



Commission of the European Communities

agriculture

Reports of the Scientific Committee for Pesticides

(Second series)



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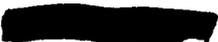
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FOREWORD

The Scientific Committee for Pesticides was set up by Commission Decision 78/436/EEC of 21 April 1978 (OJ No L 124 of 12.5.1978, p. 16) in order to provide the Commission with informed opinions on scientific and technical matters relating to the use and marketing of pesticides and to their residues, particularly in food and feedingstuffs.

The members of the Committee are independent and highly qualified in the fields of applied biology, toxicology, ecotoxicology and chemistry. The Secretariat of the Committee is provided by the Commission's Directorate-General for Agriculture.

The Committee's second series of reports, published in this volume, relate to questions put to it by the Commission on the safety in use of certain pesticides and, for a wider range of pesticides, on the maximum permitted levels of their residues in foodstuffs, in particular fruit and vegetables. Questions in this connection had arisen in the course of the Commission's work on the approximation of Member States' legislation concerning pesticides.

Composition of the Scientific Committee for Pesticides

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REPORT ON THE APPLICATION OF ETHOXYQUIN AND DIPHENYLAMINE
TO APPLES AND PEARS FOR THE TREATMENT OF SUPERFICIAL SCALD

(Opinion expressed on 9 December 1982)

1. BACKGROUND AND TERMS OF REFERENCE

Ethoxyquin and diphenylamine are used on apples and pears both within the Community and in third countries for the treatment of superficial scald. Until 1981 this use of ethoxyquin within the Community was subject to the provisions of Council Directive 70/357/EEC concerning the antioxidants authorised for use in foodstuffs intended for human consumption (1) but by amending Directive 81/962/EEC of 24 November 1981 (2) the Council decided to exclude ethoxyquin from its scope, regarding the compound as a pesticide rather than an antioxidant.

Ethoxyquin was studied in 1975 by the Scientific Committee for Food (3) which concluded that, whilst there was no toxicological evidence to oppose its use on apples and pears, continued acceptance could only be temporary and there should be no extension of use. This Committee identified inadequacies of the long-term toxicity and reproduction data and a lack of information on dietary exposure resulting from the use of ethoxyquin as an animal feedingstuffs additive.

(1) O.J. No L 157 of 18.7.1970, p. 31

(2) O.J. No L 354 of 9.12.1981, p. 22

(3) Report of the Scientific Committee for Food, 1st series, December 1975

In view of continuing uncertainties about the safety of ethoxyquin and its changed regulatory status, the Commission in June 1982 requested the Scientific Committee for Pesticides, in collaboration with the Scientific Committee for Food, to re-examine potential dietary exposure on the basis of newly available data and to advise on the safety and efficacy of ethoxyquin as well as of alternative treatments for superficial scald, particularly diphenylamine.

2. DISCUSSION

(a) Efficacy of ethoxyquin and diphenylamine

Both substances are used to control superficial scald in apples and pears. This is a physiological disorder associated with long-term storage. For most commercially important varieties of apples and pears which are to be stored for longer than 80 days, treatment is essential to prevent superficial scald. Although many possible alternatives have been tested, ethoxyquin and diphenylamine are the only satisfactory products available. Treatment, usually as a dip or drench, must be applied soon after harvest, as the induction of the disorder occurs within 4-5 weeks. Normally, only fruit destined for long-term storage will be treated.

Both ethoxyquin and diphenylamine are very effective in controlling superficial scald. For technical reasons, the choice of products depends on the variety of the fruit being treated as well as the conditions of treatment and storage. No fruit lots would be treated with both chemicals.

(b) Residues in apples and pears

Although methods of treatment and rates of application vary depending on the variety and the location, it is generally found that pre-storage deposits of the order of 2 mg/kg for ethoxyquin or 4 mg/kg for diphenylamine are necessary for satisfactory control of superficial scald. It is accepted that good agricultural practice requires maximum residue levels of 3 mg/kg for ethoxyquin and 5 mg/kg for diphenylamine immediately after treatment.

Treated food, however, is rarely offered for consumption until after a lengthy period of storage. Residues decline steadily in storage and,

after 80 days, rarely exceed 0.5 mg/kg (ethoxyquin) or 1 mg/kg (diphenylamine); levels about one-tenth of these values are more typical.

(c) Dietary exposure from other sources

In addition to possible residues in apples and pears, ethoxyquin residues may also occur in poultry products as a result of the use of ethoxyquin as a permitted feedingstuffs additive up to 150 mg/kg of the complete feedingstuff (4). On the basis of the limited information available at that time, the 1975 Report of the Scientific Committee for Food calculated that exposure from such use might greatly exceed that from residues in fruit and begin to approach toxicologically significant levels. However, recent data provided by Member States now indicate that residues in poultry products in fact rarely exceed 0.1 mg/kg and constitute a negligible source of intake of ethoxyquin, particularly after cooking.

Diphenylamine residues would not normally be expected to occur in foodstuffs other than apples and pears.

(d) Toxicology

The Committees re-examined the toxicology of both products.

(i) Ethoxyquin

Although no further modern long-term studies have been carried out, the results of a number of recent mutagenicity tests (5) suggest that ethoxyquin has no genotoxic potential. Having antioxidant properties, it shares with other compounds of this nature the anti-mutagenic and anti-carcinogenic activities related to their scavenging action. Although the available studies are not comparable to modern standards, the long-term studies in rats (6) showed no carcinogenic effect.

(4) O.J. No L 270 of 14.12.1970, p. 1

(5) (i) T. Ohta et al. Mutagenicity screening of feed additives in the microbial system. *Mutation Research* 77, 21-30 (1980)

(ii) P.E. Jøner. Butylhydroxyanisole, butylhydroxytoluene and ethoxyquin tested for mutagenicity. *Acta Vet. Scandinavia* 18, 187-93 (1977)

(6) I.I. Osler. EMIC Association 031506 (1977). Reference Overview on Toxicology of Ethoxyquin (received from Monsanto, 1 July 1982)

However, a clear no-effect level cannot be determined from the available data.

(ii) Diphenylamine

The Committees considered the Report of the 1976 FAO/WHO Joint Meeting on Pesticide Residues (7) and endorsed its conclusions on permissible diphenylamine residues. However, the Committees drew attention to the fact that diphenylamine formulations may contain as an impurity the human carcinogen 4-aminobiphenyl and the user hazard should therefore be particularly considered (8).

3. CONCLUSIONS

- (i) Dietary exposure to ethoxyquin residues resulting from use on fruit and as a feedingstuffs additive is lower than previously estimated.
- (ii) The toxicological data now available do not permit the establishment of a clear no-effect level for ethoxyquin which the Committee considers essential to judge the importance to health of the residues found in the diet. It concludes that a thorough 90-days study in rats, carried out according to modern protocol, is necessary and that the results should be made available shortly.
- (iii) Meanwhile, the internationally recommended maximum residue level of 3 mg/kg for ethoxyquin in apples and pears can be provisionally maintained.

-
- (7) Report of the 1976 Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues, WHO Technical Report. Series No 612, 1977. Plant Production and Protection Series No 8, 1977
 - (8) (i) Safe et al. Identification of toxic impurities in commercial diphenylamine. Bulletin of Environmental Contaminants and Toxicology 17, 204, 1977
 - (ii) R. Orgelyck (1975). Research finds aromatic amines exposure cause of increased number of tumours. Health and Safety. September/October p. 46 (Australia)

- (iv) The Committee endorses the maximum residue level for diphenylamine in apples and pears of 5 mg/kg, recommended by the 1976 FAO/WHO Joint Meeting on Pesticide Residues (7) but draws attention to the possible user hazard.

REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON THE USE OF NITROFEN AS A HERBICIDE

(Opinion expressed on 26 July 1983)

BACKGROUND AND TERMS OF REFERENCE

Nitrofen is used in certain Member States as a pre-emergence herbicide on cereal crops and also, to a limited extent, as a pre-emergence treatment of legumes and as an early post-emergence treatment on onions. The Commission requested the Scientific Committee for Pesticides to examine the toxicology of nitrofen in relation to its applications and to give an opinion on the following question:

"Is the use, in accordance with good agricultural practice, of nitrofen prejudicial to human health or the environment and, if so, can such dangers be eliminated by selective reduction of potential exposure?"

DISCUSSION

Nitrofen is fairly stable in some soils but the uptake by plants seems to be very limited (1). All available data indicate that there are no detectable amounts of nitrofen residues in the grains of treated wheat. However, appreciable amounts of residues have been found in lettuce and other vegetables after post-emergence treatment (1, 2). It may be concluded that the potential dietary intake is low.

Nitrofen is rapidly absorbed through the skin from solvent based formulations. It may also be taken up by inhalation and ingestion.

It has been shown to be carcinogenic in two species, producing liver tumours in mice and pancreatic tumours in rats (3). Moreover, it is a strong teratogenic (and fetotoxic) substance in mice and rats (4). In view of the information reported above an operator hazard is apparent, particularly in relation to the teratogenic danger for women operators. The risk for the consumer seems to be low, but cannot be excluded.

CONCLUSIONS

In view of the toxicological considerations mentioned above, the Committee concluded that since the potential hazards to human health associated with the use of nitrofen as a herbicide cannot be eliminated by selective reduction of exposure, the prohibition of the use of nitrofen should be envisaged. However, it was accepted that there is a possible need for a temporary derogation to cover its use as a pre-emergence herbicide on cereals in some countries, provided that strict protective precautions are taken.

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FURTHER REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON MAXIMUM LEVELS FOR CERTAIN PESTICIDE RESIDUES
IN FRUIT AND VEGETABLES

(Opinion expressed on 26 July 1983)

BACKGROUND AND TERMS OF REFERENCE

In the context of its work to revise Annex II of Council Directive 76/895/EEC of 23 November 1976, relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables (1), the Commission invited the Scientific Committee for Pesticides to examine a series of draft maximum levels for certain pesticide residues in fruit and vegetables. These draft levels had been drawn up by its departments in collaboration with experts of Member States and, before submitting proposals to the Council, the Commission requested the Committee in December 1979 to give an opinion on the following questions:

- (a) Do any of the envisaged maximum residue levels present a risk to the health of the consumer? If so, which, and what is the nature of such a risk? What lower level, if any, would be toxicologically acceptable?

- (b) Are any of the envisaged maximum residue levels unnecessarily high, having regard to the needs of good agricultural practice? If so, which, and what lower levels would be more appropriate?

The Committee made an interim report on 1 April 1981 (2) on such levels as it had been able to consider up to December 1980. Since then it has examined the levels relating to further pesticides.

OPINION OF THE COMMITTEE

The Committee examined the draft maximum levels for the pesticide residues set out in the Annex to this Report, on the basis, except where stated, of publicly available data.

The Committee is of the opinion that, save for the cases considered specifically below and for which it has made recommendations or comments, in the light of present knowledge, the draft levels submitted to it by the Commission do not present a hazard for public health and are consistent with the needs of good agricultural practice.

For the sake of clarity, the Annex to this report sets out the draft maximum residue levels of the compounds, amended where appropriate in accordance with its recommendations.

Phosalone

The Committee noted the use of phosalone on vegetables, particularly in integrated pest control and in beekeeping areas. It proposed extending the maximum residue limit of 1 mg/kg envisaged for cabbage, peas, lettuce and tomatoes to all vegetables with the exception of root vegetables and olives, for which it proposed a value at or about the limit of determination in agreement with the residues resulting from supervised trials (3). The Committee also proposed a level of 1 mg/kg for citrus and strawberries in agreement with the residues found in supervised trials.

Piperonyl Butoxide

Piperonyl butoxide is used as a synergist with natural pyrethrins, synthetic pyrethroids and other pesticides. It is one of the methylenedioxyphenyl (MDP) compounds and at high concentrations acts as an inhibitor of hepatic microsomal enzymes. It is of relatively low toxicity to rats, dogs and monkeys and multigeneration studies in rats show no effect at 10,000 mg/kg (4). Liver lesions, of the hyperplastic

type, were produced in the liver of treated animals but there were no carcinomas in rats fed up to 20,000 ppm piperonyl butoxide for 18 months and no increase in tumours in any tissues (5). Other MDP compounds are carcinogenic (safrole, dihydrosafrol myristicin, N-propyl isome) or act as co-carcinogens. In the case of 3,4 benzopyrene, this latter activity is apparently related to demonstrably delayed metabolism of the compound (6).

There have been many metabolic studies on the effects of MDP compounds on a number of chemicals used as insecticides. The normal mode of action of these synergists when used with pyrethrins and pyrethroids seems to be the blocking of oxidative detoxification reactions (2). Although these compounds occur naturally, the human dietary level is unknown. The Committee felt it would be prudent to fix a maximum residue level for piperonyl butoxide. At the present state of knowledge this should be 8 mg/kg for fruit and vegetables but the Committee considered that it is preferable to fix individual levels for various crops.

Quintozene

The Committee was informed that based mainly on environmental considerations concerning certain impurities the use pattern of quintozene in the Community has changed and it has been partly replaced by alternatives.

On the basis of the available data, the Committee concluded that there were no indications of mutagenic, teratogenic or carcinogenic activity (7). It endorsed the ADI of 0.007 mg/kg/b.w. allocated by FAO/WHO Joint Meeting on Pesticide Residues in 1975. However, the Committee, while recommending the maximum residue levels proposed, felt that these figures should also include the main degradation products pentachloroaniline and methylpentachlorophenylsulphide and stressed that the HCB level in technical quintozene should be as low as possible and should not exceed a level of 0.1%. Additionally, technical quintozene should not contain more than 1% pentachlorobenzene.

The Committee reviewed the known uses of quintozene. It noted that the highest residues were found on lettuce and endive after use of quintozene as a soil fungicide. Supervised trial data, carried out in the early 1970s, justify a maximum residue level of 3 mg/kg on lettuce and endive.

Dodine

The Committee supported the levels suggested by the Commission but felt it desirable to comment more generally on N-nitroso-compounds which may be associated with certain nitrogenous pesticides, including dodine.

N-Nitroso-Compounds Problem (8), (9), (11), (12), (13)

Some members of the class of chemicals known as N-nitroso-compounds are among the most potent cancer causing substances discovered. More than 100 N-nitroso-compounds, including nitrosamines, have been tested for carcinogenicity in a wide range of animal species and more than 80% of them have induced tumours of some kind. Most of the compounds are mutagenic in "in vitro" test systems and some of the substances have been shown to be embryotoxic or teratogenic in experimental animals. There is no epidemiological or clinical evidence that the N-nitroso-compounds are carcinogenic to man, but it seems to be highly probable that there is a risk. It is not possible to give a quantitative estimation of this risk because of lack of adequate data.

N-nitroso-compounds have been reported to be present in certain pesticide formulations as impurities (contaminants). These contaminants can be traced back to the chemical synthesis of the pesticides or could be formed in the formulations of certain pesticides due to presence of added nitrite (as a corrosion inhibitor).

In soil, N-nitroso-compounds can arise from the parent pesticides or from metabolites and other nitrogen containing compounds, such as dimethylamine, when a sufficient amount of nitrite is present or is formed by the action of nitrifying or denitrifying bacteria.

There is only limited information on N-nitroso-compounds in plants. It has been demonstrated that the compounds can be taken up by plants, but do not tend to accumulate in green plant material, and the plant level seems to decrease rapidly when the uptake ceases.

Formation of N-nitroso-compounds in animals has been demonstrated but only after administration of unrealistically high doses of nitrite and the nitroso forming agent.

The demonstrated carcinogenicity in animals of some N-nitroso-compounds suggests that human exposure to N-nitroso-compounds from pesticides should be reduced as much as possible. The risk associated with the occurrence of N-nitroso-compounds in, and in connection with the

use of some pesticides, should be related to their risk from other sources.

The Committee therefore recommends that limits on the concentration of N-nitroso-compounds in pesticide preparations, including dodine, should be set at the relevant limits of determination and residue limits for N-nitroso-compounds should also be established for relevant foods and feeds.

ANNEXMAXIMUM RESIDUE LEVELS APPROVED BY THE SCIENTIFIC COMMITTEE FOR PESTICIDES

| : Common or Chemical Name : | Maximum Level (in mg/kg (ppm)) : |
|-----------------------------|--|
| : mevinphos : | : 0.5 pome and stone fruit, leafy vegetables : |
| : : | : 0.2 other fruit, tomatoes, cucumbers : |
| : : | : 0.1 other vegetables : |
| : phosalone : | : 1 citrus and strawberries : |
| : : | : 2 other fruit : |
| : : | : 0.1 root vegetables and olives : |
| : : | : 1 other vegetables : |
| : piperonyl butoxide : | : 8 fruit and vegetables : |
| : : | : : |
| : quintozene : | : 3 lettuce and endive : |
| : including : | : 1 bananas : |
| : pentachloroaniline : | : 0.5 bulbs, tuber and root vegetables : |
| : and methylpentachloro- : | : 0.1 other vegetables : |
| : phenylsulphide : | : 0.01 other fruit : |
| : : | : : |
| : ethion : | : 2 citrus fruit : |
| : : | : 1 other products : |
| : : | : : |
| : formothion : | : 0.2 citrus : |
| : : | : 0.1 other products : |
| : : | : : |
| : dodine : | : 1 pome and stone fruit : |
| : : | : 0.2 other products : |
| : : | : : |

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REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON THE USE OF METHYL BROMIDE AS A FUMIGANT
OF PLANT GROWING MEDIA

(Opinion expressed on 27 July 1983)

BACKGROUND AND TERMS OF REFERENCE

Methyl bromide is used in certain Member States as a fumigant of soil and compost in areas out of doors and indoors. The Commission requested the Scientific Committee for Pesticides to examine the toxicology and environmental impact of methyl bromide and its conversion products in relation to its applications and to give an opinion on the following questions:

1. What are currently the incidence, nature and levels of its residues in foodstuffs and the environment, and what will be the potential exposure of man?

2. Is the use, in accordance with good agricultural practice, of methyl bromide prejudicial to public health or the environment and, if so, can such dangers be eliminated by selective reduction of potential exposure or must a prohibition be envisaged? If the former, by what means could exposure be reduced, having regard to the availability of satisfactory alternative treatments and their toxicological and technological consequences?

DISCUSSION

A. Agricultural Practice

1. Usage

Disinfestation of soil and compost is essential in modern intensive horticultural production, particularly in protected (greenhouse) culture. High capital investment and high labour costs in such intensive horticulture necessitate a high degree of crop specialisation. This involves the growing of only one, or very few kinds of crops, with year-round production and very limited crop rotation. Under these conditions, disease organisms and pests build up in the soil and become a major limiting factor if not controlled.

Control of soil-borne diseases and pests can be achieved by disinfestation of the soil or compost, by the use of replaceable growing media such as peat or rock wool, or by using a hydroponic system such as the Nutrient Film Technique (NFT). Soil disinfestation may be achieved by heat, usually applied as steam, or by chemicals such as methyl bromide.

Fumigation with methyl bromide is the most widely used method of soil disinfestation in protected cropping and is effective against nematodes, insects, fungi and weeds. A recent estimate of annual world production of methyl bromide is about 20,000 tonnes; usage in the Community accounts for 7,000 tonnes of total production (1). Methyl bromide is a gas at normal greenhouse temperatures (boiling point 3.6°C); it is available commercially in small cans or large cylinders as a liquid under pressure. It is normally released as a vapour under plastic sheeting spread over the soil surface and sealed at the edges. The low boiling point and high vapour pressure allow a deep penetration into the soil and rapid dispersion of the gas (2, 3, 4, 5). Application may be from small cans punctured under the sheeting or connected to the treatment area by a special puncturing device and delivery tube. For larger areas, methyl bromide is ducted under the sheeting from cylinders, being either pumped directly as a spray or forced through a heated vaporising coil for distribution as a gas under the sheeting (6, 1).

Current practice in many countries is the application of 50-100 g methyl bromide/m², depending on the soil type and kind of infestation, with the sheeting left in position for 48-96 hours or more. Following

removal of the sheeting, the soil is normally left undisturbed for 24 hours after which it is cultivated and this is followed by a further airing period of 48 hours or more. After this, it is normally considered that there is little risk of residual gas in the soil and planting may commence. However, to reduce the residue of inorganic bromide in the soil - which may give rise to undesirable bromide residues in edible crops or which may be toxic to certain plants, e.g. carnations - the soil needs to be leached with water after removal of the sheeting and airing of the soil. Effective leaching requires flooding of the soil with 350-500 l water/m² applied in one operation. This entails a further delay of several days to allow drying of the soil before planting.

In some countries, methyl bromide in glasshouses is now applied at lower dosage viz 20 g/m² under a gas-tight plastic cover with a longer period of covering and a longer period between application and leaching (6a).

2. Alternatives

The alternatives to methyl bromide fumigation are:

- (a) steaming of the soil
- (b) treatment with other chemicals viz methyl isothiocyanate (MIT) or MIT precursors
- (c) use of alternative growing media.

(a) Steaming - is effective against all soil-borne diseases and pests. Originally, the aim of steaming was to bring all parts of the treated soil to a temperature of 100°C. Greatest thermal efficiency was achieved by injecting the steam through perforated pipes buried below the surface. However, increasing labour costs favoured surface application under a plastic sheet covered with nylon netting. Further adaptations being considered include the use of steam-air mixtures with the aim of heating all of the soil to a lower temperature - approximately 82°C. This would have the advantage of killing most of the undesirable organisms while minimizing unwanted effects, viz destruction of organisms antagonistic to disease organisms, destruction of bacteria involved in nitrogen metabolism, and mobilization of toxic levels of manganese (7). In most

situations, steaming is a satisfactory method technically, but it cannot be used where high water levels occur or where soils have a high organic matter content. Moreover, steaming is now much more costly than methyl bromide fumigation and is not regarded as an economic alternative.

- (b) Chemical alternatives - include methyl isothiocyanate (MIT) and products which generate MIT. Three products have been available, liquid MIT, liquid metham sodium and granular dazomet (8, 8a). These products are potentially effective against fungi, nematodes and weeds; they have lower acute toxicities than methyl bromide and are also less expensive. However, MIT has a low vapour pressure (21 mm Hg at 20°C) and a resultant low rate of diffusion. Consequently, much of the MIT may be broken down before an adequate concentration builds up in all parts of the soil. This is especially so in soils with an organic matter content greater than 5%. There is also a slow dispersion of the gas so that a waiting period of at least 8-10 weeks (and sometimes many months) is necessary before planting. The MIT products are very unsuitable for protected cropping where high capital costs require year-round production with minimum breaks between crops. In fact, the use of MIT and metham sodium for glasshouse crops is now very slight, because of difficulties of application and variability in effectiveness as well as the other factors already mentioned. Dazomet, which is available in granular form, can be easily distributed and worked into the soil and is used particularly in specialised but less intensive outdoor culture or as a supplement to soil fumigation.

Certain systemic nematicides and fungicides may be used in some situations as alternatives but the action spectrum of these materials is much narrower than that of methyl bromide.

- (c) Alternative growing media - the need for soil disinfection can be overcome by the use of replaceable growing media such as peat or rock wool. In order to minimize costs, these media are used in limited amounts contained in troughs, polyethylene "pillows" and so on. The polyethylene also serves as a barrier to avoid infestation of the media from the underlying infested soil. Such arrangements are

suitable for widely spaced crops such as tomatoes or cucumbers but are generally not economic for closely planted crops such as lettuce. Similar limitations apply to the Nutrient Film Technique (NFT) where a shallow stream of liquid nutrients flows along narrow channels and bathes the plant roots.

Such systems are very costly but can be justified in some circumstances for certain crops. They have cultural advantages not related to the problem of soil disinfestation. In general, it cannot be said that they offer an all round alternative to soil disinfestation.

B. Toxicological Data

1. Methyl Bromide

(a) Acute Toxicity

Because of the chemical/physical nature of the compound only limited data are available on the acute toxicity of methyl bromide after oral application (in vegetable oils). The oral LD₅₀ is reported to be in the range 100-200 mg/kg (9). The acute effects in man and experimental animals after accidental or experimental inhalation are well documented. A concentration of 40,000 mg/m³ caused lung oedema, cyanosis, coma and death after only a few minutes exposure. Exposure to 880 mg/m³ for a few hours could be tolerated without severe effects (10, 11, 12, 13, 14, 14a, 15, 16, 17, 18, 18a, 19).

After exposure to 250 mg/m³ for 8 hours, only slight symptoms were observed (10, 20). Exposure to still lower concentrations may give rise to severe headaches, vomiting, dizziness, double vision, accommodation and fixation disturbances and tremors after a latency period of a few hours (17, 21).

(b) Dermal Acute Toxicity

After a single dermal application of liquid methyl bromide, local skin effects may appear in the form of "frost bites" due to the large temperature drop caused by the quick evaporation of the compound. Repeated exposure to gaseous methyl bromide may cause a herpetic type of skin effects, which subsequently may lead to pain, itching and blisters (22).

(c) Sub-Acute and Chronic Toxicity

Inhalation of sub-lethal concentrations of methyl bromide may lead to severe and sometimes irreversible effects on the central nervous system with the following symptoms: headache, nausea, drowsiness, "pseudo"-drunkenness, tremors, hypersensitivity to noise, vision disturbances, speech defects and insomnia. Damage to the central nervous system may lead to paralysis, muscle twitches, convulsions and loss of tactile sense. Recovery can take several months and is sometimes not complete. Watrous (22) reported that 90 labourers exposed to 140 mg/m^3 for 14 days, showed some of the symptoms mentioned above. At this concentration level the effects were reversible.

After chronic or sub-chronic exposure an increased bromide content is found in blood and urine. Furthermore, the content of thiol moieties, albumen and globulin in the blood is changed (15, 23, 24). Methyl bromide methylates the -SH groups of cystein, glutathion and several -SH containing enzymes. Methylation of the -SH groups essential to cellular oxidation has been suggested as the possible mechanism for the neurologic effects of the compound.

In inhalation experiments, animals were exposed to methyl bromide for 6 to 14 months (7-8 hours/day and 5 days/week). No toxic effects were observed in rats, guinea-pigs and monkeys at 130 mg/m^3 or in rabbits at 65 mg/m^3 (9). In more recent studies (25), rats were exposed for 3 weeks (6 hours/day) to 0, 70, 200 and $600 \text{ mg methyl bromide/m}^3$. At 70 mg/m^3 no histopathological changes were found but the animals showed slight behavioural changes. This was considered as the marginal effect level. The authors proposed a safety factor of 100 for extrapolation to man, leading to an acceptable exposure level of 0.7 mg/m^3 , not taking into account the relative difference in lung volume between man and rat and the difference in respiration frequency.

(d) Semi-Chronic Oral Toxicity

Van Velsen et al. (26, 27) studied the semi-chronic oral toxicity of methyl bromide in rats at 0, 0.4, 2, 10 and $50 \text{ mg methyl bromide/kg/day}$ administered (in groundnut oil) by stomach tube for 13 weeks.

At the highest level hyperplasia was found in the cardiac part of the stomach and carcinoma in the epithelium cells. At 0.4 mg/kg/day no toxic

effects of methyl bromide were observed. No measurable effects on the morphology and functioning of the nervous system were observed at any of the dosages. At the highest dosage, changes in the relative weight of the organs with an endocrinic function were observed (26, 27, 28).

(e) Mutagenic Effect

Kramers et al. (29) examined methyl bromide for mutagenic effect in two bacterial systems, two mammalian cells systems (in vitro) and in fruit flies (Drosophila melanogaster). At relatively high exposure rates methyl bromide showed mutagenic effects in four out of the five tests. It was concluded that the compound has to be considered as a mutagenic compound. Relevant low dose long term animal inhalation experiments are lacking; the results of such tests are required before a firm opinion can be reached regarding the potential carcinogenicity/mutagenicity of methyl bromide.

2. Inorganic Bromide

Normal sources of bromide in the diet include water, salt, bread, beer, dairy products and non-root vegetables. In the United Kingdom, intake from beer and bread is probably around 1.5 mg per day (30), and data from the Netherlands suggest that dairy products provide another 1.5 mg per day (31, 31a). It is probable that in these countries around 25% of daily bromide intake is related to the use of methyl bromide as a soil fumigant.

The FAO/WHO ADI (1 mg/kg/day) of bromide reflects the level causing the minimum pharmacological effect rather than being established on the basis of the conventional no effect level (NEL) sought in studies on most pesticides and food additives (32).

More recently, human volunteer studies have suggested that a number of physiological variables may be affected (33, 34). At dosages of 4 and 9 mg/kg/day sodium bromide for 12 weeks in excess of background intake levels, the only deviations from normal were in the blood levels of thyroxine and triiodothyroxine in females. Both of these compounds were increased compared with concurrent controls. No such effects were found in males. Small but significant changes also occurred in the EEG diagrams of both males and females in the 9 mg/kg/day group. However, there was no indication of any abnormal brain activity. No deviations

from normal were observed in the 4 mg/kg/day group; this dosage could be considered to be a no effect level for the parameters considered. Sangster et al (1983) (34) suggested, on the basis of a human volunteer study, to consider an ADI of 0.4 mg/kg by applying usual rules for ADI calculations.

The effects mentioned above may provide a means of detecting bromide exposures but the widespread use of the ion may make interpretation of the detectable physiological events problematical.

C. Dangers and Precautions in Using Methyl Bromide

Recognising the toxicity of methyl bromide itself and the occurrence of residues of inorganic bromide, possible dangers can be considered under the following headings:

1. risks to operators (fumigators) applying methyl bromide
2. pollution of air and water with methyl bromide
3. bromide ion residues in soils, water and edible crops.

1. Risks to Operators

During application of methyl bromide, there may be contamination of the working environment with methyl bromide. This may arise as regular small escapes of gas through the partially permeable polyethylene sheeting or through imperfectly sealed ducts or drains. In addition, accidental leakage through a fault in the fumigation apparatus could lead to occasional short term but severe pollution of the working environment.

To minimize these risks, it is essential that only trained personnel should carry out fumigation operations and that fumigators should wear compressed air breathing apparatus (also called autonomous air flow masks).

Since methyl bromide is colourless and odourless, 2% chloropicrin is included in some formulations to give warning should substantial leakage occur during fumigation or storage. However, the lower vapour pressure of chloropicrin means that dangerous levels of methyl bromide may occur in the atmosphere before there is sufficient chloropicrin to be detected. Therefore, it is desirable that equipment for detecting even low levels of methyl bromide should be used and that operators should undergo regular medical examination, as blood testing can indicate

whether the individual has been exposed to significant levels of methyl bromide.

2. Pollution

- (a) Air - significant air pollution is likely to occur in the glasshouse being treated and in its immediate vicinity, during fumigation and following removal of the sheeting. The first peak can be reduced by a lower application rate of methyl bromide and more gas-tight sheeting. The second peak depends on the dose and period of cover and can be avoided by extending the period of cover to 10 days. For safety of the general public it is desirable that greenhouses should be locked while fumigation is in progress and that notices be displayed prominently, warning of danger in and near the greenhouse.

Only fumigators wearing suitable gas masks should enter the greenhouse to remove the sheeting and they should carry out the airing and safe disposal of the sheeting. It should be the responsibility of the fumigator to decide when the risk area may be re-entered by other personnel.

As a result of recent studies, diffusion of gas through low density polyethylene sheeting has been quantified (35, 36, 37) and more gas-proof materials have been tested (38, 39, 40, 41). As a result, lower doses can be employed without any loss of effectiveness. The combined effect of lower dose and more gas-proof sheeting would lead to reduced levels of air pollution in and near the greenhouse during fumigation. A further reduction in air pollution may be achieved by leaving the sheeting in position for 10 days instead of the customary 3-4 days.

- (b) Water - in considering the hazards to fish and other water organisms from methyl bromide it has been found that the LC_{50} for Poecilia reticulata (48 hours) was 1.2 g/m^3 (42). The average half life of methyl bromide in water was calculated to be 6.6 hours at 11°C (43, 44). Waterways may be polluted mainly by drainage from glasshouses following leaching. Normally the polyethylene sheet is left in position for up to 4 days and leaching is carried out 2 days after removal of the sheet. It has been shown (43, 44, 45, 46, 47) that leaching at this stage led to levels of methyl bromide as high as

9.3 mg/dm³ in the drainage water. However, if the polyethylene was left in position for 10 days and leaching carried out at 4 days and 10 days after removal, the resulting levels in the drainage water were 4.4 and 0.001 mg/dm³ respectively (43, 44).

Therefore, pollution of waterways with unchanged methyl bromide can be reduced to insignificant proportions by lengthening the period between fumigation and leaching to about 20 days. Of course, the resulting prolongation of the period between fumigation and planting would add considerably to the cost of treatment.

The only record of pollution by methyl bromide of water in pipes occurred where low density polyethylene (LDPE) pipes were situated under treated glasshouses: the maximum level found was 0.4 mg/m³. Studies on permeability of water pipes showed that there was no penetration of methyl bromide through metal pipes nor through the connections thereof; there was also no penetration through polyvinyl chloride (PVC) pipes but considerable penetration through LDPE pipes (48). It was further found that the concentrations of methyl bromide occurring at 80 cm depth or at a distance of 2 m from the glasshouse would not cause penetration of measurable amounts of methyl bromide into water pipes of any kind (49). From the foregoing, it appears that the safeguarding of drinking water supplies should not pose a problem.

3. Bromide Ion Residues

- (a) Soils - naturally occurring bromides are generally present in soils at less than 10 mg/kg, the level depending on soil type and geographical situation (50). When applied to soil, methyl bromide is changed by methylation of organic material and to a lesser extent by hydrolysis, resulting in the formation of inorganic bromide. Generally, the bromide formed does not exceed 60 mg/kg, but in soils of high organic matter content much higher levels may occur. In contrast to naturally occurring bromide, that which is derived from methyl bromide is initially only slightly adsorbed to soil particles and is thus mobile in the soil. It is therefore available for uptake by plants and can also be leached. Bromide is leached readily in light soils, but leaching from heavy clay soils is very difficult.

Volumes of water varying from 350 to 500 l/m² may be necessary depending on the soil type and the crop which is to follow.

The amount of bromide which results from fumigation is related to dosage, exposure time, temperature, moisture, structure and texture, and the amount of humus (51). Other factors may also be important so that the probable amount of bromide residue in the soil is difficult to calculate in advance.

(b) Water - studies on water pollution with bromide carried out in the Netherlands based on the older system of high application rates and a short waiting period before leaching (43, 44, 45, 46, 47), resulted in levels of 8.1 g/m³ and 13-20 g/m³ in the waterways into which drainage water from fumigated glasshouses was discharged. Similar results were obtained in a Belgian survey (52). These were much higher than the background values of other surface water in the area. Natural levels found were 0.3 to 0.9 g/m³ in the larger rivers and waterways and 18.4 g/m³ in the North Sea (53, 54). Studies based on the new system of lower application rates, use of gas-tight plastic sheeting and a longer waiting period before leaching, resulted in similar amounts of inorganic bromide in the water (55). The main problem arising from intensive horticulture in the polder areas is the re-use of polluted water for soil leaching. In other areas of Europe, soil fumigation is unlikely to lead to greatly increased levels of bromide in waterways.

(c) Edible crops - the amount of bromide occurring in plant tissue at harvest depends on many factors. The soil factors include the amount of mobile bromide available in the top soil; the soil type, temperature and moisture; the form of available nitrogen; and the level of chloride present (4, 5, 56). Plant species differ in their ability to take up bromide and the distribution to different plant tissues is not uniform. More is translocated to leaves than to fruits and older leaves have higher contents (4, 5, 57-76).

Despite the difficulty of predicting bromide levels in soils or uptake by plants, it is generally found that leaf vegetables, especially when grown as the first or succeeding crop following fumigation and without leaching, very frequently have levels of

bromide in excess of the tolerance levels existing in certain EEC countries (58). Leaching with sufficient water (as dictated by the soil type) should bring about a reduction of 50-80% in bromide in the top 50 cm of the soil and will generally result in much reduced levels of bromide in the succeeding crop (51, 57, 58, 60, 62, 63, 64, 72, 74, 76).

CONCLUSIONS

1. Soil disinfection is essential in intensive horticultural production.
2. At present, there is no suitable chemical alternative to methyl bromide fumigation. Improved steaming methods and the use of artificial media could replace the use of methyl bromide in some situations but are not practical in all prevailing situations.
3. It is recognised that methyl bromide is a highly toxic substance. Its high acute toxicity is fully documented but further information is required regarding its potential carcinogenicity/mutagenicity in low dose long term animal inhalation experiments.
4. The highly toxic nature of methyl bromide coupled with its lack of odour presents a hazard to applicators. It should be applied only by trained and licenced operators equipped with compressed air breathing apparatus. Applicators should have regular medical examinations.
5. Danger to the public from pollution of the air with methyl bromide can be avoided. This necessitates the use of gas-tight plastic covers, low dosage rates and a longer covering period.
6. Pollution of surface water with methyl bromide can be avoided by allowing a longer period between application and leaching. In most circumstances, a three week period should be sufficient.

7. Methyl bromide contamination of drinking water can be avoided by not using low density polyethylene water pipes in or near glasshouses. Metal or PVC pipes are impervious to methyl bromide.
8. Bromide ion residues arising from soil fumigation may result in local water pollution e.g. in polder areas, but in most areas this is likely to be of minor importance.
9. The maximum residue level (MRL) in certain EEC countries for bromide in edible plant tissues can only be accommodated by leaching the soil after fumigation with methyl bromide.
10. The Committee is of the opinion that the necessity for soil disinfection and the absence, at the moment, of suitable alternatives justify the current uses of methyl bromide. It is considered that the risks involved are minimal provided that all recommended precautions are observed.
11. It is recommended that the use of methyl bromide for soil fumigation be reviewed at regular intervals, as acceptable alternatives become available and when low dose, long term animal inhalation experiments are completed.

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REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON THE RESIDUES OF DITHIOCARBAMATES
AND THEIR ASSOCIATED COMPOUNDS

(Opinion expressed on 25 January 1984)

BACKGROUND AND TERMS OF REFERENCE

The dithiocarbamates group of fungicides is extensively used on a world-wide basis including Member States of the European Economic Community, particularly on fruit and vegetable crops. The Commission requested the Scientific Committee for Pesticides to examine the toxicology of the group, particularly its conversion products, in relation to its applications, and to give an opinion on the following questions:

1. What are the incidence, nature and levels of its residue in fruit and vegetables, and what will be the potential exposure of man through the diet?

2. Can the use of the dithiocarbamate group be prejudicial to the consumer and, if so, what measures need to be taken to eliminate such danger by selective reduction of the potential exposure?

DISCUSSION

Dithiocarbamates, especially the ethylene bis(dithiocarbamates) are in several parts of the world, including tropical areas, the most extensively used organic fungicides. In the early seventies, concern about the safety of some of these compounds was expressed, due to the possibility of the associated occurrence of significant amounts of ethylene thiourea (ETU) or propylene thiourea (PTU) either as an impurity in the manufactured product or as a degradation product. The Committee noted the toxicity evaluations on mancozeb, maneb and zineb parent compounds of the Joint Meeting of the FAO experts on pesticide residues in food and the environment and the WHO expert group on pesticide residues (further referred to as JMPR), 1970, 1974, 1977 and 1980, especially the 1980 evaluations (1).

The Committee could accept in principle the conclusions reached in these evaluations, the recommendations made and the acceptable daily intake (ADI) established in 1980 for the parent ethylene bis(dithiocarbamates) mancozeb, maneb, and zineb i.e. 0-0.05 mg/kg body weight (bw), of which not more than 0.002 mg/kg bw may be present as ETU. The ADI applies to mancozeb, maneb and zineb individually or as the sum of any combination of them. It was recognised that in the ADI the impurity ETU occurring in the technical parent compound is taken into account. Some of the oral chronic toxicity studies on which the ADI is mainly based were carried out with technical mancozeb, maneb or zineb, containing about 0.35% ETU.

It has to be recognised that the ETU problem does not occur with regard to the dimethyl dithiocarbamates, such as ferbam and ziram, or with the related compound thiram. ETU does not occur as an impurity in these products and is not formed in the degradation process. Ethylene bis(dithiocarbamate) compounds such as mancozeb, maneb, metiram, zineb and nabam¹⁾ can contain ETU as an impurity; propineb may contain PTU as impurity, a compound which has similar toxic features. ETU is present in commercial formulations in varying amounts, ranging between 0.02-2% in the technical product. In general, mancozeb contains slightly less ETU

1) Nabam is only used as a tank-mix with zinc sulphate ($ZnSO_4$) which results in formation of zineb.

than does maneb or zineb. Further amounts of ETU can be formed before and after application and also, in particular, during cooking processes of commodities containing ethylene bis(dithiocarbamate) residues. When formulated products are stored under warm and humid conditions, the amount of ETU increases. Bontoyan and Looker, 1973 (2) found that initial amounts of 0.02-2% ETU in mancozeb, maneb and zineb increased during a severe storage experiment for 39 days at 49°C and 80% relative humidity to give final contents of 0.13-14.5% ETU. The products containing mancozeb formed the least amounts of ETU.

It is well known that ETU can affect the thyroid. The "no effect level" for the thyroid function in the rat is about 2 mg/kg bodyweight. Freudenthal et al, 1977 (3) found in an experiment on rats a no effect level of 25 mg/kg ETU in the diet, equivalent to 1.78 mg/kg bodyweight. At a feeding level of 125 mg/kg ETU in the diet (equivalent to about 9 mg/kg bodyweight) thyroid hyperplasia was observed. Extensive data on the effect of ETU dose level on the development of thyroid cancers is available (4, 5, 6, 7, 8). The latter authors established an increase of thyroid tumours in male rats in a two years study at ETU dosages of 60 and 200 mg/kg bodyweight and in female rats at 200 mg/kg bodyweight.

In the degradation process of the ethylene bis(dithiocarbamates), besides ETU, another metabolite is formed which also shows effects on the thyroid function, namely DIDT²⁾ = 5,6-dihydro-3H-imidazo-[2,1-c-]1,2,4-dithiazole-3-thione. This product is less toxic than ETU; in rats fed at 100 mg/kg in the diet no adverse effects on clinical parameters (including thyroid function) were noted and gross and histopathological examinations were negative. This level can be considered to be the "no effect level".

Since the early seventies, extensive information has become available on the toxicity of the ethylene bis(dithiocarbamates), ETU and DIDT (=EBIS), on the degradation pathways on plants, in water and soil, and on the identity of the metabolites. Also, data is available on some epidemiological studies in man, i.e. workers in rubber industries where ETU is used extensively. Extensive data also became available on the range of ETU impurities in various commercial formulations of

2) Other authors refer to this metabolite as EBIS. Vonk 1975 (9) elucidated the structure of this metabolite and proposed the code name DIDT.

ethylene bis(dithiocarbamates) shortly after manufacture and on the increase of ETU during storage. Furthermore, much information is available on the fate of the rather "transient" residue of ETU on plants and in the environment (1, 10, 11, 12, 13, 14, 15, 16, 17).

A. Safety Studies

1. Epidemiology

Parkes, 1974 and Smith, 1976 (18, 19) conducted epidemiological studies on workers in the rubber industry where ETU was used extensively. Parkes concluded, on the basis of records relating to national or regional incidence of thyroid cancer, that under the conditions in which ETU has been used in past, there is no risk of man contracting thyroid cancer as a result of industrial exposure to ETU. Smith, 1976 reached the same conclusions based on a detailed study on 1929 workers in rubber compounding plants in the Birmingham area (England). No reports of thyroid cancers were found in the health records of these workers. Bauerman et al, 1980 (20) studied a population of workers, manufacturing and formulating ethylene bis(dithiocarbamates), using a battery of thyroid function tests as well as other parameters to evaluate their health and to detect subtle thyroid function abnormalities. Based on all the available data, it was concluded that there were no abnormalities in thyroid function associated with the exposure to ethylene bis(dithiocarbamates) during their manufacture.

It seems likely that workers involved in the manufacturing and handling of ethylene bis(dithiocarbamates) will be exposed to lower levels of ETU in their daily activity than are workers in the rubber industry. Exposure levels from residues will be still lower.

A few cases of illnesses due to exposure to ethylene bis(dithiocarbamates) during agricultural application or exposure to residues on treated crops have been reported. The following symptoms have been observed: severe oedema of the laryngeal opening, contact dermatitis, eczema, skin irritation. It is unclear whether these observations are associated with the ethylene bis(dithiocarbamates) as such, or with certain adjuvants in the formulations or with ETU. It must be borne in mind that the related compound thiram has shown similar anomalies with certain agricultural workers.

2. Teratogenicity (1, 21)

An increased incidence of foetal malformations in rats was found after administering maneb, mancozeb and propineb by gavage at high dosage rates, i.e. 760 mg/kg bodyweight (bw) and above, on day eleven of gestation. At dosage rates of 380-400 mg/kg bw no malformations were found (22). In several studies, ETU has been shown to induce severe teratogenesis in rats, affecting mainly the nervous system. The existing studies show no clear relationship between thyroid dysfunction and teratogenic effects of ETU. It is suggested that the induction of teratogenicity may be related to short term peak levels of ETU in the maternal blood, shortly after exposure, but this remains unproven (23, 24, 25, 26). In rats given single oral dosages of ETU of 40 mg/kg or greater, teratogenicity was obviously prenatal, whereas only postnatal effects have been observed in offspring of rats fed with 30 mg/kg bw (27, 28). Teratogenic effects have been observed during organogenesis in hamsters at daily dosage levels of 270 mg/kg bw or higher (29), and possibly in rabbits at 80 mg/kg bw (24, 25). Considering the variability in the sensitivity of different species with regard to teratogenic effects, a threshold level for teratogenic effects in man cannot be deduced.

B. Consumer Hazards resulting from ETU Residues

1. Fresh Agricultural Commodities

From several studies and supervised trials, it is obvious that ETU residues in plants, originating from the impurities in commercial ethylene bis(dithiocarbamate) products, or formed on the plant during the degradation process, are transient. At harvest, ETU is either not detectable or present only at very low levels. Only very rarely, after observing "normal" pre-harvest intervals, will the ETU level at harvest exceed the limit of determination (for most commodities of plant origin, 0.01 mg/kg). The JMPR 1977 (1) established, on the basis of the then available data, the following guideline levels:

0.01 mg/kg (at or about the limit of determination): banana pulp,
carrots, celery, lettuce, maize, potatoes, sweet corn

0.02 mg/kg: apples and pears

0.05 mg/kg: tomatoes

0.1 mg/kg : beans (in the pod)

Levels above the limit of determination are only found when short pre-harvest intervals are observed and/or environmental conditions which are unfavourable for residue degradation occur (low temperatures, low light intensity). In general, no measurable amounts are found after observing "normal" pre-harvest intervals (i.e. two weeks; or on fruiting vegetables three days).

In the light of the above-mentioned considerations, while there is at present no urgent need to establish maximum residue limits for ETU in fresh agricultural commodities, all available data suggest that a maximum limit of 0.1 mg/kg ETU should suffice for all fruit and vegetables. However, for many fruit and vegetables lower maximum residue levels could be established without difficulty.

2. Effects of Washing and Cooking (including Heat Processed Food)

It has been shown in several detailed studies and surveys that a substantial part of the ethylene bis(dithiocarbamate) parent residues may be removed from the raw agricultural crop by following a simple washing procedure. Such procedures remove approximately 30-85% depending on the crop type and the intensity of washing. The efficiency of household washing is generally less in leafy vegetables like endive and spinach and better in such commodities as tomatoes, carrots, etc. (30, 31, 32).

ETU is found in most heat processed food, including household cooked food. Heat processing has been shown to convert from 16-23% (weight basis) of the ethylene bis(dithiocarbamate) residues to ETU. After household cooking by boiling in water, some of the ETU may be discarded with the removal of the water; however, it may be expected that with other cooking processes in which little water is used (e.g. steaming) only a small amount of the ETU present after cooking will be discarded (31, 33, 34, 35, 36, 37, 38).

It is considered that the ETU residue in heat processed food or household cooked food as it reaches the consumer's mouth should not exceed the 0.1 mg/kg level. However, the observance of this level in heat processed or household cooked food can be only indirectly controlled by determining the ethylene bis(dithiocarbamate) residue in the fresh

agricultural commodity with a specific method enabling residues arising from the ETU precursors to be distinguished from those due to other dithiocarbamates, thiram and other compounds yielding carbon disulphide (CS_2) in the usual method of analysis. The levels in the fresh commodities as described above will be generally below that level.

3. Analytical Methodology

The CS_2 evolution method is still the method of choice for determining the residues of all dithiocarbamates and any residue expressed in terms of CS_2 may include mancozeb, maneb, metiram, zineb (including zineb as a tank-mix derived from nabam + $ZnSO_4$), propineb, ferbam and ziram.

However, the analytical results may include CS_2 from other sources e.g. thiram and other compounds or natural plant ingredients yielding CS_2 in the analysis.

The CS_2 method does not distinguish between ETU precursors and other compounds yielding CS_2 in the analysis, and residues from both these sources may occur on one crop (examples are apples, endive, tomatoes). It is therefore desirable that the residue of dithiocarbamates and related compounds in commodities which are generally cooked or heat processed should be expressed both in terms of CS_2 and in terms of a specific method which separates the ETU precursors from the other dithiocarbamates, thiram etc. Such a procedure would enable the CS_2 evolution method still to be used as the routine method; only when the CS_2 level found in the fresh product exceeds the level considered to be "safe" from the point of view of ETU development by cooking would the sample need to be additionally analysed by the "specific" method for ETU precursors.

Such specific methods are now available, e.g. the method developed by Greve et al, 1978 (39) in which the residue of ETU precursors is determined and expressed as 1,2-bis(pentafluorobenzamido)ethane. A residue of e.g. 0.5 mg/kg CS_2 arising exclusively from ethylene bis(dithiocarbamates) corresponds to 1.3 mg/kg 1,2-bis(pentafluorobenzamido)ethane. The validation of this and other suitable methods in the Community by collaborative studies should be encouraged and given priority. The present maximum residue limits in terms of CS_2 for crops which are generally cooked will need some adjustment if the above procedure is adopted. Those commodities which are generally cooked or

heat processed should not contain ETU precursors which yield more than 0.5 mg/kg CS₂ by the usual method of analysis (equivalent to about 1 mg parent compound/kg).

CONCLUSIONS AND RECOMMENDATIONS

1. ETU has an effect on the thyroid which may result in tumours in this organ although probably not being a primary carcinogen. Hence, the Committee considers that some restriction on its intake is desirable.
2. In the light of the diverging toxicity of different types of dithiocarbamates, both qualitatively and quantitatively, and recognising that the consumer hazards which may arise from residues of these compounds have only been measured until now with a non-specific method of residue analysis yielding CS₂, it is highly advisable to have the availability of specific methods of analysis enabling residues arising from ETU precursors to be distinguished from those due to other dithiocarbamates, thiram or natural plant ingredients yielding CS₂ in the analysis.
3. Such specific methods of analysis are especially needed for commodities which are generally cooked and on which considerable amounts of ethylene bis(dithiocarbamate) residues may be expected at harvest.
4. Promising specific methods for the determination of ethylene bis(dithiocarbamates), the ETU precursors, are now available, e.g. the method developed by Greve et al, 1978, in which the ETU precursors are determined and expressed as 1,2-bis(pentafluorobenzamido)ethane. This method, and any other promising method, needs to be validated within EEC countries. Member States are urgently invited to take part in such validation.
5. When the method or methods mentioned under 4. are proved to be suitable, residue data on crops which are generally cooked should be obtained from supervised trials on which ethylene

bis(dithiocarbamates) were applied, whether or not together with other dithiocarbamates and related compounds and from other controlled applications. Preferably, the residues should be determined both with a specific method and a sophisticated general method yielding CS₂.

6. Based on the assessment of the data referred to in the preceeding paragraph, residues from dithiocarbamates and related compounds, on commodities which are generally cooked, should be expressed in terms of CS₂ and also in the moiety which is determined with the specific method of choice for the ethylene bis(dithiocarbamates); the latter method distinguishes ETU precursors from other CS₂ yielding sources.
7. Those commodities which are generally cooked or heat processed should not contain ETU precursors which yield more than 0.5 mg/kg CS₂ by the usual method of analysis (equivalent to about 1 mg parent compound/kg). Where practice shows this is not the case, it will be necessary to examine the use patterns of these compounds and possibly alter them.

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FURTHER REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON THE APPLICATION OF ETHOXYQUIN AND DIPHENYLAMINE TO
APPLES AND PEARS FOR THE TREATMENT OF SUPERFICIAL SCALD

(Opinion expressed on 12 July 1984)

BACKGROUND AND TERMS OF REFERENCE

Ethoxyquin was studied in 1975 by the Scientific Committee for Food (SCF) (1). It identified inadequacies of the long-term toxicity and reproduction data and noted the absence of a clear no-effect level. The Committee concluded that the continued use of ethoxyquin could be accepted on a temporary basis. Re-examination of the situation by the Scientific Committee for Pesticides (SCP) in collaboration with SCF in 1982 (2) included a review of a number of recent mutagenicity tests and new data on dietary exposure. The Committee at that time concluded that the mutagenicity tests suggested that ethoxyquin had no genotoxic potential, and that having antioxidant properties, it shares with other compounds of this nature the anti-mutagenic and anti-carcinogenic activities related to their scavenging action. The Committee noted that, although the available long-term toxicological studies in rats were not comparable with modern standards, they showed no carcinogenic effect.

The Committee also concluded that the dietary exposure to ethoxyquin residues resulting from the use on fruit and as a feedingstuffs additive was lower than previously estimated; residues in fruit after storage were found rarely to exceed 0.5 mg/kg and those in poultry products 0.1 mg/kg. The opinion of the Committee was that the toxicological data

then available did not permit the establishment of a clear no-effect level for ethoxyquin which the Committee considered essential to judge the importance to health of the residues found in the diet. It concluded that a thorough 90-days study in rats, carried out according to a modern protocol was necessary, and that the results should be made available at an early date. No such study has been carried out.

The attention of the Commission has been drawn to further more recently available toxicological data, and it has therefore requested the SCP in collaboration with the SCF to review its opinion of December 1982, "Report on the application of ethoxyquin and diphenylamine to apples and pears for the treatment of superficial scald".

DISCUSSION

Since the 1982 opinion, limited evidence of mutagenicity has been provided by the findings that ethoxyquin could induce mutations in Salmonella typhimurium strains TA 1538 and TA 98 in the presence of S-9 mix (3, 4). Furthermore, it increased the 3,2'-dimethyl-4-aminobiphenyl (DMAB) induced mutagenicity in TA 100, whereas there was no effect in TA 98. Other antioxidant compounds, such as α -tocopherol and butylated hydroxytoluene by themselves inhibited the DMAB induced mutagenicity in TA 98. In these experiments, none of the test components by themselves proved mutagenic in TA 98 or TA 100 with or without S-9 activation (5).

In model studies on the mechanism of tumour promotion, ethoxyquin was included among other antioxidants being studied. At doses of 1% and higher, ethoxyquin effectively reduced the number of γ -glutamyltranspeptidase positive foci induced by an initiating dose of the hepatic carcinogen diethylnitrosamine administered to F 344 rats (6).

Another recent event which is of significance in the re-assessment of the safety of ethoxyquin is the finding of forestomach tumours when BHA was fed to rats for two years (7) and the appearance of liver tumours in rats fed BHT for their lifespan (8). Both antioxidants had been previously reported to be non-mutagenic in a number of in vitro mutagenicity tests. These substances had long been known to have anti-mutagenic and anti-tumorigenic activity in animal experiments, so that these results following exposure at high levels for life were unexpected.

CONCLUSIONS

In the light of the newly available data, the Committee has reconsidered its earlier opinion. Whilst none of these new findings is alarming in itself, the Committee is of the opinion that in the context of an overall evaluation of the data, a 90-days study would be insufficient to assess the safety of the substance, including the establishment of a clear no-effect level. The Committee has, therefore, concluded that a chronic toxicity/carcinogenicity study according to a modern protocol taking account of the antioxidant properties of ethoxyquin would be required to evaluate fully the safety of ethoxyquin and its residues in food. While awaiting the results of such a study, the Committee can recommend that the internationally recommended maximum residue level of 3 mg/kg for ethoxyquin in apples and pears be provisionally maintained.

The SCF fully agrees with the views expressed by the SCP in this report and fully endorses the conclusions reached.

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FURTHER REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON THE MAXIMUM LEVEL OF MALEIC HYDRAZIDE IN VEGETABLES

(Opinion expressed on 12 July 1984)

BACKGROUND AND TERMS OF REFERENCE

The toxicology of maleic hydrazide was studied in 1981 by the SCP (1). The Committee was subsequently invited to review the question, particularly regarding the presence of free hydrazine in commercial formulations.

OPINION OF THE COMMITTEE

The Committee reviewed the toxicology of maleic hydrazide (MH) and concluded that there is no evidence that MH containing less than 1.5 mg/kg hydrazine is carcinogenic (2). It therefore approved the residue level of 10 mg/kg maleic hydrazide for onions, for formulations in compliance with this specification. This conclusion is only valid for residues arising from the use of the sodium or potassium salts, and is not valid for other formulations, particularly the diethanolamine salt, which show larger hydrazine variations than found either in the sodium or potassium salt formulations. Moreover, the amount of hydrazine impurity may increase during the shelf-life of the diethanolamine salt formulation (3). In the case of the sodium or potassium salt, the hydrazine content shows little or no tendency to increase, and will

remain below the recommended maximum level of 1 mg/kg; it is expected that this figure could be set at a lower level in the near future. At the moment the registration and use of formulations of maleic hydrazide other than the sodium or potassium salts should be strongly discouraged.

The Committee noted that since the usage, as far as the fruit and vegetables covered by Directive 76/895/EEC are concerned, is limited to treatment of onion haulms, the maximum level for other products should be set at or about the lower limit of determination (1 mg/kg).

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REPORT OF THE SCIENTIFIC COMMITTEE FOR PESTICIDES
ON CARBENDAZIM/BENOMYL/THIOPHANATE-METHYL RESIDUES
IN FRUIT AND VEGETABLES

(Opinion expressed on 12 July 1984)

BACKGROUND AND TERMS OF REFERENCE

In the context of its work to revise Annex II of Council Directive 76/895/EEC of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables (1), the Commission invited the Scientific Committee for Pesticides to examine draft maximum levels in and on fruit and vegetables for the group of fungicides carbendazim, benomyl and thiophanate-methyl. The draft levels were as follows

Maximum Levels in [mg/kg (ppm)]

| | | | |
|--------------------|------------------|-----|---------------------------|
| | | 7 | : citrus fruit |
| carbendazim |) sum expressed | 5 | : berries, stone and pome |
| benomyl |) as carbendazim | | fruit, leaf vegetables |
| thiophanate-methyl |) | 1 | : other fruit |
| | | 0.1 | : root vegetables |
| | | 2 | : other vegetables |

The Commission requested the Committee to give an opinion on the following questions:

- (a) Do any of the envisaged maximum residue levels present a risk to the health of the consumer? If so, which, and what is the nature of such a risk? What lower level, if any, would be toxicologically acceptable?
- (b) Are any of the envisaged maximum residue levels unnecessarily high, having regard to the needs of good agricultural practice? If so, which, and what lower levels would be more appropriate?

DISCUSSION

A full ADI (0.08 mg/kg b.w.) was allocated to thiophanate-methyl by the JMPR in 1975 (2) and reconfirmed in 1977 (3). In 1983 it established an ADI for carbendazim of 0.01 mg/kg b.w. and for benomyl of 0.02 mg/kg b.w. (4).

Recent scientific evidence indicates that some conflicting results of toxicological studies on the technical products of carbendazim and benomyl (5) may have been due to varying contents of some impurities. Two amino phenazines have been identified by (unspecified) Ames-test as mutagenic (6). Insufficient information is available on the carcinogenic potential of these impurities. Until the existing doubts on these matters are resolved, it is recommended that such impurities should be restricted to as low a level as is practicable.

From earlier toxicological studies it can be concluded that approximately the same type of toxic actions are produced by carbendazim, benomyl and thiophanate-methyl (7). Borderline-effect dosages usually cause decrease in body weight in rats and dogs and occasionally increase liver enzyme activities (AP, GPT) in the serum. Higher dose levels have, at least in some studies, clear somatic actions on the liver (histopathological changes), the testicles (reduced spermatogenesis and degeneration) and the ovaries. In addition, thiophanate-methyl has been reported to cause an increase in thyroid weight and enlarged colloidal epithelial cells.

Studies on reproduction, teratogenicity and embryotoxicity were negative with carbendazim and thiophanate-methyl but benomyl caused growth retardation after oral administration to pregnant and/or weaning

rats, weight reduction of the testicles and accessory sex glands, and terata in the pups (7, 8, 9).

From the 3-month and 2-years studies on rats and dogs, levels causing no observable toxicological effects have been derived by the JMPR for carbendazim and benomyl in 1983 (4), and for thiophanate-methyl in 1975 (2).

Carbendazim:

Rat: 500 mg/kg diet equivalent to 25 mg/kg b.w.
Dog: 100 mg/kg diet equivalent to 2.5 mg/kg b.w.

Benomyl:

Rat: 2 500 mg/kg diet equivalent to 125 mg/kg b.w.
Dog: 100 mg/kg diet equivalent to 2.5 mg/kg b.w.

Thiophanate-methyl:

Rat: 160 mg/kg diet equivalent to 8.0 mg/kg b.w.
Dog: 50 mg/kg b.w./day.

Mutagenicity and Carcinogenicity

In the majority of studies designed to measure gene mutations, benomyl and carbendazim were not mutagenic, but in some studies weak mutagenic activity was observed.

It is accepted that these compounds exhibit their fungicidal activities by binding to microtubular proteins and therefore inhibit spindle functions, but the existence of a threshold level is uncertain. Particularly in yeast and fungi this phenomenon is consistent with the function of nondisjunction. The induction of micronucleated erythrocytes may also be related to the inhibition of the spindle. No evidence exists that benomyl, carbendazim or thiophanate-methyl interfere directly with DNA (5, 12).

The presence of the two identified impurities in the technical compounds of carbendazim and benomyl used in some of the tests has been claimed to be responsible also for the contradictory results in the mutagenicity tests (6). Newer manufacturing methods of technical material have resulted in lower levels of both impurities (7).

It is possible that the hepatic carcinogenic effects, observed in some of the carbendazim and benomyl long-term mouse feeding studies, resulted from the presence of the above mentioned impurities (6, 13, 14). Furthermore, these studies showed no increased tumour rate in organs other than the liver. In the case of thiophanate-methyl, an 18 month feeding study of mice showed no increased tumour incidence. In rats and other species, long-term studies with these compounds showed no hepatic tumorigenic effects (15).

The significance of enhanced liver cell tumours observed only in mice is questionable. The induction of these tumours could also be a secondary effect resulting from hepatotoxic and/or enzyme inductive action or by means of specific metabolic pathways. The induction rate moreover varies greatly with the strain used. In studies carried out with carbendazim and benomyl on mice, hepatic tumour induction was found at dose levels of 500 mg/kg diet and higher (14, 15).

The need for elucidation of the possible mode of action of carbendazim, carbendazim precursors and their impurities on mouse liver is obvious. The Committee was uncertain about the establishment of a no-effect level with regard to the effects on the liver in mice because of the varying biological effects.

Maximum Residue Limits

The Committee concluded that the levels proposed by the Commission are of the order of the MRLs that would be appropriate to cover current usage patterns. However, it also considered that differentiated values, some at a lower level, would probably be more suitable, particularly for some berries, stone fruits and leafy vegetables, such levels being consistent with good agricultural practice.

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