were not used to the same extent. The increase may, at least partly, have been due to the fact that the animals had been given treated seed. It is now quite clear that the main problem in this connection is not the substance used for seed dressing but the way in which it is handled. Furthermore, the main risk to the population is methyl mercury in fish from certain places. This is not due to methyl mercury seed dressings but to pollution of the water by mercury compounds from industry, which may be methylated by organisms in the water and then taken up by small organisms and introduced into a feeding chain ending in man. It is quite clear that heavy consumption of fish containing much methyl mercury will lead to poisoning. Because of that, we have an extensive control of fish from different waters. As far as we know, there has been no case of poisoning from this source in Sweden.

Sažetak

UPOTREBA ORGANSKE ŽIVE KAO PESTICIDA

Prikazani su rezultati poredbenih toksikoloških istraživanja metilnih, etilnih i metoksi-etilnih spojeva žive. Istaknute su razlike u apsorpciji, distribuciji i eliminaciji pojedinih spojeva kao i specifičnosti u kliničkoj slici otrovanja.

Na temelju dugogodišnjih terenskih iskustava autor zaključuje da je profesionalnu ekspoziciju organskim živinim spojevima moguće održati unutar neopasnih granica. Pritom su jednako važne tehnološke, zaštitne i medicinske kontrolne mjere.

Autor na kraju komentira i motive zabrane metilnih živinih fungicida u Švedskoj.

Odjel za medicinu rada,
Karolinska institut, Stockholm