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THE USE OF MERCURY AND ALTERNATIVE COMPOUNDS AS SEED DRESSINGS

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JOINT FAO/WHO MEETING ON THE USE OF MERCURY
AND ALTERNATIVE COMPOUNDS AS SEED DRESSINGS

Geneva, 4-6 March 1974

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THE USE OF MERCURY AND ALTERNATIVE COMPOUNDS AS SEED DRESSINGS

A Joint FAO/WHO Meeting on the Use of Mercury and Alternative Compounds as Seed Dressings was held in Geneva from 4 to 6 March 1974. Mr J. W. Wright, Chief, Vector Biology and Control, opened the Meeting on behalf of the Directors-General of the World Health Organization and the Food and Agriculture Organization of the United Nations.

1. INTRODUCTION

A serious outbreak of organomercury poisoning due to human consumption of treated seed grain occurred in Iraq in late 1971 and early 1972. This episode was the largest but by no means the only instance where the ingestion of treated seed has caused death and permanent disability. Most of the outbreaks have been associated with alkylmercury compounds, but hexachlorobenzene was responsible for a large outbreak in Turkey between the years 1955 and 1959.

The problems ensuing from the ingestion of treated seed have been under constant review by WHO and FAO in accordance with the recommendations of the Expert Committee on Insecticides in its twentieth report (1972) dealing with the safe use of pesticides.¹ It is readily acknowledged that the serious health effects that result from ingestion are due to the misuse of treated grain, but it is apparent that the precautions taken, which included labelling and colouring the grain, have not been effective in preventing this misuse.

All of the large epidemics of poisoning have occurred in countries where the need for food was severe and improved agricultural production had a high priority. An important way of achieving a continuing high production of grain and other staple crops is the use of chemical treatments to control the seedborne pathogens to which they are subject.

It is a principle in preventive medicine that, when a compound has been proved hazardous, it should be replaced by a less hazardous compound or be used in a less hazardous way, where this is possible without serious prejudice to the purpose of its use. This Joint Meeting was convened to

¹ *Wld. Hlth. Org. techn. Rep. Ser.*, 1973, No. 513, p. 7.

consider whether a replacement for some or all of the mercury seed dressings can be recommended to national authorities and whether other means can be taken to minimize the hazard.

The use of alkylmercury compounds as seed dressings for grain has resulted in intoxication of seed-eating birds and birds of prey. This consequence has not been noted when aryl and alkoxyalkyl compounds have been used.

Grain dressed with mercury compounds and sown at normal rates adds to the soil about 1 g/ha of mercury. This may be compared with the reported average annual addition to all soils of about 5 g/ha of mercury from the atmosphere in precipitation. This addition is balanced by evaporation from the soil. Since the agricultural use of mercury is about 3-5% of the total mercury used for all purposes in industrial countries, the Meeting concluded that the use of mercury compounds as seed dressing has not played a significant part in the recycling of mercury in the environment.

A considerable amount of research data has been reported in the literature on mercury seed dressings and the alternative compounds discussed in this report. Most compounds have also been extensively reviewed by the WHO Expert Committee and the FAO Working Party of Experts on Pesticide Residues at their Joint Meetings, with a view to setting acceptable daily intakes and to recommending tolerances in food. Therefore, in this report, no attempt has been made to produce a bibliography and those seeking further data should consult the monographs prepared by the Joint Meetings and other publications referenced in the text.

2. OUTBREAKS OF POISONING

2.1 Clinical considerations

Outbreaks of poisoning associated with consumption of seed dressed with either alkylmercury compounds or hexachlorobenzene have involved illness that was delayed in onset but that potentially was severe and prolonged. Illness began only after contaminated food had been eaten for some weeks. When death occurred, it was often delayed for weeks or even years after illness began. In instances where the number of persons known to be affected was greater than one thousand, mortality was as high as 7% to 11%. Many persons who survived remained permanently crippled, disfigured, or demented. Some details of the condition caused by each compound are discussed in section 4 below.

2.2 Epidemiological patterns

Most poisoning associated with treated seed was the result of human consumption of the grain. A few instances in which people were poisoned by eating meat from domestic animals that had been fed treated grain emphasize the danger of secondary poisoning.

The occurrence of illness following the eating of grain treated with methylmercury or ethylmercury compounds could have been predicted from the earlier occurrence of occupational poisoning by these compounds. By contrast, hexachlorobenzene has not been described as an occupational hazard. In spite of the difference in occupational experience, the epidemiological pattern of poisoning caused by ingestion of alkylmercury compounds has been remarkably similar to that caused by the ingestion of hexachlorobenzene.

In a few instances the adults who ate treated seeds or who provided them for their families or for their domestic animals were not aware that the food was treated. In a few other instances it is unclear whether the victims knew that the grain was treated. In the great majority of cases those who ate grain were fully aware that it had been treated. They ate it because they were hungry and thought that they could remove the poison. The fact that visible colour could be removed by washing was falsely reassuring. In at least one instance, reassurance was gained from the fact that grain treated with DDT had been cleaned and then eaten without producing any detectable injury in the same community. In every instance the fact that no symptoms occurred when the treated grain was first consumed, or even after the grain had been eaten for several days, was taken as a demonstration of its harmlessness.

2.3 Estimated intake of seed as food

In one episode, the average intake of wheat treated with methylmercury was about 20 kg per person over a period variously estimated as 48 to 66 days. This grain must have represented a substantial part of the diet of the 6530 persons who were poisoned and admitted to hospital in this outbreak. However, some persons ate as much as 50 kg each during the same period. This corresponds to an average of 1146 or 768 g per person per day respectively, enough to supply at least 3000 kcal per day to persons whose average weight was 51 kg. Thus, in considering the prevention of poisoning, it must be remembered that misuse may involve the average daily consumption of as much as 1 kg of grain per person for extended periods.

2.4 Factors contributing to poisoning

The use of alkylmercury compounds or of hexachlorobenzene for treating seed has been a cause of poisoning only in exceptional circumstances. The total amount of mercury introduced into the country in connexion with the largest single outbreak was relatively small. It was very much smaller than that used safely each year in other countries where the use of alkylmercury seed dressing was routine for many years. In many episodes, hunger was undoubtedly an important factor leading to tragedy. However, other factors may have contributed. These include the timing of delivery of the grain and the attitude of the farmers.

In some instances, treated grain was delivered to farmers so late that they had already planted their own untreated seed and were left with little or no grain for food. However, there is no evidence that late delivery was the main factor leading to the consumption of treated seed.

It is even more difficult to evaluate the attitude of farmers as a factor in poisoning. It is certainly true that in countries where the most toxic compounds have been used safely the selection and treatment of seed was required by the farmers themselves, and commercial seed producers acted merely as their agents in this regard. Farmers were keenly aware of the agricultural value of treated seed in some instances where poisoning occurred. In fact, physicians investigating one outbreak had great difficulty in getting the peasants to reveal the source of trouble because they feared that, if they did so, they would not receive any seed grain the following year. In other instances, the farmers themselves may have preferred their own varieties rather than the more productive varieties distributed by their government.

It is possible that additional factors not yet recognized may have been involved in special instances. However, it is already clear that simple notification of each farmer that seed has been treated with a poison is not sufficient to prevent its use as food by hungry people ; notification must be supplemented by further restrictions on use.

3. AGRICULTURAL NEEDS

3.1 General objectives in using seed dressings

The application of fungicides to seeds before planting serves two purposes : the control of diseases caused by seedborne infection and the protection of germinating seeds or seedlings from soilborne pathogens. Seedborne fungus pathogens are carried on or in seeds of many commercial

food, feed, and fiber crops and appropriate seed treatment can prevent or control to a practical degree many of the diseases that would otherwise result. In addition, several fungus pathogens that occur in field soil cause seed decay, pre- or post-emergence damping-off of seedlings, or infections that persist as chronic disease of growing plants. Adding appropriate protective fungicides to the seed can prevent or minimize the harmful effects of these soilborne pathogens.

Seed treatment, therefore, has very great potential for increasing the production and quality of agricultural crops and its continued use is essential if adequate yields are to be maintained. The omission of seed treatment may in some cases result in total crop loss.

The international shipment of seed for planting involves the possibility of the introduction of new seedborne plant pathogens or pathogenic races into the importing country and the exposure of the seed to attack by unrecognized soilborne diseases. To avoid these possibilities it is essential that the seed should be effectively treated and it is sometimes a requirement of the importing country that the treatment be carried out. Such treatments are usually undertaken in the country of origin, where suitable facilities are available.

3.2 Principal crops and diseases involved

Treatments are undertaken on a wide range of seeds, including cereals (large and small grains, including sorghum and millet), flax and cotton, legumes, many vegetable seeds, and potato tubers. In the present context and bearing in mind the incidents that have already occurred, the Meeting concerned itself only with those seeds that might be used for human consumption or fed to domestic animals and that have been widely treated with fungicides, particularly with mercury compounds. The most important diseases which can be controlled by mercury are listed in Table 1.

3.3 Requirements determining choice of fungicides

With the exception of the loose smuts of wheat and barley, the organo-mercury seed treatments have controlled a wide spectrum of cereal diseases and their use has been favoured in the past by many countries. Following the widespread use of such treatments, the occurrence of many diseases, as for example, wheat bunt and barley leaf stripe, has been reduced to negligible proportions in many cereal grains. When seed treatments have been omitted for a few years, these diseases have often caused serious losses.

A broad spectrum seed treatment has the advantage that it is possible to use the same material on a range of crops against a number of different

TABLE 1. DISEASES OF IMPORTANT FOOD CROPS CONTROLLED BY SEED TREATMENT WITH MERCURY FUNGICIDES

Crop	Disease	Pathogen		
Wheat	Bunt	<i>Tilletia caries</i>		
	Bunt	<i>Tilletia foetida</i>		
	Snow mould	<i>Fusarium nivale</i>		
	Seedling blight	<i>Fusarium</i> spp.		
	Seedling blight	<i>Septoria nodorum</i>		
Barley	Covered smut	<i>Ustilago hordei</i>		
	Leaf stripe	<i>Helminthosporium gramineum</i>		
	Net blotch	<i>Helminthosporium teres</i>		
	Seedling blight	<i>Fusarium</i> spp.		
Rye	Snow mould	<i>Fusarium nivale</i>		
	Stripe smut	<i>Urocystis occulta</i>		
	Seedling blight	<i>Fusarium</i> spp.		
Oats	Loose smut	<i>Ustilago avenae</i>		
	Covered smut	<i>Ustilago levis</i>		
	Leaf spot	<i>Helminthosporium avenae</i>		
	Seedling blight	<i>Fusarium</i> spp.		
Maize	Leaf spot	<i>Helminthosporium</i> spp.		
Rice	Blast	<i>Piricularia oryzae</i> ^a		
	Stem rot	<i>Helminthosporium sigmoideum</i> ^a		
	Brown spot	<i>Cochliobolus miyabeanus</i> ^a		
Sorghum Linseed Millet	Seedling blight, dry rot, seedborne diseases, preemergence rots	<i>Fusarium</i> spp. and others		
Cotton seed			Anthracnose	<i>Glomerella gossypii</i>
Peanut			Crown rot	<i>Aspergillus niger</i>
Seed potato	Black scurf	<i>Corticium solani</i>		
	Gangrene	<i>Phoma</i> spp.		
	Skin spot	<i>Oospora pustulans</i>		
	Dry rot	<i>Fusarium caeruleum</i>		

^a For control of these pathogens, crops are also sprayed during growth.

pathogens and also that its use may be expected to have beneficial effects in situations where it has not been possible to identify with certainty all the pathogens present. When the seed has to be dressed for export purposes and in the absence of specific information on the pathogen situation to which the seed might be exposed when sown, the choice of treatment may be determined by practice in the country of origin. Because of its wide spectrum, mercury treatment has been a practical choice and this is where the main hazards have been encountered. As new varieties of cereal are now being introduced into many areas where the disease situation has not

been fully explored, it is likely that there will be a continuing need for broad spectrum compounds that can be used as alternatives to mercury.

3.4 Fungicidal properties of replacements for mercury compounds

The introduction of systemic fungicides has, for the first time, offered the possibility of controlling the loose smuts of wheat and barley carried within the seed and this, together with the pressure to find satisfactory

TABLE 2. AGRICULTURAL USES OF MERCURY AND NONMERCURY FUNGICIDES

Chemical	Effectiveness and spectrum of activity	Agricultural limitations
<i>Mercury compounds</i>		
alkylmercury	Highly effective, wide spectrum.	
alkoxyalkylmercury	Highly effective, wide spectrum.	
arylmercury	Generally effective, wide spectrum.	
<i>Chlorobenzene compounds</i>		
hexachlorobenzene	Effective for wheat bunt.	Resistant races developed in some areas
quintozene	Effective for wheat bunt, barley covered smut; <i>Rhizoctonia</i> on several crops.	Resistant races of bunt in some areas.
<i>Benzimidazole compounds</i>		
benomyl ^a	Effective for wheat bunt and wheat loose smut, rye stripe smut, potato black scurf.	Ineffective for barley leaf stripe. High cost may limit use to foundation stocks.
thiabendazole	Effective on seed and soil-borne wheat bunt.	High cost.
<i>Carbamodithioates</i>		
maneb	Effective for barley leaf smut and wheat bunt. Broad spectrum.	
mancozeb	Similar to maneb.	
thiram	Mild seed protectant, broad spectrum.	Limited effectiveness with high seed inoculum.
<i>Miscellaneous fungicides</i>		
captan	Limited effectiveness on seed-borne diseases; protectant against some soilborne seedling pathogens.	
carboxin	Highly effective against seed and soilborne wheat bunt and wheat and barley loose smuts; reported effective against barley leaf stripe in some areas but not sufficiently effective in other areas.	Expensive; restricted to seed increase in some areas.

^a Name approved by the American National Standards Institute and the British Standards Institution.

replacements for mercury compounds, has stimulated the identification and production of alternative fungicides. A number of new compounds have been introduced, but in contrast to mercury compounds the materials currently available have a limited spectrum of effectiveness, and in deciding on their use it will be necessary to identify the pathogens involved in the particular crop and situation.

The alternative materials available for consideration include chlorobenzene and benzimidazole compounds, carbamodithioates and "miscellaneous fungicides" such as captan and carboxin. Table 2 summarizes their effectiveness and agricultural limitations in comparison with the mercury compounds. It should be noted that this table does not cover the use of these materials in combination. There are indications that both fungicidal efficiency and spectrum of control may be enhanced by combined formulations.

The Meeting noted that promising results are being obtained with other materials at present in the development stage and particularly recommends the direction of future research towards the introduction of compounds of lower toxicity to man and animals.

4. TOXICOLOGICAL ASPECTS

4.1 Organomercury compounds

4.1.1 *Compounds and their characteristics*

Mercury is bivalent in the organic compounds used as fungicides. Most of these compounds fall into three major classes, depending on whether the organomercury cation contains an (a) alkyl (e.g., methyl or ethyl), (b) alkoxyalkyl (e.g., methoxyethyl), or (c) aryl group. Compounds of each group may contain a wide range of inorganic or organic anions, including: chloride, bromide, iodide, nitrate, hydroxide, acetate, dicyandiamide, toluenesulfonate, benzoate, methanedinaphthylidisulfonate, and others. For seed dressings they are formulated as powder or liquids.

Vapour pressure is an important factor determining the availability of organic mercury compounds for absorption from inhalation exposure. Table 3 shows the concentrations of mercury and some of its compounds in saturated atmospheres. Their high vapour pressure helps to explain the observed extreme occupational hazard of methylmercury compounds.

TABLE 3. SATURATED VAPOUR CONCENTRATION OF MERCURY AND CERTAIN GROUPS OF ITS COMPOUNDS AT 20°C

Group	Range of concentration mg/m ³
Metallic mercury	14
Dialkyl compounds	10 000
Methyl compounds	0.3 -94
Ethyl compounds	0.05 -9.0
Phenyl compounds	0.001-0.017
Methoxyethyl compounds	0.002-2.6

4.1.2 Alkylmercury compounds

(a) *Biochemical aspects.* Organomercury compounds are absorbed by the skin and more efficiently by the respiratory and gastrointestinal tracts. There is no indication of any significant difference in the rate of absorption of different compounds at the same rate of dosage.

After absorption, alkylmercury and arylmercury compounds are transported mainly in association with the erythrocytes. This is in contrast to inorganic mercury compounds and their ions, which are bound mainly to the plasma protein. Methoxyethyl compounds are evenly distributed between red cells and plasma.

There are striking differences in the distribution and storage of different classes of organic mercury compounds, and this appears to be the basis of the differences in their toxic effects when given in repeated doses. The mercury content of different organs of rats following repeated doses of typical compounds is shown in Table 4.

TABLE 4. AVERAGE MERCURY CONTENT OF FRESH TISSUE OF RATS FOLLOWING SUBCUTANEOUS DOSAGE AT THE RATE OF 0.1 MG OF HG PER DAY EVERY OTHER DAY FOR 2 WEEKS ^a

Compound administered	Blood (mg/litre)	Liver (mg/kg)	Kidney (mg/kg)	Brain (mg/kg)
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

^a Ulfvarson, U. (1962) *Int. Arch. Gewerbepath. Gewerbehyg.*, **19**, 412-442.

It will be seen that methoxyethyl mercuric hydroxide gives about the same concentrations of mercury in the blood and vital organs as does mercuric nitrate. However, the distribution of mercury derived from methylmercuric hydroxide is entirely different, being about 15 times as high in the brain, 100 times as high in the blood, but only one tenth as high in the kidney. The concentrations of mercury derived from phenylmercuric hydroxide are intermediate between those derived from alkylmercury and those derived from inorganic mercury, but much nearer to the latter.

It is generally assumed that the differences in the distribution and storage of organomercury pesticides are due, at least in part, to differences in solubility and perhaps to steric factors. Another factor is the greater stability of alkyl compounds. Both methoxyethyl compounds and phenyl compounds are degraded in the body to inorganic mercury. Alkylmercury also is metabolized, but very slowly.

Following injection of equivalent amounts of mercury, urinary excretion of phenyl compounds is almost twice that of inorganic mercury and over 10 times that of methylmercury. That is, the same level of excretion is achieved only at high blood and tissue levels of alkyl compounds.

The biological half-life of methylmercury in man is about 70 days.

(b) *Toxicity to man.* Acute poisoning by organomercury compounds has been reported infrequently in man, although methyl and other alkyl compounds have caused such poisoning. There have been many cases of chronic poisoning involving organomercury. Most chronic cases caused by known organic chemicals have been associated with repeated exposure in connexion with the manufacture of alkyl compounds, their use for treating seed, or the eating of treated seed. The use of alkylmercury-treated seed as food has produced epidemics of poisoning in man. The outbreaks involving feed were unusual, because the poisoning of people was entirely secondary to the poisoning of domestic animals.

The clinical picture of poisoning by alkylmercury compounds is well known. The patient may complain of headache ; paraesthesia of the tongue, lips, fingers, and toes ; and other nonspecific dysfunction. In mild cases, the symptoms do not develop beyond this point and in such instances they usually disappear gradually.

Early signs of more severe poisoning include fine tremors of the extended hands, loss of side vision, and slight loss of coordination, especially with the eyes closed, as in the finger-to-nose test. Incoordination may progress to the point of inability to stand or to carry out other voluntary movements. Occasionally there is muscle atrophy and flexure contractures. In other cases, there are generalized myoclonic movements. There may be difficulty

in understanding ordinary speech, although hearing and the understanding of slow deliberate speech often remain unaffected. Irritability and bad temper are frequently present and may progress to mania. Occasionally the mental picture deteriorates to stupor or coma. Especially in children, mental retardation may be added to the symptoms of poisoning already mentioned.

Many patients gradually become much worse after their illness has been recognized and exposure stopped. Even in those cases in which recovery occurs in the course of months or years, there may be little or no real neurological improvement, only an adaptation and reeducation. The duration of illness in fatal cases has ranged from about a month to 15 years. Intercurrent infection, aspiration pneumonia, or inanition are the immediate causes of death in protracted cases.

4.1.3 *Alkoxyalkylmercury compounds*

Poisoning by alkoxyalkylmercury compounds usually begins with loss of appetite, flatulence, and diarrhoea. The patient may complain of loss of weight, exhaustion, and headache. Albuminuria is a common finding and may be accompanied by generalized oedema. Signs of injury to the central nervous system are less prominent than in poisoning by alkylmercury compounds, but numbness of the fingers and toes and some degree of ataxia and weakness may occur. No episode of poisoning has been reported involving consumption of seed treated with an alkoxyalkylmercury compound.

4.1.4 *Arylmercury compounds*

Poisoning by arylmercury compounds usually involves the blood, with symptoms of weakness secondary to anaemia and infection secondary to leukopenia. In some instances, a nonspecific neurasthenia occurs even though anaemia is mild or absent.

Apparently the only serious illness ascribed to a phenylmercury compound was a case resembling amyotrophic sclerosis and several cases of "combined motor system involvement", but the relationship of cause and effect is difficult to evaluate in the absence of other similar cases. Although significant injury to the kidney apparently has not been reported in persons exposed to phenylmercury compounds, the results of animal studies suggest that such injury might occur. No episode of poisoning has been reported involving the eating of seed treated with an arylmercury compound.

4.1.5 *Dosage response*

The exact amount of any alkylmercury compound necessary to produce poisoning in man is not known, but is obviously small.

The concentration of alkylmercury in fish and shellfish that led to poisoning in Japan was in the range of 5 to 20 mg/kg calculated as mercury. Those who became sick gave a history of eating fish between 0.5 and 3 times per day. It has been estimated that the intake of mercury in fatal cases was at the rate of about 1.64 mg per person per day. Illness began to appear along the Minamata River about two years after mercury-containing waste from a plastics factory was diverted into the river. What part of this period was necessary for incorporation of significant levels of methylmercury into fish and shellfish and how much was required for the development of illness in man is not clear.

The average intake of persons poisoned by dressed seed was estimated at 2.7 mg per person per day and the highest intake at 8.2 mg per person per day.

Expert opinion indicates that occupational exposure to alkylmercury at a concentration of 0.01 mg/m³ does not produce poisoning. Thus a dosage of 0.1 mg per person per day is apparently safe.

4.1.6 Toxicity to domestic animals

Experiments in which pigs, calves and sheep were fed diets containing methylmercury or ethylmercury compounds equivalent to daily doses of 0.1–0.8 mg Hg/kg for 30–90 days have shown symptoms consistent with lesions of the central nervous system. In contrast, short-term studies in pigs with phenylmercury or methoxyethylmercury compounds revealed symptoms of enteritis and nephritis.

Examples of residues of mercury in organs, meat, or eggs from domestic animals fed organomercury compounds are shown in Table 5. High residues may be accumulated. For alkyl compounds the distribution is

TABLE 5. EXAMPLES OF RESIDUES OF MERCURY IN ORGANS AND EGGS AFTER REPEATED ORAL EXPOSURE OF DOMESTIC ANIMALS

Compound	Animal	Dose (mg Hg/kg)	Exposure	Residues in mg/kg			
				Liver	Kidney	Muscle	Eggs
Methylmercury	Pig	5	1 week	80	52		
	Calf	0.22	10 weeks	40	140	20	
	Chicken	0.15	12 weeks	17	14	6	
			8 weeks	16	20	8	
	Hen	0.5	7 weeks				12
Ethylmercury	Cattle	0.48	30 days	50	100	20	
Phenylmercury	Pig	4.6	13 days	72	220	1	
Methoxyethylmercury	Pig	3–5	30–60 days		50	0.1	

more nearly equal for different tissues than are the distributions for methoxyethyl or phenyl compounds, for which the concentration is especially high in the kidneys, while the level in muscle is relatively low.

4.2 Hexachlorobenzene

4.2.1 *Use as seed dressing*

Seed wheat is treated with hexachlorobenzene to destroy seedborne and soilborne spores of bunt. It has proved very effective for this purpose and is usually applied in the form of dust containing 10–40% of active ingredient, but liquid preparations are also used. Rates of application are 1–2 oz of 30% dust per bushel (330 mg/kg).

4.2.2 *Biochemical aspects*

Animal studies show that hexachlorobenzene is stored in the body to a marked degree. This property certainly contributes to the demonstrated cumulative effect of the compound.

Hexachlorobenzene causes liver injury and porphyria in man, rat, mouse, guinea-pig, and rabbit. In man, these changes are the cause of death and neurological changes have not been reported. In rodents, neurological changes are prominent and are the usual cause of death whether it occurs before or after porphyrin metabolism has been disturbed. It is possible, but not proved, that this difference is associated with dosage. The exact intake of hexachlorobenzene by persons poisoned by it is unknown, but it was (a) protracted and (b) certainly not greater than 10 mg/kg per day and probably nearer 3 mg/kg per day, or even less. One investigator estimated that the intake was 50 to 200 mg per person per day. Illness was mostly in persons 4–14 years of age. By contrast, animal experiments have involved dosing for only a few days or a few weeks at levels 100 to 2800 mg/kg per day. Apparently the effect on animals of small doses repeated for long periods is not known.

It is possible consistently to produce characteristic skin lesions by exposing shaved rats to long-wave ultraviolet lights installed in their cages after porphyria was well established. The dietary level (2000 mg/kg) of hexachlorobenzene used permitted unirradiated rats to survive for long periods. However, if an area of skin 25 cm² or larger was shaved at the beginning of the exposure period, most of the animals died in 3 to 14 days. Prolonged exposure to the same ultraviolet irradiation had no effect on porphyric rats fully covered with hair or on normal rats that were shaved repeatedly.

4.2.3 *Toxicity to man*

Between 1955 and 1959 a disease, previously unknown in the area, appeared commonly in three southeastern provinces of Turkey. The people called it "the new disease" or "black sore". In due course, the illness was shown to be caused by the prolonged consumption of grain treated with hexachlorobenzene.

The illness was characterized by blistering and epidermolysis of the skin, especially of the hands and face. The skin was unusually sensitive both to light and to minor mechanical trauma. The blisters broke easily, formed crusts, healed poorly, and often became infected. If the blisters healed, they were replaced by pigmented scars containing microcysts about 1 mm in diameter, and contractures were common in areas where tissue loss had occurred. Scarring also led to permanent alopecia or corneal opacity. In some patients, the infection involved deeper tissues with suppurative arthritis and osteomyelitis, especially of the fingers. The infection was apparently superimposed on another lesion of the joints, for eventually over half of 376 patients developed swelling and spindling of the fingers. X-ray examination of 18 patients showed osteoporosis restricted to the phalanges, the metacarpal and carpal bones, the distal metaphysis and epiphysis of both the ulna and the radius, and the corresponding bones of the lower extremities. Interphalangeal arthritis leading to a narrowing of the joint spaces was striking and somewhat reminiscent of rheumatoid arthritis. Erosion of the terminal phalanges was seen in two cases. The joint changes persisted at the last examination 1 to 2 years after clinical signs and abnormal excretion of porphyrins had disappeared.

Many patients had increased pigmentation of the skin (but not of the mucosae) most noticeable on the face and hands but also involving other parts of the body. In addition, a layer of fine dark hair often appeared around the eyes and chin and on the extremities, and occasionally over the entire body. The combination of atrophic hands, dark pigmentation, and a fine covering of hair was spoken of as "monkey disease" by the peasants.

Signs of systemic disease included hepatomegaly in the majority of hospitalized patients. The liver edge was firm, sharp and tender. The thyroid was enlarged in over 30% of cases, but there was no indication of increased function. Subnormal temperature, anorexia, weight loss, and muscle atrophy were common. Suppuration was accompanied by enlargement of regional lymph nodes. Even in the early stages of the disease, the urine of all patients was port wine red or darker in colour. No erythrodontia, no neurological or mental disturbances, and no typical abdominal crises such as those seen in some forms of porphyria were observed. However, some patients did complain of bouts of abdominal pain.

It was noticed very early that the disease ran a seasonal course, all signs tending to be worse in summer and improving in winter. Persons who were affected in 1955 or 1956 usually had relapses each summer, at least until 1959. After the cause was discovered and dosage stopped, many of the patients recovered, but in some the disease continued at least for many months after intake stopped. Many persons were seriously disfigured. The mortality was 10%. There were an estimated 3000 cases.

In the same areas where hexachlorobenzene produced the disease just described in children and adults, it produced a disease called "pembe yara" or pink sore in at least one adult but chiefly in infants of mothers who had eaten contaminated bread. The high mortality rate of about 95% almost eliminated children between 2 and 5 years in many villages in the years 1955 and 1960. Thus, the number of children surviving to have the porphyric form of the disease was greatly reduced. Although no abnormal excretion of porphyrins was observed in the infants, hexachlorobenzene was demonstrated by gas chromatography in the milk of their mothers.

The disease in infants occurred at all times of the year but was most frequent in summer. It began with diarrhoea, fever, and pink or skin-coloured papules on the back of the hands and fingers, on the wrists, and sometimes on the feet and legs, especially the knees. Later the skin lesions formed plaques and rings of different colour and texture, imperfectly reminiscent of a great many different kinds of dermatitis. The mucosa of the mouth often had white spots. X-ray examination revealed an infiltration of the lungs. The infants lost so much weight that the skin hung in folds. They were so dehydrated that they were too weak to cry. The liver was always hypertrophied. There was severe hypochromic anaemia, accompanied by leucocytosis. Some infants were saved through removal from breast feeding and attention to supportive care. Resolution of the skin lesion and improvement of general health often required 1 to 2 months.

4.3 Other compounds

The acute toxicity of drazoxolon is about that of the organomercury compounds, but benzimidazole compounds (benomyl, thiabendazole), carbamodithioates (thiram, maneb, mancozeb) and other fungicides such as captan and carboxin have a much lower acute toxicity. They are all eliminated relatively rapidly from the body, and there is no evidence that they produce delayed toxic effects. Nevertheless, none of these alternatives should be used without taking precautions to prevent the use of dressed seed as food or as feed for domestic animals. Except for carboxin and drazoxolon, the toxicities of the compounds mentioned have been evaluated

by joint WHO/FAO expert groups, and published in the monographs listed below. In addition to these evaluations the Meeting studied a number of papers giving additional human experience. Since the compounds considered in this section, when used as seed dressings, do not present the same order of hazard as the compounds already described in detail, the relevant data are summarized below.

benomyl—Oral LD₅₀: rat, 10 000 mg/kg. No effect level: rat, 125 mg/kg per day; dog, 10 mg/kg per day. Experience has revealed a few cases of contact dermatitis in users.

thiabendazole—Oral LD₅₀: rat, 3600 mg/kg. No effect level: rat, 10 mg/kg per day; dog, 20 mg/kg per day. Used as an anthelmintic drug in man at a dose of 50 mg/kg, in domestic animals, 50–100 mg/kg.

thiram—Oral LD₅₀: rat, 800 mg/kg. No effect level: rat, 2.5 mg/kg per day; dog, 5 mg/kg per day. The closely related disulfiram is used in man therapeutically at an initial dose of 21 mg/kg and a maintenance dose of 3.5–7 mg/kg per day. User experience of thiram has revealed induction of alcohol intolerance. The feeding of thiram in the diet of laying hens at a level of 80 mg/kg resulted in soft-shelled eggs and cessation of production of eggs.

maneb—Oral LD₅₀: rat, 6750 mg/kg. No effect level: rat, 12.5 mg/kg per day; dog, 20 mg/kg per day.

mancozeb—Oral LD₅₀: rat, 8000 mg/kg. No effect level: rat, 5 mg/kg per day; dog, 20 mg/kg per day.

captan—Oral LD₅₀: rat, 12 500 mg/kg. No effect level: rat 50 mg/kg per day; dog, 100 mg/kg per day. Contact dermatitis has been reported. Pigs have tolerated 500–1700 mg/kg in feed for about 20 weeks without any adverse effect.

carboxin—Acute oral LD₅₀ for rats is 3200 mg/kg; the acute dermal LD₅₀ for rabbits is 78 000 mg/kg. Albino rats fed diets containing 200 mg/kg for 90 days suffered no detectable symptoms.

drazoxolon—Reported oral LD₅₀ values vary according to species between 20 mg/kg (dog) and 129 mg/kg (mouse and rat). Studies have been published on metabolism and mode of action.

quintozene—Oral LD₅₀: rat, 1650 mg/kg. No effect level: rat, 1.25 mg/kg per day.

thiram, maneb—see FAO/WHO (1965) *Evaluation of the toxicity of pesticide residues in food*. FAO Meeting Report No. PL: 1965/10/1; WHO Food Add./27.65.

organomercury compounds—see FAO/WHO (1967) *Evaluation of some pesticide residues in food*. FAO, PL: CP/15; WHO/Food Add./67.32.

organomercury compounds, maneb, mancozeb, thiram—see FAO/WHO (1968) *1967 evaluations of some pesticide residues in food*. FAO/PL: 1967/M/11/1; WHO/Food Add./68.30.

captan, hexachlorobenzene, quintozene—see FAO/WHO (1970) *1969 evaluations of some pesticide residues in food*. FAO/PL: 1969/M/17/1; WHO/Food Add./70.38.

thiabendazole, mancozeb—see FAO/WHO (1971) *1970 evaluations of some pesticide residues in food*. FAO/AGP/1970/M/12/1; WHO/Food Add./71.42.

thiabendazole—see FAO/WHO (1972) *1971 evaluations of some pesticide residues in food*. FAO/AGP/1971/M/9/1; WHO *Pesticide Residues Series, No. 1*.

benomyl (data on residues only)—see FAO/WHO (1973) *1972 evaluations of some pesticide residues in food*. FAO/AGP/1972/M/9/1; WHO *Pesticide Residues Series, No. 2*.

5. EVALUATION OF THE RISK ASSOCIATED WITH INGESTION OF FUNGICIDES ON SEED AND RECOMMENDATIONS FOR MINIMIZING THIS RISK

5.1 Evaluation of risk

Table 6 shows the recommended rate of application of fungicides to wheat, the maximum dosage that could result from eating treated wheat, and the dosages of fungicides that are tolerated by experimental animals and by people. An estimate of the relative hazard of misuse of different fungicides can be made by (a) comparison of these tolerated values with the maximum dosage values; and (b) consideration of the kind of toxicity that each compound produces. Comparison of the tolerated value with the maximum dosage for alkylmercury compounds is entirely consistent with the demonstrated extreme danger of these materials. The same is true to a lesser degree for hexachlorobenzene. However, the delayed action of these compounds may have contributed even more than their inherent toxicity to the tragic results of their misuse. By the same token, alkoxyalkylmercury and arylmercury compounds probably would be dangerous if misused, although they exhibit distinctly less cumulative toxicity than alkylmercury compounds or hexachlorobenzene.

The benzimidazole compounds, carbamodithioates, and those called "miscellaneous fungicides" in this report, would be distinctly safer, partly because their maximum dosages are more nearly similar to their tolerated dosages and partly because the kind of illness produced is usually more unpleasant than dangerous.

It must be emphasized that no absolute guarantee of safety can be made for other compounds if they are misused in the same way that alkylmercury compounds and hexachlorobenzene have been misused. The effects of alkylmercury were predictable from animal experiments but the serious effects of hexachlorobenzene were demonstrated in animals only after they had occurred in people, and then only by employing ultraviolet irradiation—an unusual method of testing. It is therefore important that every effort be made to prevent misuse, regardless of what fungicides or combination of fungicides are chosen to protect seed.

TABLE 6. RECOMMENDED RATE OF APPLICATION OF FUNGICIDES TO WHEAT SEED, THE MAXIMUM DOSAGE THAT COULD RESULT FROM EATING TREATED WHEAT, AND DOSAGES KNOWN TO BE TOLERATED BY ANIMALS OR BY MAN.

Compound	Recommended application (mg/kg)	Maximum human dosage ^a (mg/kg per day)	No effect level		Therapeutic dosage for man (mg/kg)	Maintenance dosage for man (mg/kg per day)
			Rat (mg/kg per day)	Dog (mg/kg per day)		
<i>Organomercury compounds</i>						
methylmercury compounds	13-26 ^{b, c}	0.19-0.37				0.0014 ^d
phenylmercury acetate	81 ^e	1.16	2			
<i>Chlorobenzenes</i>						
hexachlorobenzene	208 ^f	3.0	1.25			
quintozene	260 ^f	3.7	1.25			
<i>Benzimidazole compounds</i>						
benomyl	500-1560 ^g	7.3-22	125	10		
thiabendazole	1560 ^g	22	100	100 ^h	50	
<i>Carbamodithioates</i>						
thiram	1042 ^b	15	2.5	5		
disulfiram (tetraethylthio-peroxydicarbonic diamide)					21	3.57-7.14
maneb	2190 ^b	31	12.5	20		
mancozeb	2000-2500 ^g	28-36	5	20		
<i>Miscellaneous fungicides</i>						
captan	1875 ^b	27	50	100		
carboxin	1875 ^b	27				
drazoxolon			1.5	0.5		

^a Based on a daily intake of 1.0 kg of wheat, which has an energy value of 3300 kcal.

^b From: *USDA summary of registered agricultural pesticide chemical uses, Vol. II: Fungicides-nematicides*, 3rd ed., Pesticides Regulations Division, Agricultural Research Service, 1971.

^c The concentrations shown are from summary sheets issued by the United States Department of Agriculture in 1964-1967. Methylmercury compounds are no longer recommended in the USA.

^d Rate of absorption tolerated in industry.

^e Environmental Protection Agency summary issued 21 May 1971 as supplement to the USDA summary (see footnote *b* above).

^f Leach, L. D., personal communication.

^g Walker, A. G., personal communication.

^h The animals developed a mild anaemia, but blood values had returned to normal by the end of the study. Dogs receiving 20 mg/kg per day remained entirely normal.

5.2 Recommendations

The Meeting considers that, where there is a proven case for the specific use of alkylmercury compounds, it is essential that the application of the chemical and the handling of the treated seed should be strictly controlled. These compounds should be used only on nuclear stocks of seed in the first few generations of seed multiplication. In view of the value of such

stocks it is envisaged that they will be under the direct supervision of the plant breeder of primary multiplier and will be stored and planted under carefully controlled conditions.

Until effective and preferably broad spectrum alternative fungicides are available, the Meeting recognizes that the use of alkoxyalkylmercury and arylmercury compounds will have to continue under safeguards decided upon by individual countries. The Meeting therefore recommends that, in the light of the special hazards arising from the misuse of treated seed which have resulted in very serious poisoning outbreaks in various countries, the use of alkylmercury compounds should be limited to the treatment of nuclear stocks as described above. Alkoxyalkylmercury and arylmercury compounds should be used on cereal seed only after it has been shown to be justified by an investigation and assessment of all factors, and the possible use of an alternative has been ruled out.

The movement from one country to another of seed treated with any toxic material offers a great potential hazard that is difficult to control and should be carried out only when safeguards exist to prevent such seed from being diverted for use as food.

Because of the known high toxicity of alkylmercury compounds, the Meeting recommends that their use should never be permitted for the treatment of seed to be exported for production of food. The use of alkoxyalkylmercury and arylmercury compounds should be permitted on seed for export only if safeguards exist to prevent the possibility of the seed being diverted to other uses. In these circumstances, the seed should be treated and distributed strictly in accordance with the precautions described in section 6. If there is any doubt whether these precautions will be followed, mercury compounds should be replaced by an alternative for the crop and disease situation.

Since hexachlorobenzene has also caused many cases of severe poisoning in similar circumstances, the Meeting recommends that it should be used under the same limitations as those recommended for the alkoxyalkylmercury and arylmercury compounds. In addition, it should never be used on seed to be exported for use by farmers.

6. RECOMMENDED SAFETY MEASURES

It is essential that cereal grain dressed with a seed dressing be immediately and permanently distinguishable from undressed seed and the Meeting considered the principal ways in which dressed seed can be identified in order to ascertain any ways in which precautions may be improved.

6.1 Colouring of the seed

All dressed seed should be distinctly coloured. At present this is not always the case for a variety of reasons. Even when the seed dressing has contained a dye, the treated seed is often not obviously different from untreated grain. In general, seeds treated with coloured dry dressings are not as easily distinguished as those treated with liquid dressings.

Most mercury seed dressings contain a dyestuff to mark the dressed seed and it is the responsibility of registration authorities to ensure that registered seed dressing formulations contain a dyestuff. Unfortunately, the range of dyestuffs available for this purpose is limited. Farmers and seed merchants are generally not in favour of the blue/green end of the spectrum because these give a "mouldy" appearance to the grain. Yellow dyes are barely visible on some cereal seeds, particularly if the dressing process is not an efficient one. This leaves the orange/red end of the spectrum from which to choose dyes which must not affect the germination of treated seed.

Some countries have a requirement that imported seed be coloured with specified colours, primarily to denature the grain so that it can be directed for industrial uses. Occasionally such grain is directed for animal feed and it is obviously unsatisfactory to use dyestuffs to denature if this is to be an important way of distinguishing dressed grain. In some episodes the visible colour as a warning on dressed grain has been removed by washing. This is a misleading reassurance that might be rectified by the use of dyestuffs insoluble in water.

6.2 The addition of a permanent odour or taste

The Meeting did not receive any evidence which enabled it to consider the suggestion that a suitable odour be added to dressed grain as a warning. The nonacceptability of such a "stenched" grain in transport and handling may rule out such a possibility.

On the other hand, the addition of a bitter principle to the seed dressing so that low levels persist on the treated seed would appear a possibility. One such chemical is benzyldiethyl (2,6-xylylcarbamoymethyl) ammonium benzoate, which at present is used as a denaturant for alcohol and other compounds required for industrial use. To achieve an effective amount on treated seed (approximately 1 mg/kg) it would be necessary to add the chemical to a current liquid seed dressing at approximately 1g/litre. Although this compound is stable in a variety of industrial processes, it is not known whether it is stable in seed dressing formulations, would affect germination, or would survive cooking processes. The Meeting recommends

that the possibility of adding a bitter, nauseous or similar substance to seed dressings to render the dressed seed unacceptable for consumption should be investigated.

6.3 Labelling

Bags of dressed seed must be adequately labelled with warnings to all those who handle them. It may be necessary to differentiate between the hazards in transport and distribution and those to the farmer who uses the dressed grain. Several registration authorities advise that certain precautions be taken with dressed seed, but few actually require a specific sack label. The company distributing a toxic seed dressing formulation should be required to provide sack labels together with the formulated product. It is the responsibility of the seed dressing establishment to attach such labels to the sacks of dressed seed and to ensure that they are permanent enough to survive distribution channels to the user.

Specimen phrases for such a label are :

FOR SOWING ONLY

DO NOT HANDLE seed unnecessarily

NOT TO BE USED as food or feed even after mixing with undressed seed

NOT TO BE USED for oil extraction (as applicable)

DO NOT RE-USE SACK for food or feed

WASHING DOES NOT REMOVE POISON FROM THE SEED

Seed dressed with the more toxic compounds should also be labelled with danger symbols, e.g., skull and crossbones, or other easily understood symbols, together with appropriate warning words, e.g., POISON. All written labelling should be in the language of the countries in which the dressed seed is off-loaded as well as in the language (or dialect) of the receiving region.

6.4 Precautions in transport

In principle, dressed seed should not be transported with unprotected food. Seed dressed with toxic chemicals such as organomercury compounds must, like other poisonous substances, be transported separately from food and feed, as required for example by international transport regulations.

The consignment should be provided with documentation, with copies for all stages of distribution, specifying the following information : number of packs, chemical or approved name of the active ingredient, concentration

of the dressing, and safety precautions necessary during unloading and taking into store. In the trade contract a procedure for the taking of the dressed seed into store should be settled in advance so that any misuse may be avoided. Appropriate authorities should be kept informed of the exact whereabouts of consignments of dressed seed.

6.5 Distribution to users

Distribution of imported dressed seed should be arranged in such a way that the seed may reach its destination as quickly as possible with the least number of intermediate stages. An important prerequisite is the instruction and supervision of the personnel taking delivery of the dressed seed. This procedure should be ensured at all levels of distribution down to the user himself. It may be presumed that the last but one link in the distribution should be a senior official of the authority in the area, who would be responsible for distribution to individual users and instruct them in safe handling and possible hazards. He should also be responsible for the organization of the disposal of unused seed and bags.

6.6 Educational programmes

In addition to repeating the basic advice on the bag label it is suggested that detailed instructions concerning handling and hazards should be provided, in the language of the user, in the form of a leaflet. This should contain advice against attempting to remove the dressing by washing or other means and should emphasize that treated seeds should *not*, under any circumstances, be used for food or animal feed even after mixing with undressed grain. The leaflet should also attempt to explain the consequences of consuming treated grain, including the delayed appearance of symptoms, where applicable. Education programmes to support the understanding of these leaflets would be valuable.

6.7 Safe disposal of mercury compounds

Considerable quantities of alkylmercury compounds, which it might not be possible to use for the purpose for which they were manufactured, may sometimes remain in storage. It is important that any disposal of these compounds should be carried out without hazards to the workers handling them or to the environment.

Note was taken of the work of a recent WHO meeting¹ which has prepared a Manual on Methods for Safe Storage, Transport and Destruc-

¹ Working Group on Hazards to Health and Ecological Effects of Metals and Metalloids in the Environment, Stockholm, 29 October-2 November 1973.

tion/Recovery of Organomercurials and Mercury Contaminated Waste, which sets out in detail the various chemical and other means of disposal.

The Meeting recommends that national authorities should ascertain what stocks of alkylmercury compounds are being stored in their countries, with a view to ensuring that they are being stored safely, used for an approved purpose, or disposed of in a safe manner.

7. NONCHEMICAL METHODS OF PLANT DISEASE CONTROL

7.1 Production of essentially disease-free seed

Seed transmission of many fungus and bacterial diseases is dependent not only on the presence of the pathogen in the seed field but also on climatic factors, particularly moisture and temperature, that permit contamination or invasion of seeds. It is well known that growing crops in areas unfavourable for disease development may result in seeds relatively free of certain seedborne pathogens. Use of seeds from such areas may minimize the necessity for seed treatment with highly toxic fungicides, although dressing with less toxic chemicals may still be desirable.

7.2 Disinfection of seed by nonchemical means

Improved varieties of commercial crops are frequently imported from different areas of the world in relatively small quantities to be tested under local conditions for productivity, agronomic characteristics, or disease or insect resistance. Selected cultivars are then increased to provide seed for larger scale testing or for commercial production. Elimination of all pathogens from such imported stocks is highly desirable and this can be accomplished by nonchemical means. It has been shown that aerated steam produced by a controlled mixing of air and steam can provide the temperature and moisture necessary to eliminate pathogens from many crop seeds without the necessity for subsequent drying.

7.3 Breeding for disease resistance

Plant breeders have been very successful in developing varieties of many crops that are resistant to major plant diseases. Their job has been complicated, however, by the occurrence of multiple races of certain pathogens. In some cases monogenic resistance has solved the problem

but in others multigenic resistance has proved more satisfactory. The urgency of producing disease-resistant cereal varieties has been relieved by the excellent control afforded by chemical seed treatments. Restriction on the use of alkylmercury compounds and on other highly toxic fungicides will greatly increase the need for the development of plant varieties resistant to several important cereal diseases. The appearance of races of pathogens resistant to some of the selective fungicides being used as replacements for mercury compounds adds to the desirability of producing resistant varieties of plants.

7.4 Adoption of nonchemical methods

In the light of the above considerations, the production of seeds which are relatively free from seedborne pathogens should be encouraged and methods of nonchemical disinfection should be developed, particularly for exported seed. With a view to decreasing the need for fungicides, plant breeders should pay increasing attention to the production of varieties of food grains that are resistant to seedborne diseases. In this connexion special attention should be paid to the possible introduction of varieties suitable for climatic and other conditions prevailing in developing countries.

8. SUMMARY OF RECOMMENDATIONS

1. 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. They should never be permitted for the treatment of cereal seed to be exported for the production of food (section 5.2).

2. Alkoxyalkylmercury and arylmercury compounds should be used to dress cereal seed only if the need for such a treatment has been investigated and assessed and the possible use of an alternative has been ruled out. They should be permitted for use on cereal seed to be exported for the production of food only if safeguards exist to prevent the possibility of the seed being diverted from its intended use (section 5.2).

3. Hexachlorobenzene should be used to dress cereal seed only if the need for such a treatment has been investigated and assessed and the possible use of an alternative has been ruled out. It should not be permitted for the treatment of cereal seed to be exported for the production of seed (section 5.2).

4. All dressed seed to be exported for the production of food should be distinctly dyed to identify it from food grain. Cereal grain should not be dyed for reasons other than to identify it as dressed grain (section 6.1).

5. Bags of dressed seed should be adequately labelled, as detailed in the text, for all who handle them. Detailed documentation should always accompany consignments of dressed grain and appropriate authorities should be kept informed of the whereabouts of such consignments (sections 6.3 and 6.4).

6. An instruction leaflet on the handling and hazards of dressed cereal seed should be provided for the user in the appropriate language or dialect (section 6.6).

7. National authorities should ascertain what stocks of alkylmercury compounds are being stored in their country with a view to ensuring that they are being stored safely, used for an approved purpose, or disposed of in a safe manner (section 6.7).

8. Research should be undertaken on :

(a) the development of compounds for seed dressing of low toxicity to man and animals (section 3.4) ;

(b) methods of producing pathogen-free seed by nonchemical methods, including plant breeding for disease resistance (section 7.4) ;

(c) the possibility of adding a bitter, nauseous, or similar substance to seed dressings to render the dressed seed unacceptable for use as food (section 6.2) ;

(d) development of more effective dyes for identifying dressed grain, with emphasis on those that cannot be removed by washing (section 6.1).

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