Poisoning caused by the consumption of organomercury-dressed seed in Iraq

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In 1971–72, a large outbreak of poisoning caused by the consumption of seed dressed with organomercury compounds occurred in Iraq. International assistance was requested by the Government of Iraq in investigating this outbreak. The results of the investigations to date were presented at the Conference on Intoxication due to Alkylmercury Treated Seed, held in Baghdad, Iraq on 9–13 November 1974. This paper summarizes the main findings and recommendations of the Conference.

A wide range of seeds are treated with fungicides before planting (*1*), mainly to control infection by seed- or soil-borne fungi. Insecticides may also be used to protect the seed from insect attack.

Seed dressing was mentioned by Pliny in the first century B.C., but it was not until the beginning of this century that it became important (*2*); the chemical then widely used was mercuric chloride. Around 1915, the first organomercurial seed-dressing agents appeared on the market. These compounds had two essential qualities: they protected the crop from a wide range of fungi and had a low toxicity to the seed. These dominated the market for a long time. Although non-mercurial seed dressings have been used to some extent for several decades, it is only in recent years that they have been used more widely.

The organomercurial compounds that have been used for seed treatment belong to three different groups: arylmercurials, alkoxyalkylmercurials, and alkylmercurials. In the first decades of this century only arylmercury (mainly phenylmercury) and alkoxyalkylmercury compounds were used on a large scale; arylmercury compounds now have a limited use. Among the alkoxyalkylmercury compounds, methoxyethylmercury as an acetate or silicate predominates. The alkylmercury compounds were introduced in the 1940s. Of the alkylmercury compounds, methylmercury dicyandiamide is probably the compound most widely employed, but ethylmercury chloride is also effective. Methylmercury and ethylmercury are often grouped together as the short-chain alkylmercurials.

Toxicology of mercurials

The short-chain alkylmercurials have a reputation for high toxicity. The hazards connected with their use are due to their considerable chemical stability in the environment (*3*) and to their toxicological properties (*4-8*). They are completely absorbed from the gut. A considerable fraction is distributed to the nervous system and damage to nerve cells results. In the pregnant woman, they pass the placenta and cause fetal brain damage. They are only very slowly degraded into an inorganic form and the rate of elimination from the body is slow. The chemical stability and the slow elimination of the intact organomercurials explain their tendency to accumulate in food chains.

The toxicology of mercury and mercurials is complicated (*4, 8, 9*), but in essence the very limited risk with mercurials other than short-chain alkylmercurials is due to a considerably faster breakdown into mercuric mercury, both in the environment and in the body. Mercuric mercury is not distributed to the nervous system or to the fetus, and its excretion from the body is relatively rapid.

Hazards connected with mercurial seed treatment

Hazards from mercurial seed dressings may arise either from the chemical itself or from the treated seed. The effects may be due to occupational exposure, contamination of food, or pollution of the environment. Alkylmercury compounds have been involved in all three types of hazard, whereas aryl-

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and alkoxyalkylmercury compounds are comparatively innocuous.

Cases of poisoning by short-chain alkylmercurials have been reported in personnel engaged in the production, handling, and application of the agent, and also in farmers sowing dressed seed (*8*, *10*). Contamination of food may occur accidentally during handling of the agent. Such poisonings have not been reported for other fungicides used for seed treatment, but large-scale poisoning has been caused by the insecticides endrin (*11*, *12*) and parathion (*13*, *14*). Seed treated by short-chain alkylmercurials has been eaten accidentally as bread or porridge. Poisonings have also resulted from feeding dressed seed to domestic animals that were later used as food. In the period 1955–67, at least five major (*15-19*) and several minor (*5*, *8*) outbreaks of poisoning occurred in various countries as a result of the accidental ingestion of treated seed.

The syndrome of poisoning by short-chain alkylmercurials is often called Minamata disease, and is characterized by paraesthesiae of the hands, feet, lips, and tongue, by ataxia, and by concentric constriction of the visual fields (*8*). In Minamata (*20*) and Niigata [a] in Japan, major outbreaks were caused by an industrial discharge of mercury into water. The mercury accumulated as methylmercury in fish and shellfish, the consumption of which caused the poisoning.

Seed sown in fields may be eaten by animals or birds, or grow into a crop containing minor amounts of the alkylmercurial as a residue. A low but widespread presence of alkylmercury residues has been demonstrated in countries using short-chain alkylmercury seed dressing agents, but levels high enough to constitute a hazard were found only in meat from seed-eating birds (*3*).

In 1971–72 a large outbreak of alkylmercury poisoning, caused by the ingestion of treated seed, occurred in Iraq. In November 1974, an international conference was organized in Baghdad by the World Health Organization in conjunction with the Iraqi Ministry of Health and the Swedish International Development Authority. The aims of the conference were to summarize the experience obtained from the outbreak, to discuss preventive measures to be applied in the future, and to define the action to be taken in the event of a further outbreak of chemical poisoning. A report containing abstracts of papers presented and summaries of the discussions was prepared and selected papers have been published as a separate volume (*21*). This paper summarizes and reviews the main points discussed at the Conference.

[a] Report on cases of mercury poisoning in Niigata. Unpublished document, Ministry of Health and Welfare, Tokyo, 1967, 265 pp. (Japanese).

OUTBREAK IN IRAQ

Between 15 September and the first week of December 1971, 73 000 t of wheat and 22 000 t of barley, treated with organomercury seed dressing agents, were distributed in Iraq. The seed was intended for planting but, owing to a series of unfortunate circumstances, an unknown quantity of the wheat was used by a farmer for making bread and some of the barley was fed to domestic animals, mainly sheep. On 21 December 1971, the first persons suffering from alkylmercury poisoning were admitted to hospital.

Exposure

At the height of the epidemic very little information was available on how the dressed seed had been treated. It was clear that mercury compounds had been employed, but the chemical form of the mercury was not known. Initially ethylmercury was suspected, mainly because that compound had been involved in large outbreaks of poisoning caused by dressed seed in Iraq in 1955 and 1960. The clinical picture of ethylmercury poisoning was well known and the symptoms and signs seen in the first patients fitted that pattern.

A few months after the beginning of the outbreak, wheat samples were analysed by gas chromatography and selective atomic absorption spectrometry. Methylmercury levels ranging from 2 to 16 mg/kg were found (*22*). In addition, small amounts of inorganic mercury were detected. In a few samples, minor amounts of ethylmercury were present. Experimentally, no reduction in the mercury content of bread was detected during baking. In bread baked from treated wheat, methylmercury levels ranged from 5 to 10 mg/kg.

The barley probably contained a more complex mixture of mercury compounds. By gas chromatography and selective atomic absorption, the presence of non-alkyl organomercurials was demonstrated. The main compounds present were probably methoxypropylmercury, an unusual alkoxyalkylmercury compound, and phenylmercury (*23*). In addition, inorganic mercury was found and in a few

samples traces of methyl- and ethylmercury. It is possible that four different batches of barley had received different treatments with mercury compounds.

Barley was not eaten as such but was fed to animals. Experimental feeding of sheep with barley (*24*) gave rise to high levels of mercury in various organs, including kidney and muscle. There was a rather rapid decline of levels after the end of feeding, giving a biological half-life of about 10 days. In a national survey of sheep kidney (*24*) the levels found were generally below 0.5 mg/kg, although in some cases these were up to 5 mg/kg. In kidney samples, 10% of the mercury was inorganic, which is a surprisingly low figure. In mutton too, levels were below 0.5 mg/kg (*24*). It therefore seems probable that only limited amounts of the barley were really fed to the sheep.

In other meats and in fish, the mercury levels were below 0.5 mg/kg (*24*). This was also the case with chickens and eggs, in spite of the fact that high levels were obtained in an experimental feeding with wheat (*25*). Experimentally, it was shown that the mercury level in meat decreased to about 20% of the original concentration following cooking or frying.

The outbreak affected only rural areas. An epidemiological survey (*26*) studied 1221 subjects in a severely affected area and 926 subjects in a control area where treated seed had not been distributed. The main food of the peasant families was bread baked in small outdoor ovens. The average intake was about 3 loaves per day (*27*), each of about 200 g. Animal foods were consumed less than once weekly.

It can therefore safely be concluded that the only important exposure to mercury was through bread, and that the mercury was in the form of methylmercury. This concept was strongly supported by the identification of methylmercury as the dominant form of mercury in various tissues from poisoned subjects; numerous samples were analysed (*28*).

In the epidemiological study (*26*), 473 of the 1221 persons studied in the severely affected area admitted to eating methylmercury-contaminated bread over a period of ½–3 months (median slightly more than one month). Most of these ate the bread in November and December 1971 and the first hospital admissions occurred on 21 December (*19*). The total number of contaminated loaves eaten ranged from 6 to 480, with an average of 121. The study was performed 6–12 months after the last hospital admission in March 1972, and it is therefore obvious that these results may be subject to considerable error. Nevertheless, a dose–response relationship existed between the intake of contaminated loaves and the prevalence of symptoms and signs (*27*, see also below). Of those who admitted consumption of contaminated bread, about half had symptoms and/or signs that could be attributed to methylmercury poisoning; in " control " subjects who did not admit exposure, the background frequency of such findings was about one per cent.

Course of the outbreak

There are no data on which it is possible to base a reliable estimate of the total number of cases of methylmercury poisoning in Iraq. In the period 21 December 1971 to 27 March 1972, a total of 6148 patients were admitted to hospital (*19*). This is certainly an underestimate of the total number of cases, as the hospitals soon became overcrowded. Also, the density of hospitals varies in different areas of the country. Possibly, numerous patients did not consult the medical authorities, as there was no effective therapy to be offered. The total number of hospital deaths was 452; this is also an underestimate of the total deaths, as many seriously affected patients left the hospitals.

Some impressions of the severity of the epidemic can be obtained from the epidemiological survey (*26*). In the severely affected area, the prevalence of poisoning was about 28% and the case mortality about 21%. As the distribution of treated seed varied considerably in different areas, it is not possible to calculate the total number of cases from these figures.

There can be no doubt that the 1971–72 Iraqi epidemic was the largest outbreak of alkylmercury poisoning that has ever occurred. The outbreaks in Minamata and Niigata in Japan among fishermen and their families who had eaten methylmercury contaminated fish totalled a few hundred cases including about 50 deaths, according to the original report, although it was later recognized that the number of cases was underestimated in both Japanese outbreaks, the total number being several times greater (T. Tsubaki, personal communication, 1974). The Iraqi epidemics due to consumption of ethylmercury-treated seed in 1955 and 1960 included about 200 and 1000 cases and 70 and 200 deaths, respectively.

Symptoms and signs in postnatal poisoning

The Iraqi victims had the same symptoms and signs as those shown earlier to be the main charac-

teristics of postnatal alkylmercury poisoning (*8*). In order of frequency these were: (*a*) sensory disturbances such as paraesthesiae and numbness of the hands, feet, lips, and tongue; (*b*) motor disturbances with general ataxia, seen mainly as impairment of gait and dysarthria; and (*c*) visual disturbance, namely a concentric constriction of the visual fields. It has been known for some time that in severely affected patients a number of other neurological symptoms and signs may occur. The victims of the outbreak in Iraq did, however, show some characteristics not frequently reported hitherto in methylmercury poisoning. Gastrointestinal symptoms were present in some patients (*29*). This was not the case in subjects poisoned by ingestion of methylmercury-contaminated fish, but it has been previously reported in those poisoned by seed dressed with methylmercury and ethylmercury (*8*).

A possible explanation is that the mercury compound is not as firmly bound on the seed as it is in fish, where it is thought to be present as a protein complex. There may thus be a greater possibility for the methylmercury from the dressed seed to cause irritation of the gastrointestinal mucosa. In a few cases there was an exfoliative dermatitis (*29*); this has not been reported in subjects suffering from Minamata disease, but was seen in some cases during the previous epidemics in Iraq of poisoning by seed dressed with ethylmercury. The etiology of the dermatitis is not known. Hypersensitivity to the organomercurial compound or to inorganic mercury could be a possible explanation, especially since many patients developed eosinophilia of the peripheral blood. In some cases optic atrophy was reported and in others retrobulbar optic neuritis (*30*) but, since other clinicians had not noted these signs, the relevance of the findings is not clear. Also, there was some difference of opinion (*29*, *30*) as to whether disturbances of eye muscle function were present in a significant number of patients; in Japan this was a frequent finding.

The effects of alkylmercury poisoning have generally been considered to be irreversible (*8*). This view is based upon the course seen in occupationally exposed cases and in the Japanese fishermen. The clinical course seen in Iraq (*29*, *31*) quite changes this view, at least as far as sensory and motor dysfunction is concerned. Most patients with mild symptoms recovered completely or almost completely. Those with moderate symptoms generally improved and in some cases even fully recovered. Patients with severe symptoms either died at the height of the outbreak or survived and then mostly improved, in many cases to a remarkable extent. Data on recovery from visual impairment are less clear. Soon after onset of symptoms and signs, some patients suffered a blurring of vision (*30*), in some cases progressing to total blindness. This symptom always disappeared, whereas in most cases there was no improvement in the concentric constriction of the visual fields, which sometimes also progressed to total blindness. Some clinicians reported that exceptional cases had improved somewhat, but this was not a generally accepted view among the Iraqi scientists.

The distal paraesthesiae and numbness in alkylmercury poisoning suggest involvement of the peripheral nerves. Damage to peripheral neurons has been reported in certain species such as rats and cats experimentally poisoned (*5*). In the Japanese cases, involvement of peripheral nerves was first denied (*20*), but it was subsequently found that all cases had some degree of peripheral nerve lesion, as indicated by biopsy and/or measurements of nerve conduction velocity (T. Tsubaki, personal communication 1974). Neurophysiological studies were performed in several Iraqi patients (*32-34*); there was no decrease of nerve conduction velocity and therefore no indication of peripheral nerve damage. A neuromuscular transmission failure was indicated by the electromyographic findings. Since this was similar to myasthenia gravis, neostigmine was tried as a therapeutic agent and some improvement of muscular strength and general condition was observed.

Prenatal poisoning

Six cases of prenatal methylmercury poisoning due to transplacental exposure *in utero* were studied in detail. The clinical picture seen in Iraq was similar to that described in Japan (*20*), i.e., a severe impairment of mental and physical development. There was considerable difficulty in establishing the diagnosis, since the syndrome was not at all clear-cut; it could not be distinguished by its symptoms and signs from impaired development due to a number of other causes. Sometimes, mild cases did not develop signs and symptoms until some time after birth. Thus, new cases were still being diagnosed at two years of age, i.e., at the time of the Baghdad Conference. Prenatal methylmercury poisoning seems to cause irreversible damage to the fetal brain. The symptoms and signs in the infants studied did not decrease over the two years. The infants were blind and deaf and suffered severe motor dysfunction.

Treatment

Several of the well-known antidotes employed in heavy metal poisoning were used, and because these were known not to be particularly effective, a number of new methods were tried. In a few cases dimercaprol was administered, but this caused rapid deterioration of the clinical condition. This finding confirmed earlier results in animal experiments (*35*), in which dimercaprol was shown to redistribute mercury to the central nervous system from the rest of the body, probably by forming a complex that can pass the blood–brain barrier easily. It is now clear that dimercaprol should never be given to patients poisoned by alkylmercury.

Administration of penicillamine and dimercaprol sulfonate, both of which form complexes with methylmercury, resulted in some increase of the urinary mercury excretion (*36*). There was an initial increase in the blood mercury level followed by some decrease. The same pattern was seen after administration of *N*-acetyl-*d*-*L*-penicillamine, a compound with lower toxicity than penicillamine.

In animal experiments, a considerable increase in mercury elimination has been noted after oral administration of a polythiol resin (*37*). It is well established that methylmercury is eliminated from the body mainly through the bile (*5*, *10*), but a large fraction of the mercury reaching the gut by the bile is reabsorbed by the enterohepatic circulation. If a mercury-binding polythiol compound is introduced into the gut, mercury is trapped and eliminated by the faecal route. In a few patients treated with polythiol resin, there was some decrease in blood mercury levels (*36*). A few of the prenatally exposed infants were treated by exchange transfusion, and a temporary decrease of blood mercury was noted.

It seems probable that all the above-mentioned therapeutic methods reduced the body burden of mercury only very slightly, although no data were available on this matter. None of the oral treatments caused definite clinical improvement in the patients.

Animal experiments had indicated promising results of treatment by a new method called extracorporeal complexing dialysis (*38*). In a dialyser, blood from the animal was mixed with a complexing agent and the complexed methylmercury was dialysed off in the coil together with the free complexing agent. Very good results had been obtained in experiments in which cystein was used as the complexing agent. A considerable decrease in blood mercury and in the mercury content of the head of the animal occurred, and the amount of mercury removed showed that a considerable decrease in the body burden of mercury must have taken place. The method was used in a few patients late in the outbreak. It was found possible to remove considerable amounts of mercury but no clinical improvement was noted in the patients, possibly because cellular damage was already too extensive.

No treatment affecting the clinical picture of alkylmercury poisoning has been reported, with the probable exception of physiotherapy. It may be impossible to affect the disease once damage to the brain cells has occurred. It is well known that after a single heavy exposure to methylmercury there is a latent period of several weeks before symptoms and signs of poisoning occur (*8*). The cause of this latency is not known. Perhaps treatment administered within the latency period could prevent or mitigate the disease. Such a treatment has never been tried, or at least not reported.

The Baghdad Conference recommended that research in Iraq should be continued with special attention to the follow-up of exposed affected and apparently non-affected people, adults as well as prenatally and postnatally exposed children. Also, the conference urged that rehabilitation and retraining activities for severely affected patients be intensified.

Metabolism of methylmercury

Much information on the metabolism and toxicity of methylmercury in man was collected in Iraq. In the evaluation of toxic exposures and body burdens of methylmercury, a major obstacle was that the studies started only after exposure had finished. However, analysis of sequential sections of hair was shown to be very useful (*39*). The level of methylmercury in hair correlates well with the body burden of methylmercury (*4*, *10*, *40*) at the time that the hair was formed.

From studies using labelled methylmercury in combination with whole-body counting (*41*) and from repeated analyses of blood and hair from subjects exposed through fish consumption (*42*, *43*) the biological half-life of methylmercury in man has been estimated at about 70 days. This figure was confirmed by repeated analyses of mercury in blood (*22*) and by analysis of sequential sections of hair in poisoned Iraqi subjects (*44*). Half-lives of mercury as estimated from levels in hair indicated a considerable variation in rates of elimination of methylmercury from the body, as has earlier been indicated (*42*, *43*). In about 90% of the population

studied the methylmercury half-life was 35–100 days and in about 10% it was as high as 110–120 days (*44*). Such a difference may indicate great variation in the accumulation of methylmercury at a certain exposure level and some individuals, therefore, may have a much higher risk of poisoning than others. No information was available on the cause of this variation; such data are of course crucial in defining any group at special risk.

Of great importance for the toxicological evaluation of methylmercury hazards is knowledge of the relationship between exposure, total body burden, and levels in different tissues. In one survey (*22*), the relation was studied between intake of methylmercury (as calculated from methylmercury levels in bread, daily intake of bread, and time of intake of contaminated bread) and levels in blood (as recalculated to 65 days after the end of exposure, assuming a half-life of mercury in blood of 65 days. A good correlation was obtained. In another study (*45*), the relation between the ingested amount of methylmercury and mercury levels in sequential sections of hair was studied. By assuming, at each time, a relation between the total body concentration and levels in hair formed at that time and by using the half-lives calculated from levels in different parts of the hair, the authors could calculate the peak total body concentration and the peak hair level. A good correlation was found, which made it possible in other cases to deduce peak total body concentrations from hair mercury data. The average ratio was 137 (range 82–268, $n = 30$). The data from the two studies on the relation between dose, tissue levels, and body burdens was in reasonable agreement with results from tracer–dose experiments (*41*) and observations in subjects exposed through fish consumption (*42*, *43*). The Iraqi data were used for estimations of dose–response relationships.

Dose–response relationships

In several studies in Iraq (*29*, *30*), there seemed to be poor correlation between severity of symptoms and signs on the one hand, and tissue levels of mercury on the other. However, samples for mercury determinations in most cases were obtained at different times after the end of exposure and the levels had declined. When this fact was taken into consideration, there was a good correlation between tissue levels of mercury and the clinical severity of poisoning. Blood levels recalculated to 65 days after cessation of exposure were lowest in a cohort having paraesthesiae only, higher in a group showing ataxia, and even higher in a group of fatally poisoned subjects (*22*). A similar relationship between estimated peak hair mercury levels and " mild ", " moderate ", or " severe " poisoning was found in another study (*40*). There was, of course, variation of the tissue levels in subjects having a similar clinical picture and variation of the picture in subjects having the same tissue levels, but this can be expected in any kind of poisoning. Also, the severity of poisoning increased with the number of contaminated loaves ingested, as reported in one of the epidemiological studies (*27*). As expected, here too there was considerable variation. The data on the ingestion of methylmercury are by no means exact and the differences among individuals in retention at the same exposure level as well as the variation in clinical picture at the same body burden must have affected the results.

Much effort has been spent on estimations of dose–response relationships to be used in risk evaluations of methylmercury. There are two major obstacles: (*a*) the sampling of tissues for mercury determination, as well as the enquiry on the intake of contaminated bread, was carried out only after the end of the onset of poisoning and the end of exposure; and (*b*) the earliest symptom of poisoning is paraesthesiae, a subjective symptom that is also fairly prevalent in populations not exposed to significant amounts of mercury. Therefore, the tissue levels have to be recalculated in some way to the time of onset of symptoms. Estimates of the dose from data on intake of bread are hampered by poor memory and a lack of exact knowledge on the methylmercury level in the bread actually consumed. The threshold in the dose–response curve is the point where there is an increase in the frequency of paraesthesiae above the " background ".

One set of calculations on the Iraqi data was based on the blood levels (*22*). As mentioned above, these were recalculated to a time 65 days after the end of exposure by using a half-life in blood of 65 days. A further recalculation of blood levels was not performed since the levels in a few subjects studied prior to that date did not decrease; the reason for this is not clear. This relationship was used in a larger group to transform recalculated blood levels into doses. The doses were then recalculated into total body burdens at the onset of symptoms, using an assumed half-life of 70 days (*41*). Then the relation between the body burden at the onset of symptoms and the frequencies of different symptoms and signs was studied. Dose–response relationships

were established for paraesthesiae, ataxia, and death. An increase in the frequency of paraesthesiae over the background was noted at a body burden of 0.5 mg of mercury/kg. A slightly different set of calculations indicated a body burden of 0.8 mg/kg. A full description of the diagnostic criteria was not given.

Another approach was based upon mercury levels in hair (*40*). In subjects with " mild " symptoms (diagnostic criteria were not presented), the peak hair mercury levels ranged from 120 to 600 μg/g. No strict dose–response relationship was established. However, according to the relationship between peak hair mercury levels and peak total body concentrations (see above), the low end of the hair mercury range in " mild " cases corresponds to a body concentration of 0.8 mg/kg.

A third set of calculations was made from data on frequency of symptoms and signs in cohorts which had ingested different amounts of methylmercury as estimated from an epidemiological survey (*27*). An increase of the frequency of paraesthesiae above the background occurred at a total intake of 37 mg of mercury as methylmercury (T. W. Clarkson, personal communication 1974). This corresponds to about 0.7 mg/kg of body weight. As some excretion of methylmercury occurred during the exposure time, the peak body concentration was lower but, since the time of exposure was short, the difference is not great.

Considering the possible errors, it is remarkable how well the three different sets of calculations agree. They also fit with earlier estimates, mainly based on Japanese data from the Niigata outbreak (*8*, *10*), according to which poisoning in sensitive adult subjects was assumed to occur at blood mercury levels of about 20 μg/100 ml. The latter consistency is important, since in the Japanese outbreak exposure was considerably longer than in the Iraqi one. It seems, therefore, that the most important factor is body burden and the concentration in the nervous system rather than the time for which this concentration is present. Methylmercury is often said to be an accumulating agent; however, it accumulates for only a limited time (about one year) after the start of exposure (*4*, *10*). Later, a steady state is established and no further increase in tissue levels is said to occur.

Besides blood and hair, a number of other tissues were analysed in cases of postnatal poisoning. The highest levels were found in the kidneys (*45*); most of this was inorganic. Lower levels were found in the liver (*45*), mostly as organic mercury, and in the central nervous system, chiefly in the grey matter. Evaluation of the data on autopsy tissue levels was hampered by lack of information on the time between the end of exposure and death, and by some uncertainty as to whether death was due to methylmercury poisoning in all cases from which tissues were analysed (*45*). However, the data fitted reasonably well with data from the Niigata outbreak. In Minamata, higher levels were recorded. Possible explanations are differences in exposure time, differences in survival time, and analytical errors.

Risks in fetuses and infants

It is known from animal experiments and epidemiological studies in man (*46*) that methylmercury is excreted in the milk. In Iraqi women, a close correlation was demonstrated between levels in blood and in breast milk (*22*, *47*). Some of the mercury present in breast milk is inorganic and is less of a risk for the baby since the gastrointestinal absorption of inorganic mercury is probably low in babies. The percentage of inorganic mercury in the milk decreases with higher total mercury concentrations. At toxic blood levels in the mother it makes up about 40%; the proportion of methylmercury is therefore 60% and the breast-fed baby may be exposed to considerable quantities. It was shown (*47*) that in babies not exposed *in utero* the blood content could reach toxic levels with suckling only. However, if no transplacental exposure occurred, the blood mercury levels in the baby were lower than those present in the mother.

A major concern in the toxicological evaluation of methylmercury has been prenatal poisoning. It had been assumed following the Minamata epidemic that the fetus was more susceptible than the pregnant woman (*10*). In Iraq, it was found that the blood mercury level in the newborn baby was higher than in its mother (*47*), which is consistent with findings in " normal " mother–infant pairs (*10*). It was also observed that in breast-fed infants, the decline of the blood mercury level was slower than in the mother who was no longer exposed, due probably to continuous exposure of the infant. In a pregnant woman who died by poisoning, similar mercury levels were found in the brains of the mother and the fetus (*46*).

In a clinical study of 15 mother–infant pairs followed up for two years, signs of poisoning were found in seven infants. Only in one pair was the infant poisoned but not the mother. It was obvious

that the damage present in the infants was more severe than in the mothers. Also, the diagnostic criteria used in the infants were such that an observation time of two years is probably not sufficient for a final evaluation. Additional cases of slight poisoning might well appear among the infants if they were followed up for many years.

"*Subclinical*" *effects*

In an interesting study of boys who had shown no signs of poisoning but lived in a severely affected village, school performances before and after the outbreak were related to levels of mercury in the hair (*23*). While no correlation could be established between school success before the outbreak and hair mercury levels, there was a statistically significant correlation for school performance after the outbreak in 1972. This could imply an effect of methylmercury on the mental capacity of subjects regarded clinically as non-poisoned. Such an effect has often been predicted but scientific evidence has not hitherto been available. However, it was pointed out that the data may be interpreted in another way. The effect may be due not to a direct neurotoxic effect of methylmercury but to the socioeconomic situation of children living in families severely affected by disaster. Many of the boys had seen close relatives die or become crippled by poisoning. Further studies should be encouraged in order to elucidate this important matter.

In studies of fishermen exposed to methylmercury by consumption of contaminated fish, a correlation between blood mercury levels and frequency of chromosome aberrations in lymphocytes from cultures of peripheral blood has been observed (*48*). The biological significance of this finding is not clear. In a study on 65 poisoned Iraqis and 30 unexposed controls, there was a slightly higher frequency of isochromatid breaks in the poisoned subjects, but the difference was not statistically significant. A statistical analysis showed a non-random distribution of the breaks between different chromosomes, as was reported in the exposed fishermen (*49*). There was no difference in the frequency of aneuploidy. The Iraqi data thus failed to confirm the earlier findings in exposed but non-poisoned fishermen. However, the findings are not necessarily incompatible, since the fishermen had been exposed for years, in some cases for decades, while the Iraqi victims had been exposed only for a few months or less. Since lymphocytes are known to survive in interphase in the body for decades, the exposure time might be of importance for the occurrence of lymphocyte chromosome damage.

ACTION TO PREVENT AND HANDLE OUTBREAKS OF POISONING

During the final sessions of the Baghdad Conference, a general discussion took place on the prevention of outbreaks of community poisoning and on measures to be taken if an outbreak occurs. The Conference considered the report of the 1974 Joint FAO/WHO Meeting on the use of mercury and alternative compounds as seed dressings (*1*), and urged all governments to study the recommendations [a] and to apply them strictly in their own countries in order to avoid any chance of the misuse of treated seed. The Conference especially stressed the importance of labelling bags in the local language and with locally understood warning signs. It considered that rules for the strict control of treated seed should be part of a general system of regulation of all pesticides in order to prevent misuse and accidental cases of poisoning. FAO and WHO were urged to give assistance on request to countries to establish such pesticide control programmes. Establishment of national poison control centres should be encouraged. Information on therapeutic procedures should be kept available in each country and, where these exist, stocks of antidotes held. Public health authorities should be informed before any large-scale use of pesticides occurs, and pollution aspects should always be covered by environmental monitoring.

Handling of outbreaks

Proposals for detecting a community poisoning outbreak, for establishing the cause and size, for

[a] The Joint FAO/WHO Meeting recommended that the use of alkylmercury compounds as seed dressings should be strictly limited to the treatment of nuclear stocks of cereal seed used for the first few generations of seed multiplication. Alkoxyalkylmercurials, arylmercurials, and hexachlorobenzene should be used to dress seed only if the need for such treatment has been investigated and assessed and the possible use of an alternative ruled out. Export of seed treated with these compounds should be restricted. All dressed seed to be exported for the production of food should be distinctly dyed to identify it from food grain. The possibility of adding a bitter, nauseous, or similar substance to treated seed should be studied. Bags of treated seed should be adequately labelled, and accompanied by documentation and instruction leaflets on handling and hazards. The appropriate authorities should be kept informed on consignments of treated seed and national authorities should keep records on stocks of alkylmercury compounds stored in their country.

limiting the effects, and for preventing further outbreaks were presented.

As regards the detection of outbreaks, local medical and health organizations should be encouraged to report cases of poisoning, especially if they occur in clusters. The report should state where and when the poisoning occurred and the clinical signs and symptoms. Some effects of poisoning, however, may not lead to early detection of an outbreak, for example those of a teratogenic, mutagenic, or carcinogenic nature.

When an outbreak is indicated, but before the size and cause are known, two actions are crucial: (*a*) the health service, hospitals, the general public, and in some cases other countries and international organizations should be informed that there is an outbreak, and given details of preliminary preventive measures and the acute treatment of cases; and (*b*) a preliminary epidemiological field survey should be carried out to find out rapidly the size and cause of the outbreak. An epidemiological team (director, clinician, sanitarian, epidemiologist, and laboratory personnel) is formed. A survey form (main items: sex, age, place of residence and recent absences, occupation, time of onset of disease, clinical picture, food intake, water supply, and potentially affected contacts) is prepared and used on a suitable population sample (and sometimes also on controls), together with a clinical examination. Extensive samples are taken of food, containers in which food has been kept, water, blood, urine, hair, gastric contents, faeces, and autopsy tissue. Sampling is carried out at an early stage, based on informed guesses as to the vehicle of the noxious agent. Laboratory analyses are started; sometimes considerable cooperation between different laboratories with special capacities will be needed. Since infectious disease is often the main differential diagnosis of poisoning, laboratory activities may need to include both chemical analyses and bacteriological and virological work. Studies of dose–response relationships are often crucial for the establishment of firm conclusions on the cause.

As soon as the epidemiological group has reached conclusions on the size of the outbreak, the vehicle, and the agent responsible, rapid measures are taken to limit further effects. The public, the health service, hospitals, other countries, and international organizations are informed. The treatment of choice can now be established. Measures are taken to confine the cause. Often it is advisable to perform a second epidemiological survey, which may be better planned and implemented than the preliminary survey (*50*).

Measures to prevent further outbreaks should be taken at local, central, and international levels. Laws and regulations have to be re-examined, and information and education improved. The actions taken during the outbreak must be scrutinized and emergency plans changed to increase efficiency in organization. Finally, it is very important to publish a full account of the outbreak in an international scientific journal in order to spread information on the dangers and especially to make available the data on human toxicology collected during the outbreak. Data on toxicity in humans are rare and therefore of great importance.

The World Health Organization can assist in all these matters and the Conference recommended that countries should make use of the emergency assistance provided by WHO, and that WHO should continue its assistance to countries in carrying out epidemiological surveys. As in all its activities, WHO participates only at the request of a government and assists in a spirit of cooperation with national authorities. It is essential that a government should request assistance early in an outbreak so that the resources open to the Organization can be mobilized. WHO, through its contact with its collaborating laboratories and with experts throughout the world, is in a position to add to the resources of the national administration the best facilities and brains available. No country should ever feel that any blame will attach to it for allowing an outbreak to occur. The involvement of WHO in a poisoning outbreak also means that it is able to take steps on an international level to prevent similar outbreaks in the future. The implications of assistance pass far beyond the immediate outbreak and help to bring to all peoples a means of preserving health.

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RÉSUMÉ

EMPOISONNEMENTS PROVOQUÉS PAR LA CONSOMMATION DE SEMENCES TRAITÉES PAR DES ORGANOMERCURIELS EN IRAK

En 1971–72, de très nombreux cas d'empoisonnements provoqués par la consommation de semence traitée par des organomercuriels se sont produits en Irak. Le Gouvernement de ce pays a fait appel à l'assistance internationale pour effectuer des recherches sur cette épidémie. Les résultats de ces investigations, à ce jour, ont été présenté à la Conférence sur les intoxications dues à des semences traitées par l'alkylmercure, qui s'est tenue à Bagdad, Irak, du 9 au 13 novemvre 1974.

On a d'abord soupçonné que le composé de mercure utilisé était l'éthylmercure, mais on a découvert ensuite qu'il s'agissait du méthylmercure. Cette épidémie a affecté exclusivement les régions rurales et la seule exposition d'importance au mercure venait de la consommation de pain. Entre décembre 1971 et mai 1972, 6148 malades ont été hospitalisés et 452 d'entre eux sont morts. Le nombre total de décès a été probablement plus élevé.

Les signes et symptômes étaient semblables à ceux qui ont été signalés dans les épidémies d'empoisonnements par le méthylmercure au Japon et seules des différences mineures telles que la présence de symptômes gastro-intestinaux chez certains malades ont été notées. La plupart des cas bénins ont été suivis de guérison complète ou presque. Dans les cas modérés, il y a eu généralement amélioration, et quelques guérisons. Les sujets présentant des cas graves sont décédés ou bien ont présenté une amélioration de degré variable. La netteté de la vision a dans la plupart des cas été améliorée, mais non le rétrecissement du champ visuel.

Le traitement par le dimercaprol a entraîné une détérioration clinique rapide, mais la pénicillamine et ses dérivés ont accru l'excrétion de mercure. L'utilisation d'une résine au polythiol, et une dialyse extracorporelle complexante ont, dans quelques cas, entraîné l'une et l'autre une augmentation de l'excrétion mais sans amélioration clinique, peut-être parce que le traitement avait été institué trop tard.

Des relations dose–réponse ont été établies pour un certain nombre de symptômes, sur la base d'une période biologique (demi-vie) de l'organomercuriel comprise entre 65 et 70 jours.

La prévention de nouvelles épidémies de ce type, et leur traitement, au cas où il en surviendrait, sont étudiés en détail.

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