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[1] T = Toxicology
R = Residue and analytical aspects
E = Evaluation of effects on the environment

* New compound
** Evaluation in periodic review programme

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JOINT MEETING ON PESTICIDES

Geneva, 18-27 September 1995

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ABBREVIATIONS WHICH MAY BE USED

(Well-known abbreviations are not necessarily included)

Ache	acetylcholinesterase
acute RfD	acute reference dose
ADI	acceptable daily intake
AFI(D)	alkali flame-ionization (detector)
ai	active ingredient
ALAT	alanine aminotransferase
	approx. approximate
ASAT	aspartate aminotransferase
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
bw (not b.w.)	body weight
c	centi- (x 10^{-2})
C.A.	Chemical Abstracts
CAC	Codex Alimentarius Commission
CAG	Core Assessment Group
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
ChE	cholinesterase
CNS	central nervous system
cv	coefficient of variation
CXL	Codex Maximum Residue Limit (Codex MRL). See MRL.
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-)
DP	dustable powder
DS	powder for dry seed treatment
EBDC	ethylenebis(dithiocarbamate)
EC	(1) emulsifiable concentrate
	(2) electron-capture [chromatographic detector]
ECD	electron-capture detector
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
ERL	extraneous residue limit
ETU	ethylenethiourea
F_1	filial generation, first
F_2	filial generation, second
f.p.	freezing point
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FID	flame-ionization detector
FPD	flame-photometric detector

g (not gm)	gram
ìg	microgram
GAP	good agricultural practice(s)
GC-MS gas	chromatography - mass spectrometry
G.I.	gastrointestinal
GL	guideline level
GLC	gas-liquid chromatography
GLP	Good Laboratory Practice
GPC	gel-permeation chromatography
GSH	glutathione
GV	Guideline Value (for pesticides in drinking-water)
h (not hr)	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography - mass spectrometry
IBT	Industrial Bio-Test Laboratories
i.d.	internal diameter
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IR	infrared
IRDC	International Research and Development Corporation (Mattawan, Michigan, USA)
ISO	International Organization for Standardization
i.v.	intravenous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues)
LC	liquid chromatography
LC_{50}	lethal concentration, 50%
LC-MS	liquid chromatography - mass spectrometry
LD_{50}	lethal dose, median
LOAEL	lowest observed adverse effect level
LOD	limit of determination (see also "*" at the end of the Table)
LSC	liquid scintillation counting or counter
MATC	Maximum Acceptable Toxic Dose
MFO	mixed function oxidase
ìm	micrometre (micron)
min (not min.)	minute(s)
MLD	minimum lethal dose
M	molar

mo (not mth.)	month(s)
MRL	Maximum Residue Limit. MRLs include draft MRLs and Codex MRLs (CXLs). The MRLs recommended by the JMPR on the basis of its estimates of maximum residue levels enter the Codex procedure as draft MRLs. They become Codex MRLs when they have passed through the procedure and have been adopted by the Codex Alimentarius Commission.
MS	mass spectrometry
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NCI	National Cancer Institute (United States)
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NP(D)	nitrogen-phosphorus (detector)
NTE	neuropathy target esterase
o	*ortho* (indicating position in a chemical name)
OP	organophosphorus pesticide
p	*para* (indicating position in a chemical name)
PEC	Predicted Environmental Concentration
PHI	pre-harvest interval
ppm	parts per million. (Used only with reference to the concentration of a pesticide in an experimental diet. In all other contexts the terms mg/kg or mg/l are used).
PT	prothrombin time
PTT	partial thromboplastin time
PTU	propylenethiourea
RBC	red blood cell
RfD	*see* acute RfD
rT_3	3,3′,5′-tri-iodothyronine (cf. T_3: 3,5,3′-tri-iodothyronine)
s.c.	subcutaneous
SC	suspension concentrate (= flowable concentrate)
SD	standard deviation
SE	standard error
SG	water-soluble granule
SL	soluble concentrate
SP	water-soluble powder
sp./spp.	species (only after a generic name)
sp gr (not sp. gr.)	specific gravity
t	tonne (metric ton)
T_3	3,5,3′-tri-iodothyronine (cf. rT_3: 3,3′,5′-tri-iodothyronine)
T_4	thyroxine
TADI	Temporary Acceptable Daily Intake
TER	Toxicity Exposure Ratio

tert	tertiary (in a chemical name)
TLC	thin-layer chromatography
TMDI	theoretical maximum daily intake
TMRL	Temporary Maximum Residue Limit
TPTA	triphenyltin acetate
TPTH	triphenyltin hydroxide
TSH	thyroid-stimulating hormone (thyrotropin)
UDMH	1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine)
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet
WG	water-dispersible granule
WHO	World Health Organization
WP	wettable powder
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to
*	(following residue levels, e.g. 0.01* mg/kg): level at or about the limit of determination

PESTICIDE RESIDUES IN FOOD

REPORT OF THE 1995 JOINT FAO/WHO MEETING OF EXPERTS

1. INTRODUCTION

A Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups (JMPR) was held in Geneva, Switzerland, from 18 to 27 September 1995. The FAO Panel and the Toxicological Core Assessment Group had met in preparatory sessions on 13-15 and 14-15 September respectively.

The Meeting was opened by Dr. M. Mercier, Director of the International Programme on Chemical Safety (IPCS), on behalf of the Directors-General of FAO and WHO. In his opening remarks, Dr. Mercier emphasized the consolidation and expansion of the work of the JMPR to encompass the review of studies appropriate for the assessment of occupational and public health exposure and environmental fate and ecotoxicity. He also reminded the participants of two recent consultations, one to revise the *Guidelines for predicting dietary intake of pesticide residues* and the other to consider *The application of risk analysis to food standards issues*, both of which provided recommendations that will have an impact on the work of the JMPR.

The Meeting was held in pursuance of recommendations made by previous Meetings and accepted by the governing bodies of FAO and WHO that studies should be undertaken jointly by experts to evaluate possible hazards to man arising from the occurrence of residues of pesticides in foods. The reports of previous Joint Meetings (see References, Section 7) contain information on acceptable daily intakes (ADIs), maximum residue limits (MRLs) and general principles for the evaluation of the various pesticides. The supporting documents (Residue and Toxicological Evaluations) contain detailed monographs on these pesticides and include comments on analytical methods. The present Meeting was convened to consider a further number of pesticides together with items of a general or a specific nature. These include (1) items for clarification of recommendations made at previous Meetings or for reconsideration of previous evaluations in the light of findings of subsequent research or other developments, (2) identification of issues relating to the establishment of drinking-water quality guidelines, and (3) environmental assessments of 5 pesticides.

During the Meeting the FAO Panel of Experts was responsible for reviewing pesticide use patterns (good agricultural practices), data on the chemistry and composition of pesticides and methods of analysis for pesticide residues, and for estimating the maximum residue levels that might occur as a result of the use of the pesticides according to good agricultural practices. The WHO Toxicological Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides. The recommendations of the Joint Meeting, including further research and information, are proposed for use by national governments, international organizations and other interested parties. The Environmental Core Assessment Group identified risks to organisms in the environment.

2. GENERAL CONSIDERATIONS

2.1 MODIFICATIONS TO THE AGENDA

Abamectin was added to the agenda for toxicological assessment.

Several WHO consultants considered written comments concerning the JMPR monographs on chlorothalonil (study of reproductive toxicity in rats) and azinphos-methyl (cholinesterase inhibition) raised by a member of the US Delegation at the 27th Session of the CCPR. The WHO Secretariat has replied directly to the member of the US Delegation.

2.2 JOINT MEETING ON PESTICIDES

JMPR evaluations

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has a long history of providing scientific advice to the CCPR and to FAO and WHO Member States relating to acceptable daily intakes of pesticide residues and maximum residue levels of these pesticides in food commodities. In recent years, the JMPR has comprised the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO expert groups on pesticide residues. The WHO Expert Group is supported by the International Programme on Chemical Safety (IPCS), which is a joint programme of the WHO, the United Nations Environment Programme (UNEP), and the International Labour Organisation (ILO).

Proposals of the Consultation for the Joint Meeting on Pesticides

In 1992, the IPCS convened a Consultation to advise on improved procedures for the timely and efficient assessment of pesticide safety that could reasonably be dealt with at the international level so that international organizations could be more responsive to the needs of countries and other users of information on pesticide safety. Comprehensive safety assessments should also include occupational safety and environmental hazards, with emphasis on the most timely and efficient use of available resources and on avoiding duplication of effort.

The Consultation proposed the integration of relevant pesticide activities into a *Joint Meeting on Pesticides* (JMP). These activities include those of the IPCS, in co-ordination with relevant pesticide activities of the FAO, the United Nations Industrial Development Organization (UNIDO) and the Organization for Economic Co-operation and Development (OECD). The Consultation recommended that the scientific assessment of toxicological and other relevant scientific data be undertaken primarily by a Core Assessment Group (CAG). The CAG would evaluate the toxicological data relevant to human and environmental effects, identify key studies or deficiencies, and recommend appropriate toxicological end-points and scientific issues that are to be taken into further consideration.

The Consultation recommended that the resulting evaluation would, in turn, form the basis for consideration of these pesticides by three appropriately composed panels that would convene as necessary. The panels would deal with public and occupational health, the environment, and pesticide residues in food and drinking-water. The panels would elaborate relevant guidance on exposure on the basis of their particular expertise.

The Consultation proposed that the Panel on Public and Occupational Health would consider matters such as hazard classification, labelling, directions for safe use, and first aid for acute pesticide poisoning, as well as occupational exposure limits, monitoring techniques and analytical methods for assessing occupational exposure. The proposed Panel on Residues in Food and Drinking-water would continue to serve the needs of the CCPR and would, in addition, recommend guideline limit values for contamination of drinking-water by pesticides, when necessary. It was further proposed that the Environmental Panel would assess environmental exposure, safe use and disposal, environmental monitoring, and relevant analytical methods.

Current activities

The first CAG meeting was held in Geneva in October-November 1994, at which time a summary report was produced[i]. Five Environmental Health Criteria monographs, which summarize the data on the five pesticides that were evaluated, will soon be published.

At the present Meeting activities are being expanded to include the assessment of toxicological studies in which substances are administered by the dermal route and by inhalation, and several pesticides are undergoing environmental assessment. Issues relevant to the establishment of drinking-water quality guidelines for several pesticides were also highlighted by the present Meeting.

The present Meeting identified issues relating to the establishment of drinking-water quality guidelines as an activity of the CAG, not the Residues Panel as envisaged by the Consultation. Guideline values themselves were not established, because issues other than toxicity and environmental transport, persistence and fate must be taken into account when they are established (see Annex IV).

At the present Meeting, the Residues Panel met at the same time as the CAG. This is not the procedure that was envisaged at the Consultation but is more closely related to the work of the traditional JMPR. To be consistent with the terminology that has been developed for the JMP, IPCS activities related to the toxicological and environmental assessments carried out by the traditional JMPR will now be carried out by the CAG, which supersedes the *WHO Expert Group*.

In view of the commitment of the FAO and WHO to provide expert advice to the Codex Alimentarius Commission, the Joint Meeting that considers pesticides referred to it by the CCPR will continue to concentrate on residues in food. To avoid confusion and to emphasize its mandate this Meeting will, at least in the short term, continue to refer to itself as the *Joint Meeting on Pesticide Residues* (JMPR).

2.3 TOXICOLOGICAL CRITERIA FOR ESTIMATING GUIDANCE VALUES FOR DIETARY AND NON-DIETARY EXPOSURE TO PESTICIDES

The JMPR has established procedures for the risk assessment of pesticide residues in food. The toxicological end-point used in these procedures is traditionally the ADI, which is defined as "An estimate of the amount of a pesticide that can be ingested daily over a lifetime without appreciable health risk."

As discussed in Section 2.6, concern has been expressed in recent years about the procedure to be adopted for assessing acute dietary risk. The outcome of the JMPR's consideration is the acute dietary reference dose (acute RfD), which reflects an analysis of the available data to establish a reference dose, analogous to the ADI, but relevant to acute exposure resulting from, for example, consumption of a single item or a meal-sized portion of a commodity containing a pesticide residue.

Sectors of the human population may be exposed to pesticides from sources other than food. Farm workers, for example, can be exposed during the mixing, loading and/or application of pesticides to a crop and/or during harvest. The general population may be exposed as bystanders during the commercial application of pesticides or during the use of pesticides in their own gardens.

During the evolution of the JMPR into the JMP, it was envisaged that the CAG and the associated panels would become involved in risk assessment for other sectors of the population. The first JMP and the present Meeting considered the possible processes of risk assessment to be used for exposures of consumers other than dietary exposure. There are evidently many problems which are often difficult to resolve with the available data, such as:

- integration of multiple routes of exposure
- "seasonal" occupational exposure
- route-to-route extrapolation of results of toxicological studies

In an attempt to contribute to the process of assessing risks from different sources the Meeting decided that, in addition to establishing ADIs, it would tabulate the relevant data for each pesticide in a format designed to draw attention to the crucial toxicological results relevant to human exposure. This approach is described in more detail in the report of the 1994 meeting of the CAG.

2.4 REPORT OF THE ENVIRONMENTAL CORE ASSESSMENT GROUP (ENVIRONMENTAL CAG)

The Environmental Core Assessment Group (Environmental CAG) has a role to identify risk to organisms in the environment. Effects should be identified at the levels of individual organisms, populations, communities and ecosystems where this is possible. The environmental fate of the compounds is assessed; this is only relevant to establish the likely exposure for these organisms. Where data on fate and bioaccumulation indicate likely contamination of the food chain leading to human exposure, this information will be considered by another working group - the FAO Residues Panel.

The Environmental CAG has carried out hazard identification and exposure response for the compounds. Laboratory testing, together with field studies where available, have been used for this purpose. Conditions of the tests, such as climate, have been taken into account where these

might lead to different conclusions in different climatic zones. The Evaluation for each compound has an introductory text outlining the main route of entry to, degradation in, and loss from different environmental compartments. This is followed by quantitative risk assessments for aquatic and terrestrial environments. Organisms chosen for the risk assessment are representative of these compartments. Organisms are, inevitably, those for which laboratory tests are available.

A quantitative risk assessment has been made comparing either reported or estimated concentrations of the compounds in different environmental compartments. Models for estimating Predicted Environmental Concentration (PEC) are not standardized internationally. Three different models have been used by this year's Environmental CAG: the EPPO system, the USES model from The Netherlands and a US EPA model (GENEEC). All of these approaches are broadly similar and differ only in detail. It is proposed that guidelines to authors of monographs should be established before the next Environmental CAG meeting to define acceptable approaches. Using these models, PECs have been compared with observed toxicity values in acute and chronic tests to calculate Toxicity Exposure Ratios (TERs, the toxicity value divided by the exposure concentration) as an indication of risk. A Risk Classification system has been standardized to avoid confusion to the readers of the Evaluations. The one chosen was the USES system which assigns risk phrases to the TERs at each change in the order of magnitude. The phrases are TER 0.01 to 0.1 "very large", 0.1 to 1 "large", 1 to 10 "present", 10 to 100 "low" and 100 to 1000 "negligible".

The TERs have been calculated using the PEC for the environmental compartment relevant to each selected species or group of species.

The Environmental CAG should ideally address the issues of risk to individual species (non-target organisms likely to be exposed during use in the wider environment) and to ecosystem function. Special attention should be paid to endangered or sensitive species. It has been recognized that information on which to base such wider estimation of risk is frequently lacking. The Environmental CAG has recognized this situation and presented one example risk assessment on which local assessments can be based given extra local information. For many countries, particularly in the developing world, local information will not be available. Either this can be generated as a response to the example risk assessment presented or the limitations of the risk assessment should be clear from the transparent methodology for deriving TERs. This is an unacceptable position in the long term and further discussion should be initiated internationally on possible mechanisms of extrapolation of risk assessment results.

It is clear that the Environmental CAG requires available information on both environmental fate and ecotoxicity studies in the laboratory and field from industry. Ideally, this should include data indicative of effects in tropical and other climatic zones. It is recognized that this will not be possible in the majority of cases. Industry is asked to provide data packages which have been prepared for other purposes, such as national or regional assessments of the compound. This will allow the example risk assessment to be performed. Industry is also asked to provide extra information where this is available. It is also recognized that industry is providing data on fate to both the Environmental CAG and the FAO Panel. Both will require the same data in this respect but will use them to generate different information on exposure. It will be appreciated if industry can continue to provide these data to both groups.

Additive and synergistic interactions with other chemicals should be addressed by the Environmental CAG. However, there will seldom be sufficient information available to consider such interactions. It is recommended that this question be addressed by the Secretariat for future meetings.

2.5 DATA REQUIREMENTS FOR ESTIMATING ADIs AND MRLs

2.5.1 Toxicological evaluation of pesticide exposure by the Core Assessment Group

For over 30 years, the WHO Expert Group has been evaluating the available toxicological database for the active ingredients of pesticides for the purpose of estimating Acceptable Daily Intakes (ADIs) of their residues in food and/or feed. In the past year, the Group's charge has been expanded to include, as data and circumstances dictate, an estimation of the acute dietary reference dose (acute RfD) and the characterization of additional toxicological criteria for a series of non-dietary exposures (short-term, medium-term and long-term), such as occupational situations and home use.

In the light of these new responsibilities and in order to be more transparent and explicit in articulating their data requirements for addressing all situations, the 1995 Core Assessment Group (CAG) developed the following lists of information that would be needed. They are divided into two general categories. The first category lists those data that are critical or essential to the conduct of an adequate (initial) evaluation toxicologically-based criteria for all pesticides. The second category reflects information to be developed, for example, on the basis of (1) the results of studies reviewed in Category 1; (2) the nature of the pesticide under evaluation (e.g. cholinesterase inhibitor); (3) the expectation that exposure via a specific route is possible and, potentially, a significant risk (e.g. inhalation during application of a pesticide with a high vapour pressure); and (4) desire to understand the mechanism of action underlying a particular effect.

It is acknowledged that many of these data, particularly in Category 1, are developed in accordance with “standardized” testing guidelines. The CAG supports in principle the generation of information in accordance with such guidelines, in so far as they represent the current state of the science, are accompanied by a satisfactory level of quality assurance, and retain sufficient flexibility to accommodate the unique properties of the pesticide under evaluation.

It should also be noted that, while the Core Assessment Group responsible for the toxicological evaluation of pesticides has determined the following information needs, it does not intend to review the primary data relating to all the areas cited. The Group would continue the traditional practice of evaluating the primary data only for Toxicology and metabolism, Human data and Additional data. It would rely upon the evaluations of other expert groups in the other areas. Therefore, only data developed in these three areas should be submitted to the Toxicology CAG.

CATEGORY 1

The data considered critical or essential for an initial evaluation include:

Chemical identity

ISO common name
Chemical name
CAS numbers
Empirical and structural formulae
Relative molecular mass
Specification of purity

Impurities, additives - identity, formation and range of each
Micro-contaminants (e.g. nitrosamines, dioxin)
Name of manufacturer(s) or submitter(s)

Physical and chemical properties

Physical state
pH
Density
Vapour pressure
Solubility in water
Solubility in organic solvents
Octanol-water partition coefficient (as function of Ph)
Corrosion characteristics
Stability in water (see Fate and Behaviour in the environment)

Function and Mode of action

Function (e.g. herbicide, fungicide)
Mode of action on target organisms (e.g. contact poison, systemic poison)
Field of use (e.g. food crop, greenhouse)
Plants or products to be protected

Fate and Behaviour in the environment

Hydrolysis rate, with identification of metabolites and breakdown products
Photodegradation in water
Photodegradation in soil
Rate and route of photodegradation in air
Degradation in soil, with identification of products
Biodegradation in aquatic systems (anaerobic and aerobic)

Residue chemistry

Nature of residues in plants
Nature of residues in livestock, if crop is used for feed or applied directly or indirectly to animals
Nature of residues in water

Toxicology and Metabolism [Primary data to be submitted to CAG]

Acute oral (at least two species)
Acute dermal
Acute dermal irritation
Acute eye irritation
Skin sensitization
Subchronic, oral, rat - 90 day
Subchronic, oral, non-rodent - 90 day
Developmental toxicity - rodent
Developmental toxicity - second species, preferably non-rodent
Multigeneration reproductive toxicity - rat

Toxicokinetics - rodent - (Absorption, distribution, metabolism, excretion)
Chronic toxicity - rodent
Carcinogenicity - rodent (may be combined with chronic toxicity - rodent)
Genotoxicity
1) Bacterial mutation (*Salmonella typhimurium* strains, at minimum)
2) Mammalian cell mutation (*tk* or *hprt* locus)
3) Mammalian cell chromosomal aberration or aneuploidy
4) Hepatocytes, unscheduled DNA synthesis
5) Only if positive results are obtained for (3), a mouse bone-marrow micronucleus test (with kinetochore straining if aneuploidy is suspected.

Acute delayed neuropathy by organophosphorus compounds - hen
Cholinesterase inhibition, e.g. by
Organophosphorus compounds
Carbamates
Certain dithiocarbamates

Human data [Primary data to be submitted to CAG]

Medical surveillance of manufacturing plant personnel (to include exposure estimates)
Clinical cases and reported incidents
Health records from industry and agriculture
Observations of exposure and effects in the general population or epidemiological studies

Additional data [Primary data to be submitted to CAG]

Ongoing updates of exposure and monitoring data
Any mechanistic studies that clarify effects reported in toxicity studies

CATEGORY 2

Data that may be considered desirable or necessary for conducting a full evaluation of the toxicological potential of a pesticide. (As noted above, there may be specific circumstances in which the data needs cited here would actually be considered critical or essential for the initial evaluation and, therefore, expected to be available for it.)

Physical and chemical properties

Particle size distribution (when exposure by inhalation is expected)

Function and Mode of action

Concentration of active ingredient in formulation used (generic formulation such as wettable powder or emulsifiable concentrate)

Toxicology and Metabolism [Primary data to be submitted to Toxicological CAG]

Acute inhalation
Repeated dose (e.g. 21-90 day), dermal
Repeated dose (e.g. 28-90 day), inhalation

Developmental toxicity, rodent, dermal
Toxicokinetics, human, *in vitro/in vivo*
Animal transfer studies
Dermal penetration
Chronic toxicity, non-rodent (e.g. if a subchronic study shows that dogs are more sensitive than rats)
Carcinogenicity, second species (rodent)
Additional genotoxicity tests, especially *in vivo*
Acute neurotoxicity, rat
Subchronic neurotoxicity, rat
Subchronic delayed neuropathology for organophosphorus compounds, hen
Post-natal developmental (neuro)toxicity
Toxic effects of metabolites from treated plants when different from animal metabolites

The usefulness of these data will be reviewed in the light of experience gained in their application.

2.5.2 Evaluation of pesticide residues by the FAO Panel

(i) General data requirements

The public identification of the JMPR data requirements has been mentioned as one area in which improved transparency of JMPR procedures is desirable. The failure to submit critical supporting studies, required for recommending maximum residue limits, for several chemicals reviewed at this Meeting also indicated the need for the JMPR to define the information it requires for adequate evaluation.

Although no single detailed compilation of the data requirements of the FAO Panel has been prepared, previous Meetings have given details of the data required for various aspects of the evaluation of pesticide residues in food and the environment on several occasions (Stability of residues in stored analytical samples, 1990 Report, Section 2.10; Commodity descriptions in supervised trials, 1991 Report, Section 2.7; Data requirements for periodic review, requesting submission of ..."all relevant information on use patterns...., supervised trials on residues, fate of residues (metabolism, storage and processing, stability in stored analytical samples)... 1992 Report, Section 2.3; Guidelines on the need for animal transfer studies 1993 Report, Section 2.7; Data required for estimating maximum residue levels, and The submission of data on metabolism, 1994 Report, Sections 2.4 and 2.5).

In addition, in 1994 the FAO widely distributed instructions on the preparation of data submissions for consideration by the FAO Panel, including the need for an index of data submitted and the need for a working paper to be prepared by the data submitters. It outlined the types of data to be included, including studies on the fate of residues.

As noted above, the Meeting was not able to make recommendations for maximum residue limits for some compounds (e.g. bifenthrin, buprofezin, haloxyfop, quintozene) in some or all of the commodities for which data on supervised trials were available, because of the lack of one or more critical supporting studies, such as the fate of residues in soil and their uptake by plants, studies on animal metabolism, animal transfer studies, processing studies etc.

The Meeting reconsidered the data requirements published in the reports mentioned above and confirmed that they are normally essential for full consideration of the behaviour of the residues, to allow an estimate of their nature and levels in food commodities.

(ii) Data on environmental fate

For many years data on environmental have been submitted to the FAO Panel of the JMPR to supplement other data used to estimate maximum levels of pesticide residues in food and animal feed.

In more than one submission to the 1995 JMPR the data on the environmental fate of residues were not submitted or could not be used owing to restrictions imposed by the submitter of the data. Although such data may not be needed for some applications of pesticides (e.g. seed treatments or post-harvest uses), the Meeting confirmed that studies on environmental fate must normally be included in data submitted to the FAO Panel for new and periodic review pesticides, unless a convincing rationale for their omission is provided. The Meeting agreed that the availability of the relevant studies was essential for the assessment of the potential for residues in food and feeds.

The Meeting reaffirmed the need for the continued submission of the detailed primary reports on these studies to the FAO Panel of the JMPR together with reports on other studies required, even if some of the data are also needed by the Environmental Core Assessment Group.

The FAO Panel does not need data on environmental toxicology but does need studies on environmental fate relevant to the potential for the uptake of residues by food and feed crops.

The submitted data should include:

* physical and chemical properties;

* metabolism and degradation in soil, identification of metabolites and degradation products, and an indication of their levels;

* persistence of the parent compound and its metabolites or degradation products in soil under aerobic and anaerobic conditions;

* mobility of the parent compound and its metabolites in soil;

* adsorption by various soils;

The Meeting recognised the need for, and advantages of, the closer co-operation of the FAO Panel and the Environmental CAG, and recommends that guidelines for the mutual support and harmonization of their activities should be developed at future meetings.

2.6 ASSESSMENT OF ACUTE DIETARY RISK

In 1994, the Joint Meeting outlined the approach it wished to develop for considering the risks of short-term exposure to acutely toxic pesticides. This was done in response to concerns raised at the CCPR over the appropriateness of the traditional ADI as a toxicological benchmark for this purpose. The JMPR proposed the introduction of a "short-term ADI", to be called the "acute reference dose" (acute RfD), as the basis for estimating the risk of short-term dietary exposure.

In developing this proposal, the Meeting considered the suitability of data currently available for estimating acute RfDs for monocrotophos and aldicarb, as examples of organophosphorus and methylcarbamate insecticides respectively, whose acute toxicity is due to acetylcholinesterase inhibition.

Monocrotophos

The effects of monocrotophos differ in rats and humans. The two main discrepancies are: (1) in humans, erythrocyte acetylcholinesterase is less sensitive than plasma cholinesterase to inhibition (no inhibition at a dose that inhibits plasma cholinesterase by 50%), while in rats these enzymes are equally sensitive; (2) the rates of recovery of inhibited cholinesterases are much slower in humans than in rats. A similar phenomenon has been described for the dimethyl phosphates dichlorvos and trichlorfon.

For these reasons, data on humans are most relevant for establishing an ADI or an acute RfD for monocrotophos. The 1993 JMPR established an ADI on the basis of lack of inhibition of erythrocyte acetylcholinesterase in a 28-day study in humans, as monocrotophos was not found to be carcinogenic or teratogenic and caused no toxicity other than the cholinergic syndrome in animals. In the case of short-term exposure, the acute RfD can be derived from an experiment conducted with 0.015 mg/kg bw for seven, then four days after a 3-day pause. In this case, too, no inhibition of erythrocyte acetylcholinesterase was found, but the length of treatment was too short to allow any conclusion about the effect after more prolonged treatment. None of these experiments allowed determination of an LOAEL because erythrocyte acetylcholinesterase inhibition never occurred.

The available toxicological data in humans allow the establishment of an ADI of 0-0.0006 mg/kg bw and of an acute RfD of 0.002 mg/kg bw, based on the lack of erythrocyte acetylcholinesterase inhibition and using, in both cases, the usual 10-fold safety factor.

In-vitro data on the inhibition of plasma cholinesterase and erythrocyte and brain acetylcholinesterase in rodents and in humans would facilitate assessment of the risk of monocrotophos. For instance, comparison of the sensitivity *in vitro* of human plasma cholinesterase with that of erythrocyte and brain acetylcholinesterase to inhibition by monocrotophos might allow extrapolation of an NOAEL using the available data in humans *in vivo*.

The following considerations also relate to the acute RfD. (1) Given the slow rate of reappearance of both plasma cholinesterase and erythrocyte acetylcholinesterase after inhibition by monocrotophos in humans, it is conceivable that the effect on erythrocyte acetylcholinesterase of a single dose equal to 7 x 0.015 mg/kg bw would not be significantly different (i.e. no inhibition) from that obtained with seven daily doses of 0.015 mg/kg bw. (2) Given the characteristics of the dose-response curve of cholinesterase inhibition by organophosphorus esters and the relationship between acetylcholinesterase inhibition and the appearance of the cholinergic syndrome, it can be concluded that a single dose of 7 x 0.015 mg/kg bw is well below that which would induce signs of toxicity.

An addendum to the toxicological monograph on monocrotophos was prepared.

Aldicarb

An ADI of 0-0.003 mg/kg bw was established for aldicarb in 1992 on the basis of the NOAEL for erythrocyte acetylcholinesterase inhibition in a single-dose, double-blind, placebo-controlled study in human volunteers, which was 0.025 mg/kg bw.

Aldicarb was not carcinogenic or teratogenic and caused no toxicity other than the cholinergic syndrome. The single-dose study in human volunteers was considered appropriate for establishing the ADI since the cholinesterase inhibition caused by aldicarb is rapidly reversible and any chronic exposure can be considered as a series of repeated acute exposures. The Meeting therefore concluded that the same no-effect level and safety factor should be used to derive the acute RfD (0.003 mg/kg bw). The Meeting also noted that the sulfoxide and the sulfone are metabolites of aldicarb in plants and animals, and are generally included in the measured total residue of aldicarb. If data are available in which the sulfone can be differentiated from the other components of the residue, that may allow further refinement of the risk assessment, since the sulfone is some 10-20 times less toxic than the parent aldicarb.

Conclusion

These examples confirm the expectation of the 1994 JMPR that the estimation of acute RfDs for acutely toxic pesticides may be based on studies that are different from those used to establish the ADI and that this will require consideration on a case-by-case basis.

2.7 CONSULTATION ON APPLICATION OF RISK ANALYSIS TO FOOD STANDARDS ISSUES - JMPR RESPONSE TO SPECIFIC RECOMMENDATIONS

The Meeting was provided with a report of a Joint FAO/WHO Expert Consultation on *Application of Risk Analysis to Food Standards Issues*[ii]. The Consultation had been convened at the request of the 41st Session of the Executive Committee of the Codex Alimentarius Commission (CAC) which wished to promote consistency and transparency in the establishment of Codex standards, guidelines and recommendations. Joint Meeting members received copies of the report at the Meeting and provided the following initial comments.

The Meeting endorsed the goals and concepts expressed in the recommendations of the Consultation on Risk Analysis and will pursue operational procedures to improve risk assessment.

The Meeting was encouraged by recommendations in four specific areas, directed towards the JMPR:

- exposure assessment for pesticide residues in food as an integral part of the Codex risk assessment procedure;
- a more transparent process for deriving MRLS;
- thorough documentation of the review process; and
- review of criteria for establishing safety factors.

With regard to exposure assessment, recommendations for revising the guidelines for predicting the

dietary intake of pesticide residues were recently produced by a Joint FAO/WHO Consultation[2]. The recommendations, when formulated into a set of guidelines, will be very useful to the JMPR in predicting the dietary intake of residues when pesticides are being evaluated. The Consultation recommended the best use of all available residue data, proposed the separation of intake assessment for chronic and acute effects and suggested that information on regional diets be updated periodically.

The JMPR agrees that dietary intake of pesticide residues should be assessed by member countries of Codex as recommended. National estimates of dietary intake and food consumption patterns should be submitted to the WHO, which currently undertakes estimates of international and regional dietary intake.

With regard to the transparency of the process for estimating MRLs, the FAO Panel has developed and will continue to develop procedures for explaining this process. It takes two forms.

Firstly, explanations of general principles together with specific examples are routinely provided in the JMPR general report items. For example, in the 1994 JMPR report the Meeting explained its requirements with regard to data for estimating MRLs[3]. The 1994 report also included an FAO Panel Manual[4] describing the information to be found in a residue monograph. The present Meeting has summarized the basis for its definitions of residues (Section 2.8.1) and for the estimation of maximum residue levels for multi-component residues at or about the limit of determination (Section 2.8.3).

Secondly, individual cases are explained in some detail in the evaluation of each compound. Such detailed explanations are partly responsible for the considerable increase in the size of the monographs in recent years.

The principles and processes adopted for the toxicological assessment of pesticide residues in food have been explained[5]. Substantial progress has also been made in documenting the toxicological review process undertaken by the WHO Expert Groups. This is also reflected in the expanded content and explanations given in the JMPR reports and increasingly detailed toxicological monographs in recent years.

A policy statement regarding the submission of proprietary data to the WHO for consideration by the JMPR has been published. Much of the information evaluated by the JMPR is the property of the data submitters and has previously been evaluated by national regulatory authorities. Because of its commercial value and proprietary nature, it is submitted on the mutual understanding that it will be used only for evaluation by the JMPR. The data are stored securely and returned to the submitter or destroyed after each Meeting. Neither the FAO nor the WHO is empowered to provide the data to third parties.

The JMPR agrees that the use of standardized test protocols and minimal data requirements should

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[2] WHO and FAO. 1995. Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues. Report of a FAO/WHO Consultation. Document WHO/FNU/FOS/95.11 (draft).

[3] JMPR Report. 1994. 2.4 Data required for estimating maximum residue levels.

[4] JMPR Report. 1994. 2.7 Revised order of topics in residue evaluation monographs - the FAO Panel Manual.

[5] WHO. 1990. Principles for the Toxicological Assessment of Pesticide Residues in Food. EHC 104.

be encouraged. Much of the information reviewed by the JMPR is generated in accordance with internationally accepted protocols; however, the limitations of standardized testing of chemicals should be appreciated. While standardized testing may increase confidence in the quality of the data, it cannot always ensure their adequacy or appropriateness for the assessment of the toxicological hazard of pesticide residues in the diet. The complexities of the assessment of pesticide residues often necessitate the generation of additional data to address specific problems. There may be requirements for additional toxicological or mechanistic studies for which standardized test protocols do not exist, are inappropriate, or are irrelevant.

The 1994 JMPR noted[6] that international organizations were co-operating with governments and industry to develop internationally agreed registration requirements and recommended that the attention of these organizations should be drawn to the need for the development of minimum data requirements for supervised residue trials. It further recommended that any such minimal requirements that might be developed be brought to the attention of a future JMPR. The Meeting reaffirmed the 1994 recommendations and also drew attention to the need for harmonization of the requirements for critical supporting studies (metabolism, analytical methods, frozen storage stability, processing, and animal transfer studies). The Meeting recommended that these international organizations consider developing such harmonized requirements.

The OECD has recently surveyed the data requirements for pesticide registration by its member countries[7]. These have now been reviewed at the present Meeting and the minimal data requirements of the JMPR have been outlined (*see* 2.5).

The JMPR agrees that the basis for the use of safety factors and other approaches for the inter-species extrapolation of risk should be continually reviewed in the light of contemporary knowledge.

The approach to, and principles for, the selection of safety factors used by the JMPR in the estimation of ADIs are described in EHC 104[8]. EHC 170[9] addresses the selection of guidance values in a broader context. The current approaches to the use of safety factors by different advisory bodies are under review.

The JMPR will continue to produce documents with sufficient detail and explanation to be as useful as possible to Member States and interested parties.

2.8 RESIDUES

2.8.1 Definitions of pesticide residues

A pesticide residue is defined as that combination of the pesticide and/or its metabolites, derivatives and related compounds to which the MRL applies.

Previous Joint Meetings have explained the basis for choosing definitions of residues and have

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[6] JMPR Report, 1994. 2.4 Data required for estimating maximum residue levels.

[7] OECD Environment Monograph No 77. 1994. Data Requirements for Pesticide Registration in OECD Member Countries: Survey results. OECD, Paris.

[8] [Rpt. footnote 3, p.11]

[9] WHO. 1994. Assessing Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits, EHC 170.

described some of the complexities which occur (JMPR 1982[iii], JMPR 1983[10], JMPR 1987[11]).

Questions on definitions of residues often arise at the CCPR and the 1994 Joint Meeting[12] added a specific section "Residue definition" in its new format for residue evaluation monographs. It will now be easier for the reader to find an explanation for the definition of the residue. Because of these developments and the evolution of concepts for arriving at definitions of residues the Meeting believed it was opportune to summarize the current basis for the definition of residues.

Definitions of residues are somewhat arbitrary at best. For this reason and because of the various purposes for which they are used definitions of residues established by national governments often do not agree. The first requirement is for a definition which is most suitable for monitoring compliance with GAP; another requirement is for a definition to include compounds of toxicological interest for dietary intake estimations and risk assessment. The two requirements are sometimes not compatible, and in the compromise various definitions of residues are possible.

The JMPR considers the following factors when proposing a residue definition.

The composition of the residues found in animal and plant metabolism studies.
The toxicological properties of metabolites and degradation products (for risk assessment).
The nature of the residues determined in supervised residue trials.
The fat-solubility.
The practicality of regulatory analytical methods.
Whether metabolites or analytes common to other pesticides are formed.
Whether a metabolite of one pesticide is registered for use as another pesticide[13].
The definitions of residues already established by national governments and long-established and customarily accepted definitions.

Metabolism studies establish the basic information on the composition of the residue in animal tissues and in crops. The studies identify the metabolites and provide their relative concentrations.

For enforcement purposes it is not desirable to include minor metabolites. Monitoring for additional compounds only adds to the costs of analysis, and standards for metabolites are sometimes not readily available.

The compounds determined in the supervised residue trials should have been chosen on the basis of (1) the metabolism studies, (2) the practicality of their inclusion in a regulatory method and (3) their significance for toxicology and risk assessment needs. Where possible, residue components of different toxicological significance should be recorded separately and ideally the trials should provide separate results for the parent and each important metabolite.

For some compounds it may be necessary to establish separate residue definitions for enforcement (the estimation of maximum residue levels and compliance with MRLs) and dietary intake purposes. The residue definition for dietary intake purposes should include metabolites and degradation products of toxicological concern irrespective of their source.

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[10] JMPR 1983. 2.3 Expression of maximum residue limits in terms of a single compound.
[11] JMPR 1987. 2.8 Pesticides that are also metabolites of other pesticides.
[12] JMPR 1994. 2.7 Revised order of topics in residue evaluation monographs - the FAO Panel Manual.
[13] JMPR 1987. 2.8 Pesticides that are also metabolites of other pesticides.

Metabolites arising from different sources should generally be excluded from definitions of residues for enforcement purposes unless the definition is a combined one covering the various sources. For example, *p*-nitrophenol arises from both parathion and parathion-methyl. It is often a major component of aged residues but is not included in the definitions of the residues.

Where a metabolite of one pesticide is registered for use as a second pesticide, separate MRLs would normally be established if the analytes of the two compounds were different. Preferably no compound, metabolite or analyte should appear in more than one residue definition. Triadimenol is a registered pesticide and a metabolite of triadimefon. The MRLs for triadimefon are for triadimefon only. The MRLs for triadimenol are for triadimenol only, but cover triadimenol residues arising from the use of either triadimefon or triadimenol. Before 1992 the definition of the triademefon residue included triadimenol, and an analyst detecting triadimenol in a sample could not be certain whether to compare the residue with an MRL for triadimefon or triadimenol.

The fat-solubility of a residue is primarily assessed from the octanol-water partition coefficient and the partition of the residue between muscle and fat observed in metabolism and animal transfer studies. The 1991 JMPR[14] provided guidelines for deciding whether a pesticide is fat-soluble. The words "(fat-soluble)" are included in the residue definitions of fat-soluble compounds. Sampling protocols for animal commodities depend on whether a residue is fat-soluble or not.

Ideally it should be possible to measure the residue as defined, with a limit of determination (LOD) adequate for proposed MRLs, with a high degree of specificity in a multi-residue regulatory analytical method. Although circumstances may warrant exceptions, a definition of a residue should not normally depend on a particular method of analysis, which means that the definition should not contain the words "determined as". However, the only way to produce a practical definition for residues of the dithiocarbamates is to describe the residue as ".... determined and expressed as ....".

It is generally preferable to define a residue in terms of the parent compound. Even if the residue consists mainly of a metabolite the residue should be expressed in terms of the parent pesticide after molecular weight adjustment. There have been exceptions, e.g. the current definition of amitraz, *N*-methylbis(2,4-xylyliminomethyl)amine, is expressed in terms of the metabolite *N*-(2,4-dimethylphenyl)-*N'*-methylformamidine.

If the parent compound can exist as an acid or its salts the residue is preferably expressed as the free acid. An example is 2,4-D.

Where the residue is defined as the sum of the parent compound and metabolites expressed as the parent the concentrations of the metabolites should be adjusted according to their molecular weight before being added to produce the total residue. The words "expressed as" in the residue definition signify adjustment for molecular weight. An example is the definition of methiocarb: *sum of methiocarb, its sulfoxide and its sulfone, expressed as methiocarb.*

No allowance is made for molecular weights in the definitions of residues of some older compounds. An example is heptachlor: *sum of heptachlor and heptachlor epoxide (fat-soluble).* Because such definitions are widely accepted the need for change should be carefully considered. The best time for the reconsideration of an existing residue definition is during a periodic review.

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[14] JMPR 1991. 3.3 Fat-soluble pesticides.

As far as possible the same definition of the residue should apply to all commodities. There are exceptions. For example, if the major residue in animal commodities is a specific animal metabolite a definition which includes that metabolite is needed for regulatory monitoring. But the animal metabolite is not required in the residue definition for crop commodities. Separate definitions would then be proposed for commodities of plant and animal origin. An example is thiabendazole: *thiabendazole, or, in the case of animal products, sum of thiabendazole and 5-hydroxythiabendazole.*

A major part of the residue of some pesticides is bound or conjugated, with the free residue disappearing very quickly. The bound or conjugated residue is then a better indicator for monitoring compliance with GAP. If the residue is defined as bound or conjugated there must be a clear instruction for the regulatory analyst as to how to measure it. The instruction could be to extract samples with a particular solvent under specified conditions, or perhaps to begin with a hydrolysis step, etc. An example of conjugated residues is bendiocarb: *commodities of plant origin: unconjugated bendiocarb. Commodities of animal origin: sum of conjugated and unconjugated bendiocarb, 2,2-dimethyl-1,3-benzodioxol-4-ol and N-hydroxymethyl-bendiocarb, expressed as bendiocarb.*

Recommendations

1. For new compounds and compounds in the periodic review programme, national definitions of residues and the basis for them should be supplied to the JMPR.

2. Separate definitions of residues for enforcement (the estimation of maximum residue levels and compliance with MRLs) and for dietary intake purposes should be established when the requirements are in conflict.

3. The requirements for the estimation of maximum residue levels and for the estimation of dietary intake risk assessment should be taken into account in supervised residue trials. Where possible, residue components of different toxicological significance should be recorded separately and ideally the trials should provide separate results for the parent compound and each important metabolite.

2.8.2 JMPR approach to estimating Extraneous Residue Limits (ERLs)

The term extraneous maximum residue limit (EMRL) recently introduced by the Codex Alimentarius Commission is the maximum level recommended by the Codex Alimentarius Commission to be allowed for unavoidable residues of persistent chemical contaminants in food or feed resulting from environmental contamination from previously approved uses of these chemicals as pesticides. The term ERL, used by the JMPR since 1975, has the same meaning. ERLs (EMRLs) differ from maximum residue limits (MRLs) in that MRLs are intended to regulate residues of chemicals still authorized for use as pesticides. The need for ERLs is often first determined at the national level as a result of monitoring, and if they are needed they typically replace the previous MRLs, usually at lower levels.

At the 27th Session of the CCPR (1995) the Committee was reminded of the need for the submission of national monitoring data to support estimates of extraneous residue limits (ERLs) by the JMPR (ALINORM 95/24A, paras 175-6). A request had been made by circular letter CL 1994/12 Part B3 requesting monitoring data and information on national approaches to estimating ERLs. This had elicited only a limited response.

The ensuing discussion revealed some misconceptions about the approach the JMPR generally follows and a desire for a "more transparent" policy. The Committee again requested inputs from governments and by CL 1995/13-PR 5 has again requested monitoring data and information on how national governments use such data in estimating ERLs, with the aim of developing criteria for their use for this purpose. Data requirements for the estimation of ERLs have been discussed by the JMPR (1990 Report, Section 2.7).

The Meeting welcomed the interest in and discussion of the issue at the CCPR, and the goal of developing more formal criteria for deciding on the need for ERLs and for their estimation. It strongly supported the request for the submission of better data for the estimation of ERLs. As an interim measure until any new criteria are developed and in order to increase transparency, the Meeting considered it useful to comment on the general philosophy of the JMPR, on the factors which have been taken into account in the past in estimating ERLs, and on some of the difficulties that have been encountered.

The first signal has generally been some indication that the pesticide is no longer approved for uses on food-producing crops or animals. This information often comes from manufacturers who inform the CCPR and/or the JMPR that they have discontinued production of a pesticide, or from governments that a compound is no longer approved for use as a pesticide. Chemicals for which ERLs are most likely to be needed are those which have been widely used as pesticides, which are persistent in the environment for a relatively long period after uses have been discontinued and which are expected to occur in foods or feeds at levels of sufficient concern to warrant monitoring.

Predictions of persistence in the environment (and the potential for uptake by food or feed crops) can often be based on a combination of data sources normally available for chemicals previously approved as pesticides. These may include information on their chemical and physical properties, metabolism studies, data on supervised field trials, data on environmental fate, rotational crop data, the known persistence of similar chemicals, and especially from monitoring data.

In order to make reasonable estimates to cover international trade, the JMPR needs current and geographically representative data which are often unavailable. Typically data are available from only three or four (usually developed) countries at the most, usually from developed countries. By the nature of national monitoring, data are usually received primarily on those commodities in which residues have been found at the national level and which have the potential to create trade difficulties. The Meeting confirmed the need for the submission of all relevant monitoring data (including nil results) as requested by the 1991 JMPR (Report, Section 2.3).

On receipt of the data, to the extent possible the JMPR attempts to take into account a number of factors in estimating an ERL. These include the amount of data, the relative importance of the commodity in international trade, the potential for trade difficulties or accounts thereof, the frequency positive results, a knowledge of the propensity of a particular crop to take up residues (e.g. the uptake of DDT by carrots), historical monitoring data (e.g. previous monographs), and the level and frequency of residues in similar crops, especially those in the same crop group. In some cases the estimate has turned out to be the highest level reported, especially if a relatively good database is available and the spread of results is reasonably narrow.

In recent years there has been more of a tendency to estimate a level below the highest residue found, especially if the higher values occur infrequently. For example, the 1993 JMPR recommended an ERL of 0.2 mg/kg for DDT in carrots, although 2 of 4 imported samples reported from one country were 0.4 and 0.5 mg/kg. The Meeting took into account that only 2 of over 800 imported

samples exceeded 0.2 mg/kg. A similar approach was taken for DDT in the fat of meat, where the Meeting proposed lowering an ERL of 5 mg/kg to 1 mg/kg, although some residues were reported up to 1.8 mg/kg. This approach recognizes that residues gradually decline and that monitoring data are often somewhat dated by the time they reach the JMPR. One aim of recommending ERLs lower than the highest reported levels is to discourage unauthorized uses which higher levels might accommodate. It is likely to encourage those who might not otherwise submit data to do so. If health concerns permit, the approach has to be balanced against unnecessary restrictions of trade.

The JMPR is aware that some countries use statistical approaches to estimating national ERLs, e.g. setting ERLs at a 95 percentile level. Although the JMPR may use statistical tools, it has not routinely adopted standard statistical methods. There are several reasons for this. One is the lack of internationally accepted standards for such an approach. A more operational reason is the nature and quality of the data usually available. The form in which they are provided, for example, often does not lend itself to statistical analysis, while treatments which involve more subjective judgements such as taking into account data from similar crops or the consideration of historical data are difficult to fit into a statistical approach.

As noted above, it has been the JMPR's experience and expectation that residues of these chemicals in the environment and in food and feed will decline with time. The rate will depend on a number of factors, including the nature of the chemical, the crop, the location and environmental conditions. Because residues gradually decrease, the JMPR recommends reassessment every few years. No set period has been defined: ideally it would be about 5 years, but practical considerations (e.g. data availability or scheduling) will often dictate the interval. For example, the 1992 JMPR recommended the re-evaluation of aldrin/dieldrin in 1998 and the 1993 JMPR recommended a reassessment of DDT monitoring data also in 1998, but the availability of data and expressed concerns will result in reconsideration of the proposed ERL for DDT in meat in 1996.

The intention is to continue lowering the ERLs as the results of monitoring permit, again discouraging unauthorized use and, it is hoped, encouraging the submission of national monitoring data. Eventually, the data may indicate that there is no longer a need to monitor the chemical. This view would be based on the conclusion that there is no longer a potential for significant disruption of trade and that the incidence or level of residues is no longer a significant health concern. For example, as part of the effort to discontinue limits for large commodity groups such as "vegetables" the 1990 CCPR postponed the withdrawal of ERLs for heptachlor, awaiting further data. Insufficient data were provided to the 1991 JMPR which recommended the conversion of ERLs for vegetable to temporary ERLs to encourage the submission of more data. On the basis of additional data the 1993 JMPR recommended the withdrawal of the TERLs for heptachlor on vegetables owing to the low level and incidence of the residues found in monitoring.

The Meeting looks forward to reviewing country responses to CL 1995/13-PR (5), the receipt of better and more geographically representative monitoring data and the development of internationally acceptable criteria for estimating ERLs.

2.8.3 MRLs at or about the limit of determination for multi-component residues

The limit of determination (LOD) is the lowest concentration of a compound that can be determined in a commodity with an acceptable degree of certainty.

The 1981 Meeting (Report, Section 2.4) recognized the difficulties that may arise in regulatory

laboratories analysing low level of residues in samples of unknown origin, and stated that it usually estimates a limit of determination which is achievable under those conditions and it is this figure that is proposed as a maximum reside limit “at or about the limit of determination”. This limit is often referred to as a practical limit of determination to distinguish it from the limits of determination achieved in supervised trials.

The 1989 Meeting (Report, Section 2.9) reaffirmed the 1981 statement and pointed out that "an MRL so identified does not always necessarily imply that residues of the pesticides do not occur in that commodity". The application of a more sensitive or specific method may reveal detectable residues in some commodities as shown, for example, in Tables 14 and 26 of the 1995 monograph on quintozene.

In many instances the use of a pesticide according to GAP results in a residue level in crops or commodities that is too low to be measurable by available analytical methods. Setting and enforcing MRLs for residues occurring at or about the limit of determination of analytical procedures may require different approaches depending on the composition and definition of the residues. It is emphasized that all available relevant information should be carefully considered to ensure that an MRL established at a level equivalent to a practical limit of determination of the individual residue components will fully accommodate the levels of these components which could occur in commodities following treatment according to GAP.

The Meeting considered the example of bentazone. The residue in plant commodities is defined as the sum of bentazone, 6-hydroxybentazone and 8-hydroxybentazone, expressed as bentazone. The LODs reported in supervised trials for the three components were generally 0.02 mg/kg, but the practical LODs were regarded as 0.05 mg/kg for regulatory purposes. The Meeting noted that if an MRL for bentazone was set as the sum of the practical LODs of the three components of the residue it would have to be established at 0.2 mg/kg (3 times the practical limit of determination to incorporate all three residue components). In this case, any one of the residue components could be present at 0.2 mg/kg, or all of the three at 0.06 mg/kg, without exceeding the MRL. Consequently, individual residue components could be respectively 10 and 3 times those which should arise from the recommended use of the compound but would be within the MRL. Similarly, if the sum of the LODs achieved in the supervised trials was considered an MRL of 0.1 mg/kg would be needed, which would still allow 5 times the residue that would arise from treatments complying with GAP. The Meeting concluded that when residues are undetectable in a commodity an MRL based on the sum of the LODs of the individual residue components is not appropriate for enforcement purposes.

The Meeting considered some of the situations which occur under practical conditions and used the examples to explore the possible actions in order to facilitate the elaboration of an internationally acceptable procedure.

In cases where several metabolites are included in the definition of the residue two basic situations can be distinguished.

(1) The residue components are or may be converted to a single compound or analyte by the analytical method (e.g. fenthion). The total residue is measured as a single compound and expressed as the parent compound (e.g fenthion sulfone is measured and expressed as fenthion). The MRL is set and enforced on the basis of the total measured residue. Since after the conversion of all the residue components a single compound is to be determined, the MRL can be simply enforced either at or above the LOD. This situation is similar to other cases where the residue is defined as a single compound.

(2) The residue components, for example bentazone, 6-hydroxybentazone and 8-hydroxybentazone, are determined separately by the method. The concentrations of measurable residues are adjusted for molecular weight and summed, and their sum is used for estimating the maximum residue level. In this case the foreseeable situations and the proposed approaches are illustrated with the examples given in Table 1, supposing that:

- the definition of the residue includes the parent A and metabolites B and C;
- the LOD of the analytical procedure used in supervised trials was 0.02 or 0.03 mg/kg for the components of the residue;
- taking into consideration the difficulties in the analytical procedure, the JMPR recommended for each residue component a practical limit of determination of 0.05 mg/kg for regulatory purposes.

Table 1. Examples of maximum residues detected in supervised trials, and recommended MRLs.

Example	Maximum levels (mg/kg) detected for components			Recommended MRL (mg/kg)
	A	B	C	
(a)	<0.02	<0.02	<0.02	0.05[1]
(b)	<0.02	<0.03	<0.02	0.05[1]
(c)	0.04	<0.02	<0.02	0.1
(d)	0.04	0.03	<0.02	0.1
(e)	<0.02	0.04	0.05	0.2
(f)	0.08	0.06	<0.02	0.2

[1] None of the residue components should exceed the MRL when the commodity was treated in compliance with GAP.

Actions in regulatory laboratories

The residues should be analysed by methods which determine the residues individually. "Total residue" methods are not suitable for enforcement analysis in such cases.

When the MRL is set at or about the limit of determination all individual residue components should be within the MRL for compliance.

In other cases the residues of the individual components are summed and compared with the MRL. When a component is not detected it is counted as zero, and not as its LOD.

In the future a laboratory might apply a method capable of measuring residues of 0.01 mg/kg in a commodity for which an MRL of 0.05** mg/kg was established, where the qualifier ** indicates a multi-component residue (as distinct from a single-component residue or single determined analyte) at or about the LOD, and detect the residues shown below.

Sample	Residues (mg/kg) detected		
	A	B	C

(a)	0.02	0.02	0.02
(b)	0.04	<0.01	<0.01
(c)	0.08	<0.01	<0.01

The following actions should be taken:

- in samples (a) and (b) the concentrations of the individual residue components are to be compared with the 0.05** mg/kg limit, and the lot is considered to contain residues that are within the MRL;
- in sample (c) the residue of component A exceeds the limit of 0.05* mg/kg, and the lot is considered to contain residues above the MRL.

In summary:

(a) When the residue definition includes two or more compounds which are determined as individual analytes, and no detectable residues are observed in supervised trials an MRL is established at a level equivalent to the highest practical limit of determination of the individual residue components. This type of limit is marked ** to distinguish it from those which apply to a single residue component or determined analyte.

The lot tested should be considered as being in compliance with the MRL marked ** when none of the residue components exceeds the limit even if the total residue is above the limit.

(b) When some of the residue components are detectable in supervised trials an MRL is established as the sum of the residues. The residues present below the LOD are counted as being at the LOD in estimating the maximum residue level.

For the enforcement of the MRL, a component present below the LOD is taken as zero in the sum, and not as being at its LOD.

It is pointed out that summing the individual residues inevitably increases the uncertainty of the result according to the laws of propagation of error. In this regard reference is made to the 1991 Report, Section 2.8, describing the interpretation of the results of residue analysis for comparison with an MRL.

The Meeting recommends that comments should be invited from the CCPR and member countries on national approaches to the problem, and on the proposed approach outlined in this document. The JMPR will consider the comments in the further development of the principle.

2.9 JMPR EVALUATIONS

2.9.1 Use of data by the JMPR

The CCPR periodic review programme results in the nomination of older pesticides for re-evaluation by the JMPR. Consequently, manufacturers are requested to supply all available old and new data on the nominated pesticide.

The Meeting has determined that, in the interests of maximal utilization of available resources, once

data are submitted to the JMPR they will be evaluated and a monograph will be published. It will not be possible to withdraw permission for the evaluation of data that have been submitted.

If no toxicological data are provided for the evaluation of pesticides elected for periodic review, previous toxicological monographs will be re-examined and will serve as a basis for re-evaluation.The age of previous monographs may mean, however, that the data reported therein are inadequate to permit valid re-evaluation. Under such conditions the ADI may be withdrawn. MRLs will be retained, withdrawn or revised in accordance with the periodic review procedure outlined by the CCPR (ALINORM 93/24, Appendix V, Annex III; ALINORM 93/24A, Appendix IV, Annex II) and elaborated on by the 1992 JMPR (Report Sections 2.3 and 2.4).

2.9.2 Use of JMPR evaluations by regulatory authorities

Regulatory authorities are encouraged to make use of the critical evaluations of the JMPR. When using them, however, authorities should use documentation provided by manufacturers in accordance with national laws relating to the submission and use of unpublished proprietary data to ensure that the JMPR evaluations are of pesticides manufactured by the same routes, of comparable purity and with similar impurities to the pesticides that are being registered.

The following statement is given on an introductory page of this report, which will also be included in future reports:

The summaries and evaluations contained in this report are, in most cases, based on unpublished proprietary data submitted for the purpose of the JMPR assessment. When using the evaluations for registration purposes, registration authorities should ensure that the substance to be registered is equivalent to the substance reviewed by the JMPR. Due attention should be given to the proprietary nature of registration data in accordance with national laws.

2.9.3 Shortening JMPR reports on compounds - Section on residue and analytical aspects

The Meeting noted that the "Residue and analytical aspects" sections of JMPR reports have become quite lengthy in recent years following requests for more detailed explanations of all recommendations. The requests have been met largely by combining aspects of the report and the appraisal section of the monograph into a single document, which has been used both as a report item and as the appraisal.

It is recognized that the functions of the report and the appraisal are not identical, but it is no longer feasible to produce separate long documents within the time available.

Concern has been expressed that a detailed report is not currently serving its full purpose because the CCPR does not consider the recommendations for MRLs until the monographs are available.

The Meeting suggested that the reports on residue and analytical aspects could be quite brief; they would describe in general terms the data submitted or reviewed but without detailed explanations for the recommendations. These would continue to appear in the appraisal section of the monograph. It is emphasized that there would be no loss of transparency.

A briefer report would be more economical to produce, could be published earlier, and would avoid unnecessary publication of the same text in two documents. It is envisaged that such a residue report would not normally exceed one page; a shortened report item for metiram is shown below (p. 29) as

an example.

Recommendation

It is recommended that the views of the CCPR be sought on:

- the JMPR proposal to shorten reports on compounds;
- the usefulness of the current detailed JMPR residue reports for facilitating the progress of recommendations for MRLs;
- whether the production of brief reports would meet the needs of the CCPR until the JMPR Residue Evaluations are available.

4. METIRAM (186)

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of the compound were considered for the first time by the present Meeting.

Metiram is a non-systemic fungicide with a very broad spectrum of activity and is registered for use on cereals, fruits, vegetables, tobacco and ornamental in numerous countries. It is active against downy mildews, rust fungi and a number of leaf spot fungi. Resistance to metiram has not developed during more than 30 years of use.

The Meeting received extensive information on metabolism, environmental fate in soil, methods of residue analysis, stability of residues in stored analytical samples, approved use patterns, supervised residue trials, animal transfer studies and the fate of residues during food processing.

Metabolism studies on lactating goats, laying hens, apples and potatoes were reviewed. Information was provided to the Meeting on the environmental fate of metiram in soil, including information on hydrolysis and photolysis.

The methods of residue analysis for metiram rely on acid hydrolysis to release CS_2, which is then measured colorimetrically or by gas chromatography. The methods are the same as those for the other ethylenebis(dithiocarbamate)s, mancozeb and maneb. The Meeting agreed that the residue should be defined as a dithiocarbamate residue: *The MRLs refer to total dithiocarbamates, determined as CS_2 evolved during acid digestion and expressed as mg CS_2/kg.*

Information was provided to the Meeting on the frozen storage stability of metiram and ETU on apples, wet and dry apple pomace, apple juice, sauce, baby food, tomatoes, potatoes and sugar beets.

The Meeting received residue data from supervised trials on the following commodities:

apples, pears, apricots, cherries, peaches, plums, currants, gooseberries, grapes, strawberries, and bananas;

cabbages, cauliflowers, cucumbers, tomatoes, lettuce, beans, peas, potatoes, celery; wheat, rape seed, hops, wheat forage, wheat straw.

Animal transfer studies in which lactating dairy cows were dosed with metiram were reviewed.

Processing studies were available for metiram on apples (to apple puree and apple juice), pears (to pear compote) and grapes (to grape juice, must and wine).

2.10 DIETARY INTAKE OF PESTICIDE RESIDUES

Following the general methods described in Guidelines for Predicting Dietary Intake of Pesticide Residues, Theoretical Maximum Daily Intake (TMDI) calculations have been performed for the Joint Meeting by the WHO. The results are summarized in Annex III. Processing and other factors must be reviewed before more realistic calculations can be performed on those pesticides for which the TMDI exceeds the ADI.

2.11 ISSUES RELEVANT TO THE ESTABLISHMENT OF GUIDELINES FOR DRINKING-WATER QUALITY

The Joint Meeting considered issues relevant to the establishment of Guideline Values for drinking-water for five pesticides: bentazone, diquat, chlorothalonil, diflubenzuron, and methomyl. General issues related to this activity, and individual assessments of the five pesticides, are given in Annex IV.

The Meeting recommended that the JMP should consider issues relevant to the establishment of guideline values for pesticides in drinking-water whenever full environmental and toxicological assessments are carried out.

3. SPECIFIC PROBLEMS

No specific problems were discussed.

4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE FOR HUMANS AND MAXIMUM RESIDUE LIMITS

4.1 ABAMECTIN (177)

TOXICOLOGY

Abamectin was evaluated by the 1992 and 1994 Joint Meetings. At the latter, an ADI of 0-0.0002 mg/kg bw was established on the basis of an NOAEL of 0.12 mg/kg bw per day for pup toxicity in a study of reproductive toxicity in rats. A safety factor of 500 was applied because of concern about the teratogenicity of the Ä-8,9 isomer, which is a photolytic degradation product that forms a variable proportion of the residue in crops.

The uses of abamectin as a veterinary drug were evaluated at the forty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[iv] on the basis of the toxicological assessment of this substance by the JMPR. The Committee noted that an extra safety factor had been applied by the JMPR owing to concern about the toxicity of the Ä-8,9 isomer, which, upon review of the data, the Committee concluded did not occur in animal tissues from the use of abamectin as a veterinary drug. It therefore did not seem to be appropriate to use an ADI that included an extra safety factor to account for the toxicity of the Ä-8,9 isomer as the basis for comparison when evaluating residues resulting from use as a veterinary drug.

The present Meeting confirmed that the ADI of 0-0.0002 mg/kg bw established in 1994 applies to residues in plants, after the use of abamectin as a plant protection product, which contain abamectin and varying proportions of the Ä-8,9 isomer. The Meeting agreed that this ADI was not appropriate for abamectin residues that do not contain the Ä-8,9 isomer. In order to accommodate this situation, the Meeting allocated an ADI of 0-0.001 mg/kg bw to abamectin itself, on the basis of the NOAEL of 0.12 mg/kg bw per day in the study of reproductive toxicity in rats and using a safety factor of 100.

The Meeting emphasized that MRLs that are recommended by the JMPR and JECFA should be harmonized to include residues from both the use of abamectin as a veterinary drug and the consumption of fodder containing residues of abamectin.

The Meeting reiterated the need for results of the studies identified by the 1994 JMPR that would provide information valuable for the continued evaluation of the compound. This information is necessary to characterize more clearly the toxicity of abamectin and the Ä-8,9 isomer.

A toxicological monograph was not prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Rat: 0.12 mg/kg bw per day (two-generation study of reproductive toxicity)

Estimate of acceptable daily intake for humans

Mixture of abamectin and Ä-8,9 isomer: 0-0.0002 mg/kg bw
Abamectin: 0-0.001 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound, as recommended by the 1994 JMPR

1. Data on P-glycoprotein in other species, including humans.

2. Establishment and validation of a more sensitive method to assess neurotoxic effects of avermectins in rodents.

3. Acute toxicity of the Ä-8,9 isomer in CF_1 and CD_1 mice with measurements of P-glycoprotein and blood and brain levels of the compound.

4. Teratogenicity study in CD_1 and CF_1 mice with abamectin and the Ä-8,9 isomer with concurrent measurements of P-glycoprotein, in order to correlate its presence or absence with maternal toxicity and teratogenicity.

4.2 ALDICARB (117)

TOXICOLOGY

The Meeting established an acute reference dose (acute RfD). Details are given in Section 2.6.

4.3 AZINPHOS-METHYL (002)

RESIDUE AND ANALYTICAL ASPECTS

Azinphos-methyl was originally evaluated in 1965 and has been reviewed on several occasions since. In 1991, the JMPR carried out an extensive re-evaluation and required additional data by 1993 to support the Codex maximum residue limit (CXL) for grapes. These data were not available to the 1993 Joint Meeting, which was informed that data from trials on grapes in Germany and Italy, including processing studies, would be available for the 1995 Meeting. In 1993 the CCPR recommended deletion of the CXL and it was subsequently deleted by the CAC.

At the 1994 CCPR, the delegation of Germany questioned the accuracy of the method of analysis for almonds and wheat (ALINORM 95/24, para 68). Several delegations observed that the data were not sufficient to establish an MRL for wheat. The proposed MRLs for almonds and wheat were held at step 7B pending the review of written comments by the JMPR.

An analytical method suitable for plant material was submitted together with validation data for a number of crops. Determination was by GLC with an FPD with a reported limit of determination of 0.04 mg/kg.

Information on GAP was supplied by Germany, Australia, New Zealand and the manufacturer. Information from Australia on monitoring analyses of a large number of commodities

showed that residues were all below the limit of determination (<0.1 mg/kg) except in one grape sample of 229 (reported within the range 0.1-0.4 mg/kg), and seven pear samples of 366 (<0.1-0.4 mg/kg).

Grapes. The 1991 monograph reported six US trials, carried out in one season, in which residues following treatment at 0.84 kg ai/ha were 0.22-3.37 mg/kg in samples taken 14 days after the last treatment. GAP in the USA requires a maximum application rate of 1.1-1.2 kg ai/ha with a PHI of 10 days for WP and 7 days for EC. The 1991 Meeting concluded that the additional residues data were insufficient to propose amendment to the CXL of 4 mg/kg for grapes and that residues data from countries other than the USA were desirable.

New Italian supervised trials conducted according to Italian GAP were available from the manufacturer. Residues were <0.04-0.61 mg/kg at a PHI of 20 days. However only four trials were available, conducted at three locations. The Meeting agreed that the six US trials could not support a recommendation because a combination of the low application rate and the longer PHI used in these trials might lead to an underestimate of the maximum residue, and concluded that the data were insufficient to recommend an MRL for such an important commodity. The Meeting was informed that the manufacturer was considering carrying out further trials on grapes in Southern Europe.

The new Italian trials indicate that the residues resulting from Italian GAP are likely to be lower than those resulting from US GAP.

Wheat. At the 1994 CCPR the delegation of Germany questioned the accuracy of the method of analysis used and the MRL of 0.2 mg/kg recommended by the 1991 JMPR. In addition, several delegations observed that the data were not sufficient to establish an MRL for wheat. Information was brought to the attention of the Meeting that indicated that the accuracy of the old colorimetric method of analysis used in some of these trials was inadequate. Although a new specific method of analysis was used in seven of the US wheat trials only one of the trials included results at the PHI reported as Canadian and Mexican GAP (30 days). In the other six trials the PHIs were 48-75 days. The Meeting recommended that the MRL for wheat should be withdrawn.

The 1991 JMPR had recommended the MRL for wheat to replace the CXL for cereal grains, which it concluded was not adequately supported.

Almonds. At the 1994 CCPR the delegation of Germany questioned the MRL of 0.3 mg/kg for almonds recommended by the 1991 JMPR. The Meeting was informed that the accuracy of the old colorimetric method of analysis used in some of these trials was inadequate. Data from two series of trials were presented in the 1991 JMPR monograph. Samples from the trials which appear to have been used to support the MRL of 0.3 mg/kg were analysed by the colorimetric method. In a further 24 US trials in which a new specific method of analysis was used, residues were reported as <0.02-0.04 mg/kg in the kernels and 0.04-3.65 mg/kg in the hulls. On the basis of these trials the Meeting estimated maximum residue levels of 0.05 mg/kg for almonds and 5 mg/kg for almond hulls.

When grapes containing residues of <0.04-0.07 mg/kg were processed the residues in must and wine were 0.06-0.09 and <0.04 mg/kg, respectively. However the details of the processing were submitted too late for full consideration by the Meeting and were in the form of a draft translation. The Meeting understood that the manufacturer had agreed to submit the original study report and the final translation containing the full experimental details to the FAO for future consideration by the FAO Panel.

azinphos-methyl

Recommendations are recorded in Annex I.

4.4 BENOMYL (069)

TOXICOLOGY

Benomyl was evaluated toxicologically by the Joint Meeting in 1973, 1975, 1978 and 1983. In 1983 an ADI of 0-0.02 mg/kg bw was established, after a review of data on the toxicity of carbendazim and benomyl and incorporating a higher-than-normal safety factor because of the paucity of data on individual animals in many studies. The compound was reviewed by the present Meeting within the CCPR periodic review programme, with particular attention to the recent Environmental Health Criteria monograph on benomyl (EHC 148).

Benomyl is readily absorbed by animals after oral exposure and rapidly metabolized. It is eliminated in the faeces and excreted in the urine. Ninety eight per cent of the dose was excreted by 72 h after administration. The tissue distribution showed no bioconcentration. In rats, the metabolites carbendazim and methyl 5-hydroxybenzimidazol-2-ylcarbamate (5-hydroxycarbendazim) were found in the blood and in small amounts in the testes and liver. The latter compound was the main metabolite in urine. A 50% wettable powder formulation was poorly absorbed via the dermal route by rats. After a 10-h exposure, less than 2% of a single dose of 0.2 mg was excreted in the urine.

Benomyl has low acute toxicity, with an oral LD_{50} in rats of >10,000 mg/kg bw. The clinical signs of toxicity after high single doses were generally non-specific. Testicular degeneration, with necrosis of germinal epithelium and aspermatogenesis, has been observed after single doses in rats (≥100 mg/kg bw orally) and dogs (1.65 mg/litre air by inhalation). Wettable powder formulations containing benomyl have been shown to be mildly irritating to rabbit skin and eyes and have also induced skin sensitization reactions in maximization tests. The WHO has classified benomyl as unlikely to present an acute hazard in normal use.

In a 90-day study, rats were given dietary doses of 0, 100, 500 or 2500 ppm benomyl. Increased liver weight was seen at 2500 ppm; the NOAEL was 500 ppm (50 mg/kg bw per day). Dogs were given dietary doses of 0, 100, 500 or 2500 ppm benomyl for three months or two years and rabbits were treated dermally, five days per week for three weeks, with 0, 50, 250, 500, 1000 or 5000 mg/kg bw per day. Hepatotoxicity was seen in the dogs but not in the rabbits; effects on male reproductive organs were seen in both rabbits and dogs. The NOAEL was 500 ppm (equal to 13 mg/kg bw per day) in dogs, and 500 mg/kg bw per day in rabbits.

In a two-year study, benomyl was administered in the diet to rats at 0, 100, 500 or 2500 ppm. Benomyl was not carcinogenic and showed no compound-related effects at dietary levels up to and including 2500 ppm (equal to 109 mg/kg bw per day). In a two-year feeding study in mice at dietary levels of 0, 500, 1500 or 5000 ppm, benomyl caused liver tumours, and a no-effect level could not be established for hepatocellular neoplasms. Male mice had decreased testicular weights and thymic atrophy at 5000 ppm. The lowest dietary level was equal to 64 mg/kg bw per day.

In rats treated by gavage for 62 days with 45 mg benomyl/kg bw per day, decreased testicular and epididymal weight, reduced caudal sperm reserves and decreased sperm production, with generalized disruption of all stages of spermatogenesis were observed. After mating with untreated females, no effect was seen on reproductive behaviour, weight of the seminal vesicles,

sperm mobility, or related reproductive hormones. The NOAEL was 15 mg/kg bw per day. A lowering of male fertility rates has been reported, but this effect was not seen consistently. A single dose of 100 mg/kg bw or more administered to rats by gavage had effects 70 days after exposure which included decreased testicular weight and atrophy of the seminiferous tubules. The NOAEL was 50 mg/kg bw per day. In a recent study of reproductive toxicity, rats received dietary doses of 0, 100, 500, 3000 or 10 000 ppm benomyl. The NOAEL was 500 ppm (equivalent to 37 mg/kg bw per day), on the basis of effects on pup survival and pup growth and on testicular changes. Fertility indices were not affected at dietary levels up to 10,000 ppm.

In a study of developmental toxicity, mice were exposed by gavage to benomyl at doses of 0, 50, 100 or 200 mg/kg bw per day on days 7-17 of gestation. There was no indication of maternal toxicity, but benomyl was teratogenic at doses of 100 and 200 mg/kg bw per day and fetotoxic at 50 mg/kg bw per day. The major abnormalities included hydrocephaly, cleft palate, and limb defects. In studies of teratogenicity, pregnant rats were exposed to benomyl at doses up to and including 125 mg/kg bw per day on days 7-16 of gestation. Benomyl was teratogenic, the major effects being microphthalmia and hydrocephaly. The Meeting concluded that the NOAELs in rats were 30 mg/kg bw per day for teratogenicity and fetotoxicity and 125 mg/kg bw per day for maternal toxicity. In rabbits, benomyl was not teratogenic at doses up to 180 mg/kg bw per day (the highest dose tested), and no effect was seen on maternal toxicity or fetotoxicity at 90 mg/kg bw per day.

Benomyl has been adequately tested for genotoxicity in a range of assays. The Meeting concluded that benomyl does not directly damage genetic material but does cause numerical chromosomal changes both *in vitro* and *in vivo* as a result of its interference with the mitotic spindle proteins.

In an epidemiological study of workers exposed to benomyl, there was no reduction in fertility, as indicated by the birth rates, among the study population. Spermatogenesis in the workers was not examined. Cases of dermal sensitization to benomyl have been reported.

An ADI of 0-0.1 mg/kg bw was established on the basis of the NOAEL of 13 mg/kg bw per day in the two-year study in dogs and applying a safety factor of 100. This ADI should be used when assessing exposure to benomyl itself. Since the use of benomyl on crops gives rise to residues of carbendazim and since the ADI for carbendazim is lower than that which would be derived from the data on benomyl, the Meeting concluded that the intake of residues in food should be compared with the ADI of 0-0.03 mg/kg bw for carbendazim.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: <500 ppm, equal to <64 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
50 mg/kg bw per day (study of developmental toxicity)
<50 mg/kg bw per day (fetotoxicity in a study of teratogenicity)

Rat: 2500 ppm, equal to 109 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

500 ppm, equivalent to 37 mg/kg bw per day (study of reproductive toxicity)

30 mg/kg bw per day (teratogenicity and fetotoxicity in a study of developmental toxicity)

125 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rabbit: 180 mg/kg bw per day (study of developmental toxicity)

90 mg/kg bw per day (maternal toxicity and fetotoxicity in a study of developmental toxicity)

Dog: 500 ppm, equal to 13 mg/kg bw per day (one-year study)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw (benomyl)
0-0.03 mg/kg bw (carbendazim, with which residues of benomyl in food should be compared)

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to benomy[1]

Exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral, toxicity, rat	LD_{50} >10 000 mg/kg bw
	Dermal, toxicity, rabbit	LD_{50} (50% wettable powder) >10 000 mg/kg bw
	Dermal, irritation, rabbit	50% wettable powder - irritating
	Ocular, irritation, rabbit	50% wettable powder - irritating
	Dermal, sensitization, guinea-pig	Positive in maximization test
	Inhalation, toxicity, rat	LC_{50} of 50% wettable powder >4.01 mg/litre air
Mid-term (1-26 weeks)	Oral, 62 days, rat	NOAEL=15 mg/kg bw per day; reduced spermatogenesis
	Oral, developmental toxicity, rat	NOAEL=30 mg/kg bw per day; fetotoxicity and teratogenicity
Long-term (> one year)	Dietary, two years toxicity, dog	NOAEL=13 mg/kg bw per day; hepatotoxicity

BENOMYL, CARBENDAZIM AND THIOPHANATE-METHYL - EVALUATION OF EFFECTS ON THE ENVIRONMENT

Benomyl, carbendazim and thiophanate-methyl are systemic fungicides belonging to the benzimidazole group. They are broad-spectrum fungicides used on a wide variety of crops. Because of the development of resistance, benzimidazole fungicides are usually alternated with other compounds with a different mode of action. The available formulations include wettable powders, water-dispersible granules, flowable concentrates, dusts and granules.

Benomyl and thiophanate-methyl entering the environment are converted to carbendazim, which can be regarded as the environmentally relevant compound. Their half-lives are of the order of 2-19 h for benomyl and 3-4 days for thiophanate-methyl.

The carbendazim formed is degraded in the environment with a half-life of months under aerobic and anaerobic conditions in soil and water.

Carbendazim partitions from water to soil and sediment. It binds to the mineral components of the soil, probably by the imidazole ring. Adsorption is strong, and carbendazim is not leached through the soil despite the low K_{ow}. No contamination of groundwater can be expected, as confirmed in field monitoring studies of well water.

Abiotic degradation is considered to represent a minor route of degradation of carbendazim; micro-organisms, predominantly bacteria, are the major route of loss.

Only moderate bioaccumulation of carbendazim was seen in laboratory studies at constant exposure concentrations. There is rapid depuration on transfer to clean water. No significant bioaccumulation of carbendazim is expected in the field.

Benomyl had no effect on soil bacterial populations in laboratory studies. In greenhouse studies, application rates up to 89.6 kg ai/ha had little effect on soil-nitrifying bacteria. Field studies confirm these findings, even though transient effects on soil fungi have been observed.

The NOEC for green algae was 0.5 mg/litre.

Carbendazim is very toxic to fish, aquatic invertebrates and Mysid shrimp on an acute basis (LC_{50}s 0.007 mg ai/litre for fish; 0.087 mg ai/litre for aquatic invertebrates and 0.098 mg ai/litre for shrimp). The MATCs (maximum acceptable toxic concentrations) for rainbow trout, Daphnids and Mysid shrimp were 0.019, 0.004 and 0.035 mg ai/litre, respectively.

Field application rates of carbendazim are not expected to pose an acute hazard to non-target mammalian wildlife.

Carbendazim, thiophanate-methyl and benomyl have low acute toxicity to birds, with dietary LC_{50} values >5000 mg/kg diet. Field application rates are not expected to pose a hazard to birds.

Risk assessment

Aquatic environment

A simple screening model (GENEEC - EPA/OPP/EFED, 1995) for worst-case scenarios has been used to estimate the Predicted Environmental Concentration (PEC) of carbendazim in aquatic systems. In this assessment, the following use pattern has been used: application of 0.56 kg ai/ha of carbendazim to vineyards, four treatments at 14-day intervals. In addition, the following assumptions are used in the calculation: soil K_{oc}, 250; water-solubility, 8 mg/litre; present spray drift, 5%; depth of soil incorporation, 0; soil aerobic half-life, 180 days; aquatic aerobic half-life, 61 days; longest hydrolysis half-life, 175 days; and photolysis half-life, stable.

The GENEEC model results were as follows:

Peak concentration in a water body 2 m deep	56	ìg/litre
4-day concentration in a water body 2 m deep	54	ìg/litre
21-day concentration in a water body 2 m deep	48	ìg/litre
56-day concentration in a water body 2 m deep	38	ìg/litre.

The model is basically the same as that used in the UK and The Netherlands.

Toxicity Exposure Ratios (TERS) have been calculated as in Table 1. These indicate that the risk to all aquatic organisms, on either an acute or a chronic basis, is at least present and often large. However, reduced bioavailability owing to adsorption to sediment would reduce this apparent risk.

Contamination of surface waters by benomyl, carbendazim and thiophanate-methyl must be avoided to prevent toxic effects on aquatic organisms.

Table 1. Acute and chronic risk estimates for aquatic organisms following application of carbendazim to vineyards.

Time course	Organism	PEC (ìg/litre)	Toxicity (ìg/litre)	End-point	TER	Risk classification
Acute	Invertebrate	56	87	LC_{50}	1.55	Present
Acute	Fish	56	7	LC_{50}	0.125	Large
Acute	Shrimp	56	98	LC_{50}	1.75	Present
Chronic	Invertebrate	48	27	NOEC	0.56	Large
Chronic	Fish	48	3	NOEC	0.06	Very large
Chronic	Shrimp	45	35	NOEC	0.78	Large

Terrestrial environment

The PEC used for evaluation of acute effects is based on one application of 0.6 kg ai/ha, of which 100% reaches both the canopy and the soil. The soil PEC for chronic effects is based on four successive applications of 0.6 kg ai/ha, as on vines. As the degradation rate of carbendazim in soil is of the order of months and carbendazim is not mobile, no degradation is assumed. A further assumption was that the compound is dispersed into the top 5 cm of a soil with density 1.4 g/cm^3.

The summary of acute and chronic TERs (Table 2) indicate a "large" risk to earthworms in the soil. The risk to honey bees is regarded as being low. The large risk to earthworms is confirmed by field studies; no such studies are available for arthropods.

Table 2. Acute and chronic risk estimates for terrestrial organisms following application of carbendazim to vineyards.

Time course	Organism	PEC	Toxicity	End-point	TER	Risk classific-ation
Acute	Compost worm (*Eisenia foetida)*	0.86 mg/kg soil	5.7 mg/kg	LC_{50}	6.6	Present

Time course	Organism	PEC	Toxicity	End-point	TER	Risk classific-ation
Acute	Honey bee (*Apis mellifera)*	6 ìg/cm^3	>50 ìg/bee	LC_{50}	12[1]	Low
Chronic	Compost worm (*Eisenia foetida)*	3.43 mg/kg	0.6 mg/kg soil	NOEC for reproduction	0.17	Large
Chronic	Springtail *(Folsomiacandida)*	3.43 mg/kg	>1000 mg/kg	Reproduction	>290	Negligible
Chronic	Predatory mite *(Typhlodro-mus pyri)*	6 ìg/cm^3	38% reduction at 0.69 ìg/cm^3	Reproduction	-	-

[1] Hazard ratio estimate from toxicity per bee

4.5 BENTAZONE (172)

RESIDUE AND ANALYTICAL ASPECTS

Bentazone was evaluated originally in 1991 and subsequently in 1992 and 1994. At the 27th Session of the CCPR the delegation of Germany, supported by France, suggested that the residue definition for animal products should not include metabolites, as in practice no residues of metabolites were found. These delegations were also of the opinion that the LOD was too low when metabolites were included in the residue definition for plant materials.

Metabolism studies were conducted on goats and hens. In goats dosed at 3-50 mg ai/kg bw/day for 5 and 8 days, the parent bentazone constituted about 71-96% of the total radioactive residues (TRR) in milk, 71-97% in muscle, 94-98% in fat, 91-98% in kidney, 83-84% in liver, 97-100% in urine and 71% in faeces. The bile and liver contained bentazone *N*-glucuronide in addition to the parent compound. No 6-hydroxybentazone, 8-hydroxy-bentazone or AIBA (2-amino-*N*-isopropylbenzamide) could be found in the milk or tissues. When 6-hydroxybentazone and 8-hydroxybentazone were fed separately, residues were rapidly excreted (86.1% and 91.4% within 24 hours after the last dose, respectively). The residues consisted mainly of 6-hydroxybentazone or 8-hydroxybentazone with smaller amounts of their glucuronide and sulfate conjugates.

In hens dosed at 10 mg ai/hen/day for 5 days, the major residue components were the parent bentazone and its glucuronide conjugate. No AIBA was detected.

Taking into consideration the highest residues which may occur in plant commodities and the composition of the feed of animals, it was concluded that the residues in meat, milks and eggs would not exceed the present draft MRLs of 0.05 mg/kg.

Since in the new studies no AIBA could be detected in any of the analysed tissues, milk, eggs or excreta even when extremely high doses were fed to goats and hens, the Meeting concluded that there was sufficient evidence to change the definition of the residues in animal products to bentazone alone. The change of the definition does not affect the estimated maximum residue level (0.05* mg/kg) for meat, milks and eggs.

The Meeting also reconsidered the residue definition and the recommended limits for plant products. As the recommended maximum residue limits set at or about the limit of determination indicate undetectable residues, none of the residue components (bentazone, 6-hydroxybentazone and 8-hydroxybentazone) should be present in detectable concentration, and their LODs should not be summed. Each of the residue components can be determined individually with an LOD of <0.02 mg/kg. The LOD of 0.05* mg/kg therefore gives a 250% allowance for regulatory laboratories, where the analytical conditions might not be optimized as well as in laboratories specialized in the analysis of these compounds.

The Meeting therefore confirmed its previous recommendations for plant commodities.

4.6 BIFENTHRIN (178)

RESIDUE AND ANALYTICAL ASPECTS

Bifenthrin was first evaluated at the 1992 JMPR and MRLs of 0.05* mg/kg were recommended for barley, maize and wheat to cover field applications. Information has now been made available on the use of bifenthrin as a grain protectant on stored grain.

At the 26th Session of the CCPR (ALINORM 95/24, 1994, para 295) the delegations of Germany and France considered that the available data base on dry hops was inadequate for the proposed MRL. Additional explanatory notes on bifenthrin residue trials on hops have now been made available to the Meeting. Details of recent supervised trials on hops in the UK have also been supplied.

The residue analytical method for bifenthrin in cereal grains and milling and baking products relies on acetone extraction followed by solvent partition and column chromatography for clean-up and GLC with ECD for quantitative analysis. Good analytical recoveries were achieved for bifenthrin on grain (0.1-0.4 mg/kg), bran (0.3 and 20 mg/kg) and white flour, wholemeal flour and white bread (all 0.3 mg/kg).

A similar method was used for the analysis of hops where analytical recoveries of 67-113% were achieved for 11 spiked samples over the concentration range 0.01 mg/kg to 10 mg/kg. The limit of determination was 0.01 mg/kg.

In the UK registered use bifenthrin may be applied 5 times to hops at a spray concentration of 0.004 kg ai/hl. The hops may be harvested 10 days after the final application. The hops in the UK supervised trials were harvested 7 days after the final application, which was not strictly within GAP. However, the Meeting regarded the results as being consistent with the data from the German trials and as providing additional support.

The Meeting was informed that a registration for the use of bifenthrin on hops would not be pursued for the time being in Germany. The Meeting noted that the German residues data for dried hops, where bifenthrin spray concentrations were 0.0025-0.0038 kg ai/hl and the hops were harvested 10 days after the final application, were within UK GAP and re-evaluated the data according to UK GAP. Residues on dried hops at 10 days PHI in the 12 trials were 0.1, 0.7, 0.9, 1.0, 1.8, 1.9, 1.9, 1.9, 2.5, 2.7, 2.9 and 4.2 mg/kg.

The US use pattern on hops was reported in the 1992 JMPR Residue Evaluations as pending. The US trial data on hops reported in the 1992 Evaluations were evaluated against US GAP for hops reported to the current Meeting (3 applications, 0.1 kg ai/ha, spray concentration 0.0033 kg ai/hl and 14 days PHI). Residues in dried hops in the eight US trials were 0.5, 0.5, 0.7, 0.9, 1, 5, 5 and 5 mg/kg. Residues in dried hops from the same trials harvested 28 days after the final application also ranged up to 5 mg/kg.

Bifenthrin residues in dried hops from the total of twenty trials in the USA and Germany were 0.1, 0.5 (2), 0.7 (2), 0.9 (2), 1.0 (2), 1.8, 1.9 (3), 2.5, 2.7, 2.9, 4.2, and 5 (3) mg/kg. With a number of residues from supervised trials at 5 mg/kg, it is likely that in commercial practice residues in excess of 5 mg/kg will occur. The Meeting agreed that the data supported the current recommendation of 10 mg/kg for bifenthrin in dried hops.

Bifenthrin is effective as a grain protectant. It is registered in combination with malathion for use on stored grain in Belgium, and is proposed for registration in Brazil, France, Morocco, Poland and the UK. Bifenthrin is to be used at 0.3-0.4 g ai/t in combination with malathion at 6-8 g ai/t.

Storage experiments on barley in the UK and on wheat in Belgium, France and the UK showed that bifenthrin residues are stable for 12 months on stored grain at 20°C. Other pyrethroid grain protectants have shown similar persistence. The levels of bifenthrin on the grain at the beginning and end of storage will essentially be the same.

The Meeting was reluctant to proceed with a recommendation for cereals until a number of points had been clarified. Information is needed on the efficiency of extraction of aged residues, national MRLs covering use on stored grains, and the fate of bifenthrin residues during commercial milling, baking and malting. Information should also be provided when proposed registrations become official or when new registrations for grain protectant uses are obtained.

FURTHER WORK OR INFORMATION

Desirable

1. Information on the efficiency of extraction by acetone of aged bifenthrin residues on stored grain. Acetone extraction is the first step in the analytical method.

2. Information on national MRLs for bifenthrin relating to uses on stored grains.

3. Information on the fate of bifenthrin during the commercial milling of wheat treated with it post-harvest. The studies should simulate commercial practices, including the effects of commercial cleaning.

4. Information on the fate of bifenthrin during the baking of bread.

5. Information on the fate of bifenthrin during the commercial malting of barley treated with it post-harvest. The studies should simulate the commercial process.

4.7 BUPROFEZIN (173)

RESIDUE AND ANALYTICAL ASPECTS

Buprofezin was first evaluated by the 1991 JMPR, which estimated an ADI of 0-0.01 mg/kg bw and recommended TMRLs for cucumber, tomato and oranges with 8 required and 4 desirable items of further work or information. Data were provided in response to the 1991 requirements on the fate of residues in water (acidic conditions), metabolism in ruminants and plants, additional

supervised trials on citrus, cucumber and tomatoes, and other items.

Data provided by the manufacturer allowed the Meeting to conclude that the identity of the thiobiuret metabolite formed in water under acidic conditions had been confirmed.

The 1991 JMPR reviewed data on the metabolism of buprofezin in rats and reports of the metabolic products found in the excreta of hens and proposed a tentative metabolic pathway for animals, but required a ruminant metabolism study. Such a study on a lactating Jersey cow fed the equivalent of 27 ppm in the diet of [^{14}C]phenyl-labelled buprofezin for 7 days was reviewed by the Meeting. More than 64% of the total radioactive dose was excreted in the faeces and urine, over twice as much in faeces as in urine. Tissues and milk accounted for 1.2% of the administered dose, the highest proportion in the liver (0.7%), the next highest in muscle (0.2%) and the lowest in the kidneys (0.04%).

Unchanged buprofezin and *p*-hydroxybuprofezin were the only identified residues found in the faeces, accounting for 61% of the total radioactive residue (TRR). These two, with isopropylphenylurea (IPU), hydroxy-IPU, acetamidophenol and low levels of the dione metabolite were found in urine (35% of the TRR was identified). No unchanged buprofezin was detected in the liver, kidneys, or milk. None of the several metabolites in the muscle and fat could be identified owing to the low levels present ($\leq$0.02 mg/kg buprofezin equivalent).

In liver the predominant residue was *p*-hydroxybuprofezin (11% of the TRR), with lesser amounts of IPU, hydroxy-IPU and *p*-acetamidophenol (19.1% of the TRR was identified). A similar profile of the same metabolites was found in the kidneys (33% of the TRR identified). In milk (15% of the TRR identified) the same compounds were found, but *p*-acetamidophenol was the predominant residue (9.2% of the TRR). Several unidentified metabolites were also observed in each matrix, the major one constituting 5.9, 4.5 and 4.9% of the TRR in the liver, kidneys and milk respectively.

From these findings two basic metabolic pathways are proposed for ruminants. The first is hydroxylation at the para position of buprofezin, followed by cleavage of the thiadiazinane ring and loss of the $-CH_2-S-C=N-C(CH_3)_3$ group to leave hydroxy-IPU which is degraded to N-hydroxyphenylacetamide (*p*-acetamidophenol). The second proposed route involves formation of the dione metabolite (found in urine as well as in citrus metabolism) as an intermediate before cleavage of the thiadiazinane ring with loss of $-CH_2-S-C=O$ to form IPU which is hydroxylated and metabolized by multiple steps also to the acetamidophenol. The dione was not reported in the hen study, but was found in the degradation of buprofezin in soil and water.

The metabolic pathway proposed for ruminants is consistent up to a point with that proposed by the 1991 JMPR for animals on the basis of the data on rats and hens. The difference is an additional hydroxylation of the phenyl ring in rats to form dihydroxyphenyl-buprofezin, followed by methylation of one of the hydroxy groups to form hydroxy-methoxy-buprofezin. Neither of these compounds nor the thiobiuret metabolite were among those used as reference standards in the cow metabolism study. It is possible that unidentified metabolites found in the cow study could have included them.

From these studies the Meeting concluded that the metabolism in ruminants is reasonably well understood. Even so, it would have preferred to see a higher proportion of the TRR identified in liver and kidney, since some of the unknown metabolites occurred at levels near or above some of those which were identified. For this reason and for further confirmation of

proposed metabolic pathways, the Meeting concluded that a desirable extension to the work already done would be the analysis of any reserve (or future) cow liver and kidney samples for the two additional metabolites found in rats and for thiobiuret (the major product formed in water under acidic conditions).

The Meeting confirmed the view of the 1991 JMPR that any future uses of buprofezin on major poultry feed items may require a more definitive poultry metabolism study.

The 1991 JMPR reviewed information on the metabolism in plants. On tomatoes buprofezin *per se* accounted for >90% of the residue after 7 days. In geoponic- or hydroponically-grown rice plants residues were taken up by the roots and translocated to other plant parts, the major residue being unchanged buprofezin and the major metabolite *p*-hydroxybuprofezin. In several other hydroponically-grown plants buprofezin was again the major residue, but the major metabolite was buprofezin sulfoxide, followed by the phenylbiuret. Because of these differences, the 1991 Meeting concluded that a study of metabolism by a major crop on which there was extensive use was needed, and required a citrus metabolism study. The 1991 JMPR also requested analysis for buprofezin sulfoxide, the phenylbiuret and *p*-hydroxybuprofezin in future field trials and for the thiobiuret in future metabolism or residue studies if it was found as a metabolite in citrus.

A citrus metabolism study was completed on glass-grown lemon trees at rates approximating GAP. Little translocation was found in immature fruit after applications of [^{4}C]buprofezin to leaves or stems. The manufacturer reported that the thiobiuret (BF-25), phenylbiuret (BF-11) and buprofezin sulfoxide (BF-10) were all used as reference standards in the study and were not detected. The one and two-dimensional TLC and HPLC analyses supported this with respect to buprofezin sulfoxide and the phenylbiuret, but none of the chromatograms of samples or standards provided confirmed analyses for the thiobiuret.

The Meeting concluded that there was little likelihood that significant levels of the phenylbiuret or buprofezin sulfoxide would be formed from topical applications to citrus and that this conclusion could reasonably be extended to other commodities for which temporary limits had been proposed, when taking into account the previously reviewed study on tomatoes. In view of the presence of significant levels of unidentified metabolites, proof that the thiobiuret was formed under acidic conditions and the lack of firm experimental evidence that it was not present in the citrus metabolism study, the Meeting had no basis to conclude that this compound is not formed during citrus metabolism.

As for other aspects of citrus metabolism, on day zero essentially all of the radioactivity was in or on the peel and 93-97% in the surface wash. After 14 days the proportion in the surface wash was reduced to 65% of the total and after 75 days to 16%. After these two periods the total residues in the peel (extractable + non-extractable) were 34.6 and were 82.9% respectively, indicating penetration from the surface into the peel with time. This was confirmed by the increase in the low pulp residue (from <0.4 to 1.3% of the total) over the same period.

After 14 days 66% of the TRR was unchanged buprofezin, 6% the dione metabolite (3-isopropyl-5-phenyl-1,3,5-thiadizinane-2,4-dione), 5.7% 2-amino-2-methylethyl-2-methylpropyl-4-phenylallophanate (designated as O or metabolite A), 3.6% unidentified metabolite B and 1.7% 1-isopropyl-3-phenylurea (IPU). After 75 days the levels were 18% buprofezin, 34% metabolite A, 9% metabolite B, 8% IPU and 7% dione.

On the basis of these findings the proposed metabolic pathway for plants is similar to, but more complex than, that outlined in the 1991 monograph. One route involves oxidation at the para position on the phenyl group to form hydroxybuprofezin, followed by cleavage of the heterocyclic ring to form hydroxy-IPU. A second route involves oxidation of the sulfur followed by ring cleavage to form the phenylbiuret, which is further degraded to IPU and oxidized to hydroxy-IPU.

In a third route oxidation of the *tert*-butylimino group to form the dione is followed by ring cleavage and formation of IPU, which is again oxidized to hydroxy-IPU. In the fourth route postulated hydroxylation of the *tert*-butyl group to an intermediate designated as BF-4 is followed by ring cleavage to give metabolite A, which is degraded to IPU and this again may be oxidized to hydroxy-IPU. In all cases the IPU may also be degraded to phenylurea.

Because of the multiple metabolic routes shown to occur in plants, future submissions of data on commodity groups other than fruiting vegetables and citrus should be accompanied by geoponic metabolism studies for the groups in question. The metabolism studies should be conducted before the field trials. If significant residues of additional metabolites are identified, field trials may need to include analyses for these as well.

Several extractability studies and analytical methods for buprofezin (including ICI method PPRAM 82) were provided in response to the requirement for validation of PPRAM 82, which was used for most of the trials reviewed by the 1991 JMPR. Several of the studies submitted to the present Meeting demonstrated that acetone (used in method 82) efficiently extracts buprofezin from fortified samples.

The primary response to the 1991 requirement was re-analysis of peaches which were found by PPRAM 82 in 1990 to contain 0.66 mg/kg buprofezin. The extraction procedures tested in the re-analysis were cold acetone, cold acetone/water, acetone reflux, cold methanol and methanol/water reflux. Results were similar in all cases, ranging from 0.52 to 0.78 mg/kg (mean 0.66 mg/kg), with 68-87% recoveries from 0.5 mg/kg fortifications.

The Meeting concluded that the available information sufficiently validated method 82 for the MRL levels recommended in 1991 (0.3 to 0.5 mg/kg), but agreed that additional validation was still desirable to allow an accurate estimate of a limit of determination. Full validation is needed for any future data developed with this method or others.

Another GLC method described for the determination of buprofezin and its dione and isopropylphenylurea metabolites has a limit of determination of 0.05 mg/kg in tomato products.

The 1991 JMPR required additional data from outdoor supervised trials on cucumbers and tomatoes if such uses were shown to be GAP, and additional data on oranges with analyses for *p*-hydroxybuprofezin, thiobiuret, buprofezin sulfoxide and phenylbiuret in addition to buprofezin. Unchanged buprofezin had been the only significant residue in a tomato metabolism study. Data were provided for cucumbers, tomatoes and citrus.

Citrus. The temporary MRL of 0.3 mg/kg recommended for oranges by the 1991 JMPR was based mainly on Japanese trials, since other trials did not reflect maximum GAP conditions (trials in South Africa showed <0.05 mg/kg after 127 days but the GAP PHI is 90 days) or otherwise did not comply with GAP (too many applications or excessive rates). The 1991 Meeting considered maximum residues in the Japanese trials according to GAP to be approximately 0.3 mg/kg on a

whole fruit basis, from a GAP application rate of 2.5 kg ai/ha (50 g ai/hl) and a 14-day PHI. Additional data from trials reflecting GAP were required.

The Meeting was informed that current Japanese GAP involves 5 applications at 25 g ai/hl and a 14-day PHI. Application rates are not on a kg ai/ha basis because that is volume-dependent and the volume varies according to the size of the trees. Therefore, it follows that the Japanese trials on oranges reviewed in 1991 were at twice GAP rates.

Additional citrus data from Brazil, Spain and Japan were provided to the Meeting in response to the 1991 requirement. In Brazilian trials the maximum residues in oranges were 0.04 mg/kg after 28 or 63 days and <0.01 mg/kg after 91 days from applications at 0.5 kg ai/ha (30 g ai/hl). Although the trials were according to FAO guidelines, buprofezin was reported not to be registered in Brazil and the data could not be related to the known GAP of other countries. The application rate was reported to be twice the "recommended" dosage, but it is within the range of GAP reported by some countries (either as g ai/ha or g ai/hl, not always both). Samples were adequately stored for the short period before analysis. The Meeting concluded that the Brazilian data were not sufficiently related to available GAP to estimate a maximum residue level.

In three Spanish trials maximum residues in whole oranges were 0.06 mg/kg after the Spanish 7-day GAP PHI, from an application rate of 1 kg ai/ha (25 g ai/hl), which was reported to be current Spanish GAP. This is an increase from the 10-12.5 g ai/hl rate reported as Spanish GAP in the 1991 JMPR monograph. The limit of determination for the HPLC determination was approximately 0.02 mg/kg in whole oranges for both buprofezin and *p*-hydroxybuprofezin. No residues (<0.02 mg/kg) of the latter were detected.

In a Japanese trial maximum residues on natsudaidais from GAP application rates were 0.7 and 0.4 mg/kg after 21 and 30 days respectively, the GAP PHI being 14 days. Five knapsack applications at GAP rates were made, each at 25 g ai/hl (1.25 kg ai/ha), to 2-tree plots. The trials were therefore within GAP but did not reflect the shortest GAP PHI. The reported limit of determination is 0.01 mg/kg for buprofezin and *p*-hydroxybuprofezin, but chromatograms suggest that 0.02-0.05 mg/kg may be more realistic.

Analytical samples from the Japanese trials stored at -20°C showed 80-106% recoveries of parent and *p*-hydroxybuprofezin after 58 days (pulp) or 90 days (peel). The field samples were stored at -10°C for periods ranging from 60 to 90 days for the shorter PHI samples to over twice that period for samples taken at longer intervals. Taken together with the good stability reported in 1991 of residues in apples, peaches and kiwifruit stored up to a year at -20°C, the Meeting concluded that the stability of stored samples in the Japanese trials was reasonably validated.

In the data submitted to the Meeting buprofezin residues in whole fruit were approximately 3 to 10 times those in the pulp, depending on the interval, which is consistent with the 3 to 8 times reported in the 1991 monograph. No residues of *p*-hydroxybuprofezin (<0.02 mg/kg) were detected in the peel, pulp or whole oranges in either the Spanish or Japanese trials. This is consistent with the metabolism study for this PHI and at the relative residue levels of buprofezin.

Although results have been provided from 14 supervised trials in 1991 and 1995 in 4 countries, few of them reflect GAP. The Japanese trials are the most significant because they most closely reflected maximum GAP conditions. The results from trials according to relevant GAP were South Africa, 1 trial, <0.05 mg/kg (4 results); Spain, 3 trials, 0.06 mg/kg, 2 x 0.0.03

mg/kg; Japan, 1 trial, 0.7, 0.4, 3 x 0.2, 0.08 mg/kg, giving altogether 0.7, 0.4, 0.2(3), 0.08, 0.06, <0.05(4) and 0.03(2) mg/kg.

The Meeting concluded that the available data were still insufficient to recommend an MRL for such a major commodity as citrus and recommended that the current temporary limit of 0.3 mg/kg be withdrawn. For future consideration of a citrus limit additional data reflective of GAP (including maximum application rates and shortest PHIs) need to be provided, together with confirmation of the current GAP, with labels in English or with an English translation, and all critical supporting information including a citrus processing study.

Cucumbers. The temporary MRL of 0.3 mg/kg estimated by the 1991 JMPR was based on data (mainly indoor) from The Netherlands, the UK, Greece and Japan. Maximum residues representing GAP were 0.06 mg/kg from The Netherlands (3-day PHI) and Greece (7-day PHI) and 0.21 mg/kg from trials according to proposed UK GAP (3-day PHI). Maximum residues reflecting GAP in a Japanese trial were 0.13 mg/kg after three days (the GAP PHI is 1 day), at 0.6 times the maximum permitted rate and 0.6 mg/kg at 1 day from a double rate. Residues were roughly proportional to the application rate. Because only the trials in Greece were outdoor, the Meeting required additional data from outdoor trials if outdoor uses are confirmed to be covered by GAP. Most of the GAP for cucumbers reported to the 1991 JMPR did not distinguish between field and glasshouse uses, but most of the trials were glasshouse.

No confirmation was received of non-glasshouse GAP for buprofezin uses on cucumbers, although uses listed by the 1991 JMPR for The Netherlands, the UK and Japan were confirmed (The Netherlands and UK confirmed as glasshouse uses). Accordingly there were no data from supervised field trials. However, additional data from trials according to GAP at four glasshouse sites in Japan were received. Residues at the 1-day Japanese GAP PHI were 0.4 to 0.8 mg/kg (mean 0.6 mg/kg), decreasing to a mean residue of 0.08 mg/kg after 7 days. On the basis of these new results, together with data reviewed by the 1991 JMPR, the Meeting recommended that the previous temporary MRL of 0.3 mg/kg should be replaced by an MRL of 1 mg/kg.

Tomatoes. The temporary MRL of 0.5 mg/kg recommended by the 1991 JMPR was based on trials in The Netherlands, the UK, Greece an Japan, with maximum residues reflecting GAP in The Netherlands of 0.2 mg/kg (0.3 mg/kg from a 1.3-fold rate) (GAP 0.075 kg ai/hl, 3-day PHI); UK 0.3 mg/kg (proposed GAP the same as The Netherlands) and Japan 0.4 mg/kg (GAP 1-1.9 kg ai/ha or 0.025 kg ai/hl). As with cucumbers, additional data would be required if field uses are confirmed to be GAP. GAP reported by the 1991 JMPR did not generally make a distinction, although most of the trials reviewed were glasshouse.

No specific information on GAP for field uses on tomatoes was provided to the Meeting, but additional data from Italy (field) and Japan (glasshouse) were provided. GAP in Germany, The Netherlands and the UK, and indirectly in Japan (where trials were reported as being according to GAP) was confirmed as applying to glasshouse uses. No GAP was provided for Italy, although the trials were within reported Japanese GAP. After 2 days (compared to the Japanese 1-day PHI) residues at the three Italian field locations ranged from 0.08 to 0.2 mg/kg, with no concentration reported in the juice and puree, although details of the processing were not given. No residues (<0.015 mg/kg) of *p*-hydroxybuprofezin were detected in any sample. Samples were stored appropriately to ensure their integrity.

The two applications in the Italian trials were also within the total seasonal application permitted in German GAP, although German GAP allows only one application. The rates

expressed as kg ai/hl are also compatible with GAP rates reported in 1991 for Bulgaria, former Czechoslovakia, Jordan and Poland (Jordan and Poland have a 3-day PHI; the Italian results were at 2 or 7 days). The available results show a slow decrease in residues during the first 3 days. Although the Italian results cannot be strictly related to the GAP provided, they can be considered supplementary supportive information. Residues were generally lower than in the Japanese trials (see next para.), but the application rate expressed as kg ai/ha was higher in the latter, although the kg ai/hl rate is the same. A reasonable limit of determination for the HPLC method used would be 0.02 mg/kg.

Residues in the Japanese glasshouse trials according to GAP ranged from 0.3 to 0.7 mg/kg after 1 day, decreasing to 0.1 to 0.3 mg/kg after 7 days. Controls ranged from <0.005 to 0.04 mg/kg. An LOD of 0.05 mg/kg would appear to be reasonable for the method used (GLC with NP detection), according to chromatograms provided.

Taking into account residues from GAP applications up to 0.3 mg/kg in trials reviewed by the 1991 JMPR and up to 0.7 mg/kg in the new trials, the Meeting recommended that the previously recommended temporary MRL of 0.5 mg/kg should be replaced by an MRL of 1 mg/kg.

Processing tomatoes with field-incurred residues from exaggerated application rates revealed concentration factors of 23 and 34 from unwashed fruit to wet and dry pomace respectively. No significant concentration was observed in juice, puree or paste and residues of the dione metabolite did not exceed 0.02 mg/kg in dry pomace, even from more than twice the field application rate. No residues of the isopropylphenylurea metabolite were observed.

The JMPR reported no significant loss of buprofezin from apples, peaches and courgettes and only 13% from kiwi fruit after storage up to a year at -20°C. New information showed mean recoveries of 80-106% of both buprofezin and *p*-hydroxybuprofezin from 0.5 mg/kg fortification levels after storage of citrus for 56-58 days (flesh) or 91-93 days (peel) at -20°C. In cucumbers stored for 130 days at -20°C the recovery of buprofezin at 0.2 mg/kg fortification was reported as 90%. Mean recoveries of buprofezin added to tomatoes at 0.05 mg/kg ranged from 100 to 114% at four sites after storage for periods ranging from 53 to 94 days.

Residues in animals. The 1991 JMPR reviewed a conventional 28-day dairy cow feeding study which included feeding levels of 20 and 200 ppm in the diet. No residues of buprofezin (<0.01 mg/kg) were reported in muscle, kidney, liver, fat or milk from the low dose. On the basis of these results and the 0.5 and 0.3 mg/kg temporary limits recommended for tomato and oranges respectively, the 1991 Meeting tentatively concluded that residues of buprofezin *per se* were unlikely to occur in the muscle, kidneys, liver or milk of cattle, but recommended reconsideration of this conclusion in the light of required processing information and animal metabolism studies, which were provided to the present Meeting.

A 7-day metabolism study on a dairy cow was conducted at the equivalent of 27 ppm in the diet, a similar level to the 20 ppm feeding study reviewed by the 1991 JMPR. The metabolism study supports the finding in the feeding trial that residues of buprofezin are unlikely in the muscle, offal or milk of cattle at 20 ppm feeding levels. However, it also reveals that the major residue in animal products is *p*-hydroxybuprofezin (in the liver and kidneys) or *p*-acetamidophenol (in milk), not the parent compound determined in the feeding study. In the metabolism study, *p*-hydroxybuprofezin occurred at 0.13 mg/kg in liver, 0.07 mg/kg in kidney and <0.001 mg/kg in milk with lower levels of other metabolites. In milk the highest residue was

p-acetamidophenol at 0.002 mg/kg. Residues in muscle were ≤ 0.02 mg/kg buprofezin equivalent and could not be identified.

The tomato processing study showed concentration of buprofezin by factors of 23 and 34 in wet and dry pomace respectively. With worst-case assumptions (e.g. residues at the proposed MRL level of 1 mg/kg in fruit, 34-fold concentration in dry tomato pomace, feeding levels of dry pomace of 25% of the diet in beef and 10% in dairy cattle) it can be estimated from the metabolism study that the major residue *p*-hydroxybuprofezin in cattle could occur at approximately 0.04 mg/kg in liver, 0.02 mg/kg in kidney and <0.001 mg/kg in milk, and *p*-acetamidophenol also <0.001 mg/kg in milk. Although no maximum residue level has been estimated for citrus, similar levels might be expected from the feeding of dry citrus pomace if the concentration factors are similar. Concentration in citrus pomace would be expected since most of the buprofezin residue has been shown to be in the peel. This observation and the concentration found in tomato pomace support the need for a citrus processing study.

Therefore, while the 1991 finding that no residues of buprofezin *per se* would be expected in meat, offal and milk was confirmed, there is a potential for low residues of *p*-hydroxybuprofezin in liver and kidney. Although a conventional feeding trial has been conducted it was less useful than it might have been because only buprofezin was determined, not the residues likely to occur, mainly hydroxybuprofezin.

The guidance on the need for conventional feeding studies in the 1993 JMPR report requires feeding trials if detectable residues (>0.1 mg/kg) occur in feeds and metabolism studies indicate that residues may occur at levels >0.01 mg/kg. Even if it is assumed that residues in the whole fruit before processing into pomace are likely to be ≤ 50% of the MRL (generally true for tomato and citrus), the information on buprofezin indicates that an adequate conventional animal transfer study is required.

The Meeting therefore concluded that the available data were insufficient to estimate reliable maximum residue levels for animal products. The information required would include a conventional feeding trial in which the residues determined would include at least buprofezin and *p*-hydroxybuprofezin, and preferably also *p*-acetamidophenol in milk, with details of analytical methods. A suitable definition of the residue in animal products can be determined when these data are available, should it be decided that MRLs for animal products are needed.

Because a new metabolism study on citrus and new residue data on plants were available, the Meeting reconsidered the 1991 JMPR definition of the residue for regulatory purposes as buprofezin. The 1991 conclusion was based to a large extent on the tomato metabolism study showing over 90% of the residue in tomatoes to be unchanged buprofezin after 7 days.

The citrus metabolism study showed unchanged buprofezin to account for 66% of the residues after 14 days and 18% even after 75 days. After 75 days the major residue was shown to be metabolite A (2-amino-2-methylethyl-2-methylpropyl-4-phenylallophanate). No significant residues of buprofezin sulfoxide (reported in hydroponic metabolism studies) or the phenylbiuret or thiobiuret metabolites were reported. However, as noted earlier, there was no experimental evidence provided to demonstrate that residues of the thiobiuret metabolite did not occur in citrus. In supervised trials data submitted to the Meeting no residues of *p*-hydroxybuprofezin were reported in citrus or tomato.

On the basis of these findings the Meeting confirmed the 1991 JMPR recommendation

that the definition of the residue for regulatory purposes in cucumber, tomato and oranges should be buprofezin. The Meeting was informed by the manufacturer that the definition of the residue for human foods of plant origin is buprofezin *per se* in Spain, The Netherlands, Belgium, Switzerland and Japan. The definition may need to be re-assessed if MRLs are proposed in the future for additional crop types (since metabolism varies among crops) or if the need is indicated when the desirable information listed below is provided.

Recommendations for MRLs are recorded in Annex 1.

FURTHER WORK OR INFORMATION

Desirable

1. Analysis of any reserve cow liver and kidney samples from the ruminant metabolism study for the presence of the dihydroxybuprofezin, hydroxymethoxybuprofezin and thiobiuret metabolites.

2. Further validation of PPRAM method 82 with sufficient chromatograms, recoveries and controls to permit an accurate estimate of the limit of determination.

3. Information on buprofezin and *p*-hydroxybuprofezin residues in food and commerce or at consumption, especially on buprofezin residues in commodities for which buprofezin uses are approved.

4. A conventional animal transfer study in which residues of buprofezin, *p*-hydroxybuprofezin and (in milk) *p*-acetamidophenol are determined, with suitable and validated analytical methods. Alternatively, reserve samples from the original transfer study can be analyzed for these compounds if it can be convincingly demonstrated that such analyses would still be valid after prolonged storage. These studies are highly desirable, and would be required before maximum residue levels could be estimated for animal products.

5. Further information on national definitions of the residue for MRLs for crop and animal commodities.

6. Should citrus MRLs be contemplated in a future submission, the following further work or information would be:

Desirable Experimental evidence that the thiobiuret metabolite does not occur during citrus metabolism.

Required A citrus processing study, including analyses for the major residues identified in the metabolism study (e.g. buprofezin, metabolite A and the thiobiuret derivative unless it has been shown not to be formed during citrus metabolism).

4.8 CAPTAN (007)

TOXICOLOGY

In 1984, the JMPR estimated the ADI of captan for humans to be 0-0.1 mg/kg bw on the basis of an NOAEL in a study of reproductive toxicity in rats of 12.5 mg/kg bw per day and a safety factor of 100. The 1990 JMPR reviewed additional data but did not change the ADI.

Additional information on the distribution, biotransformation, excretion, and potential for binding to DNA in rodents has been reviewed by the present Meeting. Data on genotoxicity *in vitro* and *in vivo* and on short-term toxicity were also reviewed.

The excretion profiles of male and female rats were similar, the urinary route predominating. The residual tissue concentrations seven days after dosing were negligible in animals of both sexes, the highest concentrations being found in the kidneys and blood. The metabolism of captan in rats appears to involve the evolution of thiophosgene, derived from the trichloromethylthio moiety. Thiophosgene is detoxified, at least in part, by three mechanisms: oxidation and/or hydrolysis to carbon dioxide; reaction with the cysteine moiety of glutathione to yield thiazolidine-2-thione-4-carboxylic acid; and reaction with sulfite to produce dithiobis(methanesulfonic acid). Degradation in the gastrointestinal tract appears to play a major role in the metabolism of captan.

Studies on the hyperplasia induced by captan showed that prominent crypt-cell hyperplasia was induced within 28 days in the proximal duodenum of mice fed diets containing 6000 ppm captan for 91 days or 800, 3000, or 6000 ppm for 56 days. The NOAEL was 400 ppm, the lowest dose administered for 56 days, equivalent to 60 mg/kg bw per day, on the basis of duodenal hyperplasia.

Captan has been adequately tested for genotoxicity in a range of assays, which demonstrate that it is mutagenic and clastogenic *in vitro* but not *in vivo*. The *in-vitro* responses are reduced or abolished by the presence of liver homogenates, serum, glutathione, or cysteine whenever these experimental modifications have been investigated. Studies of the genotoxicity of captan in mouse duodenum indicate that it does not bind covalently to DNA (although metabolic incorporation of the *N*-trichloromethylthio-carbon does occur) and nuclear aberrations are not induced. The Meeting concluded that captan does not present a significant genotoxic risk, owing to the presence of an efficient detoxification mechanism *in vivo*.

There appear to have been no studies on the effects of captan on glutathione levels analogous to those conducted with folpet. Dietary studies of 4-8 weeks duration have shown that irritation and consequent inflammation as well as hyperplasia occur in the proximal duodenum of mice. These data indicate that sustained proliferative stimulation of the proximal duodenum is a consequence of oral administration of captan. The Meeting concluded that this finding represents an important element in the process by which captan, which is not genotoxic *in vivo*, induces tumours in the mouse gastrointestinal tract.

The information available to the present Meeting provides no basis for altering the existing ADI for captan, which is based on an NOAEL of 12.5 mg/kg bw per day, determined in studies of reproductive toxicity in rats and monkeys, and a 100-fold safety factor.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 400 ppm, equivalent to 60 mg/kg bw per day (56-day study of toxicity)

Rat: 250 ppm, equivalent to 12.5 mg/kg bw per day (study of reproductive toxicity)

Dog: 100 mg/kg bw per day (66-week study of toxicity)

Monkey: 12.5 mg/kg bw per day (study of developmental toxicity)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

- Further observations in humans

4.9 CARBENDAZIM (072)

TOXICOLOGY

Carbendazim was evaluated toxicologically by the Joint Meeting in 1973, 1977, 1983 and 1985. In 1985, the Meeting confirmed the ADI of 0-0.01 mg/kg bw established in 1983, on the basis of a review of data on the toxicity of carbendazim and benomyl and incorporating a higher-than-normal safety factor in view of the paucity of data on individual animals in many studies. The compound was reviewed by the present Meeting within the CCPR periodic review programme, with particular attention to the recent Environmental Health Criteria monograph on carbendazim (EHC 149).

Carbendazim is readily absorbed by animals after oral exposure and rapidly metabolized. It is eliminated in the faeces and excreted in the urine. The tissue distribution showed no bioconcentration. In rats, 2-[(methoxycarbonyl)amino]-1*H*-benzimidazol-5-yl hydrogen sulfate was identified as the main metabolite. The results of comparative studies in rats and mice indicate that the detoxification capacity of mouse liver may become saturated at high doses. Carbendazim is poorly absorbed via the dermal route in rats. Within 24 h, only about 0.2% of a single dose of 0.6 mg was excreted in the urine and faeces.

Carbendazim has low acute toxicity, with an oral LD_{50} in the rat of >10,000 mg/kg bw. The clinical signs of toxicity after high single doses were generally non-specific. Testicular degeneration has been observed after single oral doses of $\geq$1000 mg/kg bw in rats. Wettable powder formulations containing carbendazim have been shown to be irritating to rabbit skin and eyes but did not induce skin sensitization in Buehler-type tests. The WHO has classified carbendazim as unlikely to present an acute hazard in normal use.

In 90-day dietary studies in rats, increased liver weight was seen at 1350 ppm (the highest dose tested in one study), without any histological change. The overall NOAEL was 500 ppm, equivalent to 50 mg/kg bw per day. In dogs treated by dietary administration for up to two years at levels up to and including 4500 ppm, hepatotoxicity (increased liver weight, hepatic cirrhosis, swollen vacuolated hepatocytes and chronic hepatitis) was seen at 500 ppm and above, and the NOAEL was 100 ppm, equivalent to 2.5 mg/kg bw per day.

Two two-year studies were conducted in rats at dietary levels of 0, 100 , 500 or 2500-10,000 ppm and 0, 150, 300 or 2000-10,000 ppm. Carbendazim did not have carcinogenic potential, but some effects were seen at the highest doses tested. In one study there was some evidence of testicular atrophy, and in the other an increased incidence of diffuse proliferation of parafollicular cells in the thyroid was seen. In the latter study, evidence of mild hepatotoxicity was seen in the absence of histopathological change. The NOAEL in both studies was equivalent to 15 mg/kg bw per day.

Three carcinogenicity studies were performed in mice. In Swiss mice and CD-1 mice treated for 80 weeks and two years, respectively, at dietary levels up to 5000 or 7500 ppm, carbendazim increased the incidence of liver tumours. Because of the minimally increased incidence of proliferative lesions of the liver at 150 or 500 ppm in the diet (the lowest doses tested), it was not possible to establish no-effect levels in these studies. In NMRKf mice, which have a low spontaneous incidence of liver tumours, no carcinogenic effect was seen at dietary levels up to and including 5000 ppm (the highest level tested for 96 weeks), but hepatotoxicity was seen at this dose. The NOAEL was equal to 34 mg/kg bw per day.

In a three-generation study of reproductive toxicity, rats were fed dietary levels of 0, 150, 300 or 2000 ppm. Carbendazim had no effect on reproduction or development at dietary levels up to and including 2000 ppm (equivalent to 120 mg/kg bw per day). Male fertility was depressed in rats given carbendazim by gavage at 200 mg/kg bw per day for 85 days. A dose of 50 mg/kg bw per day (the lowest dose tested) caused a decrease in epididymal sperm counts. After a single oral dose to rats, disruption of spermatogenesis was seen at 100 mg/kg bw but no effect was seen at 50 mg/kg bw. The effect was associated with loss of germ cells resulting from inhibition of Sertoli-cell microtubules.

Carbendazim was tested for developmental toxicity in rats at doses between 5 and 3000 mg/kg bw per day on days 6-15 of gestation. It was fetotoxic and teratogenic at 20 mg/kg bw per day and above, the main effects being microphthalmia and hydrocephaly. The NOAEL for fetotoxicity and teratogenicity was 10 mg/kg bw per day; maternal toxicity was observed at 90 mg/kg bw per day and above, and the NOAEL for maternal toxicity was 20 mg/kg bw per day. Rabbits were exposed to carbendazim by gavage at doses of 0, 10, 20 or 125 mg/kg bw per day on days 7-19 of gestation. Carbendazim was fetotoxic and teratogenic, the major effects being malformed vertebrae and ribs. The NOAELs in this species were 10 mg/kg bw per day for teratogenicity and fetotoxicity and 20 mg/kg bw per day for maternal toxicity.

Carbendazim has been adequately tested for genotoxicity in a range of assays. The Meeting concluded that it does not directly damage genetic material but causes numerical chromosomal aberrations both *in vitro* and *in vivo* as a result of its interference with the mitotic spindle proteins.

In an epidemiological study of workers exposed to carbendazim, there was no reduction in fertility, as indicated by the birth rates, among the study population. Spermatogenesis in the

workers was not examined.

An ADI of 0-0.03 mg/kg bw was established on the basis of the no-effect level of 2.5 mg/kg bw per day in the two-year study in dogs and a safety factor of 100. The resultant ADI, when compared with the LOAELs in the studies with Swiss and CD-1 mice, provides an adequate level of safety.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 300 ppm, equal to 34 mg/kg bw per day (96-week study of toxicity and carcinogenicity in NMRKf mice)
<150-500 ppm, equivalent to <22-75 mg/kg bw per day (studies of toxicity and carcinogenicity in Swiss mice (80 weeks) and CD-1 mice (two years)

Rat: 300-500 ppm, equal to 15 mg/kg bw per day (toxicity, two-year studies, of toxicity and carcinogenicity)
2000 ppm, equivalent to 120 mg/kg bw per day (study of reproductive toxicity)
10 mg/kg bw per day (study of developmental toxicity)
10 mg/kg bw per day (fetotoxicity in study of developmental toxicity)
20 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rabbit: 10 mg/kg bw per day (study of developmental toxicity)
10 mg/kg bw per day (fetotoxicity in study of developmental toxicity)
20 mg/kg bw per day (maternal toxicity in study of teratogenicity)

Dog: 100 ppm, equal to 2.5 mg/kg bw per day (two-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to carbendazim

Exposure	Relevant route, study type, species	Results/remarks
Short-term (1-7 days)	Oral, toxicity, rat	LD_{50} >10,000 mg/kg bw
	Dermal, toxicity, rat	LD_{50} >2000 mg/kg bw
	Dermal, irritation, rabbit	50% wettable powder - non-irritating
	Ocular, irritation, rabbit	50% wettable powder - irritating
	Dermal, sensitization, guinea-pig	Non-sensitizing in Buehler test
	Inhalation, toxicity, rat	LC_{50} >5.9 mg/litre air
Mid-term (1-26 weeks)	Oral, developmental toxicity, rat and rabbit	NOAEL = 10 mg/kg bw per day; fetotoxicity and teratogenicity
Long-term (> one-year)	Dietary, toxicity, dog	NOAEL = 2.5 mg/kg bw per day; hepatotoxicity

EVALUATION OF EFFECTS ON THE ENVIRONMENT

See the report on benomyl (4.3), in which the environmental effects of benomyl, carbendazim and thiophanate-methyl are discussed.

4.10 CARTAP (097)

Cartap was on the agenda for evaluation within the CCPR periodic review programme. Data were submitted to the WHO and FAO for toxicological and residue evaluations, but were subsequently withdrawn by the manufacturer.

TOXICOLOGY

Because the new data were withdrawn, the only items of information available were summaries of the studies that had been reviewed by the 1976 and 1978 Joint Meetings. An examination of these summaries by the present Meeting indicated that the only data on non-rodent species were from an antidotal study, in which 200 mg/kg bw applied dermally caused “severe toxicity” in dogs.

Because of the absence of appropriate studies in non-rodents and because of questions relating to the adequacy of some of the older studies, the Meeting concluded that the ADI could no

longer be supported, and it was therefore withdrawn.

A toxicological monograph was not prepared.

RESIDUE AND ANALYTICAL ASPECTS

Cartap was evaluated by the 1976 and 1978 Meetings, and Codex MRLs became established for a number of commodities.

Since the manufacturer withdrew the data originally provided, the residues of cartap in food could not be evaluated. The Meeting therefore withdrew its previous recommendations.

4.11 CHLORPYRIFOS (017)

RESIDUE AND ANALYTICAL ASPECTS

The use of chlorpyrifos on citrus in the USA results in higher residue levels than the current CXL for citrus fruits, 0.3 mg/kg. The Meeting reviewed available information on analytical methods, frozen storage stability, use patterns, fate during processing and supervised trials on citrus in the USA, Spain and South Africa.

At the 21st Session of the CCPR in 1993 (ALINORM 93/24A para 251) chlorpyrifos was identified as a candidate for periodic review. It was listed for periodic review but not scheduled in the report of the 1995 CCPR (ALINORM 95/24A page 99, Annex 1 of Appendix IV). Information was available to the Meeting on physical properties and metabolism but these subjects are best reviewed in the context of the entire data base in the Periodic Review Programme.

In residue analytical methods chlorpyrifos was extracted from the substrate with acetone or methanol. The extract was cleaned up by hexane-acetonitrile partitions followed by passage through a small silica gel column. Chlorpyrifos residues were analysed by GLC with photometric detection of phosphorus. Limits of determination were 0.01 mg/kg and recoveries were generally good. The method was validated on citrus peel, pulp and juice and a number of other agricultural commodities and their processed fractions.

Chlorpyrifos residues were extracted from orange pulp and peel with dichloromethane in a method used in South African trials. Clean-up was effected by solvent partitioning and Florisil column chromatography, and residues were measured by GLC with an FPD. The LOD was 0.01 mg/kg.

An analytical method was also available for the metabolite 3,5,6-trichloro-2-pyridinol. Orange substrates were heated with methanolic sodium hydroxide before extraction to convert the chlorpyrifos residues to 3,5,6-trichloro-2-pyridinol. After clean-up and formation of the trimethylsilyl derivative the residue was determined by GLC with EC detection. The method measures the total residue, chlorpyrifos + 3,5,6-trichloro-2-pyridinol. When a duplicate sample is analysed for chlorpyrifos alone the level of 3,5,6-trichloro-2-pyridinol is estimated by difference. The LOD was 0.05 mg/kg. The method was validated for citrus and citrus fractions.

Information on the frozen storage stability of chlorpyrifos and 3,5,6-trichloro-2-pyridinol residues in an extensive range of raw agricultural and processed commodities was made available to the Meeting. Residues were generally stable (>70% remaining) under the test conditions (-18°C for 3 months and longer, some samples for 4 years).

Chlorpyrifos is registered in the USA for use on citrus fruits for the control of aphids, scale, mites, cutworms, grasshoppers, thrips, and other pests. A petroleum spray oil recommended for use on citrus trees may be added to dilute spray mixtures to improve control. Information on registered uses in South Africa and Spain was also provided.

In the USA chlorpyrifos may be applied to citrus orchards at 1.1-3.9 kg ai/ha with a 21-day PHI or at 3.4-6.7 kg ai/ha with a 35-day PHI. Residues in 11 US trials on oranges treated at maximum GAP rates were 0.098, 0.11, 0.26, 0.36, 0.38, 0.38, 0.39, 0.41, 0.49, 1.3 and 2.0 mg/kg. Residues on grapefruit in 4 trials where application was at 1.4 kg ai/ha and the fruit were harvested 21 days later were 0.05, 0.067, 0.31 and 0.34 mg/kg.

In South Africa the registered use allows chlorpyrifos to be applied to citrus orchards at a spray concentration of 0.0096-0.048 kg ai/hl with a PHI of 60 days. Residues in 5 South African trials on oranges according to this use pattern were 0.05, 0.12, 0.14, 0.19 and 0.21 mg/kg.

The registered chlorpyrifos use pattern on citrus in Spain allows a spray concentration of 0.075-0.10 kg ai/hl and a 21-day PHI. In 4 Spanish trials on mandarins according to this use pattern chlorpyrifos residues were 0.40, 0.55, 0.99 and 1.2 mg/kg.

The chlorpyrifos residues from the 24 trials on oranges, grapefruit and mandarins in rank order were 0.05, 0.05, 0.067, 0.098, 0.11, 0.12, 0.14, 0.19, 0.21, 0.26, 0.31, 0.34, 0.36, 0.38, 0.38, 0.39, 0.40, 0.41, 0.49, 0.55, 0.99, 1.2, 1.3 and 2.0 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for chlorpyrifos on citrus fruits to replace the previous recommendation (0.3 mg/kg).

The pulp and peel of oranges were analysed separately in 10 South African supervised trials. In all samples, including those from trials where treatment was at exaggerated rates or harvest at intervals shorter than the official PHI, chlorpyrifos residues were not detected (<0.01 mg/kg) in the pulp. In a Spanish trial chlorpyrifos residues were not detected (<0.01 mg/kg) in the pulp of mandarins when residues in the whole fruit were 0.14 mg/kg.

Information was made available to the Meeting on the fate of field-incurred chlorpyrifos residues during the processing of oranges, grapefruit, lemons and tangelos.

In laboratory-scale extraction of juice from oranges treated at exaggerated application rates in the USA in 1977 and 1978, chlorpyrifos residues in the juice ranged up to 0.78 mg/kg with the median below the LOD (<0.01 mg/kg). Residues in the whole oranges were not measured.

Residues of chlorpyrifos were not detected (<0.01 mg/kg) in the juice of grapefruit, lemons, oranges and tangelos produced in simulated commercial processing. Residues in the initial fruit were 0.36 mg/kg in grapefruit, 0.38 mg/kg in lemons, 0.51 mg/kg in oranges, and 0.59 mg/kg in tangelos.

The Meeting concluded that chlorpyrifos levels in citrus pulp and juice produced from a crop treated with chlorpyrifos according to GAP were generally below the LOD (0.01 mg/kg).

Dietary intake studies in Australia, Belgium and Finland showed that the dietary intake of

chlorpyrifos was much less than the current ADI.

The recommended MRL for citrus fruits is recorded in Annex I.

4.12 DITHIANON (180)

RESIDUE AND ANALYTICAL ASPECTS

Dithianon is a multi-site protective fungicide which inhibits spore germination. It was first reviewed by the 1992 JMPR. At the 1994 CCPR the delegation of Germany questioned the data on which the maximum residue level of 1 mg/kg on cherries estimated by the 1992 JMPR were based.

Items of further work or information listed as desirable by the 1992 JMPR were (1) additional studies on the fate of residues in farm animals (metabolism and transfer studies), and on plant metabolism and soil degradation, and (2) GAP and residue information for uses on cereals in Germany, The Netherlands and the UK.

The present Meeting received updated information on GAP, summaries of residue trials on cherries and explanatory notes by Germany. The manufacturer provided reports of two supervised residue trials from Germany and two from France. Summarized information on GAP was made available by Finland and the UK. A summary of residue trials on apples was also provided by Finland.

The determination of residues in cherries in older trials was by the formation of a coloured morpholine adduct. In the current procedure, cherries are homogenized with acetone, hydrochloric acid and water, the homogenate is partitioned with hexane and dichloromethane and the residue cleaned up by gel permeation chromatography with cyclohexane/ethyl acetate. After addition of 0.1 ml acetic acid the solvent is evaporated and the residue dissolved in acidified dichloromethane and cleaned up further by silica gel column chromatography. The determination is carried out by HPLC with UV detection. The LOD is 0.05 mg/kg.

The information on GAP provided by Germany and the UK is basically the same as supplied in 1992. Therefore at present there is no approved use on cereals in Germany or the United Kingdom.

The present Meeting reviewed the new reports of residue trials on cherries and apples in the context of those previously reviewed.

Cherries. The 1992 JMPR estimated a maximum residue level of 1 mg/kg, based on six German and two Dutch trials (3 treatments, 0.15-0.75 kg ai/ha) with residues from 0.14 mg/kg to 0.8 mg/kg at 21-28 days after treatment. The critical GAP exists in Australia (2-4 treatments, 0.075-0.113 kg ai/hl, 21-day PHI), and Switzerland (multiple applications, 0.05-0.075 kg ai/hl, 21-day PHI), followed by The Netherlands (4 treatments, 0.049-0.052 kg ai/hl, 0.49-0.78 kg ai/ha, 28-day PHI) and Germany (3 treatments, 0.038 kg ai/hl, 0.56 kg ai/ha, 28-day PHI).

In addition to the six German trials carried out in 1985/86 and evaluated in 1992, the Meeting received data on 7 trials on sour cherries and 5 trials on sweet cherries in Germany from 1967 to 1972, which could be evaluated on the basis of Swiss GAP. Diathinon was applied three to ten times at 0.05 kg ai/hl (0.4-1.4 kg ai/ha). After PHIs of 21-23 days the residues in the fruit ranged from 0.62

to 4.3 mg/kg.

In 1993 two further trials were conducted on sour cherries in Germany which included analyses of processed products. After three applications at 0.56 kg ai/ha and a 27-day PHI the residues in the fruit were 0.48 and 0.77 mg/kg, reduced by washing to 0.24 and 0.28 mg/kg respectively. No residues above the limit of determination (0.05 mg/kg) could be detected in preserves, jam or juice.

Two new trials on sweet cherries were carried out in France in 1992 (3 treatments, 0.38 kg ai/ha, 0.038 kg ai/hl). The residues 14 or 28 days after application were 0.11 and 0.05 mg/kg.

After re-evaluation of all results from application rates of 0.038-0.075 kg ai/hl or 0.49-0.78 kg ai/ha according to the reported European GAP the Meeting estimated a maximum residue level of 5 mg/kg for cherries to replace the previous recommendation (1 mg/kg).

Apples. A short summary repot of trials on apples was made available by Finland. Dithianon was applied four or five times a year at application rates from 0.5 to 2 kg ai/ha. Residues after a PHI of 21 days ranged from 0.5 to 16 mg/kg. The high residue occurred because the last treatment was carried out about 30 days later than usual. The data do not reflect GAP in Finland but may be considered as supplementing the results provided in 1992 on which an estimated maximum residue level for pome fruit was based. The Meeting considered that they supported the previous estimate of 3 mg/kg.

The revised recommendation for cherries is recorded in Annex I.

FURTHER WORK OR INFORMATION

Desirable

Additional studies on the fate of residues in farm animals (metabolism and transfer studies), and on plant metabolism and soil degradation (from 1992).

4.13 DITHIOCARBAMATES (105)

Mancozeb, maneb and propineb were reviewed in the CCPR periodic review programme in 1993 and MRLs for dithiocarbamates were recommended.

Metiram, another dithiocarbamate, has now been evaluated as a new compound. The maximum residues arising from the use of metiram according to GAP do not exceed the currently recommended dithiocarbamate MRLs, but additional MRLs are needed for some commodities without existing recommendations for dithiocarbamates.

The 1993 JMPR had estimated a maximum residue level of 2 mg/kg for dithiocarbamates in mangoes arising from the use of mancozeb, but the entry had been inadvertently omitted from Annex I.

The Meeting noted that there is a CXL for dithiocarbamates in endives, but no recommendation had been made during the 1993 periodic review of mancozeb, maneb and propineb. In the absence of adequate data the 1993 Meeting should have recommended withdrawal of the

previous recommendation. Accordingly, the present Meeting recommends deletion of the CXL for endive.

A consolidated list of current JMPR recommendations for dithiocarbamates, including those arising from the use of metiram, is included in Annex I.

4.14 ETHEPHON (106)

TOXICOLOGY

Ethephon was last reviewed toxicologically by the 1993 JMPR, which established an ADI of 0-0.05 mg/kg bw was established. At that time, the Meeting noted that ethephon was a dibasic phosphonic acid and could therefore not phosphorylate hydrolases at the serine residue. Inhibition of plasma and erythrocyte, but not brain, cholinesterase has however been seen *in vivo*. Neither data on the pure compound nor the results of *in-vitro* studies were available. The Meeting considered that the effects on cholinesterase required clarification and recommended re-evaluation of the compound in 1995.

The Meeting was aware that pure and technical-grade ethephon and six manufacturing impurities in technical-grade ethephon are being tested for cholinesterase inhibition in rat plasma and erythrocytes *in vitro*. As a final report on this study is expected to be available in April 1996, the Committee recommended re-evaluation of ethephon in 1997.

The meeting maintained the ADI of 0-0.05 mg/kg bw.

A toxicological monograph was not prepared.

4.15 FENARIMOL (191)

(±)-2,4′-dichloro-á-(pyrimidin-5-yl)benzhydryl alcohol

Fenarimol is a pyrimidin-5-yl benzhydrol systemic fungicide, which is available in several formulations, the most important being emulsifiable concentrates, suspension concentrates, and wettable powders. It is registered for use on many crops world-wide. It was considered for the first time by the present Meeting.

TOXICOLOGY

Fenarimol given orally to rats was rapidly absorbed, distributed and excreted. Elimination occurred principally in the faeces (76-83%), mainly as a result of biliary excretion, and to a lesser extent in the urine (6.5-9.2%). Residue levels in tissues were relatively low. Dermal absorption of fenarimol by monkeys was low (about 2.5%). There was some barrier to placental transport of fenarimol-derived radiolabel in rats during part of the gestation period. Although the levels of the radiolabel in the milk of lactating rats were three to five times those in the plasma, only a very small proportion of the dose (< 0.1%) was eliminated in the milk of a lactating goat.

Fenarimol is extensively metabolized to many metabolites. The major pathways are

oxidation of the carbinol-carbon atom, the chlorophenol rings, and the pyrimidine ring. Repeated oral administration to rats had no effect on the elimination of fenarimol or its metabolites.

Fenarimol has low acute oral and dermal toxicity, the LD_{50} in rats and rabbits being 2550 and >2000 mg/kg bw respectively. After inhalation the LC_{50} was >2 mg/litre (1-h exposure). Fenarimol did not irritate skin or eyes and was not a skin sensitizer in guinea-pigs in a maximization test. The WHO has classified fenarimol as unlikely to present an acute hazard in normal use.

In a 14-day pilot study in mice given dietary concentrations of 25-12,800 ppm, liver toxicity was observed at 800 ppm and above. In a three-month study in mice given dietary concentrations of 0, 360, 620, 1100, 2000 or 3300 ppm, toxicity was observed mainly in the liver, seen as increased liver weight, hepatic enzyme induction, centrilobular hypertrophy, and hepatomegaly. The NOAEL was 360 ppm, equivalent to 52 mg/kg bw per day, on the basis of an increase in liver weight at 620 ppm.

In two 14-day pilot studies in rats given dietary concentrations of 25-12,800 ppm, liver toxicity was observed at 200 ppm and above. Dietary administration of fenarimol to rats for three months at 0, 50, 200 or 800 ppm also resulted in liver toxicity at and above 200 ppm, seen as increased liver weight, hepatic enzyme induction, centrilobular hypertrophy, and fatty changes in the liver. The NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw per day, on the basis of induction of liver enzymes. In another three-month study in rats, with dose levels of 0, 140, 200, 280, 360 or 500 ppm, the NOAEL was 200 ppm, equivalent to 10 mg/kg bw per day, on the basis of an increase in liver weight and induction of hepatic enzymes at 280 ppm and above.

In a three-month study in dogs, oral administration of fenarimol in gelatin capsules at doses of 0, 1.2, 5 or 20 mg/kg bw per day resulted in no systemic toxicity. In a one-year study in which dogs were given 0, 1.2, 12, or 120 mg/kg bw per day, toxicity was observed at the highest dose. This included liver toxicity and, in female dogs, a transient enlargement of the mammary gland and increased ovarian weight; an increase in the occurrence of soft stools was observed at all doses. The NOAEL was 12 mg/kg bw per day.

In a study of chronic toxicity, mice were administered fenarimol at dietary levels of 0, 50, 170 or 600 ppm for 12 months. The NOAEL was 170 ppm, equivalent to 24 mg/kg bw per day, on the basis of decreased body-weight gain and effects on the liver at 600 ppm. In a two-year study of carcinogenicity, mice were given diets containing 0, 50, 170 or 600 ppm fenarimol. The NOAEL was 170 ppm, equivalent to 24 mg/kg bw per day, on the basis of a slight decrease in body weight gain in males at 600 ppm. There was no evidence of carcinogenicity.

Two studies of chronic toxicity were performed in which rats were administered dietary concentrations of fenarimol at 0, 50, 130 or 350 ppm for 12 or 18 months. In both studies, the main effects at the highest dose were a decrease in the leucocyte count, increased liver weight, and decreased spleen weight. In the 12-month study, the NOAEL was 130 ppm, equal to 6 mg/kg bw per day. In the 18-month study, the NOAEL was 50 ppm, equal to 2.3 mg/kg bw per day on the basis of a reduction in body weight.

Three carcinogenicity studies were performed in rats. In the first, rats were administered diets containing 0, 50, 130 or 350 ppm fenarimol. A small increase in the incidence of hepatic-cell adenoma was seen at the highest dose. A no-effect level was not observed owing to a slight increase in fatty changes and hyperplastic nodules in the liver at all doses. No clear treatment-related effect on tumour incidence was seen. Two further studies were performed at lower doses (0, 12, 25 or 50 ppm).

In the first study the survival was very low, owing to an outbreak of chronic respiratory disease. There was evidence of reduced body weight gain and an increased incidence of fatty changes in the liver at 50 ppm. No adverse effect was observed in the second study. The overall NOAEL for all three studies was 25 ppm, equal to 1.2 mg/kg bw per day. There was no evidence of carcinogenicity.

A three-generation study of reproductive toxicity in mice given dietary levels of 0, 35, 70 or 140 ppm fenarimol revealed no adverse effects on parental mice or offspring. In earlier pilot studies, however, doses of 170 ppm and above reduced fertility and live-born litter size and lengthened the gestation period. The NOAEL was 140 ppm, equivalent to 20 mg/kg bw per day.

In a two-generation study of reproductive toxicity in which guinea-pigs were given 0 or 400 ppm fenarimol in the diet (equal to 33 mg/kg bw per day), parental toxicity was seen and there was equivocal evidence of a slight effect on the proportion of live-born progeny. In a single-generation study of reproductive toxicity with a cross-over design, rabbits were treated orally with fenarimol at a level of 0 or 35 mg/kg bw per day. There was no evidence of general systemic toxicity or of effects on reproduction.

Two multi-generation studies of reproductive toxicity have been performed in rats. In a two-generation study rats were exposed to dietary concentrations of 0, 50, 130 or 350 ppm, and in a three-generation study to 0, 12, 25 or 50 ppm. Fenarimol reduced fertility, caused dystocia, reduced live-born litter size and lengthened the gestation period. In the first study, cross-over data showed that the reduction in fertility was clearly mediated through the male and was only slightly reversible. The overall NOAEL for general systemic toxicity was 25 ppm, equivalent to 1.2 mg/kg bw per day, on the basis of reduced body weight gain in F_1 males at 50 ppm and above. The overall NOAEL for reproductive toxicity was 12 ppm, equivalent to 0.62 mg/kg bw per day, on the basis of a reduction in live-born litter size at 25 ppm and above.

Three single-generation studies of reproductive toxicity with a cross-over design have been conducted in rats, which were exposed orally to fenarimol at doses 0 or 35 mg/kg bw per day. These studies showed that the effects on reproduction were not strain-dependent, the effects on fertility were clearly male-mediated and the reduction in live-born litter size (probably due to an increased incidence of still births) was female-mediated. No correlation was found between fertility and the levels of prolactin, luteinizing hormone and testosterone, organ weights, histopathological findings, or sperm morphology.

The single- and multi-generation studies of reproductive toxicity show that fenarimol has adverse effects on reproduction in rats and (at higher dose levels) in mice, but not in guinea-pigs or rabbits. A number of studies were performed to investigate the mechanism of the adverse effects on reproduction, and particularly those on fertility. The results of these studies and of others in the open literature show that fenarimol affects male sexual differentiation and subsequent behaviour indirectly by inhibiting the aromatase-catalysed conversion of testosterone to estradiol-17ß within the hypothalamus. Data from the literature strongly indicate that while estradiol-17ß is the central regulator of sexual differentiation in rats, human male sexual behaviour is controlled by dihydrotestosterone, which is formed from testosterone by the enzyme 5-á-reductase. There is also evidence that the effect of fenarimol in female rats (delayed parturition) is also due to inhibition of aromatase, as this inhibition results in a sustained level of circulating progesterone and prolonged corpus luteal function, thus leading to delayed parturition. In contrast to rats, the same mechanism for an abrupt decrease in progesterone secretion is not required for parturition in guinea-pigs or humans. The Meeting concluded that although not clear-cut, there is sufficient evidence that the adverse effects on the organization and expression of sexual behaviour in male rats and on delayed parturition in

female rats are not relevant for humans.

In a study of developmental toxicity, pregnant rats were given fenarimol by gavage at doses of 0, 5, 13 or 35 mg/kg bw per day. There was evidence of developmental toxicity (hydronephrosis) but no signs of maternal toxicity at the high dose. In a study in which some females were also allowed to litter and wean their progeny, pregnant rats were exposed to 0 or 35 mg/kg bw per day during days 6-15 of gestation. There were adverse effects on reproductive performance (increased length of gestation, dystocia) and developmental toxicity (increased hydronephrosis), but no evidence of general systemic maternal toxicity. The increased incidence of hydronephrosis appeared to be due to delayed development and was not considered a teratogenic effect. Overall, the NOAEL for maternal toxicity was 35 mg/kg bw per day and that for embryo- and fetotoxicity was 13 mg/kg bw per day.

In a study of developmental toxicity in which rabbits were administered fenarimol by gavage at doses of 0, 3, 10, or 35 mg/kg bw per day, no signs of toxicity were observed in dams or fetuses. In a second study rabbits were exposed orally to doses of 0, 15, 50 or 150 mg/kg bw per day. The NOAEL for maternal toxicity was 50 mg/kg bw per day, on the basis of reductions in body weight and food consumption and an increased incidence of abortions. The NOAEL for embryo- and fetotoxicity was also 50 mg/kg bw per day, on the basis of a reduced number of live fetuses and an increased incidence of extra ribs. There was no evidence of teratogenic potential.

Fenarimol has been adequately tested for genotoxicity in a series of assays *in vitro* and *in vivo*. The Meeting concluded that fenarimol is not genotoxic.

The Meeting concluded that the effects of fenarimol in male rats (reduced fertility) and female rats (delayed parturition) are due to inhibition of aromatase, an enzyme that is not involved in these aspects of human reproduction. It therefore decided that it would be inappropriate to use the NOAEL seen in studies of reproductive toxicity in determining the ADI. An ADI of 0-0.01 mg/kg bw was established on the basis of an overall NOAEL of 1.2 mg/kg bw per day, seen in several studies of carcinogenicity in rats, and a safety factor of 100.

A toxicological monograph was prepared, summarizing the data that were reviewed by the present Meeting.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 24 mg/kg bw per day (12-month study of chronic toxicity)
20 mg/kg bw per day (three-generation study of reproductive toxicity)

Rat: 1.2 mg/kg bw per day (three studies of carcinogenicity)
0.62 mg/kg bw per day (multigeneration study of reproductive toxicity)*
13 mg/kg bw per day (embryo- and fetotoxicity in study of developmental toxicity)

Dog: 12 mg/kg bw per day (one-year study of toxicity)

Rabbit: 50 mg/kg bw per day (maternal and embryo- or fetotoxicity in a study of developmental toxicity)

*Data considered irrelevant for evaluation with respect to human health.

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to fenarimol

Exposure	Relevant route, study type, species	Result/remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Not irritating
	Eye, irritation, rabbit	Not irritating
	Skin, sensitization, guinea-pig	Not sensitizing
	Oral, toxicity, rat	LD_{50} = 2550 mg/kg bw
	Dermal, toxicity, rabbit	LD_{50} = >2000 mg/kg bw
	Inhalation, toxicity, rat	1-h LC_{50} = >2 mg/litre
Medium term (1-26 weeks)	Dermal, toxicity, 21-day, rabbit	No systemic effect; no irritation at 1000 mg/kg bw
	Dietary, three-month, toxicity, rat	NOAEL = 2.5 mg/kg bw hepatic enzyme induction
	Dietary, three-generation, reproductive toxicity, rat	NOAEL = 0.625 mg/kg bw; reduced live-born litter size
	Gavage, developmental toxicity, rat	NOAEL = 13 mg/kg bw hydronephrosis; no maternal toxicity
Long-term (> one year)	Dietary, two-year, toxicity, rat	NOAEL = 1.2 mg/kg bw; fatty change in liver

EVALUATION OF EFFECTS ON THE ENVIRONMENT

Fenarimol is a systemic fungicide and its use covers a wide range of fruit and vegetables, hops and wheat. It is registered in many countries.

Fenarimol is rapidly adsorbed to soil or sediments, and a series of laboratory experiments showed that the compound has no tendency to leach and stays in the top few centimetres of the soil profile. Its high persistence (several months) in soil was confirmed in the field. Photolysis was shown to occur but owing to many factors, including the type of use and the ready adsorption to soil and

sediments, it is not considered to be a significant mechanism of degradation. Fenarimol is very slowly degraded according to field experiments and laboratory studies conducted in both aerobic and anaerobic conditions (the half-life is of the order of months to more than a year). Hydrolysis has been shown only at extreme Ph. The compound is therefore highly persistent and not mobile.

There is very limited bioaccumulation and depuration of contaminated tissues takes place in a few days for both aquatic and terrestrial organisms (fish and earthworms).

The data indicated no effects of fenarimol on soil respiration and nitrification processes at levels much higher than normal application rates; similar results were obtained on sewage treatment sludges.

Fenarimol has shown in aquatic toxicity tests LC_{50}/EC_{50}s of 0.82 mg/l, 0.18 mg/l and 0.76 mg/l for the most sensitive fish, aquatic invertebrate and algae respectively. In chronic experiments with fish and aquatic invertebrates the NOECs were 0.43 mg/l and 0.113 mg/l.

Fenarimol was of low acute toxicity to honey bees with acute oral and contact LD_{50}s of >10 and >100 ìg/bee respectively. Tests on earthworms demonstrated a very low toxicity both on acute (LC_{50} 200-300 mg formulation/kg, equivalent to 25-37 mg ai/kg) and reproductive effects (NOEC = 1.89 kg ai/ha).

The compound was reported also to be of low acute oral toxicity to birds with LD_{50} and NOEL of >2000 mg/kg bw and 2000 mg/kg bw respectively. In bird dietary toxicity studies reduced body weight was observed and the NOEC of 250 mg ai/kg food for fenarimol was proposed. In several studies on reproductive toxicity values between 250 and 300 mg ai/kg food were indicated as NOECs for different birds. However, it should be noted that at the dose level of 50 mg ai/kg there was a mean reduction of 27% in the number of eggs laid but this was not statistically significant. No data were submitted on the toxicity of fenarimol to wild mammals; the LD_{50} for laboratory mammals was 2500 mg ai/kg bw.

Risk assessment

At application rates equivalent to 28 times the maximum recommended application rate for fenarimol (4 x 1.5 kg ai/ha on turf) there was no significant effect on soil respiration or soil microbial processes, indicating a low risk to such processes.

Using spray drift or overspray contamination arising from tractor mounted spray boom application to turf (4 x 1.5 kg ai/ha) and air-assisted spray applications to orchards (14 x 0.072 kg ai/ha) as examples of reasonable worst-case risk uses, the risk to aquatic organisms was assessed and is presented in Tables 1 and 2 below. Details of the PEC calculations are given in the evaluation of fenthion.

Table 1. Summary of acute risk to aquatic organisms from spray drift or overspray contamination arising from applications of fenarimol by tractor boom or air-assisted spray.

Organism	LC_{50}/EC_{50} (mg ai/l)	Use Type	Acute PEC (mg ai/l)	Acute TER	Risk classification
Fish	0.8	Tractor boom spray	0.025*	32	Low
Fish	0.8	Air-assisted spray	0.04#	20	Low
Aquatic invertebrates	0.18	Tractor boom spray	0.025*	7.2	Present**
Aquatic invertebrates	0.18	Air-assisted spray	0.04#	4.5	Present**
Algae	0.76	Tractor boom spray	0.025*	30	Low
Algae	0.76	Air-assisted spray	0.04#	19	Low

All PEC values based on 1 application
#Overspray PEC values
*Spray drift PEC values
** Although the risk is classified as "present" it is considered low risk owing to the small scale and localized nature of turf applications.

Table 2. Summary of chronic risk to aquatic organisms from spray drift or overspray contamination arising from multiple applications of fenarimol by tractor boom or air-assisted spray.

Organism	NOEC (mg ai/l)	Use Type	Chronic PEC (mg ai/l)	Chronic TER	Risk classification
Fish	0.43	Tractor boom spray	0.0125*	34	Low
Fish	0.43	Air-assisted spray	0.02#	21	Low
Aquatic invertebrates	0.113	Tractor boom spray	0.0125*	9	Present**
Aquatic invertebrates	0.113	Air-assisted spray	0.02#	5.7	Present***
Sediment invertebrates	0.113[a]	Tractor boom spray	0.04*	2.8	Present**
Sediment invertebrates	0.113[a]	Air-assisted spray	0.04#	2.8	Present**

All PEC values based on maximum recommended applications
[a] Based on *Daphnia* chronic toxicity data # Overspray PEC * Spray drift PEC
** Although the risk is classified as "present", it is considered to be low owing to the small scale and localized nature of turf applications.
*** Although the risk is classified as "present", overspray is the worst case and spray drift is more likely. This results in a chronic PEC of 0.006 and TER of 18.8, representing a low risk.

The summary of acute and chronic TERs for aquatic organisms reported above indicate that fenarimol presents a low risk to aquatic life except for the orchard-type multiple application which may present a medium/high chronic risk to sediment-dwelling invertebrates.

The risk to bees was considered to be low since the hazard ratios reported for the highest application rates recommended (1.5 kg ai/ha) were >15 and >150 for acute oral and acute contact exposure respectively. The recommended timing of application is when bees are unlikely to be foraging. The risk to non-target arthropods cannot be fully assessed from the limited non-target arthropod data available. On the basis of the high application rate to turf (1.5 kg ai/ha) and the multiple applications made to orchards (14 x 0.072 kg ai/ha), a worst-case short-term TER for earthworms of 23-35 and long-term TER of 139-208 were reported respectively, indicating a low risk.

The risk to insectivorous, grazing and fruit-eating birds and mammals was assessed and is presented in Tables 3 and 4 below, using the same applications to turf and orchards together with applications to strawberries of 4 x 0.084 kg ai/ha as worst-case risk uses.

Table 3. A summary of the risk to insectivorous, grazing and fruit-eating birds from the use of fenarimol on turf and in orchards.

Organism	Use	Food type	Food residue (mg ai/kg)	LC_{50} (mg ai/kg food)	TER	Risk classification
Goose	Turf	Vegetation	170*	>6250	>37	Low
Song thrush	Turf	Earthworms	8.6#	>6250	>730	Negligible
Starling	Orchard	Cherries	0.89#	>6250	>7000	Negligible

* Food residue information calculated from EPPO/COE vertebrate risk assessment scheme.
\# Food residue based on actual residue data.

Table 4. A summary of the risk to insectivorous, grazing and fruit-eating mammals from the use of fenarimol on turf and soft fruit.

Organism	Use	Food type	Food residue (mg ai/kg)	Expected daily intake (mg ai/kg bw)	LD_{50}	TER	Risk classification
Shrew	Turf	Earthworms	8.6	8.6	2500	290	Negligible
Rabbit	Turf	Grass	168*	70	2500	36	Low
Wood mouse	Soft fruit	Strawberries	0.14*	0.06	2500	>10,000	Negligible

*Food residue based on EPPO/COE vertebrate risk assessment scheme calculations.
#Food residue based on actual residue data.

The TERs reported for mammals and birds in tables 3 and 4 indicate a low risk (i.e. TERs >100), except for the risk to both grazing birds and mammals from the high use of fenarimol on turf (TERs <100). However, information from wildlife monitoring in the United Kingdom indicates that no poisoning incidents have been associated with such a use, so the actual risk may be low.

Using the same exposure levels for birds as in Table 3 the TERs for reproduction in birds were 22.7 for insectivorous birds and 56 for fruit-eating birds, indicating a low risk to reproducing birds.

FURTHER RESEARCH

Data on the chronic toxicity of fenarimol-contaminated sediment to sediment-dwelling invertebrates.

RESIDUE AND ANALYTICAL ASPECTS

Fenarimol is a crystalline solid of moderately low melting point and volatility. It has low solubility in water and is soluble in medium polarity solvents. The octanol/water partition coefficient indicates that the compound has the potential to accumulate to a moderate extent. It is photolabile in air and water and is not flammable, autoflammable, explosive or oxidizing.

In rats the major metabolic routes are oxidation of the carbinol, the chlorophenyl rings and the pyrimidine ring.

In goats a number of metabolites were formed, but they occurred at very low levels and would be unlikely to exceed 0.01 mg/kg following the feeding of crops (e.g apple pomace) which had been treated according to current GAP. The metabolites included *o*-chlorobenzoic acid and the methyl sulfone derivative of fenarimol, neither of which were identified as rat metabolites. Fenarimol was also detected in liver and kidney samples at low levels, and was the major component of the residue in pigs. In a poultry metabolism study the highest total residue occurred in the liver and kidneys. No identification of the residue was attempted although intakes by chickens from treated crops are likely to low (<0.1 ppm in the diet).

In apples and grapes fenarimol was degraded to numerous unidentified compounds at very low levels. These are likely to be photo-degradation products as they generally show very similar chromatographic characteristics. They do not occur in rats. The major component of the radioactive residue in apples, grapes and cucumbers was fenarimol. Six hours, 29 days and 49 days after spraying apples with [á-^{14}C]fenarimol, the majority of the radioactive residue (81-92%) was associated with the peel.

A number of analytical methods were reported for a variety of substrates. Although these used different extraction and clean-up techniques, the determination in all was by GLC with an ECD, achieving LODs of 0.002-0.05 mg/kg.

Since the studies of metabolism by plants and livestock indicated that unchanged fenarimol was the major component of the residue, the Meeting concluded that the residue should be defined as fenarimol.

Residues in wine, grapes and cherries were found to be stable for at least 370, 370 and 104 days, respectively, following storage at ca. -20°C. Additional data on the storage stability of residues were available for fortified peaches, tomatoes and melons, but were submitted too late for consideration by the Meeting: they will be evaluated by a future Meeting.

Important experimental details were missing from several of the residue trials. In cases where weather data, example chromatograms, crop variety or full details of the method of analysis for the particular trial were not provided the trials data were used, where applicable, to estimate maximum residue levels, since these omissions were not considered critical. However, where analytical recoveries associated with a trial were outside the range 70-120% the results were generally ignored. Similarly, if laboratory samples were stored frozen for more than 6 months or the duration and conditions of storage were unspecified the analytical results were not considered reliable. The exception to this was fruit crops for which data on the storage stability of residues were available. Finally in all cases a study report was considered necessary; a simple trial sheet was not considered to give sufficient information and such submissions as were not used in the estimation of maximum residue levels.

Apples. The results of a large number of trials were available from several countries around the world. The highest residues were found in trials according to Dutch GAP, but since the Dutch data were submitted only in summary form they were not used to estimate maximum residue levels. 16 Northern European trials reflected German GAP (0.0036 kg ai/hl, 21 days PHI) with residues of 0.02-0.21 mg/kg. A number of other German trials were reported but only summary sheets were submitted. US GAP was followed in eight trials in the USA, several of which were replicated, with residues 29-42 days after the final treatment of 0.002-0.059 mg/kg.

Eight trials according to GAP reported for Denmark, the UK and Ireland showed residues of 0.02-0.18 mg/kg. In further trials according to GAP in New Zealand, Brazil and Chile residues were 0.002-0.09 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg.

Pears. Four trials according to GAP were reported from the USA with residues of 0.01-0.04 mg/kg. Two trials were available with residues up to 0.13 mg/kg reflecting Italian and German GAP: the analytical recoveries associated with these trials were low at 63 and 67% respectively. The Meeting took into account the large number of trials on apples and the similar use patterns on the two crops, and estimated a maximum residue level of 0.3 mg/kg for pome fruits.

Peaches. Five peach trials in Spain and Italy according to Spanish GAP gave residues of 0.03-0.3 mg/kg at 7 days. In two of these trials the volume of spray per hectare was not clear and the results can therefore only be used as supplementary information. A further 1988 Spanish trial on apricots according to Spanish GAP for peaches with a residue of 0.36 mg/kg at 7 days provides support. The highest residues were from trials in which high water volumes were used but these complied with GAP. In a single Chilean nectarine trial according to Argentinian GAP residues were below the LOD at 2 days. No trials were available with results at the Japanese GAP PHI of one day. The Meeting estimated a maximum residue level of 0.5 mg/kg for peaches.

Cherries. Nine trials (3 with replicates) according to US GAP showed residues of 0.06-0.89 mg/kg at a 0- or 1-day PHI. It was recognised that no account was taken of the weights of the stones and the residues in the whole cherries would have been somewhat lower. The Meeting estimated a maximum residue level of 1 mg/kg for cherries.

Currants. Only 5 trials were available from The Netherlands and only one of these was according to GAP in Denmark, Ireland, The Netherlands or the UK. Furthermore, since the Dutch data were submitted only in summary form they could not be used. The Meeting concluded that there were insufficient data to estimate a maximum residue level for currants.

Gooseberries. Only one Dutch trial, reported in summary form only, was available: it complied with GAP reported for Ireland, The Netherlands and the UK. The Meeting concluded that there were insufficient data to estimate a maximum residue level.

Grapes. Residues in grapes treated according to GAP in the USA, Australia and France were generally low with residues of 0.003-0.06 mg/kg, 0.01-0.08 mg/kg and 0.02 mg/kg, respectively. A number of German trials were submitted of which six (2 with replicates) reflected German GAP (0.023 kg ai/ha, 35 days PHI). The residues were 0.01-0.15 mg/kg in samples taken 35 days after the final treatment. Seven of the German trials (two with replicates) which accorded with UK GAP (0.04 kg ai/ha, PHI 14 days) gave residues of 0.02-0.24 mg/kg in samples taken 14 days after the final treatment. There were no southern European trials at the highest GAP rate (0.06 kg ai/ha) or the shortest PHI (7 days). The Meeting estimated a maximum residue level of 0.3 mg/kg for grapes.

Strawberries. Residue trials data were available from Italy, Japan, Spain and The Netherlands. Three Italian trials were according to GAP (0.048 kg ai/hl, 7-day PHI), with residues of 0.12-0.18 mg/kg. Dutch trials reflecting GAP (0.084 kg ai/ha, treatment before flowering) showed residues of <0.01-0.02 mg/kg, but the data were submitted in summary form only and were therefore not considered further. Higher residues would result from Spanish GAP which has the shorter PHI of 3 days (0.0048 kg ai/hl) and which was represented by one trial with a residue of 0.25 mg/kg. Seven field trials were according to Japanese indoor GAP with a PHI of 1 day (0.03 kg ai/ha or 0.003 kg ai/hl). Residues in crops sampled one day after the final treatment were 0.04-0.56 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg for strawberries.

Raspberries. Only one residues trial was available from the UK and this was at a higher application rate than the GAP reported for Ireland and the UK. There were insufficient data to estimate a maximum residue level.

Bananas. Residue trials in Ecuador, Costa Rica and Honduras demonstrated that residues in unbagged bananas were generally higher than in bagged bananas. Six trials according to GAP in Honduras and Nicaragua (0.12 kg ai/ha, PHI 0 days) showed residues in unbagged bananas 0 or 1 day after the final treatment of <0.01-0.19 mg/kg. Six further trials at twice the registered application rate led to residues of 0.03-0.3 mg/kg in unbagged fruit. Residues were determined in the edible pulp. Although these were generally lower than those in the peel some were higher. The Meeting concluded that there was no consistent partition factor between the pulp and peel. It estimated a maximum residue level of 0.2 mg/kg.

Cucumbers. Only very limited data were available with one trial according to UK and Irish GAP (0.002 kg ai/hl, 2-day PHI) and one according to GAP in Uruguay. Residues were 0.03 mg/kg after 2 days and 0.003 mg/kg after 4 days respectively. The Meeting concluded that there were insufficient data to estimate a maximum residue level for cucumber.

Gherkins. GAP for gherkins in The Netherlands was reported as 0.0024 kg ai/hl, 6-day PHI, for both protected and field use. Two Dutch trials were reported with the high application concentration of 0.24 kg ai/hl but with the rate per hectare unspecified. However, since the data were submitted in summary form only they were unsuitable. The Meeting concluded that there were insufficient data to estimate a maximum residue level.

Melons (including cantaloupe) and watermelons. Data were available from two Spanish indoor trials but these were with a higher spray concentration than the reported Dutch GAP. Two trials were according to Brazilian GAP (0.024 kg ai/ha, 4-day PHI); the residues were 0.005 mg/kg in melons and "not detected" in watermelons.

Four French trials on melons were according to Greek GAP for "cucurbits" (0.024 kg ai/ha, 1-day PHI) with residues of <0.01 mg/kg in the pulp and up to 0.11 mg/kg in the peel of samples taken 2 days after the final treatment. However, no information was available on the weight ratio of the peel to the pulp. The manufacturer suggested a 30% peel to fruit weight ratio based on melon samples taken from other trials. Whilst the Meeting would not normally consider it appropriate to use an assumed weight ratio, this was considered an exceptional case since the residues were very low and calculations of the residues in whole melons from the trial with the highest residue level in the peel, based on an assumed peel:fruit weight ratio of 20-40%, would lead to values of 0.03-0.05 mg/kg if the residues in the pulp were at the limit of determination. Other trials were available which, although they did not correspond exactly to reported GAP (usually they were with exaggerated doses), indicated that residues were generally low. The Meeting estimated a maximum residue level of 0.05 mg/kg for melons. Since there were relatively few results the Meeting did not consider it appropriate to extrapolate this estimate to other cucurbits.

Pumpkins, courgettes and squashes. Only limited data were available, with no indoor trials according to Dutch indoor GAP.

Only one trial in Brazil, with a residue of 0.005 mg/kg, conformed to outdoor GAP in Argentina and Uruguay. Single Australian replicated trials on zucchini and pumpkins were according to Australian GAP for cucurbits. Residues were very low: 0.001-0.01 mg/kg three days after the final treatment. The Meeting concluded that there were insufficient data to estimate a maximum residue level for pumpkins, courgettes or squashes.

Tomatoes. Two indoor trials in The Netherlands were comparable to Danish GAP (0.036 kg ai/ha or 0.0048 kg ai/hl, 2-day PHI). Residues in both were 0.03 mg/kg at 2 days. Italian and Spanish outdoor GAP (0.0048 and 0.006 kg ai/hl, 7-day PHI) was reflected in two Italian trials and one Spanish trial with residues of 0.03, 0.03 and 0.05 mg/kg at 7 days. There were no outdoor trials according to Japanese GAP, which has a PHI of 1 day. Should submissions be made in the future, processing data will be required. There were insufficient data to estimate a maximum residue level.

Peppers. There were 6 trials in Italy and Spain according to Italian and Spanish GAP (the same as for tomatoes). The residues were 0.03 and 0.07 mg/kg in the Italian trials and 0.07, 0.08, 0.12 and 0.5 mg/kg in the Spanish trials, in samples taken 7 days after the final treatment. The Meeting estimated a maximum residue level of 0.5 mg/kg for peppers.

Aubergines. Only one Italian trial was available in which the residue was <0.01 mg/kg 15 days after treatment. This was insufficient to estimate a maximum residue level.

Beetroots and carrots. The only GAP reported for beetroots and carrots was the Dutch GAP for "vegetables" (0.036 kg ai/ha or 0.0024 kg ai/hl, 3-day PHI). Although one Netherlands trial was available for each of these crops, neither reflected GAP since samples were taken 27 days after treatment. No maximum residue level could be estimated.

Artichoke, Globe. Six Italian trials were considered to reflect Italian GAP (0.0048 kg ai/hl or 0.038 kg ai/ha, 7-day PHI) with residues of <0.01-0.06 mg/kg. Two of these trials (in 1979 with residues of <0.01 and 0.03 mg/kg) had a low associated analytical recovery (61%) and were therefore not considered reliable. A further Spanish trial gave a higher residue of 0.26 mg/kg at 7 days but a high volume of water (2,500 l/ha) was applied and the spray concentration (0.006 kg ai/hl) was higher than that registered in Italy. The Meeting estimated a maximum residue level of 0.1 mg/kg for globe artichokes.

Witloof chicory. Only one replicated trial in The Netherlands was available which complied with Dutch GAP for "vegetables". Residues were <0.01 mg/kg in samples taken 60 days after treatment. The Meeting concluded that there were insufficient data to estimate a maximum residue level for witloof chicory.

Pecans. Twelve trials were carried out in the USA of which four (one replicated) had application rates of 0.074-0.12 kg ai/ha, close to the registered rate in the USA (0.098 kg ai/ha). Residues in the kernels, to which the MRL applies, were <0.002 mg/kg at 35-153 days. In a further series of trials, residues in the kernels were all <0.002 mg/kg except in one trial with 0.02 mg/kg, at an exaggerated application rate (0.14-0.197 kg ai/ha). The residue of 0.02 mg/kg may have resulted from physical transfer from the shell. Recognising the need to establish MRLs at levels suitable for routine analysis by monitoring and enforcement laboratories, the Meeting estimated a maximum residue level of 0.02* mg/kg for pecans.

Hops. Four trials in Germany were all according to German GAP (0.06 kg ai/ha or 0.0015 kg ai/hl, 10-day PHI). The residues in dry hops harvested 10 days after the final treatment were 2.22-3.55 mg/kg, but in all the trials the hop samples were stored for 13 months before analysis. Brewing with these hops gave residues in the beer of <0.01 mg/kg. The results appeared very consistent and would suggest a maximum residue level of 5 mg/kg in dry hops, but in the absence of data confirming the stability of fenarimol in stored samples of a leafy crop the Meeting decided not to recommend an MRL: it was informed that a storage stability study on hops was now available.

Apple pomace. Processing data on apples indicated a concentration of residues from whole apples to dry pomace of 5-20-fold, with a median concentration factor of 14. Apple samples in several of the trials were "soak-washed" before analysis of the whole apples. The Meeting considered the data from these samples unsatisfactory. In the seven remaining trials with unwashed apples the median and mean concentration factors were 15 and 17 respectively. Although it was noted that the analytical recoveries from dry apple pomace were variable (68, 68, 76, 83, 108, 132 and 132%) the Meeting estimated a maximum residue level of 5 mg/kg for apple pomace, dry.

Dried grapes. Processing data on grapes indicated concentration factors for residues in whole grapes to those in raisins of 0.2-2.1. By applying the median concentration factor of 0.6 to the estimated maximum residue level of 0.3 mg/kg for grapes, the Meeting estimated a maximum residue level of 0.2 mg/kg for dried grapes.

Grape pomace, dry. Processing grapes to dry grape pomace increased the residues about 12-15 times, but as there were only two suitable results and residues in the grapes were low the Meeting could not establish a reliable concentration factor and therefore did not estimate a maximum residue level.

In a livestock feeding study beef cattle and pigs were fed for 28 days with fenarimol at various rates up to 1 ppm in the diet. At this dose residues of fenarimol in all tissue except liver were ≤0.01 mg/kg. Residues in the liver reached a maximum level of 0.03 mg/kg in pigs and 0.05 mg/kg in cattle. At rates of 0.1 and 0.3 ppm all tissue residues were <0.01 mg/kg.

Livestock will obtain fenarimol from wheat grain and straw, peas and pea straw, and fruit pomace. Of these items sufficient data on residues were available only for dry apple pomace (estimated maximum residue level 5 mg/kg). Dairy and beef cattle consume a maximum of 30% of their dietary dry matter as fruit pomace, whereas it is not generally fed to pigs. The maximum intake of fenarimol by beef cattle from fruit pomace would therefore be approximately 1 ppm in the diet. The Meeting recognized the need to establish MRLs at levels suitable for routine analysis by monitoring and enforcement laboratories, and estimated maximum residue levels of 0.02* mg/kg for cattle meat and kidney and 0.05 mg/kg for cattle liver.

There were insufficient data on pig feed items to estimate a maximum residue level for the meat or edible offal of pigs.

Although data on the environmental fate of fenarimol in soil were submitted to the Environmental Core Assessment Group at the present Meeting they were not, as would normally be expected, submitted for the consideration of the FAO Panel. The manufacturer agreed to submit the data to the FAO, for future consideration by the FAO Panel, as soon as possible. The Meeting concluded that in these circumstances temporary MRLs should be recommended, with a requirement for the studies on environmental fate.

Recommendations for temporary MRLs are listed in Annex I.

FURTHER WORK OR INFORMATION

Required (by 1996)

Data on the environmental fate of fenarimol in soil.

Desirable

1. Full details of the methods of analysis used in all the residue studies where this information was not given. Validation of the methods of analysis for which validation data were not submitted.

2. A study to assess the likely residues in relevant succeeding or rotational crops or an explanation of why residues would not be expected.

3. Information on the melting point, octanol/water partition coefficient, solubility and specific gravity of pure fenarimol.

4. Submission of the study reports supporting the trials on apples, gooseberries, currants, gherkins and strawberries conducted in The Netherlands.

4.16 FENPROPIMORPH (188)

RESIDUE AND ANALYTICAL ASPECTS

(±)-*cis*-4-[3-(4-*tert*-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine

Fenpropimorph is a fungicidal pesticide whose major use is for the control of diseases in cereals. It is formulated into more than 49 products, mostly in mixtures with other fungicides, although the EC formulation is reported to be the most commonly used. Typically 1-3 field applications are made at rates of 0.3 to 0.75 kg ai/ha. Fenpropimorph was reviewed for the first time at the 1994 JMPR which considered toxicological aspects. Owing to the late receipt of residue data the FAO Panel review was postponed until 1995.

The fate of residues has been studied in animals, plants, soil, water and soil/water systems. The metabolism in plants is similar to that in animals to the extent that oxidation is the first stage of metabolism, followed by degradation of the morpholine ring. There are differences, especially in that generally fenpropimorph is the main residue in plants but is not found in animals (fenpropimorph reported in hen kidney is an exception).

The metabolites referred to by codes are identified below.

BF 421-1 4-{3-[4-(2-hydroxy-1,1-dimethyl)ethylphenyl]-2-methylpropyl}-*cis*-2,6-dimethylmorpholine
BF 421-2 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionic acid
BF 421-2-Me methyl 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionate
BF 421-2 conjugate 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)-propyl]phenyl}propionic acid conjugate
BF 421-3 2-methyl-2-{4-[2-methyl-3-(*cis*-2-hydroxymethyl-6-methylmorpholin-4-yl]propyl)phenyl}propionic acid
BF 421-4 2-methyl-2-{4-[2-methyl-3-(2-hydroxypropyl)aminopropyl]-phenyl}propionic acid
BF 421-7 [3-(4-*tert*-butylphenyl)-2-methylpropyl](2-hydroxypropyl)amine
BF 421-10 *cis*-2,6-dimethylmorpholine
BF 421-13 4-[3-(4-*tert*-butylphenyl)-2-methyl-1-oxopropyl]-*cis*-2,6-dimethylmorpholine
BF 421-15 4-[3-(4-*tert*-butylphenyl)-2-methylpropyl]-*cis*-2,6-dimethylmorpholine-3-one
BF 421-16 2-methyl-2-[4-(carboxyphenyl)]propan-1-ol
BF 421-17 2-methyl-2-[4-(2-carboxypropyl)phenyl)]propionic acid

The Meeting noted that the animal metabolites (and/or their conjugates) BF 421-3, BF 421-4, BF 421-16 and BF 421-17 had not been reported in plants. The plant metabolites BF 421-2-Me, BF 421-7, BF 421-10, BF 421-13 and BF 421-15 have not been reported in animals. Residues of most of these would be expected to be less than 1/4 of those of the parent compound, although BF 421-7 has been reported in one study of wheat metabolism to be at a similar level to the parent compound in wheat straw under some conditions. In any future animal metabolism studies it may be prudent to analyze for these plant metabolites.

Studies on rats, goats and poultry show rapid absorption from the gastrointestinal tract and rapid elimination of residues in faeces, urine or excreta, slightly less in urine than faeces. High bile residues were consistent with a high rate of faecal elimination.

The three test animals showed similar but not identical metabolism, consisting mainly in progressive oxidation of methyl groups of both the *tert*-butyl group and the morpholine ring. Further metabolism of the morpholine ring was demonstrated by the expiration of significant amounts of $^{14}CO_2$ by the rat. The expiration of $^{14}CO_2$ was not measured in goats or hens.

In animals, residues of the parent compound were detected only in hen kidneys. The highest residues of identified metabolites were in the liver and kidneys. The main metabolites were BF 421-1, detected in goat fat and faeces and hen plasma, BF 421-2 detected in several goat tissues and milk and hen kidneys and liver, and BF 421-3 detected in goat and hen kidneys and goat fat.

No conjugates were detected in hens, whereas conjugates of BF 421-2 were found in goat liver and a conjugate of BF 421-3 was found only in rat urine, faeces and bile. Metabolites BF 421-16 and BF 421-17 were detected only in rat urine, kidney and faeces.

Although the faeces and urine were by far the predominant routes of elimination of residues, approximately 50% of the material administered to goats in one study was not accounted for by analyses of urine, faeces, milk, bile, cage washes, and tissues or organs, and was assumed to remain in the gastrointestinal tract. This was not documented nor was radioactivity measured in expired CO_2, which had been shown to be a significant route of elimination in rats. Elimination in the faeces and urine combined was reported to be about 84% in a separate study in which animals were killed 24 hours after the last dose as compared with 5 hours in the first study.

In studies of <u>cereal metabolism</u> fenpropimorph with the benzylic carbon labelled was applied to leaf surfaces. Over 60% of the residue on the day of application was on the leaf surface and was mainly unchanged fenpropimorph. After three weeks about 30% of the applied radioactivity was absorbed into the leaf and only about 7% of that was unchanged fenpropimorph. Low levels of radioactivity were translocated to untreated plant parts. With the ring-labelled compound (either ring) most of the radioactivity was extractable and fenpropimorph was generally by far the main residue, although BF 421-7 was sometimes of the same order in straw, depending on the conditions. Other metabolites identified in cereal plants included BF 421-1, BF 421-2, <u>BF 421-2-Me</u>, <u>BF 421-10</u>, <u>BF 421-13</u> and <u>BF 421-15</u>. The underlined compounds were not reported in studies of animal metabolism.

The radioactivity in cereal grains was too low for identification and was mainly associated with the starch fractions, although it did not appear to be incorporated into the glucose units. Less was associated with protein and polysaccharide fractions.

Rotational crop plantings in soil containing 0.42 mg/kg [^{14}C]fenpropimorph resulted in residues in the mature crop of $\leq$0.01 mg/kg fenpropimorph equivalents in spinach and sugar beet tops, <0.02 mg/kg in green wheat plants and 0.004 mg/kg in mature sugar beets. Since metabolism studies showed relatively rapid degradation of fenpropimorph, the rotational crop data suggest that, at least in sandy loam soil, only trace residues would be expected in rotational crops after the previous crops had been sprayed with fenpropimorph.

Under neutral conditions fenpropimorph is largely stable in water. Degradation in soil

proceeds by oxidation and opening of the morpholine ring to give BF 421-2, BF 421-7, BF 421-8 and BF 421-10. In addition, BF 421-13 and BF 421-15 can result from the photolysis of soil residues. The half-life of fenpropimorph in soil varies according to the conditions, ranging from 10 to 90 days. In aerobic water/sediment systems degradation is similar, except that the morpholine ring is not opened.

Analytical methods are available for the determination of fenpropimorph in plant materials, soil and water. For plants the emphasis in method development has been on cereals (grain, plant, forage and straw) and citrus. Most methods rely on extraction with methanol, chloroform, methylene chloride or other solvents and concentration, with or without clean-up by cation exchange, alumina chromatography or liquid/liquid partition. Determination is generally by GLC with an NPD or occasionally HPLC with UV detection or GC-MS, depending on the method and the matrix being analyzed. A limit of determination of 0.05-0.1 mg/kg should be achievable in most cases and perhaps lower, especially for water, soil and grain. However, for some methods sufficient information was not available for an independent estimate of the limit of determination.

Methods for fenpropimorph acid (BF 421-2) in soil depend on methylation with diazomethane before determination by GLC with an NPD or by GC-MS.

The stability of fenpropimorph in stored analytical samples of wheat grain, green plants and straw and of fenpropimorph and its acid in soil was investigated over a 2-year period. The maximum losses of the parent compound or its acid were about 25%, but generally less than 10%.

Because residues in plants are generally mainly the parent compound the Meeting concluded that for regulatory purposes the residue in plants should be defined as fenpropimorph. For risk assessment purposes, the data suggest that the total residues of fenpropimorph plus its major plant metabolites will almost certainly be no more than 3 times the level of fenpropimorph alone, but more likely less than twice that level. Consideration of a definition of the residue in animal products must await further information. The Meeting was informed by the manufacturer that national definitions of the residue in foods and feeds of plant origin include only fenpropimorph. This is also the definition for residues in meat and milk in The Netherlands.

Supervised residue trials gave the following results.

Beans. Residues in fresh ripe bean seeds in 6 trials in 1983 in the UK at GAP rates were <0.05, <0.1 or 0.07 mg/kg after 26-72 days compared to the 28-day UK PHI. Residues in 3 UK trials, also according to GAP, were 0.06(2) and 0.09 mg/kg in whole plants. The results suggest that residues are unlikely to exceed 0.1 mg/kg in fresh shelled beans, but because the data were relatively old and limited and the residue reports did not include information on method(s) of analysis, sample chromatograms, control values, or analytical recoveries, the Meeting concluded that the information was insufficient to support a limit.

Carrots. The Meeting did not use summary data submitted from Norway in the absence of detailed reports, acknowledged to be unavailable.

Cereals. Data from many supervised trials with a wide geographical distribution (mainly Western Europe) were available. A significant number of the reports were not sufficiently documented for full confidence in the validity of the data, but because over half of the reports were considered reasonably well documented and because of the similarity and mutual support of the results among the cereals, the Meeting concluded that limits could reasonably be recommended, even when discounting the less well documented studies. In most cases grain residues were less than 0.05 mg/kg.

Most of the trials were on barley and wheat. While the results were minimal for oats and somewhat scanty for rye, the Meeting considered the data on cereal grains to be mutually supportive.

Barley. Over 100 supervised trials were conducted in 9 Western European countries and New Zealand, covering the range of reported GAP including 1-3 applications, usually of EC formulations, at rates ranging from 0.38 to 0.75 kg ai/ha and PHIs ≥30 days. Data were also available for exaggerated rates and shorter PHIs. Residues in barley grain judged by the Meeting to be from treatments according to GAP, expressed as mg/kg with the number of results in parentheses were: ≤0.05 (62), <0.08 (2), 0.06 (3), 0.07 (4), 0.08 (3), 0.09 (4), 0.1 (12), 0.2 (8), 0.3 (2), 0.4 (2) and 0.5 (1), with a median of <0.05 mg/kg. The residues of 0.3 mg/kg (from the same trial), 0.5 mg/kg and one of 0.4 mg/kg were from German trials according to German GAP, but with 3 applications instead of the two allowed. GAP in the UK allows three applications if the last two are after January as they were in these trials. The distribution in barley straw was ≤0.1 (29), 0.2-0.5 (23), 0.6-1 (19), 1.1-1.5 (13), 1.8 (4), 1.9 (1), 2.2 (1) and 4.2-4.8 (2). The last two residues were from the same German trial as the residues of 0.3 mg/kg in the grain. In whole barley plants residues from applications according to GAP at the days PHI in parentheses were 2.4-31 mg/kg (0), 7.3 mg/kg (7-9), 0.2-2.6 (14-18), 0.08-2 (20-25), 0.09-1.8 (26-30), 0.05-0.2 (30-40) and 0.04-0.07 mg/kg (40-50).

Although there was an adequate number of results, there were deficiencies in the detail provided for a significant number of the trials. For example, the sample handling and storage conditions and analytical recovery values were not provided, nor were analytical methods identified for about a third of the studies. No sample chromatograms were provided for any of the field studies, although representative chromatograms from grain and straw analyses were provided in separate validations of one of the methods used (Method 840-MD-02).

By putting greater weight on the better documented studies and noting that data among the cereals were similar and mutually supportive, the Meeting estimated a maximum residue level of 0.5 mg/kg for barley grain. No data on moisture content were available to estimate a maximum level in fodder on a dry weight basis, but with maximum expected residues of 2 mg/kg in fresh barley forage from GAP treatments, and assuming 30% dry matter, a theoretical level of 7 mg/kg could be estimated for dry fodder. Observing that median residues in fresh forage after the shortest GAP PHI would be <0.5 mg/kg, and noting maximum residues in barley straw of 4.8 mg/kg, the Meeting estimated a maximum residue level of 5 mg/kg for dry barley straw and fodder.

Wheat. Over 150 supervised trials were conducted in 10 Western European countries and in New Zealand. Some of the German trials were with higher application rates than reported German GAP, but as they were according to the GAP of neighbouring countries the Meeting considered that they should not be disregarded. The distribution of residues, with the number of results within reported GAP in parentheses, were for grain <0.05 (203), 0.05-0.09 (18) and 0.1-0.4 (20), with a median of <0.05 mg/kg, and for straw <0.05 (9), 0.05-0.09 (31), 0.1-0.4 (59), 0.5-0.9 (39), 1-2 (32), 2.1-2.9 (26), 3-4 (9), 4.1-5 (7) and 5.9 mg/kg, with a median of 0.7 mg/kg. Residues in whole plants were 0.08-39 mg/kg at day 0, decreasing to about 0.05-1 mg/kg at 30-60 days.

As in the case of barley some of the studies were not well documented, especially with respect to sample handling and storage conditions and the identification or provision of the analytical methods used. In approximately 6 cases the interval from sampling to analysis was ≥2 years and in four trials the plot size was only 5 m^2. No representative chromatograms were provided with the supervised trials data although, as with barley, they were provided with some method validations. The Meeting considered the documentation for approximately 7% of the 150 trials to be unacceptable.

Approximately 50% were reasonably well documented and another 40% fairly well documented.

As with barley, the Meeting gave greater weight to the better documented studies, took into account the similarities among the different cereals, and estimated a maximum residue level of 0.5 mg/kg for wheat grain. Noting that only one residue (of 5.9 mg/kg) in over 250 barley and wheat straw samples exceeded 5 mg/kg, the Meeting concluded that it was unlikely that residues in straw would exceed 5 mg/kg.

Again, no moisture contents were available to estimate fodder residues on a dry weight basis. Assuming 25% moisture in the whole plants, and estimating a maximum residue of 2 mg/kg in fresh wheat fodder (whole plants), a theoretical maximum level of 8 mg/kg could be estimated for the fodder on a dry weight basis. Observing that, as in the case of barley,the median residue in fresh fodder after the minimum 30-day GAP PHI is likely to be less than 0.5 mg/kg compared with the estimated maximum of 2 mg/kg, the Meeting estimated a maximum residue level of 5 mg/kg for wheat straw and fodder, dry.

Oats. Data were available from three supervised trials in the UK in 1980, all within reported UK GAP for the EC formulation (2 x 0.75 kg ai/ha; 30-day PHI). Residues in grain were <0.05 (2) and 0.4 mg/kg after 35 days and <0.05 mg/kg after 81-83 days, in straw 1.2 and 0.8 mg/kg after 83 and 35 days respectively, and in green plants up to 1.1 and 0.5 mg/kg after 38 and 49 days respectively. The studies were reasonably well documented, except that the analytical method used was not identified. Taking into account the mutual support of the barley and wheat data, the Meeting estimated maximum residue levels of a 0.5 mg/kg for oat grain and 5 mg/kg for oat straw and fodder, dry.

Rye. Data were available for about 12 supervised trials conducted in 1980-84 in Germany, the UK and Sweden. Swedish trials with EC formulations were according to GAP reported for the UK and Germany, which allows up to two 0.75 kg ai/ha applications of the EC with a 35-day PHI.

Four of the Swedish trials with an SC formulation were within reported UK GAP for SC but two trials giving residues of 0.3 and 0.4 mg/kg after 82 days were from two applications at 0.75 kg ai/ha whereas UK GAP allows only one at that rate (2 are permitted at 0.56 kg ai/ha). At PHIs at or longer than the 35-day German and UK GAP and relating Swedish results to GAP in those countries, the residues which reflected GAP were <0.05 (11 results), 0.09 and 0.1 mg/kg in grain and 0.05, 0.09, 0.2, 0.3, 0.4, 0.6, 1 and 1.3 mg/kg in straw. Residues in whole plants were 2.7 and 3.8 mg/kg on the day of application. Most of the studies were reasonably well documented, although as with oats in several cases information was lacking on the analytical methods used or on analytical recoveries and representative chromatograms were not provided with the trials. Taking these results into account and with the support of those for barley and wheat, the Meeting estimated maximum residue levels of 0.5 mg/kg for rye grain and 5 mg/kg for rye straw and fodder, dry.

Leeks. Residues in whole leeks in eight supervised trials in the UK in 1982-3 (6 locations) were 0.1 to 0.4 mg/kg 20 to 38 days after 3-5 GAP applications of 0.75 ai/ha. The GAP PHI is 21 days. There appears to be little correlation between the number of applications or PHI (3-28 days) and residue levels. With one exception the interval from sampling to analysis was ≤6 months and the samples were reported to have been deep frozen. In the absence of more detailed information on sample handling and methods of analysis (the data suggest that there were more than one), sample chromatograms, analytical recoveries and control values, the Meeting could not estimate a maximum residue level. If adequate supporting information can be provided to a future Meeting, the data may support an estimate of 0.5 mg/kg for leeks.

Onions. The Meeting did not use summary data submitted from Norway in the absence of detailed reports, which were acknowledged to be unavailable.

Sugar beets. Over 25 supervised trials (1982-89) were conducted in 6 Western European countries at GAP rates (0.38-1.1 kg ai/ha), with samples of sugar beet and sugar beet leaves taken at PHIs ranging from 0 to 113 days. GAP for sugar beets was reported only for Belgium, Denmark, Greece, Luxembourg and Switzerland but the trials, which were in Belgium, France, Greece, Italy, Sweden and Switzerland, cover the full range of reported GAP for Western Europe, in which the minimum PHI is 7 days (Greece). In all cases 6 or more days after the last application residues were reported as ≤0.05 mg/kg in the roots and ≤1 mg/kg (0.09 mg/kg median) in the leaves, with leaf residues approaching 1 mg/kg in several trials. Where they were provided, control values for both roots and leaves were <0.05 mg/kg. No data were available for sugar beet molasses or pulp.

The Meeting was not satisfied with the level of information provided in approximately half the trials on one or more of the following items: sample handling and storage conditions, recovery data, control values and plot sizes. More often than not this was because only the analytical reports (without the corresponding field reports) were submitted.

In most cases the analytical method was identified as being one of those for which information was supplied to the Meeting, although no sample chromatograms were provided for sugar beets. They were provided for other crops in separate method validations. Analyses were generally conducted within 14 months of sampling, usually less. No storage stability studies were provided for sugar beet, although fenpropimorph has been shown to be stable for over a year in soil and wheat grain, straw and plants under frozen storage.

Although the Meeting found the overall submission to be only marginally acceptable, because several of the trials in different geographical areas and in different years were relatively well documented it concluded that maximum residue levels could be estimated. The Meeting considered the submission of validation of methods specifically for sugar beet roots and leaves, and of storage stability studies for a root crop to be highly desirable for a future JMPR evaluation in order to confirm the estimates. The Meeting estimated that fenpropimorph residues are unlikely to exceed 0.05 mg/kg (limit of determination) in sugar beet roots or 1 mg/kg in sugar beet leaves when GAP is followed.

Animal products. Of the crops for which maximum residue levels were estimated by the Meeting, those which may be fed to animals include the grain (0.5 mg/kg), straws and fodders of cereals (5 mg/kg), cereal grain forage (2 mg/kg) and sugar beet tops (1 mg/kg). No information was available on sugar beet molasses or pulp.

Assuming worst-case feeding situations for the above crops and maximum residue levels in them, maximum theoretical fenpropimorph levels in the feed would be 1.3 ppm for beef cattle, 1.7 ppm for dairy cattle and 0.35 ppm for poultry.

No conventional feeding trials data were provided to the Meeting. It is possible to make a crude estimate of total residues as fenpropimorph equivalents in cattle and poultry using the above estimates in conjunction with residue levels found in the metabolism studies on goats and hens. With these assumptions the total residues (mg/kg) in cattle/poultry would be muscle 0.01/0.003, fat 0.03/0.01, liver 0.3/0.03, kidney 0.08/0.02, milk 0.02 and eggs 0.01.

There are several obstacles to recommending reliable MRLs for fenpropimorph in animal products. One is the lack of data on sugar beet pulp and molasses, although the studies provided

suggest that residues in the roots, if present, may not exceed 0.01 mg/kg. A more serious obstacle is the lack of conventional feeding studies.

The guidance on livestock transfer studies in the 1993 JMPR report states that such studies are required (1) when detectable residues are found in feed items and metabolism studies indicate that significant residues (>0.01 mg/kg) may occur in edible tissues, and generally (2) where significant residues (generally >0.1 mg/kg) occur in crops or commodities fed to animals. Both situations occur with fenpropimorph. The guidance allows the possibility of using metabolism studies to serve as transfer studies when only low residue levels (<0.1 mg/kg) are found in feed items, but this does not apply to fenpropimorph. The situation does not lend itself to waiving the need for transfer studies.

Another complicating factor is the indication in metabolism studies that fenpropimorph *per se* is unlikely to occur in animal products with the possible exception of hen kidney. The studies indicate that low residues of metabolites may occur, especially in liver and kidney. None of the analytical methods provided to the Meeting is suitable for animal products and none determines metabolites (except fenpropimorph acid in soil). The Meeting was advised that an analytical method for the determination of fenpropimorph *per se* in animal tissue is available but it was not provided. There would be little point in recommending limits for the parent compound in animal products when its residues would not normally be expected.

No method has been provided for enforcing limits based on a definition of the residue which includes the most likely animal metabolites BF 421-1 (hydroxy-fenpropimorph) BF 421-2 (fenpropimorph acid) and BF 421-3 (hydroxymethyl-fenpropimorph acid). The Meeting was informed that a method for the determination of fenpropimorph acid is expected to be completed by the end of 1995, but it has not yet been decided whether feeding trials employing this method will be conducted.

The Meeting concluded that the data were insufficient to estimate maximum residue levels for animal products. For that purpose conventional transfer studies are needed for cattle and poultry, following Codex guidance and with analyses for the parent compound and likely metabolites by validated methods.

Fenpropimorph residues were reduced by 20 and 60% in Washington navel oranges and Hernandina clementines respectively held in storage for 30 days at 5°C. In the processed fractions residues increased slightly in the pulp over the same period, remained the same in the albedo and decreased by 10 and 46% respectively in the peel.

A summary report of a wheat processing study suggests fenpropimorph losses of >30% when processing wheat grain containing 0.07 mg/kg into bran, wholemeal or white flour. In this and three other summary reports bread baked from grain with residues of 0.05 to 0.08 mg/kg was reported to contain residues of <0.05 mg/kg. The Meeting could not confirm the results reported for the processed products in the absence of the detailed processing procedures. Processing studies on wheat grain containing residues near the estimated maximum level would be desirable for a clear picture of the extent of residue reduction.

With regard to the edible portions of food commodities, cereal grains are the main items for which MRLS are recommended. Trials showed that median residues in grain are likely to be <0.05 mg/kg and maximum residues unlikely to exceed 0.5 mg/kg. As noted above, summary reports suggest that residues in processed grain fractions and bread are likely to be less than in grain and probably not detectable (<0.05 mg/kg) in bread baked from grain containing expected median

residues. This needs to be confirmed.

Although no MRLs are recommended for beans, leeks or citrus fruits, the data suggest that residues may not exceed 0.5 mg/kg from approved uses in leeks or 0.1 mg/kg in fresh beans. Although data were not provided for estimating a maximum residue level for citrus, the available information indicates that residues in citrus pulp are likely to be less than 10% of the residue in the whole fruit.

No information was provided on residues in commodities in commerce or at consumption.

The Meeting estimated the maximum residue levels recorded in Annex 1.

FURTHER WORK OR INFORMATION

Desirable

1. Details (preferably in English) of the procedures used in the BASF wheat processing studies described in reports Nos. 79/10261, 79/10262, 79/10263 and 86/10411 for review at a future Meeting.

2. Conventional livestock and poultry feeding (transfer) studies with determination of fenpropimorph and the major metabolites identified in metabolism studies (e.g. BF 421-1, BF 421-2 and BF 421-3).

3. Validated analytical regulatory methods (including representative chromatograms) for the determination of fenpropimorph and its major metabolites in animal products.

4. Information on fenpropimorph residues in commodities in commerce or at consumption.

5. A study of the frozen storage stability of analytical samples of a root crop.

6. Validation of analytical methods used in the sugar beet trials.

4.17 FENPYROXIMATE (192)

tert-butyl (*E*)-á-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-*p*-toluate

Fenpyroximate is a non-systemic selective acaricide for the control of immature and adult stages of spider mites. It is registered in many countries around the world, mainly for the control of European red mites (*Panonichus ulmi*) and two-spotted mite (*Tetranichus urticae*) in citrus fruits, pome fruits, grapes and hops.

Fenpyroximate was evaluated for the first time by the present Meeting.

TOXICOLOGY

Fenpyroximate was relatively well absorbed by rats after oral administration. Absorbed fenpyroximate was excreted predominantly via the biliary route, with lesser amounts in urine. The residual levels in organs and tissues after 168 h were low. There was no evidence of bioaccumulation.

Fenpyroximate was extensively metabolized in rats; 23 metabolites were identified. No parent compound was found in the urine. Metabolites found in the excreta represented 0-11% of the administered dose. Multiple pathways have been proposed for the metabolism of fenpyroximate, including oxidation, hydroxylation, demethylation, hydrolysis and isomerization.

Fenpyroximate has slight to moderate acute oral toxicity (oral LD_{50} = 440-520 mg/kg bw in mice and 245-480 mg/kg bw in rats); it is acutely toxic by inhalation (LC_{50} in rats = 0.21-0.36 mg/m^3). The WHO has not classified fenpyroximate for acute toxicity.

In a 13-week study in rats in which fenpyroximate was administered in the diet at concentrations of 0, 20, 100 or 500 ppm, the NOAEL was 20 ppm, equal to 1.3 mg/kg bw per day, and was based on decreased body weight gain and lowered plasma protein levels in females fed 100 ppm. In a 13-week study in dogs, fenpyroximate was administered orally in capsules at doses of 0, 2, 10 or 50 mg/kg bw per day. The NOAEL was 2 mg/kg bw per day, on the basis of decreased body weight gain and clinical signs such as an increased incidence of diarrhoea, emaciation and slight bradycardia at 10 mg/kg bw per day. In a 52-week study of similar design, with doses of 0, 0.5, 1.5, 5 or 15 mg/kg bw per day the NOAEL was 5 mg/kg bw per day, on the basis of decreased body weight gain and total protein levels at 15 mg/kg bw per day.

In an 18-month study of carcinogenicity in mice given dietary concentrations of 0, 25, 100, 400 or 800 ppm, the NOAEL was 100 ppm, equal to 9.5 mg/kg bw per day, and was based on decreased body weight gain, absolute body weight and food consumption in animals of each sex at 400 ppm. There was no evidence of carcinogenicity. In a 104-week study in rats given dietary concentrations of 0, 10, 25, 75 or 150 ppm, the NOAEL was 25 ppm, equal to 1 mg/kg bw per day, based on decreased body weight and body weight gain in males at 75 ppm. There was no evidence of carcinogenicity.

In a two-generation (one litter per generation) study of reproductive toxicity in rats given dietary concentrations of 0, 10, 30 or 100 ppm, the NOAEL for maternal and developmental toxicity was 30 ppm, equal to 2 mg/kg bw per day, on the basis of decreased body weight gain in animals of the F_0 and F_1 generations at 100 ppm.

In a study of developmental toxicity in rats given doses of 0, 1, 5 or 25 mg/kg bw per day by gavage, the NOAEL for maternal toxicity and fetotoxicity was 25 mg/kg bw per day, the highest dose tested. There was no evidence of embryotoxicity or teratogenicity. In a study of developmental toxicity in rabbits given doses of 0, 1, 2.5 or 5 mg/kg bw per day by gavage, there was no evidence of embryo- or fetotoxicity or teratogenicity at any dose. The NOAEL for maternal toxicity was 2.5 mg/kg bw per day on the basis of minor effects at 5 mg/kg bw per day.

Fenpyroximate has been adequately tested for genotoxicity in a range of tests *in vitro* and *in vivo*. The Meeting concluded that it is not genotoxic.

Two high doses, given 21 days apart, to hens did not cause gait abnormalities or morphological changes in the nervous system.

An ADI of 0-0.01 mg/kg bw was established on the basis of the NOAEL of 1 mg/kg bw per

day for reductions in body weight gain and plasma protein concentration in the 104-week study in rats and a safety factor of 100.

A toxicological monograph was prepared, summarizing the data that were reviewed by the present Meeting.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 100 ppm, equal to 9.5 mg/kg bw per day (18-month study of carcinogenicity)

Rat: 25 ppm, equal to 1 mg/kg bw per day (104- week study of carcinogenicity)
30 ppm, equal to 2 mg/kg bw per day (study of reproductive toxicity)

Rabbit: 2.5 mg/kg bw per day (maternal toxicity in study of developmental toxicity)

Dog: 5 mg/kg bw per day (52-week study of toxicity)

Estimate of acceptable daily intake for humans

0 - 0. 01 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to fenpyroximate

Exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral, lethality, mouse and rat	LD_{50}, 245-520 mg/kg bw
	Eye, irritation, rabbit	Irritating
	Eye, irritation, human	Irritating
	Skin, sensitization, guinea-pig	Sensitizer
	Dermal, lethality, rat	$LD_{50} > 2000$ mg/kg bw
	Inhalation, lethality, rat	$LC_{50} = 0.21 - 0.36$ mg/m^3
Medium-term	Repeated 21-day toxicity, dermal, rat	NOAEL = 300 mg/kg bw per day based on reduced body weight gain and increased liver weight
	Repeated 4-week inhalation, toxicity, rat	NOAEL = 2 mg/m^3 based on increased lung weight and mucosal change in nasal passage
	Repeated 13-week dietary, toxicity, rat	NOAEL = 1.3 mg/kg bw per day based on reduced body weight gain and lowered plasma protein level
Medium-term	Dietary, two-generation reproductive and developmental toxicity, rat	NOAEL = 2 mg/kg bw per day for maternal and developmental toxicity
	Gavage, developmental toxicity, rat, rabbit	NOAEL = 2.5 mg/kg bw per day for maternal toxicity; no fetotoxicity or teratogenicity
Long-term	Repeated dietary, two-year toxicity and carcinogenicity, mouse, rat	NOAEL = 1 mg/kg bw per day based on reduced body weight gain and lowered body weight; no carcinogenicity

RESIDUE AND ANALYTICAL ASPECTS

The fate of fenpyroximate has been studied in rats, mandarins, apples, grapes, soil and water.

The principal metabolites identified are indicated below.

A: *tert*-butyl (*Z*)-á-(1,3,-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-*p*-toluate
C: (*E*)-á-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-*p*-toluic acid
F: 1,3-dimethyl-5-phenoxypyrazole-4-carbaldehyde
H: 1,3-dimethyl-5-phenoxypyrazole-4-carboxylic acid

K: 1,3-dimethyl-5-phenoxypyrazole-4-carbonitrile
L: *tert*-butyl (*E*)-á-(3-methyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-*p*-toluate

Male and female rats were dosed orally once with fenpyroximate labelled with ^{14}C in both the pyrazole and benzyl rings at a 2 mg/kg or 400 mg/kg bw. Another group of animals received a daily dose of 2 mg/kg bw of the unlabelled compound for 14 days, followed by a single administration of [*pyrazole*-^{14}C]fenpyroximate at the same level. Fenpyroximate was rapidly excreted in the urine and faeces.

Following [*pyrazole*-^{14}C]fenpyroximate administration at 2 mg/kg, radioactivity was rapidly excreted in faeces and urine. After 168 hours, 70-85% of the dose had been excreted in the faeces and 12-18% in the urine. Negligible amounts of radioactivity were expired as CO_2 or volatile organic compounds. Similar results were obtained after multiple dosing with unlabelled fenpyroximate followed by a single dose of fenpyroximate at 2 mg/kg.

Although slower excretion was observed after a single administration at 400 mg/kg, 75-77% of the dose was excreted in the faeces and 11-12% in the urine after 168 hours. Tissue residues were generally low at 168 hours, and the highest concentration of radioactivity (1-4% of the dose) was in the gastrointestinal tract. The major urinary metabolites were 1,3-dimethyl-5-phenoxypyrazole-3-carboxylic acid (H) and 4-cyano-1-methyl-5-phenoxypyrazole-3-carboxylic acid. High levels of unchanged fenpyroximate were present in the faeces, owing to the excretion of the unabsorbed compound.

A similar pattern of excretion and tissue distribution were observed after administration of [*benzyl*-^{14}C]fenpyroximate. The major urinary metabolite was terephthalic acid and large amounts of unchanged fenpyroximate were found in the faeces.

The principal metabolic pathways were isomerization, cleavage of the oxime ether bond between the benzyl and pyrazole rings, hydrolysis of the ester, oxidation of the *tert*-butyl group and *N*-demethylation of the pyrazole ring.

Low residues were found in the tissues: liver 0.1-0.25%; kidney 0.05-0.1 %; and fat 0.4-0.8% of the initial dose.

No metabolism studies were submitted for other animals.

The fate of residues in plants was studied in mandarins, apples and grapes, using [*pyrazole*-^{14}C] and [*benzyl*-^{14}C]fenpyroximate. Labelled fenpyroximate was applied to mandarins at approximately the recommended rate, and samples were collected at 0, 3, 7, 14, 28 and 137 days after treatment. Radioactivity was not detected in the pulp (LOD 0.03 mg/kg at 28 days and 0.004 mg/kg at 137 days after treatment). The radiocarbon concentration on and in treated leaves gradually decreased. Loss from the peel was slower. The half-life of fenpyroximate was 38.4 days in the peel and 8.8 days in the leaves. The principal ^{14}C residues were fenpyroximate and its *Z*-isomer, although *N*-demethyl-fenpyroximate was found at analytically significant levels in early trials on mandarins.

The *Z*- isomer (compound A) generally occurred at levels of ≤10% of those of fenpyroximate in the peel and leaves at short PHIs (3-7 days). *N*-demethyl fenpyroximate (compound L) occurred at comparable or slightly higher levels at PHIs of 28-137 days.

Labelled fenpyroximate was applied to apples at the maximum recommended field rate of 7.5 g ai/hl, and samples were analyzed at intervals. Fenpyroximate and its *Z*-isomer were the main ^{14}C residues in apples at harvest. Several metabolites were also found, but were of minor importance. The total radioactivity in the fruits decreased from 0.13 mg fenpyroximate equivalents/kg at day 0 to 0.003 mg/kg at day 57 (harvest).

Metabolism studies on grapes were carried out using pyrazole- and benzyl-labelled fenpyroximate. Fenpyroximate and its *Z*-isomer were again the main residues in grapes and stems at harvest. Several metabolites were detected at lower levels. After the application of labelled fenpyroximate at the recommended rate (37.5 g ai/ha) the highest total radioactivity found in grape bunches was 0.19 mg/kg fenpyroximate equivalents at day 7, and 0.08 mg/kg at day 57 (harvest).

In summary, plant metabolism studies indicated that the major residual compounds in crop commodities are unchanged fenpyroximate and its *Z*- isomer. Although the proportion of the *Z*-isomer increased with time, its residues were generally less than 20% of the fenpyroximate levels in fruits at PHIs up to 28 days. Leaves showed the same pattern of metabolites as fruits, but with higher levels of ^{14}C. Residues of *N*-demethyl-fenpyroximate (compound L) were of the same order as, or slightly higher than, those of the *Z*-isomer.

Although compounds A and L were the main metabolites in plants, compound A was a minor metabolite in animals and compound L was not found.

Studies of the fate of fenpyroximate in soil (sandy, silty and clay) showed that the degradation pathways consist of hydrolysis of the ester, isomerization or cleavage of the oxime group, *N*-demethylation, oxidation of the methyl group at the 3-position on the pyrazole ring and hydroxylation of the phenyl ring, with final mineralization to CO_2. Compounds A, C, H and K were the major degradation products. The half-life was 10 to 50 days, except in sandy soil where it was 159 days. Fenpyroximate was strongly adsorbed to soil, to an extent depending on the content of soil organic matter.

The adsorption/desorption of [*pyrazole*-^{14}C]fenpyroximate was studied in four different soil types. The K_{oc} values were all 37,000 or more, showing that fenpyroximate is immobile in all the soils tested (loamy sand, sandy loam, clay loam and loam).

The leaching behaviour of fenpyroximate and its aged residues was studied in various soils. The results showed that small amounts of fenpyroximate move only through very sandy soils with low organic matter contents. The compound can therefore be classified as weakly mobile.

Environmental fate in water. The hydrolysis of fenpyroximate was studied in buffered sterile and unsterilized aqueous solutions at various Ph values and temperatures. Compounds A, C and F were identified as degradation products. The studies were too short to estimate half-lives.

The photolysis of fenpyroximate in solution was studied with irradiation by sunlight and a xenon lamp. The predominant product of photodegradation was compound A. Degradation was apparently by isomerization, oxime-ether cleavage and hydrolysis. The half-life was 2.6 days in sunlight and 1.5 hours under irradiation with a xenon lamp (603 watts, 290-300 nm) at pH 7.

The analytical methods for fenpyroximate and its isomer used in the reported studies were based on extraction with methanol or acetone, partitioning with hexane or acetonitrile, and clean-up on some combination of C_{18} cartridges, SX-3 gel, silica gel and alumina columns. Determination was

by GLC or HPLC. The GLC methods determine fenpyroximate and its *Z*-isomer, while HPLC (with UV detection) determines fenpyroximate, its *Z*-isomer and *N*-demethyl-fenpyroximate in the same extract.

Recoveries of fenpyroximate and its *Z*-isomer from fruits were above 70% with LODs of 0.02-0.05 mg/kg. The limits of determination reported for other commodities were 0.1 mg/kg for dregs and yeast, 1 mg/kg for dried hops, 0.5 mg/kg for green hops, and 0.01 mg/kg for beer.

The storage stability of pyrazole-labelled fenpyroximate was investigated on apples and grapes stored at -20ºC. After about 3 years approximately 65% of the initial residue remained. In another study apples and grapes fortified with a solution of fenpyroximate and its metabolites were stored at -20ºC. The proportions of the original residues remaining in apples after 145 days were fenpyroximate 68%, *Z*-isomer 71%, and *N*-demethyl fenpyroximate 60%, and in grapes stored for 77 days fenpyroximate 76%, *Z*-isomer 87%, and *N*-demethyl-fenpyroximate 50%.

The stability of fenpyroximate residues at -20ºC was also studied in citrus samples (peel and pulp) fortified with fenpyroximate and its *Z*-isomer. The proportions of both compounds remaining were 65% in pulp stored for 140 days and 72% in peel stored for 188 days. Fenpyroximate and the *Z*-isomer were stable in hops (dried cones) stored at -18ºC for 2 years with about 100% of the residues remaining. The studies showed that fenpyroximate can be considered to be reasonably stable during these periods.

Results of residue trials were available for citrus (oranges and mandarins), apples, grapes and hops. For many trials only summary reports were supplied and few trials were according to GAP. Often representative chromatograms were not provided although control values and percentage recoveries were submitted.

Fenpyroximate is registered for use on citrus fruits in Brazil, Chile, Greece, Italy, Japan, Peru and Spain with application rates from 0.1 to 0.2 kg ai/ha, and PHIs of 14-15 days. The Meeting received data from supervised trials in Brazil, Greece and Italy: residues were determined separately and the peel/pulp ratios were not reported. Supervised trials on mandarins treated at the recommended rate (0.005 kg ai/hl) were carried out in Japan in greenhouses, this being a minor use in that country. These trials were the only ones in which residues in the whole fruit were reported. Since the other trials showed that the residues occur principally in the peel and pulp:peel ratios were not reported, the Meeting could not estimate a maximum residue level.

Apples. Numerous field trials have been conducted in Australia, Belgium, France, Germany, Japan and New Zealand. No GAP was reported for Australia. A trial in Belgium was evaluated against GAP in France and Switzerland. Several trials in France and Germany were carried out according to GAP in those countries (0.008 kg ai/hl, 21 days PHI). In supervised trials in Japan fenpyroximate was applied at the recommended rate (0.005 kg ai/hl). The *Z*-isomer was determined in most of these trials and was below the limit of determination in almost every sample. Supervised trials according to GAP carried out in New Zealand showed parent residues from <0.01 to 0.13 mg/kg at the New Zealand PHI of 14 days; the *Z*-isomer was not determined. The storage period before analysis was not reported. The Meeting estimated a maximum residue level of 0.2 mg/kg.

Grapes. Supervised trials on vines were conducted in France, Germany, Italy and Japan. Those in France and Italy which approximated Portuguese GAP showed residues of <0.02 and 0.08 mg/kg (France) and 0.07, 0.17 and 0.47 mg/kg (Italy). Residues in two (greenhouse) trials in Japan in accordance with GAP were 0.38 to 0.53 mg/kg. Residues of fenpyroximate in all the trials complying

with GAP ranged from <0.02 to 0.53 mg/kg. The Meeting concluded that the data were insufficient to estimate a maximum residue level for a major crop.

Hops. Results of nine German trials (1989-1991) were submitted to the Meeting, but only one trial was in accordance with GAP. The Meeting could not estimate a maximum residue level.

The Meeting received data from processing studies on apples. Residues of fenpyroximate in apple puree and cider were below the limit of determination. In two domestic processing trials with fruit containing 0.06 mg/kg and 0.15 mg/kg, the fenpyroximate residues in wet pomace were concentrated by factors ranging from 2.2 to 2.6. In the absence of the study details and because the studies did not represent a commercial process, the Meeting could not draw conclusions from the data.

Supervised trials on grapes were carried out in Germany to study the fate of fenpyroximate in processed products. Only summary reports were available, where critical supporting information was lacking. Residues of fenpyroximate in wine were below the limit of determination (<0.01 mg/kg), when made from grapes containing residues of fenpyroximate of 0.13-0.15 mg/kg. No data on processing to pomace were provided. In the absence of the study details the Meeting could not draw conclusions from the data.

Processing studies on hops showed that even with high fenpyroximate residues in the hops no residues could be detected in beer. A residue of 0.4 mg/kg was found in yeast, which is of minor importance in the human diet. The highest residue found in spent hops was 6 mg/kg, from dried hops with a fenpyroximate residue of 37.4 mg/kg.

No information was provided on residues of fenpyroximate occurring in commerce or at consumption.

Since metabolism studies showed that the *Z*-isomer was always less than 20% of the residue and in almost all supervised trials its residues were near the limit of determination, the Meeting concluded that the residue should be defined as fenpyroximate.

The Meeting considered the need to include livestock metabolism and animal transfer studies in accordance with FAO guidelines in future submissions. The Meeting was informed that animal studies were not available. Additional residue data on citrus fruits (oranges, whole fruit) with relevant information on GAP are needed, as are additional supervised trials data on grapes and hops reflecting GAP. Complete trial details should be provided, including the analytical methods used, validations thereof, and sample chromatograms.

Owing to the lack of critical supporting data, although the Meeting estimated a maximum residue level for apples, this is not recommended for use as an MRL.

FURTHER WORK OR INFORMATION

Desirable

1. An additional processing study on apples, conducted with apples containing residues at or above the estimated maximum residue level (0.2 mg.kg), reflecting commercial processing.

2. An additional study on processing grapes to wine and raisins, including data on by-products. Complete trial details should be provided.

3. Information on residues of fenpyroximate in foods in commerce or at consumption.

4.18 FENTHION (039)

TOXICOLOGY

Fenthion was evaluated toxicologically by the Joint Meeting in 1971, 1975, 1978, 1979, and 1980. An ADI of 0-0.001 mg/kg bw was allocated in 1980, on the basis of an NOAEL of 0.09 mg/kg bw per day for cholinesterase inhibition in a two-year dietary study in dogs. The compound was evaluated at the present Meeting within the CCPR Periodic Review Programme.

A single dose of ^{14}C-radiolabelled fenthion was readily absorbed and rapidly excreted in the urine and faeces of rats and no ^{14}C was detectable in the expired CO_2. About 90% of the radiolabel was eliminated within 48 h of dosing. The excretion profiles were similar regardless of sex, dose level, or route of administration (oral or intravenous). Urine was the main route of elimination (>90% of the total ^{14}C), and only minor amounts were recovered in the faeces. Little ^{14}C was retained in the tissues, suggesting that fenthion does not accumulate in the body of rats.

[^{14}C]Fenthion was extensively metabolized in rats. No unchanged parent compound was detected in the urine and very little (<2%) in the faeces. The major group of metabolites (accounting for ~60% of the total recovered ^{14}C) comprised three phenols (fenthion phenol (4-methylthio-*m*-cresol) and its sulfoxide and sulfone) and their glucuronide and sulfate conjugates. Four demethyl metabolites (accounting for ~30% of the recovered ^{14}C) and the sulfoxide of fenthion oxon (constituting 1-4%) were also identified.

Fenthion is moderately toxic (LD_{50} = 50-500 mg/kg body weight) to mice, rats, guinea-pigs, and rabbits when given orally, intraperitoneally, dermally, or by inhalation. It is highly toxic to avian species (especially to the wild mallard duck) when given orally. The LC_{50} in rats for 4-h exposure by inhalation was 0.5-0.9 mg/litre. Fenthion caused cholinergic toxicity with a long recovery time. Fenthion did not irritate rabbit skin and was minimally or not irritating to the rabbit eye; it did not sensitize guinea-pig skin. The WHO has classified fenthion as "highly hazardous".

Fenthion potentiated the acute toxicity of other cholinergic chemicals, such as malathion, dioxathion, and coumaphos, in rats. In mice and dogs, pre-treatment with fenthion inhibited the metabolism and detoxification of 2-*sec*-butylphenyl methylcarbamate, resulting in significant potentiation of its acute toxicity. There was no evidence that other cholinergic chemicals potentiate the toxicity of fenthion.

Repeated short-term administration of fenthion (orally to mice, rats, dogs and monkeys; dermally to rabbits; by inhalation to rats) and its metabolite fenthion sulfoxide (orally to mice and rats), resulted primarily in inhibition of cholinesterases. The NOAEL for oral administration of fenthion, based on toxicologically significant depression of acetylcholinesterase activity in the brain (>10%) and/or erythrocytes (>20%), was 5 ppm (equivalent to 0.25 mg/kg bw per day) in rats (treated for three months or one year), 3 ppm (equal to 0.09 mg/kg bw per day) in dogs (treated for two years) and 0.07 mg/kg bw per day in monkeys (treated for two years). The NOAEL for fenthion was 50 mg/kg bw per day applied dermally to rabbits for 21 days on the basis of inhibition of brain acetylcholinesterase activity. The NOAEL for fenthion in rats exposed by inhalation for 21 days was 0.001 mg/l, on the basis of clinical signs of cholinergic toxicity and inhibition of brain acetylcholinesterase at higher doses. The NOAEL for fenthion sulfoxide administered orally to rats for four weeks was 3 ppm (equivalent to 0.15 mg/kg bw per day) on the basis of significant inhibition of brain and erythrocyte acetylcholinesterase. An NOAEL was not determined for fenthion or its metabolite in mice; the LOAEL for fenthion was 150 ppm (equal to 83 mg/kg bw per day) in mice exposed in the diet for four weeks, and the LOAEL for fenthion sulfoxide in mice similarly exposed was 3 ppm (equivalent to 0.45 mg/kg bw per day).

In a carcinogenicity study, fenthion was administered in the diet to mice at 0, 0.1, 1, 5 or 25 ppm for 102 weeks. The NOAEL for chronic toxicity was 5 ppm (equal to 2 mg/kg bw per day) on the basis of toxicologically significant inhibition of brain and/or erythrocyte acetylcholinesterase. There was no evidence of carcinogenicity.

In two studies of chronic toxicity and carcinogenicity, rats received fenthion at dietary concentrations of 0, 3, 15 or 75 ppm or 0, 5, 20 or 100 ppm for 24 months. The NOAEL for chronic toxicity was 3 ppm (equal to 0.14 mg/kg bw per day) on the basis of toxicologically significant inhibition of brain and/or erythrocyte acetylcholinesterase. The compound was toxic to the eye in rats at 100 ppm (equal to 5.2 mg/kg bw per day), inducing an increased incidence of retinal atrophy, posterior subcapsular cataract formation, corneal mineralization, and mineralization and optic nerve atrophy, especially in females. No ocular toxicity was seen at doses ≤20 ppm (equal to 0.8 mg/kg bw per day). There was no evidence of carcinogenicity.

In a two-generation study of reproductive toxicity (one litter per generation), rats were fed diets containing fenthion at levels of 0, 1, 2, 14 or 100 ppm. The NOAEL for systemic toxicity in the parent generation was 2 ppm (equal to 0.16 mg/kg bw per day) on the basis of consistent inhibition of brain and erythrocyte acetylcholinesterase. The NOAEL for reproductive toxicity was 14 ppm (equal to 1.2 mg/kg bw per day) on the basis of decreased fertility, implantation sites, litter size, pup viability and growth at 100 ppm.

Two studies of developmental toxicity were performed in which rats were exposed by gavage to fenthion at doses of 0, 1, 3 or 10 mg/kg bw per day or 0, 1, 4.2 or 18 mg/kg bw per day on days 6-15 of gestation. No NOAEL for maternal toxicity was determined owing to toxicologically significant inhibition of brain and erythrocyte acetylcholinesterase activity at ≥1 mg/kg bw per day. The NOAEL for embryo- and fetotoxicity and teratogenicity was 18 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity in rabbits, fenthion was administered by gavage at doses of 0, 1, 2.8 or 7.5 mg/kg bw per day, on days 6-18 of gestation. The NOAEL for maternal toxicity was 1 mg/kg bw per day, on the basis of toxicologically significant inhibition of brain and erythrocyte acetylcholinesterase activity at ≥2.8 mg/kg bw per day. The NOAEL for embryo- and fetotoxicity and

teratogenicity was 7.5 mg/kg bw per day, the highest dose tested.

Fenthion has been adequately tested for genotoxicity in a range of assays *in vivo* and *in vitro*. While most showed no significant response, positive results were obtained in two critical assays. The Meeting concluded that fenthion is weakly genotoxic.

Fenthion did not cause delayed neuropathy in hens at doses higher than the LD_{50}.

In a four-week study of male volunteers, the NOAEL was 0.07 mg/kg bw per day, the highest dose tested, on the basis of no inhibition of erythrocyte acetylcholinesterase. In two investigations of workers regularly exposed to fenthion, no evidence of neurotoxicity was observed.

An ADI of 0-0.007 mg/kg bw was established on the basis of the NOAEL of 0.07 mg/kg bw per day in the four-week study of human volunteers, using a safety factor of 10. The ADI provides a margin of safety of >100-fold for chronic ocular toxicity and for reproductive toxicity observed in rodents.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 5 ppm, equal to 2.0 mg/kg bw per day (two-year study of carcinogenicity)

Rat: 3 ppm, equal to 0.14 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
2 ppm, equal to 0.16 mg/kg bw per day (maternal toxicity in a two-generation study of reproductive toxicity)
14 ppm, equal to 1.2 mg/kg bw per day (two-generation study of reproductive toxicity)
18 mg/kg bw per day (embryo- and fetotoxicity and teratogenicity in a study of developmental toxicity)

Rabbit: 1 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
7.5 mg/kg bw per day (embryo- and fetotoxicity and teratogenicity in a study of developmental toxicity)

Dog: 3 ppm, equal to 0.09 mg/kg bw per day (two-year study of toxicity)

Monkey: 0.07 mg/kg bw per day (two-year study of toxicity)

Human: 0.07 mg/kg bw per day (four-week study of toxicity)

Estimate of acceptable daily intake for humans

0-0.007 mg/kg bw

Estimate of acute reference dose

The available data did not allow the Meeting to establish an acute reference dose different from the ADI (0-0.007 mg/kg bw). It should be noted, however, that the ADI is derived from a study of human volunteers in which 9-36% inhibition of plasma cholinesterase but no inhibition of erythrocyte acetylcholinesterase was found at the highest dose tested (0.07 mg/kg bw per day for 25 days). In occupationally exposed workers, about 50% plasma cholinesterase inhibition was found in the absence of erythrocyte acetylcholinesterase inhibition. It follows that the acute reference dose is likely to be somewhat higher than the ADI. Data on the sensitivity to inhibition of plasma cholinesterase and erythrocyte and brain acetylcholinesterase *in vitro* by the active metabolites of fenthion might allow extrapolation to an LOAEL in humans.

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to fenthion

Exposure	Relevant route, study type, species	Result, remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Not irritating
	Eye, irritation, rabbit	Minimally or not irritating
	Skin, sensitization, guinea-pig	Not a skin sensitizer
	Inhalation, 4-h, toxicity, rat	LC_{50} = 0.5-0.9 mg/litre
	Oral, toxicity, mouse, rat, guinea-pig, rabbit	LD_{50} = 50-500 mg/kg bw
	Oral, dermal, subcutaneous, single doses, cholinesterase activity, rat	NOAEL (all routes) = 5 mg/kg bw per day based on inhibition of brain and erythrocyte acetylcholinesterase.
Medium-term (1-26 weeks)	Repeated dermal, 21 days, toxicity, rabbit	NOAEL = 50 mg/kg bw per day for systemic toxicity on the basis of inhibition of brain acetylcholinesterase
	Repeated inhalation, 21 days, toxicity, rat	NOAEL = 0.001 mg/litre per day for systemic toxicity on the basis of clinical signs of cholinergic toxicity
	Repeated dietary, 13-16 weeks, toxicity, rat	NOAEL = 0.25 mg/kg bw per day, based on inhibition of brain acetylcholinesterase
	Repeated gavage developmental toxicity, rabbit	NOAEL = 1 mg/kg bw per day for maternal toxicity on the basis of inhibition of brain and erythrocyte acetylcholinesterase; no embryo or fetotoxic or teratogenic effects
	Repeated oral (gelatin capsules), four weeks, toxicity, human	NOAEL = 0.07 mg/kg bw per day on the basis of no inhibition of erythrocyte acetylcholinesterase
Long-term (≥1 year)	Repeated dietary, two years, toxicity, dog	NOAEL = 0.09 mg /kg bw per day on the basis of inhibition of brain and erythrocyte acetylcholinesterase

EVALUATION OF EFFECTS ON THE ENVIRONMENT

Fenthion is an organophosphorus pesticide used for both agricultural and non-agricultural purposes. Its major application is to control insect pests (maximum application rate 1.25 kg ai/ha) but it is also used as a veterinary product for the control of external parasites on domestic animals and as a pesticide against birds (application rate 2.4 kg ai/ha). Spraying for bird control is with a special formulation not available commercially but used only under governmental control. Usually formulated as an emulsifiable concentrate, the pesticide is applied by ground (80-85%) and aerial (15-20%) spraying. It is also formulated as granules or as a paste for the control of urban birds. It can enter the environment beyond the intended application zone either by spray drift, as residues in birds which are food items of birds of prey and, presumably, by loss of surface residues from domestic animals.

Fenthion entering the environment is rapidly adsorbed to soil and sediment. The binding is strong, though the mechanism is poorly understood. The compound can be regarded as immobile in soil; leaching of the parent compound below the top few centimetres of the soil profile is unlikely.

Although photodegradation occurs under laboratory conditions, it is not regarded as a significant route of breakdown in the field. Hydrolysis occurs slowly and is dependent on pH; half-lives of fenthion in sterile buffers range between 30 and 60 days with slower degradation at low pH.

Fenthion is degraded by micro-organisms in soil with a half-life of 10 days in the laboratory; field degradation is slower with approximately half of the compound degraded to carbon dioxide in six months in temperate climates. Generally, breakdown is slower in water-sediment systems than in soil. The pesticide has been measured in surface waters in untreated areas at concentrations up to 0.12 ìg/l. The properties outlined above would not suggest that fenthion enters the aquatic environment by leaching or run-off; there is no satisfactory explanation for the aquatic residues.

There is no significant bioaccumulation, despite the high fat-solubility of the compound, since metabolism and elimination is rapid in organisms.

Because of its relatively rapid breakdown in the environment, the acute toxicity of the compound is of relevance to organisms. Chronic exposure is not expected for most species. The binding to soil and sediment particles would be expected to reduce the bioavailability of the compound.

Fenthion and its formulations were shown to be toxic to highly toxic to micro-organisms with 4-day EC_{50} values of 550 and 1100 ìg/l respectively. No acute toxicity data were reported for algae. Fenthion has a low toxicity for algae after chronic exposure. Screening tests have indicated no phytotoxicity.

The acute and chronic toxicity for crustaceans was shown to be high with an EC_{50} value of 5.7 ìg/l and a NOEC value of 0.018 ìg/l. Fenthion was also shown to be very toxic to fish: LC_{50} = 830 ìg/l and MATC (maximum acceptable toxic concentration) = 20 ìg/l.

One study showed toxicity to amphibian larvae at 0.84 ìg/l.

Fenthion is moderately toxic to toxic for birds with an LD_{50} value of 7.2 mg/kg bw and a 5-day LC_{50} value of 60 mg/kg feed. The substance is also toxic to honey bees, contact LD_{50} = 0.16 ìg/bee, and slightly toxic to earthworms: 14-day LC_{50} = 723 mg/kg dry weight.

Risk assessment

Exposure concentrations have been derived from the results of monitoring programmes or field experiments simulating common agricultural practice on the one hand and on the other hand based on a simple model calculation after spraying the substance on to ornamental. Basically, the same model for calculating predicted environmental concentrations (PECs) is currently used by the Environmental Protection Agency in the USA, the Pesticides Safety Directorate in the United Kingdom and in the model of the Uniform System for the Evaluation of Substances (USES) of The Netherlands. The method is presented in Figure 1, a and b. The data of a 2-year monitoring programme that have been used for calculation (the upper section of Table 1), refer to 15 freshwater locations in The Netherlands where fenthion was detected. The emission routes leading to these concentrations are not clear. Other monitoring data (e.g. concentrations in surface water) were not available. The data of field experiments that have been used for the hazard evaluation refer to the aerial application of fenthion for mosquito control (lower section of Table 1). Other field experiments giving concentrations in surface water were not available. No data on residues in sediment have been included, as these also were not available.

Concentrations that refer to chronic exposure are assumed to result from dissipation in accordance with first-order kinetics.

(a) monitoring programme and salt marsh (see Table 1):

(b) spraying example (see Table 2):

with:

with:	PEC_I	= initial predicted environmental concentration (ìg/l)
	PEC_T	= mean predicted concentration after the interval T (ìg/l)
	T	= test period in chronic toxicity studies (days)
	f	= emission factor (fraction of aerial dose reaching water)
	D	= dose (kg ai/ha)
	d	= water depth (m)
	DT_{50}	= dissipation half-life of ai in water (days)
	n	= number of applications during growing season
	ÄT	= application interval (days)

The following data are used in the example calculations for the situations (a) and (b):

1. water depth d is 0.3 m
2. worst-case application rate in ornamental:
3 times 1 kg ai/ha with 7 days spray interval which, taking into account a half-life of 7 days, gives a deposit of 1.75 kg ai/ha
3. emission factor: 0.05 spray drift at 1 m distance
4. test periods: 4 days for algae
21 days for crustaceans
88 days for fish

The half-life time used is the longest value of the half-life times reported. This can be considered as a realistic worst-case value.

The lowest LC_{50} or EC_{50} and NOEC values for algae, crustaceans and fish have been taken from the toxicity tests reported.

It should be noted that only a limited data-set is available with respect to concentrations in the environment and toxicity values. Only the water compartment and a few species living in the open water have been included. Apart from 3-methyl-4-methylsulfinylphenol and 3-methyl-4-methylsulfonylphenol, no toxicity data on transformation products for aquatic organisms are available.

The exposure concentrations are calculated for the time-points equalling the duration of an experiment (e.g. the 21 days NOEC for water fleas must be compared with the $PEC_{21\text{-days}}$, calculated as described above).

Table 1 compares the estimated mean and maximum exposure concentrations in the field with the lowest reported $L(E)C_{50}$ and NOEC values for acute and chronic exposure of organisms in the open water for the monitoring programme and the salt marsh results respectively. The ratio of the effect concentration to the exposure concentration (Toxicity Exposure Ratio, TER) has been calculated. The Table is meant as a guide to establishing possible risk classification in the field and is not intended to estimate the degree of effect likely to be seen in the field. The "possible risk" classification is a simple one using different classification phrases for order-of-magnitude segments of the ratios.

As can be seen from Table 1, possible risk for aquatic organisms can be expected for crustaceans, following either acute or chronic exposure. Fish and algae appear not to be at risk from fenthion. The few field observations available confirm this risk for crustaceans. However, these field experiments should be considered less reliable as the description of some relevant test conditions (e.g. physico-chemical characteristics of the water, temperature, actual concentrations of fenthion) is incomplete.

In Table 2 the results are summarized for the example spraying of ornamental. It can be seen that again crustaceans are the organisms at risk after either acute or chronic exposure. Algae are not affected and the effect on fish can be considered as low.

It should be noted that the possible risk calculations in Tables 1 and 2 refer to realistic worst-case conditions: the data showing the highest toxicity are included; the slowest reported dissipation rate is included; the concentrations used for calculating the mean estimated exposure concentration are only those referring to sites where fenthion was actually detected; the concentration used as the maximum estimated exposure concentration refers to aerial application for mosquito control.

On the other hand, only four groups of aquatic organisms are included (e.g. no sediment-living organisms), adjuvants and transformation products are not taken into account, and the possible hazards do not refer to water temperatures exceeding 22°C.

Table 1. Indications of environmental hazard for aquatic organisms by technical grade fenthion.

Effect	Organisms	Estimated exposure concn. (ìg/l)	Toxicity data (ìg/l)	End-point	Toxicity exposure ratio	Risk classific-ation

Effect	Organisms	Estimated exposure concn. (ìg/l)	Toxicity data (ìg/l)	End-point	Toxicity exposure ratio	Risk classific-ation
Mean estimated exposure concentration (monitoring programme)						
Acute	Crustaceans	0.020	EC_{50} = 5.7	Immobilisation	285	Negligible
Acute	Fish	0.020	LC_{50} = 830	Mortality	>1000	Negligible
Acute	Amphibia	0.020	LC_{50} = 0.84	Mortality	42[2]	Low[2]
Chronic	Algae	0.017	EC_{50} = 550	Biomass decrease	>1000	Negligible
Chronic	Crustaceans	0.0084	NOEC = 0.018	Reproduction	2.1	Present
Chronic	Fish	0.0023	MATC = 20[1]	Reproduction	>1000	Negligible
Maximum estimated exposure concentration (salt marsh)						
Acute	Crustaceans	1.7	EC_{50} = 5.7	Immobilisation	3.4	Present
Acute	Fish	1.7	LC_{50} = 830	Mortality	488	Negligible
Acute	Amphibia	1.7	LC_{50} = 0.84	Mortality	0.5[2]	Large[2]
Chronic	Algae	1.4	EC_{50} = 550	Biomass decrease	393	Negligible
Chronic	Crustaceans	0.71	NOEC = 0.018	Reproduction	0.03	Very large
Chronic	Fish	0.2	MATC = 20[1]	Reproduction	100	Negligible

[1] This is the mean of 13 and 27 ìg/l

[2] This is based on a single study which may over-estimate the toxicity of fenthion to amphibia

Table 2. PEC-based risk assessment for the highest recommended agricultural application rate.[1]

Effect	Organism	PEC (ìg ai/l)	Toxicity (ìg ai/l)	Endpoint	TER	Risk classification
Acute	Crustaceans	29	EC50 = 5.7	Immobilization	0.2	Large
Acute	Fish	29	LC50 = 830	Mortality	29	Low
Acute	Amphibia	29	LC50 = 0.84	Mortality	0.03	Very large
Chronic	Algae	23.9	EC50 = 550	Biomass	23	Low
Chronic	Crustaceans	12.2	NOEC = 0.018	Reproduction	0.0015	Very large
Chronic	Fish	3.3	MATC = 20	Reproduction	6.1	Present

[1] Worst-case application rate in ornamental: 3 times 1 kg active ingredient/ha with 7 days spray interval, which with a half-life of 7 days gives 1.75 kg active ingredient/ha 14 days after the first application.

Reports of field and laboratory studies on beneficial insects show that fenthion kills some predators, though results are variable. Less effect was noted in the field than the laboratory. Fenthion is not considered hazardous to earthworms at recommended application rates. The risk to honey bees is considered negligible provided it is not applied to foraging bees.

Fenthion has high acute toxicity to birds and is used as an avicide at high application rates. Risk assessment has been carried out for avicidal and general agricultural use.

Use of fenthion as an avicide

A single study reports secondary poisoning of a bird of prey following the ingestion of poisoned house sparrows. The reported dietary LC_{50} to bobwhite quail is 60 mg/kg diet. On the basis of comparative body weight and food consumption figures, LC_{50}s for predatory birds eating avian prey can be estimated at 267 mg/kg diet for the European kestrel and 282 mg/kg diet for the sparrowhawk using the following equations:

$$\text{[Test species] } LD_{50} \text{ (mg/kg/day)} = \frac{\text{[Test species]} LC_{50} \text{ (mg/kg diet) x (food consumption, kg/day)}}{\text{bw (kg)}}$$

$$LC_{50} \text{ (mg/kg dry weight diet/day)} = \frac{\text{[Test species]} LD_{50} \text{ (mg/kg/day) x bw (kg)}}{\text{food consumption (kg)}}$$

The total daily intake of fenthion leading to death is 4.2 and 4.8 mg for the two species respectively. Reported residues in house sparrows poisoned by fenthion used as an avicide are 6, 631 and 1152 micrograms/g for carcase, feather and skin, and feet respectively. The total fenthion content of the carcase would be 166 micrograms based on a body weight for the sparrow of 27.7 g. Ingestion of a whole carcase of a sparrow should not lead to a lethal dose. However, ingestion of residues from the feathers and feet during plucking of prey could lead to a lethal intake. There may, therefore, be comparable sensitivity to fenthion across a range of bird species. It can, therefore, be assumed that any bird-eating raptor would be killed by eating contaminated prey.

Agricultural use

Predicted environmental concentrations (PEC) were calculated using the European and Mediterranean Plant Protection Organisation/Council of Europe (EPPO/COE) vertebrate scheme. The highest recommended agricultural application rate of 1.25 kg/ha was used, giving PECs for grass, insects, and grains of 140, 3.4 and 3.4 mg/kg, respectively, soon after spraying. Estimated LC_{50}s for bird species eating these as food were derived from the reported bobwhite quail dietary toxicity test results as above. Toxicity Exposure Ratios are given in Table 3.

Table 3. Toxicity exposure ratios (TER) for birds following application of fenthion to crops at 1.25 kg/ha.

Species	Type of food	Estimated LC_{50} (ppm in the diet)	PEC mg/kg	TER	Risk classification
Common quail *Coturnix coturnix*	Wheat and grass seed	211	140	1.5	Present
Greylag goose *Anser anser*	Vegetation	658	140	4.7	Present
Wren *Troglodytes troglodytes*	Small insects, spiders and seeds	46	3.4	13.5	Low
Jackdaw *Corvus monedula*	Insects, spiders, seeds and grains	285	3.4	84	Low
Reed bunting *Emberiza shoeniclus*	Seeds, snails and insects	73	3.4	21.5	Low
Red legged partridge *Alectoris rufa*	Vegetation	355	3.4	104	Very low

The use of fenthion at the highest recommended application rate would, therefore, be likely to lead to deaths in birds. The most susceptible species are vegetation feeders with low body weights.

RESIDUE AND ANALYTICAL ASPECTS

Fenthion was first evaluated in 1971 and has been reviewed several times since, most recently in 1989. It was scheduled for re-evaluation in 1995 in the CCPR periodic review programme (ALINORM 91/24, para 241 and Appendix V).

The Meeting received information on GAP, the metabolic fate in laboratory and farm animals and in plants, environmental fate, analytical methods, supervised residue trials, animal transfer studies, fate during processing and storage, and residues in food in commerce and at consumption.

Laboratory animal metabolism

Rats. Rats multiply dosed intraperitoneally with ^{32}P-labelled fenthion (10 mg/kg body weight) eliminated 80% of the administered dose within 20 days after the first injection. Acetonitrile-extractable residues in tissues were below the limit of determination of the assay (0.05 mg/kg) after 3 days. Rats eliminated 86% of a single oral dose of ^{32}P-labelled fenthion (100 mg/kg body weight) within 7 days and had tissue levels of chloroform-extractable radioactivity of less than 0.2 mg/kg at day 3. The majority (96-99%) of the radiolabel in urine or faeces was in hydrolysis products.

After single oral or subcutaneous doses of [^{35}S]fenthion (25 mg/kg body weight), elimination by rats was primarily in the urine irrespective of the route of administration. Urine metabolites after both treatments were mainly hydrolysed products. Liver and kidney had the highest residue levels. Fenthion and its oxygen analogue, sulfoxide and sulfone were identified in tissues.

After single intravenous (0.13 or 2 mg/kg body weight) or single or multiple oral doses (0.3, 1.5 or 10 mg/kg body weight) of [^{14}C]fenthion, rats excreted 80% or more of the administered radioactivity in the urine between 24 and 72 hours after dosing. Faecal elimination was a minor route of excretion. Tissue levels were low, generally less than <0.1 mg/kg or <0.001 mg/kg depending on the limit of determination reported. The major urine metabolites included fenthion phenol, its sulfoxide and sulfone, their glucuronide and sulfate conjugates, and demethylated metabolites.

Rabbits. After a single oral or subcutaneous dose of [^{35}S]fenthion (25 mg/kg body weight), elimination was primarily by the urine irrespective of the route of administration. The majority of the recovered radiolabel was water-soluble in all animals. The liver and kidney had the highest reported residue levels and fenthion, its oxygen analogue and their sulfoxides and sulfones were identified in the tissues.

Farm animal metabolism

Lactating cattle. Lactating Jersey cows were given dermal (14 mg/kg body weight) or intramuscular (9 mg/kg body weight) treatments with [^{32}P]fenthion and killed 14 or 21 days after treatment respectively. Peak concentrations in the urine occurred within 24 hours of treatment in both groups and more than 95% of the radioactivity in the urine was associated with hydrolysis products. Elimination via the faeces was of minor importance.

In dermally treated cows, the highest organoextractable residues were in the subcutaneous fat. Organoextractable residues in the muscle, omental fat and liver were <0.001 mg/kg. Residue levels in intramuscularly treated animals were higher, with the maximum value reported in the liver.

Approximately 1% of the dermally administered dose was eliminated in the milk. The maximum acetonitrile-extractable level in the milk was 0.25 mg/kg fenthion equivalents, 18 hours after treatment. After 7 days, the level was 0.009 mg/kg. In the intramuscularly treated animals, about 2% of the administered dose was eliminated in the milk. The maximum acetonitrile-extractable level was 0.5 mg/kg fenthion equivalents, 8 hours after treatment. After 14 days, the level was 0.014 mg/kg. Fenthion, fenthion sulfone and fenthion oxon sulfoxide and sulfone were major residues with fenthion sulfoxide and fenthion oxon identified as minor metabolites. In the urine 95% of the radiolabel was in hydrolysis products with dimethyl phosphorothioate and dimethyl phosphate present as major metabolites.

[^{32}P]Fenthion was given to two dairy cattle orally at the rate of approximately 1.5 mg/kg body weight for 14 days. Two other cows were treated daily by backline application for 7 days with 50 ml of a 1% [^{32}P]fenthion solution. Animals were killed 7 days after the last dose. Maximum acetonitrile-extractable residues in milk in the orally treated animals were observed on day 2 in one cow (0.24 mg/kg) and day 13 in the other (0.36 mg/kg). Residues in milk were <0.01 mg/kg in both animals within 2 days of stopping treatment. In the backrubber trials, acetonitrile-extractable residues in the milk peaked at 4 days (0.15 mg/kg) and 6 days (0.47 mg/kg). Residue levels were <0.01 mg/kg in the milk by three to five days after cessation of treatment. In animals from the feeding study, the highest levels were in the kidney and liver (0.02-0.04 mg/kg). Residues in the fat were 0.01-0.02 mg/kg and in muscle 0.006-0.01 mg/kg. In the backline-treated animals, subcutaneous fat had the highest levels (0.14 and 0.26 mg/kg). Omental and renal fat levels were <0.1 mg/kg. Levels in the kidney, liver and muscle were ≤0.02 mg/kg. Eighty to ninety-six per cent of the radiolabel was identified as fenthion or its metabolites.

When a lactating Jersey cow was given a single dermal (backline, top of shoulders to base of

tail) treatment with [*phenyl*-1-^{14}C]fenthion at 5.1 mg/kg body weight and killed 18 hours after treatment, the average ^{14}C residues were: treatment site hair 16,200 mg/kg; non-treatment site hair 2.3 mg/kg, treatment site skin 106 mg/kg; non-treatment site skin 0.1 mg/kg; subcutaneous fat at treatment site 6.3 mg/kg, at non-treatment site 1.8 mg/kg; peritoneal fat 0.3 mg/kg; liver 0.1 mg/kg; kidney 0.1 mg/kg, and muscle 0.3 mg/kg fenthion equivalents. Milk residues were 0.03 mg/kg fenthion equivalents 6 and 18 hours after treatment and 0.05 mg/kg 12 hours after treatment. In the urine the mean radiocarbon level was 3.9 mg/kg fenthion equivalents. Fenthion was the major component (typically >90% of the radiolabel present in all tissues). The kidney and liver contained significant amounts of unidentified metabolites (44 and 22% respectively), fractions of which were tentatively associated with the glucuronides of fenthion phenol sulfoxide or sulfone. Fenthion sulfoxide accounted for up to 5% of the radiocarbon in hair, skin, muscle and fat but was not present in the kidney or liver.

Goats. A lactating goat was dosed orally by capsule once daily for three consecutive days with [*phenyl*-1-^{14}C]fenthion at 20 mg/kg body weight and slaughtered 3.5 hours after the final dose. Fifty-two per cent of the administered ^{14}C was recovered: urine 44%, faeces 6.3%, milk 0.2% and edible tissues an estimated 1%. A large part of the final dose remained unquantified in the gastrointestinal tract. Levels of ^{14}C expressed as fenthion in the tissues were: liver 3 mg/kg; kidney 24 mg/kg; muscle 0.6 mg/kg, and fat 3 mg/kg (residues of fenthion sulfoxide and fenthion sulfone in the fat were 0.5 mg/kg, supporting a description of the residue as "fat soluble"). Residues in the kidney were probably associated with the major elimination route in the urine. In milk the residue level peaked within 8 hours of dosing. The metabolites identified included fenthion phenol and its sulfoxide and sulfone, demethylated fenthion oxon and its sulfoxide, and demethyl-fenthion and its sulfoxide and sulfone. Fenthion sulfoxide and sulfone were major metabolites in fat.

Pigs. A male and female pig were given a single oral dose of [*phenyl*-1-$^{13/14}$C]fenthion (5 mg/kg body weight). After 7 days the female pig was dosed at 10 mg/kg per day for two consecutive days and the male pig for 3 consecutive days. The animals were killed at 6 (male) and 30 (female) hours after the last dose. Excretion in the urine and faeces was rapid in both male and female with the majority (about 85%) of the initial dose eliminated within 30 hours and 91-95% by 54 hours in both pigs. The urine was the major route of elimination, faecal elimination accounting for 10% or less of the total radiolabel. Urinary metabolites were present as conjugated phenols. Fenthion phenol sulfoxide and sulfone were the major urinary products. Levels of the radiolabel (expressed as fenthion) in the tissues of the male pig were kidney 8.4 mg/kg, liver 8.6 mg/kg, fat 4.7 mg/kg, muscle 2.9 mg/kg, brain 2.4 mg/kg, and heart 3.1 mg/kg. Residues in the female pig 30 hours after the last dose were substantially lower (kidney 1.2 mg/kg, liver 0.9 mg/kg, fat 1.6 mg/kg and muscle, brain and heart 0.2 mg/kg each), indicating effective elimination from the tissues. In the tissues fenthion and fenthion oxon and their sulfoxides and sulfones were all found in varying proportions. Fenthion phenol sulfoxide and sulfone were present in the kidney and liver.

In a pig given a backline treatment with [*phenyl*-1-^{14}C]fenthion (14 mg fenthion/kg body weight) and slaughtered 18 hours after the dose, mean ^{14}C residue levels as fenthion equivalents were liver 0.2 mg/kg, kidney 0.3 mg/kg, muscle 0.1 mg/kg, non-treatment site fat 0.8 mg/kg, and peritoneal fat 0.6 mg/kg. Treatment site hair, skin and subcutaneous fat contained 1400, 134 and 3.9 mg/kg respectively. Over 96% of the treatment site residue was fenthion. In kidney, liver, muscle and peritoneal fat, fenthion was present as 26, 69, 88 and 81% of the residues identified, respectively. Fenthion sulfoxide was 12% of the muscle residue and 11% of the peritoneal fat residue. Fenthion oxon sulfone (approximately 7%) was present in the kidney. The kidney and liver contained an unidentified metabolite, representing 67 and 31% respectively of the total residue, tentatively associated with glucuronide conjugates of fenthion phenol sulfoxide or sulfone.

Plant metabolism

Plant metabolism studies on olives, guavas, beans, cabbages, alfalfa, tea, maize, rice, Bahia grass and Coastal Bermuda grass were made available to the Meeting.

Olive plants. In olive plants treated once or twice with fenthion at 0.5 kg fenthion/ha and harvested over a 28 days period after the final treatment, fenthion and fenthion sulfoxide were the major residues found in the olive pulp, oil and pomace. Fenthion sulfone and fenthion oxon were also present. Residue levels were higher in the olives and olive products after two treatments. A half-life of about 11 days was calculated for fenthion under these trial conditions.

Olive trees were foliar-sprayed (with added bait) at 0.2 kg ai/hl 3 times (approximately 75 g fenthion/ha/spraying), or 5 times (approximately 100 g fenthion/ha/spraying). Samples of olives (2-3 kg, 200-300 olives/plant) were taken over a 54-day period after the last sprayings. Fenthion residues were degraded slowly in both trials with a half-life of about 38 days. Residue levels from 5 treatments were generally higher than those from 3. Fenthion, fenthion sulfoxide and fenthion oxon sulfoxide were the major residues.

Guava. When a guava tree was sprayed once with a 0.06% solution of [^{14}C]fenthion labelled in the ring-1 position, 88% of the radiolabel was found on the peel. Fenthion (59% of the total ^{14}C present) and fenthion sulfoxide (26%) were the major residues in the peel at day 0. After 32 days, demethyl-fenthion sulfoxide (52%) and fenthion phenol sulfoxide (12%) were the major metabolites. Pulp activity reached a maximum after 7 days (18% of the total ^{14}C). Demethyl-fenthion sulfoxide was the major metabolite (5.5% of the ^{14}C) at day 32. Nearly 100% of the activity was identified. The major metabolites were fenthion sulfoxide at earlier intervals and demethyl-fenthion sulfoxide at the later stages.

Cabbage. When cabbages were sprayed with ^{32}P-labelled fenthion at 9 kg fenthion/ha, 80% of the radiolabel initially present (46 mg/kg) had disappeared within 3 days. After 7 days, fenthion sulfoxide and sulfone accounted for about 50% of the ^{14}C.

Beans. In beans treated with a 0.2% emulsion containing [^{32}P]fenthion, the majority of the radiolabel was initially chloroform-extractable (about 150 mg/kg fenthion equivalents) with about 20 mg/kg water-extractable. After 8 days the relative amounts were 15 mg/kg and 45 mg/kg, indicative of conversion to water-soluble compounds. Fenthion concentrations were about 100 mg/kg at day 0 and decreased over 8 days to about 17% of the original active ingredient level. Fenthion sulfoxide was the major metabolite identified (20 mg/kg initially, about 5 mg/kg after 8 days).

Maize. Maize plants were treated with single applications of fenthion emulsifiable concentrate at 0.56, 1.1 and 2.2 kg fenthion/hectare. Maize silage was prepared from maize sampled one day after treatment. In the maize plants, extensive oxidation of fenthion to its metabolites (principally fenthion sulfoxide) occurred rapidly and after 21 days fenthion sulfoxide, fenthion sulfone and fenthion oxon sulfone were major metabolites.

In maize silage prepared from treated maize plants, residues were found to be more persistent with less oxidation than in the field samples. Fenthion and fenthion sulfoxide were the major residues.

Rice. When rice, at different growth stages, was treated with a 0.07% water emulsion of ^{32}P-labelled fenthion, most of the label was chloroform-extractable initially. By day 7, the chloroform-extractable

radiolabel was <10% of that initially applied. Fenthion sulfone and fenthion sulfoxide were identified as chloroform-extractable metabolites. In the ears of the rice plants, fenthion sulfoxide was the major component with lesser amounts of fenthion sulfone. In rice grains the bulk of the radiolabel was in the bran (60 mg/kg total fenthion equivalents, 0.9 mg/kg chloroform-extractable) with lesser amounts in the polished rice (total 5.7 mg/kg, 0.1 mg/kg chloroform-extractable) and husk (total 2.4 mg/kg, no chloroform-extractable activity). Phosphoric acid, thiophosphoric acid, dimethyl phosphoric acid, *O,O*-dimethyl thiophosphoric acid, and *O*-methyl *O*-(3-methyl-4-methylmercaptophenyl) thiophosphoric acid were identified in water extracts of rice grains.

Alfalfa. In alfalfa sprayed with [^{13}C] and [^{14}C]fenthion labelled in the ring-1 position at a concentration of 0.42 kg fenthion/ha and harvested 7 and 30 days later, there was a total of 13 mg/kg of radioactivity expressed as fenthion equivalents at day 7 and 6.6 mg/kg at day 30. Organosoluble radioactivity decreased (7 days approximately 56%, 30 days approximately 30%) as water-soluble activity increased (approximately 40% at 7 days and approximately 62% at 30 days). Fenthion sulfoxide and demethyl-fenthion sulfoxide were major metabolites at various times. The glucosides of fenthion phenol sulfoxide and sulfone were also identified as being present throughout the experiment.

Bahia grass. When bahia grass was sprayed with [*phenyl*-U-^{14}C]fenthion at a rate of about 110 g/ha/spraying (4 applications), the residue did not accumulate in the soil (<0.1 mg/kg fenthion 1 day after spraying). Levels of ^{14}C (as fenthion) in the grass 1 day and 66 days after the final application were 16 and 0.5 mg/kg respectively. At day 1 fenthion sulfoxide and fenthion constituted 65% and 13% of the ^{14}C respectively. On day 66, fenthion phenol sulfoxide and sulfone were the major metabolites constituting 62% and 27% of the ^{14}C respectively. Carryover of residues into rotational crops (spinach, silver beet and wheat) did not occur.

Coastal bermuda grass. Coastal bermuda grass was sprayed with fenthion at 0.56 kg fenthion/hectare and sampled over a 21-day period. Fenthion, present at 7.7 mg/kg after spraying, steadily disappeared with 0.01 mg/kg remaining at day 14 and 0.006 mg/kg at day 21. Fenthion sulfoxide was the major metabolite initially present (19 mg/kg). After 21 days, fenthion sulfoxide (0.15 mg/kg) and fenthion sulfone (0.32 mg/kg) were the major metabolites. Residue levels from spray treatments at 1.1 and 2.2 kg ai/ha were generally higher than those at 0.56 kg ai/ha.

Tea. Fenthion residues in tea bushes sprayed with [^{32}P]fenthion at 9 kg fenthion/ha decreased quickly with the accompanying formation of fenthion sulfoxide and sulfone. Initial levels of the radiolabel (as fenthion equivalents) were 43 mg/kg in younger tea leaves and 90 mg/kg in older. After 3 days the amount of radiolabel had decreased by 50-60% of the amount initially present and continued to decrease. Fenthion was the only compound identified at day 0 but at day 7 it accounted for <1% of the chloroform-soluble radiolabel present. Fenthion sulfoxide and sulfone were major metabolites from day 3 onwards.

Environmental fate

The photodegradation of fenthion applied to sandy loam soil at 53 mg/kg was rapid when the soil was exposed to sunlight, with a half-life of 6-7 hours. Fenthion sulfoxide was the major product with fenthion sulfone, fenthion oxon sulfoxide and fenthion phenol sulfoxide detected as minor components.

Fenthion applied to sterile soils at 50-200 mg/kg and exposed to sunlight was readily converted to fenthion sulfoxide with about 45-80% of the original fenthion remaining after 4 days.

After 9 days aerobic incubation of [*phenyl*-1-^{14}C]fenthion (1 mg/kg) in a non-sterile loam soil at room temperature, the major products were fenthion sulfoxide (34% of the total ^{14}C) and fenthion phenol sulfoxide (17%), with fenthion sulfone and fenthion phenol sulfone present as minor components. After 9 days comparable incubation in sterile soil, fenthion remained the major component (74% of the total ^{14}C) with fenthion sulfoxide (16%) as the major product.

[*Phenyl*-1-^{13,14}C]fenthion (1 mg/kg soil) was applied to soil and incubated under aerobic (30 days) and anaerobic (60 days) conditions. Sterilized soil was also treated with 1 mg/kg of labelled fenthion and incubated for 30 days. Light was excluded during the incubations. Treated soil samples were also incubated anaerobically for 60 days. Under aerobic conditions fenthion was very rapidly degraded on soil with a half-life of about one day. After 120 days 50% of the radiolabel present was $^{14}CO_2$, 8% was organosoluble and 42% was unextractable. The compounds identified were fenthion sulfoxide and sulfone, fenthion phenol sulfoxide and sulfone, and *O*-methyl fenthion phenol sulfone (3-methyl-4-(methylsulfonyl)anisole). Under anaerobic conditions degradation was slower and fenthion phenol sulfone was the major product. In the sterile soil, fenthion had a half-life of 14 to 21 days. Fenthion sulfoxide was the major product (4% of the total ^{14}C initially and 34% after 30 days).

Fenthion (2 mg/kg soil) was added to soils containing 2.6 and 0.6% of organically bound carbon. After 10 days at 22°C less than 10% of the original material remained. Calculated half-lives were 1.7 and 0.5 days. Fenthion sulfoxide was the main product.

[*Phenyl*-U-^{14}C]fenthion (2 mg/10 g soil) was aged in soil for 30 days in an environment protected from light. The soil was then treated for 45 days with water simulating rainfall. Approximately 4% of the radiolabel was eluted without significant concentration in any of the water samples. About 87% of the applied radiolabel remained in the soil with the majority (67%) found in the top 3 inches.

[*Phenyl*-U-^{14}C]fenthion (10 mg/kg soil) was aged in soil for 30 days at room temperature and then treated for 45 days with water simulating rainfall. Sixteen per cent of the recovered radiolabel was in the leachate and 55% in the top 4 cm of the soil. In the leachate fraction, fenthion phenol, fenthion phenol sulfoxide and fenthion phenol sulfone were identified as major products and fenthion sulfoxide, fenthion sulfone and fenthion oxon sulfone as minor components.

[*Phenyl*-1-^{13,14}C]fenthion (1 mg/kg soil) was added to soil and sand, incubated aerobically at 22-24°C for 4 or 25 days and then continuously leached with aqueous calcium chloride solution over a two-day period during which time light was excluded from the soils. Leaching was minimal with the majority of the radiolabel found in the top 6 cm of each soil. The proportion of radiolabel in the leachate was 5% or less in all samples. In sand 36% of the radiolabel was leached in 4 days and 46% in 25 days. Ninety-five to 98% of the recovered radiolabel was retained in the soils and about 63% (4 days) and 54% (25 days) in the sand. After 25 days approximately 7% of the applied radiolabel was present as $^{14}CO_2$. Fenthion sulfoxide was the major product in all 4-day samples (29-38% of the radiolabel found). Fenthion and its sulfone and fenthion phenol sulfoxide and sulfone were minor components. Fenthion sulfoxide and fenthion phenol sulfoxide and sulfone were major components at 25 days.

Fenthion was not found in the leachate from the sand. Fenthion sulfoxide, fenthion phenol sulfoxide and fenthion phenol sulfone were identified as major products in the leachate from the sand at various times.

Labelled fenthion applied to thin-layer plates coated with various soil types demonstrated low soil mobility.

Fenthion spray concentrate (about 11 kg/ha) was added to three soils (loam and two silty clay loams) and leached by percolating water through the treated soils. Run-off water and soils were analyzed for residues. Insignificant leaching occurred. The majority of the fenthion residues remained in the top centimetre of the soils. Residues in the run-off water were less than 1% of the amount applied. Fenthion and fenthion sulfoxide were identified in the soils with only limited migration away from the point of application.

[*Phenyl*-1-^{14}C]fenthion was added to three soil types at concentrations of 0.5 to 10 mg/kg and adsorption data indicated that fenthion was strongly adsorbed to the soils. Freundlich adsorption constants were calculated to be between 19 and 39. These values were considered high and suggestive of strong soil adsorption coupled with lowered mobility through the soil. The percentage of fenthion adsorbed in all the soils was high (79 to 91%).

An adsorption/desorption study of [*phenyl*-1-^{13},^{14}C]fenthion (at nominal concentrations of 1, 5, 7.5 and 10 mg/kg of soil) with four soil types in which the soil was equilibrated with a solution of the labelled fenthion, showed Freundlich constants between 6 and 16. These values were associated with low mobility through the soil. Desorption constants were also calculated and confirmed that fenthion was resistant to leaching from the soil.

<u>Aquatic fate</u>

Fenthion (10 mg/kg) was added to phosphate buffers at pH 5, 7, and 9 at 30° and 50°C and samples were analyzed for residues of fenthion and its products over a period of 16 days. Fenthion had half-lives of 23-31 days at 30°C and 2-6.5 days at 50°C. No sulfoxides, sulfones or oxons were detected.

In a simulated field water system (made from pond water, stored outside and exposed to full sunlight), fenthion had a half-life of about 1-1.5 days. No degradation products were observed in the water. Fenthion sulfone was identified in silt from the pond water used.

A study of the stability of [*phenyl*-U-^{14}C]fenthion (5 mg/kg) in sterile aqueous phosphate buffers at 5, 25 and 40°C and pH 5, 7 and 9 showed maximum stability at acidic pH and 5°C where the half-life was 133 weeks. At pH 9 and 40°C, the half-life was about 2 weeks. Fenthion, fenthion sulfoxide and sulfone, fenthion oxon and its sulfoxide and sulfone, and fenthion phenol sulfoxide and sulfone were detected. Although the relative proportions of these compounds varied with the pH, temperature and time of sampling, fenthion sulfoxide was the principal product.

Fenthion at 3.6 to 5.1 ìg/ml was incubated in citrate buffer (pH 4), phosphate buffer (pH 7), and borate buffer (pH 9) at 50, 60 and 70°C. Half-lives were shorter at higher pH and temperature. The half-life of fenthion at 22°C was calculated to be about 200 days at pH 7. Fenthion phenol was identified in acidic and basic media.

When [*phenyl*-U-^{14}C]fenthion was added to pond water and silt at 10 mg/l, the fenthion had a half-life of less than 2 days in the water and 20 days in the silt. Fenthion sulfoxide was the major product in the water phase.

[*Phenyl*-1-^{14}C] was added to water-sediment samples at a concentration of 1.5 mg

fenthion/litre and the systems were kept at 20-24°C under aerobic and anaerobic conditions for 66 and 190 days respectively. In the aerobic system, the majority of the radiolabel was unextractable at the end of the trial (approximately 75% of the ^{14}C content at that time) and 15-20% of the radiolabel had been incorporated into carbon dioxide.

Carbon dioxide was the principal product in the anaerobic system (about 50% of the radiolabel present at the end of the experiment). A small amount of labelled methane was produced.

In the aerobic system the major products were fenthion sulfoxide and demethyl-fenthion oxygen analogue sulfone. In the anaerobic system, fenthion phenol sulfoxide and fenthion phenol were the main products with 3-methylphenol and methane detected at lower levels.

Fenthion labelled in the ring-1 position with ^{14}C and ^{13}C (1.5 mg/l) was added to two pond water and sediment samples. The test systems were open to the atmosphere and maintained with shaking in the dark at 20-24°C. Samples were taken during 66 days. The majority of the radioactivity (56 and 74% of the applied radioactivity at 66 days) transferred to the sediment and was not extractable with organic solvents. Carbon dioxide, produced in both systems, accounted for 9.5-13% of the final radioactivity. Degradation of fenthion was rapid in both systems with half-lives of about a week. The majority of the products were in the aqueous phases. Fenthion sulfoxide, demethyl-fenthion oxon sulfone, fenthion phenol sulfoxide and fenthion phenol sulfone were all major products at times during the experiment. Fenthion sulfone, demethyl-fenthion and its sulfoxide and sulfone, fenthion oxon, and demethyl-fenthion oxon sulfone were all found at lower levels.

Water and sediment from a pond were incubated anaerobically in the dark at about 22°C for 360 days with [*phenyl*-1-^{14}C]fenthion, added at the rate of 1.5 mg/kg. The radiolabel rapidly appeared in the sediment (28% of the total 14C content at one hour after application). In water, fenthion concentrations decreased from about 72% of the radiolabel initially present to about 7% 30 days later. Fenthion was a major component in the sediment. Between 120 and 190 days, carbon dioxide accounted for about 50% of the radiolabel added. At 120 days methane accounted for about 4% of the total radiolabel added. The major products were fenthion phenol and its sulfoxide. Demethyl-fenthion, its sulfoxide and 3-methylphenol were minor components.

Fenthion (at 200 ìg/litre) was added to salt marsh water and sediment systems (one sterilized by formalin without plants, one non-sterile without plants and one non-sterile with plants). The systems were kept at 20°C for 190 hours in the light and in darkness. Fenthion levels in the non-sterile systems approached zero by 200 hours. In sterile systems fenthion residues were still present in the water at 200 hours at a level between 50 and 100 ìg/litre. Half-lives were about 4 days in the sterile system and about 33-35 hours in the two non-sterile systems.

Fenthion was added to river water at the rate of 10 ìg/litre and kept for a period of 8 weeks under laboratory conditions in natural and artificial light. Within one week, 50% of the original fenthion was left, at 2 weeks 10% was present and none was detected after 4 weeks. In similarly treated distilled water, no fenthion loss was reported over the same period.

<u>Photolysis</u>

When [*phenyl*-U-^{14}C]fenthion at 5 mg/l in distilled water was irradiated with artificial light sources approximating the spectral wavelengths of sunlight, rapid breakdown was observed with half-lives of fenthion at 5°C and 25°C of 55 and 15 minutes respectively. The identified degradation products

identified were fenthion sulfoxide and sulfone, fenthion oxon and its sulfoxide, and fenthion phenol and its sulfoxide and sulfone. Fenthion sulfoxide and polar degradation products were formed at significant levels in all systems.

Irradiation of a 3.5 mg/l solution of fenthion in distilled water for 10 minutes with a high-pressure mercury vapour lamp showed a half-life of 4.5 minutes for fenthion. A solution of fenthion in distilled water exposed to summer sunlight had a half-life of four hours and numerous photoproducts were formed. Fenthion sulfoxide and fenthion phenol were identified as products of photolysis.

When [*phenyl*-1-^{13,14}C]fenthion (7 mg/l) in a pH 5, sterile sodium acetate buffer was irradiated with an artificial light source for 4 hours, extensive degradation of fenthion occurred and a half-life of about 30 minutes was calculated. Fenthion phenol, fenthion sulfoxide, fenthion phenol sulfoxide and fenthion phenol sulfonic acid were major photoproducts. Other products identified were fenthion sulfone and fenthion oxon sulfone.

In an investigation of the direct photodegradation of organic compounds in water under environmental conditions, fenthion had experimental half-lives of 4 hours in summer and 11 hours in autumn compared to calculated half-lives of 3 hours (summer value) and 14 hours (autumn value).

Analytical methods

Individual components of the fenthion residue (fenthion, fenthion sulfoxide and sulfone, fenthion oxon sulfoxide and sulfone) can be cleaned up by gel permeation chromatography on a polystyrene gel.

In the early supervised trials, plant material was solvent-extracted and the extract chromatographed successively on aluminium oxide and activated carbon columns. Fenthion residues with the P=S group were oxidized by potassium permanganate to fenthion sulfone. Quantification was by infra-red spectrophotometry or total phosphorus determination. Limits of determination were <0.1 mg/kg, with recoveries of 78-83% for cherries, apples, and cole crops, 80% for peas, 40-50% for guavas and 75% for olives and olive oil. For grapes at a fortification level of 0.23 mg/kg the recovery was 130%. For crops with lower chlorophyll content, the plant material was solvent-extracted and partitioned, and total phosphorus was determined colorimetrically after column chromatography. Methods which determined total phosphorus have been replaced by methods which specifically measure fenthion or its oxidative metabolites, either as total residues or individually.

Organophosphorus pesticides containing thioether groups when present as the parent compound and/or its sulfoxide and sulfone in fruits and vegetables were determined by solvent extraction and oxidation of fenthion and fenthion sulfoxide to fenthion sulfone with potassium permanganate. This step removed most of the interfering plant material and column clean-up was not routinely needed. Fenthion sulfone was determined by gas chromatography on a packed column with a phosphorus-specific alkali flame-ionization detector. Recoveries were generally >70% for fruits and vegetables at 0.01-0.1 mg/kg.

Fenthion can be determined in plant material by extraction with ethyl acetate followed by gas chromatography with phosphorus-specific detection without further clean-up. Limits of determination were 0.01-0.05 mg/kg, with recoveries >80%.

Fenthion residues in capsicums, mangoes, tomatoes and zucchini were determined by

extraction with acetone, sweep co-distillation of a hexane extract of the aqueous residue left after evaporation of the acetone, and GLC with a flame-photometric detector. Cucumbers and rockmelons did not require the co-distillation step. Limits of determination were 0.01-0.02 mg/kg. Recoveries were >80% at levels of fortification between 0.1 and 1.2 mg/kg.

Fenthion residues in animal tissues were extracted with acetone followed by chloroform and partitioned with *n*-hexane and acetonitrile to remove contaminating material. Residues were oxidized with *m*-chloroperbenzoic acid to fenthion oxon sulfone. This was hydrolysed and the resulting phenol derivatized and determined by gas chromatography with electron-capture detection. Recoveries in animal tissues were between 71 and 108% at the 0.1 mg/kg level. The method was also suitable for milk with a limit of determination of 0.01 mg/kg (81-114% recoveries).

This method was developed further by omitting the hydrolysis and derivatization steps and determining fenthion and its metabolites as fenthion oxon sulfone by gas chromatography with a thermionic detector. The LOD was 0.05 mg/kg. Recoveries from cattle tissues and organs were greater than 80% at the 0.1 mg/kg level except from bovine liver (64%). In poultry tissues and organs recoveries were 87-118% at 0.1 mg/kg. The method was free from interference from 42 other pesticides. The use of *m*-chloroperbenzoic acid as the oxidizing agent allows total fenthion residues to be determined by conversion of P=S and P=O compounds to the fenthion oxon sulfone.

Fenthion residues in animal tissues can be determined after extraction with acetone/acetonitrile, evaporation of the filtered extract, and partitioning with hexane and acetonitrile. Fenthion is determined in the acetonitrile phase by GLC with phosphorus-specific detection. LODs are 0.01-0.04 mg/kg, with recoveries between 66 and 120%.

In a qualitative TLC method to detect fenthion an ethyl acetate extract of the tissues is chromatographed. The developed plate is sprayed with bromine and a homogenate of bee heads, then with naphthyl acetate and a dye precursor. The cholinesterase from the bee heads hydrolyses the ester and the liberated naphthol forms a coloured dye. If fenthion is present, the hydrolysis cannot occur and a white spot is seen on a pink background.

Fenthion and fenthion sulfone residues in sheep liver, kidney, muscle and subcutaneous fat were determined after extraction of the tissues with acetonitrile, solvent partitioning of the extract with *n*-hexane and acetonitrile and chromatographic clean-up. HPLC was used to determine fenthion and fenthion sulfone. The limit of determination for both compounds was 0.02 mg/kg and the limit of detection 0.005 mg/kg. Fenthion recoveries from muscle, subcutaneous fat and organs at 0.04 and 0.1 mg/kg levels were between 60 and 96%. Fenthion sulfone recoveries at the same levels were between 68 and 110%.

Total fenthion residues in eggs and milk were determined after solvent extraction, partitioning, and oxidation of the extract with *m*-chloroperbenzoic acid. The fenthion oxon sulfone formed was partitioned into chloroform and determined by GLC with a flame-ionization detector. The LOD was 0.005 mg/kg. Recoveries at the 0.01 and 0.005 mg/kg levels were between 74 and 128%.

Total fenthion residues were determined in citrus fortified at 0.1 mg/kg by *m*-chloroperbenzoic acid oxidation and gas chromatography after solvent extraction and partitioning. Recoveries were 86% from the fruit and 106% from the peel. Changes in the extraction process improved the limit of determination to 0.01 mg/kg, where recoveries of 73-77% from peel, 96% from juice, and 80-120% from marmalade were reported.

In apples. apple products, pears and pear preserve, total fenthion residues were determined by gas chromatography on a megabore column with a flame-photometric detector optimized for phosphorus, after extraction with acetone, partitioning with dichloromethane and oxidation with *m*-chloroperbenzoic acid to the oxon sulfone. Apple juice was cleaned up by column chromatography and the residues oxidized to fenthion oxon. Recoveries at the 0.01 mg/kg level were apples 90 and 94%, apple purée 78 and 86%, apple juice 84%, apple pomace 79-124%, pears 65 and 75%, and pear preserve 86 and 89%.

Using similar extraction procedures and *m*-chloroperbenzoic acid oxidation, total fenthion residues were determined in cherries and peaches at the 0.1 mg/kg level. A 78% recovery was reported for cherries (limit of determination 0.05 mg/kg) and 74-81% for peaches (limit of determination 0.01 mg/kg).

The determination of fenthion residues in olives and olive oil has been thoroughly investigated. Initial methods involved solvent extraction, partitioning, and alumina and activated carbon column chromatography to remove interfering substances. Total phosphorus was determined colorimetrically. The lower limits of determination were reported as 0.05 mg/kg for olives and 0.1 mg/kg for olive oil, with recoveries of 75-80%. The determination was made more specific by using *m*-chloroperbenzoic acid oxidation and gas chromatography to determine fenthion oxon. Recoveries at the 0.1 mg/kg level were 74% from olives and 94% from the oil.

To determine fenthion, fenthion sulfoxide and fenthion sulfone residues in olive oil, a hexane solution of the oil was partitioned into acetonitrile and the residue oxidized with potassium permanganate. This milder oxidizing agent converted fenthion and its sulfoxide to fenthion sulfone. Fenthion sulfone and oxon sulfone were then determined separately by gas chromatography on a packed column with a nitrogen-phosphorus detector. For the whole method, recoveries were >79%. Limits of determination were 0.005 mg/kg for fenthion sulfone and 0.01 mg/kg for the oxon sulfone.

Fenthion, its sulfoxide and sulfone, and fenthion oxon were determined in olives after solvent extraction, partitioning with *n*-hexane and acetonitrile and column-chromatographic clean-up by gas chromatography on a capillary column with a nitrogen-phosphorus detector. Parathion-methyl was added as an internal standard. Olive oil was directly analyzed after dilution with ethyl acetate. Recoveries were stated to be about 80% with detection limits of 5 to 10 ìg/kg for fenthion and the products.

When a megabore column and a flame-photometric detector optimized for phosphorus were used to determine fenthion oxon after solvent extraction, partitioning and *m*-chloroperbenzoic acid oxidation, recoveries at the 0.01 mg/kg level were 81% from olives and 81-85% from olive oil. The limit of determination was 0.01 mg/kg.

In rice, total fenthion residues were determined after extraction with acetone and chloroform, evaporation of the solvent, and *m*-chloroperbenzoic acid oxidation. Determination was by GLC with a phosphorus-sensitive detector. Recoveries at the 0.1 mg/kg level were ≥75%. The LOD was ≤0.05 mg/kg. In a development of this method, the rice was extracted with acetone and the acetone extract partitioned with dichloromethane. The residue left after evaporation of the dichloromethane was partitioned with hexane and acetonitrile. The acetonitrile phase was evaporated and the residue taken up in dichloromethane. Fenthion was determined by GLC after cleaning up the solution on a Florisil column. The dichloromethane extract was treated with aqueous potassium permanganate to form fenthion sulfone and fenthion oxon sulfone, which were partitioned into dichloromethane and

determined by GLC with a flame-photometric detector. Minimum detectable limits for both sulfones and fenthion were 0.005 mg/kg. Recoveries at the 0.1 mg/kg level were between 88 and 106%.

Fenthion residues in rice were also determined after a thin-layer chromatographic clean-up by GLC with a flame-photometric detector. Recovery at the 0.1 mg/kg level was 97%. The limit of detection was ≤0.005 mg/kg.

Total fenthion residues in soil were determined by GLC after extraction of an aqueous suspension of the soil with acetone. The limit of determination was 0.05 mg/kg with a 90% recovery at the 0.5 mg/kg level.

To determine total fenthion residues in leachate water, the water was extracted with dichloromethane, the residue was oxidized with *m*-chloroperbenzoic acid and the product determined by GLC. The limit of determination was 0.05 mg/kg with 80% recovery at the 0.5 mg/kg level.

For the determination of total fenthion residues in drinking-water, column clean-up of the water was followed by solvent extraction. The fenthion residues were oxidized with *m*-chloroperbenzoic acid to the oxon sulfone. This was determined by GLC on a megabore column with a flame-photometric detector optimized for phosphorus. The limit of determination was 0.01 mg/kg with recoveries of 90 and 94% at that level.

Fenthion was determined in water after solid-phase extraction on alkyl-modified silica gel. The residue was desorbed and determined by gradient elution on HPTLC silica gel plates with detection by derivatization and UV, with internal and external standards. The limit of determination was 0.05 ìg active ingredient/litre with fenthion recoveries at a fortification level of 0.1 ìg/l of 59-69%. By changing the elution solvent recoveries of 68-93% at 0.05 ìg/l were achieved.

In animal tissues and plants, solvent extraction and partitioning followed by *m*-chloroperbenzoic acid oxidation to fenthion oxon sulfone and gas-chromatographic determination is suitable for the determination of total fenthion residues in a wide variety of commodities. The method has acceptable sensitivity and recoveries are generally at least 70% and frequently better. By measuring a single entity, the method is simplified and also determines the sulfoxides and sulfones which are more toxic than fenthion itself.

Stability of stored analytical samples

Fenthion, fenthion sulfoxide, fenthion sulfone, fenthion oxon sulfoxide and fenthion oxon sulfone were stable in olives and olive oil fortified at 0.2 mg/kg of each (total 1 mg/kg) and stored below -20°C up to 380 days. Samples fortified with fenthion at the 2 mg/kg level and stored at room temperature (17 to 23°C) for a year were also stable. Total residues of >0.5 mg/kg in samples of virgin olive oils taken during monitoring studies and stored at 17 to 23°C were stable for 13 months.

Orange peel and pulp fortified with fenthion, fenthion sulfoxide, fenthion sulfone, and fenthion oxon sulfoxide and sulfone (each at 0.2 mg/kg, total 1 mg/kg), were stored below -20°C for 433 days (peel) and 448 days (pulp). Residues of all the compounds were stable over this period.

Cattle brain, fat, heart, kidney, liver and muscle were fortified with ^{32}P-labelled fenthion or fenthion oxon sulfone and stored at -18°C up to four weeks (fenthion) or six weeks (oxon sulfone). Fenthion was stable in all tissues. Fenthion oxon sulfone was stable in brain, heart, muscle and fat for

six weeks but was not stable in liver (29.5% of the original material was extractable with chloroform after 4 weeks storage). Stability in the presence of kidney tissue was marginal with 68.6% of the original material being extractable with chloroform after storage for one month.

In cattle muscle, liver and fat fortified with fenthion or fenthion oxon at 1 mg/kg and stored at room temperature for 6 hours, fenthion recoveries from liver and muscle were 96% and from fat 83%. Fenthion oxon sulfone was stable in steak and fat but was rapidly lost from liver with 15% remaining after 4 hours.

In a metabolism study on a goat using radiolabelled fenthion, further degradation to oxidized, demethylated and dephosphorylated products occurred in organs and tissues stored for an unspecified time at about -20°C.

In sheep liver, kidney, muscle and subcutaneous fat fortified with fenthion, 50% or less of the fenthion remained in all the tissues after storage at approximately -20°C for 51 weeks. Fenthion sulfone was found to be stable under these conditions. Fenthion and fenthion sulfone residues in sheep tissues incurred from dermal application were also stable.

Definition of the residue

The data on metabolism and environmental fate and the existence of satisfactory analytical methods, indicated that no change was needed to the current Codex residue definition. This conclusion takes account of the identification of fenthion and its oxidative metabolites in the animal and plant metabolism studies and the demonstration of fat-solubility in metabolism studies on farm animals and in supervised residue trials on animals. The definition is practical for regulatory analytical purposes and also allows for the determination individually of fenthion and its oxidative metabolites should these be required for dietary intake studies or risk assessments in which differences in toxicity between fenthion and its oxidative metabolites may be important.

The Meeting recommended no change to the current definition of the fenthion residue as the "sum of fenthion, its oxon and their sulfoxides and sulfones, expressed as fenthion (fat soluble)".

Residues resulting from supervised trials

Mandarins and oranges. Data were available on fenthion residues in mandarins and oranges from 15 trials in Spain. The residues in mandarins and oranges were generally similar for the same use pattern and were considered mutually supportive. Eight supervised trials were according to GAP: oranges were sprayed once at 0.05 kg ai/ha in 5 trials and mandarins at the same rate in 3 trials using aerial application. GAP for citrus in Spain requires a single aerial application of 0.06 kg ai/ha with a 3-day PHI. The highest residues in the whole fruit from each trial according to GAP were <0.01, <0.01, 0.02, 0.04, 0.05, 0.15, 0.18, and 0.21 mg/kg. Residues in the pulp were all <0.01 mg/kg. The Meeting noted that the total fenthion residues in orange juice made from the treated oranges were <0.01 mg/kg.

The data did not support the current maximum residue limit of 2 mg/kg for citrus fruit and indicated that a lower value would be appropriate. Because a number of the results were close to 0.2 mg/kg it was considered that this value was too low and could lead to unnecessary residue violations. A maximum residue level of 0.5 mg/kg for oranges and mandarins was estimated to replace the previous recommendation of 2 mg/kg for fenthion in citrus fruits. The Meeting also agreed to withdraw the previous recommendation for fenthion in citrus juice (0.2 mg/kg), noting that maximum

residue limits for juices had not usually been recommended.

<u>Cherries</u>. Residue data on cherries were available from 10 supervised trials in Germany. Seven of the trials were according to German GAP (single application at 0.05 kg ai/hl with a 14-day PHI). The highest residues in the fruit from each trial according to GAP were 0.38, 0.5, 0.55, 0.6, 0.65, 0.8, and 1 mg/kg.

The Meeting agreed to maintain the current recommendation of 2 mg/kg.

<u>Peaches</u>. Residue data were available from 4 supervised trials in Spain and one in South Africa. The trials were considered to be according to GAP. Peaches were sprayed in South Africa with single applications of 0.06 kg ai/hl with a 14-day PHI. South African GAP is 0.04-0.05 kg ai/hl, 1-3 sprays, 10-day PHI. The Spanish trials with 2 applications at 0.075-0.1 kg ai/hl with a 14-day PHI were according to GAP (0.1 kg ai/hl, 1-2 sprays, 14-day PHI). In the trials there were no results after 10 days from South Africa and only one after 14 days from Spain. The highest residues in the fruit from each trial according to GAP were 0.12, 0.16, 0.24, 0.48, and 1.1 mg/kg. The Meeting was informed that additional trials on peaches were being planned and results would be available in the near future.

The Meeting considered that there were too few results to estimate a maximum residue level for a stone fruit as important as peaches and agreed to withdraw the current recommendation (2 mg/kg).

<u>Olives</u>. Data were available from supervised trials in Spain (four), Greece (four) and Italy (three). One of the Spanish, three of the Greek and the three Italian trials were according to relevant GAP. The Spanish trial (0.3 kg ai/ha, three applications) was evaluated against Italian GAP of 0.25-0.5 kg ai/ha, 2-3 applications and a 28-day PHI. In the Greek trials olives were sprayed from the air 4 times at 0.09 kg ai/ha. Greek GAP for olives sprayed aerially is 3-5 treatments at 0.09 kg ai/ha with a 21-day PHI. Olives in the Italian trials were sprayed by ground application 2 or 3 times at 0.05 kg ai/hl (0.5 kg/ha). Italian GAP is 2-3 treatments at 0.025-0.05 kg ai/hl with a 28-day PHI.

The highest residues in the olives from each trial according to GAP were 0.01, 0.04, <0.1(2), 0.26, 0.36, and 0.87 mg/kg.

The Meeting was informed that additional Greek trials on olives, begun in May 1995, were in progress and results would be available in the near future.

The Meeting agreed to maintain the current recommendation of 1 mg/kg.

<u>Rice</u>. About 40 analyses of hulled rice were available from supervised trials in Japan, using dustable powder, emulsifiable concentrate and granule formulations, conducted between 1969 and 1978. Twenty-eight of the results were from trials according to Japanese GAP. Three of the reported residues were in polished rice. Dustable powder trials were conducted at 0.6-0.9 kg ai/ha with 1 or 3 applications. Japanese GAP for dustable powders is 0.6-0.8 kg ai/ha, 1-2 applications, 21-day PHI. The trials with emulsifiable concentrates were conducted at 0.5-0.75 kg ai/ha, 1-3 applications: GAP for emulsifiable concentrates is 0.375-0.75 kg ai/ha, 1-2 applications, 30-day PHI. Granular treatments were at 2 kg ai/ha with 2 applications. The Japanese GAP for this type of formulation is 1.5-2 kg ai/ha, 1-2 applications, 45-day PHI.

Residues in rice grains without husks from 31 supervised trials conducted according to Japanese GAP for the EC and DP formulations in 1994 were also presented. Single or double

applications of dustable powder (DP) formulations were made 21 days before harvest at 0.6 or 0.8 kg ai/ha (Japanese GAP is 1-2 applications, 0.6-0.8 kg ai/ha, 21-day PHI). Single applications followed an earlier application of a GR formulation. Emulsifiable concentrate (EC) formulations were applied as a single 0.75 kg ai/ha treatment with a 30-day PHI following the earlier application of a GR formulation. The Japanese GAP for emulsifiable concentrates is 0.375-0.75 kg ai/ha, 1-2 applications, 30-day PHI.

The results from the 1969-1978 and 1994 trials were considered together because "hulled rice" (i.e. rice without hulls) is the same product as "husked rice" (i.e. rice grains without husks).

The total fenthion residues in the rice in each of the trials according to GAP were <0.001 (17), <0.002 (2), 0.008, 0.009, 0.01 (2), 0.012, <0.014 (8), <0.015 (17), <0.016 (2), <0.017, 0.018, <0.019 (2), <0.02, <0.023, <0.024 (5), and <0.028 (2) mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg for fenthion in "Rice, husked" to replace the previous recommendation for "Rice" of 0.1 mg/kg.

Post-harvest uses

Data on residues of fenthion only and not its oxidative metabolites were available from single supervised post-harvest disinfestation trials on mangoes, rockmelons, cucumbers, zucchini, capsicum peppers and tomatoes conducted at and above the Australian GAP rate. Residues in these commodities were generally similar for the same use pattern and were considered to be mutually supportive. Australian GAP is a single flood spray or dip at 0.041 kg ai/hl without a withholding period. The highest residues from each trial according to GAP were mango 1.4 mg/kg; rockmelon 2.1 mg/kg; cucumber 2.0 mg/kg; zucchini 1.2 mg/kg; capsicum 2.6 mg/kg; tomato 1.3 mg/kg.

The Meeting considered that the measurement of fenthion alone might not be justified in view of its demonstrated conversion to oxidative metabolites. It was also considered that, although the use patterns were similar, a single trial on each commodity was insufficient. It was further concluded that a level of 5 mg/kg, which might be estimated on the basis of the higher results, would be excessive for some of the commodities. For these reasons no maximum residue limits could be recommended.

Animal commodities

Meat. Data on total fenthion residues in cattle fat, muscle and offal from 7 supervised trials in the USA were presented. Of these, five were considered to be according to registered use patterns which allow approximately 4-16 mg ai/kg body weight as a pour-on or spot-on application with withholding periods of 10, 14, 15, 21, 35 or 45 days depending on the country concerned. Residues after 7 days were considered to be just relevant to a 10-day withholding period. The highest residues from each trial according to registered use patterns in the fat were <0.05, 0.07, 0.47, 0.84, and 3.9 mg/kg, and in offal 0.02, 0.06, <0.1, and 0.15 mg/kg. The corresponding residues in muscle were 0.03, 0.04, 0.2, and 0.31 mg/kg. Because one of the valid trials reported only residues in fat there are only four results for offal and muscle. There were no data from withholding periods of 10 days and only one set of results from a 14-day withholding period.

The Meeting recalled that a metabolism study had been submitted in which the nature of the residues in the skin and tissues after a dermal application to a pig had been determined. In a supervised trial in the USA pigs were given a pour-on treatment at approximately 9.5 mg ai/kg body

weight and the animals were slaughtered during a 7- to 45-day period after treatment. Registered use patterns are 5 mg ai/kg body weight and an 8-day withholding period in Belgium and 9.8 mg ai/kg body weight with a 14-day withholding period in Canada. The highest residues from registered use patterns were 0.09 mg/kg in composite fat (omental and renal) and back fat, 0.03 mg/kg in offal, and 0.02 mg/kg in muscle.

Sheep in the UK were dermally treated, but there was no UK use pattern and the treatment rate used was four times that in the only use pattern available for sheep (South Africa). The trial could therefore not be used to estimate a maximum residue level.

The Meeting noted that although there were sufficient valid trials and the pig study could be considered with the cattle studies, there were no results for cattle at a 10-day withholding period and the residue levels appeared to be changing rapidly between 7 and 10 days after treatment in these animals. The Meeting was therefore unable to recommend a maximum residue level for fenthion in meat and agreed to withdraw the previous recommendation (2 mg/kg in the fat).

Milk. Data on fenthion residues in milk were available from 15 trials in which cattle had been treated with fenthion. Twelve of the trials were considered to be according to registered GAP and involved treatment levels between 3.5 and 11.8 mg ai/kg body weight. Withholding periods were from less than a day ("zero") to 5 days and longer. Results were from individual cows or pooled samples. Withholding periods in registered GAP are zero, 5, or 7 days. The maximum dose rate allowed is 16 mg fenthion/kg body weight. The highest residues in the milk after each withholding period were 0.04, 0.06, 0.07(2), 0.09, 0.1, 0.14, 0.2, 0.47, and 0.95 mg/kg at 0 days (10 valid trials), 0.012, 0.022, and 0.07 mg/kg at 5 days (3 valid trials), and 0.01 and 0.05 mg/kg at 7 days (2 valid trials).

The Meeting noted that extensive information on the total fenthion residues in milk after the dermal treatment of cows had been presented, and observed that the highest residues occurred within 24 hours of treatment. The Meeting also noted that although a number of results from a zero withholding period were around 0.1 mg/kg, there was evidence that significantly higher residues occurred within the first day after treatment.

The Meeting concluded that the data supported an increase in the maximum residue level and estimated a maximum level of 1 mg/kg to replace the previous estimate of 0.05 mg/kg.

Maximum residue limits recommended for withdrawal

Because residue data from supervised trials on apples, bananas, cabbages (head), cauliflowers, common beans, grapes, lettuce (head), bulb onions, pears, peas, plums, potatoes, squash (summer), strawberries, sweet potatoes, wheat, and winter squash had not been provided, the Meeting agreed to withdraw the recommendations for apples (2 mg/kg), bananas (1 mg/kg), cabbages, head (1 mg/kg), cauliflowers (1 mg/kg), common bean (pods and/or immature seeds) (0.1 mg/kg), grapes (0.5 mg/kg), lettuce, head (2 mg/kg), onion, bulb (0.1 mg/kg), pear (2 mg/kg), peas (0.5 mg/kg), plums (including prunes) (1 mg/kg), potatoes (0.05 mg/kg), squash, summer (0.2 mg/kg), strawberry (2 mg/kg), sweet potato (0.1 mg/kg), wheat (0.1 mg/kg), and winter squash (0.2 mg/kg).

Farm animal transfer studies

Animal transfer studies with cattle and lactating cows were made available to the Meeting.

Hereford steers were fed fenthion-treated feed for six consecutive days at 2.5 mg fenthion/kg

body weight (approximately 1 g fenthion/animal). Residues of fenthion (total) were not detected (<0.1 mg/kg or less than the control value) at day 7 or 10 in the brain, heart, liver, kidney, muscle (loin, round, and flank), or fat (omental, renal, and back). Although the daily food consumption was not reported, it was estimated by the sponsor that the concentration in the feed was approximately 80 ppm.

Six dairy cattle weighing 990-1265 kg were fed feed containing 5 ppm fenthion for 28 days. Milk samples taken on days 28 and 29 contained no detectable residues (<0.01 mg/kg in whole milk, not fat).

Jersey cows were fed diets spiked with 0, 25, 50 or 100 ppm fenthion (dry weight basis) for 28 days. Residue concentrations in the milk, urine and faeces were still increasing after 28 days. The total fenthion residues in the milk at 28 days were 0.018, 0.049 and 0.099 mg/kg for the 25, 50, and 100 ppm dietary levels respectively. Seven days after feeding fenthion ceased, residues were not detectable (<0.002 mg/kg) in whole milk, faeces or urine

The Meeting noted that although critical animal feeding studies had been submitted, they were inadequate because of the uncertainty of the actual fenthion level in one study and the continued increase in residue levels in another. It was also observed that while there were some data available on total fenthion residues in orange and mandarin pulp, there was a general lack of information on residue levels likely to be found in animal feeds. The Meeting considered that the major source of exposure of animals would probably be from dermal treatment rather than forage or fodder intake. The Meeting was informed that a transfer study on lactating cows would be available in the near future.

The Meeting was unable to estimate maximum residue levels arising from the consumption of treated feed because of the deficiencies in the data submitted and the lack of detailed knowledge of likely residue levels in animal fodder or forage.

Fate of residues in processing

Information on the fate of residues during the processing of apples, oranges, and olives was made available to the Meeting.

In the simulated industrial preparation of apple juice and apple sauce, washing removed approximately 45% of the residues on the apple peel. Residues were carried through the process into the sauce and clarified juice with little concentration.

Orange juice made by a simulated industrial process contained <0.01 mg/kg total fenthion residues. In a small-scale preparation of marmalade, the total fenthion residues in the marmalade were similar to those in the whole oranges.

The Meeting was informed that the results of a new citrus processing study in the USA would be available in the near future.

Washing olives treated with fenthion resulted in no significant change in residue levels.
Residues in crude olive oil prepared by the small-scale pressing of treated olives were 1.5-6.6 times those in the olives from which the oils were prepared.

By applying a median concentration factor of 3 to the maximum residue level of 1 mg/kg

estimated for olives, the Meeting estimated a maximum residue level of 3 mg/kg for olive oil, virgin.

Residues in refined virgin olive oil were 51-79% of those found in the unrefined oil. Residues in fermented olives were approximately 45-55% of those in the treated olives.

Residues in food in commerce or at consumption

In residue monitoring in Australia between 1989 and 1994 fenthion residues were not detected in butter (476 samples), cheese (937), milk (204), milk powder (fat basis, 750), eggs (780), beef fat (39,933), pig fat (15,933), sheep fat (29,361), or poultry fat (2168).

In a two-year Greek monitoring programme on fenthion residues in virgin olive oil following fenthion treatment the majority of the samples had total fenthion residue levels below 0.1 mg/kg even when samples taken in the second year of the programme were from locations where residues were relatively high in the first year. Four to six per cent of the samples contained residues above 1 mg/kg, the Greek and Codex maximum residue limit for olive oil.

Recommendations for MRLs and withdrawals of MRLs are given in Annex I.

FURTHER WORK OR INFORMATION

Desirable

1. Full details of olive trials in Greece, begun in May 1995.

2. Additional information on residue levels in treated animal feeds.

3. Additional information on residues in meat and offal arising either from dermal treatment or consumption of fenthion-treated animal feeds in transfer studies.

4. Information on the measured octanol/water partition coefficients of the oxidative metabolites of fenthion.

4.19 FLUSILAZOLE (165)

TOXICOLOGY

Flusilazole was previously evaluated toxicologically by the Joint Meeting in 1989. An ADI of 0-0.001 mg/kg bw was allocated, on the basis of a NOAEL of 0.14 mg/kg bw per day for hepatic toxicity in a one-year dog dietary study in dogs. Additional data were reviewed by the present Meeting.

In rats, orally administered ^{14}C-labelled flusilazole was readily absorbed and rapidly excreted in the urine and faeces, with little radiolabel recovered in expired air. Over 90% of the administered dose was eliminated within 96 h. ^{14}C from phenyl-labelled material was excreted predominantly in the faeces (87% in males and 59% in females), while that from triazole-3-labelled material was recovered primarily in the urine (72% in each sex). Tissue retention of ^{14}C was low (<1%, excluding the carcase). [^{14}C]Flusilazole was extensively metabolized in rats. After absorption, it was cleaved at

the triazole ring. Recovered parent compound accounted for only 2-11% of the administered dose, and was found predominantly in faeces, the urinary level being <1%.

Flusilazole is slightly toxic to mice, rats and rabbits when given as a single oral dose and is minimally toxic to rats and rabbits when given dermally or by inhalation. The oral LD_{50} in rats was > 500 mg/kg bw, the dermal LD_{50} in rabbits was >2000 mg/kg bw and the inhalation LC_{50} in rats was 6.8-7.7 mg/litre. Flusilazole was minimally irritating to the eyes and skin of rabbits, and it was practically non-irritating to the skin and not a dermal sensitizer in guinea-pigs. The WHO has classified flusilazole as "slightly hazardous".

Repeated oral administration of flusilazole to mice (90 days), rats (90 days) and dogs (90 days and one year) resulted primarily in lesions of the liver (hepatocellular hypertrophy and hyperplasia and vacuolation) and urinary bladder (urothelial hyperplasia and vacuolation). On the basis of the hepatic and/or urinary bladder changes, the NOAEL was 25 ppm (equal to 4 mg/kg bw per day) in mice, 125 ppm (equal to a mean of 8.1 mg/kg bw /day in two 90-day studies) in rats and 5 ppm (equal to 0.14 mg/kg bw per day) in dogs (one-year study). Repeated dermal application of flusilazole to rabbits for 21 days did not result in treatment-related systemic toxicity at doses up to and including 200 mg/kg bw per day.

In two 18-month studies of carcinogenicity, flusilazole was administered at dietary concentrations of 0, 5, 25 or 200 ppm to mice of both sexes in the first study and at 0, 100, 500 or 1000 ppm to males and 0, 100, 1000 or 2000 ppm to females in the second study. The overall NOAEL for the two studies was 25 ppm (equal to 3.4 mg/kg bw per day) on the basis of hepatotoxicity and urinary bladder hyperplasia in males at 100 ppm. In the second study, an increased incidence of hepatocellular tumours (adenomas and carcinomas) was observed in males at ≥100 ppm (equal to 14 mg/kg bw per day) and in females at ≥1000 ppm (equal to 200 mg/kg bw per day), doses at which lesions of the liver (focal necrosis, hepatocellular hypertrophy and hyperplasia and vacuolation) were evident. Flusilazole was carcinogenic in the second study.

In two two-year studies of chronic toxicity and carcinogenicity, rats received dietary concentrations of flusilazole at 0, 10, 50 or 250 ppm (first study) or 0, 125, 375 or 750 ppm (second study). In the first study, the NOAEL was 10 ppm (equal to 0.4 mg/kg bw per day) on the basis of mild nephrotoxicity (pyelonephritis in females and hydronephrosis in males) at 50 ppm. In the second study, an increased incidence of urinary bladder transitional-cell tumours (papillomas and carcinomas) in rats of each sex and testicular Leydig-cell tumours in males were observed at 750 ppm (equal to 31 mg/kg bw per day), doses at which lesions of the urinary bladder (urothelial necrosis, exfoliation and hyperplasia) were clearly demonstrated. Flusilazole was carcinogenic in the second study.

A special two-week study to investigate the possible mechanism by which testicular Leydig-cell tumours are induced was conducted in rats. Flusilazole caused a dose-dependent lowering of serum testosterone and estradiol levels at ≥20 mg/kg bw per day *in vivo* and a dose-related decrease in testosterone and androstenedione production in cultured testicular Leydig cells by inhibiting enzymes involved in steroid biosynthesis.

In a two-generation study of reproductive toxicity, rats were fed diets containing flusilazole at concentrations of 0, 5, 50 or 250 ppm. The NOAEL for systemic (parental) toxicity was 5 ppm (equal to 0.34 mg/kg bw per day) on the basis of hepatic lesions at 50 ppm. The NOAEL for reproductive toxicity was 50 ppm (equal to 4.0 mg/kg bw per day) on the basis of treatment-related mortality during parturition, increased length of gestation, reduced numbers of live-born pups per

litter and decreased pup growth at 250 ppm.

Three studies of developmental toxicity were performed in rats at doses of 0, 10, 50 or 250 mg/kg bw per day in the first study, 0, 0.4, 2, 10, 50 or 250 mg/kg bw per day in the second study, and 0, 0.2, 0.4, 2, 10 or 100 mg/kg bw per day in the third study. A study of developmental toxicity was also conducted in which rats were fed flusilazole at dietary levels of 0, 50, 100, 300 or 900 ppm (equal to 0, 4.6, 9, 27 and 79 mg/kg bw per day) on days 7-16 of gestation. The NOAEL for maternal toxicity was 10 mg/kg bw per day, on the basis of a slight reduction in body-weight gain and food consumption during treatment at ≥27 mg/kg bw per day. The NOAEL for embryo- and fetotoxicity was 4.6 mg/kg bw per day on the basis of increased resorption, increased length of gestation, reduced litter size and a higher incidence of skeletal variations or anomalies at ≥9 mg/kg bw per day. At 250 mg/kg bw per day, an increased incidence of cleft palate was observed. The NOAEL for teratogenicity was 100 mg/kg bw per day.

In three studies of developmental toxicity in rabbits, animals were treated with flusilazole at 0, 2, 5 or 12 mg/kg bw per day (first study), 0, 12 or 35 mg/kg bw per day (second study), or 0, 7, 15 or 30 mg/kg bw per day (third study) on days 7-19 of gestation. The NOAEL for maternal and embryo- or fetal toxicity was 12 mg/kg bw per day on the basis of clinical signs of toxicity and an increased incidence of abortion and total resorptions at ≥15 mg/kg bw per day. There was no evidence of teratogenicity at doses up to and including 15 mg/kg bw per day, the highest dose at which an adequate number of live litters was available for the assessment of teratogenicity.

Flusilazole has been adequately tested for genotoxicity in a series of assays *in vivo* and *in vitro*. The Meeting concluded that flusilazole is not genotoxic.

An ADI of 0-0.001 mg/kg bw was established on the basis of the NOAEL of 5 ppm, equal to 0.14 mg/kg bw per day, in the one-year dietary study in dogs, and a safety factor of 100.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 25 ppm, equal to 3.4 mg/kg bw per day) (18-month study of toxicity and carcinogenicity)

Rat: 10 ppm, equal to 0.4 mg/kg bw per day) (two-year study of toxicity and carcinogenicity)
5 ppm, equal to 0.34 mg/kg bw per day (maternal toxicity in a two-generation study of reproductive toxicity)
50 ppm, equal to 4 mg/kg bw per day (two-generation study of reproductive toxicity)
4.6 mg/kg bw per day (embryo- or fetotoxicity in a study of developmental toxicity)
100 mg/kg bw per day (teratogenicity in a study of developmental toxicity)

Rabbit: 12 mg/kg bw per day (maternal and embryo- or fetal toxicity in a study of developmental toxicity)
15 mg/kg bw per day (teratogenicity in a study of developmental toxicity)

Dog: 5 ppm, equal to 0.14 mg/kg bw per day one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.001 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to flusilazole

Exposure	Relevant route, study type, species	Result/remarks
Short-term (1-7 days)	Dermal, irritation, rabbit	Minimally irritating
	Eye, irritation, rabbit	Minimally irritating
	Skin, sensitization, guinea pig	Not a skin sensitizer
	Oral, toxicity, rat	LD_{50} = > 500 mg/kg bw
	Dermal, toxicity, rabbit	LD_{50} = > 2000 mg/kg bw
	4-h, Inhalation, toxicity, rat	LC_{50} = 6.8 - 7.7 mg/litre
Medium-term (1-26 wks)	Repeated dermal, 21-day, toxicity, rabbit	NOAEL = 200 mg/kg bw per day, highest dose tested for systemic toxicity
	Repeated dietary, reproductive toxicity, rat	NOAEL = 0.34 mg/kg bw per day on the basis of hepatic toxicity
	Repeated gavage, developmental toxicity, rabbit	NOAEL = 7 mg/kg bw per day for maternal, embryo- or fetal toxicity; NOAEL = ≥15 mg/kg bw per day for teratogenicity
Long-term (≥ one year)	Repeated dietary, one year, toxicity, dog	NOAEL = 0.14 mg/kg bw per day for primarily liver toxicity

4.20 FOLPET (041)

TOXICOLOGY

Folpet was evaluated toxicologically by the Joint Meeting in 1969, 1973, 1982, 1984, 1986, 1990 and 1993. A temporary ADI of 0-0.16 mg/kg bw was established by the 1969 JMPR. In 1973, an ADI of 0-0.1 mg/kg bw was allocated. In 1982 the ADI was made temporary because it was based almost exclusively on studies performed by Industrial Biotest Laboratories Inc. which had not been validated. In 1984 the Meeting withdrew the temporary ADI because no useful additional data had become available. In 1986, when the occurrence of gastrointestinal neoplasms in mice was considered to be the result of "swamping" of the gut and the passage of large amounts of an irritant through the small bowel, a temporary ADI of 0-0.01 mg/kg bw was allocated. This temporary ADI was confirmed by the 1990 JMPR, pending the results of further investigations of the relevance of the metabolism in animals for humans, further studies to elucidate the mechanism of the induction of gastrointestinal tract tumours in mice, and studies designed to establish an NOAEL in mice. In 1993, new data from a study of carcinogenicity in mice designed to elucidate the mechanism of tumour induction were reviewed. Relevant further studies were known to be in progress, so the temporary ADI of 0-0.01 mg/kg bw was extended to 1995.

The present Meeting reviewed additional information on effects on enzymes, acute toxicity, long-term toxicity and carcinogenicity, and delayed cutaneous hypersensitivity.

Excretion of orally administered folpet by mice and rats is about 45-55% in urine, 30-40% in expired air and 11-17% in faeces; very little biliary excretion occurs, particularly in mice.

Important degradation pathways of folpet in rodents result in the formation of phthalimide and thiophosgene. The latter is detoxified, at least in part, by three mechanisms: oxidation and/or hydrolysis to carbon dioxide; reaction with the cysteine moiety of glutathione to yield thiazolidine-2-thione-4-carboxylic acid; and reaction with sulfite to produce dithiobis(methanesulfonic acid).

A study in which rats were exposed by acute inhalation indicated an LC_{50} of 0.39 (male) to 0.43 (female) mg/litre. The WHO has classified folpet as unlikely to present an acute hazard in normal use.

A two-year study of carcinogenicity in mice with dietary concentrations of 0, 1000, 5000, or 10,000 ppm showed a dose-related increase in the incidence of atypical duodenal hyperplasia, adenomas and adenocarcinomas, leading to partial obstruction of the duodenal lumen in animals of both sexes. A no-effect level was not observed. In another two-year study of carcinogenicity, mice were given dietary concentrations of 0, 150, 450, or 1350 ppm. A treatment-related decrease in male body weight gain was seen. There was a higher incidence of duodenal masses and thickening of the stomach wall in females and reduced liver weight in males at 1350 ppm. Microscopic changes at 1350 ppm and to a minor degree at 450 ppm included benign papillomas in the keratinized region of the stomach, benign adenomas in the duodenal mucosa, villous hyperplasia in the duodenal and jejunal mucosa, and hyperplasia of the lamina propria of the duodenum. Administration of folpet in the diet at a concentration of 1350 ppm induced tumours in the upper parts of the gastrointestinal tract (non-glandular stomach and duodenum) of mice of both sexes. The NOAEL was 150 ppm, equal to 16 mg/kg bw per day.

Folpet has been adequately tested for genotoxicity in a range of assays, which demonstrate that it is mutagenic and clastogenic *in vitro* but not *in vivo*. The *in-vitro* responses were reduced or abolished by the presence of liver homogenates, serum, glutathione, or cysteine whenever these experimental modifications have been investigated. The Meeting concluded that folpet does not present a significant genotoxic risk, owing to the presence of an efficient detoxification mechanism *in vivo*.

Oral administration of folpet causes time-dependent changes in the glutathione content and glutathione *S*-transferase activities of different regions of the gastrointestinal tract of mice and rats, with consequent effects on the detoxification of folpet. As early as three to four weeks after initiation of treatment with a tumour-inducing dose of folpet, both protein and non-protein thiol concentrations are increased throughout the duodenum of mice. Reaction with protein thiol is important for toxicity, while reaction with glutathione is important for detoxification. At the same time, some hyperplasia and hypertrophy were observed and the concentration of cyclin-dependent kinase was increased, but only in the proximal half of the duodenum, a result supported by assaying for proliferating cell nuclear antigen. These data indicate that sustained proliferative stimulation of the proximal duodenum is a consequence of oral folpet administration. The Meeting concluded that this finding describes an important element in the process by which folpet, which is not genotoxic *in vivo*, induces tumours in the mouse gastrointestinal tract.

A maximization test indicated that folpet is a sensitizer and irritant in guinea-pig skin.

An ADI of 0-0.1 mg/kg bw was allocated on the basis of the NOAEL of 10 mg/kg bw per day in the two-year study of toxicity and carcinogenicity in rats, the one-year study of toxicity in dogs and studies of reproductive toxicity in rats and rabbits, and a safety factor of 100.

A toxicological monograph was prepared, summarizing the data that were reviewed by the present Meeting and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 150 ppm, equal to 16 mg/kg bw per day (104-week study of toxicity and carcinogenicity)

Rat: 190 ppm, equivalent to 10 mg/kg bw per day (104-week study of toxicity and carcinogenicity)

800 ppm, equivalent to 40 mg/kg bw per day (two-generation study of reproductive toxicity)

10 mg/kg bw per day (maternal toxicity of developmental toxicity)

Rabbit: 10 mg/kg bw per day (maternal and fetotoxicity in study of developmental toxicity)

Dog: 10 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to folpet

Exposure	Relevant route, study type, species	Results, Remarks
Short-term (1-7 days)	Skin, sensitization, guinea-pig	Sensitizer and irritant in maximization test
	Oral, toxicity, rat	LD_{50} >5000 mg/kg bw
	Inhalation, 4-h lethality, rat	LC_{50} = 0.4 mg/litre
	Dermal, toxicity, rabbit	LD_{50} >23 000 mg/kg bw
Medium-term (1-26 weeks)	Repeated oral, 13-week toxicity, rat	NOAEL = 300 mg/kg bw per day based on reduced body weight, irritation of proximal gastrointestinal tract, and other effects
	Repeated oral, reproductive toxicity, rat	NOAEL = 40 mg/kg bw per day based on reduced body weight
	Oral, developmental toxicity, rabbit	NOAEL = 10 mg/kg bw per day based on reduced body weight and food consumption; no fetotoxicity or teratogenic effect
Long-term (≥ one year)	Repeated oral, one year, toxicity, dog	NOAEL = 10 mg/kg bw per day based on reduced body weight and food consumption and serum biochemical changes

4.21 HALOXYFOP (193)

(*RS*)-2-[4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid

Haloxyfop is a substituted phenoxypropionic acid derivative which has been developed as a selective herbicide for the control of grass weeds in broad-leaf crops. In the first formulations produced, the active substance was either racemic haloxyfop ethoxyethyl ester or the racemic methyl ester. When applied to plants, the ester is rapidly hydrolysed to the acid which has herbicidal activity. As it has been demonstrated that the (*R*)- isomer of haloxyfop is the herbicidally active compound, with essentially no activity associated with the (*S*)- isomer, a resolved methyl ester has been developed which is approximately 98% (*R*)- isomer.

Haloxyfop was evaluated for the first time by the present Meeting.

TOXICOLOGY

After oral administration of the racemic mixture to rats, 98% of the parent compound was in the form of the (*R*)- isomer, indicating rapid conversion of the (*S*)- enantiomer *in vivo*.

Various studies on the fate of haloxyfop (acid) and its esters have been conducted in mice, rats, dogs, monkeys and humans. Haloxyfop is rapidly absorbed and eliminated primarily as the unchanged parent compound after oral administration. A marked sex difference in the excretion pattern was noted in rats, the principal route of excretion being the faeces in males and the urine in females. The major route of elimination was also faecal in mice and dogs (only males studied), whereas in monkeys (only males studied) the main elimination route was the urine. The plasma elimination half-lives were lowest in female rats (one day) and longest in male rats (six days). Comparative pharmacokinetic investigations with haloxyfop (acid) and its esters in rats showed very similar patterns of absorption and excretion. The esters were rapidly converted to the parent acid. Pharmacokinetic studies in men after oral administration revealed rapid absorption. The plasma elimination half-life was about six days. Urine was the main excretory route. Dermal absorption was estimated to be about 3% of an applied dose.

After a single oral dose to rats haloxyfop and its esters showed similar, moderate toxicity. The LD_{50} was about 300 mg/kg bw for the acid and its methyl ester and about 500 mg/kg bw for the ethoxyethyl ester. The WHO has classified haloxyfop as ‘moderately hazardous’.

Two short-term studies were conducted in mice. In one study the diet provided dose levels of 0, 0.002, 0.02, 0.2 or 2 mg/kg bw haloxyfop per day over 13 weeks; in the other study the dose levels were 0, 0.02, or 2 mg/kg bw per day over 36 weeks. At 2 mg/kg bw per day in both studies effects in the liver consisted of increases in serum alkaline phosphatase activity (in males), increased liver weights, hepatocellular enlargement, and increased eosinophilia. In addition, in the 36-week study, the kidneys of high-dose males showed a decrease in cytoplasmic vacuolation. The NOAELs were 0.2 mg/kg bw per day in the 13-week study and 0.02 mg/kg in the 36-week study.

Two short-term dietary studies were conducted in rats. In the 16-week and 37-week studies the dose levels were 0, 0.002, 0.02, 0.2 or 2 mg/kg bw per day and 0, 0.02 or 2 mg/kg bw per day respectively. At 2 mg/kg bw per day in both studies, changes including an increase in serum alkaline phosphatase activity, liver enlargement, an increase in liver weight, a slight decrease in testicular weights, and histopathological changes in the liver (hepatocellular enlargement and increased cytoplasmic homogeneity) were observed. In male rats, treatment-related effects on the liver were observed at 0.2 mg/kg bw per day in the 16-week study. The NOAEL was therefore 0.02 mg/kg bw per day in both studies.

In a 13-week study in dogs, doses of 0, 2, 5, or 20 mg haloxyfop/kg bw per day haloxyfop were given in the diet. At 5 mg/kg bw per day and above, changes in biochemical parameters (reduced thyroid hormone levels, decreased cholesterol concentration), decreased thyroid and parathyroid weights and histopathological changes in the liver (hepatocellular enlargement) and thyroid gland (decrease in follicular size, hypertrophy of follicular epithelial cells) were observed. At 20 mg/kg bw per day decreased body weight gain, reductions in various haematological parameters and increases in liver and kidney weights were found. The NOAEL was 2 mg/kg bw per day.

In a 12-month dietary study in dogs at dose levels of 0, 0.05, 0.5 or 5 mg/kg bw haloxyfop per day, a decrease of the serum cholesterol concentration was found in both sexes at 5 mg/kg bw per

day. The NOAEL was 0.5 mg/kg bw per day.

In a 13-week study in monkeys at dose levels of 0, 2, 10 or 30 mg/kg bw haloxyfop per day, oral administration of 30 mg/kg bw per day resulted in a decrease of the cholesterol concentration, an increase of liver and kidney weights, a decrease of thyroid weights, hepatocellular hypertrophy, increased content of cytoplasmic lipid and in females a decrease in the size of the thyroid follicles and hypertrophy of the follicular epithelial cells. At 10 mg/kg increased kidney weights and slight hepatocellular enlargement were observed. The NOAEL was 2 mg/kg bw per day.

A two-year dietary study of carcinogenicity in mice at dose levels of 0, 0.03, 0.065 or 0.6 mg/kg bw haloxyfop per day revealed a dose-dependent increase in the incidence of hepatocellular tumours at 0.065 and 0.6 mg/kg bw per day in both sexes. Statistically significant increases in the incidence of adenomas in males and carcinomas in females were observed at 0.6 mg/kg bw per day. Other histopathological effects on the liver including altered cytoplasmic staining properties of centrilobular hepatocytes and a decrease in cytoplasmic vacuolization were observed at 0.6 mg/kg bw per day. The NOAEL was 0.03 mg/kg bw per day on the basis of an increased incidence of liver tumours at higher doses.

In a two-year study of carcinogenicity, rats were given diets providing doses of 0, 0.01, 0.03, 0.065, or 0.1 mg/kg bw per day for males and 0, 0.001, 0.03, 0.065, or 1 mg/kg bw per day for females. Treatment-related effects on the liver at 0.1 mg/kg bw per day and above included transient organ weight increases, hepatocellular enlargement and increased eosinophilia. There was no evidence of carcinogenic potential. The NOAEL was 0.065 mg/kg bw per day.

In a study of developmental toxicity in rats at oral dose levels of 0, 0.1, 1 or 7.5 mg/kg bw haloxyfop (sodium salt) per day, maternal toxicity was observed at 7.5 mg/kg bw per day as evidenced by reduced body weight gain and reduced food consumption. In the fetus, ossification was delayed at 7.5 mg/kg bw per day. No evidence for teratogenicity was observed. The NOAEL for maternal toxicity and embryotoxicity was 1 mg/kg bw per day.

In two studies of developmental toxicity in rabbits at doses of 0, 1, 7.5 or 20 mg/kg bw per day and 0, 3, 7.5 or 15 mg/kg bw per day, maternal toxicity (maternal deaths) occurred at 15 mg/kg bw per day and above. Embryotoxicity was seen at 20 mg/kg bw per day, as indicated by an increased incidence of resorptions. The results gave no evidence of teratogenic potential. The NOAEL was 7.5 mg/kg bw per day for maternal toxicity and 15 mg/kg bw per day for embryotoxicity.

In a two-generation study, rats were treated with diets providing dose levels of 0, 0.01, 0.065 or 1 mg/kg bw haloxyfop per day. Reduction in body weight gains were observed in weanlings of the F_1 and F_2 generation at 1 mg/kg bw per day. Reproduction was not affected by the treatment. The NOAEL in this study was 1 mg/kg bw per day for reproduction and 0.065 mg/kg bw per day for body weight changes in neonates.

Haloxyfop has been adequately tested for genotoxicity in a range of tests *in vivo* and *in vitro*. The Meeting concluded that it is not genotoxic.

In order to study the mechanism of hepatocarcinogenesis in mice, several short-term studies were conducted to investigate the effect of haloxyfop on hepatocellular peroxisomes. Peroxisome induction was evidenced by histopathological and electron microscopical changes and increased activities of enzymes involved in the ß-oxidation of fatty acids and hepatic carnitine acetyl transferase in mice at a dose of 1 mg/kg bw per day and in rats at 0.5 mg/kg bw per day. The increase in liver

tumour incidence observed at 0.065 mg/kg bw per day in the long-term study of carcinogenicity in mice indicates that peroxisome proliferation is not an important part of the mechanism by which this non-genotoxic compound is carcinogenic.

An ADI of 0-0.0003 mg/kg bw was established on the basis of the NOAEL of 0.03 mg/kg bw per day in the two 2-year studies in mice, using a safety factor of 100.

A toxicological monograph was prepared, summarizing the data that were reviewed at the present Meeting.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 0.03 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 0.065 mg/kg bw per day (two-year study of toxicity and carcinogenicity and study of reproductive toxicity)
1 mg/kg bw per day (maternal, embryo- and fetotoxicity in study of developmental toxicity)

Rabbit: 7.5 mg/kg bw per day (maternal toxicity, in study of developmental toxicity)

Dog: 0.5 mg/kg bw per day (12-month study of toxicity)

Monkey: 2 mg/kg bw per day (13-week study of toxicity)

Estimate of acceptable daily intake for humans

0-0.0003 mg/kg bw

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to haloxyfop

Exposure	Route, study type, species	Result, Remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Irritating
	Eye, irritation, rabbit	Irritating
	Skin, sensitization, guinea-pig (Buehler and Magnusson/Kligman)	No sensitization
	Oral, toxicity, rat	LD_{50} = 340 - 550 mg/kg bw per day
	Dermal, toxicity, rat, rabbit	LD_{50} >2000 mg/kg bw per day
Medium-term (1-26 weeks)	Repeated dietary, one month, dog	NOAEL = 5 mg/kg bw per day, reduced body weight gain, reduced cholesterol and increased liver and kidney weights
	Repeat dietary, 16 weeks, rat	NOAEL = 0.02 mg/kg bw per day, increase in liver weights and histopathological changes in liver
	Oral, developmental toxicity, rat	NOAEL = 1 mg/kg bw per day, reduction of maternal body weight gain, delayed ossification
	Dietary, reproductive toxicity, rat	NOAEL = 0.065 mg/kg bw per day, reduced neonatal body weight gain
Long-term (≥ one year)	Repeat dietary, two years, toxicity and carcinogenicity, mouse	NOAEL = 0.03 mg/kg bw per day; increased incidence of liver tumours

RESIDUE AND ANALYTICAL ASPECTS

Supervised trials were carried out on a wide range of crops with methyl, ethoxyethyl and butyl esters of haloxyfop or haloxyfop-R (the resolved (*R*)-isomer), but the results can be evaluated on the basis of the acid because the esters are rapidly hydrolysed in plants, animals and soils, and the (*S*)-isomer is rapidly converted to the (*R*)-isomer in animals and soils.

Metabolic studies on several species of animals and plants show that the major residues are haloxyfop and its conjugation products; the conjugates are easily hydrolysed to yield haloxyfop under mild alkaline conditions. The residue analytical method used in all the trials included the hydrolysis process.

The fate of haloxyfop was studied in four soils under aerobic conditions. The soils were treated at a rate equivalent to 104 g/ha haloxyfop. The methyl ester of haloxyfop-R was degraded rapidly in all soils. One day after application only 1.3-5.0% of the applied radioactivity (AR) was present as the ester. Haloxyfop (acid) was degraded to 4-[(3-chloro-5-trifluoromethyl)-2-pyridinyloxy]phenol (referred to as the phenol), which further decomposed to 3-chloro-5-trifluoromethylpyridin-2-ol (referred to as the pyridinol). The phenol and pyridinol reached maximum

concentrations of 7-12.6% and 35.5-52.4% of the AR between 3 and 14 days and about 90 days after treatment, respectively. Three unidentified metabolites were detected. One accounted for 2.0-9.3% of the AR at 182 days after treatment; the other two were below 1%. The evolved CO_2 amounted to 6.5-24% of the AR by day 182. The level of unextractable residues increased continuously and ranged between 23.3 and 34.7% of the AR on day 182. The half-lives of haloxyfop ranged from 9 to 20 days. Under anaerobic conditions the methyl ester was rapidly degraded to haloxyfop which remained stable during the following 300 days.

The behaviour of the residues was studied in lysimeters under field conditions. Sugar beet was sown in the soils, which were treated at rates of 112 and 212 g/ha haloxyfop equivalents. The leachate contained 0.29-0.71% of the AR. No methyl ester, haloxyfop or pyridinol could be detected in the leachate. The radioactivity in the leachate consisted of an unknown compound at 0.03-0.15 ìg haloxyfop equivalent/l. Most of the soil residues remained in the top 30 cm. No haloxyfop could be detected (<0.00009 mg/kg), while the pyridinol was present at concentrations of 0.00027-0.0019 mg/kg.

The total radioactivity in the edible parts of the plants at harvest amounted to 0.01-1.0% of the AR, equivalent to 0.004-0.013 mg/kg haloxyfop.

In water/sediment systems under aerobic conditions haloxyfop ethoxyethyl ester was steadily converted to the pyridinol which reached its maximum concentration within 2-4 weeks.

The residue analytical procedure consists in extraction and hydrolysis of the ester or conjugate of haloxyfop with alkaline methanol, acid organic-phase partitioning, alkaline extraction, a second acid organic partitioning, and conversion to the methyl or butyl ester. Further clean-up of the sample is achieved on a Florisil column before quantification by gas chromatography with electron-capture detection.

The Meeting agreed to define the residue as the sum of haloxyfop esters, haloxyfop and its conjugates, expressed as haloxyfop.

The residue data from supervised trials were evaluated as follows.

Fruits

Orchard crops

Haloxyfop is used in orchards to control grass weeds. Since the application is directed at the weeds growing at the base of the trees, residues in fruits will only be caused by drift contamination or translocation after the uptake of soil residues by the roots. The Meeting therefore concluded that orchard crops should be evaluated as a single group.

Citrus fruits. Supervised trials were carried out on oranges in Brazil and Italy and lemons and grapefruit in New Zealand, with application rates of 0.21-1.9 kg ai/ha of racemic haloxyfop or 0.16-0.42 kg ai/ha of haloxyfop-R with PHIs of 28-206 days.

Information on GAP was not available from these countries, but was submitted from Argentina, Bolivia, Paraguay and Peru for citrus (racemic haloxyfop: post weed emergence at 2-4 leaves stage with an application rate of 0.06-0.3 kg ai/ha) and from Australia, Czech Republic, Poland and Slovakia for orchards (racemic haloxyfop up to early weed tillering at 0.21-0.83 kg ai/ha;

haloxyfop-R up to early weed tillering or closing canopy at 0.052-0.21 kg ai/ha).

The residues were <0.02, <0.03 and <0.1 mg/kg.

Pome fruits. Two Italian and one New Zealand residue trials on apples were carried out with application rates of 0.1-0.42 kg ai/ha at PHIs of 29-132 days with racemic haloxyfop. Information on GAP was submitted from Australia for orchards (up to early weed tillering at 0.21-0.83 kg ai/ha) and from Argentina, Bolivia, Paraguay and South Africa for pome fruit (post weed emergence at 2-4 leaves stage at 0.06-0.31 kg ai/ha).

The residues were <0.02 mg/kg and <0.01 mg/kg from the trials in Italy and New Zealand respectively.

Grapes. Six supervised trials were carried out in Australia and France with racemic haloxyfop according to GAP (Australia: orchard, up to early weed tillering at 0.21-0.83 kg ai/ha; France: up to early weed tillering at 0.16-0.62 kg ai/ha).

The residues were <0.01-0.03 mg/kg.

Three supervised trials were carried out in Italy with haloxyfop-R at 0.21 kg ai/ha. There was no information on GAP. The residues were <0.05 mg/kg.

Bananas. Two supervised trials were carried out in Australia, one with racemic haloxyfop and one with haloxyfop-R under approved use conditions (orchard, up to early weed tillering with application rates of 0.21-0.83 kg ai/ha of racemic haloxyfop and 0.1-0.21 kg ai/ha of haloxyfop-R). The residues were <0.05 mg/kg in both cases.

The meeting estimated a maximum residue level of 0.05* mg/kg for citrus fruits, pome fruits, grapes and banana.

Vegetables

Garlic, onion, cabbage, Brussels sprouts, cauliflower, melon, tomato, fennel, lettuce, spinach, carrot, globe artichoke and asparagus. There were too few trials or insufficient information on GAP to estimate maximum residue levels.

Beans and peas. Data on beans and peas (legume vegetables and their fodders) were received by the Meeting but the exact Codex commodities to which the data applied were not clear. The Meeting agreed not to estimate maximum residue levels until the commodity descriptions were clarified (the report of the 1991 JMPR, Section 2.7, explains the need for descriptions of commodities according to the *Codex Classification of Foods and Animal Feeds*).

Pulses (dry). Haloxyfop is registered for several varieties of pulses. The Meeting concluded that the supervised trials on pulses could be evaluated together because of the similarities in the use patterns and residue behaviour.

Broad bean (dry). Two supervised trials were carried out in Australia with racemic haloxyfop. The trial conditions (PHI 103-171 days with application rates of 0.078-0.21 kg ai/ha) were slightly different from GAP in Australia (PHI 147 days with application rates of 0.052-0.1 kg ai/ha) for Faba beans, but the data could be evaluated because the residues were negligible.

One supervised trial was carried out in France with racemic haloxyfop. Information on French GAP was not submitted to the Meeting, but the trial conditions (PHI 46 days with application rate of 0.21 kg ai/ha) were comparable to Spanish GAP (legumes, post weed emergence at 2-4 leaves with application at 0.1-0.21 kg ai/ha). Residue data from Greece could not be related to any available GAP because the application was made at a late growth stage. The residues were <0.05 mg/kg and 0.03 mg/kg in the Australian and French trials respectively.

Chick-pea (dry). Three supervised trials in Australia reflected GAP (PHI 98 days with application rates of 0.052-0.1 kg ai/ha). The residues were 0.03-0.04 mg/kg after 78-99 days.

Common bean (dry). Two supervised trials were carried out in Australia in 1986 and 1989 with racemic haloxyfop. The maximum residue was 0.03 mg/kg from GAP application timed according to the growth stage.

Two supervised trials were carried out with racemic haloxyfop in Brazil and one in the UK, but no information on relevant GAP was available.

One supervised trial was carried out in Germany with haloxyfop-R and one in the UK in 1989-1991 but information on GAP was not submitted.

In general residues seem to depend on the growth stage of the crop rather than on the PHI. The residues were 0.03 mg/kg and <0.05 mg/kg for applications at an early growth stage and 0.2-0.41 mg/kg for applications at early budding or the end of flowering. However, in practice application at early budding or the end of flowering is not GAP.

Field pea (dry). Four supervised trials were carried out with racemic haloxyfop in Australia and two of them were according to GAP (PHI 91 days with application at 0.052-0.16 kg ai/ha). Six supervised trials were carried out in France at application rates of 0.1-0.21 kg ai/ha of racemic haloxyfop but information on GAP was not submitted. However the trial conditions were comparable to Spanish GAP (legumes, post weed emergence at 2-4 leaves stage with application rates of 0.1-0.21 kg ai/ha).

The residues were <0.01 mg/kg and <0.02-0.14 mg/kg in the Australian and French trials respectively.

Two supervised trials in Australia with haloxyfop-R were according to GAP (PHI 91 days, application rate 0.04-0.078 kg ai/ha). Six supervised trials were carried out in France and four in Germany with application rates of 0.052-0.1 kg ai/ha of haloxyfop-R. No information on GAP was available from these countries, but the trial conditions were comparable to GAP in East European countries (peas, up to closing of canopy or PHI of 60 days with application rates of 0.052-0.156 kg ai/ha). The residues were <0.01 mg/kg, <0.02-0.10 mg/kg and <0.02-0.03 mg/kg in the Australian, French and German trials respectively.

Lupin (dry). Ten supervised trials were conducted in Australia with racemic haloxyfop. The residues from three trials with application rates of 0.12-0.16 kg ai/ha and PHIs of 99-115 days, conditions close to Australian GAP (0.052-0.1 kg ai/ha with a PHI of 119 days), were <0.05, 0.03, and 0.04 mg/kg.

Only one supervised trial was conducted with haloxyfop-R in Australia in accordance with Australian GAP (PHI 119 days with application at 0.04-0.052 kg ai/ha). The residue at 92 days from

an application rate of 0.052 kg ai/ha was 0.05 mg/kg.

Pigeon pea (dry). Data from two supervised trials were submitted to the Meeting, but without information on GAP.

Soya bean (dry). Four supervised trials in Australia with racemic haloxyfop were according to GAP (PHI 119 days with application rate of 0.1-0.16 kg ai/ha). Eleven supervised trials were carried out in Brazil with racemic haloxyfop and five of them accorded with GAP (PHI 98 days with application rate of 0.096-0.12 kg ai/ha). The residues from 18 US supervised trials were <0.05-0.22 mg/kg for pre-bloom and <0.05-3.08 mg/kg for in-bloom applications, but information on US GAP was not submitted.

The residues from the trials in Australia and Brazil which were in accordance with GAP were <0.03 mg/kg and <0.05-0.07 mg/kg.

Four and six supervised trials were carried out with haloxyfop-R in France and Italy respectively. The residues in the ten trials from applications according to French GAP were <0.02-0.09 mg/kg.

On the basis of the combined residue data, the meeting estimated a maximum residue level of 0.2 mg/kg for dry pulses.

Potato. Twenty-one supervised trials were carried out in Belgium, Germany, The Netherlands, Norway, Sweden and the UK with racemic haloxyfop. Information on GAP was not submitted for these countries but the trial conditions could be compared with Irish GAP (up to 60 cm height of crop with an application rate of 0.21 kg ai/ha).

Twelve supervised trials were carried out in Germany with haloxyfop-R. The application rate (0.1 kg ai/ha) was lower than the approved rates in East European countries (0.13-0.21 kg ai/ha). The residues were <0.01-0.1 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg.

Sugar beet (roots). The Meeting concluded that supervised trials on sugar beet and fodder beet could be evaluated together because the use pattern of haloxyfop on these crops is the same and the residue behaviour is expected to be similar.

Twelve of 14 supervised trials carried out in France with racemic haloxyfop were according to GAP (up to early weed tillering with application at 0.1-0.21 kg ai/ha).

Eight supervised trials were carried out in Germany with racemic haloxyfop according to GAP (PHI 90 days with application rate of 0.16-0.21 kg ai/ha).

Fourteen supervised trials were carried out in the UK at application rates of 0.1-0.83 kg ai/ha with racemic haloxyfop. Information on GAP was not submitted, but the treatments were comparable to French GAP (up to early weed tillering with application rates of 0.1-0.21 kg ai/ha).

The residues were <0.02-0.1 mg/kg (application at 0.21 kg ai/ha at 2-8 leaves stage), <0.005-0.16 mg/kg (application at 0.21 kg ai/ha at PHI of 76-108 days) and <0.01-0.23 mg/kg (application rate of 0.21 kg ai/ha at 2-10 leaves stage) from the French, German and UK trials respectively.

Eight supervised trials were carried out in France, Germany and Italy with haloxyfop-R. No information on GAP in Germany or Italy was available, but the trial conditions were comparable to French GAP (up to early weed tillering with the application rates of 0.052-0.1 kg ai/ha).

The residues were <0.02-0.06 mg/kg from application at 0.1 kg ai/ha at the 2-9 leaves stage.

The Meeting estimated a maximum residue level of 0.3 mg/kg.

Cereal grains

Rice. Nine supervised trials were carried out in Brazil, Colombia, Mexico and Costa Rica under conditions comparable to GAP in Argentina, Ecuador and Uruguay with application rates of 0.09-0.11 kg ai/ha at early post-planting (after weed emergence and at 2-4 leaves stage). The residues were <0.01 mg/kg in both husked rice and polished rice following applications at rates of 0.03-0.24 kg ai/ha with PHIs of 98-140 days.

The Meeting noted that the residues of haloxyfop in husked rice and polished rice were below 0.01 mg/kg, but concluded that a maximum residue level of 0.02* mg/kg was a more appropriate estimate for both commodities.

Oilseed

Cotton seed. Four supervised trials were carried out in Australia with racemic haloxyfop according to GAP (PHI 119 days, application rate 0.1-0.16 kg ai/ha) and four trials in Brazil with racemic haloxyfop approximated GAP in Paraguay (post weed emergence at 2-4 leaves stage with and application rate of 0.072-0.18 kg ai/ha).

A single supervised trial was carried out in Spain with haloxyfop-R, but only GAP for racemic haloxyfop was submitted to the Meeting.

The residues from the trials with racemic haloxyfop were <0.05-0.2 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg for cotton seed.

Peanuts. Six supervised trials were carried out in Argentina and Australia with racemic haloxyfop according to GAP. The residues were <0.03, <0.05 and 0.03 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg for peanut.

Rape seed. Two supervised trials were carried out in Australia with racemic haloxyfop. The residues were <0.03-0.07 mg/kg at an application rate (0.16 kg ai/ha) slightly higher than Australian GAP (application rate 0.052-0.1 kg ai/ha, PHI 119 days).

Eight and five supervised trials were carried out with racemic haloxyfop in France in autumn and spring (February or March) respectively according to French GAP. The residues were <0.05-0.09 mg/kg from the autumn and <0.05-0.66 mg/kg from the spring application, at the approved application rate of 0.21 kg ai/ha.

Spanish GAP allows a higher application rate of 0.42 kg ai/ha at post weed emergence at the

2-4 leaves stage. The residues from trials carried out in France which corresponded to Spanish GAP were <0.05-1.68 mg/kg.

Seven and five supervised trials were carried out in Germany with racemic haloxyfop in autumn and spring (March and April) respectively according to German GAP (application rate 0.21 kg ai/ha). The residues were <0.05-0.13 mg/kg and 0.1-0.77 mg/kg at approved or slightly lower application rates (0.16-0.21 kg ai/ha) from the autumn and spring applications respectively.

Twenty and five supervised trials were carried out in the UK in the autumn and spring respectively, but information on GAP was not submitted. The residues were <0.05 mg/kg for autumn and 0.06-0.64 mg/kg for spring (up to March) at the rate of 0.21 kg ai/ha approved in France and Germany.

Five supervised trials in Norway and Sweden showed residues higher than those in other countries, but no information on GAP was available.

Five supervised trials were carried out in France and Germany with haloxyfop-R in the autumn. The residues were <0.05-0.07 mg/kg at the application rate approved in France.

The Meeting estimated a maximum residue level of 2 mg/kg for rape seed.

Sunflower seed. Nine supervised trials were carried out in Argentina, Australia and France according to GAP. The residues were <0.03-0.16 mg/kg and 0.07 mg/kg for racemic haloxyfop and haloxyfop-R respectively. The Meeting estimated a maximum residue level of 0.2 mg/kg.

Animal feed

Alfalfa. Four supervised trials were carried out in Australia in 1984, 1988 and 1989. Two of them were almost in conformity with GAP (PHI 21 days, application rate 0.052-0.16 kg ai/ha) with a slightly higher application rate.

The residues were 2.45-3.7 mg/kg for racemic haloxyfop and 1.8-2.2 mg/kg for haloxyfop-R. The Meeting estimated a maximum residue level of 5 mg/kg.

Fodder beet, Sugar beet leaves or tops. The Meeting evaluated the data for sugar beet and fodder beet together since both crops and use patterns are similar.

The residues in normally treated and harvested sugar beet leaves or tops were <0.01-0.3 mg/kg (21 trials) and <0.02-0.14 mg/kg (four trials) for racemic haloxyfop and haloxyfop-R respectively.

Five supervised trials were carried out on fodder beet in Germany at 1982 and 1983 according to GAP (PHI 90 days, application rate 0.21 kg ai/ha). The residues were <0.02-0.05 mg/kg in tops and <0.01-0.03 mg/kg in roots at PHIs of 78-106 days.

The Meeting estimated a maximum residue level of 0.3 mg/kg for sugar beet leaves or tops, fodder beet tops and fodder beet roots.

Peanut fodder. The residue in the fodder from a normally treated and harvested crop was 0.03 mg/kg (one result).

The Meeting concluded that a single result was not sufficient to estimate a maximum residue level.

Rape fodder. Residues in rape fodder treated according to GAP and harvested at maturity were <0.05-0.12 mg/kg.

Pasture. Four supervised trials with racemic haloxyfop and two with haloxyfop-R were carried out in Australia in 1988 and 1989 according to GAP.

The residues were 0.49-3.35 mg/kg from racemic haloxyfop and 0.99-1.47 mg/kg from haloxyfop-R.

Processing studies

Sugar beet. No residues of haloxyfop (<0.01 mg/kg) were found in sugar derived from sugar beet containing 0.07-0.11 mg/kg.

Soya beans. Concentration factors were 0.37-1.25 for crude oil and 0.22-1.2 for refined oil. The Meeting estimated maximum residue levels for both crude and refined soya bean oil of 0.2 mg/kg, the same level as soya bean (dry).

Rice. The residues in rice bran processed from normally treated and harvested rice were <0.02 mg/kg.

The Meeting estimated a maximum residue level of 0.02* mg/kg for rice bran, unprocessed.

Cotton seed. When cotton seed containing residues in the range 0.06-0.1 mg/kg was processed to oil the concentration factors varied from 0.88 to 1.6.

The Meeting estimated a maximum residue level of 0.5 mg/kg for crude cotton seed oil.

Sunflower seed. Three processing studies were carried out, but two of them were with seed containing residues below the LOD. The concentration factors found in the third study were 1.8 and 2.2 for crude and refined oil respectively. The processing data were insufficient to estimate a maximum residue level for sunflower seed oil.

Rape seed. Six processing studies were carried out, two with seeds containing residues below the limit of determination. The mean concentration factors from the other four studies were 1.7 for crude and 2.1 for refined oil. The Meeting estimated a maximum residue level of 5 mg/kg for both crude and refined oil.

Animal feeding studies

Cattle. Fodder beet, alfalfa, pasture, sugar beet tops, pulses, rape fodder and processed fractions of oil seed can be used as feed for beef and dairy cattle. The maximum residues found in these items from treatments according to GAP were 2.45-3.71 mg/kg in alfalfa and 0.49-3.35 mg/kg in pasture. The estimated intake of haloxyfop from these sources was comparable to that in 28-day dietary intake studies conducted with beef calves and lactating cows at 5 ppm and 2.5 ppm feeding levels respectively.

In these studies the residues were 0.01 mg/kg in beef muscle, 0.14-0.15 mg/kg in beef liver, 0.35-0.51 in beef kidney, 0.06-0.09 in beef fat, 0.03-0.04 mg/kg in milk and 0.38-0.43 mg/kg in cream.

The Meeting estimated maximum residue levels of 0.01 mg/kg for cattle meat, 0.5 mg/kg for edible offal of cattle, 0.1 mg/kg for cattle fat, and 0.05 mg/kg for cattle milk.

Poultry. Pulses and oil seeds can be used as poultry feed. The maximum proportion pulses and oil seed meal in the diet was assumed to be 30% and 20% respectively. Rape seed meal is not thought to be a poultry feed item. On the basis of these assumptions and the levels residue levels estimated for poultry feed items the Meeting concluded that the intake of haloxyfop by poultry would not exceed 0.1 ppm in the diet. The lowest feeding level (0.25 ppm) in the poultry feeding study was used to estimate the maximum levels in poultry. The residues found were <0.01 mg/kg in muscle, 0.01-0.09 mg/kg in liver, <0.01-0.03 mg/kg in fat and <0.01 mg/kg in eggs.

The Meeting estimated maximum residue levels of 0.01* mg/kg for chicken meat, 0.1 mg/kg for edible offal of chicken and 0.01* mg/kg for chicken eggs.

The Meeting was unable to complete the evaluation of the ruminant and poultry metabolism studies provided in the time available. The studies will therefore be evaluated by the 1996 JMPR. The residue data have been reviewed on the assumption that metabolism in ruminants and poultry is essentially the same as indicated in the metabolism studies provided for rats, mice, dogs, monkeys and humans.

Information is needed on the uptake by crops of haloxyfop and its soil degradation products or metabolites from soil.

Because of the lack of critical supporting data on the uptake of the soil degradation products by crops the Meeting concluded that the estimated maximum residue levels could not be recommended as MRLs. The maximum residue levels estimated are recorded in the evaluation.

FURTHER WORK OR INFORMATION

Desirable

1. Sugar beet processing data with specific regard to the concentration of haloxyfop residues in processing to molasses.

2. Sunflower seed processing data with specific regard to the concentration of haloxyfop residues in the oil.

3. Data on residues in peanut fodder resulting from supervised trials.

4.22 IPRODIONE (111)

TOXICOLOGY

Iprodione, a dicarboximide fungicide, was previously evaluated toxicologically by the JMPR in 1977

and 1992. An ADI of 0-0.2 mg/kg bw was allocated in 1992. Since that time, long-term carcinogenicity studies in rats and mice that included higher doses and supplemental studies of the possible mechanism of tumorigenicity have become available and were evaluated by the present Meeting.

In a study of carcinogenicity in mice, iprodione was administered over 99 weeks at dietary concentrations at 0, 160, 800, or 4000 ppm. At 800 ppm, non-neoplastic lesions were seen that included hepatocellular enlargement and hypertrophy of interstitial cells in the testis. At 4000 ppm, reduced body weight gain, increased liver weights and increased levels of alanine and aspartate transaminases were observed. An increased incidence of liver tumours in animals of both sexes and an increased incidence of luteomas of the ovaries were observed at 4000 ppm. The NOAEL was 160 ppm, equal to 23 mg/kg bw per day.

In a 104-week study of carcinogenicity in rats, the dietary concentrations were 0, 150, 300, or 1600 ppm of iprodione. At 300 ppm, increased liver weights and changes in the male reproductive system, including an increased incidence of interstitial-cell hyperplasia in the testis and hypertrophic changes in the adrenals of male rats, were observed. At 1600 ppm, reduced body weight gain and an increased incidence of interstitial-cell tumours of the testis were noted. The NOAEL was 150 ppm, equal to 6 mg/kg bw per day.

A number of studies have been conducted *in vitro* and *in vivo* to investigate the possible mechanism of tumorigenicity. Two studies *in vitro* to investigate the competitive binding capacity of iprodione to rat androgen receptors and possible inhibition of gonadotrophin-stimulated testosterone secretion in porcine Leydig cells indicated that iprodione may act by both mechanisms. The results of endocrine studies in rats *in vivo* also provide some evidence that iprodione may interfere with androgen biosynthesis.

An ADI of 0-0.06 mg/kg bw was established on the basis of an NOAEL of 6 mg/kg bw per day in the most recent two-year study of carcinogenicity in rats and a safety factor of 100.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 160 ppm, equal to 23 mg/kg bw per day (99-week study of toxicity and carcinogenicity)

Rat: 300 ppm in the diet, equal to 21 mg/kg bw per day (two-generation study of reproductive toxicity) (1992 JMPR)
150 ppm equal to 6 mg/kg bw per day (104-week study of toxicity and carcinogenicity)

Rabbit: 20 mg/kg bw per day (maternal toxicity in study of developmental toxicity) (1992 JMPR)

Dog: 400 ppm, equal to 18 mg/kg bw per day (one-year study of toxicity) (1992 JMPR)

<u>Estimate of acceptable daily intake for humans</u>

0-0.06 mg/kg bw

<u>Information that would be valuable for the continued evaluation of the compound</u>

Observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to iprodione

Exposure	Relevant route, study type, species	Result/Remarks
Short-term (1-7 days)	Dermal, irritation, rabbit	No irritation
	Eye, irritation, rabbit	Eye irritation
	Inhalation 4-h, lethality, rat	LC_{50} > 3.29 mg/litre
	Oral, lethality, rat	LD_{50} > 2000 mg/kg bw
	Dermal, lethality, rabbit	LD_{50} > 2000 mg/kg bw
Medium-term (1-26 weeks)	Repeated dietary, four weeks, mouse	NOAEL = 115 mg/kg bw per day; gross liver changes
Medium-term (1-26 weeks)	Repeated dietary, three months, two-generation study of reproductive toxicity, rat	NOAEL = 21 mg/kg bw per day; microscope adrenal hypertrophy and reduced parental body weight
	Repeated dietary, developmental toxicity, rabbit	NOAEL = 20 mg/kg bw per day for maternal toxicity; 60 mg/kg bw per day for embryotoxicity. No teratogenicity
Long-term (≥ one year)	Repeated dietary, carcinogenicity, rat	NOAEL = 6 mg/kg bw per day for increased liver weight; interstitial-cell hyperplasia in testis, adrenal hypertrophy; interstitial-cell tumours at highest dose

4.23 METALAXYL (138)

RESIDUE AND ANALYTICAL ASPECTS

Metalaxyl was first evaluated in 1982 and has been reviewed several times since, most recently in 1992. At the 1994 CCPR the delegations of France, Germany and the EU questioned the basis for the maximum residue level for strawberry originally estimated by the 1985 JMPR and confirmed in 1992 (ALINORM 95/24 para 252). The Session was informed that the proposed MRL of 0.2 mg/kg would not cover all uses in the EU and the USA. The MRL was held at step 7B pending review by the 1995 JMPR.

Since metalaxyl has been proposed for periodic review, the Meeting considered only the MRL for strawberry. Other available information will be kept on file for consideration as part of the periodic review.

The Meeting received updated information on GAP, eight new residue reports and an overall assessment of the residue situation for strawberries by the manufacturer. Information on GAP for strawberries was provided by Canada and the UK. The Netherlands provided information on GAP, analytical methods and data on residues resulting from supervised trials.

The parent compound metalaxyl has been determined after extraction with dichloromethane, evaporation of the solvent and solution in hexane by GLC with nitrogen-specific detection (LOD 0.04 mg/kg). Metalaxyl and the metabolites containing the 2,6-dimethylaniline moiety were determined by GLC with nitrogen-specific detection (LOD 0.03 mg/kg) after extraction with dichloromethane, partitioning into water, acid hydrolysis of metalaxyl and the metabolites to 2,6-dimethylaniline, followed by bromination to 4-bromo-2,6-dimethylaniline. The LOD was 0.03 mg/kg.

The 1992 JMPR concluded that the available data did not support changing the MRL of 0.2 mg/kg. The present Meeting reviewed the new residue data in the context of earlier information.

The use of metalaxyl in strawberries is registered world-wide for foliar spray and broadcast or soil drench application. The Meeting noted the US tolerance for metalaxyl in strawberries (10 mg/kg) and was informed that although US GAP and data supporting the US tolerance were documented they had not been provided to the JMPR. This situation highlights the need for submission of all relevant data to the JMPR.

Only two outdoor residue studies approximating GAP were received. These were from The Netherlands (1 treatment of 0.38 kg ai/ha, 42-day PHI), with maximum residues of 0.06 mg/kg 42 days after treatment. The six new studies carried out in 1993 in Spain and the two from Switzerland were not in accord with current GAP, and the reports provided to previous JMPRs could not be used because the trials they described were not conducted according to current GAP.

In view of the known incompleteness of the submitted information on GAP and the lack of sufficient residue data to estimate a maximum residue level based on European GAP, the Meeting agreed to withdraw the previous recommendation of 0.2 mg/kg for strawberries.

FURTHER WORK OR INFORMATION

Desirable

Residue data from supervised trials carried out in accordance with current use patterns on broccoli, cabbages and cauliflower (from 1992).

4.24 METIRAM (186)

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of the compound were considered for the first time by the present Meeting.

Metiram is a non-systemic fungicide with a very broad spectrum of activity and is registered for use on cereals, fruits, vegetables, tobacco and ornamental in numerous countries. It is active against downy mildews, rust fungi and a number of leaf spot fungi. Resistance to metiram has not developed in more than 30 years of use.

The Meeting received extensive information on metabolism in farm animals, apples and potatoes, environmental fate in soil, methods of residue analysis, the stability of residues in stored analytical samples, approved use patterns, supervised residue trials, animal transfer studies and the fate of residues during food processing.

When [*ethylenediamine*-^{14}C]metiram or [*thiocarbamoyl*-^{14}C]metiram was fed to lactating goats much of the ^{14}C was excreted in the faeces and urine. In the first study only ethyleneurea (EU) and ethylenethiourea (ETU) were positively identified as metabolites, and a major metabolite was not identified.

In a later metabolism study on lactating goats with [*ethylenediamine*-^{14}C]metiram most of the ^{14}C in the tissues and milk was accounted for. The levels of ^{14}C in the milk rapidly reached a plateau, within 1-2 days, and the total ^{14}C excreted in milk accounted for approximately 0.77% of the dose. Jaffe's base, 1-(2-imidazolin-2-yl)-2-imidazolidinethione, was a major metabolite in the milk, kidneys and muscle, while ETU constituted 9.4% of the residue in the fat. Other identified metabolites were ethylenebisisothiocyanate sulfide (EBIS), ethyleneurea (EU) and ethylenediamine (EDA). A considerable percentage of the ^{14}C in all the tissues and milk had been incorporated into natural products such as lactose, amino acids and lipids.

When [*ethylenediamine*-^{14}C]metiram was fed to laying hens, the metabolic pattern was reminiscent of that found from mancozeb and maneb metabolism (1993 JMPR). The metabolites were similar to those found in goats, but ethyleneurea was the major metabolite in the tissues and eggs. ETU was consistently present in the tissues at 2-5% of the total ^{14}C. Lipids and proteins contained ^{14}C, showing that some of the [^{14}C]metiram had been converted to natural products.

Ethylenethiourea (ETU) and Jaffe's base do not produce CS_2 during the CS_2 generating step of the metiram analytical methods. Ethylenebisisothiocyanate sulfide (EBIS) does produce CS_2.

When apples were treated 5 times with [*ethylenediamine*-^{14}C]metiram at 1.4 kg ai/ha and harvested 82 days after the final treatment, the highest ^{14}C residues were in the peel with lesser levels in the flesh and core, showing that the residue is mainly on the surface.

Methanol extracted 56-75% of the total ^{14}C in each fraction but only 27-37% of the total ^{14}C in each fraction was soluble in acetone. The possible metabolites ethylenethiourea (ETU), ethylenebisisothiocyanate sulfide (EBIS), ethylenethiourea-*N*-thiocarboxamide (ETT), ethylenediisothiocyanate (EDTC), ethyleneurea (EU) and hydantoin could not be detected in the acetone extract. From the peel about 42% and 28% of the methanol-soluble ^{14}C corresponded on TLC to the metiram complex and oxalic acid respectively, but proof of identity was not possible.

In a further experiment with apples with a shorter pre-harvest interval, 4 days, results were similar. The residue levels of ^{14}C expressed as metiram were 0.57 and 20 mg/kg in the flesh and peel respectively, again demonstrating that the residue was mostly on the surface. Aqueous methanol and dichloromethane extracted 46% of the total ^{14}C in the apple. ETU, EBIS, ETT, EDTC, EU and hydantoin could not be positively identified as metabolites. About 44% of the extractable ^{14}C corresponded on TLC to the metiram complex, but the identification could not be confirmed.

Potatoes were harvested 28 days after the plants had been treated with [*ethylenediamine*-^{14}C]metiram. Most of the ^{14}C remained in the tops with only 0.2% in the tubers, demonstrating that the residues were mainly immobile. From the tubers 60% of the ^{14}C residues were extractable with aqueous methanol. The potential metabolites ETU, EBIS, ETT and EDTC could not be detected in the extracts, but traces of EU, hydantoin and EDA were possibly present. From the tops 34% of the ^{14}C was extractable into aqueous methanol; 60% of this corresponded on TLC to the metiram complex, and approximately 6% to ETU.

Results were very similar in another potato study in which metiram was labelled with ^{14}C in the thiocarbonyl group. Residues of ^{14}C expressed as metiram were 0.12 and 1150 mg/kg in the tubers and dry tops respectively. From the tubers 54% of the ^{14}C residues were extractable with aqueous methanol, but no metabolites were positively identified. Of the ^{14}C extracted from the tops about 67% corresponded on TLC to the metiram complex or a compound only slightly modified, but the identification could not be confirmed.

Information was provided on the environmental fate of metiram in soil, including information on its hydrolysis and photolysis. ETU was the main product of hydrolysis in the presence of soil. ETU and EU were important products of photolysis.

Metiram ([^{14}C]ethylenediamine label) disappeared quickly from soil under aerobic conditions. ETU, EBIS, EU, carbimid and hydantoin were identified as products. They, in turn, declined within a few days. The mineralization rate was high with 42-43% of the ^{14}C volatilized within 1 year of aerobic incubation. The mineralization rate under anaerobic conditions was slightly lower.

ETU, IMD (2-imidazoline), EU, hydantoin, glycine and oxalic acid were identified as [^{14}C]metiram metabolites in the leachates from soil columns. Substantial amounts of the ^{14}C remained at the top of the columns, with 15%, 35%, 80% and 70% of the dose remaining in the top 2.5 cm of sand, sandy loam, clay and silt loam columns respectively.

Analytical methods for metiram rely on acid hydrolysis to release CS_2, which is then measured colorimetrically or by gas chromatography. The methods are the same as those for the other ethylenebis(dithiocarbamate)s, mancozeb and maneb. Limits of determination are generally in the range 0.02-0.2 mg/kg depending on the substrate.

Metiram will be included in the residue definition of dithiocarbamates. In the regulatory analytical methods for dithiocarbamates residues of metiram will behave in the same way as those of other dithiocarbamates. An analyst using an enforcement method will measure the total evolved CS_2 produced by acid digestion of a sample. The evolved CS_2 will be measured irrespective of its source.

The Meeting proposed a revised definition of dithiocarbamate residues:

The MRLs refer to the total dithiocarbamates, determined as CS_2 evolved during acid digestion and expressed as mg CS_2/kg.

Methods for the residue analysis of ethylenethiourea were reviewed in the 1993 monograph on mancozeb.

Information was provided to the Meeting on the stability during frozen storage of metiram and ETU on apples, wet and dry apple pomace, apple juice, sauce and baby food, tomatoes, potatoes and sugar beets. Studies of the frozen storage stability of ETU in a number of commodities were reviewed in 1993 and are included the 1993 monograph on mancozeb.

Incurred metiram residues in whole apples were stable (80% remaining) when stored at -20°C for 12 months. ETU was formed during storage and accumulated at the longer intervals, demonstrating that ETU residues in whole apples were stable under these conditions.

When diced apples were spiked with metiram the residues were stable for 12 months at -20°C, but when spiked with ETU the residues disappeared within weeks. Metiram was adequately stable at -20°C for 12 months in apple sauce, fresh apple juice, cooked apple juice, apple baby food, wet apple pomace, dry apple pomace, tomatoes, diced raw potatoes and diced sugar beet. The levels of ETU produced during storage were low. ETU residues were adequately stable in most of these matrices but disappeared rapidly from wet apple pomace, and within weeks from diced raw potatoes and diced sugar beet.

Residues in supervised trials have been determined by methods which measure the CS_2 evolved during acid digestion.

The Meeting received residue data from supervised trials on the following crops and commodities:

apples (*Australia, Brazil, Canada, Germany, Hungary, Italy, UK*), pears (*Germany*)
apricots (*Australia*), cherries (*Australia, Germany*), peaches (*Australia*), plums (*Germany*)
currants (*Germany, UK*), gooseberries (*UK*), grapes (*Austria, France, Germany, Hungary, Italy*), strawberries (*Germany, Switzerland, UK*)
bananas (*Australia*)
cabbages (*Germany*), cauliflowers (*Germany*)
cucumbers (*Hungary, UK*)
tomatoes (*France, Germany, Hungary*)
lettuce (*Australia, France, Germany*)
beans (*Germany*), peas (*Germany*)
potatoes (*Belgium, Germany*)
celery (*Germany*)
wheat (*Germany, Hungary*)

rape seed (*UK*)
hops (*Germany*)
wheat forage (*Germany*), wheat straw (*Germany, Hungary*)

Metiram-complex is the old name for the technical material which contains 89% metiram. Old labels and use patterns quoting 80% ai are equivalent to modern labels quoting 70% ai. Most of the application rates and spray concentrations in the trials are quoted on the old (metiram-complex) basis. The difference should be taken into account when comparing trial data with modern labels.

In Germany metiram is registered for application to pome fruit at a spray concentration of 0.12 kg ai/hl, with a 28-day PHI. In Denmark, Hungary and The Netherlands metiram is registered for use on apples at 1.8 kg ai/ha with a PHI of 28-30 days. In Belgium and Switzerland the use rate is 1.8-1.9 kg ai/ha with a 21-day PHI. The apple trials in Germany were evaluated against this use pattern. Application rates up to 2.8 kg ai/ha are included in the evaluation, which allows for the two ways of expressing active ingredient content + 30% excess in measured application rates.

Metiram residues (as CS_2) in 62 German trials within this use pattern (one result per trial according to GAP) were 0.06, 0.10, 0.10, 0.12, 0.16, 0.18, 0.18, 0.20, 0.21, 0.21, 0.22, 0.22, 0.24, 0.25, 0.25, 0.27, 0.29, 0.30, 0.33, 0.34, 0.35, 0.36, 0.37, 0.37, 0.38, 0.39, 0.40, 0.40, 0.40, 0.40, 0.41, 0.42, 0.43, 0.45, 0.48, 0.60, 0.62, 0.63, 0.67, 0.67, 0.67, 0.68, 0.70, 0.70, 0.78, 0.79, 0.80, 0.81, 0.82, 0.83, 0.84, 0.89, 0.93, 1.0, 1.1, 1.3, 1.4, 1.5, 1.6, 1.9, 2.0 and 2.0 mg/kg.

The Australian use pattern on apples requires a spray concentration of 0.16 kg ai/hl and a 21-day PHI. Two supervised residue trials were available according to this use pattern, where the metiram residues (as CS_2) were 1.0 and 2.1 mg/kg.

In Canada metiram is registered for use on apples at 4.8 kg ai/ha with a PHI of 45 days. Five Canadian trials were available, but the application rates were lower (2.2 kg ai/ha) and the PHI was 88 days. Residues of metiram (as CS_2) on apples were 0.3, 0.4, 0.4, 0.5 and 0.5 mg/kg.

In a Hungarian trial on apples according to the official use pattern (1.8 kg ai/ha, PHI 30 days) the highest metiram residue (as CS_2) was 0.45 mg/kg.

Metiram is registered for use on apples in Italy at a spray concentration of 0.14 kg ai/hl with a PHI of 28 days. The highest metiram residues (as CS_2) from each of the 5 trials according to GAP were 0.15, 0.34, 0.34, 0.67 and 2.6 mg/kg.

Eight apple trials were available from the UK according to the UK use pattern (metiram in combination with another fungicide). The application rate in the UK is low (0.038 kg ai/ha), and the metiram residues were low: <0.02, <0.02, <0.02, 0.03, <0.05, <0.05, <0.05 and 0.08 mg/kg (as CS_2).

The Meeting estimated a maximum residue level of 5 mg/kg for dithiocarbamates in apples arising from the use of metiram, and noted that this value was the same as the recommendation of the 1993 JMPR for dithiocarbamates in pome fruits.

In Germany metiram is registered for application to pome fruit at a spray concentration of 0.12 kg ai/hl, with a 28-day PHI. In Denmark and The Netherlands the registration on pears allows metiram application at 1.8 kg ai/ha with a 28-day PHI. The 5 German trials were evaluated against this use pattern and the metiram residues (as CS_2) were 0.24, 0.36, 0.47, 0.49 and 0.53 mg/kg.

The Meeting noted that an estimated maximum residue level for dithiocarbamates in pears arising from the use of metiram would not exceed the 1993 recommendation for pome fruits of 5 mg/kg.

Australian trails on stone fruits could not be evaluated because the official PHI is 21 days but the longest interval between final application and harvest in the trials was 7 days. The PHI in Germany for metiram on stone fruits is 21 days, after application of a spray concentration of 0.12 kg ai/hl, but the PHI for plums is 28 days. Metiram residues (as CS_2) from the 4 cherry trials in Germany according to GAP for stone fruits were 0.5, 0.7, 1.0 and 1.0 mg/kg, and from the two plum trials 0.08 and 0.40 mg/kg.

The Meeting agreed that 4 trials on one variety of cherry (but in 2 seasons) were insufficient coverage of possible conditions to make a recommendation. The plum trials were also too few to make a recommendation.

In German GAP grapes are sprayed up to 6 times at 0.16 kg ai/ha followed by a 56-day PHI. Austrian and German trials were evaluated against German GAP and the metiram residues as CS_2 from 7 trials were 0.06, <0.2, 0.26, 0.28, 0.61, 0.96 and 3.0 mg/kg. In a trial in Hungary the metiram residue (as CS_2) was 2.4 mg/kg. The Italian trials on grapes did not comply with GAP because there were too many applications.

The Meeting estimated a maximum residue level of 5 mg/kg for dithiocarbamates in grapes arising from the use of metiram, and noted that this was the current CXL for dithiocarbamates in grapes.

No information on GAP was available which was suitable for evaluating supervised residue trials on strawberries in Germany, Switzerland and the UK, or trials on gooseberries in the UK.

Metiram is registered for use on red currants in Germany at a spray concentration of 0.12 kg ai/hl with a PHI of 35 days. Trials on black currants were used to support the data on red currants and 0.16 kg ai/hl was considered to comply with GAP. Metiram residues (as CS_2) in the 6 German trials on currants were 0.5, 0.5, 0.88, 1.0, 1.1 and 2.0 mg/kg.

A maximum residue level similar to that for grapes would probably be required, but the Meeting noted that the proposed Draft MRL at Step 5 for dithiocarbamates on black, red and white currants (10 mg/kg) would cover the use of metiram on currants.

Metiram trials on bananas were carried out in Australia, but residues were determined in the pulp, not in the commodity of trade on which an MRL would be based.

Trials in Germany on cabbages and cauliflowers were not according to GAP and the residues could not be evaluated.

No suitable information on GAP was available for evaluating trials on cucumbers in Hungary and the UK.

German registration allows 4 applications of metiram on tomatoes at 2.9 kg ai/ha with a 5-day PHI. Metiram residues (as CS_2) from 12 German trials according to GAP were 0.03, <0.2, 0.2, <0.2, 0.22, 0.32, 0.50, 0.61, 0.74, 0.8, 1.0 and 1.4 mg/kg. Two more trials with 6 and 7 applications produced residues of 0.54 and 0.75 mg/kg 7 days after the final application. A greenhouse use in Hungary allows metiram application at 1.4 kg ai/ha with a 7-day PHI. Metiram residues (as CS_2) in a trial 6 days after the final application were up to 0.78 mg/kg. A maximum residue level of 2 mg/kg would be estimated if there were no current recommendation, but the Meeting noted that the current Draft MRL at Step 5 for dithiocarbamates in tomatoes (5 mg/kg) would cover the use of metiram.

Metiram may be used in Germany on lettuce at 0.96 kg ai/ha with a PHI of 21 days. Metiram residues (as CS_2) from the 9 German trials complying with GAP were <0.02, <0.02, <0.02, 0.02, 0.05, 0.16, <0.2, 0.77 and 0.88 mg/kg. The French trials on lettuce could not be evaluated because no comparable GAP was available. Residues in 1 Australian trial according to GAP were <0.2 mg/kg. A maximum residue level of 1 mg/kg would be estimated if there were no current recommendation, but residues in head lettuce arising from the use of metiram would be covered by the current Draft MRL at Step 5 for head lettuce of 10 mg/kg.

In Germany metiram is registered for use on dwarf beans at 0.96 kg ai/ha with a 7-day PHI. The data from supervised trials on beans in Germany were evaluated against this use pattern. Metiram residues (as CS_2) from the 6 German trials according to GAP were 0.07, 0.08, 0.15, 0.18, 0.26 and 0.78 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg for dithiocarbamates in common beans.

No information on GAP was available to evaluate the metiram trials on peas.

Metiram may be applied 5 times to potatoes in Germany at 1.3 kg ai/ha and harvested 14 days after the final application. For the purposes of residue evaluation 6 applications were considered equivalent to 5. Metiram residues (as CS_2) from the 12 German trials according to GAP were <0.05, <0.05, <0.05, <0.05, 0.08, 0.09, <0.1, <0.1, <0.1, <0.1, 0.12 and 0.13 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg for dithiocarbamates in potatoes arising from the use of metiram, and noted that this value agreed with the current Draft MRL at Step 5.

There was only one trial on celery in accord with current GAP, and this was insufficient to make a recommendation.

Metiram is registered for use on cereals in Belgium and Luxembourg at 1.4 kg ai/ha with harvest 28 days after the final application. The German trials on spring and winter wheat and a Hungarian trial on spring wheat were evaluated against this use pattern. In Hungary the metiram use rate is 1.4 kg ai/ha but the PHI is 56 days. Metiram residues (as CS_2) from the 8 trials according to GAP were <0.05, <0.1, <0.1, <0.1, <0.1, 0.13, 0.13 and 0.15 mg/kg. The Meeting noted that an estimated maximum residue level for dithiocarbamates on wheat arising from the use of metiram would not exceed the current Draft MRL (1 mg/kg).

Four UK trials on rape seed were reported and residues were not detected (<0.05 mg/kg as CS_2), but 4 trials in one year were considered insufficient to make a recommendation.

Metiram may be applied 12 times to hops in Germany at a spray concentration of 0.16 kg ai/hl. Harvest is permitted 35 days after the final application. In the trials for residue evaluation 14 applications were considered sufficiently close to 12 applications. Metiram residues (as CS_2) on dry hops from the 7 trials according to German GAP were 4.3, 5.9, 7.1, 13, 19, 25 and 28 mg/kg.

The Meeting estimated a maximum residue level of 30 mg/kg for dithiocarbamates in dry hops.

The Meeting was not able to make recommendations for wheat forage because the number of trials matching GAP was too limited.

As in the evaluation of wheat, the residue data on wheat straw were evaluated against the registered uses in Belgium, Luxembourg and Hungary. Metiram residues (as CS_2) on wheat straw from the 7 trials in Germany and 1 in Hungary were <0.1, <0.2, 0.2, 0.23, 0.23, 0.64, 0.9 and 0.9 mg/kg. The Meeting noted that an estimated maximum residue level for dithiocarbamates on wheat straw arising from the use of metiram would not exceed the current recommendation for dithiocarbamates in wheat straw and fodder, dry (25 mg/kg).

ETU residues were usually undetectable (<0.02 or <0.01 mg/kg) or at 0.01-0.02 mg/kg in most commodities in the supervised trials where metiram had been used according to GAP. The highest ETU levels recorded in the apple, grape and tomato trials were 0.06, 0.13 and 0.10 mg/kg respectively under GAP conditions.

Higher ETU residues were reported in hops (<0.1-0.54 mg/kg) and wheat straw (0.03-0.29 mg/kg) when metiram use was according to label recommendations. In some wheat straw samples ETU exceeded the dithiocarbamate levels.

Groups of lactating dairy cows were fed metiram equivalent to 8, 40, 80 and 4000 ppm (equivalent to dithiocarbamates, as CS_2, at 4.5, 23, 45 and 2300 ppm) in the diet for 32 consecutive days. Dithiocarbamate residues were present in milk only in the highest dose group. They reached a plateau after about 20 days and disappeared quickly when dosing ceased.

The "dithiocarbamate" residue in the animal commodities is unlikely to be metiram itself, but probably mainly a metabolite such as EBIS (ethylenebisisothiocyanate sulfide) which has been shown to liberate CS_2 during analysis for dithiocarbamates.

ETU residues were essentially absent from the milk produced by cows in the three lower dose groups. In the highest dose group they quickly reached a plateau of 3-5 mg/kg and declined quickly when dosing ceased.

There was little difference between the dithiocarbamate tissue residues resulting from the three lower doses. Residues were not detected in the muscle and residues in the liver, kidneys and fat were not much above the limit of determination. ETU residues were mainly undetectable in tissues from animals on the lowest three doses.

Residues in this feeding study agree with those in a study of mancozeb in dairy cows reviewed by the JMPR in 1993. The estimated maximum residues for the milks, meat and edible mammalian offal were 0.05*, 0.02* and 0.1 mg/kg respectively, based on animals eating 45 ppm mancozeb (25 ppm dithiocarbamates as CS_2) in the diet.

Residues of metiram (as CS_2) and ETU were measured in puree and juice produced from apples in 42 supervised field trials in Germany. In many samples residues were undetectable, but where they were detected processing factors could be estimated. The results suggest that metiram EBDC residues in apple juice and puree are likely to be 6% and 21% of the apple residues respectively, while ETU levels in the juice and puree are likely to be 3% and 18% respectively of the levels of metiram (as CS_2)in the apples.

Residues of metiram (as CS_2) and ETU were measured in pear compote (stewed fruit) produced from pears in 6 supervised field trials in Germany. EBDC residues had generally disappeared in the stewed product, and ETU was not produced.

Residues of metiram (as CS_2) and ETU were measured in grape juice produced from grapes in 8 supervised field trials in Germany. The results suggested that metiram EBDC residues in grape juice were likely to be twice as high as in the originating grapes, but the ETU level in the juice was likely to be only 3% of the metiram level (as CS_2) in the grapes.

Must and wine were produced from grapes field-treated with metiram in Germany. Dithiocarbamate residues (as CS_2) in the must and wine were likely to be 67% and 4% respectively of the levels in the grapes, and ETU levels 3% and 4% respectively of the dithiocarbamate residues in the grapes.

Gentle boiling of potatoes, dwarf beans, runner beans, apples and tomatoes treated in the field with metiram or maneb converted some of the EBDC to ETU.

Various commercial juices, wine and puree were surveyed in Germany in 1976 for residues of ETU. The survey showed that ETU was present in many of the products tested. The highest level of 0.09 mg/kg was recorded in a sample of tomato puree. In 1985 in Greece 16 samples of canned apple juice and 20 samples of canned peach juice with pulp were surveyed for ETU. No residues above the LOD (0.02 mg/kg) were detected.

Recommendations for MRLs for dithiocarbamates including metiram are listed in Annex I.

4.25 MONOCROTOPHOS (054)

TOXICOLOGY

The Meeting established an acute reference dose (acute RfD). Details are given in Section 2.6.

4.26 PARATHION (058)

TOXICOLOGY

Parathion was last evaluated toxicologically in 1967. An ADI of 0-0.005 mg/kg bw was established on the basis of findings in humans in which the NOAEL was 0.05 mg/kg. A safety factor of 10 was applied. Parathion was re-evaluated toxicologically by the present Meeting within the CCPR periodic review programme.

Parathion is readily absorbed from the respiratory and digestive tracts and is excreted primarily in the urine. Two hypotheses have been proposed for the metabolism of parathion; however, the metabolic spectrum is the same in both. Parathion is metabolized to paraoxon and diethyl phosphorothioic acid. Paraoxon is further metabolized, and following its oral administration to rats diethyl phosphate, diethyl phosphorothioate, desethyl-paraoxon, and *p*-nitrophenol were identified in the urine. In cattle, rumen micro-organisms are believed to be responsible for the production of aminoparathion and aminoparaoxon.

Parathion is extremely hazardous when given orally (LD_{50} = 2 mg/kg bw) or by inhalation (4-h LC_{50} = 0.03 mg/litre) and moderately hazardous when given dermally (LD_{50} = 73 mg/kg bw). The compound has been characterized in studies in laboratory animals as a mild dermal and ocular irritant and as a non-sensitizing agent. When it was administered with other OPs, its toxic effects were not potentiated. The WHO has classified parathion as “extremely hazardous”.

In a three-week study in rabbits treated dermally, the NOAEL was 0.1 mg/kg bw per day on the basis of depression of plasma, erythrocyte and brain cholinesterase activities at 2 mg/kg bw per day. In a three-week study by inhalation in rats, the NOAEL was 0.9 mg/litre on the basis of decreases in brain, plasma and erythrocyte cholinesterase activity. In a 14-day study in dogs, parathion was administered orally at doses of 0, 1.5, 3 or 6 mg/kg bw per day. No NOAEL could be determined, as clinical cholinergic signs were observed at the lowest dose tested. Cholinesterase activity was not monitored in this study. In a 90-day study in dogs at doses of 0, 0.3, 1 or 3 mg/kg bw per day, the NOAEL was 3 mg/kg bw per day. Cholinesterase activity was not measured.

In a 29-day study in mice at doses of 0, 100, 200 or 400 ppm (equivalent to 15, 30 and 60 mg/kg bw per day), clinical signs of toxicity were reported in all groups. Cholinesterase activity was not determined, and no NOAEL was seen. In a 90-day study in mice at dietary concentrations of 0, 15, 50, or 100 ppm, the NOAEL was 50 ppm (equivalent to 7.5 mg/kg bw per day) on the basis of decreased body weights of males. Cholinesterase activity was not monitored. When parathion was administered to rats for 90 days at dietary concentrations of 0, 2.5, 25 or 75 ppm, the NOAEL was 2.5 ppm (equal to 0.2 mg/kg bw per day), on the basis of depression of brain acetylcholinesterase. In a one-year study in dogs at doses of 0, 0.01, 0.03 or 0.1 mg/kg bw per day, no NOAEL could be determined as brain acetylcholinesterase was decreased at the lowest dose tested.

In a two-year study in rats, parathion was not associated with carcinogenicity when administered at dietary concentrations of 0, 0.5, 5 or 50 ppm. The NOAEL for systemic toxicity was 5 ppm (equivalent to 0.25 mg/kg bw per day) on the basis of decreases in brain, plasma and erythrocyte cholinesterase activity, retinal atrophy and increased severity of degenerative changes in the sciatic nerve. In another study in rats, given dietary levels of 0, 2, 8 or 32 ppm for two years, there was again no evidence of carcinogenicity. The NOAEL for systemic toxicity was 8 ppm (equivalent to 0.4 mg/kg bw per day) on the basis of decreases in brain acetylcholinesterase activity and retinal atrophy. No effects on sciatic nerves were reported at the highest dose tested.

In mice receiving dietary concentrations of parathion at 0, 60, 100, or 140 ppm for 18 months, no NOAEL could be determined as cholinergic signs were seen at all doses.

Two studies of developmental toxicity were conducted in rats. In the first study, parathion was administered by gavage at doses of 0, 0.25, 1 or 1.5 mg/kg bw on gestation days 6-19. The NOAEL for maternal toxicity was 1 mg/kg bw per day on the basis of increased mortality, and the NOAEL for developmental toxicity was 1.5 mg/kg bw per day. In the second study, parathion was administered by gavage at doses of 0, 0.1, 0.3 or 1 mg/kg bw per day on gestation days 6-15. The NOAEL for developmental toxicity was 1 mg/kg bw per day and that for maternal toxicity was 0.3 mg/kg bw per day on the basis of increased mortality and clinical signs of toxicity.

Two studies of developmental toxicity were conducted in rabbits. In the first study, parathion was administered by gavage on gestation days 7-19 at 1, 4 or 16 mg/kg bw per day. The NOAEL for developmental toxicity was 16 mg/kg bw per day, and the NOAEL for maternal toxicity was 4 mg/kg bw per day on the basis of decreased body weight gain. In the second study, parathion was administered by gavage on days 6-18 of gestation at 0, 0.03, 0.1 or 0.3 mg/kg bw per day. The NOAEL for both maternal and developmental toxicity was 0.3 mg/kg bw per day.

In a two-generation study of reproductive toxicity in rats, doses of 0, 0.5, 5 or 25 ppm were administered in the diet. Dams at the highest dose had tremors, and a reduction in body weight was seen during premating, gestation and lactation. The NOAEL for reproductive toxicity was 25 ppm (equivalent to 1.2 mg/kg bw per day); the NOAEL for maternal toxicity was 5 ppm (equivalent to 0.25 mg/kg bw per day) on the basis of the observation of tremors in F_0 and F_1 females. In the second study, parathion was administered at dietary concentrations of 0, 1, 10 or 20 ppm. The NOAEL for reproductive toxicity was 20 ppm (equivalent to 1 mg/kg bw per day); the NOAEL for perinatal toxicity was 10 ppm (equivalent to 1 mg/kg bw per day) on the basis of reduced body weights; and the NOAEL for maternal toxicity was 1 ppm (equivalent to 0.05 mg/kg bw per day) on the basis of decreased brain acetylcholinesterase activity. Special studies were conducted to assess the ocular toxicity of parathion. When parathion was administered to dogs at doses of 0, 0.002, 0.008 or 0.8 mg/kg bw per day for six months, no functional impairment of the eye was observed. The NOAEL was 0.008 mg/kg bw per day on the basis of depression in brain and retinal cholinesterase activity. In a three-month study of toxicity in female rats, parathion was administered at levels of 0, 0.04, 0.4 or 4 mg/kg bw per day. The NOAEL was 0.4 mg/kg bw per day on the basis of depression of brain acetylcholinesterase activity. No significant effects on ocular toxicity were reported at any dose.

Parathion was not associated with organophosphorus-induced delayed neurotoxicity in hens but it induced demyelination in the peripheral nerves of rats at a dietary level of 50 ppm (equivalent to 2.5 mg/kg bw per day). The NOAEL was 0.25 mg/kg bw per day.

In a study conducted earlier in humans, an NOAEL of 7.5 mg/day was determined on the basis of lack of effect on erythrocyte acetylcholinesterase.

Parathion has been adequately tested for genotoxicity in a range of tests *in vitro* and *in vivo*. The Meeting concluded that parathion is not genotoxic.

An ADI of 0-0.004 mg/kg bw was established on the basis of an NOAEL of 0.4 mg/kg bw per day in the two-year study in rats for retinal atrophy and inhibition of brain acetylcholinesterase at the higher dose. A safety factor of 100 was used. Lower NOAELs in animals, based only on inhibition of erythrocyte of brain acetylcholinesterase, were not considered relevant because of the availability of an NOAEL for erythrocyte acetylcholinesterase inhibition in humans, which was 0.1 mg/kg bw per day.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 50 ppm, equivalent to 7.5 mg/kg bw per day (90-day study of toxicity)

Rat: 1 ppm, equivalent to 0.05 mg/kg bw per day (study of reproductive toxicity)
2.5 ppm, equal to 0.18 mg/kg bw per day (90-day study of toxicity)
8 ppm, equivalent to 0.4 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Dog: 0.008 mg/kg bw per day (six-month study of toxicity)

Estimate of acceptable daily intake for humans

0-0.004 mg/kg bw

Estimate of acute reference dose

An acute reference dose of 0.01 mg/kg bw was derived by applying the usual 10-fold safety factor to an NOAEL of 7.5 mg/day (highest oral dose), corresponding to about 0.1 mg/kg bw per day, in humans. This was based on the absence of inhibition of erythrocyte acetylcholinesterase.

Studies that would provide information valuable for the continued evaluation of the compound

Further observation in humans

Toxicological criteria for setting guidelines for dietary and non-dietary exposure to parathion

Exposure	Relevant route, study type, species	Results/Remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Irritating
	Eye, irritation, rabbit	Irritating
	Skin, sensitization, guinea-pig	Non-sensitizing
	Oral, toxicity, rat	LD_{50} = 2 mg/kg bw
	Dermal, toxicity, rat	LD_{50} = 73 mg/kg bw
	Inhalation, toxicity, rat	LC_{50} = 0.03 mg/litre
Medium-term (1-26 weeks)	Repeated dermal, 21 days, toxicity, rabbit	NOAEL = 1 mg/kg bw per day, based on decreased brain acetylcholinesterase. No dermal effect
	Repeated inhalation, 21 days, toxicity, rat	NOAEL = 0.92 mg/m^3 based on decreased brain acetylcholinesterase
	Repeated oral, reproductive, toxicity, rat	NOAEL = 0.05 mg/kg bw per day for maternal toxicity, decreased brain cholinesterase; NOAEL ≥1 mg/kg bw per day for reproductive toxicity; NOAEL for perinatal toxicity 1 mg/kg bw per day based on reduced body weight
	Repeated oral, developmental, toxicity, rat	NOAEL = 1 mg/kg bw per day for developmental toxicity; NOAEL = 0.3 mg/kg per day for maternal toxicity based on increased mortality and cholinergic signs (rats)
Medium-term (1-26 weeks)	Repeated oral, developmental, toxicity, rabbit	NOAEL ≥0.3 mg/kg bw per day for maternal and developmental toxicity

Exposure	Relevant route, study type, species	Results/Remarks
Long-term (≥ one year)	Repeated oral, two years, long-term toxicity and carcinogenicity, rat	NOAEL = 0.25 mg/kg bw per day based on lowered brain acetylcholinesterase. No carcinogenicity

RESIDUE AND ANALYTICAL ASPECTS

Parathion was originally evaluated by the JMPR in 1965 and was extensively re-evaluated in 1991.

At the 25th Session of the CCPR (1993, ALINORM 93/24A, para 81) the delegation of Germany informed the Committee that the manufacturer would seek re-registration and indicated that a higher MRL for pome fruit was necessary. The proposed MRL was held at step 7B by the 1994 CCPR (ALINORM 95/24, para 150) pending the review by the 1995 JMPR. At the 27th Session of the CCPR (1995, ALINORM 95/24A, para 103) the manufacturer indicated that additional studies on apples were in progress and would not become available until 1996.

The 1994 CCPR (ALINORM 95/24, para 149) decided to request the JMPR to reconsider the limits of determination of parathion. It also decided to advance the proposals for cotton seed, maize, sorghum, soya bean and sunflower seed to Step 7C awaiting further information from the USA on registered uses.

Information was provided to the Meeting by the manufacturer on the current use patterns in the USA and on supervised trials on cereals and canola, supported by processing trials, freezer storage stability data and validation of analytical methods. The current review was scheduled to deal with commodities held at Step 7B or 7C: apple, cotton seed, maize, sorghum, soya bean (dry) and sunflower seed. The Meeting reviewed only those studies that included the commodities at Step 7, analytical methods to deal with the question on the limits of determination, a report on plant metabolism and recent reports on estimates of dietary intake.

In a plant metabolism study parathion was the major component of the residue (62% of the ^{14}C) in wheat grain harvested 7 days after the second application of ring-labelled parathion to the plant. Paraoxon was not detected in the grain and 4-nitrophenol comprised 7.4% of the ^{14}C. Parathion, paraoxon and 4-nitrophenol accounted for 37%, 1.2% and 13% of the ^{14}C in the wheat straw respectively. In the straw and grain 72% and 82% respectively of the ^{14}C was extractable with aqueous methanol.

The GLC methods used in the USA to determine residues of parathion and paraoxon in the majority of crops in the 1991 Evaluations had LODs of 0.05 mg/kg for each compound.

Information was provided on a procedure suitable as a regulatory method for determining residues of parathion, paraoxon and 4-nitrophenol in a range of substrates. The sample is extracted with aqueous methanol acidified with HCl, the entire mixture is refluxed for 30 minutes, then filtered and concentrated, removing the methanol. The residues are extracted into ethyl acetate, the extract is concentrated and the parathion and paraoxon residues determined by GLC with an FPD. An aliquot of the ethyl acetate extract is cleaned up on a Florisil Sep-Pak and the 4-nitrophenol residue

determined by HPLC with UV detection at 315 nm. Variations of the method are needed for some substrates. The LOD for each compound was 0.05 mg/kg. Recoveries were found to be satisfactory at this concentration and higher in approximately 50 substrates including vegetables, fruits, nuts, cereals, processed commodities and feeding materials.

A similar procedure for parathion and paraoxon residues in cereal commodities was described in another report. The LOD was 0.02 mg/kg. When the method was applied to canola and its processed commodities the LOD for parathion was 0.02 mg/kg, but that for paraoxon was 0.05 mg/kg.

When additional identification of residues is needed, capillary GC-MS may be used with selected ion monitoring at m/z = 109, which corresponds to a fragment derived from 4-nitrophenol and occurs with parathion, paraoxon and 4-nitrophenol.

The regulatory method was tested for interferences from other potential pesticide residues. Fenthion and chlorpyrifos came through the extraction and clean-up and interfered with the parathion GLC peak. Similarly phosphamidon, chlorpyrifos-methyl and parathion-methyl interfered with the paraoxon peak.

The storage stability of parathion, paraoxon and nitrophenol residues was measured after adding a mixture of 1 mg/kg of each to macerated snap beans, kidney beans, cotton seed, almond kernels, apples, clover, oranges, plums, spinach, strawberries, sunflower seed and sweet peppers and storing in a freezer for 24 months at approximately -20°C. The three compounds were stable under these conditions, but occasionally the amount of paraoxon remaining after long-term storage was less than 70%, particularly in snap beans.

Parathion is registered in the USA only for aerial application to field crops. The use patterns reported in 1995 for alfalfa, cotton, maize, sorghum, soya beans, sunflowers and wheat are essentially the same as those recorded in the 1991 Residue Evaluations. Use patterns for the additional crops barley, rapeseed or canola and sweet corn have now been reported.

Dietary intake studies in Australia, Belgium and Finland showed that the dietary intake of parathion was much less than the current ADI.

4.27 PARATHION-METHYL (059)

TOXICOLOGY

Parathion-methyl was last evaluated toxicologically by the Joint Meeting in 1984. An ADI of 0-0.02 mg/kg bw was allocated. Parathion-methyl was re-evaluated by the present Meeting within the CCPR periodic review programme, with particular attention to the recent Environmental Health Criteria monograph on parathion-methyl (EHC 145).

Parathion-methyl is absorbed through the skin, and from the respiratory and digestive tracts. Differences between its oral and intravenous toxicity have been reported and are believed to be associated with first-pass effects in the liver. The compound is rapidly excreted; negligible amounts of the labelled dose were present in the blood, tissues and organs at 48 h. Conversion of parathion-methyl to paraoxon-methyl has been shown to occur within minutes after oral administration to rats.

Detoxification is achieved by *O*-demethylation or hydrolysis to *p*-nitrophenol. In humans the primary urinary metabolites were *p*-nitrophenol and dimethyl phosphate.

Parathion-methyl is acutely toxic at low doses when administered either orally (LD_{50} = 4 mg/kg bw) or by inhalation (LC_{50} = 0.13 mg/litre). The compound is slightly irritating to the skin and the eyes and has not been demonstrated to be a sensitizing agent. The WHO has classified parathion-methyl as 'extremely hazardous'.

In a 90-day study in mice at dietary levels of 0, 10, 30 or 60 ppm, the NOAEL was 10 ppm (equivalent to 1.5 mg/kg bw per day) on the basis of significant decreases in absolute and relative testicular weights. Cholinesterase activity was not measured in this study. In a 90-day study in rats, the NOAEL was 2.5 ppm (equivalent to 0.12 mg/kg bw per day) on the basis of significant decreases in plasma, erythrocyte and brain cholinesterase activities at 25 ppm (equivalent to 1.2 mg/kg bw per day).

Two 13-week studies were conducted in dogs, in which parathion-methyl was administered at dietary levels of 0, 0.3, 1 or 3 mg/kg bw per day in one study and 0, 0.03, 0.3 or 3 mg/kg bw per day in the other. In both studies, the LOAEL was 3 mg/kg bw per day on the basis of decreases in erythrocyte, plasma and brain cholinesterase activity. The NOAELs were 1 and 0.3 mg/kg bw per day, respectively. In a one-year study in dogs, the NOAEL was also 0.3 mg/kg bw per day, the highest dose tested.

In a one-year study in rats to determine the ocular and neurotoxic effects of parathion-methyl, dietary levels of 0, 0.5, 2.5, 12 or 50 ppm were administered. Ocular toxicity was not observed. Degenerative changes of the sciatic nerve and its extensions consistent with demyelination were observed at the two highest doses. The LOAEL was 12 ppm, equal to 0.5 mg/kg bw per day. The NOAEL was 2.5 ppm, equal to 0.1 mg/kg bw per day.

In a two-year study in mice, parathion-methyl was not carcinogenic at dietary levels up to 50 ppm (equal to 9.2 mg/kg bw per day). The NOAEL was 7 ppm, equal to 1.6 mg/kg bw per day, on the basis of significant decreases in erythrocyte, plasma and brain cholinesterase activities. In a study of toxicity and carcinogenicity in rats fed parathion-methyl at dietary levels of 0, 2, 10 or 50 ppm, there was no evidence of carcinogenicity. The NOAEL was 2 ppm (equivalent to 0.1 mg/kg bw per day) and the LOAEL was 10 ppm (equivalent to 0.5 mg/kg bw per day), on the basis of a reduction in brain acetylcholinesterase activity. In another two-year study in rats, parathion-methyl did not induce carcinogenic effects. The NOAEL was 5 ppm (equivalent to 0.25 mg/kg bw per day) on the basis of the observation of tremors, anogenital staining, reduced body weight, retinal degeneration, sciatic nerve degeneration, decreased packed cell volume and haemoglobin and erythrocyte counts, and decreased brain cholinesterase activity in males and females at 50 ppm (equivalent to 2.5 mg/kg bw per day).

Two developmental studies were conducted in rats. In one study, rats received parathion-methyl by gavage at doses of 0, 0.3, 1 or 3 mg/kg bw per day. The NOAEL for maternal and developmental toxicity was 1 mg/kg bw per day on the basis of increased numbers of deaths, ataxia and dyspnoea in dams and delayed ossification in fetuses. In another study, the NOAEL for maternal and developmental toxicity was 0.3 mg/kg bw per day on the basis of significant decreases in maternal body weight gain during treatment and gestation and an increased incidence of stunted fetuses at 1 mg/kg bw per day. In studies of developmental toxicity in rabbits, decreased erythrocyte and plasma cholinesterase activities were reported in dams receiving 3 mg/kg bw per day by gavage. No developmental effects were reported that could be attributed to the administration of parathion-

methyl. The NOAEL for maternal toxicity was 1 mg/kg bw, and that for developmental toxicity was 3 mg/kg bw.

In a multigeneration study in rats, dietary levels of 0, 2, 10 or 50 ppm were administered. Slight effects on pup survival were reported in animals receiving 10 ppm, equivalent to 0.5 mg/kg bw per day. The NOAEL was 2 ppm, equivalent to 0.1 mg/kg bw per day. In another study, in which dietary levels of 0, 0.5, 5, or 25 ppm were administered, decreases in maternal body weights during the lactation period were observed at 25 ppm. The NOAEL was 5 ppm, equivalent to 0.25 mg/kg bw per day. The overall NOAEL in the two studies of reproductive toxicity was 5 ppm, equivalent to 0.25 mg/kg bw per day.

Parathion-methyl was mutagenic in bacteria, but there was no evidence of genotoxicity in a limited range of studies in mammalian systems.

The NOAEL derived from the combined results of several studies conducted in humans, based on the depression of erythrocyte and plasma cholinesterase activities, was 0.3 mg/kg bw per day.

An ADI of 0-0.003 mg/kg bw was established on the basis of the NOAEL of 5 ppm, equivalent to 0.25 mg/kg bw per day, in the two-year study in rats for retinal degeneration, sciatic nerve demyelination, reduced body weight, anaemia, and decreased brain acetylcholinesterase activities. A safety factor of 100 was used. Since the toxicological end-points seen in animals were other than acetylcholinesterase inhibition, a safety factor of 10 could not be applied to the NOAEL in humans.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 7 ppm, equal to 1.6 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 5 ppm, equivalent to 0.25 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
5 ppm, equivalent to 0.25 mg/kg bw per day (study of reproductive toxicity)
0.3 mg/kg bw per day (maternal, embryo- and fetotoxicity and teratogenicity in study of developmental toxicity)

Rabbit: 1 mg/kg bw per day (maternal toxicity in study of developmental toxicity)
3 mg/kg bw per day (no embryo- or fetotoxicity or teratogenicity in study of developmental toxicity)

Dog: 0.3 mg/kg bw per day (one-year study of toxicity and carcinogenicity)

Human: 0.3 mg/kg bw per day

Estimate of acceptable daily intake for humans

0-0.003 mg/kg bw

Estimate of acute reference dose

An acute reference dose of 0.03 mg/kg bw was derived by applying the usual 10-fold safety factor from an NOAEL of 19 mg/kg bw (highest oral dose), corresponding to about 0.3 mg/kg bw per day, in humans. This was based on the absence of inhibition of erythrocyte acetylcholinesterase.

Studies that would provide information valuable for the continued evaluation of the compound

Observations in humans, particularly reports of poisoning incidents and/or evaluation of potential long-term neurological/behavioural effects.

Toxicological criteria for setting guidelines for dietary and non-dietary exposure to parathion-methyl

Exposure	Relevant route, study type, species	Results/Remarks
Short-Term (1-7 days)	Skin, sensitization, guinea-pig	Non-sensitizing
	Eye, sensitization, rabbit	Slightly irritating
	Skin, irritation, rabbit	Slightly irritating
	Inhalation 4-h, toxicity, rat	LC_{50} = 0.13 mg/litre
	Oral, toxicity, rat	LD_{50} = 4-62 mg/kg bw
	Dermal, toxicity, rat	LD_{50} = 480 mg/kg bw
	Acute neurotoxicity, one dose, rat	NOAEL = 0.025 mg/kg bw per day
Medium-term (1-26 weeks)	Repeated dermal, 21-day, toxicity, rabbit	NOAEL = 10 mg/kg bw per day, based on decreases in brain acetylcholinesterase activity
	Repeated oral, 90-day, toxicity, rat	NOAEL = 0.125 mg/kg bw per day
	Oral, developmental toxicity, rat	NOAEL = 0.3 mg/kg bw per day, for decreased maternal body weights, decreased fetal weights, stunted growth
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.25 mg/kg bw per day on the basis of slight effects on pup survival
Long-term (≥ one year)	Repeated oral, two-year toxicity and carcinogenicity, rat	NOAEL = 0.25 mg/kg bw per day

4.28 PENCONAZOLE (182)

RESIDUE AND ANALYTICAL ASPECTS

Penconazole is a systemic triazole fungicide first evaluated in 1992.

At the 1994 CCPR the delegation of Germany stated that German GAP for grapes and pome fruits had been changed, and questioned the interpretation by the JMPR of the figures presented in the 1992 evaluation. The delegation of France requested clarification of the GAP for cucumbers, strawberries and tomatoes with respect to glasshouse and field applications.

The 1992 JMPR requested processing studies on apples and tomatoes and a method for the determination of residues of penconazole and its metabolites containing the 2,4-dichlorophenyl moiety in field-grown apples and grapes, because residues of the parent compound were found in metabolism studies on apples and grapes at only 10-15 % of the total residue levels.

The Meeting received updated information on GAP, the results of additional residue trials on pome fruits and grapes, a new analytical method, a study of freezer storage stability and an overall assessment of the residue situation for pome fruits and grapes by the manufacturer. Information on GAP for pome fruits, residue data and detailed comments were provided by Germany, and information on GAP by Australia, The Netherlands, New Zealand and the UK. Analytical methods, residue data and national MRLs were also provided by The Netherlands.

In addition to the analytical methods described in the 1992 evaluation a method for determining total residues of penconazole and all metabolites containing the 2,4-dichlorobenzyl group as 2,4-dichlorobenzoic acid (DCBA) has been used in some of the trials. Determination is by HPLC with UV detection. The LOD for plant material except straw was 0.02 mg/kg as DCBA corresponding to 0.03 mg/kg calculated as penconazole, and for straw 0.04 mg/kg as DCBA corresponding to 0.06 mg/kg as penconazole. The overall mean recovery at 0.06 and 0.3 mg/kg fortification levels was 67%.

Penconazole was stable for at least 16 months in apples and grapes under frozen conditions.

The Meeting was informed that GAP for cucumbers, tomatoes and strawberries refers to field treatments but the indoor use of penconazole on cucumbers is authorized in Switzerland.

GAP for the world-wide use of penconazole on all commodities was reported by the 1992 JMPR. The Meeting received updated information on GAP for pome fruits and grapes from Germany. The information on GAP provided by Australia, France, Greece, Italy and the United Kingdom was basically the same as in 1992.

Penconazole is applied to pome fruits and grapes by foliar spray as EC, WP or tablet (TP) formulations, alone or mixed with other fungicides. Up to 10 or more spray treatments with maximum rates of 0.07 kg ai/ha (Italy) or 0.09 and 0.15 kg ai/ha (South Africa, Morocco) are allowed.

The present Meeting reviewed the new residue data on pome fruits and grapes in the context of previous reviews.

Pome fruits. The 1992 JMPR estimated a maximum residue level of 0.2 mg/kg for pome fruits, based on numerous European trials with residues generally below 0.1 mg/kg, but also up to 0.17 mg/kg.

In addition to the trials evaluated in 1992, the present Meeting received reports of twelve German residue trials on apples and seven on pears from 1986-87 which accorded with German GAP (10-12 treatments with 0.038 kg ai/ha, 14-day PHI), but total residues were determined instead of those of the parent compound. Although the PHI for pears is 28 days (because a mixed formulation with mancozeb is used and the PHI is determined by ETU residues from mancozeb) the Meeting considered the 14-day residues on pears because the residue behaviour on apples and pears is comparable. Penconazole was applied 11 or 12 times at 0.037 kg ai/ha. After 14 days the total residues in apples ranged from 0.05 to 0.35 mg/kg and in pears from 0.05 to 0.29 mg/kg. As the

residue is defined as penconazole the total residues were not used in estimating a maximum residue level, but were noted as useful additional information. The Meeting agreed to maintain the current recommendation of 0.2 mg/kg for pome fruits.

Grapes. The 1992 JMPR estimated a maximum residue level of 0.2 mg/kg for penconazole in grapes, based on a large number of trials with residues generally below 0.2 mg/kg four weeks after the last treatment.

The present Meeting received data from numerous new trials according to GAP. In French trials in 1993 penconazole was applied eight times a season at rates from 0.014 to 0.028 kg ai/ha. Residues at PHIs of 28-30 days ranged from <0.02 to 0.04 mg/kg for the parent, and from <0.07 to 0.24 mg/kg for total residues. In three trials in South Africa (1 treatment, 0.03-0.045 kg ai/ha) total residues 14 days after the last treatment were from 0.08 to 0.14 mg/kg. Eleven German trials (6 treatments with 0.006-0.036 kg ai/ha) showed maximum total residues of 0.43 mg/kg and parent residues of 0.04 mg/kg (35-day PHI) and ten Italian trials (5-10 treatments with 0.002-0.003 kg ai/hl, 0.02-0.08 kg ai/ha) gave total residues from 0.1 to 0.32 mg/kg and parent residues from <0.02 to 0.07 mg/kg at a 14-day PHI.

Because the parent penconazole is the relevant residue with regard to consumer safety, the total residues determined as DCBA were not used for the estimation of a maximum residue level. The Meeting agreed to maintain the current recommendation of 0.2 mg/kg for grapes.

Raisins and grape pomace. Processing studies were carried out on grapes. Although parent residues were not detectable in wine and juice, they were found in raisins and wet pomace. Residues of the parent compound in 2 Italian trials were concentrated in raisins and dry pomace by factors of 2-3 and 22 respectively. Total residues as DCBA in 6 trials showed concentration factors ranging from 2 to 6 for raisins and from 4.5 to 11 for dry pomace. The Meeting estimated a maximum residue level of 0.5 mg/kg for dried grapes (raisins).

The recommended MRLs are recorded in Annex I.

FURTHER WORK OR INFORMATION

Desirable

Processing studies on apples and tomatoes (from 1992).

4.29 PIPERONYL BUTOXIDE (062)

TOXICOLOGY

Piperonyl butoxide was evaluated toxicologically by the JMPR in 1965, 1966, 1972 and 1992. An ADI of 0-0.03 mg/kg bw was allocated in 1972 on the basis of a one-year study in dogs. The 1992 JMPR confirmed the existing ADI and recommended that piperonyl butoxide be reviewed again in 1995 following submission of the results of studies of acute toxicity and teratogenicity in rats, appropriate studies of genotoxicity, an on-going one-year study in dogs, an on-going study of carcinogenicity in mice, studies of carcinogenicity in rats and mice performed by the US National Toxicology Program and observations in humans.

Piperonyl butoxide was re-evaluated by the present Meeting within the CCPR periodic review programme.

Piperonyl butoxide is metabolized by oxidation of the methylene group of the methylenedioxyphenyl moiety to yield carbon dioxide. The remainder of the molecule undergoes further degradation and is excreted mainly in the urine. As it is an alternative substrate (and therefore a competitive inhibitor) for the microsomal P450 system, piperonyl butoxide inhibits the metabolism of several drugs and pesticides. The mechanism of action of this inhibition has been elucidated in several studies.

In male rats, after single oral doses of about 500 mg/kg bw of [*methylene*-á-^{14}C]piperonyl butoxide, the label reached a peak in blood 3-12 h after dosing; the level dropped by about 50% within 24 h. The highest levels of radiolabel were found in the gastrointestinal tract and its contents, suggesting that enterohepatic circulation occurs. High levels of radioactivity were also found in the lung, liver, kidney, fat, prostate, and seminal vesicles. The excretion pattern was unchanged after 14 repeated doses of piperonyl butoxide.

Piperonyl butoxide has negligible acute toxicity, and it has been classified by the WHO as unlikely to present an acute hazard in normal use.

Both short-term and long-term studies show that the target organ of the toxicity of piperonyl butoxide is the liver. Males were slightly more sensitive than females. In a number of short-term studies in rodents, liver toxicity was characterized by liver enlargement with associated hypertrophic hepatocytes, focal necrosis and, at times, alteration of some clinical chemical parameters. The NOAEL for liver toxicity was about 100 mg/kg bw per day.

In rats exposed to piperonyl butoxide by inhalation at 0, 15, 74, 155 or 512 mg/m^3 for 6 h per day on five days a week for 13 weeks, effects were seen on the liver at the highest dose. Irritation of the upper airways was seen at all doses, with squamous metaplasia of the larynx.

In a one-year study in dogs fed diets containing 0, 100, 600 or 2000 ppm piperonyl butoxide, reduced body weight gain, increased liver weight with hypertrophic hepatocytes and alteration of some clinical chemical parameters were observed at 2000 ppm. The NOAEL in this study was 600 ppm, equal to 16 mg/kg bw per day.

Several carcinogenicity studies have been conducted in mice and rats, some of which were considered to be inadequate. In a 112-week study, mice were given diets containing 5000 or 10,000 ppm of piperonyl butoxide during weeks 1-30 and 500 or 2000 ppm during weeks 31-112. No increases in tumour incidence were observed. Mice were fed diets that gave a daily intake of 0, 30, 100, or 300 mg/kg bw for 78 weeks. Eosinophilic foci and adenomas with eosinophilic cells were observed more frequently in the livers of mid-dose males and high-dose males and females. The NOAEL in this study was 30 mg/kg bw per day on the basis of effects on the liver.

In a 12-month study of carcinogenicity in the liver, male mice were fed diets containing 0, 6000 or 12,000 ppm of piperonyl butoxide. Body weight was reduced in a dose-related manner and increased mortality was observed in high-dose animals. Hepatocellular adenomas and carcinomas were observed in treated groups. Piperonyl butoxide was carcinogenic at doses which were toxic to the liver and caused general toxicity.

In a two-year study in rats at dietary concentrations adjusted to achieve doses of 0, 30, 100 or 500 mg/kg bw per day, increased liver weights with corresponding hyperplasia and hypertrophy of hepatocytes, morphological changes, and lesions in the endocrine and hormone-sensitive organs were observed at 100 and 500 mg/kg bw per day. These effects were considered to be secondary to the ability of piperonyl butoxide to induce hepatic P450 enzymes. Piperonyl butoxide was not found to be carcinogenic in this study. After reconsideration of the data on testes in this study, previously evaluated by the 1992 JMPR, and taking into account the results of other long-term studies, the Meeting concluded that the NOAEL was 30 mg/kg bw per day on the basis of effects on the liver.

Two studies of carcinogenicity were conducted in rats fed diets containing 0, 5000, or 10,000 ppm of piperonyl butoxide. No significantly increased incidence of neoplasias was found in treated rats. Effects on body weight and mortality were observed at the highest dose. In one study, ileocaecal lesions were observed in both dose groups. Another study of carcinogenicity was conducted in rats fed diets containing 0, 6000, 12,000 or 24,000 ppm. Increased mortality was observed in mid-dose females. Absolute liver weight was increased in females at the low dose and in animals of both sexes at the high dose. Nodular lesions of the liver were observed in treated animals, and their incidence and severity were related to the dose. Hepatocellular adenomas and carcinomas were observed in the mid- and high-dose groups. Gastric and caecal haemorrhages, kidney lesions, anaemia, and platelet alteration were observed in treated animals. Piperonyl butoxide was carcinogenic at doses causing general toxicity.

In a 104-week study in rats, piperonyl butoxide (2,000 ppm) was given in the diet in combination with pyrethrins (400 ppm). A slight reduction in the body weights of treated females was the only adverse effect observed.

A two-generation study of reproductive toxicity, with one litter per generation, was conducted in mice fed diets containing 0, 1000, 2000, 4000, or 8000 ppm of piperonyl butoxide. An NOAEL could not be established because of reduced pup weight at all doses. Pup viability was reduced at the highest dose. In a two-litter, two-generation study of reproductive toxicity in rats at dietary levels of 0, 300, 1000, or 5000 ppm, the NOAEL for parental toxicity and pup development was 1000 ppm (equal to 68 mg/kg bw per day) on the basis of lower body weight at 5000 ppm. Embryo- and fetotoxicity were observed when pregnant mice were given single doses of 0, 1070, 1390, or 1800 mg piperonyl butoxide/kg bw by gavage on day 9 of gestation.

Piperonyl butoxide was not embryotoxic or teratogenic in rats or rabbits. Maternal toxicity was found in rats at 500 mg/kg bw per day and above. The NOAEL was 200 mg/kg bw per day in a study of developmental toxicity in rabbits given 0, 50, 100 or 200 mg piperonyl butoxide/kg bw per day by gavage. The incidence of common developmental variations, such as a greater number of full ribs and more than 27 presacral vertebrae was increased in all dosed groups. Since a clear dose-effect relationship was lacking, the relationship of this finding to treatment was considered dubious. The NOAEL for maternal toxicity was 50 mg/kg bw per day.

Piperonyl butoxide was not a skin sensitizer and was a mild skin and eye irritant in rabbits.

Piperonyl butoxide was adequately tested for genotoxicity in a range of assays *in vivo* and *in vitro*. The Meeting concluded that it is not genotoxic.

A single dose of 0.71 mg/kg bw of piperonyl butoxide did not alter antipyrine metabolism in humans. A study in which a formulation containing 3% piperonyl butoxide was spread on the ventral forearm of adult male volunteers indicated that about 8% of the applied dose would be absorbed

through the human scalp. These data did not contribute directly to the establishment of the ADI.

An ADI of 0-0.2 mg/kg bw was established on the basis of the NOAEL of 600 ppm (equal to 16 mg/kg bw per day) in the one-year study in dogs, with a 100-fold safety factor.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 30 mg/kg bw per day (78-week dietary study of toxicity and carcinogenicity)

Rat: 30 mg/kg bw per day (two-year dietary study of carcinogenicity)
200 mg/kg bw per day (maternal toxicity in study of developmental toxicity)
500 mg/kg bw per day (embryo- and fetotoxicity in study of developmental toxicity)
1000 ppm, equal to 68 mg/kg bw per day (study on reproductive toxicity)

Rabbit: 50 mg/kg bw per day (study of developmental toxicity)
200 mg/kg bw per day (embryo- and fetotoxicity and teratogenicity in study of developmental toxicity)

Dog: 600 ppm, equal to 16 mg/kg bw per day (one-year toxicity study)

Estimate of acceptable daily intake for humans

0-0.2 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

1. Further observations in humans
2. Short-term studies with mixtures of piperonyl butoxide and other active ingredients, in ratios relevant to human exposure

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to piperonyl butoxide

Exposure	Relevant route, study type, species	Results, Remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Mildly irritating
	Eye, irritation, rabbit	Irritating
	Skin, sensitization, guinea-pig	Not sensitizing
	Inhalation, lethality, rat	Lacrimation, salivation, nasal discharge and laboured breathing at 5.9 mg/l for 4 h. No mortality.
	Oral, lethality, mouse, rat, cat, dog	LD_{50} = 4-14 g/kg bw

Exposure	Relevant route, study type, species	Results, Remarks
	Dermal, lethality, rabbit	LD_{50} = >2 g/kg bw
Medium-term (1-26 weeks)	Repeated oral, toxicity, mice and rats	3-13 week studies; NOAEL _100 mg/kg bw per day (liver effects)
	Repeated inhalation, toxicity, rats	13-week study; irritant to upper airways at 15 mg/m^3 for 6 h per day, 5 days per week, with squamous metaplasia of the larynx; effects on the liver at 512 mg/m^3
Medium-term	Oral, developmental toxicity, rabbit	NOAEL = 50 mg/kg bw per day for maternal toxicity; no fetotoxicity or teratogenicity
	Oral, reproductive toxicity, rat	NOAEL = 68 mg/kg bw per day; maternal and pup toxicity
Long-term (≥ one year)	Repeated oral, toxicity, dog	One-year study; NOAEL = 16 mg/kg bw per day

4.30 PROFENOFOS (171)

RESIDUE AND ANALYTICAL ASPECTS

Profenofos was reviewed by the JMPR in 1990, 1992 and 1994. At the 1995 CCPR questions were raised concerning the basis for the limits recommended for cotton seed and meat, which were held at Step 7B, and for tea which was held at step 6. The Meeting reviewed additional information provided for cotton seed and tea and considered the question on meat on the basis of information in earlier JMPR monographs. The Meeting also considered information provided to clarify GAP for green peppers in the context of data evaluated by the 1994 JMPR.

Cotton seed. The Meeting received confirmation that residues up to 2.8 mg/kg after 14 days reported in 1990 had been erroneously recorded as being from GAP treatments, whereas in fact the applications had been at twice the GAP rate. The original reports show that maximum residues after 14 days from the GAP application rate were ≤1.2 mg/kg. The Meeting noted that several results from a relatively limited number of trials were very close to or slightly above 1 mg/kg, concluded that although a 3 mg/kg limit was not required, a 1 mg/kg limit might be too low, and recommended reduction of the 3 mg/kg proposal to 2 mg/kg. The Meeting saw no need to revise the current proposal of 0.05 mg/kg (at the limit of determination) for edible cotton seed oil.

Meat. The Meeting re-examined the text of the 1990 JMPR monograph to resolve the question raised at the 1995 CCPR, on the limit of determination for profenofos in meat. The recommendation recorded in 1990 is 0.02* mg/kg, but the 1990 monograph makes it clear that the limit of determination in meat is 0.05 mg/kg. The Meeting concluded that 0.02 mg/kg had been recorded in error and recommended that the estimate of 0.02 mg/kg should be changed to 0.05 mg/kg.

Teas (tea and herb teas). The 1994 JMPR had confirmed the temporary maximum residue level of 0.5 mg/kg estimated by the 1990 JMPR for tea. The 21-day PHI used for the estimate was questioned at the 1995 CCPR. The Meeting was informed that the GAP PHI had since been revised to 30 days.

Because the available data no longer accorded with GAP the Meeting recommended withdrawal of the previous estimate.

Peppers, Sweet. The 1994 JMPR concluded that the available data on green peppers could support an estimate of a maximum residue level of 0.5 mg/kg after 28 days if the application rates of 0.2-0.65 kg ai/ha used in the trials could be related to Italian GAP. Information provided to the present Meeting confirmed that the applications were equivalent to 0.04 to 0.05 kg ai/hl, which is the concentration specified in Italian GAP (one application at 0.04-0.05 kg ai/hl, equivalent to 0.24-0.4 kg ai/ha, with a 28 day PHI). With this confirmation that GAP had been followed and the observation that even at exaggerated rates residues only slightly exceeded 0.5 mg/kg the Meeting endorsed the 1994 JMPR view and estimated a maximum residue level of 0.5 mg/kg.

The revised recommendations for cotton seed, green peppers and meat are recorded in Annex I.

4.31 QUINTOZENE (064)

TOXICOLOGY

Quintozene (pentachloronitrobenzene) was evaluated toxicologically by the JMPR in 1969, 1973, 1975 and 1977. An ADI of 0-0.007 mg/kg bw was allocated in 1973, and confirmed in 1977.

Quintozene was re-evaluated by the present Meeting within the CCPR periodic review programme.

Quintozene produced in the past was frequently contaminated with high levels (up to 11%) of hexachlorobenzene, a pesticide for which the conditional ADI of 0-0.0006 mg/kg was withdrawn by the JMPR in 1978. Hexachlorobenzene is both tumorigenic and teratogenic. Its presence in the older technical-grade quintozene was probably responsible for the toxic effects that were observed. The present review of the data on the toxicity of quintozene is therefore predicated mainly on new data from studies of quintozene containing less than 0.1% hexachlorobenzene.

Quintozene is absorbed relatively slowly after oral administration in rats and mice, peak blood levels being observed about 74 h after dosing. ^{14}C from labelled quintozene is eliminated mainly in the faeces in animals of both sexes although females excrete greater amounts in the urine than males. In goats, low doses (30 mg/kg bw) were excreted mainly in the urine, but faecal elimination predominated at higher doses (100 mg/kg bw). Bile levels in ruminants were high, and enterohepatic circulation is probable. Excretion was more rapid and complete in chickens than in mammals. There was no evidence of tissue accumulation in any species.

The biotransformation of quintozene was virtually complete. Two general metabolic pathways were apparent, one involving reduction of the nitro group to an amino group and subsequent formation of secondary metabolites, and the second involving replacement of the nitro group with a sulfur-containing group (e.g. a thio- or methylthio-glucuronide or *N*-acetylcysteine group). Metabolic studies in several species have been reported for quintozene.

The acute oral LD_{50} of quintozene was greater than 1.5 g/kg bw in both rats and dogs. The dermal LD_{50} exceeded 5 g/kg bw in rabbits, and the 4-h LC_{50} in rats exceeded 1.7 mg/litre air.

Quintozene was mildly irritating to the rabbit eye and not irritating to rabbit or human skin, but it was a mild dermal sensitizing agent in guinea-pigs and humans. The WHO has classified quintozene as unlikely to present an acute hazard in normal use.

In a single 13-week study in mice at dietary concentrations of 0, 1250 (males only), 2500, 5000, 10,000, 20,000 or 40,000 (females only) ppm, 5-8% decreases in terminal body weight were seen at 10,000 ppm and above, and increased absolute liver weights were seen in animals of both sexes at all doses. All mice at 40,000 ppm died.

Four short-term studies in rats were available; in only one of them was quintozene containing less than 0.1% hexachlorobenzene used. Dietary concentrations of 0, 50, 3000 or 6000 ppm administered for 13 weeks resulted in an NOAEL of 50 ppm (equal to 3.1 mg/kg bw per day) on the basis of a slight (6-8%) reduction in terminal body weight, increased liver weight and decreased alanine aminotransferase activity at higher doses.

Five short-term studies in dogs (lasting four weeks to two years) were available, only one of which met the purity specification. In this one-year study at dietary concentrations of 0, 15, 150, or 1500 ppm, increased liver weight and hepatocellular hypertrophy were seen at 1500 ppm, which were accompanied by increased serum alkaline phosphatase and cholesterol levels and decreased alanine aminotransferase activity and creatinine levels. The NOAEL was 150 ppm, equal to 4.2 mg/kg bw per day.

A 70-day study in monkeys at a dietary concentration of 2 ppm did not reveal any adverse effects.

In a 21-day study in rabbits, with application to the skin of doses of 0, 30, 300 or 1000 mg/kg bw of quintozene for 6 h per day, significantly decreased alanine aminotransferase activity was seen at 1000 mg/kg bw per day. No irritation or other adverse effect was observed.

Four long-term (72-103-week) studies by oral administration in mice were available, only one of which met the contamination criterion. This 103-week study at dietary concentrations of 0, 2500 or 5000 ppm showed decreased terminal body weight in males (4 and 10% at 2500 and 5000 ppm) and females (18 and 21% at 2500 and 5000 ppm). Since the body weight losses in the females exceeded 10% at 2500 ppm only after week 92 of the study, the NOAEL was considered to be 2500 ppm (equal to 360 mg/kg bw per day), although the interpretation was complicated by *Klebsiella* infection. No evidence of carcinogenicity was seen.

In a study in which technical-grade quintozene (purity unknown) was applied dermally twice weekly (0.2 ml of 0.3% quintozene in acetone) to mice for 12 weeks, followed by twice-weekly dermal applications of croton oil for 20 weeks, no tumour induction was seen in the absence of a promoting agent.

Of four available long-term (two-year studies) in rats, only one met the contaminant specification. In this study, at doses of 0, 20, 3000 or 6000 ppm, thyroid follicular adenomas were seen at 3000 and 6000 ppm and possibly carcinomas at 6000 ppm (especially in males). Hepatocellular hypertrophy (mainly centrilobular), indistinguishable from that arising from increases in drug metabolizing enzyme activity, was also seen at 3000 and 6000 ppm. In the two-year study, the absolute and relative (to body and brain) weights of the thyroid and parathyroid were increased at the two highest doses in most instances. A special 90-day study on thyroid hormones showed hepatocellular hypertrophy, which was only minimal, after 90 days exposure at 20 ppm. Complete

reversibility was seen after 90 days withdrawal. Thyroid and parathyroid weights were decreased only after 30 days exposure. At 6000 ppm, T_3 and T_4 levels were decreased and levels of thyroid-stimulating hormone (TSH) were increased significantly at most intervals during dosing; the level of rT_3 was reduced at 90 days. All changes were reversible within 90 days after withdrawal. The changes in thyroid hormone levels are consistent with increased microsomal enzyme activity, resulting in increased excretion of T_3 and T_4 and subsequent disruption of the hypothalamic-pituitary-thyroid axis, causing increased circulating levels of TSH. TSH initiates increased production of T_3 and T_4 with follicular hyperplasia in the thyroid, leading to adenoma and, more rarely, carcinoma. Quintozene was thus carcinogenic. The induction of thyroid tumours appears to be secondary to the disruption of thyroid function as indicated by increased levels of TSH. The NOAEL for this effect was 20 ppm, equivalent to 1 mg/kg bw per day.

One of two multigeneration studies in rats met the criterion for the level of contamination. In this study, with dietary concentrations of 0, 20, 3000 or 6000 ppm and two litters per generation for two generations, dietary concentrations of 3000 and 6000 ppm reduced pup and adult body weights. The NOAEL was 20 ppm, equivalent to 1 mg/kg bw per day.

In studies of developmental toxicity, 13 mice (in part of a study investigating incidences of cleft palate and renal agenesis, subsequently shown to be induced by hexachlorobenzene contamination) received doses of 500 mg/kg bw per day by gavage on days 7-16 of gestation. Abortions occurred, and a low incidence of cleft palate (2%) and a high incidence (23%) of club foot were noted. Marked maternal toxicity was seen. Further, the administered material formed a solution, and not a suspension as in all other studies. The study was not considered in establishing the ADI.

Of three studies of developmental toxicity in rats, only one, using dose levels of 0, 30, 600 or 1200 mg/kg bw per day, was acceptable. The NOAEL for maternal and developmental toxicity was >1200 mg/kg bw per day. There was no evidence of the induction of malformations.

In a developmental toxicity study in rabbits given doses of 0, 12, 120 or 250 mg/kg bw per day or 0, 6.2 or 120 mg/kg bw per day, maternal toxicity was seen at 120 mg/kg bw per day and embryofetal toxicity at 250 mg/kg bw per day, including reduced pup weight, increased resorptions and increased stillbirth incidence; no increase in malformations was seen at any dose.

In a number of studies (e.g. mouse long-term, rat long-term, rat two-generation reproductive toxicity), the incidences of infection appeared to be slightly increased at high doses. Although the available histopathological examinations do not indicate effects on the immune system, it would be useful if studies could be performed to investigate the potential for quintozene to affect the immune system.

Quintozene has been tested in a range of studies for genotoxicity *in vitro.* An acceptable *in-vitro* assay is required to investigate the increase in chromosomal aberration frequency observed in cultured cells.

An ADI of 0-0.01 mg/kg bw was allocated on the basis of the NOAEL of 1 mg/kg bw per day in the two-year study, the study of thyroid toxicity and the two-generation study in rats, using a 100-fold safety factor.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and containing re-evaluations of the studies evaluated in previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 2500 ppm, equal to 390 mg/kg bw per day (103-week study of carcinogenicity)

Rat: 20 ppm, equivalent to 1 mg/kg bw per day (24-month of carcinogenicity study, multigeneration study and study of thyroid toxicity)
1200 mg/kg bw per day (study of developmental toxicity)

Dog: 150 ppm, equivalent to 4.2 mg/kg bw per day (one-year study of toxicity)

Rabbit: 12 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
120 mg/kg bw per day (embryo- and fetal toxicity in a study of developmental toxicity)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw, for quintozene containing less than 0.1% hexachlorobenzene

Studies that would provide information valuable for the continued evaluation of the compound

1. Assays of genotoxicity *in vivo* to assess possible chromosomal aberrations

2. Studies to assess the potential of quintozene to interfere with the immune system

3. Further observations in humans

Toxicological criteria for setting guidelines for dietary and non-dietary exposure to quintozene containing less than 1% hexachlorobenzene

Exposure	Relevant route, study type, species	Results/Remarks
Short-term (1-7 days)	Skin irritation, rabbit	Not irritating
	Eye irritation, rabbit	Minimally irritating
	Skin sensitization, guinea-pig (modified Buehler)	Mild sensitizer
	Dermal irritation, human	No irritation with 75% formulation
	Skin sensitization, human	Sensitization in 13/50 individuals
	4-h inhalation, toxicity, rat	LC_{50} >1.7 mg/litre air
	Oral, toxicity, rat and dog	>1.5 g/kg bw
Mid-term (1-26 weeks)	Dermal irritation, 21-day, rat	No irritation; body weight, food intake, haematology, clinical chemistry (except decreased alanine aminotransferase), urinalysis, organ weights and liver and kidney

Exposure	Relevant route, study type, species	Results/Remarks
		histopathology unaffected at doses up to 1000 mg/kg bw per day.
	Repeat oral, toxicity, 13-week, rat	NOAEL = 3.1 mg/kg bw per day; minimal changes in body and liver weight and reduced alanine aminotransferase
	Dietary, developmental toxicity, rabbit	NOAEL = 12.5 mg/kg bw per day for maternal toxicity, 125 mg/kg bw per day for embryo- and fetal toxicity, >250 mg/kg bw per day for teratogenicity
Long-term studies (≥ one year)	Dietary, toxicity or carcinogenicity, rat	NOAEL = 1 mg/kg bw per day, follicular adenomas of the thyroid and hepatocellular adenomas).

RESIDUE AND ANALYTICAL ASPECTS

Quintozene, originally evaluated by the JMPR in 1969 and re-evaluated for residues several times up to 1977, is included in the CCPR periodic review programme. The 1991 CCPR scheduled the periodic review for 1995 because new data were reported to be available (ALINORM 91/24A, para 316 and Appendix VI, para 15).

The Meeting received studies of animal and plant metabolism, analytical methods, updated information on GAP, data from supervised residue trials on vegetables and oilseed, and information on residues after storage and processing from the manufacturer. Information on analytical methods and national MRLs was also made available by The Netherlands, and on GAP by Australia, Canada and the UK. Germany and The Netherlands do not have registered uses.

The metabolism of quintozene was investigated in rats, goats, and chickens. In general, the metabolic pathways in all these species were similar. The major routes were (1) displacement of the nitro group by the sulfhydryl group of reduced glutathione or SH-containing amino acids and peptides, or by hydroxyl to yield pentachlorophenol; (2) reduction of the nitro group to form *N*-hydroxypentachloroaniline and conjugated pentachloroaniline; (3) dechlorination to yield tetrachloro analogues of the above compounds.

A feeding study on goats showed that quintozene was converted mainly to pentachloroaniline (PCA) and its glucuronide conjugate. Other metabolites formed in much smaller amounts were tetrachlorothioanisole, pentachlorothiophenol, and methyl tetrachlorophenyl sulfoxide. The majority of the activity was eliminated in the urine and faeces (38.3% and 19.2%, respectively). Milk and fat contained only one metabolite, identified as PCA. No quintozene was detected in the tissues, milk or urine.

When quintozene was fed to laying hens, pentachlorothioanisole (methyl pentachlorophenyl sulfide, PCTA), pentachlorothiophenol and pentachlorothiophenol conjugates with cysteine, malonylcysteine, pyruvate and acetate were identified in various tissues, eggs and excreta. Other metabolites found included tetrachlorothioanisole, tetrachlorothioanisole sulfone,

pentachlorothioanisole sulfoxide and tetrachloromethylsulfinylaniline ("methyl tetrachloroaniline sulfoxide"). A second pathway involved reduction of the nitro group to produce pentachloroaniline and *N*-hydroxypentachloroaniline.

Metabolism studies in plants (cabbage, potato and peanut) showed three major pathways similar to those in animals: reduction of the nitro group to form *N*-hydroxypentachloroaniline and pentachloroaniline, displacement of the nitro group by the sulfhydryl group of glutathione to give a glutathione adduct which is metabolized further or, to a lesser extent, by a hydroxyl group to give pentachlorophenol, and reductive or oxidative dechlorination, replacing chlorine by hydrogen or hydroxyl.

In cabbages grown in soil treated with [^{14}C]quintozene, the highest levels of radioactivity were found in the outer leaves. Seven metabolites were identified in leaf extracts, the two major ones being methyl tetrachlorophenyl sulfoxide and sulfone. Five minor components were identified as a methyl trichlorophenol sulfone, *N*-hydroxylated pentachloroaniline, methyl pentachlorophenyl sulfoxide and pentachlorothioanisole.

In potatoes grown in soil treated with [^{14}C]quintozene applied by pre-plant incorporation, only 6.4% of the total radioactivity was located in the potato pulp and 94% in the peel. The chloroform-soluble substances were identified mainly as pentachloronitrobenzene and pentachloroaniline with lesser amounts of pentachlorothioanisole, tetrachloronitrobenzene, tetrachlorophenol, and *N*-hydroxypentachloroaniline. Ether- and water-soluble residues were mainly conjugates of pentachlorothiophenol.

In peanuts planted in soil treated with [^{14}C]quintozene, the highest levels of ^{14}C were found in the roots (97%). The vines, shells and nuts had residues ranging from 2.7% in vines to 0.3% in nuts. Extraction with aqueous methanol removed 64-88% of the ^{14}C. The extract contained seven metabolites. The two major metabolites were identified as *S*-pentachlorothiophenyl-2-*N*-malonylcysteine and tetrachloroaniline, which were found in the roots, vines and shells.

No information on environmental fate was received. For this reason the Meeting recommended the withdrawal of all existing MRLs.

For residue analysis samples are extracted with hexane and cleaned up by liquid-liquid partition, GPC and Florisil column chromatography. Determination is by GLC with electron-capture detection. Limits of determination for quintozene, hexachlorobenzene (HCB), pentachlorobenzene (PB), pentachlorothioanisole (PCTA) and pentachloroaniline (PCA) in vegetables, nuts, oilseeds, milk, animal tissues and eggs ranged from 0.0005 to 0.05 mg/kg, and recoveries from 86 to 104% at fortification levels from 0.025 to 0.2 mg/kg.

The Meeting considered differences between the analytical conditions in specified laboratories and concluded that 0.01 or 0.05 mg/kg, depending on the commodity, were practical limits of determination of the parent compound for enforcement. For risk assessment purposes the Meeting noted that the total residues were relevant.

The residue was defined by a former JMPR as the sum of quintozene, PCTA and PCA. The present Meeting considered that the residue definition for risk assessment purposes for plant and animal commodities should be the sum of quintozene, PCTA and PCA, expressed as quintozene. This definition is also suitable for animal commodities for enforcement purposes since the parent quintozene is not an appropriate indicator compound for such commodities. Quintozene alone is a

suitable definition of the residue for enforcement purposes for crops. On the basis of the metabolism and animal transfer studies the Meeting agreed that quintozene should be described as fat-soluble. The rationale for the definition of residues is given in Section 2.8.1 of this report.

Studies of the stability of stored analytical samples showed that quintozene and its metabolites or impurities are stable as residues in head cabbages, kidney beans, potatoes, wheat, cotton seed and peanuts when stored at -20°C up to one year. Residues decreased to approximately 60-70% of the initial levels in peppers, tomatoes (including processed products), maize and soya beans after storage for six to eight months.

Quintozene is applied to garlic, beans, other vegetable seeds, potatoes, cereals and oilseed as a single seed treatment with DS, EC, FS, LS, PS or WP formulations, and to bulb, brassica, fruiting, leafy, legume, root and tuber vegetables, pulses, oilseed and coffee beans as one or two soil or plant treatments before or at planting with EC, DP, GR, SC or WP. The PHI depends on local conditions and is not relevant where the application is before or at the time of planting.

Primary food commodities of plant origin

The Meeting reviewed data on US supervised residue trials involving soil or plant treatments of broccoli, head cabbages, peppers, tomatoes, beans, potatoes, cotton seed and peanuts, and seed treatments of sugar beet, peas, barley, maize and soya beans. Residues of quintozene, the metabolites PCTA and PCA, and the impurities HCB and PB were detected.

In the calculation of total residues, the molecular weights of quintozene (295) and PCTA (296) are effectively the same. The molecular weight of PCA is 265 and a factor of 1.1 is used to express PCA as quintozene. Where concentrations of the individual metabolite PCA are given below these have been corrected by this factor and are therefore expressed as quintozene.

Bananas. No residue data were available. The Meeting was informed that quintozene was not used on bananas and agreed to withdraw the previous recommendation of 1 mg/kg.

Broccoli, Head cabbages. The US residue trials were according to US GAP for brassica vegetables (max. 34 kg ai/ha soil treatment broadcast) and approximately according to Australian GAP (37-56 kg ai/ha).

Broccoli plants were harvested at maturity, at PHIs of 64-83 days. 48 samples were analysed with a maximum total residue of 0.094 mg/kg (0.05 mg/kg quintozene, 0.044 mg/kg PCA, 0.004 mg/kg PCTA). PB and HCB could not be determined (<0.002 mg/kg). On the basis of these data the Meeting estimated maximum residue levels of 0.1 mg/kg total residue and 0.05 mg/kg parent compound to replace the previous recommendation (0.02 mg/kg).

In the cabbage trials plants were grown to maturity and harvested 67-125 days after application. 70 samples of white and savoy cabbage were analysed. In the samples without wrapper leaves the maximum total residue was 0.02 mg/kg (0.016 mg/kg quintozene, <0.002 mg/kg PCA and PCTA) and the residues of the impurities PB and HCB <0.002 mg/kg. In the samples with wrapper leaves, the maximum total residue was 0.11 mg/kg (0.062 mg/kg quintozene, 0.045 mg/kg PCA, 0.006 mg/kg PCTA) and the residues of the impurities 0.003 mg/kg PB and <0.002 mg/kg HCB. The Meeting estimated maximum residue levels of 0.2 mg/kg total residue and 0.1 mg/kg parent compound for head cabbages, based on the residues in samples with wrapper leaves, to replace the previous recommendation (0.02 mg/kg).

Other brassica vegetables. Quintozene is registered for soil treatment in Australia, the UK and the USA for brassica vegetables and in New Zealand for vegetables, but residue data were not available. The Meeting agreed that residue data from head brassicas and broccoli could not be extrapolated to cauliflower, Brussels sprouts or kohlrabi. A maximum residue level could not be estimated.

Sweet peppers, Tomatoes. The US residue trials were in accord with US GAP (max. 8.4 kg ai/ha).

In the trials on peppers the plants were harvested at maturity, at PHIs of 71-104 days. In the 20 samples analysed, the residues of quintozene, PB, HCB, PCA and PCTA were below the limits of determination (<0.05 mg/kg). The Meeting estimated maximum residue levels of 0.2* mg/kg total residue and 0.05* mg/kg parent compound as being practical limits of determination to replace the previous recommendation (0.01 mg/kg).

In the trials on tomatoes the fruits were harvested at maturity, at PHIs of 73-113 days. In the 18 samples analysed the maximum total residue was 0.016 mg/kg (0.012 mg/kg quintozene, <0.002 mg/kg PCA and PCTA). PB and HCB were below the limit of determination of 0.002 mg/kg. The Meeting estimated a maximum residue level of 0.02 mg/kg (both total residue and parent compound), to replace the previous recommendation (0.1 mg/kg).

Head lettuce. The use of quintozene on lettuce is registered in Australia as a soil application at singling, with a maximum of 0.11 kg ai/hl, and in New Zealand under the general GAP for vegetables. No residue data were received. The Meeting was informed that new studies were being considered but agreed to withdraw the recommendation of 3 mg/kg.

Common bean (pods and/or immature seeds), Common bean (dry). The trials at three US test locations (with treatment with three different formulations on each site) were in accordance with US GAP (1 soil treatment at max. 1.7 kg ai/ha).

Fresh beans were harvested at maturity, at PHIs of 42 to 62 days. In the samples analysed (from 18 trials) the maximum total residue was 0.093 mg/kg (0.081 mg/kg quintozene, 0.011 mg/kg PCA, <0.0005 mg/kg PCTA). PB and HCB were below the limit of determination (0.0005 mg/kg). In addition, 26 results from trials at exaggerated application rates were received. On the basis of the GAP trials, the Meeting estimated a maximum residue level of 0.1 mg/kg (both total residue and parent compound) to replace the previous recommendation (0.01 mg/kg).

In the 18 trials on dry beans the beans were harvested at maturity, at PHIs of 77 to 106 days. 18 samples were analysed with a maximum total residue of 0.03 mg/kg (0.02 mg/kg quintozene, 0.008 mg/kg PCA, 0.002 mg/kg PCTA). PB and HCB were below the limit of determination of 0.0005 mg/kg. Results of 19 trials at exaggerated rates were also received. On the basis of the GAP trials, the Meeting estimated maximum residue levels of 0.03 mg/kg total residue and 0.02 mg/kg parent compound for common bean (dry) to replace the previous recommendation (0.2 mg/kg).

Peas (dry). Results of eight US seed treatment trials on peas (0.12 kg ai/100 kg seed) were received, approximately in accordance with US GAP (0.096 kg ai/100 kg seed). The maximum total residue in dried peas was 0.017 mg/kg (0.007 mg/kg quintozene, <0.005 mg/kg PCA and PCTA). The Meeting estimated maximum residue levels of 0.02 mg/kg total residue and 0.01 mg/kg parent compound for dry peas.

Soya bean (dry). Sixteen US seed treatment trials on soya beans (0.1 kg ai/100 kg seed) approximated

US GAP (0.096 kg ai/100 kg seed). No residues of quintozene, PB, HCB, PCA or PCTA were found above the LOD of 0.005 mg/kg in the beans at harvest. The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound for soya bean (dry) as being practical limits of determination.

Potatoes. Quintozene is registered in Australia, Cyprus, Israel, Saudi Arabia and South Africa, but no residue data were received. US residue results based on single applications of 28 kg ai/ha (broadcast, 28 values) and 11 to 13 kg ai/ha (in-furrow, 22 values) were provided. The potatoes were harvested at maturity, at PHIs of 82 to 135 days. The maximum total residue was 1.5 mg/kg (0.96 mg/kg quintozene, 0.28 mg/kg PCA, 0.24 mg/kg PCTA). In the same sample, 0.064 mg/kg PB and 0.033 mg/kg HCB were determined. The Meeting was informed that new studies were being considered but concluded that as the US residue data could not be related to reported GAP it could not estimate a maximum residue level and agreed to withdraw the previous recommendation of 0.2 mg/kg.

Sugar beet. In eight US seed treatment trials according to GAP (0.19 kg ai/100 kg seed) no residues of quintozene were found above the LOD of 0.005 mg/kg in green leaves, or in roots or leaves at harvest. The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound for sugar beet as being practical limits of determination.

Barley. Six US seed treatment trials on barley (0.13 kg ai/100 kg seed) showed no residues of quintozene, PB, HCB, PCA and PCTA above the LOD of 0.005 mg/kg in the grain. The trials were approximately in accord with GAP in Spain (0.04-0.2 kg ai/100 kg seed) and the USA (max. 0.11 kg ai/100 kg seed). The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound for barley as being practical limits of determination.

Maize. In 12 US seed treatment trials on maize (0.052 kg ai/100 kg seed) no residues of quintozene, PB, HCB, PCA and PCTA were found above the LOD of 0.005 mg/kg in the grain. The trials accorded approximately with GAP in Spain (0.04-0.2 kg ai/100 kg seed) and the USA (0.048 kg ai/100 kg seed). The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound for maize as being practical limits of determination.

Wheat. Seed treatment with quintozene is registered in Brazil at 0.19 kg ai/100 kg seed and in the USA at 0.048 kg ai/100 kg seed. 20 US seed treatment trials at an application rate of 0.052 kg ai/100 kg seed showed a maximum total residue of 0.016 mg/kg (0.0061 mg/kg quintozene, <0.005 mg/kg PCA and PCTA) in the grain. No residues of PB or HCB were found above the LOD of 0.005 mg/kg. The Meeting estimated maximum residue levels of 0.02 mg/kg total residue and 0.01 mg/kg parent compound.

Cotton seed. The available US trials were in accordance with US GAP (1 soil treatment in-furrow at planting, maximum 2.3 kg ai/ha). Cotton seed was harvested at maturity, approximately five months after treatment. 36 samples were analysed with a maximum total residue of 0.028 mg/kg (0.008 mg/kg quintozene, 0.015 mg/kg PCA, <0.005 mg/kg PCTA). No residues of PB or HCB (<0.002, <0.005 mg/kg) were found. The Meeting estimated the previous MRL of 0.03 mg/kg as the total maximum residue level and estimated a maximum residue level of 0.01 mg/kg for the parent compound.

Peanuts. The available US trials approximated US GAP (maximum 2 soil applications of 5.6 kg ai/ha). Peanuts were harvested at maturity, 45 to 47 days after the last treatment. 32 samples of peanut kernels and hulls were analysed. In the hulls the maximum total residue was 1.3 mg/kg (0.94 mg/kg quintozene, 0.18 mg/kg PCA, 0.19 mg/kg PCTA). The same sample showed residues of 0.032 mg/kg

PB and 0.013 mg/kg HCB. In the kernels the maximum total residue in any one sample was 0.45 mg/kg (0.15 mg/kg quintozene, 0.18 mg/kg PCA, 0.12 mg/kg PCTA). The same sample contained 0.046 mg/kg PB and 0.017 mg/kg HCB. The maximum residue of the parent quintozene was 0.25 mg/kg, found in another sample (0.077 mg/kg PCA, 0.04 mg/kg PCTA, 0.045 mg/kg PB, 0.006 mg/kg HCB). No results were available for whole peanuts. The Meeting estimated a maximum residue level of 0.5 mg/kg (both total residue and parent compound) for peanuts to replace the previous recommendation (2 mg/kg), and agreed to withdraw the previous recommendation for whole peanuts of 5 mg/kg.

Animal products

Cattle. The Meeting reviewed a feeding study on dairy cows in which quintozene was fed at levels of 0.1, 1 and 10 ppm for 12-15 weeks. In the samples from the 0.1 and 1 ppm levels, no residues were found above the LOD of quintozene, PB or PCA in milk (<0.01, <0.001 and <0.005 mg/kg), kidney, liver, muscle (<0.05 mg/kg quintozene and PCA, <0.004 mg/kg PB), or fat (<0.1, <0.008 and 0.08 mg/kg). PCTA could not be quantified. Only HCB was detected in milk at the 1 ppm feeding level, with maximum residues at days 28-56 of 0.002-0-003 mg/kg. No HCB above the LOD of 0.02 mg/kg was found in the tissues, but fat showed a maximum residue of 0.1 mg/kg. Because PCTA was not analysed and the residue is defined as the sum of quintozene, PCA and PCTA the results are insufficient to estimate maximum residue levels for milk, meat or other edible products of cattle.

Chickens. Chickens were fed quintozene at levels of 0.05, 1, 5, 15, 75 and 300 ppm in the diet for four months. No residues of quintozene, PCA or PCTA were found above the LODs of 0.01 mg/kg in egg yolk and white, 0.04 mg/kg in meat and 0.03 mg/kg in liver, in the 0.05, 1, 5 or 15 ppm groups. In fat, no quintozene residues above 0.04 mg/kg could be found at levels up to 5 ppm. PB could not be found up to the 1 ppm feeding level in egg yolk (<0.005 mg/kg), egg white (<0.002 mg/kg), meat (<0.01 mg/kg) or liver (<0.006 mg/kg); 0.008 mg/kg was found in fat. HCB was determined in the 0.05 ppm group in fat (0.05 mg/kg) and liver (0.017 mg/kg) and in the 1 ppm group in egg yolk, fat and liver (0.012, 0.06 and 0.03 mg/kg), but not in egg white (<0.005 mg/kg) or meat (<0.01 mg/kg). No residues would be expected in practice from the use of quintozene, because the estimated maximum residue levels (both total and parent) in potential feeding-stuffs are generally less than 0.5 mg/kg. On the basis of the feeding levels up to 5 ppm and a maximum residue of 0.5 mg/kg to be expected in the diet, the Meeting estimated maximum total residue levels of 0.03* mg/kg for eggs and 0.1* mg/kg for chicken meat and edible offal as practical limits of determination.

Cereal fodders and straws

US seed treatment trials on barley, maize and wheat are described above, with details of the relevant GAP. Residues in the animal feed commodities were evaluated as follows.

Barley straw and fodder, dry. Four US trials on barley showed no residues of quintozene, PB, HCB, PCA or PCTA above the LOD of 0.005 mg/kg in barley straw. The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound as being practical limits of determination for barley straw and fodder, dry.

Maize forage and fodder. Thirteen results were received. No residues of quintozene, PB, HCB, PCA or PCTA were found above the LOD of 0.005 mg/kg in maize forage or fodder, except one residue of 0.006 mg/kg quintozene in the fodder. The Meeting estimated maximum residue levels of 0.02* mg/kg total residue and 0.01* mg/kg parent compound as being practical limits of determination for maize forage, and of 0.02 mg/kg (total residue) and 0.01 mg/kg (parent compound) for maize fodder.

Pea hay (dry). Results of eight US seed treatment trials on peas (0.12 kg ai/100 kg seed) were received, which were approximately according to US GAP (0.096 kg ai/100 kg seed). Quintozene residues were found in dried pea hay at <0.005 (4), 0.013, 0.015, 0.016 and 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg as parent compound for pea hay (dry), based on the rather small database, with four of the eight results at or about 0.02 mg/kg of the parent quintozene. The maximum total residue was 0.042 mg/kg (0.02 mg/kg quintozene, 0.017 mg/kg PCA, <0.005 mg/kg PCTA). PB and HCB could not be determined above the LOD of 0.005 mg/kg. The Meeting estimated a maximum total residue level, also of 0.05 mg/kg.

Soya bean fodder and forage. Sixteen US seed treatment trials on soya beans (0.1 kg ai/100 kg seed) were approximately in accord with US GAP (0.096 kg ai/100 kg seed). In whole green plants no residues of quintozene, PB, HCB, PCA or PCTA were found above the LOD of 0.005 mg/kg. The Meeting estimated maximum residue levels for soya bean forage of 0.02* mg/kg total residue and 0.01* mg/kg parent compound for soya bean forage as being practical limits of determination.

No residues of quintozene, PB, HCB, PCA or PCTA were found above the LOD of 0.005 mg/kg in hay or the whole plant at harvest (except one PCA residue of 0.015 mg/kg expressed as quintozene). The maximum total residue in the fodder was calculated as 0.025 mg/kg (0.015 mg/kg PCA, <0.005 mg/kg quintozene and PCTA). The Meeting estimated maximum residue levels for soya bean fodder of 0.03 mg/kg total residue and 0.01* mg/kg parent compound.

Wheat straw and fodder, dry. 20 trials on wheat showed a maximum total residue in straw of 0.033 mg/kg (0.023 mg/kg quintozene, <0.005 mg/kg PCA and PCTA). There were no residues of PB or HCB (except 1 of 0.014 mg/kg) in any sample. The Meeting estimated maximum residue levels of 0.05 mg/kg total residue and 0.03 mg/kg parent compound.

Processing studies were conducted on tomatoes and potatoes. Processing data on cotton seed and peanuts were also provided, but not evaluated because the validity of the studies was called into question.

Tomatoes were treated at 42 kg ai/ha (5 times the maximum label rate), but residues were too low to show the effects of processing. The study is being repeated.

Potatoes were treated with two, five or ten times the maximum label rate. Residues in the processed potato chips, granules and flakes did not exceed those in the whole raw potatoes (tubers or sliced raw chips). In only two of the eight trials, quintozene residues in cooked potato chips were higher than in the raw commodity. The results indicate that quintozene and its metabolites and impurities would not be concentrated by processing.

Because of the lack of critical supporting data on environmental fate the Meeting could not recommend the maximum residue levels it estimated for use as MRLs and, as mentioned above, recommended the withdrawal of existing MRLs.

Any future reconsideration of recommendations for MRLs will require the submission of data on bioaccumulation and soil degradation and metabolism. Processing studies on tomatoes, cotton seed and peanuts will also be required. Details of the data required are given above in Section 2.5.2.

4.32 THIOPHANATE-METHYL (077)

TOXICOLOGY

Thiophanate-methyl was evaluated toxicologically by the Joint Meeting in 1973, 1975 and 1977. In 1977 the Meeting confirmed the ADI of 0-0.08 mg/kg bw established in 1973. The compound was reviewed by the present Meeting within the CCPR periodic review programme.

Thiophanate-methyl was rapidly absorbed after oral exposure of mice, rats, and dogs. Most of the administered radiolabel was recovered within 24 h of dosing, predominantly in the urine. Carbendazim and 5-hydroxycarbendazim were among the metabolites of thiophanate-methyl identified *in vivo* and *in vitro*.

Thiophanate-methyl has low acute toxicity in rats, with an oral LD_{50} of about 7000 mg/kg bw. Clinical signs of toxicity after acute dosing with thiophanate-methyl were generally non-specific. The WHO has classified thiophanate-methyl as unlikely to present an acute hazard in normal use.

In a six-month study of toxicity, mice were given dietary doses of 0, 13, 64, 320, 1600 or 8000 ppm thiophanate-methyl. The NOAEL was 320 ppm, equivalent to 48 mg/kg bw per day, on the basis of haematological effects and hepatotoxicity. In a six-month study, rats were exposed to thiophanate-methyl in the diet at levels of 0, 13, 64, 320, 1600 or 8000 ppm. Reduced erythrocyte counts, reduced body weight gain, and evidence of hepatotoxicity and thyroid stimulation were seen at 8000 ppm. The NOAEL was 1600 ppm, equivalent to 80 mg/kg bw per day. Dogs were exposed to thiophanate-methyl by administration in capsules at doses of 0, 50, 200 or 400 mg/kg bw per day for 13 weeks or 0, 8, 40 or 200 mg/kg bw per day for one year or 0, 2, 10, 50 or 250 mg/kg bw per day for two years. Treatment-related thyroid hyperplasia was seen in all three studies; the overall NOAEL was 10 mg/kg bw per day.

In a two-year study of carcinogenicity in mice fed dietary levels of 0, 10, 40 160 or 640 ppm, there was no evidence of any carcinogenic response; the NOAEL was 160 ppm (equal to 24 mg/kg bw per day) on the basis of reduced body weight gain. In a subsequent 18-month study in mice fed dietary levels of 0, 150, 640, 3000 or 7000 ppm, the NOAEL was 150 ppm (equal to 29 mg/kg bw per day) on the basis of treatment-related hepatotoxicity and hepatocellular tumours. In a two-year study of carcinogenicity in rats fed dietary levels of 0, 10, 40, 160, or 640 ppm, effects were seen in the testes (mainly hypospermatogenesis), thyroid gland, and growth rate at 640 ppm; the NOAEL was 160 ppm (equivalent to 8 mg/kg bw per day). In a two-year study in rats fed dietary levels of 0, 75, 200, 1200 or 6000 ppm, the NOAEL was 200 ppm (equal to 9 mg/kg bw per day). Thyroid hyperplasia and thyroid tumours were seen at higher doses, together with parathyroid hyperplasia, nephrotoxicity, hepatotoxicity, and lipidosis of the adrenal cortex.

In a three-generation study of reproductive toxicity in which rats received dietary doses of 0, 40, 160 or 640 ppm, reductions in total litter size and weight at birth and at weaning were seen at 640 ppm; the NOAEL was 160 ppm, equivalent to 8 mg/kg bw per day. In a two-generation study in which rats received dietary doses of 0, 200, 630 or 2000 ppm, there was no evidence of a treatment-related effect on reproduction. The lowest dose tested in the study, equivalent to 10 mg/kg bw per day, was a minimal-effect level on the basis of hepatocyte hypertrophy, thyroid follicular-cell hypertrophy, and hyperplasia at all treatment levels.

The teratogenic potential of thiophanate-methyl was investigated in mice, rats, and rabbits. In mice exposed by gavage to thiophanate-methyl at doses of 0, 40, 200, 500 or 1000 mg/kg bw per day

on days 1-15 of gestation, there was no evidence of teratogenicity or maternal toxicity at the highest dose, although embryo- and fetotoxicity were seen at this dose. In rats exposed by gavage to thiophanate-methyl at doses of 0, 100, 300 or 1000 mg/kg bw per day on days 6-19 of gestation, there was no evidence of fetotoxicity or teratogenicity, but maternal toxicity, expressed as reduced body weight gain, was seen at the highest dose. In rabbits exposed by gavage to thiophanate-methyl at doses of 0, 2, 6 or 20 mg/kg bw per day on days 6-19 of gestation, maternal toxicity (reduced growth rate) was seen at 6 mg/kg bw per day and above. A dose-related trend of increased fetal skeletal abnormalities (ribs, vertebrae, and pelvis) at 6 and 20 mg/kg bw per day indicated an NOAEL for developmental toxicity of 2 mg/kg bw per day.

Thiophanate-methyl was adequately tested for genotoxicity in a series of assays *in vivo* and *in vitro*. The only significant response was a very small increase in the frequency of micronuclei characterized by their large size in mouse bone-marrow cells, which was not associated with the induction of structural chromosomal aberrations. This is indicative of a weak aneugenic effect. The Meeting concluded that thiophanate-methyl is not genotoxic.

Studies on the effects of thiophanate-methyl on the liver and thyroid of rats showed liver enzyme induction, reductions in thyroid hormones (T_3 and T_4), and increases in the level of thyroid-stimulating hormone and in thyroid and liver weights. Thyroid hypertrophy and increases in thyroid-stimulating hormone levels associated with treatment with thiophanate-methyl were suppressed by concomitant treatment with T_4. Thiophanate-methyl was shown to inhibit porcine thyroid microsomal peroxidase, an enzyme involved in thyroid hormone synthesis. Thyroidal and hepatic changes, including tumours, observed in the studies of toxicity may be due to increased hepatocyte turnover, reductions in the thyroid hormones T_3 and T_4 as a result of liver enzyme induction, and inhibition of thyroid microsomal peroxidase.

Workers involved in manufacturing products containing thiophanate-methyl showed no evidence of any treatment-related adverse local (skin or eyes) or systemic effects.

An ADI of 0-0.02 mg/kg bw was established on the basis of the NOAEL of 2 mg/kg bw per day for developmental toxicity in rabbits and a safety factor of 100.

The Meeting noted that the use of thiophanate-methyl on crops gives rise to residues of carbendazim, although thiophanate-methyl can also be detected as part of the residue to which consumers of treated produce are exposed. Since the toxicity of thiophanate-methyl is qualitatively and quantitatively (when corrected for relative molecular mass) different from that of carbendazim, the Meeting concluded that the intake of residues in food should initially be compared with the ADI for thiophanate-methyl. If further refinement of the risk assessment is necessary, the different components of the residue (carbendazim and thiophanate-methyl) may be characterized.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 150 ppm, equal to 29 mg/kg bw per day (18-month study of toxicity and carcinogenicity)
1000 mg/kg bw per day (maternal toxicity and teratogenicity in study of reproductive toxicity)
500 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)

Rat: 200 ppm, equal to 9 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
160 ppm, equivalent to 8 mg/kg bw per day (study of reproductive toxicity)
1000 mg/kg bw per day (teratogenicity and fetotoxicity in study of developmental toxicity)
300 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rabbit: 2 mg/kg bw per day (maternal toxicity and teratogenicity in a study of developmental toxicity)

Dog: 10 mg/kg bw per day (studies of toxicity up to two years)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

1. Comparison of metabolism of thiophanate-methyl to carbendazim among different species, including humans

2. Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to thiophanate-methyl

Exposure	Relevant route, study type species	Results/remarks
Short-term (1-7 days)	Oral, toxicity, rat	LD_{50} = 7000 mg/kg bw
	Dermal, toxicity, rat	LD_{50} = >10,000 mg/kg bw
	Dermal, irritation, rabbit	Not irritating
	Ocular, irritation, rabbit	Mildly irritating
	Dermal, sensitization, guinea- pig	Sensitizing in maximization test; not sensitizing in Buehler test
	Inhalation, toxicity, rat	LC_{50} = 1.8 mg/litre air

Exposure	Relevant route, study type species	Results/remarks
Mid-term (1-26 weeks)	Oral, reproductive toxicity, rabbit	NOAEL = 2 mg/kg bw per day; maternal and developmental toxicity
Long-term (> one year)	Dietary, toxicity and carcinogenicity, two years, rat	NOAEL = 9 mg/kg bw per day; thyroid tumours and hepatotoxicity
	Oral, toxicity, two years, dog	NOAEL = 10 mg/kg bw per day; hepatotoxicity and thyroid effects

EVALUATION OF EFFECTS ON THE ENVIRONMENT

See the report on benomyl (4.3), in which the environmental effects of benomyl, carbendazim and thiophanate-methyl are discussed.

4.33 TRIADIMEFON (133)

RESIDUE AND ANALYTICAL ASPECTS

Triadimefon has been reviewed many times since the first evaluation in 1979. MRLs were recommended for combined residues of triadimefon and triadimenol until 1989. Triadimenol being the principal metabolite of triadimefon and a pesticide in its own right. Triadimenol was evaluated for the first time in 1989, when a number of maximum residue levels were estimated to accommodate its direct use. On the basis of somewhat limited data the 1992 JMPR recommended separate MRLs for triadimefon and triadimenol. That Meeting considered additional data desirable.

The present Meeting reviewed comprehensive new data on the post-harvest use of triadimefon on pineapples to address a concern expressed at the 1994 CCPR (ALINORM 95/24, para 244) that the separate maximum residue levels of 1 mg/kg estimated for triadimefon and triadimenol were not supported by recent data. Other residue data and information on GAP submitted to the 1995 JMPR will be held on file in the FAO for evaluation by a future Meeting.

The Meeting confirmed that the limited data available to the 1992 JMPR were consistent with a ratio of triadimefon to triadimenol in the residue of 1:1 (or at most 2.5:1 from excessive applications). However, more recent results from 10 supervised post-harvest trials according to GAP support the views expressed at the CCPR that the ratio should be higher. The new data indicated that the triadimefon:triadimenol ratio from post-harvest dips according to GAP with a dry flowable formulation is 18 ± 5:1 under the conditions of the experiments in which samples were taken for analysis immediately after treatment.

The average residues of triadimefon in the whole fruit (calculated from separate analyses of peel and pulp) were 12.5 times those in the pulp and triadimenol residues were over 7 times those in the pulp, although the latter estimate is not exact since only one residue in pulp was measurable (0.01 mg/kg). The calculated residues in the whole fruit (peel + pulp, crown removed)

of triadimefon ranged from 0.8 to 1.7 mg/kg (mean, 1.2 S.D. ± 0.33) and those of triadimenol from 0.05 to 0.1 mg/kg (mean 0.07 ± 0.02). The Meeting gave greater weight to the new data which show that shortly after dipping triadimefon residues are likely to exceed 1 mg/kg, and recommended that the current 1 mg/kg proposal be increased to 2 mg/kg.

The situation with triadimenol is less clear. The recent data clearly show that the triadimefon:triadimenol ratio shortly after treatment is much higher than in the 3 studies reviewed previously, which indicated a ratio of 1:1 or at the most 2.5:1. The recent data alone would support a maximum residue level of triadimenol of 0.1 mg/kg or perhaps 0.2 mg/kg, since most of the residues are close to 0.1 mg/kg. A level of 0.2 mg/kg might also be supported in view of the variability shown in the 10 trials (the ratio of triadimefon to triadimenol varied from 13.6:1 to 29:1).

However, because samples were taken immediately after treatment, the Meeting was concerned that the results did not reflect the maximum triadimenol residues likely to occur in commercial practice after storage. The Meeting therefore concluded that the new trials did not provide an adequate basis for revising the MRL of 1 mg/kg recommended by the 1992 JMPR for triadimenol and confirmed that recommendation.

Because it seemed that triadimenol residues could increase during commercial storage after treatment, the Meeting considered that information on triadimefon and triadimenol residues in commerce or at consumption was desirable for further confirmation of the estimates.

The analytical method used for triadimefon included enzymatic incubation to allow the determination of conjugated residues. Determination was by GLC with NP detection and the limit of determination was approximately 0.01 mg/kg in whole pineapples.

Only summary data from studies of the storage stability of analytical samples were provided with the report of the pineapple trials. These were not with pineapples, but with triadimefon or triadimenol on grapes, wheat grain and forage, tomatoes and potatoes. Generally the results would give credence to the pineapple trials if confirmed by the original reports. The Meeting concluded that any future periodic review of triadimefon and triadimenol would require submission of the full reports of storage stability studies, not only summary data.

The recommendation for pineapple is recorded in Annex I.

FURTHER WORK OR INFORMATION

Desirable

Information on residues of triadimefon and triadimenol in pineapples in commerce or at consumption.

4.34 TRIADIMENOL (168)

RESIDUE AND ANALYTICAL ASPECTS

At the 1994 CCPR attention was drawn to the availability of recent data on the use of triadimefon

as a post-harvest dip, which were reported to show that the maximum residue levels of 1 mg/kg estimated by the 1992 JMPR for triadimefon and triadimenol resulting from the use of triadimefon on pineapples were inappropriate. The Meeting evaluated these data with other previously reviewed information and confirmed the previous estimate of 1 mg/kg for triadimenol.

A complete appraisal of the available data on triadimefon and triadimenol residues in pineapples is given above in the report on triadimefon (4.33).

FURTHER WORK OR INFORMATION

Desirable

Information on residues of triadimefon and triadimenol in pineapples in commerce or at consumption.

4.35 VINCLOZOLIN (158)

TOXICOLOGY

Vinclozolin was evaluated toxicologically by the Joint Meeting in 1986 and 1988. In 1986, although the data were considered incomplete, sufficient information was provided to establish a temporary ADI of 0-0.04 mg/kg bw on the basis of an NOAEL of 7 mg/kg bw per day in a six-month study in dogs and a 200-fold safety factor. It was noted that a plant metabolite (metabolite T) had been identified which was not found in rats. In 1988, the Meeting evaluated limited toxicity data on metabolite T and noted that the chemical had been found as a transient residue in only two commodities. An ADI of 0-0.07 mg/kg bw was established on the basis of the same no-effect level as that used in 1986 and a safety factor of 100. Since that time, more information has become available and brought to the attention of the JMPR at sessions of the CCPR. The compound was therefore reviewed by the present Meeting.

Vinclozolin is well absorbed after oral administration to rats and extensively metabolized. The majority of the administered radiolabel was found in the bile, and no unchanged vinclozolin was excreted in the urine. After single oral doses of radiolabelled vinclozolin, excretion was rapid; after multiple doses there was no significant accumulation. Vinclozolin is only moderately absorbed via the dermal route in rats: over 72 h, about 17% of a dose of 0.13 mg/kg bw was excreted in the urine.

Vinclozolin has low acute toxicity, with an oral LD_{50} in rats of >15,000 mg/kg bw. The clinical signs of toxicity after acute dosing with vinclozolin were generally non-specific and there were no consistent treatment-related findings at necropsy. Vinclozolin is not irritating to rabbit skin or eyes, but induced skin sensitization in a maximization study in guinea-pigs. The WHO has classified vinclozolin as unlikely to present an acute hazard in normal use.

Studies of repeated administration were carried out in mice, rats, rabbits and dogs in which vinclozolin and/or its metabolites caused toxic effects indicative of anti-androgenic activity. In two three-month feeding studies in different strains of mice at dietary levels between 100 and 5000 ppm, the NOAEL was equivalent to 20 mg/kg bw per day in both studies, on the basis of signs of hepatotoxicity, signs consistent with anti-androgenicity and changes in the

adrenal glands. In two recent three-month feeding studies in rats (at levels of 0, 300, 1000 and 3000 ppm and 0 and 50 ppm) vinclozolin caused changes qualitatively similar to those seen in mice; however, effects on the adrenal glands (including lipidosis) were seen at 300 ppm, and the NOAEL was confirmed in the second study as 50 ppm, equal to 4 mg/kg bw per day. In a 12-month feeding study in dogs using dietary levels of 0, 35, 75 150 or 1500 ppm, the NOAEL was 75 ppm, equal to 2.4 mg/kg bw per day, on the basis of pathological changes in the liver, spleen, prostate, testes and adrenals. The results of studies incorporating withdrawal periods indicate that the anti-androgenic effects of vinclozolin are reversible on cessation of treatment.

In a recent study of carcinogenicity in C57Bl/6 mice at dietary levels of 0, 15, 150, 3000 or 8000 ppm, hepatocellular carcinomas were seen at 8000 ppm. There was evidence of toxicity at 3000 ppm, including hepatotoxicity, Leydig-cell hyperplasia, atrophy of accessory sex glands, atrophic uteri and lipidosis in the cortico-medullary region of the adrenals. The NOAEL was 150 ppm, equal to 24 mg/kg bw per day. In an earlier study in NMRI mice at levels of 0, 160, 490, 1460 or 4370 ppm, survival was adversely affected at the highest dose, and the NOAEL was 490 ppm on the basis of increased liver weight, without histological change. In rats, the long-term toxicity and carcinogenicity of vinclozolin has recently been investigated in three studies using dietary levels between 25 and 4500 ppm. Cataracts and other lenticular changes were seen in rats treated with 50 ppm or more. (Mice and dogs were closely examined for ocular changes, but vinclozolin did not affect the eyes in these species.) An increased incidence of Leydig-cell tumours was seen in rats treated with 150 ppm and more, together with atrophy of accessory sex glands. Benign sex cord stromal tumours in the ovaries were seen in rats treated at 500 ppm and above, and uterine adenocarcinomas were detected at 3000 ppm (the highest dose tested in the carcinogenicity study). Adrenal tumours were seen at 1500 ppm and above. Hepatocellular carcinomas were seen in males treated with 4500 ppm, and signs of hepatotoxicity were seen in rats treated with 150 ppm or more. The NOAEL was 25 ppm, equal to 1.4 mg/kg bw per day.

In multi-generation studies, vinclozolin led to infertility of males, owing to feminization of the outer genital organs, at dietary levels of 1000 ppm or more. At 300 ppm, although all males were eventually proved fertile, the observed effects may have indicated sub-fertility. At 50 ppm, the only adverse effect was a reduction in epididymal weight (with no associated morphological changes) in F_2 offspring. The NOAEL was 40 ppm, equivalent to approximately 4 mg/kg bw per day. Recent investigations of developmental toxicity have been conducted in rats and rabbits. In rats, the most sensitive indicator of teratogenicity was a reduction in the anogenital distance; in a series of studies, the NOAEL for a change in anogenital distance was 15 mg/kg bw per day. The NOAEL for fetotoxicity was about 100 mg/kg bw per day, on the basis of signs of developmental delay, while the NOAEL for maternal toxicity was about 400 mg/kg bw per day, on the basis of clinical signs of toxicity.

Three studies of developmental toxicity have been conducted in rabbits. In the first, there were no signs of maternal toxicity, fetotoxicity or teratogenicity at doses up to and including 300 mg/kg bw per day. In the second study, with doses up to and including 800 mg/kg bw per day, toxicity led to extensive mortality at the highest dose, precluding any reliable assessment at this dose level. The NOAEL for maternal toxicity was 50 mg/kg bw per day, and that for fetotoxicity was 200 mg/kg bw per day; there was no evidence of teratogenicity at this dose (the highest dose available for assessment). The third study involved only one dose, 400 mg/kg bw per day. The number of female offspring exceeded the number of males, but there was no treatment-related change in the appearance of the male fetal genital organs. An increase in separated origins of the carotid arteries indicated potential teratogenicity at this maternally toxic dose.

Vinclozolin has been tested for genotoxicity in a range of tests *in vivo* and *in vivo*. The Meeting concluded that vinclozolin is not genotoxic. It noted that positive results were obtained in a study of cell transformation, but the process giving rise to this effect is unknown. One study suggests that vinclozolin may be a promoter in rat liver *in vivo*, which may indicate the mechanism by which liver tumours were induced in rats at a high dose.

Studies have been conducted that confirm the anti-androgenic properties of vinclozolin, which are likely to be associated with binding to the androgen receptor. This proposed mechanism of action could account for the results seen in studies of reproductive toxicity with vinclozolin and for the results of long-term toxicity studies.

In an epidemiological study of manufacturing plant personnel it was concluded that there was no evidence that vinclozolin had induced health effects in employees with possible long-term exposure to vinclozolin.

An ADI of 0-0.01 mg/kg bw was established on the basis of the NOAEL of 1.4 mg/kg bw per day in the two-year study of carcinogenicity in rats and a safety factor of 100.

A toxicological monograph was prepared, summarizing the previous evaluation and including summaries from the previous monograph and monograph addendum.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 100 ppm, equal to 20 mg/kg bw per day (three-month study of toxicity)
490 ppm, equivalent to 63 mg/kg bw per day (112-week study of toxicity and carcinogenicity in NMRI mice)
150 ppm equal to 24 mg/kg bw per day (18-month study of toxicity and carcinogenicity in C57Bl/6 mice)

Rat: 50 ppm, equal to 4 mg/kg bw per day (three-month study of toxicity)
25 ppm, equal to 1.4 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
40 ppm, equivalent to 4 mg/kg bw per day (study of reproductive toxicity)
15 mg/kg bw per day (study of developmental toxicity)
100 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)
400 mg/kg bw per day (maternal toxicity, in a study of developmental toxicity)

Rabbit: 50 mg/kg bw per day (maternal toxicity, in a study of developmental toxicity)
200 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)

Dog: 75 ppm, equal to 2.4 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to vinclozolin

Exposure	Relevant route, study type, species	Results/remarks
Short-term (1-7 days)	Oral, toxicity, rat	LD_{50} >15,000 mg/kg bw
	Dermal, toxicity, rat	LD_{50} >5000 mg/kg bw
	Dermal, irritation, rabbit	Non-irritating
	Ocular, irritation, rabbit	Non-irritating
	Dermal, sensitization, guinea-pig	Sensitizing in maximization test
	Inhalation, toxicity, rat	LC_{50} >29 mg/litre air
Mid-term (1-26 weeks)	Oral, developmental toxicity, rat	NOAEL = 15 mg/kg bw per day; teratogenicity
Long-term (> one year)	Dietary, two years, toxicity and carcinogenicity, rat	NOAEL = 1.4 mg/kg bw per day; signs of anti-androgenicity
	Dietary, one year, toxicity, dog	NOAEL = 2.4 mg/kg bw per day; signs of anti-androgenicity

5. RECOMMENDATIONS

5.1 In the interests of public health and agriculture and in view of the needs of the Codex Committee on Pesticide Residues, the Meeting recommended that Joint Meetings on Pesticide Residues should continue to be held annually.

5.2 (Section 2.7) The Meeting endorsed the recommendations in the report of the Joint FAO/WHO Expert Consultation on *Application of Risks Analysis to Food Standards Issues* (1) that dietary intake of pesticide residues should be assessed by Codex member countries and (2) that the use of standardized test protocols and minimal data requirements should be encouraged.

5.3 (Section 2.7) The Meeting re-affirmed the 1994 JMPR recommendation that international organizations, industry and governments should be encouraged to develop internationally agreed minimum data requirements for supervised residue trials, and recommended that these international organizations consider the development of harmonized requirements for critical supporting studies (metabolism, analytical methods, frozen storage stability, processing and animal transfer studies).

5.4 (Section 2.8.1) The Meeting recommended that:

(1) For new compounds and compounds in the periodic review programme, national definitions of residues and the basis for them should be supplied to the JMPR.

(2) Separate definitions of residues for enforcement (the estimation of maximum residue levels and compliance with MRLs) and for dietary intake purposes should be established when the requirements are in conflict.

(3) The requirements for the estimation of maximum residue levels and for the estimation of dietary intake should be taken into account in supervised residue trials. Where possible, residue components of different toxicological significance should be recorded separately and ideally the trials should provide separate results for the parent compound and each important metabolite.

5.5 (Section 2.8.3) The Meeting recommended that comments should be invited from the CCPR and member countries on national approaches to estimating MRLs for multi-component residues at or about the limit of determination and on an approach suggested by the 1995 JMPR.

5.6 (Section 2.9.3) The Meeting recommended that views of the CCPR be sought on:

(1) The JMPR intention to shorten reports on compounds.

(2) The usefulness of the current detailed JMPR residue reports for facilitating the progress of MRL recommendations.

(3) Whether the production of brief reports would meet the needs of CCPR until the JMPR Residue Evaluations are available.

5.7 (Annex IV) The Meeting recommended that:

(1) The JMP should consider issues relevant to the establishment of guideline values (GVs) for pesticides in drinking-water whenever full environmental and toxicological assessments are being performed.

(2) Whenever the need arises for recommending a GV for a specific pesticide that has not been evaluated previously or recently, the WHO drinking-water expert groups should request the JMP to conduct a new or updated environmental and toxicological assessment of the pesticide in question.

6. FUTURE WORK

The following items should be considered at the 1996 or 1997 Meeting. The compounds listed include those recommended for priority attention by the 26th or earlier Sessions of the CCPR, as well as compounds scheduled for re-evaluation in the CCPR periodic review programme.

6.1 1996 Meeting (tentative)

Toxicological evaluation

New compounds

Flumethrin
Tebufenozide

Periodic review compounds

Carbaryl (008)
Carbofuran (096)
2,4-D (020)
Dimethoate (027)
Ferbam
Maleic hydrazide
Mevinphos (053)
Triforine (116)
Ziram

Other evaluations

Phorate (112)

Residue evaluation

New compounds

Flumethrin
Tebufenozide
Teflubenzuron

Periodic review compounds

Chlorfenvinphos (014)
Ferbam
Phosmet (103)
Thiram
Ziram

Other Evaluations

Acephate (095)
Aldicarb (117)
DDT (021)
Diazinon (022)
Fenarimol (192)
Haloxyfop (193)
Methamidophos (100)
Propoxur (075)

6.2 1997 Meeting (tentative)

Toxicological evaluation

New compounds

Chlorpropham
Fenbuconazole

Periodic review compounds

Amitrole (079)
Chlormequat (015)
Fenamiphos (085)
Guazatine (114)
Malathion (049)

Other evaluations

Ethephon (106)
Lindane (048)
Phosalone(060)

Residue evaluation

New compounds

Chlorpropham
Fenbuconazole

Periodic review compounds

Carbofuran (096)
Demeton-S-methyl (073)
Demeton-S-methylsulphon (164)
Dodine (084)
Guazatine (114)
Mevinphos (053)
Oxydemeton-methyl (166)
Thiabendazole (065)

Other evaluations

Abamectin (177)
Carbosulfan (145)
Chlorothalonil (081)

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1976a of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Plant Production and Protection Series, No.1; WHO Technical Report Series, No. 592.

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1977a of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues.
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CORRECTIONS TO REPORT OF 1994 JMPR

Additions and changes are shown **bold**. Minor typographical errors are not included.

P. iii (Table of Contents)
4.9 Chlorfenvinphos:
Insert double asterisk to read **4.9 Chlorfenvinphos ** (T)**
Footnote:
Change * evaluation in the periodic review programme
** new compound
to *** new compound**
**** evaluation in the periodic review programme**

P. iv (Table of Contents)
4.17 Dimethoate:
Delete the double asterisk to read **4.17 Dimethoate (R)**
4.34 Parathion-methyl:
Insert double asterisk to read **4.34 Parathion-methyl ** (R)**
4.46 Tolclofos-methyl:
Insert T (for Toxicology) to read **4.46 Tolclofos-methyl * (T,R)**

P. 7, last para, line 2
Insert "no" to read "usually lead to **no** detectable residues..."

P. 27 (aldicarb), para 3, line 5
Change "...rates up tok 56 kg ai/ha..." to "...rates up **to 60 kg ai/tree**..."
P. 34 (aldicarb)
Add below last para:

FURTHER WORK OR INFORMATION

Required (by 1996)

Submission of all available data on residues in potatoes from trials reflecting current use patterns.

P. 156 (pirimiphos-methyl), last line
Change "the 1976 JMPR" to "the 19**85** JMPR"

P. 162 (propiconazole), para 2
Change the last sentence to read:
"The manufacturer does not recommend use on melons, peppers **or tomatoes**." (The same change should be made to the Appraisal in the 1994 Evaluations. The Explanation section of the evaluation has been corrected.)

Corrigenda

P. 163 (propiconazole), para 2

Change the last line to read:

"measurable**: 0.07-0.43** and <0.05-0.15 mg/kg after **5 and 6** weeks respectively."

P. 195 (tolclofos-methyl)

Replace para 3 with the following:

A study on peanuts was carried out in parallel with the study on cotton. The treatments included a foliar application (4.2 and 22 mg ai/plant) 75 days after soil treatment. The extraction of the leaves was preceded by a solvent wash to determine surface deposits. The radioactive residues on the surface of the leaves at maturity from the high treatment rate **amounted to 2.6-3.7% of the ^{14}C. Its average composition was TM 2.8%, TM-CH_2OH 7.0%, PH-CH_2OH 16.6%, and polar conjugates 59.9%. In the leaves the main residues were PH-CHO 18.2%, TM-CH_2OH 11.3%, PH-CH_3 3.7%, TMO 1.9% and three unidentified components 9.8%. The parent compound was not detected. Between 10 and 18% of the extracted residue remained at the origin on TLC separation and this was hydrolysed with cellulase to liberate PH-CH_2OH (55%) and TM-CH_2OH (29%) with smaller amounts of TMO, PH-CHO and TMO-CH_2OH**. The level of radioactivity in the nuts was too small to identify the residues. The residues in the hulls included TM (5.8%), DM-TMO (9.8%) and two unknowns (12.1 and 5.5%). About 67% of the radioactivity remained at the origin on the TLC plate.

P. 215 (Annex I, preamble)

Delete both sentences (they repeat the last two sentences on p. 214).

P. 228 (Annex I, Tecnazene)

Change the new recommendation for potatoes to "20[1] Po" to indicate that it refers to potatoes washed before analysis.

P. 237 (Annex II, FENPROPIMORPH)

The Codex Classification Number should be shown as **188**.

Annex IV, p. 14, Item 8.2

The first line should read "The items listed as required or desirable should be numbered if there are **more** than one."

Annex IV, p. 15, Item 12, para 1, line 3

The phone and fax number should read "+44**1**81 769 0435".

Annex IV, Index

The pagination is incorrect. Substitute the following.

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ANNEX I

ACCEPTABLE DAILY INTAKES AND RESIDUE LIMITS PROPOSED AT THE 1995 MEETING

The Table of recommendations includes maximum Acceptable Daily Intakes (ADIs) and Maximum Residue Limits (MRLs). It should be noted that MRLs include draft MRLs and Codex MRLs (CXLs). The MRLs recommended by the JMPR on the basis of its estimates of maximum residue levels enter the Codex procedure as draft MRLs. They become Codex MRLs when they have passed through the procedure and have been adopted by the Codex Alimentarius Commission.

In general, the recommended MRLs listed for compounds which have been reviewed previously are additional to, or amend, those recorded in the reports of earlier Meetings. For compounds re-evaluated in the CCPR periodic review programme however, both new and previous recommendations are listed because such re-evaluations are regarded as replacing the original evaluation rather than supplementing it.

Limits recommended at meetings from 1965 to 1977 inclusive are summarized in document FAO/WHO 1978c.

Some ADIs are temporary: this is indicated by the letter T and the year in which re-evaluation is scheduled in parenthesis below the ADI. All recommended MRLs for compounds with temporary ADIs are necessarily temporary, but some recommendations are designated as temporary (TMRLs) until required information has been provided and evaluated, irrespective of the status of the ADI. Such recommendations are followed by the letter T in the table. (See also the list of qualifications and abbreviations below.)

The following qualifications and abbreviations are used.

* following recommended MRL	At or about the limit of determination
* following name of pesticide	New compound
** following name of pesticide	Compound reviewed in CCPR periodic review programme
E	Extraneous Residue Limit (ERL).
F following recommendations for milk	The residue is fat-soluble and MRLs for milk and milk products are derived as explained in the introduction to Part 2 of the Guide to Codex Maximum Limits for Pesticide Residues and to Volume II of the Codex Alimentarius.
(fat) following recommendations for meat	The recommendation applies to the fat of the meat.
Po	The recommendation accommodates post-harvest treatment of the commodity.

PoP following recommendations for processed foods (classes D and E in the Codex Classification)	The recommendation accommodates post-harvest treatment of the primary food commodity.
T following ADIs	The ADI is temporary, and due for re-evaluation in the year indicated.
T following MRLs	The MRL is temporary, irrespective of the status of the ADI, until required information has been provided and evaluated.
V following recommendations for commodities of animal origin	The recommendation accommodates veterinary uses.
W in place of an MRL	The previous recommendation is withdrawn.

If a recommended MRL is an amendment, the previous value is also recorded. The absence of a figure in the "Previous" column indicates that the recommendation is the first for the commodity or group concerned.

The Table includes the Codex Classification Numbers (CCNs) of both the compounds and the commodities listed, to facilitate reference to the Guide to Codex Maximum Limits for Pesticide Residues and other Codex documents.

Commodities are listed in alphabetical order. This is a change from earlier practice where commodities were listed in the order of the "Types" in the Codex Classification of Foods and Animal Feeds, and in alphabetical order within each Type.

The change has been made to facilitate checking and comparison with the CCPR Tables of MRLs, which are in alphabetical order.

ACCEPTABLE DAILY INTAKES (ADIs) AND MAXIMUM RESIDUE LIMITS (MRLs)

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
Abamectin	0.001[1] 0.0002[2]				
		[2] for mixture of abamectin and Ä-8,9 isomer			
Azinphos-methyl	0.005	TN 0660	Almonds	0.05	0.3
(002)		AM 0660	Almond hulls	5	-
		GC 0654	Wheat	W	0.2
		Residue: azinphos-methyl			
Benomyl** (069)	0.1				
		Periodic review was for toxicology only.			
Bentazone (172)	0.1				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity CCN	Commodity Name	Recommended MRL or ERL (mg/kg) New	Recommended MRL or ERL (mg/kg) Previous
		Notes: Note changed definition of residue for animal products, formerly "sum of bentazone an			
Buprofezin	0.01	VC 0424	Cucumber	1	0.3 T
(173)		FC 0004	Oranges, Sweet, Sour	W	0.3 T
		VO 0448	Tomato	1	0.5 T
		Residue: buprofezin			
Captan (007)	0.1	Note: previous ADI maintained			
Carbendazim** (072)	0.03	Periodic review was for toxicology only			
Cartap**	No ADI	VB 0041	Cabbages, Head	W	0.2
(097)		TN 0664	Chestnuts	W	0.1
		VL 0467	Chinese cabbage, type "Pe-tsai"	W	2

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		HS 0784	Ginger, root	W	0.1
		FB 0269	Grapes	W	1
		DH 1100	Hops, dry	W	5
		FT 0307	Persimmon, Japanese	W	1
		VR 0589	Potato	W	0.1
		VR 0494	Radish	W	1
		CM 0649	Rice, husked	W	0.1
		VO 0447	Sweet corn (corn-on-the-cob)	W	0.1
		DT 1114	Tea, Green, Black (black, fermented and dried)	W	20
		All previous recommendations for MRLs withdrawn. Not record			
Chlorpyrifos	0.01	FC 0001	Citrus fruits	2	0.3
(017)		Residue: chlorpyrifos (fat-soluble)			
Dithianon	0.01	FS 0013	Cherries	5	1
(180)		Residue: dithianon			
Dithiocarbamates		AM 0660	Almond hulls	20 mb[1,2]	-
(105)		TN 0660	Almonds	0.1*[2] mz, mb	-
		VS 0621	Asparagus	0.1[2] mz	-
		FI 0327	Banana	2[2] mz	1
		GC 0640	Barley	1[2] mz	-
		AS 0640	Barley straw and fodder, dry	25[2] mz, mb	-
		VB 0041	Cabbages, Head	5[2] mz, mb	-
		VR 0577	Carrot	1[2] mz	0.5
		VS 0624	Celery	W[2]	5
		FS 0013	Cherries	W[2]	1
		VP 0526	Common bean (pods and/or immature seeds)	1[3] mt	W[2]
		VL 0510	Cos lettuce	10[2] mb	-
		FB 0265	Cranberry	5[2] mz	-
		VC 0424	Cucumber	2[2] mz, mb	0.5
		FB 0021	Currants, Black, Red, White	10 mz mt	10[2]
		MO 0105	Edible offal (mammalian)	0.1 mz mt	0.1[2]
		PE 0112	Eggs	0.05*[2] mz	-
		VL 0476	Endive	W[4]	1
		VA 0381	Garlic	0.5[2] mz	-
		FB 0269	Grapes	5 mz mt, mb, pb	5

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		DH 1100	Hops, dry	30[3] mt	-
		VL 0480	Kale	15[2] mz, mb	-
		VA 0384	Leek	0.5[2] mz	-
		VL 0482	Lettuce, Head	10 mz, mb, mt	10[2]
		AS 0645	Maize fodder	2[2] mz	-
		FC 0003	Mandarins	10[2] mz	-
		FI 0345	Mango	2[3] mz	-
		MM 0095	Meat	0.02* mz, mt	0.02*[2]
		VC 0046	Melons, except Watermelon	0.5[2] mz, pb	1
		ML 0106	Milks	0.05* mz, mt	0.05*[2]
		VA 0385	Onion, Bulb	0.5[2] mz, pb	-
		FC 0004	Oranges, Sweet, Sour	2[2] mz	-
		FI 0350	Papaya	5[2] mz	-
		FS 0247	Peach	W[5]	3
		SO 0697	Peanut	0.1*[2] mz	-
		AL 0697	Peanut fodder	5[2] mz	-
		VO 0445	Peppers, Sweet	1[2] mz, mb	-
		FS 0014	Plums (including Prunes)	W[2]	1
		FP 0009	Pome fruits	5 mz mt, pb	5[2]
		VR 0589	Potato	0.2 mz, mt, mb, pb	0.2[2]
		PM 0111	Poultry, Edible offal of	0.1[2] mz	-
		PO 0110	Poultry meat	0.1[2] mz	-
		VC 0429	Pumpkins	0.2[2] mz	-
		VA 0389	Spring onion	10[2] mb	-
		VC 0431	Squash, Summer	1[2] mz	-
		FB 0275	Strawberry	W[5]	3
		VR 0596	Sugar beet	0.5[2] mz, mb	-
		AV 0596	Sugar beet leaves or tops	20[2] mz, mb	-
		VO 0447	Sweet corn (corn-on-the-cob)	0.1*[2] mz	-
		VO 0448	Tomato	5 mz mt, mb, pb	5[2]
		VC 0432	Watermelon	1[2] mz, mb	-
		GC 0654	Wheat	1 mz, mb, mt	1[2]
		AS 0654	Wheat straw and fodder, dry	25 mz, mb, mt	25[2]
		VC 0433	Winter squash	0.1[2] mz	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		[5] Withdrawal recommended by 1993 JMPR; withdrawn by 21st			
Ethephon (106)	0.05	Note: previous ADI maintained			
Fenarimol*	0.01	AB 0226	Apple pomace,dry	5 T	-
(192)		VS 0620	Artichoke, Globe	0.1 T	-
		FI 0327	Banana	0.2 T	-
		MO 1280	Cattle, kidney	0.02* T	
		MO 1281	Cattle, liver	0.05 T	
		MM 0812	Cattle meat	0.02* T	
		FS 0013	Cherries	1 T	-
		DF 0269	Dried grapes (= Currants, Raisins and Sultanas)	0.1 T	-
		FB 0269	Grapes	0.3 T	-
		VC 0046	Melons, except Watermelon	0.05 T	-
		FS 0247	Peach	0.5 T	-
		TN 0672	Pecan	0.02* T	-
		VO 0445	Peppers, Sweet	0.5 T	-
		FP 0009	Pome fruits	0.3 T	-
		FB 0275	Strawberry	1 T	-
		Residue: fenarimol			
Fenpropimorph*	0.003	GC 0640	Barley	0.5	-
(188)		AS 0640	Barley straw and fodder, dry	5	-
		AV 1051	Fodder beet leaves or tops	1	-
		GC 0647	Oats	0.5	-
		AS 0647	Oat straw and fodder, dry	5	-
		GC 0650	Rye	0.5	-
		AS 0650	Rye straw and fodder, dry	5	-
		VR 0596	Sugar beet	0.05*	-
		AV 0596	Sugar beet leaves or tops	1	-
		GC 0654	Wheat	0.5	-
		AS 0654	Wheat straw and fodder, dry	5	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		Note: First review of residue and analytical aspects. Toxicology was reviewed in 1993.			
Fenpyroximate* (193)	0.01	Note: The Meeting estimated a maximum residue level for apples, but owing to the lack of cr			
Fenthion**	0.007	FP 0226	Apple	W	2
(039)		FI 0327	Banana	W	1
		VB 0041	Cabbages, Head	W	1
		VB 0404	Cauliflower	W	1
		FS 0013	Cherries	2	2
		FC 0001	Citrus fruits	W	2
		JF 0001	Citrus juice	W	0.2
		VP 0526	Common bean (pods and/or immature seeds)	W	0.1
		FB 0269	Grapes	W	0.5
		VL 0482	Lettuce, Head	W	2
		FC 0003	Mandarins	0.5	2[1]
		MM 0095	Meat	W	2 (fat) V
		ML 0106	Milks	W	0.05 F V
		OC 0305	Olive oil, virgin	3	1
		FT 0305	Olives	1	1
		VA 0385	Onion, Bulb	W	0.1
		FC 0004	Oranges, Sweet, Sour	0.5	2[1]
		FS 0247	Peach	W	2
		FP 0230	Pear	W	2
		VP 0063	Peas (pods and succulent = immature seeds)	W	0.5
		FS 0014	Plums (including Prunes)	W	1
		VR 0589	Potato	W	0.05
		GC 0649	Rice	W	0.1
		CM 0649	Rice, husked	0.05	
		VC 0431	Squash, Summer	W	0.2
		FB 0275	Strawberry	W	2
		VR 0508	Sweet potato	W	0.1

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		VO 0448	Tomato	W	0.5
		GC 0654	Wheat	W	0.1
		VC 0433	Winter squash	W	0.2

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
Flusilazole (165)	0.001	Note: previous ADI maintained			
Folpet (041)	0.1	Note: previous temporary ADI 0.01 mg/kg bw			
Haloxyfop* (194)	0.0003	Note: the Meeting estimated a number of maximum residue levels, but owing to the lack of cı			
Iprodione (111)	0.06	Note: previous ADI 0.2 mg/kg bw			
Metalaxyl	0.03	FB 0275	Strawberry	W	0.2
(138)		Residue: metalaxyl			
Metiram* (186)					

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
Parathion** (058)	0.004				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		Periodic review was for toxicology only			
Parathion-methyl** (059)	0.003				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		Periodic review was for toxicology only			
Penconazole (182)	0.03	DF 0269	Dried grapes (= Currants, Raisins and Sultanas)	0.5	-
		Residue: penconazole			
Piperonyl butoxide** (062)	0.2				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		Periodic review was for toxicology only.			
Profenofos	0.01	SO 0691	Cotton seed	2	3
(171)		MM 0095	Meat	0.05*	0.02*
		VO 0445	Peppers, Sweet	0.5	-
		DT 0171	Teas (Tea and Herb teas)	W	0.5
		Residue: profenofos			
Quintozene**	0.01	FI 0327	Banana[1]	W	1
(064)		VB 0400	Broccoli	W	0.02
		VB 0041	Cabbages, Head	W	0.02
		VD 0526	Common bean (dry)	W	0.2
		VP 0526	Common bean (pods and/or immature seeds)	W	0.01
		SO 0691	Cotton seed	W	0.03
		VL 0482	Lettuce, Head[1]	W	3
		SO 0697	Peanut	W	2
		SO 0703	Peanut, whole	W	5
		VO 0445	Peppers, Sweet	W	0.01
		VR 0589	Potato[1]	W	0.2
		VO 0448	Tomato	W	0.1

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		[1] These recommendations are also withdrawn because uses have been discontinued and			
Thiophanate-methyl** (077)	0.02				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		Periodic review was for toxicology only.			
Triadimefon	0.03	FI 0353	Pineapple	2 Po	1 Po
(133)		Residue: triadimefon			
Vinclozolin (159)	0.01	Note: previous ADI 0.07 mg/kg bw.			

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

ABAMECTIN (177) 1992 (T,R), 1994 (T,R), 1995 (T)

ACEPHATE (095) 1976 (T,R), 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R)

ACRYLONITRILE 1965 (T,R)

ALDICARB (117) 1979 (T,R), 1982 (T,R), 1985 (R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1994 (R), 1995 (T)

ALDRIN (001) 1965 (T), 1966 (T,R), 1967 (R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)

ALLETHRIN 1965 (T,R)

AMINOCARB (134) 1978 (T,R), 1979 (T,R)

AMITRAZ (122) 1980 (T,R), 1983 (R), 1984 (T,R), 1985 (R), 1986 (R), 1989 (R), 1990 (T,R), 1991 (R & corr. to 1990 R evaluation)

AMITROLE (079) 1974 (T,R), 1977 (T), 1993 (T,R)

ANILAZINE (163) 1989 (T,R), 1992 (R)

AZINPHOS-ETHYL (068) 1973 (T,R), 1983 (R)

AZINPHOS-METHYL (002) 1965 (T), 1968 (T,R), 1972 (R), 1973 (T), 1974 (R), 1991 (T,R), 1992 (corr. to 1991 rpt), 1993 (R), 1995 (R)

AZOCYCLOTIN (129) 1979 (R), 1981 (T), 1982 (R),1983 (R), 1985 (R), 1989 (T,R), 1991 (R), 1994 (T)

BENALAXYL (155) 1986 (R), 1987 (T), 1988 (R), 1992 (R), 1993 (R)

BENDIOCARB (137) 1982 (T,R), 1984 (T,R), 1989 (R), 1990 (R)

BENOMYL (069) 1973 (T,R), 1975 (T,R), 1978 (T,R), 1983 (T,R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)

BENTAZONE (172) 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1995 (R)

BHC (technical) 1965 (T), 1968 (T,R), 1973 (T,R) (see also lindane)

BIFENTHRIN (178) 1992 (T,R), 1995 (R)

BINAPACRYL (003)	1969 (T,R), 1974 (R), 1982 (T), 1984 (R), 1985 (T,R)
BIORESMETHRIN (093)	1975 (R), 1976 (T,R), 1991 (T,R)
BIPHENYL	see diphenyl
BITERTANOL (144)	1983 (T), 1984 (R), 1986 (R), 1987 (T), 1988 (R), 1989 (R), 1991 (R)
BROMIDE ION (047)	1968 (R), 1969 (T,R), 1971 (R), 1979 (R), 1981 (R), 1983 (R), 1988 (T,R), 1989 (R), 1992 (R)
BROMOMETHANE (052)	1965 (T,R), 1966 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R), 1992 (R)
BROMOPHOS (004)	1972 (T,R), 1975 (R), 1977 (T,R), 1982 (R), 1984 (R), 1985 (R)
BROMOPHOS-ETHYL (005)	1972 (T,R), 1975 (T,R), 1977 (R)
BROMOPROPYLATE (070)	1973 (T,R), 1993 (T,R)
BUTOCARBOXIM (139)	1983 (R), 1984 (T), 1985 (T), 1986 (R)
BUPROFEZIN (173)	1991 (T,R), 1995 (R)
sec-BUTYLAMINE (089)	1975 (T,R), 1977 (R), 1978 (T,R), 1979 (R), 1980 (R), 1981 (T), 1984 (T,R: withdrawal of TADI, but no evaluation)

CADUSAFOS (174)	1991 (T,R), 1992 (R), 1992 (R)
CAMPHECHLOR (071)	1968 (T,R), 1973 (T,R)
CAPTAFOL (006)	1969 (T,R), 1973 (T,R), 1974 (R), 1976 (R), 1977 (T,R), 1982 (T), 1985 (T,R), 1986 (corr. to 1985 rpt), 1990 (R)
CAPTAN (007)	1965 (T), 1969 (T,R), 1973 (T), 1974 (R), 1977 (T,R), 1978 (T,R), 1980 (R), 1982 (T), 1984 (T,R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1995 (T)
CARBARYL (008)	1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (T,R), 1970 (R), 1973 (T,R), 1975 (R), 1976 (R), 1977 (R), 1979 (R), 1984 (R)
CARBENDAZIM (072)	1973 (T,R), 1976 (R), 1977 (T), 1978 (R), 1983 (T,R), 1985 (T,R), 1987 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)
CARBOFURAN (096)	1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R)
CARBON DISULFIDE (009)	1965 (T,R), 1967 (R), 1968 (R), 1971 (R), 1985 (R)
CARBON TETRACHLORIDE (010)	1965 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R)

CARBOPHENOTHION (011)	1972 (T,R), 1976 (T,R), 1977 (T,R), 1979 (T,R), 1980 (T,R), 1983 (R)
CARBOSULFAN (145)	1984 (T,R), 1986 (T), 1991 (R), 1992 (corr. to 1991 rpt), 1993 (R)
CARTAP (097)	1976 (T,R), 1978 (T,R), 1995 (T,R)
CHINOMETHIONAT (080)	1968 (T,R) (as oxythioquinox), 1974 (T,R), 1977 (T,R), 1981 (T,R), 1983 (R), 1984 (T,R), 1987 (T)
CHLORBENSIDE	1965 (T)
CHLORDANE (012)	1965 (T), 1967 (T,R), 1969 (R), 1970 (T,R), 1972 (R), 1974 (R), 1977 (T,R), 1982 (T), 1984 (T,R), 1986 (T)
CHLORDIMEFORM (013)	1971 (T,R), 1975 (T,R), 1977 (T), 1978 (T,R), 1979(T), 1980(T), 1985 (T), 1986 (R), 1987 (T)
CHLORFENSON	1965 (T)
CHLORFENVINPHOS (014)	1971 (T,R), 1984 (R), 1994 (T)
CHLORMEQUAT (015)	1970 (T,R), 1972 (T,R), 1976 (R), 1985 (R), 1994 (T,R)
CHLOROBENZILATE (016)	1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R), 1980 (T)
CHLOROPICRIN	1965 (T,R)
CHLOROPROPYLATE	1968 (T,R), 1972 (R)
CHLOROTHALONIL (081)	1974 (T,R), 1977 (T,R), 1978 (R), 1979 (T,R), 1981 (T,R), 1983 (T,R), 1984 (corr. to 1983 rpt and T evaluation), 1985 (T,R), 1987 (T), 1988 (R), 1990 (T,R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R)
CHLORPROPHAM	1965 (T)
CHLORPYRIFOS (017)	1972 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1981 (R), 1982(T,R), 1983 (R), 1989 (R), 1995 (R)
CHLORPYRIFOS-METHYL (090)	1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990 (R), 1991 (T,R), 1992 (T) and corr. to 1991, 1993 (R), 1994 (R)
CHLORTHION	1965 (T)
CLETHODIM (187)	1994 (T,R)
CLOFENTEZINE (156)	1986 (T,R), 1987 (R), 1989 (R), 1990 (R), 1992 (R)
COUMAPHOS (018)	1968 (T,R), 1972 (R), 1975 (R), 1978 (R), 1980 (T,R), 1983(R),1987 (T), 1990 (T,R)
CRUFOMATE (019)	1968 (T,R), 1972 (R)

CYANOFENPHOS (091)	1975 (T,R), 1978 (T: ADI extended, but no evaluation), 1980, (T), 1982 (R), 1983 (T)
CYCLOXYDIM (179)	1992 (T,R), 1993 (R)
CYFLUTHRIN (157)	1986 (R), 1987 (T and corr. to 1986 rpt), 1989 (R), 1990 (R), 1992 (R)
CYHALOTHRIN (146)	1984 (T,R), 1986 (R), 1988 (R)
CYHEXATIN (TRICYCLOHEXYLTIN HYDROXIDE) (067)	1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R), 1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T), 1989 (T), 1991 (T,R), 1992 (R), 1994 (T)
CYPERMETHRIN (118)	1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985(R), 1986 (R), 1987 (corr. to 1986 evaluation), 1988 (R), 1990 (R)
CYROMAZINE (169)	1990 (T,R), 1991 (corr. to 1990 R evaluation), 1992 (R)
2,4-D (020)	1970 (T,R), 1971 (T,R), 1974 (T,R), 1975 (T,R), 1980 (R), 1985, (R), 1986 (R), 1987 (corr. to 1986 rpt, Annex I)
DAMINOZIDE (104)	1977 (T,R), 1983 (T), 1989 (T,R), 1991 (T)
DDT (021)	1965 (T), 1966 (T,R), 1967 (T,R),1968 (T,R), 1969 (T,R), 1978 (R), 1979 (T), 1980 (T), 1983 (T), 1984 (T), 1993 (R), 1994 (R)
DELTAMETHRIN (135)	1980 (T,R), 1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986, (R), 1987 (R), 1988 (R), 1990 (R), 1992 (R)
DEMETON (092)	1965 (T), 1967 (R), 1975 (R), 1982 (T)
DEMETON-S-METHYL (073)	1973 (T,R), 1979 (R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R)
DEMETON-S-METHYLSULFON (164)	1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R)
DIALIFOS (098)	1976 (T,R), 1982 (T), 1985 (R)
DIAZINON (022)	1965 (T), 1966 (T), 1967 (R), 1968 (T,R), 1970 (T,R), 1975 (R), 1979 (R), 1993 (T,R), 1994 (R)
1,2-DIBROMOETHANE (023)	1965 (T,R), 1966 (T,R), 1967 (R), 1968 (R), 1971 (R), 1979 (R), 1985 (R)
DICHLOFLUANID (082)	1969 (T,R), 1974 (T,R), 1977 (T,R), 1979 (T,R), 1981 (R),1982 (R), 1983 (T,R), 1985 (R)
1,2-DICHLOROETHANE (024)	1965 (T,R), 1967 (R), 1971 (R), 1979 (R), 1985 (R)
DICHLORVOS (025)	1965 (T,R), 1966 (T,R), 1967 (T,R), 1969 (R), 1970 (T,R), 1974 (R), 1977 (T), 1993 (T,R)

DICLORAN (083)	1974 (T,R), 1977 (T,R)
DICOFOL (026)	1968 (T,R), 1970 (R), 1974 (R), 1992 (T,R), 1994 (R)
DIELDRIN (001)	1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (R), 1970, (T,R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)
DIFLUBENZURON (130)	1981 (T,R), 1983 (R), 1984 (T,R), 1985 (T,R), 1988 (R)
DIMETHIPIN (151)	1985 (T,R), 1987 (T,R), 1988 (T,R)
DIMETHOATE (027)	1965 (T), 1966 (T), 1967 (T,R), 1970 (R), 1973 (R in evaluation of formothion), 1977 (R), 1978 (R), 1983 (R) 1984 (T,R) 1986(R), 1987 (T,R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1994 (R)
DIMETHRIN	1965 (T)
DINOCAP (087)	1969 (T,R), 1974 (T,R), 1989 (T,R), 1992 (R)
DIOXATHION (028)	1968 (T,R), 1972 (R)
DIPHENYL (029)	1966 (T,R), 1967 (T)
DIPHENYLAMINE (030)	1969 (T,R), 1976 (T,R), 1979 (R), 1982 (T), 1984 (T,R)
DIQUAT (031)	1970 (T,R), 1972 (T,R), 1976 (R), 1977 (T,R), 1978 (R), 1994 (R)
DISULFOTON (074)	1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R)
DITHIANON (180)	1992 (T,R), 1995 (R)
DITHIOCARBAMATES (105)	1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R, propineb and thiram), 1984 (R, propineb), 1985 (R), 1987 (T, thiram), 1988 (R, thiram), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T, thiram), 1993 (T,R), 1995 (R)
DNOC	1965 (T)
DODINE (084)	1974 (T,R), 1976 (T,R), 1977 (R)

EDIFENPHOS (099)	1976 (T,R), 1979 (T,R), 1981 (T,R)
ENDOSULFAN (032)	1965 (T), 1967 (T,R), 1968 (T,R), 1971 (R), 1974 (R), 1975 (R), 1982 (T), 1985 (T,R), 1989 (T,R), 1993 (R)
ENDRIN (033)	1965 (T), 1970 (T,R), 1974 (R), 1975 (R), 1990 (R), 1992 (R)
ETHEPHON (106)	1977 (T,R), 1978 (T,R), 1983 (R), 1985 (R), 1993 (T), 1994 (R), 1995 (T)
ETHIOFENCARB (107)	1977 (T,R), 1978 (R), 1981 (R), 1982 (T,R), 1983 (R)

ETHION (034)	1968 (T,R), 1969 (R), 1970 (R), 1972 (T,R), 1975 (R), 1982 (T), 1983 (R), 1985 (T), 1986 (T), 1989 (T), 1990 (T), 1994 (R)
ETHOPROPHOS (149)	1983 (T), 1984 (R), 1987 (T)
ETHOXYQUIN (035)	1969 (T,R)
ETHYLENE DIBROMIDE	see 1,2-dibromoethane
ETHYLENE DICHLORIDE	see 1,2-dichloroethane
ETHYLENE OXIDE	1965 (T,R), 1968 (T,R), 1971 (R)
ETHYLENETHIOUREA (ETU) (108)	1974 (R), 1977 (T,R), 1986 (T,R), 1987 (R), 1988 (T,R), 1990 (R), 1993 (T,R)
ETOFENPROX (184)	1993 (T,R)
ETRIMFOS (123)	1980 (T,R), 1982 (T,R[15]), 1986 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)
FENAMIPHOS (085)	1974 (T,R), 1977 (R), 1978 (R), 1980 (R), 1985 (T), 1987 (T),
FENARIMOL (192)	1995 (T,R,E)
FENBUTATIN OXIDE (109)	1977 (T,R), 1979 (R), 1992 (T), 1993 (R)
FENCHLORPHOS (036)	1968 (T,R), 1972 (R), 1983 (R)
FENITROTHION (037)	1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R)
FENPROPATHRIN (185)	1993 (T,R)
FENPROPIMORPH (188)	1994 (T), 1995 (R)
FENPYROXIMATE (193)	1995 (T,R)
FENSULFOTHION (038)	1972 (T,R), 1982 (T), 1983 (R)
FENTHION (039)	1971 (T,R), 1975 (T,R), 1977 (R), 1978 (T,R), 1979 (T), 1980 (T), 1983 (R), 1989 (R), 1995 (T,R,E)
FENTIN COMPOUNDS (040)	1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R), 1993 (R), 1994 (R)
FENVALERATE (119)	1979 (T,R), 1981 (T,R), 1982 (T), 1984 (T,R), 1985 (R), 1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)
FERBAM	see dithiocarbamates, 1965 (T), 1967 (T,R)

[15]R evaluation omitted. Published 1986.

FLUCYTHRINATE (152)	1985 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1993 (R)
FLUSILAZOLE (165)	1989 (T,R), 1990 (R), 1991 (R), 1993 (R), 1995 (T)
FOLPET (041)	1969 (T,R), 1973 (T), 1974 (R), 1982 (T), 1984 (T,R), 1986 (T), 1987 (R), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1993 (T,R), 1994 (R), 1995 (T)
FORMOTHION (042)	1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R)

GLUFOSINATE-AMMONIUM (175)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R)
GLYPHOSATE (158)	1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1994 (R)
GUAZATINE (114)	1978 (T.R), 1980 (R)

HALOXYFOP (194)	1995 (T,R)
HEPTACHLOR (043)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R), 1974 (R), 1975 (R), 1977 (R), 1987 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1993 (R), 1994 (R)
HEXACHLOROBENZENE (044)	1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)
HEXACONAZOLE (170)	1990 (T,R), 1991 (R and corr. to 1990 R evaluation), 1993 (R)
HEXYTHIAZOX (176)	1991 (T,R), 1994 (R)
HYDROGEN CYANIDE (045)	1965 (T,R)
HYDROGEN PHOSPHIDE (046)	1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1971 (R)
IMAZALIL (110)	1977 (T,R), 1980 (T,R), 1984 (T,R), 1985 (T,R), 1986 (T), 1988 (R), 1989 (R), 1991 (T), 1994 (R)
IPRODIONE (111)	1977 (T,R), 1980 (R), 1992 (T), 1994 (R), 1995 (T)
ISOFENPHOS (131)	1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986 (T,R), 1988 (R), 1992 (R)
LEAD ARSENATE	1965 (T), 1968 (T,R)
LEPTOPHOS (088)	1974 (T,R), 1975 (T,R), 1978 (T,R)
LINDANE (048)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R) (published as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R)

MALATHION (049)	1965 (T), 1966 (T,R), 1967 (corr. to 1966 R), 1968 (R), 1969 (R), 1970 (R), 1973 (R), 1975 (R), 1977 (R), 1984 (R)
MALEIC HYDRAZIDE (102)	1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R)
MANCOZEB (050)	1967 (T,R), 1970 (T,R), 1974 (R), 1977 (R), 1980 (T,R), 1993 (T,R)
MANEB	see dithiocarbamates, 1965 (T), 1967 (T,R), 1987 (T), 1993 (T,R)
MECARBAM (124)	1980 (T,R), 1983 (T,R), 1985 (T,R), 1986 (T,R), 1987 (R)
METALAXYL (138)	1982 (T,R), 1984 (R), 1985 (R), 1986 (R), 1987 (R), 1989 (R), 1990 (R), 1992 (R), 1995 (R)
METHACRIFOS (125)	1980 (T,R), 1982 (T), 1986 (T), 1988 (T), 1990 (T,R), 1992 (R)
METHAMIDOPHOS (100)	1976 (T,R), 1979 (R), 1981 (R), 1982 (T,R[16]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R)
METHIDATHION (051)	1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,R), 1994 (R)
METHIOCARB (132)	1981 (T,R), 1983 (T,R), 1984 (T), 1985 (T), 1986 (R), 1987 (T,R), 1988 (R)
METHOMYL (094)	1975 (R), 1976 (R), 1977 (R), 1978 (R), 1986 (T,R), 1987 (R), 1988 (R), 1989 (T,R), 1990 (R), 1991 (R)
METHOPRENE (147)	1984 (T,R), 1986 (R), 1987 (T and corr. to 1986 rpt), 1988 (R), 1989 (R)
METHOXYCHLOR	1965 (T), 1977 (T)
METHYL BROMIDE (052)	see bromomethane
METIRAM (186)	1993 (T), 1995 (R)
MEVINPHOS (053)	1965 (T), 1972 (T,R)
MGK 264	1967 (T,R)
MONOCROTOPHOS (054)	1972 (T,R), 1975 (T,R), 1991 (T,R), 1993 (T), 1994 (R), 1995 (T)
MYCLOBUTANIL (181)	1992 (T,R)
NABAM	see dithiocarbamates, 1965 (T), 1976 (T,R)
NITROFEN (140)	1983 (T,R)

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[16]R evaluation omitted. Published 1989.

OMETHOATE (055)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1979 (T), 1981(T,R),1984 (R), 1985 (T), 1986 (R), 1987 (R), 1988 (R), 1990 (R)
ORGANOMERCURY COMPOUNDS	1965 (T), 1966 (T,R), 1967 (T,R)
OXAMYL (126)	1980 (T,R), 1983 (R), 1984 (T), 1985 (T,R), 1986 (R)
OXYDEMETON-METHYL (166)	1965 (T, as demeton-S-methyl sulfoxide), 1967 (T), 1968 (R), 1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R)
OXYTHIOQUINOX	see chinomethionat

PACLOBUTRAZOL (161)	1988 (T,R), 1989 (R)
PARAQUAT (057)	1970 (T,R), 1972 (T,R), 1976 (T,R), 1978(R), 1981 (R), 1982 (T), 1985 (T), 1986 (T)
PARATHION (058)	1965 (T), 1967 (T,R), 1969 (R), 1970 (R), 1984 (R), 1991 (R), 1995 (T,R)
PARATHION-METHYL (059) (059)	1965 (T), 1968 (T,R), 1972 (R), 1975 (T,R), 1978 (T,R), 1979 (T), 1980 (T), 1982 (T), 1984 (T,R), 1991 (R), 1992 (R), 1994 (R), 1995 (T)
PENCONAZOLE (182)	1992 (T,R), 1995 (R)
PERMETHRIN (120)	1979 (T,R), 1980 (R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985 (R), 1986 (T,R), 1987 (T), 1988 (R), 1989 (R), 1991 (R), 1992 (corr. to 1991 rpt)
2-PHENYLPHENOL (056)	1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 1990 (T,R)
PHENOTHRIN (127)	1979 (R), 1980 (T,R), 1982 (T), 1984 (T), 1987 (R), 1988 (T,R)
PHENTHOATE (128)	1980 (T,R), 1981 (R), 1984 (T)
PHORATE (112)	1977 (T,R), 1982 (T), 1983 (T), 1984 (R), 1985 (T), 1990 (R), 1991 (R), 1992 (R), 1993 (T), 1994 (T)
PHOSALONE (060)	1972 (T,R), 1975 (R), 1976 (R), 1993 (T), 1994 (R)
PHOSMET (103)	1976 (R), 1977 (corr. to 1976 evaluation), 1978 (T,R), 1979 (T,R), 1981 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1994 (T)
PHOSPHINE	see hydrogen phosphide
PHOSPHAMIDON (061)	1965 (T), 1966 (T), 1968 (T,R), 1969 (R), 1972 (R), 1974 (R), 1982 (T), 1985 (T), 1986 (T)
PHOXIM (141)	1982 (T), 1983 (R), 1984 (T,R), 1986 (R), 1987 (R), 1988 (R)

PIPERONYL BUTOXIDE (062)	1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1972 (T,R), 1992 (T,R), 1995 (T)
PIRIMICARB (101)	1976 (T,R), 1978 (T,R), 1979 (R), 1981 (T,R), 1982 (T), 1985 (R)
PIRIMIPHOS-METHYL (086)	1974 (T,R), 1976 (T,R), 1977 (R), 1979 (R), 1983 (R), 1985 (R), 1992 (T), 1994 (R)
PROCHLORAZ (142)	1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (corr. to 1990 rpt, Annex I, and evaluation), 1992 (R)
PROCYMIDONE (136)	1981 (R), 1982 (T), 1989 (T,R), 1990 (R), 1991 (corr. to 1990 Annex I), 1993 (R)
PROFENOFOS (171)	1990 (T,R), 1992 (R), 1994 (R), 1995 (R)
PROPAMOCARB (148)	1984 (T,R), 1986 (T,R), 1987 (R)
PROPARGITE (113)	1977 (T,R), 1978 (R), 1979 (R), 1980 (T,R), 1982 (T,R)
PROPHAM (183)	1965 (T), 1992 (T,R)
PROPICONAZOLE (160)	1987 (T,R), 1991 (R), 1994 (R)
PROPINEB	1977 (T,R), 1980 (T), 1983 (T), 1984 (R), 1985 (T,R), 1993 (T,R)
PROPOXUR (075)	1973 (T,R), 1977 (R), 1981 (R), 1983 (R), 1989 (T), 1991 (R)
PROPYLENETHIOUREA (PTU) (150)	1993 (T,R), 1994 (R)
PYRAZOPHOS (153)	1985 (T,R), 1987 (R), 1992 (T,R), 1993 (R)
PYRETHRINS (063)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T), 1972 (T,R), 1974 (R)

QUINTOZENE (064)	1969 (T,R) 1973 (T,R), 1974 (R), 1975 (T,R), 1976 (Annex I, corr. to 1975 R), 1977 (T,R), 1995 (T,R)

2,4,5-T (121)	1970 (T,R), 1979 (T,R), 1981 (T)
TEBUCONAZOLE (188)	1994 (T,R)
TECNAZENE (115)	1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R), 1994 (T,R)
TEFLUBENZURON	1994 (T)
TERBUFOS (167)	1989 (T,R), 1990 (T,R)

THIABENDAZOLE (065)	1970 (T,R), 1971 (R), 1972 (R), 1975 (R), 1977 (T,R), 1979 (R), 1981 (R)
THIODICARB (154)	1985 (T,R), 1986 (T), 1987 (R), 1988 (R)
THIOMETON (076)	1969 (T,R), 1973 (T,R), 1976 (R), 1979 (T,R), 1988 (R)
THIOPHANATE-METHYL (077)	1973 (T,R), 1975 (T,R), 1977 (T), 1978 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)
THIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1970 (T,R), 1974 (T), 1977 (T), 1983 (R), 1984 (R), 1985 (T,R), 1987 (T), 1988 (R), 1989 (R), 1992 (T)
TOLCLOFOS-METHYL (189)	1994 (T,R)
TOLYLFLUANID (162)	1988 (T,R), 1990 (R), 1991 (corr. to 1990 rpt)
TOXAPHENE	see camphechlor
TRIADIMEFON (133)	1979 (R), 1981 (T,R), 1983 (T,R), 1984 (R), 1985 (T,R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1989 (R), 1992 (R), 1995 (R)
TRIADIMENOL (168)	1989 (T,R), 1992 (R), 1995 (R)
TRIAZOLYLALANINE	1989 (T,R)
TRIAZOPHOS (143)	1982 (T), 1983 (R), 1984 (corr. to 1983 rpt, Annex I), 1986 (T,R), 1990 (R), 1991 (T and corr. to 1990 evaluation), 1992 (R), 1993 (T,R)
TRICHLORFON (066)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1987 (R)
TRICHLORONAT	1971 (T,R)
TRICHLOROETHYLENE	1968 (R)
TRICYCLOHEXYLTIN HYDROXIDE	see cyhexatin
TRIFORINE (116)	1977 (T), 1978 (T,R)
TRIPHENYLTIN COMPOUNDS	see fentin compounds

VAMIDOTHION (078)	1973 (T,R), 1982 (T), 1985 (T,R), 1987 (R), 1988 (T), 1990 (R), 1992 (R)
VINCLOZOLIN (159)	1986 (T,R), 1987 (R and corr. to 1986 rpt and R evaluation), 1988 (T,R), 1989 (R), 1990 (R), 1992 (R), 1995 (T)

ZINEB (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1993 (T)

ZIRAM (105) see dithiocarbamates, 1965 (T), 1967 (T,R)

ANNEX III

INTAKE PREDICTIONS

At the request of the Meeting, WHO calculated the predicted intakes of residues on the agenda of the Joint Meeting, based on the methods described in Guidelines for Predicting Dietary Intake of Pesticide Residues with following two exceptions which were among the recommendations of a Joint FAO/WHO Consultation on Guidelines for Predicting Dietary Intake of Pesticide Residues held 2-6 May 1995 in York, United Kingdom. These were:

a) the Theoretical Maximum Daily Intake (TMDI) should be calculated using MRLs that have been established at or below the limit of detection rather than using zero.

b) the use of the "global" diet should be replaced by appropriate "cultural" diets. For the 1995 JMPR, the TMDIs for both the "global" and existing "cultural" diets have been calculated.

More realistic calculations were not performed on those pesticides for the TMDI (Theoretical Maximum Daily Intake), based on "global" or "cultural" diets, exceeded the ADI, because there was insufficient opportunity at the Joint Meeting to review the detailed processing and other data on the compounds of interest. The results of these calculations will be made available to the Twenty-eight Session of the Codex Committee on Pesticide Residues (CCPR) in April 1996.

The TMDI calculations were based on the ADIs and MRLs proposed by the Meeting and existing and pending MRLs in the Codex system. For the following compounds the TMDI did not exceed the ADI for the "global" or "cultural" diets:

abamectin, azinphos-methyl, benomyl, buprofezin, captan, carbendazim, chlorpyrifos, dithianon, dithiocarbamates, ethephon, fenarimol, fenpropimorph, fenthion, flusilazole, iprodione, metalaxyl, metiram, parathion, penconazole, piperonyl butoxide, profenofos, thiophanate-methyl, and triadimefon.

The TMDI did not exceed the ADI for the "global" diet, but did exceed the ADI for one or more of the "cultural" diets for the following compound:

vinclozolin.

The TMDI exceeded the ADI for both the "global" diet and one or more of the "cultural" diets for the following compound (information on processing and other factors must be reviewed before more realistic estimated intakes can be calculated):

parathion-methyl.

The TMDI was not calculated for the following compounds for which no MRLs have been proposed or where all existing MRLs have been proposed for withdrawal:

cartap, fenpyroximate, quintozene.

The TMDIs calculated grossly over-estimate the true pesticide residue intake. It should, therefore, not be concluded that the MRLs proposed by the Meeting are unacceptable when the TMDI exceeds the ADI. Instead, TMDI calculations should be used as a screening tool that may eliminate the need for further calculations of the intake of a pesticide when its value is below the ADI. When the TMDI exceeds the ADI, more realistic calculations should be performed.

In order to assess the potential of acute toxic episodes (poisonings), the JMPR established Acute Reference Doses for the following compounds:

aldicarb, fenthion, monocrotophos, parathion and parathion-methyl

Based on the recommendations of the Joint FAO/WHO Consultation mentioned above, large portion weights for the commodities concerned will be obtained and the maximum possible exposure due to one MRL/commodity combination will be determined. This information will be provided to the Twenty-eighth Session of the CCPR.

ANNEX IV

JMP ASSESSMENT OF PESTICIDE RESIDUES IN DRINKING-WATER

Introduction

In 1992, a Consultation convened by the IPCS recommended that the Joint Meeting on Pesticides address the issue of pesticide residues in drinking-water. In making this recommendation the Consultation recognized the fact that the primary site of international expertise on the health effects of and exposure to pesticides is within the Joint Meeting on Pesticides.

As far as possible, drinking-water sources should be protected from contamination with pesticides and other chemicals. It is recognized however, that pesticides and their degradation products may occur in drinking-water temporarily or for long periods through accidents, misuse, leaching or run-off, or from the direct application of herbicides and insecticides to water for weed or disease vector control. For these reasons, WHO has developed Guideline Values (GVs) for pesticides in drinking-water (WHO, 1993).

The GVs recommended by WHO in the *Guidelines for drinking-water quality* are intended to be both practical and feasible to implement as well as protective of public health. A GV represents the concentration of a contaminant that does not result in any significant risk to the health of the consumer over a lifetime of consumption. Short-term deviations above the GVs do not necessarily mean that the water is unsuitable for consumption. The amount by which, and the period for which, any GV can be exceeded without affecting public health depends upon the specific substance involved. The WHO GVs are advisory in nature, and are intended to be used as a basis for the development of national drinking-water standards (WHO, 1993).

The Meeting did not consider it appropriate to propose GVs, as information additional to toxicity, environmental fate and transport (e.g. analytical capabilities and practical water treatment technology) would have to be considered. It was deemed appropriate to address issues relative to the establishment of GVs, so that guidance can be provided to the appropriate WHO drinking-water expert groups for the development of GVs.

Evaluated information that is best addressed by the JMP and is of direct relevance to the further development of GVs includes, but is not limited to:

- the fate of the pesticide in the environment (persistence, transport and transformation), with particular reference to the nature and persistence of degradation products in water;

- toxicological evaluation of degradation products;

- levels found in food, dietary intake studies, and calculated theoretical maximum daily intake (TMDI);

- levels found in water; and
- relevance of the ADI, which is usually based on studies of ingestion in the diet, to an alternative toxicological evaluation based on studies of ingestion in drinking-water and other considerations relevant to drinking-water.

Recommendations

The JMP should consider issues relevant to the establishment of GVs for pesticides in drinking-water whenever full environmental and toxicological assessments are being performed.

Whenever the need arises for recommending a GV for a specific pesticide that has not been evaluated previously or recently, the WHO drinking-water expert groups should request the JMP to conduct a new or updated environmental and toxicological assessment of the pesticide in question.

Comments on specific pesticides

The present Meeting considered five pesticides that had been previously evaluated, and provided additional guidance relevant to the derivation of GVs.

Bentazone

Bentazone is a contact herbicide used on a variety of crops including cereals, maize, peas, rice, and soya beans. It is absorbed by the green parts of leaves and acts by inhibiting photosynthesis. It is soluble in water up to 570 mg/l. It can be analyzed by high-performance liquid chromatography of a derivative. In soil, short-lived hydroxy compounds are formed which rapidly undergo further degradation. It is photodegraded in sunlight. The average half-life of bentazone in the field is about two weeks. Owing to its high solubility, bentazone can be leached to underground waters, although the risk from this is mitigated by its limited half-life.

On the basis of Codex MRLs dietary exposure to bentazone is expected to be low, the TMDI being only 1% of the ADI.

Toxicology

Bentazone was last evaluated toxicologically by the JMPR in 1991 (FAO/WHO, 1992). It is rapidly absorbed from the gastrointestinal tract; 90% of the dose is excreted in the urine as unchanged bentazone. Small quantities of 6- and 8-hydroxybentazone have been identified.

The acute toxicity of bentazone is moderate to low (oral LD_{50} 500-2500 mg/kg bw). In a long-term study in rats, the NOAEL was 9 mg/kg bw per day (males) and 11 mg/kg bw per day (females) on the basis of changes in urine volume and colour, prothrombin time in males and clinical chemical parameters. The NOAEL in a long-term study in mice was 12 mg/kg bw per day on the basis of changes in male pituitary weight and prothrombin time. There was no increase in the incidence of tumours in either species. There was no evidence of genotoxicity. The NOAEL in a one-year study in dogs was 10 mg/kg bw per day on the basis of increased prothrombin time and reduced spermiogenesis. The ADI, established by the JMPR on the basis of an NOAEL of 10 mg/kg bw per day in the long-term study in rats and the use of a 100-fold safety factor, is 0-0.1 mg/kg bw. This ADI was considered by the present Meeting to be relevant for the derivation of a

drinking-water GV. The 1991 JMPR recommended additional studies (genotoxicity and a 90-day feeding study in rats) on the 6-hydroxy metabolite, and these data are of relevance to the definition of the residue to be used for dietary exposure assessment. The dietary exposure assessment for bentazone may need to be re-evaluated once these additional studies have been submitted and reviewed.

Chlorothalonil

Chlorothalonil is a fungicide with a broad spectrum of activity. It is used on pome and stone fruit, citrus, currants, berries, bananas, tomatoes, green vegetables, coffee, peanuts, potatoes, onions and cereals. It is also used in wood preservatives and paints. It can be analyzed by gas-liquid chromatography with electron-capture detection. It has low water solubility (0.9 mg/litre) and low mobility in soil. It is rapidly degraded in soil and in water, with a half-life of a few days and production of the 4-hydroxy metabolite. The half-life of this metabolite is also relatively short.

Dietary exposure to chlorothalonil is expected to be low. The TMDI is 20% of the ADI. Crop residues are composed mainly of the parent compound. Total diet studies and individual food analyses in several countries have shown undetectable or low concentrations of chlorothalonil.

Toxicology

Chlorothalonil was last evaluated toxicologically by the 1992 JMPR (FAO/WHO, 1993c) and the 1994 Core Assessment Group (WHO, 1995). It is poorly absorbed from the gastrointestinal tract. It is conjugated with glutathione in the liver and gastrointestinal tract. Conjugates are transported to the kidneys where they are converted by cytosolic â-lyase to thiol analogues that are excreted in the urine. Dogs and monkeys excrete little or none of these derivatives in the urine.

Chlorothalonil has low acute oral and dermal toxicity in rats and rabbits, with LD_{50}s above 10,000 mg/kg bw. It irritates the skin and eye. The main effects of chlorothalonil are observed in the stomach and kidney and lesions in these tissues were observed in two-year studies in rats, mice, and dogs. In rats, hyperplasia of the kidney and forestomach was observed at doses of 3.8 mg/kg bw per day and above. The NOAEL was 1.8 mg/kg bw per day. Similar effects were observed in mice in which the NOAEL was 1.6 mg/kg bw per day. The NOAEL in the dog was 120 ppm, equivalent to 3 mg/kg bw per day.

Chlorothalonil was not mutagenic in several tests *in vitro* and *in vivo* but gave positive results in a small number of assays. It was concluded by the 1992 JMPR that chlorothalonil does not show a genotoxic hazard for humans.

Stomach tumours and renal tubular tumours (adenomas and carcinomas) were found in both rats and mice. The rodent forestomach tumours were attributed to the irritancy of chlorothalonil. Similarly, the metabolic conversion of chlorothalonil to glutathione conjugates with subsequent conversion to thiol metabolites that are toxic to the kidney is more marked in rodents than in dogs or monkeys. For these reasons the results of a two-year feeding study in dogs, with a NOEL of 120 ppm, equivalent to 3 mg/kg bw per day, were used by the 1992 JMPR to establish the ADI. Applying a 100-fold safety factor, an ADI of 0-0.03 mg/kg bw was established. This ADI was considered by the present Meeting to be relevant for the derivation of a drinking-water GV.

Diflubenzuron

Diflubenzuron is a member of the benzoylphenylurea group of insecticides. It is sparingly soluble in water (0.2 mg/litre at 20°C). Diflubenzuron can be measured in water by high-performance liquid chromatography with ultraviolet detection or by gas chromatography with electron-capture detection. It is used in agriculture, forestry and public health to control insect pests and vectors. Diflubenzuron is applied directly to plants and water and is quickly and strongly adsorbed by soil and sediments. It is rapidly degraded in soil, with a half-life of less than seven days. It is unlikely to be leached. The main degradation pathway in soil is hydrolysis leading to 2,6-difluorobenzoic acid and 4-chlorophenylurea. Free 4-chloroaniline has not been detected in soil.

The 1994 CAG (WHO, 1995) concluded that exposure to diflubenzuron is negligible in food. The TMDI is 9% of the ADI.

Toxicology

Diflubenzuron was evaluated by the Core Assessment Group in 1994. It is absorbed from the digestive tract and to a lesser extent through the skin. There is saturable absorption in the rat gastrointestinal tract. The major route of metabolism in rats is hydroxylation; 80% of the metabolites are (2,6-difluoro-3-hydroxy)diflubenzuron, (4-chloro-2-hydroxy)diflubenzuron and (4-chloro-3-hydroxy)diflubenzuron. Little or no 4-chloroaniline is formed in rats. The metabolic pathway in humans is unknown.

Diflubenzuron has low acute toxicity after administration by any route. It causes methaemoglobinaemia after oral or dermal administration or inhalation. The NOAEL for this end-point is 2 mg/kg bw per day in rats and dogs and 2.4 mg/kg bw per day in mice. There was no increase in the incidence of tumours at doses up to 10,000 ppm, the highest dose tested, in rats and mice. 4-Chloroaniline is both mutagenic and carcinogenic.

After reviewing the available data, the CAG concluded that diflubenzuron is not genotoxic.

In view of the toxicological characteristics of diflubenzuron, the CAG concluded that on the basis of the NOAEL of 2 mg/kg bw per day in mice, rats and dogs, and applying a 100-fold safety factor, 0.02 mg/kg bw per day will probably not cause adverse effects in humans whatever the route of exposure. This value was considered by the present Meeting to be relevant to the derivation of a drinking-water GV.

Diquat

Diquat (1,1′-ethylene-2,2′-bipyridylium) is a herbicide used on a wide variety of crops. It is a quick-acting contact herbicide and plant desiccant. It is used to control floating and submerged weeds in water, and for pre-harvest desiccation of seed crops and cotton. It was reviewed by the JMPR in 1993 and 1994 (FAO/WHO, 1994a, 1995a).

Diquat is very soluble in water (700 g/litre). It is stable in acid and neutral solutions but unstable under alkaline conditions. Metabolic break-down does not occur in plants. It is rapidly and completely adsorbed to soil and sediments. It is photodegradable and slowly mineralized in water and sediments.

The TMDI for existing MRLs exceeds the ADI (170% of the ADI).

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recommended that diquat be evaluated in the next revision of the Guidelines.

Toxicology

Diquat was last evaluated toxicologically by the 1993 JMPR (FAO/WHO, 1994a).

Diquat is poorly absorbed from the gastrointestinal tract and is eliminated primarily via the faeces during the first 24 h. The primary product excreted in both urine and faeces is the parent compound; diquat monopyridone and dipyridone and picolinic acid are excreted in small amounts.

Diquat is moderately toxic after acute administration, with LD_{50} values of 125-250 mg diquat ion/kg bw. In two-year studies in mice, the NOAELs were 3.6 and 4.5 mg ion/kg bw per day on the basis of reduced growth and increased kidney weight or hepatic vacuolation at higher doses. In rats, the NOAEL was equal to 0.19 mg/kg bw per day on the basis of cataract formation at doses of 0.6 mg diquat ion/kg bw per day and above.

There was no evidence of carcinogenicity in rats or mice.

Diquat has been tested in a series of genotoxicity assays *in vivo* and *in vitro*. Chromosomal aberrations were induced *in vitro* but there was no other evidence of genotoxicity. The 1993 JMPR concluded that diquat is not genotoxic.

An ADI of 0-0.002 mg/kg bw was established by the 1993 JMPR on the basis of an NOAEL of 0.19 mg diquat ion/kg bw per day identified in a two-year study in rats, using a safety factor of 100. This ADI was considered by the present Meeting to be relevant for the establishment of a drinking-water GV. A more accurate determination of potential dietary exposure would be useful in setting a drinking-water guideline.

Methomyl

Methomyl is a carbamate insecticide used on a wide range of crops including fruit, vines, hops, vegetables, cereals, soya beans, cotton and ornamental plants. Methods that can be used for its analysis include high-performance liquid chromatography and gas-liquid chromatography. Methomyl is highly soluble in water (55 g/litre). It is poorly adsorbed to soil and is expected to be mobile and reach ground-water. It is, however, rapidly degraded in soil and water, with a half-life of a few days.

Low levels of methomyl are present in food and other crops at harvest. The residue consists mainly of methomyl. The TMDI is 30% of the ADI.

Toxicology

Methomyl was evaluated by the 1994 Core Assessment Group (WHO, 1995). The absorption, metabolism and excretion of methomyl after oral administration to rats is very rapid, the processes being completed within a few days. The proposed metabolic pathway of methomyl includes displacement of the S-methyl group by glutathione, followed by enzymic transformation to give the mercapturic acid derivative.

Methomyl has high acute oral toxicity with an oral LD_{50} in the rat of 17-45 mg/kg bw. The signs of acute toxicity are those expected of a cholinesterase inhibitor. Recovery is rapid. In a 2-

year study in mice, the NOAEL was 8.7 mg/kg bw per day, based on increased mortality and decreased haemoglobin and erythrocyte counts at higher doses. In a long-term study in rats, decreased body-weight gain and lower haemoglobin and packed cell volumes were observed at 20 mg/kg bw per day. The NOAEL was 5 mg/kg bw per day. In a two-year study in dogs, slight to moderate anaemia was observed. The NOAEL was equivalent to 3 mg/kg bw per day.

There were no treatment-related tumours in two-year studies in rats or mice.

Methomyl was not mutagenic and did not induce primary DNA damage in bacterial or mammalian cells *in vitro*, whereas it had cytogenetic potential in human lymphocytes *in vitro,* as evidenced by increased frequencies of micronuclei and chromosomal aberrations. The Meeting concluded that methomyl was not genotoxic.

Methomyl has not shown delayed neurotoxicity. *In vitro*, human erythrocyte acetylcholinesterase activity was six times as sensitive to the inhibitory action of methomyl as that of the rat.

In poisoning incidents in humans, a dose as low as 13 mg/kg bw was lethal. No other relevant information in humans is available.

NOAELs of 5 mg/kg bw in rats, 8.7 mg/kg bw in mice and 3 mg/kg bw in dogs were identified by the CAG. It was concluded on the basis of the NOAEL of 3 mg/kg bw per day in dogs and applying a 100-fold safety factor, that 0.03 mg/kg bw per day would probably not cause adverse effects in humans. This value was considered by the present Meeting to be relevant for the derivation of a drinking-water GV; however, consideration should also be given to including cholinesterase-inhibiting degradation products in applying the GV.

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[I].See also toxicological criteria for carbendazim when considering dietary exposure to residues

). = Toxicology

R = Residue and analytical aspects

E = Evaluation of environmental fate by the Environmental Core Assessment Group