RESIDUE REVIEWS

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RESIDUE REVIEWS

Residues of Pesticides and Other
Contaminants in the Total Environment

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Preface

That residues of pesticide and other contaminants in the total environment are of concern to everyone everywhere is attested by the reception accorded previous volumes of "Residue Reviews" and by the gratifying enthusiasm, sincerity, and efforts shown by all the individuals from whom manuscripts have been solicited. Despite much propaganda to the contrary, there can never be any serious question that pest-control chemicals and food-additive chemicals are essential to adequate food production, manufacture, marketing, and storage, yet without continuing surveillance and intelligent control some of those that persist in our foodstuffs could at times conceivably endanger the public health. Ensuring safety-in-use of these many chemicals is a dynamic challenge, for established ones are continually being displaced by newly developed ones more acceptable to food technologists, pharmacologists, toxicologists, and changing pest-control requirements in progressive food-producing economies.

These matters are of genuine concern to increasing numbers of governmental agencies and legislative bodies around the world, for some of these chemicals have resulted in a few mishaps from improper use. Adequate safety-in-use evaluations of any of these chemicals persisting into our foodstuffs are not simple matters, and they incorporate the considered judgments of many individuals highly trained in a variety of complex biological, chemical, food technological, medical, pharmacological, and toxicological disciplines.

It is hoped that "Residue Reviews" will continue to serve as an integrating factor both in focusing attention upon those many residue matters requiring further attention and in collating for variously trained readers present knowledge in specific important areas of residue and related endeavors involved with other chemical contaminants in the total environment. The contents of this and previous volumes of "Residue Reviews" illustrate these objectives. Since manuscripts are published in the order in which they are received in final form, it may seem that some important aspects of residue analytical chemistry, biochemistry, human and animal medicine, legislation, pharmacology, physiology, regulation, and toxicology are being neglected; to the contrary, these apparent omissions are recognized, and some pertinent manuscripts are in preparation. However, the field is so large and the interests in it are so varied that the editors and the Advisory Board earnestly solicit suggestions of topics and authors to help make this international book-series even more useful and informative.

"Residue Reviews" attempts to provide concise, critical reviews of timely advances, philosophy, and significant areas of accomplished or needed endeavor in the total field of residues of these and other foreign chemicals in any segment of the environment. These reviews are either general or specific, but properly they may lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, regulation, and toxicology; certain affairs in the realm of food technology concerned specifically with pesticide and other food-additive problems are also appropriate subject matter. The justification for the preparation of any review for this book-series is that it deals with some aspect of the many real problems arising from the presence of any "foreign" chemicals in our surroundings. Thus, manuscripts may encompass those matters, in any country, which are involved in allowing pesticide and other plant-protecting chemicals to be used safely in producing, storing, and shipping crops. Added plant or animal pest-control chemicals or their metabolites that may persist into meat and other edible animal products (milk and milk products, eggs, etc.) are also residues and are within this scope. The so-called food additives (substances deliberately added to foods for flavor, odor, appearance, etc., as well as those inadvertently added during manufacture, packaging, distribution, storage, etc.) are also considered suitable review material. In addition, contaminant chemicals added in any manner to air, water, soil or plant or animal life are within this purview and these objectives.

Manuscripts are normally contributed by invitation but suggested topics are welcome. Preliminary communication with the editors is necessary before volunteered reviews are submitted in manuscript form.

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July 19, 1976

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J.D.G.

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By

G. VETTORAZZI*

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I. Introduction

The present review includes the carbamate and organophosphorus (OP) compounds considered by the WHO Expert Committee on Pesticide Residues and the FAO Working Party of Experts on Pesticide Residues (also referred to as the Joint Meeting) up to 1974 and represents the second in a series of general reviews comprising the major categories of pesticide chemicals evaluated by the Joint Meeting[1].

Repeatedly the Joint Meeting has recommended the issuing of a single volume containing monographs of all pesticides for which a toxicological evaluation has been carried out by the meeting (WHO/FAO 1969 a, p. 12; 1970 a, p. 14; 1971 a, p. 20). While awaiting the implementation of this recommendation this review has been designed to assist those working in

* Food Additives (Food Safety) Unit, World Health Organization, Geneva, Switzerland.

[1] For the first review see Residue Reviews 56, 107 (1975).

this field in identifying and locating important aspects related to the toxicology of carbamate and OP pesticides. The reader's attention is called to the following points which should be kept in mind while perusing the present review: (a) the page numbers indicated after a quotation refer to the English text of the document, (b) acceptable daily intake (ADI) figures are reported by indicating only the maximum value for the sake of brevity, (c) similarly, the sources of information have been condensed into two acronyms (WHO/FAO) and should be read "Joint FAO/WHO Meeting on Pesticide Residues" while, in quotations, WHO (World Health Organization) preceeds FAO (Food and Agriculture Organization) to indicate that the source refers to the document issued by WHO (in this respect, it should be noted that the same document is published by FAO and WHO separately), (d) the sources of information contain the collective views of international groups of experts and do not necessarily represent the decisions or the stated policy of the two organizations involved, and (e) an attempt has been made by the Joint Meeting to indicate in each monograph what further information would assist in making a complete assessment of the possible consumer hazard; when the meeting recommended ADIs or tolerances on only a "temporary" basis, due to insufficiency of information on any particular question, the nature of such additional information has been indicated and has been described as "required" because it is considered to be essential before ADIs or tolerances can be recommended or confirmed; in other cases the information is stated to be "desirable."

It is hoped that this work will be of help to the scientific community to which these reviews are directed.

II. Cholinesterase-inhibiting substances

a) Criteria for evaluation

The major criterium for evaluation of some OP compounds and carbamates is the *in vivo* inhibition of ChE and aliesterase (WHO/FAO 1969 a, p. 9). In discussing on which elements an establishment of acceptable daily intake should be based the Joint Meeting observed that, in the past, ADIs have occasionally been established for pesticides for which the results of long-term studies in animals were not available. The scientific literature contains an increased number of examples of substances that have been presumed to be safe solely on the basis of chemical, metabolic, and short-term toxicological information, but that have subsequently been shown to exhibit toxic effects in long-term studies in laboratory animals. The meeting therefore agreed that only in exceptional circumstances should ADIs be established in the absence of satisfactory data from long-term animal studies. However, for some OP pesticides it may still be logical to base ADIs on data from adequate short-term *in vivo* studies of anti-ChE activity, since such activity is the most sensitive criterion of effect for these com-

pounds. Nevertheless, data from long-term experiments are usually required to provide assurance of the safety of moieties of molecules other than those responsible for the anti-ChE activity (WHO/FAO 1972 a, p. 7).

For animals exposed to OP compounds that inhibit ChE, depression of ChE activity in plasma, erythrocytes, and various other tissues is usually the most sensitive measure of toxicity. However, a few OP compounds with low acute toxicity and certain carbamates produce reversible inhibition of ChE. Measurement of depression of ChE activity in blood or tissues may then be unreliable as an indicator of potential toxicity. The Meeting felt that because the anti-ChE effect of certain carbamates was reversible and because many of them have only short half-lives, information on plasma concentrations and biological half-lives of such compounds was required. Such information is needed to elucidate discrepancies between signs of cholinergic stimulation and measurements of apparent *in vivo* inhibition of ChE activity by such compounds as propoxur (WHO/FAO 1974 a, pp. 14–15). The Meeting, more recently, recommended that ChE activity in the brain, as well as erythrocytes and plasma, should be measured in the future during short- and long-term feeding studies on ChE-inhibiting pesticides (WHO/FAO 1975 a, p. 11). In this regard, a WHO Scientific Group noted that ChEs in both plasma and erythrocytes are markedly reduced by a number of substances, including many OP compounds used as pesticides. There is, however, poor correlation between the ChE levels and the signs and symptoms of toxicity. Blood ChE levels may be useful as an indication of exposure to a substance with anti-ChE activity, but not as an invariable guide to the degree of intoxication present or predicted. In general, lack of correlation between the activity of a particular enzyme, or the level of a chemical or one of its metabolites at some specific site (e.g., in blood), and the occurrence of toxic signs or symptoms may be due to the fact that the more significant change in activity or concentration is occurring at some other site (e.g., at nerve endings). Thus, the changes being measured may correlate with changes at the more significant site only over a small part of the range. Alternatively, some other enzyme, chemical, or metabolite may be more closely related to the toxic mechanism. Although changes in blood ChE levels may be helpful in toxicological studies, it is important that further research should be done to relate the indices used as closely as possible to the biochemical changes concerned in bringing about the toxic effects (*WHO Scientific Group* 1967, pp. 17–18). In this respect, the desirability of determining the usefulness of aliesterases inhibition, and of electroencephalographic criteria for assessing the effects of the ChE-inhibiting pesticides, was mentioned (WHO/FAO 1973 a, p. 8; 1975 a, p. 11). Furthermore, to permit evaluation or reevaluation of certain OP compounds, there is a need for information from pharmacokinetic and enzyme kinetic studies, for information on the time-course of ChE inhibition *in vivo*, and for studies of aliesterase inhibition and of interactions with other organophosphates. Information is also needed on the influence of exposure to enzyme-inducing agents on the response to OP compounds (WHO/FAO 1974 a, p. 14).

b) Potentiation

The problem of interactions between pesticides, between pesticides and drugs, and between pesticides and other environmental chemicals has been examined in detail (WHO/FAO 1968 a, pp. 37–40; 1971 a, p. 9). It was recognized that data from acute potentiation studies on ChE-inhibiting pesticides are of little direct value in assessing ADIs for man. However, they are of value in assessing potential hazards to persons applying pesticides. It has been noted that no evidence of potentiation was detected when several acutely synergistic pairs of compounds were administered in short-term tests on experimental animals at low dietary levels. It has been suggested that consideration be given to the usefulness of inhibition of carboxylesterases ("aliesterases") as a criterion for assessing a no-effect level of these compounds, which inhibit carboxylesterases at lower concentrations than those that inhibit cholinesterases. Recent short-term feeding studies have demonstrated that a large number of OP insecticides are more potent inhibitors of liver and serum carboxylesterases than of cholinesterases. Although there is strong evidence that inhibition of carboxylesterases is a factor in the potentiation of the acute toxicity of insecticides and other chemicals that depend upon these enzymes for their detoxification, the physiological significance of carboxylesterase inhibition is still unknown (WHO/FAO 1973 a, p. 8).

c) Other aspects

The importance of observations in man which may influence and allow use of considerably smaller safety factors (WHO FAO 1969 a, p. 10; 1970 a, p. 15; 1971 a, p. 20; 1975 a, p. 9) and the role of data from accidental poisoning (WHO/FAO 1971 a, p. 9) have been repeatedly described. The general principles adopted in the evaluation of metabolites may be found in WHO/FAO (1969 a, p. 7; 1970 a, p. 3; 1974 a, p. 16). For problems connected with the variability of composition of certain pesticides and impuirites in technical grade products which may account for toxic effects, refer to WHO/FAO (1969 a, p. 7; 1970 a, pp. 4–5; 1975 a, p. 15). The mechanism of action of carbamate and OP compounds is described in WHO (1962, p. 8; 1967, pp. 10–11). Signs and symptoms of poisoning diagnosis of intoxication as well as causes of death in anti-ChE poisoning may be found in WHO (1962, pp. 9–11 and 14; 1967, pp. 11–14). Therapy of poisoning by ChE-inhibitors (WHO, 1962, pp. 11–14; 1967, pp. 23–26 and pp. 58–59; 1973, pp. 49–50), methods for determining the activity of ChEs in human blood (WHO 1967, pp. 14–22; 1975, pp. 15–16) as well as methods for determining metabolites in urine (WHO 1967, pp. 22–23) are other chapters that may be usefully consulted.

III. Toxicological reviews

Table I supplies a listing of the carbamate and OP pesticides for which an ADI has been established by the Joint Meeting up to and including 1974. The names used are either the names recommended by the International

Organization for Standardization (ISO) or the chemical names. The latter are in accordance with the rules of the International Union of Pure and Applied Chemistry (IUPAC) as interpreted by the American Chemical Society in *Chemical Abstracts*. Table II contains an alphabetical list of common names and chemical names included in this review.

The summaries presented here indicate the existing reviews on each compound as a result of the activities of the Joint Meeting and provide, in a condensed manner, the most important conclusions, deliberations, and comments made by the Joint Meeting in carrying out the toxicological evaluation of pesticide chemicals. Based on the information contained in the documents reviewed, reference is also made to the toxicological studies available to the Joint Meeting and brief remarks are made with regard to major uses, technical product and formulations, and the natures of residues in food.

Concerning references to WHO specifications for pesticides for public health use, FAO specifications for pesticides for agricultural use, and CIPAC methods of analysis, the reader is referred to the excellent review published by LOWE and STILES (1974)[2].

a) Carbamates

1. Benomyl.—Benomyl is a relatively new systemic broad-spectrum fungicide. It is marketed as wettable powders and used in foliar applications, seed treatments, and post-harvest dipping procedures on a great number of food and forage crops.

The compound is easily hydrolyzed into the relatively stable methyl-2-benzimidazole (MBC) which is considered to be the major fungitoxic principle of benomyl. The formulated compound may hydrolyze if not kept dry in storage.

A fungicidal effect additional to the MBC activity is claimed to be connected with the simultaneous release of volatile butyl isocyanate. A further metabolic product found in plants is 2-aminobenzimidazole formed from MBC. Cow feeding trials show that hydroxylated methyl benzimidazole carbamates are formed from benomyl with MBC as the probable intermediate metabolite. MBC and possibly 2-AB are likely to be the primary chemical entities to be absorbed from the alimentary tract following the ingestion of benomyl residues (WHO/FAO 1974 b, p. 46).

No acceptable daily intake (ADI) was established for benomyl because the data available for consideration by the Joint Meeting were not sufficient to permit a toxicological assessment of this compound (WHO/FAO 1974 a, p. 19). The work deemed necessary before an ADI for man can be established comprises full toxicological data. In addition, areas indicated as worth pursuing include further development of analytical methods to permit separate determination of benomyl and metabolites when present together,

[2] D. A. LOWE and A. R. STILES (1974); Progress in standardization: 1. Pesticides, Nomenclature, specifications, analysis, use and residues in food. Bull. Wld. Hlth. Org. **49**, 169–204 (1973).

Table I. *Listing of carbamate and organophosphorus pesticides and their toxicological evaluation.*

Compound	Maximum acceptable daily intake for man (mg/kg bw)	Remarks
azinphos-methyl	0.0025	The ADI is not applicable to the ethyl derivatives nor to the oxygen analogue (WHO/FAO 1969 b).
bromophos	0.006	Temporary evaluation: the compound is scheduled for reevaluation in 1977 (WHO/FAO 1973 b).
bromophos-ethyl	0.003	Temporary evaluation: the compound is scheduled for reevaluation in 1975 (WHO/FAO 1973 b).
carbaryl	0.01	
carbophenothion	0.005	Temporary evaluation: the compound is scheduled for reevaluation in 1976 (WHO/FAO 1973 b). ADI relates to carbophenothion, its sulfoxide, and its sulfone, together with the corresponding oxygen analogue, if present, expressed as carbophenothion (WHO/FAO 1973 b).
chlorfenvinphos	0.002	Expressed as the sum of *alpha* and *beta* isomers of chlorfenvinphos (WHO/FAO 1973 a—Annex 1).
chlorpyrifos	0.0015	—
coumaphos	0.0005	Temporary evaluation: the compound is scheduled for reevaluation in 1975 (WHO/FAO 1973 b).
crufomate	0.1	—
demeton and related compounds (-*S*-methyl, -*S*-methylsulfon, oxydemeton-methyl)	0.005	The total demeton-*S*-methyl, demeton-*S*-methyl sulfone and oxydemeton-methyl (demeton-*S*-methyl sulfoxide) should not exceed this figure (WHO/FAO 1974 b).
diazinon	0.002	To be determined and expressed as the parent compound (WHO/FAO 1973 a—Annex 1).
dichlorvos	0.004	—
dimethoate	0.02	As dimethoate and its oxygen analogue expressed as dimethoate (WHO/FAO 1973 a—Annex 1).
dioxathion	0.0015	*Cis*- and *trans*-isomers of principal active ingredient to be determined and expressed as sum of both (WHO/FAO 1973 a—Annex 1).
disulfoton	0.001	Temporary evaluation: the compound is scheduled for reevaluation in 1975 WHO/FAO 1974 b). To be determined as disulfoton (WHO/FAO 1973 a—Annex 1).
ethion	0.005	To be determined as ethion and its oxygen analogue and expressed as ethion (WHO/FAO 1973 a—Annex 1).
fenamiphos	0.0006	It refers to fenamiphos, its sulfoxide, and its sulfone, expressed as fenamiphos (WHO/FAO 1975 a—Annex 1).
fenchlorphos	0.01	It refers to fenchlorphos and oxygen analogue: to be expressed as fenchlorphos (WHO/FAO 1973 a—Annex 1).

Table I. (*Continued*)

Compound	Maximum acceptable daily intake for man (mg/kg bw)	Remarks
fenitrothion	0.005	It refers to fentrothion and its oxygen analogue (WHO/FAO 1975 a—Annex 1).
fensulfothion	0.0003	It refers to fensulfothion, its oxygen analogue, the oxygen analogue sulfone, and the sulfone to be determined and expressed as fensulfothion (WHO/FAO 1973 a—Annex 1).
fenthion	0.0005	Temporary evaluation: this compound is scheduled for reevaluation in 1975 (WHO/FAO 1972 b).
formothion	0.02	ADI is applicable only to the parent compound. The metabolites dimethoate and omethoate should be referred to separately established ADIs (WHO/FAO 1973 a—Annex 1).
malathion	0.02	—
methidathion	0.005	Temporary evaluation: this compound is scheduled for reevaluation in 1975 (WHO/FAO 1973 b).
mevinphos	0.0015	*Cis*- and *trans*-isomers to be determined and expressed as the sum of both (WHO/FAO 1973 a—Annex 1).
monocrotophos	0.0003	—
omethoate	0.0005	Temporary evaluation: this compound is scheduled for reevaluation in 1975 (WHO/FAO 1972 b). See also related compounds, dimethoate and formothion.
parathion	0.005	—
parathion-methyl	0.001	Temporary evaluation: this compound is scheduled for reevaluation in 1975 (WHO/FAO 1973 b). The ADI is applicable to the oxygen analogue as well (WHO/FAO 1969 b).
phosalone	0.006	—
phosphamidon	0.001	Expressed as the sum of phosphamidon and its desethyl derivative (WHO/FAO 1973 a—Annex 1).
pirimiphos-methyl	0.005	Temporary evaluation: this compound is scheduled for reevaluation in 1976 (WHO/FAO 1975 b).
propoxur	0.02	—
thiometon	0.005	Temporary evaluation: this compound is scheduled for reevaluation in 1976 (WHO/FAO 1974 b). To be determined as thiometon-sulfone and expressed as thiometon (WHO/FAO 1974 a—Annex 1).
thiophanate-methyl	0.08	To be determined as thiophanate-methyl and its metabolite MBC and expressed in terms of the latter (WHO/FAO 1974 a—Annex 1).
trichlorfon	0.01	Temporary evaluation. See under ferbam.

Table II. *Common and chemical names of pesticides mentioned in text.*

Common or trade name	Chemical name
azinphos-ethyl	phosphorothioic acid, *O,O*-diethyl *S*-[(4-oxo-1,2,3-benzotriazin-3(4*H*) methyl] ester
azinphos-methyl	phosphorothioic acid, *O,O*-dimethyl *S*-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl) methyl ester
benomyl	carbamic acid, [1-[(butylamino) carbonyl]-1*H*-benzimidazol-2-yl] methyl ester
bromophos	phosphorothioic acid, *O*-(4-bromo-2,5-dichlorophenyl) *O,O*-dimethyl ester
bromophos-ethyl	phosphorothioic acid, *O*-(4-bromo-2,4-dichlorophenyl) *O,O*-diethyl ester
carbaryl	1-naphthalenol methylcarbamate
carbendazim	carbamic acid, 1*H*-benzimidazol-2-yl methyl ester
carbophenothion	phosphorothioic acid, *S*-[[4-chlorophenyl)thio]methyl] *O,O*-diethyl ester
chlorfenvinphos	phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl)-ethenyl diethyl ester
chlorpropham	carbamic acid, (3-chlorophenyl)-1-methylethyl ester
chlorpyrifos	phosphorothioic acid, *O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) ester
Chlorthion®	phosphorothioic acid, *O*-(3.chloro-4-nitrophenyl) *O,O*-dimethyl ester
coumaphos	phosphorothioic acid, *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) *O,O* diethyl ester
crufomate	phosphoramidic acid, methyl-2-chloro-4-(1,1-dimethylethyl)-phenyl methyl ester
demeton-*S*-methyl	phosphorothioic acid, *S*-2-(ethylthio)ethyl *O,O*-dimethyl ester
demeton-*S*-methylsulfone	phosphorothioic acid, *S*-[2-(ethylsulfonyl)ethyl]*O,O*-dimethyl ester
diazinon	phosphorothioic acid, *O,O*-diethyl *O*-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] ester
dichlorvos	phosphoric acid, 2,2-dichloroethenyl dimethyl ester
dimethoate	phosphorodithioic acid, *O,O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] ester
dioxathion	phosphorodithioic acid, *S,S'*-1,4-dioxane-2,3-diyl-*O,O,O',O'*-tetraethyl ester
disulfoton	phosphorodithoic acid, *O,O*-diethyl *S*-[2-(ethylthio) ethyl] ester
ethion	phosphorodithioic acid, *S,S'*-methylene *O,O,O',O'*-tetraethyl ester
fenamiphos	phosphoramidic acid, (1-methylethyl)-ethyl 3-methyl-4-(methylthio)-phenyl ester
fenchlorphos	phosphorothioic acid, *O,O*-dimethyl *O*-(2,4,5-trichloro-phenyl) ester
fenitrothion	phosphorothioic acid, *O,O*-dimethyl *O*-(3-methyl-4-nitrophenyl) ester
fensulfothion	phosphorothioic acid, *O,O*-diethyl *O*-[4-(methylsulfinyl)-phenyl ester
fenthion	phosphorothioic acid, *O,O*-dimethyl *O*-[3-methyl-4-(methylthio)phenyl] ester

Table II (*Continued*)

Common or trade name	Chemical name
formothion	phosphorodithioic acid, *S*-[2-formylmethylamino)-2-oxo-ethyl] *O*,*O*-dimethyl ester
leptophos	phosphonothioic acid, phenyl-*O*-(4-bromo-2,5-dichlorophenyl) *O*-methyl ester
malathion	butanedioic acid, [(dimethoxyphosphinothioyl)-thio]-diethyl ester
methidathion	phosphorodithioic acid, *S*-[(5-methoxy-2-oxo-1,3,4-thiadiazol-3(2*H*)-yl)methyl] *O*,*O*-dimethyl ester
mevinphos	2-butenoic acid, 3-[dimethoxyphosphinyl)oxy]-methyl ester
monocrotophos	phosphoric acid, dimethyl 1-methyl-3-(methylamino)-3-oxo-1-propenyl ester
omethoate	phosphorothioic acid, *O*,*O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl ester
oxydemeton-methyl	phosphorothioic acid, *S*-[2-(ethylsulfinyl)ethyl] *O*,*O*-dimethyl ester
parathion	phosphorothioic acid, *O*,*O*-diethyl *O*(4-nitrophenyl) ester
parathion-methyl	phosphorothioic acid, *O*,*O*-dimethyl *O*-(4-nitrophenyl) ester
phosalone	phosphorodithioic acid, *S*-[(6-chloro-2-xox-3(2*H*)-benzoxazolyl) methyl] *O*,*O*-diethyl ester
phosphamidon	phosphoric acid, 2-chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester
pirimiphos-methyl	phosphorothioic acid, *O*-[2-(diethylamino)-6-methyl-4-pyrimidinyl] *O*,*O*-dimethyl ester
propham	carbamic acid, phenyl-1-methylethyl ester
propoxur	phenol 2-(1-methylethoxy)-methyl carbamate
thiometon	phosphorodithioic acid, *S*-[2-(ethylthio)ethyl] *O*,*O*-dimethyl ester
thiophanate-methyl	carbamic acid, [1,2-phenylenebis(iminocarbonothioyl)] bis-dimethyl ester
trichlorfon	phosphonic acid, (2,2,2-trichloro-1-hydroxyethyl)-dimethyl ester
trichloronat	phosphonothioic acid, ethyl-*O*-ethyl *O*-)2,4,5-trichlorophenyl ester
vamidothion	phosphorothioic acid, *O*,*O*-dimethyl *S*-[2-[[1-methyl-2-(methyalamino)-2-oxoethyl]thio]-ethyl]

information on residues in food in commerce, and on the nature and level of residues in poultry and eggs following the feeding of benomyl residues in ratios (WHO/FAO 1974 a, p. 34 and b, p. 46).

No review on the toxicology of this compound is available; however, one review on its residues in food can be found in WHO/FAO 1974 b, p. 33.

2. Carbaryl.—Carbaryl is a methyl carbamate insecticide extensively used around the world on a variety of agricultural crops, ornamentals, turf, forest, livestock, and poultry as well as on certain other nonagricultural pests. It has been in use since 1959 and the strongest influence on the use patterns of carbaryl in recent years has been a marked reduction in the general use of certain low-cost organochlorine insecticides for which it is often

selected as a replacement. This pesticide is metabolized by a similar route in the man, rat, guinea-pig, sheep, pig, and monkey. However, it is metabolized in a different manner in the dog (WHO/FAO 1967 b, p. 17).

It has been reported that carbaryl has adverse effects on reproductive physiology in several animal species and an increased urinary amino acid to creatinine ratio in man were regarded as matters of concern. Several studies on the effect of carbaryl on reproduction were reviewed in 1973 (WHO/FAO 1974 b, p. 146). No effect on reproduction was observed in Rhesus monkeys. Studies in several species of animals showed that administration by gavage is more likely to affect reproduction than administration in the diet. Further work was reported which indicated disturbance in the thyroid gland following short-term treatment. In longer term studies, disturbances of carbohydrates and protein metabolism, liver function and endocrine function and effects on gonads were observed. In addition, behavioral changes have been reported indicating possible sympathomimetic effects on peripheral systems. However, new data with respect to the effects of carbaryl on renal function have not been reported. Toxicological data were considered sufficient for recommending an ADI for man of 0.01 mg/kg bw. No-effect levels were determined in rat (10 mg/kg bw) and man (0.06 mg/kg bw), respectively (WHO/FAO 1974 b, p. 146).

Regarding occupational or accidental exposure, about 50 known cases of illness allegedly due to carbaryl, but no fatalities, have been reported. Fewer than 12 of the cases showed clear-cut ChE inhibition. Three cases were due to accidental ingestion by children and one to an intentional overdose taken by an experimenting scientist (an oral dose of 250 mg resulting in moderately severe poisoning); the remaining cases were related to overexposure to dusts or sprays by process workers, formulators, or applicators. In the applicators, onset of illness consistently resulted in cessation of work. Symptoms were usually subsiding by the time medical observation was obtained and were gone within 3 or 4 hr, whether or not atropine was administered (WHO 1967, pp. 45–46). The estimation of free and conjugated 1-naphthenol excreted in the urine has been used to measure exposure of workers to carbaryl. This metabolite is measured colorimetrically or by a GLC technique (WHO 1975, p. 13).

Several carbaryl metabolites have been identified in mammals after administration of ^{14}C-labelled carbaryl.

In plants, several carbaryl metabolites are essentially similar to metabolites that have been identified in mammalian metabolism studies. These metabolites occur as glycosides in plants whereas they occur as glucuronides and sulphates in animals (WHO/FAO 1968 b, p. 17). Acute LD_{50} and 7-day no-effect levels for these metabolites in rats have been determined and demonstrate that they possess lower toxicities than the parent compound (WHO/FAO 1970 b, p. 51).

Extensive data show that the metabolic pathways of carbaryl are the same whether the pesticide is absorbed into plants or applied by surface treatments. Data are available which showed that residues on fruit and vegetables were greatly reduced (up to 75%) by home processing or canning

(WHO/FAO 1970 b, p. 53). Data on the behavior of carbaryl residues make it appear that (1) storage would have little effect on residues and (2) washing, heating, cooking, or baking would likely reduce levels by a substantial amount (WHO/FAO 1974 b, p. 168). Areas of research indicated as worth pursuing include further studies to elucidate the effects of carbaryl on renal function and further studies to resolve the differences on observations of different investigators on reproductive physiology, especially with regard to neuro-endocrine and behavioral changes (WHO/FAO 1974 a, p. 37; b, p. 170).

Six reviews on the toxicology of this compound (WHO/FAO 1964, p. 132; 1965 b, p. 31; 1967 b, p. 31; 1968 b, p. 15; 1970 b, p. 45; 1974 b, p. 141), six reviews on its residues in food (WHO/FAO 1967 b, p. 39; 1968 b, p. 18; 1969 b, p. 35; 1970 b, p. 51; 1971 b, p. 3; 1974 b, p. 147), and one review on its safe use (WHO 1967, pp. 45–46) are available.

3. Carbendazim.—Carbendazim, or methyl-2-benzimidazole carbamate (MBC), was introduced as a commercial fungicide in 1972 for specific treatments. It is available as wettable powder formulations or as dispersions containing 60 to 20% a.i., respectively. It is recognized as the chemical entity which is mainly responsible for the fungitoxic activity of the systemic benzimidazole fungicides, benomyl and thiophanate-methyl. In effect, MBC is formed as the major metabolite in and on plant material. Accordingly, the antifungal effects of carbendazim are described as practically similar to the two mentioned chemicals, *i.e.*, it is a broad-spectrum, systemic fungicide which is active against molds, rots, and blight. It is claimed effective against apple scab, powdery mildew, botrytis, and penicillium-induced decay of citrus fruits.

This compound has low acute toxicity. Its fate in animals is not known and needs to be clarified. Limited studies on mice and rats have indicated no mutagenic potential or adverse effect on the male sex organs, although high levels resulted in testicular damage. In short-term studies in the rat and the dog an increase in the liver weight was the most significant finding. No histological changes were seen in the liver. Because of the observed effect on the liver and as no long-term or reproduction studies were available an ADI for man was not established (WHO/FAO 1974 b, p. 184).

The residue levels reported generally reflect the dosages applied and the decline of residue levels mostly follows the pattern which characterizes growth dilution. It is chemically stable and metabolizes to a limited extent in plants and soils. The only detected metabolite is 2-aminobenzimidazole which constitutes less than 5% of the total residues in leaves. It is readily absorbed through the root systems of plants and, accordingly, there may be a possibility of unintentional uptake into subsequent crops. Data are available which indicate that carbendazim may not reach through the soils into ground water (WHO/FAO 1974 b, p. 189). Indicated areas for further research include long-term studies to investigate chronic toxicity and carcinogenicity, reproduction and teratogenicity studies, metabolic and distribution studies in several species, elucidation of the effect on the liver in female rats and dogs, information on the nature and level of residues in meat, milk, and eggs,