Food and Agriculture Organization of the United Nations

World Health Organization

ISSN 0259-2517

FAO PLANT PRODUCTION AND PROTECTION PAPER

122

Pesticide residues in food 1993

Joint FAO/WHO Meeting on Pesticide Residues

REPORT

1993

Rome, 1993

CONTENTS

[1] T = Toxicology; R = Residue and analytical aspects

* = evaluation in the periodic review programme

** = new compound

1993 FAO/WHO JOINT MEETING ON PESTICIDE RESIDUES

Geneva, 20-29 September 1993

PARTICIPANTS

WHO Expert Group on Pesticide Residues

Prof. U.G. Ahlborg
Division of Environmental Toxicology
Karolinska Institutet
Institute of Environmental Medicine
Box 210
S-17177 Stockholm
Sweden
Tel: (46 8) 728 7530
Fax: (46 8) 343 849

Dr A.L. Black
Medical Services Adviser in Toxicology
Department of Health, Housing, Local Government
and Community Services
GPO Box 9848
Canberra 2601 ACT
Australia
Tel: (61 6) 289 8464
Fax: (61 6) 289 7802

Professor J.F. Borzelleca (Chairman)
Pharmacology, Toxicology
Medical College of Virginia
Virginia Commonwealth University
Box 613
Richmond 23298-0613 Virginia
USA
Tel: (1 804) 786 8409
Fax: (1 804) 285 1401

Mr D.J. Clegg
142 Corkery Woods Drive
RR 2
Carp K0A 1LO Ontario
Canada
Tel: (1 613) 256 4518
Fax: (same as telephone. Call first)

Dr Penelope A. Fenner-Crisp (Rapporteur)
Director, Health Effects Division
Office of Pesticide Programs (H7509C)
US Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460
USA
Tel: (1 703) 305 7351
Fax: (1 703) 305 5147

Dr E.M. den Tonkelaar
Toxicologist
Toxicology Advisory Centre
National Institute of Public Health and Environmental Protection
Antonie van Leeuwenhoeklaan 9
P.O. Box 1
Bilthoven 3720 BA
Netherlands
Tel: (31 30) 743 000
Fax: (31 30) 291 492

Dr Peipei Yao
Professsor of Toxicology
Consultant of ICAMA
Institute of Occupational Medicine, CAPM
Ministry of Public Health
29 Nan Wei Road
Beijing 100050
China
Tel: (86 1) 301 6891 / 303 8761 256 / 301 0863
Fax: (86 1) 301 4322 / 301 1875

FAO Panel of Experts on Pesticide Residues in Food and the Environment

Dr. D.C. Abbott
AOAC International, Liaison Representative
80 Chaffers Mead
Ashtead, Surrey
KT21 1NH
United Kingdom
Tel. & fax: (44) 372-274856

Dr. A. Ambrus (Rapporteur)
Budapest Plant Health & Soil Conservation Station
H-1519
P.O. Box 340
Budapest
Hungary
Tel: (361) 1851 177/(361) 1851 110/(361) 1850 782
Fax: (361) 1869 276/(361) 1869 116

Dr. Ursula Banasiak
Stahnsdorfer Damm 81
D-14532 Kleinmachnow
Germany
Tel: (49) 33203/22423 or 22586 or 22128
Fax: (49) 33203/22278

Mr. D.J. Hamilton
Senior Principal Scientist
Agricultural Chemistry
Queensland Department of Primary Industries
Meiers Road, Indooroopilly
Brisbane, Queensland 4068
Australia
Tel: (61 7) 877 9484
Fax: (61 7) 371 6436

Mr. N.F. Ives (Vice-Chairman)
Health Effects Division (H7509C)
US Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460
USA
Tel: (703) 305-6378
Fax: (703) 305-5147

Dr. J.-R. Lundehn
Federal Biological Research Centre for Agriculture and Forestry (BBA)
Messeweg 11-12
D-38104 Braunschweig
Germany
Tel: (49) 531 299-3450
Fax: (49) 531 299-3003

Mr. K. Voldum-Clausen
Tingmosen 5
3500 Varlöse
Denmark
Tel: (45) 42 48 08 95
Fax: (45) 39 66 01 00

Ms. H.F. Yeoh
Residue Section
Pesticides Control Branch
Dept. of Agriculture
Jalan Gallagher
Kuala Lumpur 50632
Malaysia
Tel: 603-2983077 ext. 104
Fax: 603-2983646

Secretariat

Mrs P.H. Arentzen (WHO Temporary Adviser)
National Institute of Public Health and Environmental Protection
Antonie van Leeuwenhoeklaan 9
P.O. Box 1
3720 BA Bilthoven
Netherlands
Tel: (31 30) 749 111
Fax: (31 30) 742 971

Dr Elisabeth Bosshard (WHO Temporary Adviser)
Federal Office of Public Health
Division of Food Science
c/o Institute of Toxicology
Schorenstrasse 16
Schwerzenbach 8603
Switzerland
Tel: (41 1) 825 75 11 / (41 1) 825 74 19
Fax: (41 1) 825 04 76

Mrs M. Caris (WHO Temporary Adviser)
Toxicological Evaluation Division, Bureau of Chemical Safety
Health and Welfare Canada
Room 2-2, HPB Bld.
Tunney's Pasture
Ottawa K1A OL2 Ontario
Canada
Tel: (1 613) 957 1688
Fax: (1 613) 941 2632

Dr K. Fujimori (WHO Temporary Adviser)
Division of Pharmacology
Biological Safety Research Center
National Institute of Health Sciences
18-1, Kamiyoga 1-chome
Setagaya-ku
Tokyo 158
Japan
Tel: (81 3) 3700 1141
Fax: (81 3) 3707 6950

Dr H. Galal-Gorchev
International Programme on Chemical Safety
World Health Organization
1211 Geneva 27
Switzerland
Tel: (41 22) 791 3537
Fax: (41 22) 788 1949 / 791 0746

Dr J.L. Herrman (WHO Joint Secretary)
International Programme on Chemical Safety
World Health Organization
1211 Geneva 27
Switzerland
Tel: (41 22) 791 3569
Fax: (41 22) 788 1949 / 791 0746

Dr A. Kocialski (WHO Temporary Adviser)
Health Effects Division
Office of Pesticide Programs (H7509C)
US Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460
USA
Tel: (1 703) 305 7396

Fax: (1 703) 305 5147

Dr Jens-Jörgen Larsen (WHO Temporary Adviser)
Head, Department of General Toxicology
Institute of Toxicology
National Food Agency of Denmark
19, Mörkhöj Bygade
Söborg 2860
Denmark
Tel: (45 39) 69 66 00 ext 4100
Fax: (45 39) 39 66 01 00

Prof. M. Lotti (WHO Temporary Adviser)
Università di Padova
Istituto di Medicina del Lavoro
via Facciolati 71
Padova 35127
Italy
Tel: (39 49) 75 01 55
Fax: (39 49) 82 16 644

Mr A.F. Machin (FAO Consultant)
Boundary Corner
2 Ullathorne Road
London SW16 1SN
UK
Tel. & fax: (44 81) 769 0435

Dr T.C. Marrs (WHO Temporary Adviser)
Medical Toxicology and Environmental Health
Department of Health
Skipton House
80 London Road
Elephant and Castle
London SE1 6LW
UK
Tel: (44 71) 972 5328 / 972 5300
Fax: (44 71) 972 5156

Dr D. McGregor
Unit of Carcinogen Identification and Evaluation
International Agency for Research on Cancer
150 cours Albert-Thomas
69372 Lyon Cedex 08
France
Tel: (33) 72 73 84 85
Fax: (33) 72 73 85 75

Dr A. Moretto (WHO Temporary Adviser)
Università di Padova
Istituto di Medicina del Lavoro
via Facciolati 71
Padova 35127
Italy
Tel: (39 49) 82 16 644
Fax: (39 49) 82 16 644

Dr G. Moy
Food Safety
World Health Organization
1211 Geneva 27
Switzerland
Tel: (41 22) 791 3698
Fax: (41 22) 791 0746

Mr W.J. Murray (FAO Joint Secretary)
Plant Protection Service
Plant Production & Protection Division
Food and Agriculture Organization of the United Nations (FAO)
Via delle Terme di Caracalla
Rome 00100
Italy
Tel: (39 6) 5797 3222
Fax: (39 6) 5797 3152

Dr R. Plestina
International Programme on Chemical Safety
World Health Organization
1211 Geneva 27
Switzerland
Tel: (41 22) 791 3592
Fax: (41 22) 788 1949 / 791 0746

Dr A. Takanaka (WHO Temporary Adviser)
Head
Division of Pharmacology
Biological Safety Research Center
National Institute of Health Sciences
18-1, Kamiyoga 1-chome
Tokyo 158 Setagaya-ku
Japan
Tel: (81 3) 700 1141
Fax: (81 3) 707 6950

Dr W.H. van Eck
Chairman, Codex Committee on Pesticide Residues
Food and Product Safety Division
Ministry of Welfare, Health and Cultural Affairs
Postbox 3008
Sir Winston Churchillaan 362
2280 MK Rijswijk
The Netherlands
Tel: (70) 340 69 66
Fax: (70) 340 5177

Dr G. Vettorazzi (WHO Temporary Adviser)
International Toxicology Information Centre (ITIC)
Paseo Ramón Maria de Lilí, 1, 4°-D
20002 San Sebastian
Spain
Tel: (34 43) 32 04 55
Fax: (34 43) 32 04 87

Mr M. Walsh (WHO Temporary Adviser)
Principal Administrator EEC
Commission of the European Communities
Législation des produits végétaux et de nutrition animale
VI/B/II.1
Rue de la Loi 200
Brussels 1049
Belgium
Tel: (32 2) 235 11 11
Fax: (32 2) 236 59 63

Mr M. Watson (WHO Temporary Adviser)
Head, Risk Evaluation Branch
Pesticide Safety Directorate
Ministry of Agriculture, Fisheries and Food
Rothamsted
Harpenden, Herts AL5 2SS
UK
Tel: (44 582) 462 100
Fax: (44 582) 462 919

Dr Y. Yamada
Food Standards Officer
Joint FAO/WHO Food Standards Programme Group
Food and Agriculture Organization of the United Nations (FAO)
via delle Terme di Caracalla
Rome 00100
Italy
Tel: (39 6) 5797 5443
Fax: (39 6) 5797 4593

ABBREVIATIONS WHICH MAY BE USED

AChE	acetylcholinesterase
ADI	acceptable daily intake
AFI(D)	alkali flame-ionisation (detector)
ai	active ingredient
ALAT	alanine aminotransferase
approx.	approximate
ASAT	aspartate aminotransferase
at. wt.	atomic weight
b.p.	boiling point
bw	body weight
c	centi - (x 10^{-2})
°C	degree Celsius (centigrade)
CCPR	Codex Committee on Pesticide Residues
ChE	cholinesterase
cm	centimetre
CNS	central nervous system
cu	cubic
cv	coefficient of variation
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-; preceding a chemical name)
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	gram
ìg	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography - mass spectrometry
G.I.	gastrointestinal
GL	guideline level
GLC	gas-liquid chromatography
GPC	gel-permeation chromatography
GSH	glutathione

h	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre
HPLC	high-performance liquid chromatography
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)
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)
k	kilo- (x 10^3)
kg	kilogram
l	litre
LC	liquid chromatography
LC_{50}	lethal concentration, 50%
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
m	metre
MFO	mixed function oxidase
mg	milligram
ìg	microgram
ìm	micrometre (micron)
min	minute(s)
ml	millilitre
MLD	minimum lethal dose
mm	millimetre
M	molar
mo	month(s)
m.p.	melting point
MRL	Maximum Residue Limit (this term replaces "tolerance")
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NCI	National Cancer Institute (United States)
NMR	nuclear magnetic resonance
no.	number
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)
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/1 are used).
PT	prothrombin time
PTT	partial thromboplastin time
PTU	propylenethiourea
RBC	red blood cell
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	specific gravity
sq	square
t	tonne (metric ton)
T_3	tri-iodothyronine
T_4	thyroxine
TADI	Temporary Acceptable Daily Intake
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
v/v	volume ratio (volume per volume)
WG	water-dispersible granule
WHO	World Health Organization
wk	week
WP	wettable powder
wt	weight
wt/vol	weight per volume
w/w	weight per weight
yr	year
<	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

2. GENERAL CONSIDERATIONS

2.1 AMENDMENTS TO THE AGENDA

Benomyl (069)*, Carbendazim (072)*, Dimethoate (027), Diquat (031)*, Ethephon (106)*, Ethion (034)*, Iprodione (111)*, Profenofos (171), Propiconazole (160) and Thiophanate-methyl (077)* were originally scheduled for review by the FAO Panel. The draft evaluations of these compounds had been completed by the Panel members, but they could not be given adequate consideration in the time available to the Meeting. In the interests of maintaining the high standard of the evaluations the review of these compounds was postponed to the 1994 Joint Meeting.

The toxicological evaluation of captan was postponed until 1995 when folpet, a closely-related compound, will be reviewed. Chlorpropham was not evaluated owing to lack of data.

* Periodic review compounds

2.2 RISK ASSESSMENT PROCEDURES USED BY THE JMPR

The Codex Alimentarius Commission, at its 20th Session, considered a working paper entitled *Risk assessment procedures used by the Codex Alimentarius Commission, and its subsidiary and advisory bodies* (ALINORM 93/37). The expert committees, including the JMPR, that advise the Commission were characterized as forming a bridge between those who carry out scientific research and the risk managers (usually Codex Committees), and it was stated that the expert committees are ideally suited to perform risk assessment.

In its discussions, the Commission reiterated the importance of increasing the transparency of the work of the Joint Meeting in, for example, the identification of hazards and the choice of safety factors used in safety evaluations. The Commission noted that the characterization of exposure relative to dietary intake suffered from a lack of information and consistent methods of risk assessment, and needed to be improved. In addition, the needs of special "at risk" groups should be taken into account. It was also recommended that more attention be given to quantifying uncertainty in specific risk assessments carried out by the Expert Committees that advise the Codex Alimentarius Commission. The Commission recommended that the paper should be brought to the attention of the JMPR.

In responding to the report of the Commission, the Joint Meeting emphasized the importance of maintaining a distinction between risk assessment, which is performed by the FAO/WHO expert committees, and risk management. In this way the Codex Alimentarius Commission will have unbiased scientific advice on which to base its decisions.

Recommendations have been made at a number of conferences in recent years that FAO and WHO expert committees should be more "transparent". The Joint Meeting has responded by describing in more detail the data that it is reviewing and explaining more clearly the basis for its decisions. With regard to toxicological assessments the safety factors that are applied to the NOAELs in the studies that are reviewed represent the uncertainty inherent in the assessments and in extrapolating results from one species to another. WHO Environmental Health Criteria (EHC) 104 [i] explains the basis of the standard safety factor, and when this is not used the reasons are explained in the individual evaluations. FAO is in the process of producing a document that describes the scientific bases for its assessments.

The Joint Meeting recognized the need for improved dietary intake data, and stressed that it is dependent upon Member States to provide them. Better intake data for specific population groups, such as infants and children, are required. On the assessment side, the International Programme on Chemical Safety (IPCS) has published an EHC document that

outlines special approaches that should be taken for infants and children [2], and other organizations have considered this issue more recently [3,4].

Intake predictions have been made in recent years using the *Guidelines for predicting dietary intake of pesticide residues* [5]. Although these guidelines are generally accepted and remain valid, IPCS is considering the possibility of convening a consultation to revise them in the light of the experience gained in using them, taking into account suggestions that have been made by the Codex Committee on Pesticide Residues (CCPR) and others. The Joint Meeting stressed that theoretical predictions of maximum dietary intake should be used only as a screen to identify those pesticides whose intake may have the potential to exceed the ADI, and that theoretical predictions should not be a substitute for more realistic intake estimates based upon actual residue levels and food intake at the national and/or local level, when such information is available.

With reference to paragraph 68 in the report of the Codex Alimentarius Commission (ALINORM 93/40) the Meeting stressed that MRLs for both pesticides and veterinary drugs are based on different data bases from those on which ADIs are based, and that there is no direct relationship between them. The purpose of MRLs is to ensure that good agricultural practice in the use of pesticides or good practice in the use of veterinary drugs has been followed. They cannot be used for making realistic estimates of pesticide or veterinary drug intake.

The Meeting agreed with recommendation 6 of the working paper (ALINORM 93/37) that "it is currently impracticable (and probably not necessary) to achieve uniformity in risk analysis activities between the expert groups, and between the Codex committees. However, it is important that the principles for risk assessment be the same, or where differences exist these should be justified."

The Meeting agreed on the importance of a paper such as this to improve transparency of the Codex/Expert Committee process. However, the Meeting recommended that the working paper (ALINORM 93/97) should not be published or distributed further in its present form. A revised paper should be prepared that would take into account new developments in the dynamic field of risk assessment and recent Codex developments. That paper should then be circulated to national and international organisations to give them the opportunity to comment before publication or wider distribution.

2.3 IMPROVING THE ASSESSMENT OF DIETARY RISK OF PESTICIDES

The understanding of the potential risk of exposure to pesticide residues in food is of critical interest internationally. National governments and other organizations with responsibilities or interests in this issue are continually striving to upgrade their information base so as to improve the quality of their assessments. While current risk assessment procedures make the best use of all the available data and there is no evidence that dietary exposure to pesticide residues as a consequence of approved uses presents a risk to human health in any population group, the JMPR continually seeks to be responsive to enhancement of the scientific basis of dietary risk assessment by incorporating valid new information into its deliberations.

---

[2] *Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach*. WHO Environmental Health Criteria, No. 59. Geneva, World Health Organization, 1986.

[3] *Similarities and differences between children and adults: implications for risk assessment*. Washington, International Life Sciences Institute Press, 1992.

[4] *Pesticides in the diets of infants and children*. National Academy of Sciences. Washington, National Academy Press, 1993.

[5] *Guidelines for predicting dietary intake of pesticide residues*. Geneva, World Health Organization, 1989.

The attention of the Meeting was drawn to a report recently released by the National Research Council of the National Academy of Sciences (NAS) in the United States [ii]. The approaches to evaluating health risks from chemicals during infancy and early childhood have also been discussed in an EHC document [6].

An overview of the recommendations put forth in the NAS report was presented to the Meeting. These recommendations addressed areas pertinent to the conduct of the assessment of the risk of pesticide exposures in food, with particular emphasis on the consideration of differences that may exist in sensitivities or exposures to pesticides between infants and young children and the adult population.

Particular emphasis was placed upon effecting improvements in: 1) the manner in which toxicity testing is performed to understand better the potential for hazard to the unborn and very young, 2) the magnitude and quality of information related to exposure (i.e. food consumption data and residue data on raw and processed foods) and 3) risk characterization methods for integrating the hazard and exposure data to reduce uncertainties in predicting risk. While these changes should improve the current ability to assess dietary exposure to pesticide residues, the need to gather and collate data on an international basis remains, especially for population groups of special concern such as infants and children. The Meeting strongly recommended that governments address this need by conducting appropriate dietary surveys.

The Meeting should remain aware of progress made with respect to these important issues of risk assessment. Information developed as a consequence of these recommendations by the NAS may be included in the data on individual pesticides submitted for consideration by future Joint Meetings.

2.4 ADIs BASED ON SHORT-TERM EXPOSURE

The *ad hoc* Working Group on Acceptances at the 25th Session of the Codex Committee on Pesticide Residues (CCPR), when considering the situation in which an ADI is based upon the NOAEL in a short-term exposure study (such as a teratogenicity study), concluded that estimates of the intakes of pesticides should be based upon different measures of food consumption from those appropriate to a long-term effect. The Working Group requested JMPR (WHO Group) to develop guidelines for assessing the toxicological significance of dietary exposure where adverse health effects may result from single or short-term exposure and to consider the definition of the ADI when it is based on an adverse health effect following single or short-term exposure (ALINORM 93/24A, Appendix III).

It should be emphasized that, even though the numerical value of the ADI is derived from the NOAEL in a specific study or studies, it is based on all the data on the pesticide. Even if the effect seen at the lowest dose above the NOAEL is an acute one (such as acetylcholinesterase inhibition) or the study on which the ADI is based is a short-term one (such as a teratogenicity study) the total database provides confidence that long-term exposure is safe. Therefore, the Joint Meeting did not consider it appropriate to use different terminology in such situations.

With those pesticides on which the ADI is based on acute effects or short-term exposure, it may be appropriate to compare the ADI with short-term intake. When predicting intakes for such pesticides, the basis of the ADI, which is explained in the report, should be consulted to ensure that the appropriate comparisons are made. The CCPR was invited to

---

6 *Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach*. WHO Environmental Health Criteria, No. 59. Geneva, World Health Organization, 1986.

request advice from the Joint Meeting in specific instances in which it is not clear which comparisons should be used. The IPCS will consider the types of food intake data that represent short-term intake when the *Guidelines for Predicting Dietary Intake of Pesticide Residues* are revised, and it is expected that guidance on evaluating acute exposures will be incorporated into them. Procedures for the evaluation of the potential for acute toxicity in the context of acute exposure scenarios should then be incorporated into efforts to improve toxicological evaluations in general.

2.5 CONCOMITANT PESTICIDE AND VETERINARY USES OF CHEMICALS

During the discussion of thiabendazole, the 25th Session of the CCPR requested the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the JMPR to discuss the potential for problems when a chemical is used both as a pesticide and for veterinary purposes. This resulted from a suggestion that the CCPR should use the more recent thiabendazole ADI estimate of the JECFA as opposed to the older JMPR estimate. The JECFA and the JMPR were also requested to discuss the need to provide participants in both the CCPR and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) with information on the evaluations of both the JECFA and the JMPR in these situations and to propose a procedure for consideration by both Codex Committees (draft ALINORM 93/24A, paragraph 88).

The Joint Meeting recommended that the Codex Alimetarius Commission and the FAO/WHO Secretariats of the expert committees develop procedures to ensure consistency and appropriate exchange of information among the committees involved. To this end, when either the JMPR or JECFA is scheduled to review a chemical that has been reviewed by the other Committee, the Meeting also recommended that the Joint Secretaries of the JMPR and JECFA obtain and make available copies of pertinent evaluations to their respective Meetings and in advance to the appropriate data reviewers. In a similar manner when an MRL is at Codex Step 3 for discussion the Meeting recommended that the Codex Secretariat, with co-ordination and advice from the Joint Secretaries of the JECFA and the JMPR, arrange distribution of the pertinent evaluations to country contact points for both committees. Contact points should be requested to make copies available to the national committee delegation and/or other national officials responsible for providing comments.

The Meeting drew attention to MRLs related to veterinary uses (indicated in the MRL table by V) for compounds in the CCPR periodic review programme. In a periodic review, veterinary uses will be treated in the same way as all other uses and if information is not supplied, the FAO Panel will recommend withdrawal of the MRLs. The Meeting recommended, for periodic review compounds, that full information on approved veterinary uses and data from residue trials according to the approved uses, together with metabolism data in plants and animals, be included in the submission to the FAO Panel.

2.6 VALIDATION OF STUDIES

Reports of several studies that had been performed by Industrial Bio-Test (IBT) Laboratories were submitted to the present Meeting by sponsors of pesticides that were on the agenda. In most cases no indication was given as to whether they had been validated, either by the US Environmental Protection Agency (USEPA) or Health and Welfare Canada, the two organizations that have attempted to validate most of the IBT studies. Only those studies that were found at the Meeting to have been validated by either the US EPA or Health and Welfare Canada were included in the evaluations.

The Joint Meeting requested that in future sponsors provide the validation status of IBT studies by government agencies, when they submit them to the JMPR for review.

Future Joint Meetings should consider the appropriate course of action to be taken if similar situations arise in the future. Only official government validations of any suspect data will be considered.

2.7 GUIDELINES ON THE NEED FOR ANIMAL TRANSFER STUDIES IN ESTIMATING PESTICIDE MAXIMUM RESIDUE LEVELS

In the course of the 1992 Session of the Codex Committee on Pesticide Residues (CCPR) it was recognized that there was a need to define better the criteria to be considered in determining the need for animal transfer studies when estimating pesticide maximum residue levels. It was decided to request countries to submit information on national approaches in order that some general rules might be elaborated (ALINORM 93/24, para 189). Governments were requested by circular letter (CL 1992/12-PR) to submit this information. A single submission, from the United Sates, was received. The request for this information was reiterated at the CCPR in 1993 (ALINORM 93/24A, para 18) and two further responses were received, from Norway and the United Kingdom. This information was used as the basis for developing some general guidance in this area for the FAO Panel of the JMPR.

General guidance with respect to the role of livestock metabolism and feeding studies in the estimation of pesticide maximum residue levels by the JMPR may be found in the *Codex Guidelines on Pesticide Residue Trials to Provide Data for the Registration of Pesticides for the Establishment of Maximum Residue Limits* (FAO 1986). The document states that:

- "animal metabolism studies are required whenever a pesticide is applied directly to livestock, animal premises are to be treated, or residues occur in crops or crop parts used for feed;"

- "separate feeding studies are required for a ruminant and poultry whenever residues occur in items of feed for these animals."

Because of the development of more sensitive methods of analysis, low or trace pesticide residues are found with increasing frequency in animal feed items. The question arises as to the need for animal transfer studies where livestock are expected to be exposed to low levels of pesticide residues in feed.

The definition of what constitutes a "trace level" in an animal feed commodity or diet is not possible as the judgement involves a number of factors, not only the residue level. It is unlikely that agreement will be reached on a general cut-off level for residues in feed, below which livestock feeding studies will not be required. The definition of some trigger or guidance values would be consistent with the accepted practices of national governments. In addition this would alert industry to this potential need and give them the opportunity to consider these questions in preparing their submissions to the JMPR.

<u>Guideline on the need for animal transfer studies</u>

Livestock (ruminant and/or poultry) metabolism studies are required whenever a pesticide is applied directly to livestock, to animal premises or housing, to crops or commodities used in animal feed, to forage crops, or to any plant parts that could be used in animal feeds.

Livestock transfer studies are required when detectable residues are found in feed items from crop field trials reflecting the proposed use of the pesticide (maximum rate, minimum pre-harvest interval) and the metabolism studies indicate that significant residues (>0.01 mg/kg) may occur in edible tissues (taking into account estimated residue intake from the total livestock diet) and/or the potential for bioaccumulation.

Livestock transfer studies are generally required where significant residues (generally >0.1 mg/kg) occur in crops or commodities fed to animals.

When only low levels (<0.1 mg/kg) of residues are found in feed items the anticipated dietary burden and the results of the metabolism studies must be considered. The latter may indicate that residues in animal commodities would be well below detection limits and thus serve as feeding studies.

2.8 GUIDELINES ON THE PREPARATION OF DATA SUBMISSIONS TO THE FAO PANEL OF THE JMPR

The Meeting was provided with a copy of a working paper concerning the preparation of data submissions to the FAO Panel of the Joint Meeting. The proposal outlined the format and information to be provided to the Joint Meeting. This should include an index or directory of the information to be submitted and a working paper. It will be used as the basis for the submission of information to the FAO Panel of the 1994 Joint Meeting. The formats proposed for the index or directory, the working paper and the organization of the submission are intended as guides and will be amended on the basis of comments received and experience gained in their implementation. Copies of these guidelines are available from the FAO Joint Secretary.

2.9 CHOICE OF DOSE LEVELS IN TOXICOLOGY STUDIES

The Meeting was asked to evaluate a number of toxicological studies in which one or two very low dose levels were used together with one or two high dose levels. Examples in this report are a long-term study in rats (dose levels 0, 0.1, 1.5, 125 or 250 ppm diazinon), a one-year study in dogs (0, 0.1, 0.5, 150 or 300 ppm diazinon), a long-term study in rats (0, 0.5, 2.5, 5 or 125 ppm ethylenethiourea) and a one-year study in dogs (0, 30, 80, 1000 or 3000 ppm metiram).

From a scientific point of view, the selection of doses with such a wide span between the low and high levels can create problems in establishing NOAELs. One of the main factors in interpreting toxicological data is the dose-response relationship. The determination of this becomes difficult when the doses employed in the study under review are not relatively evenly spaced across the range. The determination of the NOAEL, then, is very imprecise if effects are observed at the high doses, but no effects of concern are observed at the low doses. The "true" NOAEL would be somewhere in the broad, untested region between the low and high doses. The dose range should be selected in such a way that the highest dose gives a clear effect on the target organ, the middle dose(s) give some effect(s) and the lowest dose is the NOAEL.

It should be stressed again (see 1987 JMPR report, Section 2.5) that at very high dose levels the kinetics and nature of the biotransformation of a substance may be substantially different from those that occur at low dose levels. This can also have an influence on the evaluation of toxicological data in which only very low and very high doses have been tested because different forms of toxicity might arise as a result of these differences.

2.10 MODE OF ACTION, MECHANISM OF TOXICITY AND TOXICOLOGICAL EVALUATION

The Meeting drew attention to previous comments (1986 JMPR Report, Section 2.3) on the importance of an understanding of the mode of action of a pesticide in the evaluation of its toxicity. This understanding can provide insight into the biological activity of a pesticide and assist in the assessment of its toxicity to non-target species, even when the mechanism differs. For this reason, the Meeting recommended that, where known, information on the mode of pesticidal action as well as on the mechanism of toxicity in non-target species should be made available for consideration in the overall toxicological evaluation of the pesticide.

2.11 DIETARY INTAKE OF PESTICIDE RESIDUES

Following the methods described in *Guidelines for Predicting Dietary Intake of Pesticide Residues* [iii], Theoretical Maximum Daily Intake (TMDI) calculations have been performed for the Joint Meeting by WHO. The results are summarized in Annex III. Processing factors must be reviewed before Estimated Maximum Daily Intake (EMDI) calculations can be performed on those pesticides for which the TMDI exceeded the ADI.

3. SPECIFIC PROBLEMS

3.1 MEASUREMENT OF RADIOACTIVE IODINE UPTAKE AS IN INDICATION OF THYROID FUNCTION

Study of the mechanisms of toxicity frequently involves measurements of dynamic processes. In order to avoid invalid conclusions from such measurements, they must be made at multiple and well-spaced time points.

An example is the measurement of the degree of ^{131}I-uptake by the thyroid in experiments with goitrogenic compounds (see amitrole, ethylenethiourea (ETU) and ethylenebis(dithiocarbamate)s (EBDCs). The time at which the iodine uptake is measured is very important. When the thyroid is enlarged and overactive initially (for instance after six hours) the uptake is high, but then it decreases very rapidly. After 48 hours the value is much lower than in the controls. After 24 hours, it can be lower, the same, or still higher than the control value. With a moderately activated thyroid the uptake remains, in general, above the control value (see the results of experiments carried out by den Tonkelaar and Kroes (1974) as described under short-term studies in the monograph on amitrole). In many experiments, measurements are made only after 24 hours. These can give a false impression of the uptake, especially at higher dose levels. The time of measurement should therefore always be taken into account when interpreting ^{131}I-uptake data.

3.2 EVALUATION OF THE DITHIOCARBAMATES

The Joint Meeting evaluated toxicologically four ethylenebis(dithiocarbamate)s (EBDCs), mancozeb, maneb, metiram and zineb, as well as ethylenethiourea (ETU), the major common metabolite, degradation product and contaminant of the EBDCs. A group ADI was established for the EBDCs, and an ADI was allocated to ETU. In addition, the Meeting evaluated propineb and propylenethiourea (PTU), the major metabolite of propineb. An ADI was allocated to propineb and a temporary ADI was allocated to PTU.

The Meeting also evaluated residue and analytical aspects of mancozeb, maneb and propineb, and of ETU and PTU. Because the individual dithiocarbamates cannot be distinguished by the regulatory analytical method used, the recommended MRLs for mancozeb, maneb and propineb are covered by recommendations for the dithiocarbamates as a group and are listed in Annex I under that heading.

Because residues of propineb, which has been allocated a substantially lower ADI than the group ADI for the EBDCs, cannot be distinguished by regulatory analytical methods from residues of the EBDCs, it is strongly recommended that the development of additional regulatory analytical methods should be aggressively pursued to differentiate propineb residues from those arising from the use of EBDCs.

In the absence of such a specific analytical method, consideration should be given to the use of the ADIs for propineb/PTU when comparing the toxicological significance of dietary exposure to residues of all pesticides giving rise to carbon disulphide on analysis.

Details of the evaluations may be found in Section 4 under the general heading DITHIOCARBAMATES (4.15) and under the individual compounds ETHYLENETHIOUREA (4.18), MANCOZEB (4.28), MANEB (4.29), METIRAM (4.30), PROPINEB (4.35), PROPYLENETHIOUREA (4.36) and ZINEB (4.39).

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

4.1 ALDICARB (117)

RESIDUE AND ANALYTICAL ASPECTS

At the 24th Session of the CCPR (1992) a proposed MRL of 0.05 mg/kg for aldicarb in Brussels sprouts was held as a TMRL at step 7B awaiting more data from supervised trials.

Data from 5 sites in the UK were available to the Meeting. Aldicarb was applied at 3.8, 5.1 and 7.7 g ai/100 m row: 5.1 g/100 m row is the registered use in the UK. Residues were <0.01-0.03 mg/kg except in one trial with the application rate of 5.1 g/100 m, where the level was 0.1 mg/kg. In another trial with the dosage of 7.7 g ai/100m the residue was 0.09 mg/kg.

The Meeting recommended that the TMRL of 0.05 mg/kg should be replaced by an MRL of 0.1 mg/kg.

4.2 AMITROLE (079)

TOXICOLOGY

Amitrole was evaluated in 1974 when a conditional ADI of 0-0.00003 mg/kg bw was allocated. This was extended in 1977. The compound was re-evaluated by the present Meeting in the periodic review programme. The International Programme on Chemical Safety (IPCS) has reviewed amitrole recently and will soon be producing an Environmental Health Criteria document on it.

Amitrole is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration to rats and mice. It is rapidly distributed throughout most body tissues, but with a slight accumulation in tissues with a rapid cell turnover (bone marrow, spleen, thymus, gastrointestinal tract). In a study with pregnant mice it was observed that amitrole passes through the placenta into the fetus with the same distribution pattern as in the mothers. Excretion is rapid after oral exposure. Within 24 hours, 70-95% of the administered radioactivity is excreted via the urine, mainly as the parent compound.

The metabolic transformation in mammals produces two minor metabolites detectable in the urine. The metabolism of amitrole occurs mainly in the liver and involves substitution of the hydrogen atom in the 5 position. The metabolites identified were 3-amino-5-mercapto-1,2,4-triazole and 3-amino-1,2,4-triazolyl-5-mercapturic acid.

Amitrole has a low acute toxicity when tested in several species by various routes of administration. In old studies, amitrole was reported to have slight irritating effects on the skin and eyes. Evidence of a moderate sensitizing potential was observed in a Magnusson-Kligman test but not in a Klecak open epicutaneous test. WHO has classified amitrole as unlikely to present acute hazard in normal use.

Oral exposures up to four weeks in rats revealed that effects on the thyroid occurred at levels $\geq$ 60 ppm in the diet or 104 ppm in drinking water. No effects were observed at 30 ppm in the diet (equivalent to 3 mg/kg bw/day) or 10 ppm in drinking water (equivalent to 1.3 mg/kg bw/day). Furthermore, it was shown that after a recovery period the effects on the thyroid were reversible.

In a 30-day study in mice at concentrations in drinking water of 0, 5000, 10000 or 20000 mg/l, histopathological changes in the liver were observed at all dose levels.

Several short-term oral studies were performed with rats. These were mainly focused on the effects on the thyroid, as this is the target organ in rats.

Only two oral studies were suitable for assessment. In one, male rats were exposed to dietary concentrations of 0, 2, 10 or 50 ppm for 13 weeks or to 0, 0.25 or 0.50 ppm for 11 weeks. The NOAEL was 2 ppm (equivalent to 0.1 mg/kg bw/day), based on histological changes in the thyroid (appearance of follicular cells, contents of colloid and capillary density). Decreases in protein-bound iodine (PBI) were not considered to be biologically significant.

The other study consisted of four short-term experiments in female rats. Dietary concentrations in one experiment were 0, 2, 20 or 200 ppm with exposure for six weeks, in two subsequent experiments 0, 20, 50 or 200 ppm with exposure for six or 13 weeks and in the fourth experiment 0, 20, 50, 200 or 500 ppm with exposure for six weeks. From these four experiments the overall NOAEL was 2 ppm (equivalent to 0.1 mg/kg bw/day), based on increased iodine uptake (shortly after injection), increased thyroid weight and histopathological changes of the thyroid (goitre and clearly activated thyroids).

From several short-term studies in rats with administration in drinking-water, slight effects on the thyroid (moderate stimulation of the thyroid epithelium) were seen at the lowest concentration tested, 50 ppm.

In a one-year study in dogs, no effects on the thyroid were observed at the highest dose tested (12.5 mg/kg bw/day). The only effect observed at this level was pale-coloured pancreases. The test, however, was performed with a small number of animals.

Long-term and/or carcinogenicity studies have been performed in mice, rats, and golden hamsters. Studies in mice were focused on induction of liver and thyroid tumours. In a carcinogenicity study in mice with only one but a very high dose level (1000 mg/kg bw/day by gavage), survival time was significantly reduced and liver and thyroid tumours were observed in all treated mice. A slight increase in the incidence of liver tumours was observed in a special carcinogenicity study in which offspring were treated for a period of 90 weeks at a level of 500 ppm in the diet.

In a carcinogenicity study in mice at levels of 0, 1, 10 or 100 ppm in the diet, an increased incidence of tumours was not observed. In this study, a thyroid function test was also performed with a small number of animals. At 100 ppm an increase in thyroid weight and in iodine accumulation in the thyroid was observed. The NOAEL was 10 ppm (equivalent to 1.5 mg/kg bw/day).

In a carcinogenicity study in rats with levels of 0, 1, 10 or 100 ppm in the diet, a slight decrease in survival time, an increase in the incidence of thyroid tumours and an increase in the incidence of (mainly benign) pituitary tumours were observed at 100 ppm. In this study, a thyroid function test was also performed with a small number of animals. At 100 ppm, thyroid weight was increased during the whole study period as was the percentage accumulation of radioiodine in the thyroid. The NOAEL was 10 ppm (equivalent to 0.5 mg/kg bw/day).

In another limited long-term study in rats, the NOAEL was 10 ppm (equivalent to 0.5 mg/kg bw/day), based on thyroid hyperplasia. A clearly enhanced thyroid tumour incidence was found at 50 and 100 ppm. In this study, animals suffered from apparent respiratory infection.

In a third study in rats, thyroid hyperplasia and thyroid tumours were observed in animals fed 100 ppm (during the first 40 weeks of the 115-120 week study, the dose level was 5 ppm). In rats treated at pulsed intervals (alternate four week periods) at levels of 60 ppm (first 3 ppm) and 200 ppm (first 10 ppm) thyroid tumours were also observed. Slight thyroid hyperplasia was also observed at the lowest dose level of 20 ppm (first 1 ppm; intermittent dosing regimen). An NOAEL could not be established.

In a carcinogenicity study in Syrian hamsters at dietary concentrations of 0, 1, 10 or 100 ppm, the NOAEL was 10 ppm (equivalent to 1 mg/kg bw/day), based on decreased body-weight gain and increased mortality. No effects on the thyroid were observed at 100 ppm. There was no evidence of carcinogenic potential.

A well performed reproduction study was not available. From a limited study in rats at dietary concentrations ranging from 25 to 1000 ppm, effects on reproductive capability were observed at 500 ppm and above. Reduction of liver weight and thyroid hyperplasia were the most sensitive effects observed at the lowest dose level (25 ppm, equivalent to 1.3 mg/kg bw/day).

In a teratogenicity study, rats were exposed by gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day on days 6 to 15 of gestation. No effects were observed in this study. The NOAEL for maternal toxicity and embryo/fetotoxicity was 1000 mg/kg bw/day.

In another teratogenicity study, rats were exposed by gavage at doses of 0, 100, 500 or 1000 mg/kg bw/day. Slight maternal toxicity (reduced weight gain and food consumption and increased thyroid weights) was observed at doses of 500 and 1000 mg/kg bw/day. Reduced fetal body weight/litter and reduced skeletal ossifications were observed in the high-dose group. Increased incidences of enlarged and/or dark thyroids were seen in fetuses at 500 and 1000 mg/kg bw/day. The NOAEL for maternal toxicity and embryo/fetotoxicity was 100 mg/kg bw/day. Amitrole was considered not to be teratogenic in rats at dose levels up to 1000 mg/kg bw/day.

In a teratogenicity study in rabbits the animals were exposed by gavage to dose levels of 0, 4, 40 or 400 mg/kg bw/day. Decreased weight gain during the gestation period was observed at 40 and 400 mg/kg bw/day and increased liver weight at 400 mg/kg bw/day. A dose-related increased incidence of abortions was observed in all treated groups. Embryo/fetotoxicity were observed at 40 and 400 mg/kg bw/day. Increased incidences of irreversible structural changes were also found at these dose levels, which involved mainly the head and limbs. The NOAEL for maternal toxicity, embryo/fetotoxicity and teratogenicity was 4 mg/kg bw/day.

In a dermal teratogenicity study in rabbits at dose levels of 0, 1000, 1500 or 2000 mg/kg bw/day, maternal toxicity (decreased body weight and food consumption, thin appearance and anorexia) was observed at 2000 mg/kg bw/day. At this level, irreversible structural changes (anencephaly and microphthalmia) were observed. The NOAEL for maternal toxicity, embryo/fetotoxicity and teratogenicity after dermal exposure was 1500 mg/kg bw/day.

Amitrole has been tested adequately in series of *in vitro* and *in vivo* genotoxicity assays. Positive responses were obtained in a number of mutation assays in bacteria, recombinogenicity assays in yeast and some mammalian cell assays for mutation, sister-chromatid exchange and cell transformation. No genotoxicity was demonstrated *in vivo*. The Meeting concluded that the genotoxic potential of amitrole was equivocal.

Amitrole is a goitrogen in mice, rats and sheep but not in Syrian hamsters, dogs, or cattle at the doses that have been tested. The mechanism of thyroid toxicity involves inhibition of thyroid peroxidase. This inhibition results in decreases in circulating levels of T_4 and T_3, which stimulate the pituitary to increase secretion of TSH which in turn may cause thyroid hypertrophy, hyperplasia and neoplasia. Threshold doses have been identified in the sensitive species. Amitrole is not genotoxic in *in vivo* assays.

The Meeting withdrew the conditional ADI and established a temporary ADI, based on the NOAEL of 0.5 mg/kg bw/day in the 24-month dietary study in rats, pending the evaluation of the required data (see below). Because of the inadequacy of the existing data a safety factor of 1000 was used.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and containing relevant data from the previous monograph and monograph addendum on amitrole.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:	10 ppm, equivalent to 1.5 mg/kg bw/day	(18-month study)
Rat:	10 ppm, equivalent to 0.5 mg/kg bw/day	(24-month study)
	100 mg/kg bw/day	(teratogenicity study)
Hamster:	10 ppm, equivalent to 1 mg/kg bw/day	(18-month study)
Dog:	12.5 mg/kg bw/day	(12 month study)

Estimate of temporary acceptable daily intake for humans

0-0.0005 mg/kg bw

Studies without which the determination of a full ADI is impracticable

Results to be submitted to WHO by 1996 (all known to have been initiated):

1. Two-generation reproduction study in rats.
2. One-year study in dogs.
3. Oral teratogenicity study in rabbits.
4. Metabolism study in rats.

Studies which will provide information valuable in the continued evaluation of the compound

1. Further observations in humans.
2. Comparative biotransformation (including humans).
3. Clarification of the genotoxic potential of amitrole.

RESIDUE AND ANALYTICAL ASPECTS

Amitrole was evaluated by the JMPR in 1974 and 1977 and is included in the CCPR periodic review programme. A conditional ADI was allocated in 1974 and confirmed in 1977. An MRL for raw agricultural commodities was recommended at the limit of determination in 1974, but the 17th Session of the CCPR (1987) recommended that the MRL should be withdrawn and replaced by a note that uses of amitrole should be restricted to those where residues in food would not be expected to occur.

Information on registered uses was received from Australia, Belgium, Canada, France, Germany, The Netherlands, Portugal and Spain. The compound is applied to the ground and directly on to weeds and usually with a long PHI, so residues should not be detectable in crops grown on treated soil.

The Meeting received only one report from supervised trials, but was informed that new trials on apples, grapes, and pears were in progress. Most of the studies would be supplied to the JMPR in the near future.

Several reports were available from studies on the metabolism or degradation of amitrole (aminotriazole) in plants, animals and soil. In plants after direct applications to the leaves or stem the main metabolite was aminotriazolylalanine, 3-(3-amino-1,2,4-triazol-1-yl)-D-alanine. Two other metabolites were found, but not identified. The same metabolites were present in rats. After treatment of the soil surrounding plants only small amounts of aminotriazole and its metabolites were translocated to the plant. In apples residues of the parent compound and the metabolite triazolylalanine were undetectable or very low: when present the compounds were in both free and conjugated forms. In cell suspension cultures from apples 3,5-dihydroxy-1,2,4-triazole was produced.

In soil rapid degradation occurs with CO_2 as the main degradation product. Degradation in soil is strongly influenced by the presence of micro-organisms, and does not occur under anaerobic conditions. From laboratory experiments it was possible to propose a degradation scheme for amitrole in soil. The ring is opened after metabolism to 5-hydroxyaminotriazole, and via cyanamide the compound is decomposed to CO_2 and ammonia. Because of the rapid degradation only small amounts of aminotriazole are leached into soil. Leaching is most pronounced in sandy soil with a low content of organic material.

New analytical methods for the determination of residues of amitrole have been developed using gas chromatography with a nitrogen-specific detector, thin layer chromatography and high performance liquid chromatography with fluorescence or electrochemical detection. The limits of determination are 0.01 - 0.02 mg/kg for residues in fruit, vegetables and soil.

A complete re-evaluation of amitrole has not been possible because new data from supervised trials were not available. Although the registered uses reported to the Meeting are similar to the application conditions in some supervised trials examined by the JMPR in 1974, the data from the trials currently in progress should be taken into consideration. No reports from studies of storage stability were available, but the Meeting was informed that the results of such studies will be available in 1995. Reports of animal transfer studies were also lacking, but as residues of amitrole in crops are obviously very low and usually below the limit of determination, there is a very limited need for such studies.

No Codex residue limits are established for amitrole in food commodities. The Meeting is aware that the compound is in use. A realistic limit of determination for the general monitoring of amitrole would be 0.05 mg/kg.

FURTHER WORK OR INFORMATION

Desirable

1. Residue data from supervised trials on apples, pears and grapes known to be in progress.

2. Reports from experiments on the storage stability of amitrole known to be in progress.

4.3 AZINPHOS-METHYL (002)

RESIDUE AND ANALYTICAL ASPECTS

Azinphos-methyl was evaluated in 1965 and several times since. In 1991 a re-evaluation resulted in recommendations to withdraw or change several MRLs. New residue data from trials carried out according to GAP were required for apricots, black currants, citrus fruits, strawberries, kiwifruit and bulb and spring onions. The data from trials according to GAP on apricots, citrus fruits and kiwifruit were so limited that withdrawal of the existing MRLs was proposed, and this recommendation was accepted by the 25th Session of the CCPR (1993). Residue data from trials according to GAP on blueberries, cherries and grapes were also desirable as the data available were from only one country, the USA.

The Meeting received summarized residue data from Spain from trials on mandarins and oranges according to registered use in Spain. Residue data on apricots were also available from Spain, but the dosage used was about 3 times the registered rate.

Residue data from trials on cherries were received from Denmark, but samples were taken more than 50 days after the last treatment whereas the registered PHI in Denmark is 21 days. Information was received on several trials on cherries carried out in the USA, which supported the MRL of 2 mg/kg proposed by the 1991 JMPR. The Meeting was informed that data from trials on grapes in Germany and Italy, including processing studies, would be available in 1995.

At the 1991 JMPR a temporary residue limit was proposed for wheat straw and fodder. As no supplementary data were received the Meeting proposes that the temporary limit should be withdrawn.

FURTHER WORK OR INFORMATION

Desirable

1. Detailed information from trials on citrus fruits carried out in Spain.

2. Residue data from trials on citrus fruits from other countries.

4.4 BENALAXYL (155)

RESIDUE AND ANALYTICAL ASPECTS

Benalaxyl was first reviewed for residues by the 1986 JMPR, which estimated Guideline Levels and listed desirable information. Guideline Levels were changed to MRLs when an ADI was allocated by the 1987 JMPR. Over several years various limits (in particular on grapes) were questioned at the CCPR. Submission of additional unspecified data has been promised. Several submissions were made to the Meeting in response to requests of the 1986 JMPR or concerns expressed at the CCPR, some with and some without the detailed reports.

Grapes. The 0.5 mg/kg limit estimated by the 1986 JMPR was lowered to 0.2 mg/kg by the 1990 CCPR. Although no outstanding issues remained, extensive recent data from the use of benalaxyl on grapes were provided to the Meeting. Much of the summarized information could not readily be related to the more detailed reports provided owing to its code numbering format, except in the case of the Italian data.

Most of the submitted grape data do not closely reflect reported current GAP. In particular, most of the results (except at day 0) were at intervals significantly longer than the reported 7-day Italian GAP PHI (the shortest non-0-day PHI was 11 days and most PHIs were longer). The few results within GAP (GAP rates and $\geq$ 11 day PHI) were consistent with the current 0.2 mg/kg CXL. However, extrapolation from Italian residue decline curves strongly suggests that residues exceeding 1 mg/kg are likely to occur from Italian GAP at a 7-day PHI. Extrapolation of previously provided and additional data from German supervised trials also suggests that residues may approach 1 mg/kg when related to Italian GAP. However, the Meeting was informed that the manufacturer is to request that the 7-day Italian PHI be revised to 10-28 days. With that revision residues would be within the current limit. The Meeting was also informed that applications are only on small immature fruit.

Residues in must and wine were ≤0.02 mg/kg, mostly ≤0.01 mg/kg. No data were provided for grape pomace, a possible animal feed item.

Potatoes. The adequacy of previously submitted analytical methods to support the current 0.01 mg/kg CXL for potatoes has repeatedly been questioned at the CCPR. The Meeting concluded (see below) that 0.02 mg/kg is a reasonable limit of determination for the new analytical method reported, and noted that the limit of "detection" for much of the additional summary data reported (but not reviewed) is 0.02 mg/kg. The Meeting therefore proposed that the MRL should be increased to 0.02 mg/kg.

In addition to substantial supervised trials data for grapes, the Meeting received summary data on benalaxyl residues in cucumber, potatoes and tomatoes. Because summary data without accompanying detailed reports are not suitable for estimating maximum residue levels the Meeting did not review these summaries apart from considering the limit of determination for potatoes. The Meeting was informed that the detailed reports would be submitted for review at a future meeting.

The Meeting also received a limited response to the 1986 request for additional information on levels of metabolites in plants. Noting unsuccessful efforts to analyze the GX1A and GX1B glucoside metabolites in crops, the Meeting was informed of a method for the determination of these metabolites in white wine (unsuccessful in red wine). No data were provided except the results of recovery studies.

Residues in animal products. In response to a JMPR request for information on residues in cattle and pigs the manufacturer expressed the view that metabolism studies and the low residues expected in feed items would make residues in meat from cattle and pigs unlikely. Since (1) significant residues could occur: they have been found in the offal of goats and hens in metabolism studies (e.g. up to 1 and 1.8 mg/kg in the liver of goats and hens fed at 50 ppm in the feed); (2) information on the possible concentration of residues in feed items derived from processing was lacking; and (3) the duration of the metabolism study feeding periods (7 days for cattle, 14 days for hens) was relatively short, the Meeting could not with certainty come to the same conclusion. While the Meeting agreed that residues in animals would be likely to be low, there is the potential for finite residues.

Processing. Apart from data on residues of benalaxyl in wine and must, no information was provided in response to the 1986 JMPR request for information on the effect of processing on residues in crops. Processing studies would also provide insight into the likelihood of residues in animal products. The Meeting was informed that processing studies would be scheduled for 1994.

Analytical methods. A published analytical method based on acetone extraction, liquid-liquid partitioning, alumina clean-up and GLC with NPD detection was provided in response to CCPR concerns that no published enforcement method was available and doubt concerning the reported 0.01 mg/kg limit of determination in potatoes in the method previously reviewed. The published method was tested on several crops, wine, must and water. Recoveries of $\geq$95% were reported.

The Meeting received excellent documentation of what appears to be a suitable enforcement method. While the reported limits of determination (0.01 mg/kg in crops and 0.01 mg/l in wine and must) may be attainable in the author's laboratory, on the basis of sample chromatograms, reported control values and fortification levels, the Meeting concluded that a more realistic limit of determination for Codex purposes would be of the order of 0.05 mg/kg in crops (0.02 mg/kg in potatoes) and 0.05 mg/l in wine and must. Detection is possible at lower levels.

A description of an analytical method for the determination of the glucoside metabolites GX1A and GX1B in white wines was also provided (chromatograms suggest that routine analyses down to 0.05 mg/kg should be feasible). An analytical method based on column chromatography clean-up and GLC with AFID detection for determining benalaxyl in wine was also provided, with the capability of analyses at 0.02 to 0.05 mg/kg.

FURTHER WORK OR INFORMATION

Desirable

1. Submission of revised Italian GAP for grapes for the next scheduled review.

2. Submission of detailed reports of trials on cucumber, potato and tomato corresponding to summary data provided to the 1993 Meeting, reported in a manner to permit easy comparison of the summary data and the detailed reports and in the working language of the Meeting.

3. Submission on completion of processing studies which are scheduled for 1994.

(From 1986 JMPR)

4. Information on residues in meat from pigs and cattle fed a diet containing benalaxyl.

4.5 BROMOPROPYLATE (070)

TOXICOLOGY

Bromopropylate was previously evaluated by the Joint Meeting in 1973, when an ADI of 0-0.008 mg/kg bw was allocated. That Meeting recommended further desirable work as follows: 1) studies to elucidate the effects on survival rate of rats in long-term feeding studies; 2) long-term studies in a second animal species; 3) studies on the effects of bromopropylate on the liver. The results of these studies and additional data were submitted for the present evaluation.

After oral administration of [U-^{14}C]phenyl bromopropylate, most of the radioactivity was eliminated in the faeces, with lower amounts of radioactivity excreted in the urine. The routes of elimination were sex- dependent.

Bromopropylate was metabolized preferentially by cleavage of the isopropyl ester linkage, and to a minor extent by oxidation reactions attacking the phenyl ring and the isopropyl group.

Bromopropylate has the properties of a phenobarbital-like inducer of cytochrome P-450 in the mouse liver. In a DNA-binding study conducted with mice no radioactivity was detectable in liver DNA, indicating that bromopropylate is devoid of genotoxic potential in this organ.

Bromopropylate has a low acute toxicity in rats and rabbits. WHO has classified bromopropylate as unlikely to present acute hazard in normal use.

In a one-year study in dogs at dietary concentrations of 0, 100, 400 or 2,000 ppm, the NOAEL was 100 ppm (equal to 2.7 mg/kg bw/day), based on depressed body-weight gain at 400 ppm and above.

In a study in mice using dietary concentrations of 0, 30, 150, 1,000 or 3,000 ppm for 24 months, the NOAEL was 150 ppm (equal to 16 mg/kg bw/day), based on increased absolute

and relative liver weights and hepatocellular neoplastic lesions at 1,000 ppm and above.

Long-term toxicity/carcinogenicity studies in rats were reviewed. The study considered by the 1973 Joint Meeting was found to be unacceptable. In a new study at dietary concentrations of 0, 100, 700 or 5,000 ppm, the NOAEL was 100 ppm (equal to 3.7 mg/kg bw/day), based on increased water consumption and increased relative liver and thyroid weights at 700 ppm and above. Increased incidences of focal hepatocellular hypertrophy and fatty changes and pigmentation of hepatocytes were also observed at 700 ppm and above.

In a reproduction study in rats using dietary concentrations of 0, 165, 750 or 2,250 ppm, the NOAEL was 165 ppm (equal to 9 mg/kg bw/day), based on increased liver weight and hypertrophy of hepatocytes in F_1 animals at 750 ppm and above.

Teratogenicity studies were conducted with rats and rabbits. In the study in rats at doses of 0, 50, 300 or 700 mg/kg bw/day, depressed maternal body-weight gain and an increased incidence of skeletal variations of fully formed 14th ribs and rudimentary 14th ribs were recorded at 300 mg/kg bw/day and above. The maternal NOAEL in this study was 50 mg/kg bw/day. There was no evidence of embryo/fetotoxicity or teratogenicity. In the study in rabbits at doses of 0, 20, 60, or 120 mg/kg bw/day, mean body-weight gain was depressed at 60 mg/kg bw/day. The NOAEL for maternal toxicity was 20 mg/kg bw/day, and no embryo/fetotoxic or teratogenic effects were found.

After reviewing the available genotoxicity data, the Meeting concluded that bromopropylate was not genotoxic.

An ADI was established, based on the NOAEL of 2.7 mg/kg bw/day in the one-year study in dogs, using a 100-fold safety factor.

A toxicological monograph was prepared, summarizing the data that have been reviewed since the previous evaluation and incorporating relevant studies from the previous monograph.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 150 ppm, equal to 16 mg/kg bw/day (two-year study)
Rat: 100 ppm, equal to 3.7 mg/kg bw/day (two-year study)
Dog: 100 ppm, equal to 2.7 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Bromopropylate was scheduled by the CCPR for periodic review at the 1993 JMPR (ALINORM 93/24A, para 93). It was first considered by the JMPR in 1973 when residue data on apples, pears, plums, grapes, bananas, strawberries, citrus, hops, tea, cotton, egg plant and tomatoes were evaluated and MRLs for apple, banana, cherry, citrus fruits, cotton seed, grapes, hops, nectarine, peach, pear, plum, strawberry, tea and vegetables were established. Since then,

more residue trials on some of the same crops as well as additional ones such as artichokes, beans, celery, cucurbits, guavas, maize, onions, papaya, peaches, peanuts, peas, sweet peppers, pineapples and sugar beet have been conducted by the manufacturer in various countries as well as the authorities of The Netherlands and Spain. Further information has also been provided by the manufacturer, Spain, The Netherlands and Australia on current uses. Australia has also indicated that the pesticide had not been marketed since 1986.

The manufacturer has indicated that there were no current uses on nectarines, bananas or cherries. The Meeting recommended the withdrawal of the MRLs for these commodities.

Additional plant metabolism studies on apples and citrus showed that the parent compound was the residue of importance, particularly in the edible parts, although minor metabolites, mainly 4,4′-dibromobenzilic acid, were found in the leaves.

No information on the fate in animals has been submitted but the Meeting noted that adequate information on animal transfer studies for dairy cows and beef cows had been reported by the 1973 JMPR.

In water, bromopropylate was found to have a half-life of 20-40 days. Bromopropylate and its metabolites were concluded to have low mobility in sandy loam, silty loam and sandy soils on the basis of leaching studies. The half-life in silty loam and sandy loam soils was about 45 days, the major metabolite being 4,4′-dibromobenzophenone.

Residues in the juice of apples and mandarin oranges, and in wine and beer were reported to be below the limit of detection, (0.02 mg/kg in all cases, except beer 0.005 mg/kg).

Bromopropylate residues in samples of tea, tomatoes, tomato puree, oranges, grapefruit, orange juice, orange oil, apples, peaches and cherries were found to remain stable up to 2 years under freezer conditions at -18^{o}C.

GAP information was not available for guavas, papayas, pineapples, onions, celery, maize, peanuts or sugar beet, so residue data on these crops could not be evaluated.

GAP information and residue trials data on peas, tomatoes, egg plants, artichokes and sweet peppers were too limited for the Meeting to estimate maximum residue levels.

The available information for cotton seed, hops and tea was also too limited to support the present MRLs. The Meeting agreed to withdraw the recommendations for these commodities.

For citrus, the trials data on residues in the pulp and peel confirmed earlier findings that most of the residues are concentrated in the peel. Results from Australia, South Africa and Morocco were not supported by GAP information, while in data from Spain, China and Israel trials rates were expressed differently from the national GAP. Six trials in Brazil on oranges and mandarin oranges were evaluated in the light of the national GAP. At 14 days after the last application, residues ranged from 0.6 to 5.8 mg/kg in the peel and 0.2 to 0.4 mg/kg in the pulp. Assuming that the peel weight is 30% of the fruit's weight the calculated residues in whole fruit would be less than 2 mg/kg. In trials on lemons in Spain rates between 1.6 and 5.2 kg ai/ha were used, which were within Spanish GAP. At 14 days, residues ranged from 0.5 to 1.3 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for bromopropylate in citrus fruits with a PHI of 14 days, to replace the current MRL of 5 mg/kg.

The residue trials data on apples from Brazil and Canada were not evaluated because no information on registered uses was available from these countries. Trials from Chile were also not evaluated because the registered use was supplied in terms of spray concentration while the trials application rates were expressed as kg ai/ha. Trials in The Netherlands, France and Germany on apples and pears were within the GAP of The Netherlands and France, and

residues at 21 days were within the range of 0.18 - 1.6 mg/kg. Data on apples and pears were mutually supporting. The Meeting recommended an MRL of 2 mg/kg for pome fruits at a pre-harvest interval of 21 days, based on the data from France, Germany and The Netherlands.

For peaches, trials data from Brazil and Switzerland were submitted, and for plums, data from ten trials in Germany. Data from Switzerland and Germany were evaluated on the basis of the GAP of Switzerland (stone fruits) and The Netherlands (plums). At 21 days after the last application, the highest residue obtained was 1.6 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for plums at a pre-harvest interval of 21 days. Data from peach trials were insufficient to recommend an MRL but provided some additional support for the plum estimate.

Additional data on grapes from trials in Australia, France, Hungary, Israel, South Africa and Switzerland were submitted. As there was no information on registered uses in Australia and South Africa, the data from these countries could not be evaluated. Trials rates in Hungary were expressed differently from GAP in Hungary. The trials rates in France, Israel and Switzerland covered the national recommendations. The data from France showed that by 27 days residues in grapes were all less than 2 mg/kg, and in wine <0.02 mg/kg. The Meeting recommended an MRL of 2 mg/kg for grapes at a pre-harvest interval of 28 days.

Residue trials data on strawberries had been submitted from Brazil, Israel, Italy, Japan and Spain. Although trial rates in Spain and Italy did not cover the maximum rates under the GAP of the two countries, on the basis of the trials data the Meeting recommended an MRL of 2 mg/kg for strawberries with a PHI of 14-21 days.

For beans, evaluation of the residue trials data from Italy and Spain was based on the GAP of Spain. Residue levels at 7 days ranged from 0.26 to 2.5 mg/kg. The Meeting recommended an MRL of 3 mg/kg for common beans at a pre-harvest interval of 7 days.

Residue data from Italy on cucumbers, melons and summer squash were evaluated on the basis of the GAP of Spain. The Meeting recommended an MRL of 0.5 mg/kg for cucumber, melons and summer squash at a pre-harvest interval of 7 days.

The Meeting recommended withdrawal of the MRL for vegetables, to be replaced by MRLs for the specific commodities beans, cucumber, melons and summer squash.

FURTHER WORK OR INFORMATION

Desirable

1. Information on the occurrence of bromopropylate residues in food in commerce or at consumption.

2. Information on residues in the pomace of citrus fruit, apples and grapes, which may be used as animal feeds.

4.6 CARBOFURAN (096)

RESIDUE AND ANALYTICAL ASPECTS

The 1992 CCPR held the 2 mg/kg carbofuran citrus limit at Step 7B pending a JMPR review of country comments to be submitted. The Meeting considered comments from Germany on the proposed citrus limit, as well as supervised trials data for potatoes, onions and tomatoes. In addition to being only summarized, the data for potato did not reflect the GAP PHI. No GAP

information was provided for onions. For tomato important information was missing for two of four trials. The Meeting did not consider the summary data with no additional supporting information from limited trials sufficient for estimating maximum residue levels.

The Meeting took note of its recommendation to withdraw the 2 mg/kg temporary limit for carbosulfan in citrus fruits (see 4.7 below), and further noted that the current 2 mg/kg citrus limit for carbofuran was recommended to accommodate residues resulting from the use of carbosulfan. The Meeting therefore recommended withdrawal of the current temporary limit for carbofuran in citrus fruits.

4.7 CARBOSULFAN (145)

RESIDUE AND ANALYTICAL ASPECTS

Carbosulfan was first reviewed for residues by the 1984 JMPR. Although extensive data were reviewed for a number of commodities, the Meeting recommended only a temporary limit for citrus fruits pending the submission of required and desirable information, in particular critical supporting studies and GAP information.

The 1991 Meeting recommended that limits for carbosulfan should be for carbosulfan *per se* and that separate limits should be set for the sum of carbofuran and 3-hydroxy-carbofuran to accommodate residues resulting from the use of carbosulfan or carbofuran. Keto-carbofuran was deleted from the definition. The 1991 JMPR decided not to propose a new limit for citrus fruits, pending the review of additional data received too late for consideration. Additional requirements were added to those listed by the 1984 Meeting.

The Meeting received a discussion paper, summary comments and selected pages and summary tables from a number of reports on the identification and fate of residues in animal products in response to the 1984 JMPR requirements. The Meeting did not review these documents in the absence of the complete reports from which the summaries came. The required information on brassica vegetables was not provided. GAP information and trials data on a number of commodities were also provided, much but not all of which had been reviewed by the 1984 JMPR.

Citrus. The 1984 JMPR recommended a 2 mg/kg temporary limit for citrus fruits, pending the submission of required information. The definition of the residue was revised to separate the limits for carbosulfan from those of its metabolites by the 1991 JMPR, resulting in separate limits at 2 mg/kg for carbosulfan *per se* and 2 mg/kg for the sum of carbofuran and 3-hydroxy-carbofuran. No change in the carbosulfan numerical level was proposed, pending the review of additional information. Clarification of apparent discrepancies in Spanish GAP was also requested but the GAP has not been fully clarified. One Codex delegation provided written comments explaining its view that a 2 mg/kg limit was not justified for carbosulfan or carbofuran, citing the general lack of data reflecting GAP and the low residues of carbosulfan in particular. In order to address the issues the Meeting considered newly submitted information on GAP and new and re-submitted residue trials data, and took into account data reviewed by the 1984 JMPR as well as the Codex comments.

The most extensive data (1984 JMPR) are those from trials in the USA. However, the use is not yet GAP in the United States and the Meeting could not with confidence relate the data to the GAP of other countries. Further, new data on peel and pulp residues in Spanish trials did not include important information, precluding a determination of whether the data reflected Spanish GAP (which is itself still in question). If future submissions show that all of the Spanish data reflect GAP, maximum whole fruit residues of <0.05 mg/kg carbosulfan and 0.3 mg/kg carbofuran plus 3-hydroxy-carbofuran would be indicated, assuming a peel to pulp ratio of 30:70. Re-submitted Brazilian data (<0.05 mg/kg carbosulfan, carbofuran, or 3-hydroxy-

carbofuran) could not be related to the Brazilian GAP information provided.

The only data that could be related to GAP with some confidence were from Italian trials reviewed in 1984 which could be compared to Spanish GAP and Israeli data which could be compared to Israeli GAP. The Italian trials according to Spanish GAP resulted in maximum residues of 0.7 mg/kg carbosulfan and 1.7 mg/kg for the sum of carbofuran and 3-hydroxy-carbofuran. Maximum residues reflecting Israeli GAP were 0.05 mg/kg carbosulfan and 0.2 mg/kg for the sum of carbofuran and 3-hydroxy-carbofuran, although requested information on the interval from sampling to analysis to give greater confidence in the results was not provided.

Because the requested clarification of GAP and the sampling-to-analysis intervals still have not been supplied, because only a relatively small data base is available which can be compared GAP, and because of a large discrepancy between the two sets of results which were comparable to GAP, the Meeting concluded that insufficient information had been provided to support a citrus limit for carbosulfan or carbofuran. The Meeting was informed that additional supervised citrus trials would be conducted in Spain, Brazil and Mexico.

Hops. German data for green and dry hops, spent hops and beer that were reviewed by the 1984 JMPR were re-submitted to the Meeting, together with GAP for Spain and Germany. No GAP information was provided to the 1984 Meeting. The data indicate that dry hop residues are unlikely to exceed 3 mg/kg for carbosulfan and 7 mg/kg for combined residues of carbofuran and 3-hydroxy-carbofuran after the 28-day Spanish PHI from the 37.5 g ai/hl used in the supervised trials. No data were available for the maximum 75 g ai/hl reported to be Spanish GAP. Maximum residues 21 days (German GAP PHI) after 6 applications at 37.5 ai/hl resulted in carbosulfan residues of 0.04-3.4 mg/g in dry hops and 0-2.2 mg/kg in green hops. Corresponding residues of carbofuran plus 3-hydroxy-carbofuran were 1.4-11.3 mg/kg in dry hops and 1-9.9 mg/kg in green hops. Because 6 applications were used, compared to GAP of one application, the Meeting was unable to estimate a limit for hops.

Melons. Data (indoor) were available from only two trials in one country (two results at the GAP PHI) with only one trial at the maximum application rate. No analyses were conducted for 3-hydroxy-carbofuran and critical supporting information on sample storage conditions and the interval from sampling to analysis were lacking. It was therefore concluded that the data were insufficient to support an MRL for melons. The Meeting was informed that supervised trials on melons are being conducted in Spain.

Pome fruit. The 1984 JMPR reviewed data on apples and pears from three countries, but did not estimate a limit for pome fruit because the data base could not be related to available GAP and critical supporting information (e.g. storage conditions and intervals) was not provided. Summaries of some of the data reviewed by the 1984 JMPR were provided to the present Meeting as well as additional summary data not previously reviewed. Because only summary information was provided, because most of the old and new data could not be compared to the available Spanish GAP, and because the desirable critical supporting information still had not been provided, the Meeting concluded that the data were insufficient to support limits for pome fruit.

Potatoes. Fairly extensive data from Italy, France and the UK were reviewed by the 1984 JMPR. Summaries of these data were provided to the Meeting, but 11 of the 13 trials did not reflect the (Spanish) GAP PHI of 28 days. A discussion document and selected pages from a sugar beet metabolism study were provided in response to the 1984 JMPR requirement for a root metabolism study from both foliar and soil treatments. The Meeting concluded that data reflecting GAP were not adequate to recommend an MRL and that submission of the complete metabolism study would be needed before that requirement could be regarded as satisfied.

Stone fruit. Summary data from a substantial number of trials were available, but were not

adequately reported and many of the trials did not reflect GAP PHIs for use in recommending MRLs. The trials most adequately reported were based on an 83-day PHI, whereas GAP is 28 days. The Meeting concluded that data reflecting GAP were inadequate and inadequately reported to recommend MRLs.

Sugar beet. Extensive data were reviewed by the 1984 JMPR but critical supporting information was sketchy or in some cases missing, data were not relevant to available GAP information and a root metabolism study was required. Information provided to the Meeting indicated that Spanish GAP was similar to that used in the French and UK trials reviewed in 1984, except that the Spanish PHI is 60 days whereas most of the trials results were at $\geq$104 days. Summary discussion information and selected pages from a sugar beet root metabolism study provided to the Meeting did not meet a 1984 JMPR root metabolism requirement. The full reports need to be submitted. Summary Italian data from trials at application rates greater than the Spanish GAP rates and at longer intervals than the minimum Spanish PHI were also provided. The Meeting concluded that data reflecting GAP were still inadequate to support an MRL for sugar beets. When the complete metabolism study and the detailed Italian data are provided the Meeting can reconsider the position.

Metabolism. The Meeting was informed that metabolism studies on oranges, rats, and goats and an animal transfer study on cows are being conducted.

4.8 CHLOROTHALONIL (081)

RESIDUE AND ANALYTICAL ASPECTS

Chlorothalonil was first evaluated in 1974. This evaluation has been prepared as part of the programme of periodic reviews agreed by the CCPR.

Information on current GAP and residue trials data were made available to the Meeting by one of the manufacturers; GAP information was also provided by Australia, Canada and the EC.

At the initiation of this review there were 35 MRLs for chlorothalonil; all were CXLs except the MRL for grapes which was at step 7B.

The fate of chlorothalonil has been studied in lettuce, tomato, carrot and celery. Chlorothalonil was the major characterised component of the residue in all cases; small amounts of 4-hydroxy-2, 5, 6-trichloroisophthalonitrile (SDS-3701) were also found.

Data from supervised residue trials carried out in a number of countries and on a range of crops were available.

No GAP was reported for citrus fruit, so the Meeting recommended that the CXL of 5mg/kg should be withdrawn.

The CXL of 10 mg/kg for cherries was proposed in 1974; it was based on US GAP with a 7-day pre-harvest interval and residue data from trials carried out in the USA. Since use so close to harvest is no longer GAP in the USA the CXL is obsolete and the Meeting considered that it should be withdrawn. Results from a series of trials carried out in accordance with current GAP in the USA were available at the Meeting. Residues up to 0.5 mg/kg were found. The Meeting recommended that an MRL of 0.5 mg/kg was appropriate for this use.

For peaches, the CXL of 25 mg/kg was again based on US GAP permitting use up to 7 days before harvest and residue trials data from the USA. This US GAP is now obsolete and therefore the CXL was not acceptable. Supervised trial data on peaches from Italy, Spain and

the USA were made available to the Meeting. Residues up to 0.12 mg/kg were found when chlorothalonil was used according to current US GAP, and up to 0.98 mg/kg in Italian trials within Spanish and Greek (1.5kg ai/ha and 14-15 days PHI) and Italian (1.0 kg ai/ha and 21-day PHI) GAP. The Meeting recommended an MRL of 1 mg/kg for peaches.

Chlorothalonil residues up to 4.1 mg/kg were found in cranberries harvested 50-70 days after treatment at 5.9 kg ai/ha (within US GAP) in a series of trials in the USA in the 1980s. The Meeting recommended an MRL of 5 mg/kg for cranberry.

The CXLs of 25 mg/kg for raspberries (red and black) and currants (black, red and white) and 10 mg/kg for blackberries were based on GAP and trials in the USA. Since this GAP is no longer current the Meeting recommended that these CXLs should be withdrawn.

For grapes, the draft MRL, at step 7B, is 10 mg/kg. This proposal was based on Austrian GAP of 0.11 kg ai/ha with a PHI of 7 days and on data from supervised trials carried out in Germany; this GAP is no longer current. A 1.6 kg ai/ha, 7-day PHI GAP has been reported for Australia and in one trial in 1973/4 chlorothalonil residues up to 5.6 mg/kg were found in supervised trials after treatment within this GAP. However, GAP in France (0.4 kg ai/ha, 30 days PHI) yielded much more recent data that were consistent and were deemed more suitable as the basis for a recommendation. The Meeting therefore recommended an MRL of 0.5 mg/kg, based on the data from France.

For banana the GAP on which the CXL of 0.2 mg/kg was based is not clearly described in the 1973 evaluations. The data base considered by the present Meeting was not sufficient to support a soundly based MRL and the Meeting recommended that the CXL should be withdrawn.

The CXL of 5 mg/kg for bulb onions was based on trials data for green onions; the Meeting therefore concluded that it needed revision. Chlorothalonil residues up to 0.57 mg/kg were found in bulb onions harvested 7 days after treatment at 1.5 - 1.75 kg ai/ha (within US GAP) and up to 0.52 mg/kg 14 days after treatment at 1.5 kg ai/ha (within other countries' GAP), although most results were lower than these. The Meeting recommended an MRL of 0.5 mg/kg.

The CXL of 5 mg/kg for cabbages was based on residue data from US trials where crops were harvested on the day of the last treatment. Since current US GAP specifies a minimum PHI of 7 days the CXL should be revised. Chlorothalonil residues up to 0.7 mg/kg were reported from trials using treatment regimes within US, UK and Irish GAP. The Meeting recommended an MRL of 1 mg/kg.

For broccoli, the CXL of 5 mg/kg is based on a 7-day PHI and results from US trials. This GAP is still current in the USA and Canada but although results were reported from two further US trials where treatments were within GAP, the Meeting considered the data were inadequate and recommended that the CXL of 5 mg/kg should be withdrawn.

The CXL of 5 mg/kg for Brussels sprouts was based on a PHI of 7 days and data from the USA. Chlorothalonil residues up to 4.3 mg/kg were reported for samples harvested 6-7 days after treatment at 1.3-2.5 kg ai/ha. The Meeting recommended that the CXL should be maintained.

For cauliflower, the CXL of 5 mg/kg was based on a PHI of 7 days and residue data from the USA. Chlorothalonil residues up to 0.47 mg/kg were reported from trials where treatments were within current GAP in the USA, UK and Ireland. The Meeting recommended an MRL of 1 mg/kg.

For kale, the CXL of 10 mg/kg was based on US GAP and residue data. Since this GAP is

no longer current the Meeting recommended withdrawal of the CXL.

The CXL of 5 mg/kg for melons except watermelon was based on US trials data and a 1-day PHI. Chlorothalonil residues up to 1.45 mg/kg were found in samples treated in accordance with US GAP. The Meeting recommended an MRL of 2 mg/kg but recognised that additional data on residues on different types of melons would be desirable.

For cucumbers, the CXL of 5 mg/kg is based on a 1-day PHI. Chlorothalonil residues up to 4.3 mg/kg were reported from trials where treatments were in accordance with US GAP and the Meeting recommended that the CXL should be maintained.

The CXLs of 5 mg/kg for summer and winter squash and pumpkins were based on a 1-day PHI. Chlorothalonil residues up to 3.6 mg/kg were found in samples of summer and winter squash treated in accordance with current US GAP. The Meeting recommended that MRLs of 5 mg/kg were appropriate for summer and winter squash. No residue data were presented for pumpkins and therefore that CXL should be withdrawn, although pumpkins appear to be covered in the Codex Classification by the MRL for winter squash.

For sweet corn, the CXL of 1 mg/kg was based on a 1-day PHI which is no longer GAP. Residue data reflecting current US GAP were available from only one trial; these were not sufficient to estimate a maximum residue level. The Meeting recommended withdrawal of the CXL.

The CXL for tomato is 5 mg/kg, based on US data and GAP. Chlorothalonil residues up to 4.6 mg/kg were found in trials where treatments were within GAP. The Meeting recommended that the CXL should be maintained.

The CXL of 10 mg/kg for peppers was based on US GAP and residue data. Since use on peppers is no longer GAP in the USA the Meeting recommended withdrawal of this recommendation.

The CXLs for endive, lettuce and witloof chicory (sprouts) were based on US GAP and residue data. Since use on these crops is no longer GAP in the USA the Meeting recommended withdrawal of these CXLs.

The CXL of 5 mg/kg for common bean (pods and/or immature seeds) was based on US GAP and residue data. In supervised trials residue levels in crops treated in accordance with GAP were up to 3.1 mg/kg. The Meeting recommended that the CXL should be maintained.

The CXL for lima beans (dry) was based on US GAP and residue data. Since this use is no longer GAP in the USA the Meeting recommended withdrawal of the CXL.

The CXL of 1 mg/kg for carrots was based on GAP and residue data from the USA. Residues up to 0.96 mg/kg were reported from trials where treatments were within GAP. The Meeting recommended that the CXL should be maintained.

The CXL of 0.1 mg/kg for potato was based on a 0-day PHI. Residues up to 0.18 mg/kg were reported from trials where treatments were within GAP although only one result exceeded 0.1 mg/kg. The Meeting recommended an MRL of 0.2 mg/kg.

The CXL of 1 mg/kg for sugar beet was based on a 1-day PHI; this is no longer GAP. Residues reflecting current GAP were up to 0.1 mg/kg in the root. The Meeting recommended an MRL of 0.2 mg/kg for sugar beet root. Corresponding residues in the leaves reached 14 mg/kg. The Meeting recommended an MRL of 20 mg/kg for sugar beet leaves or tops but realised that appropriate animal transfer studies were lacking.

The CXL of 15 mg/kg for celery was based on a 7-day PHI. Chlorothalonil residues up to 9.8 mg/kg were found in trials where treatments reflected current GAP. The Meeting recommended an MRL of 10 mg/kg.

Barley grain from crops treated in accordance with GAP contained up to 1.4 mg chlorothalonil/kg. Most results however were much lower than this. The Meeting decided that the data reflecting use up to 1.4 kg ai/ha were not sufficient to support a soundly based MRL and recommended an MRL of 0.1 mg/kg for grain, based on application rates up to 1.0 kg ai/ha. The Meeting also recommended an MRL of 20 mg/kg for barley straw; animal transfer studies are desirable.

Wheat grain from crops treated in accordance with GAP contained up to 0.09 mg chlorothalonil/kg. The Meeting recommended that the MRL should be established at 0.1 mg/kg for grain and 20 mg/kg for wheat straw, recognising that animal transfer studies were desirable.

GAP was not reported for any other cereal grain. The Meeting recommended that the CXL for cereal grains should be withdrawn.

The CXLs for whole peanut and peanut kernels were based on a 1-day PHI; this is no longer GAP. Chlorothalonil residues up to 0.03 mg/kg were found in crops treated in accordance with current GAP. The Meeting recommended an MRL of 0.05 mg/kg for peanut and withdrawal of the CXL for whole peanuts.

Information on residue distribution between the inedible and edible portions of the commodity was available for banana; chlorothalonil is essentially a surface residue and transfer to pulp was insignificant.

Processing studies are available for cherry, peach, grape, cabbage, cucumber, squash, tomato, snap bean, carrot, potato, celery and peanut.

Washing cherries, peaches, cucumbers, tomatoes and snap beans removed 45-95% of the residue. Residue reductions of 75-98% occurred in cabbages, cucumbers, tomatoes and celery during distribution from the farm gate to retail outlets. Residue levels in canned cherries, canned pickled cucumber and tomato juice made from treated crops were very low (1-2% of initial residues). Residues were not found in canned peach puree, wine, squash-based baby food, tomato paste, canned or frozen snap beans, carrot-based baby food, potato crisps, dried potato or refined peanut oil prepared from crops with incurred residues.

Chlorothalonil residues were stable during freezer storage for one year in cherries, cucumbers, tomatoes, carrots, potatoes, celery and wheat grain.

FURTHER WORK OR INFORMATION

Desirable

1. Additional residue data from supervised trials on different types of melons.

2. Animal transfer studies assuming a residue equivalent to the recommended MRL of 20 mg/kg in sugar beet leaves or tops, barley straw and wheat straw.

3. Additional residue data on grapes treated according to GAP in Australia.

4.9 CHLORPYRIFOS-METHYL (090)

RESIDUE AND ANALYTICAL ASPECTS

Data evaluated by the 1991 JMPR showed residues of chlorpyrifos-methyl in crude and refined maize oil as high as approximately 100 mg/kg, produced from maize containing only 3.8 mg/kg. The 1991 JMPR therefore required further information on the influence of commercial refining processes on residues of chlorpyrifos-methyl in oil from maize and a full description of the processes used.

As a maximum residue limit of 10 mg/kg is established for chlorpyrifos-methyl in rape seed, and it would be expected that residue levels in oil produced from treated rape seed would also be high, information was required on the levels of residues occurring in rape seed oil.

In response to the requirement for information about commercial processes used for producing and refining maize oil a detailed description of the milling, refining and deodorization procedures generally used in the USA was received. Two studies of the fate of residues of chlorpyrifos-methyl during the processes of milling, refining and deodorization were also supplied. The compound is concentrated in the oil produced from maize grain and it does not disappear during the process of refining, but it disappears almost completely when the oil is deodorized. The procedure used for deodorizing is to heat the oil to 175-230° C in a vacuum. In this process chlorpyrifos-methyl is volatilized, and in one of the experiments the vapours were trapped and 95% of the chlorpyrifos-methyl originally present in the oil was collected as the unchanged compound.

No information was available to the Meeting on the levels of chlorpyrifos-methyl in rape seed oil either from trials or from monitoring. The Meeting therefore recommends withdrawal of the existing temporary MRL of 10 mg/kg for chlorpyrifos-methyl in rape seed.

Information was received from Spain on registered uses of chlorpyrifos-methyl and summarized residue data from trials on lemons, mandarins and oranges. The applications in the trials were in accordance with registered uses in Spain, except those on mandarins where the dosage was a little lower in the trials. All residues were low, between 0.01 and 0.13 mg/kg after 14 days, and lower than the proposed limit of 0.5 mg/kg for oranges. The proposed residue limit for oranges was confirmed, but the Meeting was unable to propose a residue limit for the whole group of citrus fruits as details from the trials in Spain were not available.

FURTHER WORK OR INFORMATION

Desirable

Submission of details from trials on citrus fruits in Spain and further information on GAP for citrus fruits in Spain.

4.10 CYCLOXIDIM (179)

RESIDUE AND ANALYTICAL ASPECTS

Cycloxidim, a systemic cyclohexanedione herbicide, was reviewed for the first time by the 1992 JMPR. However, the time available did not allow adequate evaluation of the extensive residue data provided by the manufacturer. These data have been reviewed by the present Meeting.

Residue data were reported from supervised trials of cycloxidim carried out in 15 countries and on over 40 commodities. Although many of these trials were according to registered and/or recommended use patterns, some crop/ application rate combinations were not registered or

the resultant data were very limited. In addition, residue data on bulb onions, parsnip, sunflower seed and hay were obtained using an analytical procedure with the comparatively high limit of determination of 0.5 mg/kg while that for Brussels sprouts was 0.25 mg/kg; determinations on all other commodities could be made down to 0.05 mg/kg.

Cycloxidim is applied as a foliar spray directly to the growing crop and also to soil as a surface application. Owing to its systemic properties some uptake and distribution is to be expected although the extent is likely to be variable as it is dependent on the growth stage; this is borne out by the wide variations observed in the residue data presented. As there is little alteration in residue level with time after application, the PHIs are of little real significance.

These factors combined to make the estimation of suitable maximum residue levels for this compound rather complicated. However, despite these potential drawbacks the residue data were deemed to be sufficient to allow recommendations for MRLs to be made for 16 commodities. They were regarded as being inadequate, for various reasons, to support recommendations for the other commodities for which residue data were available. Data on citrus, pome and stone fruits were sparse, as were those on tropical fruits, cucurbits and some root and stem vegetables. Despite the absence of processing data on grapes, potatoes and sugar beet the Meeting felt able to recommend MRLs for those crops.

Residue data on beans (dry), rape seed and soya bean (dry) were deemed adequate and mutually supportive for a maximum residue level of 2 mg/kg to be estimated for each commodity. Similarly, despite the inherent variability, residue data on Brussels sprouts, cabbage and cauliflower were taken together to estimate a maximum level of 2 mg/kg for brassica vegetables. Data on common bean together with those for peas (in pod) supported a maximum residue level of 1 mg/kg for each, while for shelled peas (green) a level of 2 mg/kg was suggested; for peas (dry) the results were too variable to interpret with any degree of assurance. Residue data on carrot, leek, lettuce (head and leaf) and strawberry were also found to be adequate for the recommendations given in Annex I to be made.

FURTHER WORK OR INFORMATION

Desirable

1. Residue data from supervised trials on bulb onions, parsnip, sunflower seed and hay, using an analytical procedure with a lower limit of determination of about 0.05 mg/kg.

2. Processing studies on grapes, potatoes and sugar beet treated with cycloxidim in supervised trials.

4.11 DDT (021)

RESIDUE AND ANALYTICAL ASPECTS

At the 22nd and 23rd Sessions of the CCPR (1991 and 1992) it was agreed that countries should be requested to provide information on registered or recommended uses of DDT and also on residue levels from trials with registered uses or from monitoring. At the 23rd Session the existing Extraneous Residue Limits for DDT in cereal grains, eggs, meat and milk were converted to temporary limits, and the general MRL for DDT in fruits and vegetables was withdrawn. Residue data were necessary to support the existing ERLs and possibly to develop ERLs for DDT in commodities in the fruits and vegetables groups.

The Meeting has received no information about registered or recommended uses of DDT on crops or animals. Monitoring data for residues of DDT in fruits, vegetables, cereal grains

and products of animal origin were received from the governments of Canada, Denmark, The Netherlands and the USA.

It was obvious from the monitoring data that residues are not often present in fruit, vegetables and cereal grains, but the incidence observed is of course dependent on the limit of determination used in the monitoring. In Canada, The Netherlands and the USA the limit of determination was 0.01 mg/kg, while the limit in Denmark was 0.02 mg/kg. In Canada DDT was present in 29 of 1100 samples. In Denmark no residues were found in any of 4300 samples. In The Netherlands DDT was present in 54 of 37,500 samples, and in the USA in 369 of 15,445 samples. In most cases residues were low and mostly below 0.1 mg/kg. The frequency of residues in fruit and vegetables seems to be highest in carrots, probably owing to the occurrence of DDT in the soil from earlier uses and the ability of carrots to take up pesticides from the surrounding soil. In Canada and the USA DDT was present in 64 of a total of 452 samples of carrots, which is approximately 14%. It is more surprising that DDT residues were also present in several samples of apples.

Residue data from monitoring cereal grains were available only from the USA. In 579 samples of cereal grains DDT was present in 5 samples with the highest residue at 0.09 mg/kg.

Residue data were available from many samples of animal products such as butter, milk, cheese, eggs and the fat of cattle, pigs, poultry, sheep, goats and horses. Residues of DDT and its metabolites occurred more frequently in animal products than plant products. Residues were mostly at very low levels, but in some samples up to 0.5 mg/kg and in a few samples even higher with a maximum of 1.8 mg/ kg in fat from cattle.

Residues in the monitoring data available to the Meeting were usually considerably lower than the existing temporary ERLs. Residues in the fat of meat were as mentioned above much lower than the existing limit of 5 mg/kg. In eggs residues with a few exceptions were below the limit of determination (0.01 or 0.02 mg/kg), and were at the level of 0.11 and 0.20 mg/kg in only two samples of egg powder. For milk the existing TMRL is 0.05 mg/kg, approximately 1 mg/kg in milk fat. All residues in samples from the monitoring studies were considerably lower, and generally below the limit of determination. Residues in butter and cheese, calculated as the levels in milk fat, were always considerably lower than 1 mg/kg.

The incidence of detection of environmental contaminants is expected to increase if lower limits of determination are employed. The Meeting noted the remarks made at the 24th Session of the CCPR (ALINORM 93/24, 29) concerning realistic limits of determination, that using methods with low limits of determination was costly and not the best use of resources. The Meeting concluded that for the general monitoring of DDT and the metabolites included in the definition, a suitable limit of determination for the total residue would be 0.02 mg/kg.

As the production of the compound ceases and environmental residues decrease, extraneous residues in food will also decrease. The Meeting therefore recommended that monitoring data should be evaluated again in 1998, with the possibility of lowering the ERLs for DDT.

FURTHER WORK OR INFORMATION

Desirable

Residue data from monitoring DDT in fruit and vegetables in other countries.

4.12 DIAZINON (022)

TOXICOLOGY

Diazinon was previously evaluated by the Joint Meeting in 1963, 1965, 1966 and 1970. An ADI of 0-0.002 mg/kg bw was allocated in 1966, based on an NOAEL of 0.02 mg/kg bw/day in human volunteers. The compound was reviewed at the present Meeting on the basis of the CCPR periodic review programme.

Following oral administration to rats, diazinon was almost completely absorbed and eliminated, mainly in the urine.

The main degradative pathway includes the oxidase/hydrolase-mediated cleavage of the ester bond leading to the pyrimidinol derivative 4-hydroxy-2-isopropyl-6-methylpyrimidine, which is further oxidized to more polar metabolites.

Diazinon has moderate acute oral toxicity to mice and rats. The clinical signs observed were consistent with cholinesterase inhibition and included sedation, tremors, convulsions and ataxia. It is classified by WHO as moderately hazardous.

In an oral 90-day feeding study in rats at dietary concentrations of 0, 0.5, 5, 250 or 2500 ppm, the NOAEL was 5 ppm (equal to 0.4 mg/kg bw/day), based on erythrocyte and brain cholinesterase inhibition at 250 ppm and above.

In short-term studies in dogs, diazinon was administered at dietary concentrations of 0, 0.1, 0.5, 150 or 300 ppm for either 90 days or 52 weeks. In both studies, the NOAEL was 0.5 ppm (equal to 0.02 mg/kg bw/day), based on erythrocyte and brain cholinesterase inhibition at 150 ppm and above.

In a carcinogenicity study in mice, diazinon was administered at dietary concentrations of 0, 100 or 200 ppm over 103 weeks. There was no evidence of carcinogenicity.

In a carcinogenicity study in rats diazinon was administered at dietary concentrations of 0, 400 or 800 ppm for 103 weeks. There was no evidence of carcinogenicity.

In a long-term toxicity/carcinogenicity study, rats were maintained on a diet containing diazinon at concentrations of 0, 0.1, 1.5, 125 or 250 ppm for up to 99 weeks. The NOAEL was 1.5 ppm (equal to 0.07 mg/kg bw/day), based on inhibition of erythrocyte and brain cholinesterase at 125 ppm and above. There was no evidence of carcinogenicity.

A multigeneration reproduction study was conducted in rats using dietary concentrations of 0, 10, 100 or 500 ppm. The NOAEL was 10 ppm (equivalent to 0.5 mg/kg bw/day), based on a reduction in parental body-weight gain in the F_1 generation and a reduced survival rate and reduced body weight of F_1 pups at 100 ppm.

In a teratogenicity study in rats, diazinon was orally administered at dose levels of 0, 10, 20 or 100 mg/kg bw/day. Maternal toxicity, indicated by weight loss correlated with reduced food consumption, became evident at 100 mg/kg bw/day. Effects on the fetuses at this dose level consisted of retarded ossification and an increased incidence of rudimentary ribs. The NOAEL was 20 mg/kg bw/day, based on maternal toxicity and fetotoxicity. There was no evidence of teratogenicity.

A teratogenicity study in rabbits conducted with oral dose levels of 0, 7, 25 or 100 mg/kg bw/day revealed clinical signs of maternal toxicity, increased mortality and reduced body-weight gain at 100 mg/kg bw/day. The NOAEL was 25 mg/kg bw/day. There was no evidence of teratogenicity.

A neurotoxicity study performed with hens treated at dose levels of 13 or 28 mg/kg bw/day (protected by atropine pre-treatment) did not reveal evidence of delayed neurotoxicity.

Diazinon has been adequately tested in a series of genotoxicity assays. Chromosomal aberrations were induced in cultured mammalian cells, but there were no other indications of genotoxicity. The Meeting concluded that diazinon was not genotoxic.

Diazinon was evaluated in four human male volunteers who received 0.025 mg/kg bw/day of diazinon in capsules for 34-36 days. There were no consistent treatment-related effects on plasma or erythrocyte cholinesterase activity, blood chemistry or urinalysis. No clinical effects were reported. The NOAEL was 0.025 mg/kg bw/day.

The ADI of 0-0.002 mg/kg bw was maintained, which is based on the NOAEL of 0.025 mg/kg bw/day in the study in humans, using a 10-fold safety factor.

A toxicological monograph summarizing the data received since the previous evaluation and containing relevant data from the previous monograph and monograph addenda was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 5 ppm, equal to 0.4 mg/kg bw/day (90-day study)
1.5 ppm, equal to 0.07 mg/kg bw/day (99-week study)
10 ppm, equivalent to 0.5 mg/kg bw/day (reproduction study)
20 mg/kg bw/day (maternal toxicity in teratogenicity study)

Rabbit: 25 mg/kg bw/day (maternal toxicity in teratogenicity study)

Dog: 0.5 ppm, equal to 0.02 mg/kg bw/day (one-year study)

Human: 0.025 mg/kg bw/day (34-36-day study)

Estimate of acceptable daily intake for humans

0-0.002 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Diazinon, originally evaluated by the JMPR in 1967 and re-evaluated for residues several times up to 1979, is included in the CCPR periodic review programme.

The general CXLs for fruits and vegetables (0.5 mg/kg) were retained by the 1990 CCPR, to await review by the 1993 JMPR.

Information on current world-wide GAP and extensive residue data were provided by one manufacturer and several countries.

Diazinon is an organophosphorus insecticide with a broad spectrum of activity against a

wide range of pests: sucking, chewing and boring insects, including soil-living insects. It is effective mainly by contact and stomach action. The product has been introduced world-wide in many countries and is used on numerous crop groups or commodities. It is generally used as a foliar or soil spray or applied as a granule to the soil.

Major target crops are leafy, fruiting, stem and root vegetables, deciduous fruit, rice and maize. Minor crops include berries, cereals, citrus, grapes, mushrooms, nut trees, olives and sugar beet. Additional uses for non-food crops are on ornamentals, grass and turf, and in nurseries.

Citrus fruits

Only limited data were available for oranges and mandarins which the Meeting felt were not sufficient to estimate a maximum residue level. Evidently the PHI (14-21 days) does not much influence residue levels. The Meeting recommended withdrawal of the CXL (0.7 mg/kg).

Pome fruits

The Meeting estimated a maximum residue level of 2 mg/kg (PHI 14 days), based on available trials from Germany, Switzerland and the USA on apples and pears.

Stone fruits

Cherries. Trials at dosage rates of 3.3 kg ai/ha applied 5 times showed residues up to 0.73 mg/kg 10 days after the last application. The Meeting recommended an MRL of 1 mg/kg.

Peaches. Taking into account data from Germany (PHI 14 days) and the USA (PHI 20 days), the Meeting estimated a maximum residue level of 0.2 mg/kg.

Plums (including Prunes). Trials at dosage rates of 3.3 kg ai/ha applied 5 times showed residues up to 0.78 mg/kg 10 days after the last application. The Meeting proposed an MRL of 1 mg/kg.

Prunes [dry]. US trials with dried prunes showed residues up to 1.9 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg.

Berries

Grapes. On the basis of the data available the Meeting felt unable to estimate a maximum residue level because the data do not match relevant GAP.

Strawberry. After observing the recommended PHI of 5 days the residues were below 0.1 mg/kg except one of 35 results, at 0.12 mg/kg. A maximum residue level of 0.1 mg/kg was estimated.

Cranberry. No results were reported within the reported GAP.

Currants, Black, Red, White. Results of trials in Germany and Switzerland showed residues up to 0.21 mg/kg at the recommended PHI of 14 days. The Meeting estimated a maximum residue level of 0.2 mg/kg.

Blackberries, Boysenberry, Raspberries. On the basis of US data and GAP for caneberries (PHI 7 days) the Meeting recommended an MRL of 0.1 mg/kg for blackberries and boysenberry, and 0.2 mg/kg for raspberries.

Olives. Because too few of the available residue data reflect current GAP the Meeting felt

unable to estimate a maximum residue level on olives or olive oil although processing studies are available which indicate an accumulation of diazinon in crude oil by a factor of 3-5. The Meeting recommended withdrawal of the CXLs for olives (2 mg/kg) and olive oil, virgin (2 mg/kg).

Tropical fruits

Persimmons. Only one trial reflected the reported GAP in New Zealand.

Banana. Only two trials reflected the current GAP in Costa Rica. Although no residues were found the Meeting felt unable to estimate a maximum residue level on such limited data.

Kiwifruit. On the basis of 6 new trials from New Zealand (PHI 28 days) the Meeting estimated a maximum residue level of 0.2 mg/kg.

Pineapple. Seven days after application (the PHI in Costa Rica) trials in Honduras and Costa Rica showed residues up to 0.07 mg/kg. Reported results from the USA were not taken into account because exaggerated application rates were used. The Meeting estimated a maximum residue level of 0.1 mg/kg.

Bulb vegetables

Onion, Bulb. At the recommended rate of application and the recommended PHI of 10 days residues were below 0.05 mg/kg, which was estimated as the maximum residue level.

Spring onion. The range of residue levels found in a series of trials was wide, between <0.01 and 0.65 mg/kg. A maximum residue level of 1 mg/kg, after the recommended PHI of 10 days, was estimated.

Brassica vegetables

Broccoli. Results of 10 trials from the USA within recommended GAP (PHI 7 days) showed residues up to 0.23 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg.

Cabbages, Head. On the basis of several trials from the USA within the recommended GAP (PHI 7 days) the Meeting estimated a maximum residue level of 2 mg/kg.

Cauliflower. The Meeting concluded that the reported data were insufficient to estimate a maximum residue level. Most of the trials were in Germany where there is no GAP. These results could be related to GAP in Switzerland (PHI 14 days), but only three trials included this PHI.

Kohlrabi. On the basis of the available trials and GAP in Switzerland (14 days PHI) the Meeting estimated a maximum residue level of 0.2 mg/kg.

Fruiting vegetables

Cucumber. On the basis of a PHI of 7 days (GAP in the USA) the Meeting estimated an MRL of 0.1 mg/kg. One value of 0.4 mg/kg was assumed to be an outlier because in that trial only 0.2 mg/kg was found 3 days after application.

Cantaloupe. Seven days after application (GAP in he USA) residues up to 0.18 mg/kg were found in the reported USA trials. The Meeting estimated a maximum residue level of 0.2 mg/kg.

Squash, Summer. In US trials residues up to 0.05 mg/kg were found 7 days after application.

An MRL of 0.05 mg/kg was recommended by the Meeting.

Mushrooms. Limited data from The Netherlands do not reflect the current PHI. The Meeting felt unable to estimate a maximum residue level.

Peppers, Sweet. Although no data were available for the recommended PHI of 5 days in the USA, the data from USA trials at PHIs of 3-7 days clearly show that 5 days after application residues would not exceed 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg for sweet peppers.

Sweet corn (corn-on-the-cob). No residues of diazinon were detectable (<0.01 mg/kg) 10-14 days after the last application. Seven days after the last application residues were small, <0.01-0.02 mg/kg. The Meeting proposed an MRL of 0.02 mg/kg.

Maize forage. Residues were detectable at levels of 0.04-7.95 and <0.01-4.95 mg/kg 7 and 14 days after the last application. The Meeting estimated a maximum residue level of 10 mg/kg.

Leafy vegetables

Tomato. On the basis of reported US data and a PHI of 1 day, the Meeting estimated a maximum residue level of 0.5 mg/kg.

Chinese cabbage; Kale, Chinese. Reported trials from Thailand on Chinese cabbage did not include the national PHI of 14 days but data from Thailand on Chinese kale showed residues below 0.02 mg/kg 14 days after application. Taking all the data on both commodities into account, the Meeting felt able to estimate a maximum residue level of 0.05 mg/kg for both Chinese cabbage and kale.

Lettuce, Head; Lettuce, Leaf. No data were available covering the PHI of 10 days registered in the USA where most of the trials were done. However, the great number of results at sampling intervals of 7-14 days clearly show that 10 days after application residues will be below 0.5 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg for both head and leaf lettuce.

Spinach. The Meeting concluded that the residue situation is comparable to that of lettuce and proposed an MRL of 0.5 mg/kg (PHI 10 days).

Legume vegetables

Common beans (pods and/or immature seeds). At a PHI of 7 days residues were at levels up to 0.2 mg/kg, which was estimated as a maximum residue level.

Garden pea, shelled. Residue results from the USA showed a comparable situation to that of common beans. The Meeting estimated a maximum residue level of 0.2 mg/kg (PHI 7 days).

Root vegetables

Carrot. After PHIs of 7 and 14 days residues were below 0.5 and 0.3 mg/kg, respectively. A maximum residue level of 0.5 mg/kg was estimated, covering the recommended PHI of 7 days.

Celeriac; Parsley, Turnip rooted. The results of only one trial were reported for each commodity. The Meeting therefore did not propose an MRL.

Potatoes. After the recommended PHI of 14 days residues were below the reported limit of determination. A maximum residue level of 0.01* mg/kg was estimated.

Radish. After PHIs of 7 and 14 days residues were below 0.1 mg/kg. A maximum residue level of 0.1 mg/kg was estimated, covering the recommended PHI of 10 days.

Sugar beet. At a PHI of 14 days residues were at levels up to 0.1 mg/kg, which was estimated as a maximum residue level.

Sugar beet leaves or tops. On the basis of the reported data and a PHI of 14 days a maximum residue level of 5 mg/kg was estimated.

Stalk and stem vegetables

Artichoke. Limited data available from Spain (3 results, one location) were insufficient to recommend an MRL.

Witloof chicory (sprouts). In the one trial reported no residues were detectable (<0.01 mg/kg) 14 days after application. No MRL was proposed.

Cereal grains

Maize. In all reported trials there were no detectable residues (<0.02 mg/kg) in the grain. Taking into account the reported results on sweet corn, the Meeting estimated a maximum residue level of 0.02* mg/kg.

Rice. Seven trials were conducted in India, Indonesia and Pakistan. No residues were detectable (<0.02 or <0.03 mg/kg) in the grain or the unhusked grain 23-59 days after the last application. Low residues were detectable in the straw, up to 0.04 mg/kg. Because the data did not match GAP in most of the countries the Meeting agreed not to recommend an MRL. The Meeting recommended withdrawal of the CXL for polished rice (0.1 mg/kg).

Tree nuts

Almonds. All results from the USA clearly show that normally there will be no residues in the nuts (<0.01 mg/kg). However in several cases residues up to 0.03 mg/kg occurred owing to contamination. The Meeting proposed an MRL of 0.05 mg/kg.

Almonds, hull. The available data were at PHIs of 14-45 days (and some at 0 days). The Meeting estimated a maximum residue level of 5 mg/kg (PHI 14-45 days).

Walnuts. On the basis of the available results of 24 supervised trials it is clear that no residues occur in nuts. The Meeting proposed the limit of determination as the MRL (0.01* mg/kg).

Oilseed

Cotton seed. On the basis of only four trials from one year and one country the Meeting felt unable to estimate a maximum residue level and recommended withdrawal of the CXL for cotton seed (0.1 mg/kg).

Animal products

Meat and milks. Residues in the milk and tissues of cattle were reported after applying ear tags to the animals (registered use in Canada).

Two ear tags (6% cypermethrin, 11% diazinon), one per ear, were attached to each of three Holstein dairy cows. Milk samples were taken five hours before application, and 5 h and 1, 3, 7, 14, 21, and 28 days after application.

Residues of diazinon in milk samples were not detectable (<0.0005 mg/kg) until three days after tag application. The residues remained consistently less than 0.002 mg/kg for the entire residue study.

Three Hereford steers were treated with two ear tags (6% cypermethrin, 9.6% diazinon), one per ear. After 14 days, one animal was slaughtered and samples of blood, liver, tongue, muscle, back fat, and kidney fat were analysed; after 100 days the remaining two treated animals were killed and similar samples were analysed.

Diazinon was found on the hair, but in the analysed tissues it was detectable only in the back fat and kidney fat of the animal killed 14 days after tag attachment. The levels were low, 0.032 and 0.035 mg/kg respectively. No residues (<0.01 mg/kg) were found in the back fat, kidney fat, liver, muscle and tongue 100 days after treatment, indicating that there was no accumulation.

Four Hereford steers were treated with two ear tags (20% diazinon) - one per ear. After 7 days, one animal was killed and samples of blood, liver, tongue, muscle, centre back fat, and kidney fat were analysed; a second steer was killed after 14 days and the remaining two after 28 days, all animals being sampled in the same fashion.

Residues were detectable in the centre back and kidney fat of all the animals. The highest levels were 0.045 and 0.041 mg/kg, respectively, on day 14. There were still detectable residue levels of diazinon in the centre back and kidney fat on day 28 at 0.02-0.03 mg/kg.

Data from planned animal transfer studies are not yet available. The Meeting recommended withdrawal of the established MRLs.

Withdrawal of the CXLS for Barley, Fruits (except ...), Hazelnuts, Leafy vegetables, Meat of cattle, pigs and sheep, Milks, Peanut, Pecan, Safflower seed, Sunflower seed, Vegetables (except ...), and Wheat is recommended because available residue data are insufficient although GAP is reported.

Metabolism in plants

Metabolism studies have been carried out on apples, beans, sweet corn, lettuce, potatoes and rice.

In processing

Processed fractions were prepared from apples, grapes, lettuce, endive, maize, pineapples, potatoes, sugar beet and tomatoes. Wine was made in some cases from harvest grapes and olive oil (crude) was prepared from olives in one trial. Generally residues of diazinon are reduced or not detectable in processed commodities with importance for human consumption: juice, sugar, and wine.

A concentration of residues was observed in crude olive oil and in pomace-type fractions, with the latter having a potential use as animal feed.

Residues in the edible portion of food commodities

No information was available about the partition of residues between the pulp and peel in citrus fruit, pineapple or cantaloupe.

No residues were detectable in the whole fruit or in separate samples of pulp and peel when diazinon was applied to bananas.

Residues in almonds (kernels) were low, ranging from <0.01 to 0.03 mg/kg 28-45 days after the last application.

Stability of pesticide residues in stored analytical samples

The stability of diazinon and the metabolites diazoxon (G-24576) and hydroxydiazinon (CGA 14128) under freezer storage conditions was determined in maize, tomatoes, potatoes, apples, strawberries, lettuce, soya beans (dry), refined corn oil, tomato paste and sugar beet molasses.

Residues of diazinon are generally stable in crops and processed commodities for a minimum of twenty-six months of freezer storage. A slight decline was observed in strawberries after three months storage, which continued at a much slower rate through twenty-six months.

Residues of diazoxon are unstable in crop and processed fraction substrates, but are stable in maize oil.

Residues of hydroxydiazinon are generally stable in crop substrates and processed fractions. A decline in residues was observed in apples and strawberries after three months of storage and continued at a much slower rate through twenty-six months.

The stability of diazinon under freezer storage conditions was further tested in some animal tissues, namely muscle, liver, kidney and fat of sheep. Diazinon was found to be stable for at least 8 months of storage.

Methods of residue analysis have been described for commodities of plant and animal origin with a limit of determination of 0.01 mg/kg in most commodities. Diazinon is classified as fat-soluble (octanol/water partition coefficient 3.95). In a large number of studies residues of the potential metabolites diazoxon (G 24576) and hydroxydiazinon (CGA 14128) were determined besides parent diazinon. Since these two compounds were practically not found in crops at harvest or in processed commodities it can be concluded that the use of the product according to GAP may be reliably monitored by determining the parent compound alone.

The data now available from the various metabolism studies show that major metabolites identified in plant and soil metabolism, namely 4-hydroxy-2-isopropyl-6-methylpyrimidine (G 27550), 4-hydroxy-2-(2-hydroxyprop-2-yl)-6-methylpyrimidine (GS 31144), and diazoxon (G 24576), also occur in animal metabolism (rat). Thus there is no need to include compounds other than diazinon in the residue definition.

FURTHER WORK OR INFORMATION

Desirable

1. Results of ongoing residue studies on citrus fruits, hazelnuts, hops, pecans and peanuts.

2. Data from dairy cattle transfer studies reported to be completed.

3. Additional information on registered veterinary uses including residue data.

4.13 DICHLORVOS (025)

TOXICOLOGY

Dichlorvos has been previously evaluated by the Joint Meeting in 1965, 1966, 1967, 1970 and 1977. An ADI of 0-0.004 mg/kg bw was allocated in 1966 and was maintained at subsequent Meetings. The compound was re-evaluated by the present Meeting in the CCPR periodic review programme.

Dichlorvos is rapidly absorbed by all routes of exposure and rapidly degraded. The metabolic pathways of dichlorvos are similar in mammalian species, including humans. Metabolites are rapidly excreted or incorporated into natural enzymatic pathways.

Dichlorvos has a marked acute oral toxicity with typical cholinergic signs and has been classified by WHO as highly hazardous.

Rat erythrocyte and brain cholinesterase inhibited by dichlorvos spontaneously reactivates with a half-life of about two hours both *in vitro* and *in vivo*.

Several carcinogenicity studies in mice and rats using routes other than gavage were negative, even when doses causing signs of toxicity were used. It should be noted that two squamous-cell carcinomas of the oesophagus have been observed in treated mice in one study.

In a two-year feeding study in rats (0, 0.1, 1, 10, 100 or 500 ppm), no neoplastic lesions were attributed to treatment. The NOAEL, based on brain cholinesterase inhibition, was 100 ppm (actual concentration 47 ppm, equivalent to 2.4 mg/kg bw/day).

In a carcinogenicity study in mice dichlorvos, administered by corn oil gavage (0, 10 or 20 mg/kg bw/day to males, and 0, 20 or 40 mg/kg bw/day to females), caused forestomach papillomas (statistically-significant positive trend with increased incidence in the high-dose female group). Elements of the mechanism by which these papillomas might arise have not been established, but the induction of hyperplasia in the forestomach was demonstrated. Additionally, genotoxic effects might occur at high local concentrations of dichlorvos (see below) as can be obtained in gavage dosing but not in dietary exposure. On the basis of the increased incidence of forestomach papillomas, the NOAEL was 10 mg/kg bw/day.

In a carcinogenicity study in Fisher 344 rats, dichlorvos administered by corn oil gavage (0, 4 or 8 mg/kg bw/day) caused an increased incidence of pancreatic adenomas (statistically significant in males only), mononuclear cell leukaemias (statistically significant in males only, no dose-response relation) and mammary gland adenomas or fibroadenomas (females only, no dose-response relation, statistically significant in the low dose group only). The Meeting observed that the incidence of pancreatic acinar adenomas in male control rats was unusually high and therefore the higher incidence found in treated animals was considered of questionable biological significance. The increased incidence of mononuclear cell leukaemia, which is usually high and variable in this strain of rat, was also of questionable biological significance. The doses used significantly inhibited plasma, but not erythrocyte, cholinesterase activity when measured three hours after treatment. However, given the rapid recovery of erythrocyte cholinesterase activity after inhibition by dichlorvos, the timing might have underestimated the inhibition.

Dichlorvos has been adequately tested in a series of *in vitro* and *in vivo* genotoxicity assays. The data indicate that dichlorvos is genotoxic in bacteria and cultured mammalian cells, but that it is not clastogenic *in vivo* except under conditions where an unusually high tissue dose can be attained. Dichloroacetaldehyde, a major metabolite of dichlorvos, is a weak bacterial mutagen. Positive results have been reported in mice given a dose of dichloroacetaldehyde far greater than that which could derive from sublethal doses of dichlorvos. Dichlorvos has been shown to methylate DNA *in vitro* at a rate that is 8-9 orders of magnitude lower than the rate of phosphorylation. DNA alkylation is therefore not likely to occur at doses of dichlorvos which are not inhibitory to erythrocyte/brain cholinesterase.

A three-generation reproduction study in rats was negative at doses up to 235 ppm in the diet, equivalent to 12 mg/kg bw/day. A one-litter, one-generation study in mice in which dichlorvos was administered by inhalation at doses which caused >90% plasma cholinesterase inhibition, but no signs of toxicity, was negative. Dichlorvos caused reversible damage of seminiferous tubules, Leydig and Sertoli cells at oral doses of 10 mg/kg bw daily for 18 days in mice and at 5 mg/kg bw and above every other day for 8 weeks in rats.

Dichlorvos appeared not to be teratogenic in mice, rats and rabbits at doses which caused maternal toxicity.

Dichlorvos caused delayed polyneuropathy in hens at doses much higher than the unprotected LD_{50}. Cases of delayed polyneuropathy also have been reported in humans after severe intoxications.

In humans, the rate of dichlorvos hydrolysis by plasma is similar to that in rats. The rate of recovery of inhibited erythrocyte and plasma cholinesterase activity in humans given dichlorvos is much slower than in rats. Half-lives of recovery are about 15 days in humans and about two hours in rats. A daily dose of 1 mg/kg bw to male human volunteers for seven days caused 5-30% inhibition of erythrocyte cholinesterase. The NOAEL in humans, based on the absence of erythrocyte cholinesterase inhibition in 12 volunteer males for 21 days, was 0.04 mg/kg bw/day.

In 1986, the Joint Meeting discussed the significance of carcinogenicity studies for organophosphorus pesticides and the requirements for further studies (Section 3.1 of the report). At that time none of the organophosphorus pesticides had caused a carcinogenic response in experimental animals. The 1986 Meeting recommended that, depending upon future evaluation on a case-by-case basis, further consideration should be given to the need for carcinogenicity studies for organophosphorus compounds.

In assessing the potential hazard to humans of residues of dichlorvos, the following considerations were taken into account in view of the weakly positive results in the gavage carcinogenicity study in mice.

Organophosphorus esters used as insecticides react with biological molecules by phosphorylation of serine hydrolases and alkylation of macromolecules. Phosphorylation of acetylcholinesterase and alkylation of DNA are considered to account for the acute cholinergic toxicity and initiation of the carcinogenic process, respectively. These biochemical reactions occur at different rates. When the rate of phosphorylation is substantially higher than the rate of alkylation, *in vivo* genotoxic effects are unlikely to occur because effective doses cannot be achieved owing to acute toxicity. Dichlorvos meets these criteria, the rate of phosphorylation of acetylcholinesterase being much faster (eight orders of magnitude) than that of alkylation of several macromolecules, including DNA. Hence positive mutagenicity tests were seen only *in vitro* and, as indicated in the 1986 Joint Meeting report, carcinogenicity studies are unlikely to give more information. The weak carcinogenic response of dichlorvos obtained in mice in a corn oil gavage study should be interpreted as a local effect of dichlorvos.

Information on comparative cholinergic toxicity might be of critical relevance for the extrapolation of toxic effects (other than acute effects) of organophosphates in experimental animals to humans. The characteristics of the interactions of a given compound with acetylcholinesterase (rates of phosphorylation, spontaneous reactivation and ageing) from different species can be compared *in vitro*. Also, the *in vivo* rate of reappearance of blood acetylcholinesterase activity can be measured. In some cases, metabolic degradation of organophosphates can be assessed comparatively by measuring the level of serum A esterase which hydrolyses a given compound. All these data make possible an improved assessment of the cholinergic toxicity of organophosphorus compounds in different species.

This knowledge may be of special significance in the case of dimethyl phosphates since the rates of *in vivo* reactivation vary substantially across species. Therefore, chronic dosing is more critical for extrapolation from animal data to humans. In a repeated dose regime, the longer the half-life of reactivation the more rapid and/or more toxic will be the resulting effect (hence in a chronic dosing regime, humans will be intoxicated by doses of dichlorvos which, when given alone, cause much less inhibition of erythrocyte/brain cholinesterase than rodents can tolerate). Therefore, comparison between the *in vivo* rates of recovery of enzyme activity will allow an assessment of the repeated doses of compounds and the resulting cholinesterase inhibition, which would represent the limiting factors for other toxicities (including mutagenicity and carcinogenicity).

In the case of dichlorvos the Meeting considered the relevance of carcinogenicity data derived from rodents to human safety, and concluded that the compound would not cause chronic human health hazards at doses below those which inhibit acetylcholinesterase.

The Meeting maintained the ADI, which is based on studies in humans with an NOAEL of 0.04 mg/kg bw/day, using 10-fold safety factor.

Some of the data that served as the basis for this review are summarized in WHO Environmental Health Criteria 79. A toxicological monograph summarizing new or not previously reviewed data as well as relevant data from previous monographs and monograph addenda on dichlorvos was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 10 mg/kg bw/day (two-year study)

Rat: 47 ppm in the diet, equivalent to 2.4 mg/kg bw/day (two-year study)

Human: 0.04 mg/kg bw/day (21-day study)

Estimate of acceptable daily intake for humans

0-0.004 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Dichlorvos was previously evaluated at the 1965, 1966, 1967, 1969, 1970 and 1974 Joint Meetings and it is included in the CCPR periodic review programme.

Dichlorvos, an organophosphorus insecticide, combines both contact and stomach action and has a marked vapour action. It is effective against a broad spectrum of insect pests in the field and in stored products. In addition to plant and stored product protection, it is often used in public health vector control and in animal health for ectoparasite control. The compound is registered for use on over 30 commodities in many countries.

Residues from supervised field trials or specific studies were evaluated for 45 commodities.

Following foliar application at recommended or double rates, the residues in most of the plant commodities tested (apples, avocados, beans, Brussels sprouts, cacao beans, cabbages, cauliflower, chilli peppers, cotton seed, cucumbers, dates, egg plants, lettuce, onions, peanuts, peas, rice, sorghum, soya beans, strawberries, tea, tomatoes, witloof chicory) were below the limit of determination (0.01-0.04 mg/kg, except tea 0.1 mg/kg). Detectable residue were reported in four commodities with maximum values of 0.05 mg/kg in cherries, 0.15 mg/kg in peaches, 0.08 mg/kg in grapes and 0.04 mg/kg in kale.

Residues in samples of endive, celery, spinach, cauliflower, leeks, cucumbers, paprika, tomatoes, radishes and blackberries moving in commerce in The Netherlands were below the limit of determination (<0.05 mg/kg). A residue of 0.1 mg/kg was found in one of 10 lettuce samples.

Following the post-harvest or indoor application of dichlorvos, residues were present in detectable amounts in beans (1.85 and 1.48 mg/kg after 14 and 21 days), wheat (0.41-5.0 mg/kg after 1-2 months), barley (0.14-0.74 mg/kg after 21 days), rice (0.12-0.23 mg/kg after 23-24 days), lettuce (0.2-0.4 mg/kg after 3-4 days) and mushroom (0.02-0.12 mg/kg after 1 day). The results of supervised trials on barley, wheat and rice were supported by the extensive studies in India on a wide variety of stored commodities including cereals.

The very limited data base for most of the crops and/or the discrepancy between the trial conditions and current GAP for beans, cacao beans, coffee beans, cotton seed, egg plant, indoor lettuce, peanuts, peppers and soya beans did not allow the estimation of maximum residue levels, although the Meeting took into account that the results are mutually supportive for many commodities.

The Meeting was also concerned about the lack of frozen storage stability tests of residues in fruit and vegetable samples in view of the period of several months which often elapsed between sampling and analysis, and the substantial decrease of dichlorvos residues in wheat samples stored at -15^{o}C.

In the absence of this information and as a result of the limited residue data, the previous recommendations for fruits and vegetables were withdrawn.

The animal metabolism studies showed that dichlorvos is readily absorbed, hydrolysed and effectively eliminated. The metabolic pathway was identical in the mammalian species studied. The studies on laboratory animals are discussed as part of the toxicological evaluation.

Residues of dichlorvos in the eggs of hens receiving a mist spray three times at a rate of 50 mg/m^3 were first detected 2 days after the first treatment. The residue concentration varied from <0.03 to 0.11 mg/kg during the trial. There was no increase in the concentration following consecutive treatments, and the residue declined below the limit of determination 3 days after the last application. Three birds were killed 18 hours after the 3rd treatment and the breast and leg muscle analysed. The residues found were between <0.01 and 0.05 mg/kg. Egg production was not affected by the treatments.

Various tissues of pigs which had received a single oral dose of vinyl-1-^{14}C-dichlorvos (ca. 40 mg dichlorvos/kg feed) were analysed at 2, 7 and 14 days after the treatment. The ^{14}C content of the tissues expressed as dichlorvos varied from 2.5 mg/kg (in brain) to 33 mg/kg (in liver) after 2 days, and from 1.9 mg/kg to 9.7 mg/kg after 14 days, but no dichlorvos, demethyl-dichlorvos, dichloroacetaldehyde or dichloroacetic acid could be detected.

Three cows were sprayed for 31 consecutive days with 59 ml of 1% dichlorvos solution for the control of horn fly and mosquitoes. Milk samples were collected at 2 hours and 1, 2, 4, 8, 16, 24 and 31 days. Tissue and blood samples were taken one day after the final treatment.

No dichlorvos was detected in any milk samples (<0.003 mg/kg) or body tissues (<0.002 mg/kg) from the treated cows.

Dairy cows were dosed orally at rates of 1.3, 1.8 and 2.6 mg/kg body weight with dichlorvos in the form of polyvinyl chloride pellets. The PVC formulation prevents substantial absorption by the animal, but may release the compound only much later in the manure. As the absorbed amount is unknown the non-detectable dichlorvos residues (<0.04 mg/kg) in milk samples, collected between 1 and 14 days, cannot be related to the dose.

In a dermal application experiment, six cattle and two dairy cows were sprayed once with 15 litres of an emulsion of NUVAN 100 EC at a concentration of 1500 mg/kg. Cattle were slaughtered 1, 3 and 7 days after treatment. Milk samples from two dairy cows were taken 6 h and 1, 3 and 7 days after treatment (control 1 day before treatment). No measurable residues of dichlorvos were found in milk (<0.005 mg/kg) or in muscle, liver, kidney or fat (<0.02 mg/kg).

In plants, the main routes of degradation of dichlorvos were found to be cleavage of the P-C bond to form the major metabolite dimethyl phosphate, demethylation to monomethyl phosphate and phosphoric acid, demethylation to demethyl-dichlorvos (a minor pathway), and loss by volatilization.

Cotton plants of the Deltapine Smooth leaf variety were grown in a glasshouse and treated by injecting aqueous solutions of ^{32}P-labelled dichlorvos (100 µg) into the petioles of individual, fully expanded leaves. Leaf samples were collected 1, 24 and 48 hours after the treatment. The analyses showed 81.2% loss as volatiles, 12.3% as dimethyl phosphate (the major metabolite), 2.2% as phosphoric acid + methyl phosphate and 0.1% as demethyl-dichlorvos (minor metabolites) within 48 hours of application. No parent residue was detectable at this time. Non-extractable residues corresponded to less than 5% of the applied radioactivity.

Greenhouse-grown bean, potato, and tomato plants of 15 cm height, with or without roots, were placed in formulated 0.1-0,2% ^{32}P-dichlorvos. Dichlorvos was degraded with a half-life of 6.8, 4.6 and 6.8 hours on beans, tomatoes and potatoes, respectively. Dimethyl phosphate was a major metabolite detected during the 24-hour test period. Volatile radioactivity amounted to about 60% in all three plant species.

Wheat grain at moisture levels of 18% and 10.6% was topically treated with ^{14}C-dichlorvos at a rate of 40 ìg ai/10 g sample. Treated samples were stored in sealed glass jars in darkness at 20°C and sampled over a period of 10 days. the uptake of dichlorvos was rapid at the higher moisture level. Within 2 days the aqueous-extractable bound activity reached a maximum and remained stable for 7 days, after which the phosphorylated protein was converted to a more stable demethyl form. The uptake rate decreased once all the protein had been phosphorylated, so excess dichlorvos would be lost from the grain by volatilization.

Dichlorvos broke down rapidly on grain to give mainly dimethyl phosphate (about 2 mg/kg at day 10) and phosphorylated protein derivatives, which are mainly water-soluble. Lesser amounts of demethyl-dichlorvos (about 0.5 mg/kg at day 10), monomethyl phosphate (about 0.2-0.25 mg/kg at day 10) and traces of phosphoric acid (undetectable-0.05 mg/kg at day 10) were also found.

The hydrolysis of dichlorvos at a concentration of 10 mg/l in aqueous media follows first order kinetics. The rate of hydrolysis appears to be strongly influenced by the ionic strength of the solution. Half-lives at 30°C determined at pH 1, 5, 7, 9 and 13 are of the order 74, 50, 18, 16 and 0.65 hours respectively. At 20°C and pH 13, the half-life value is 1.3×10^{-2} hours.

In micro-ecosystems containing sediments from a recultivated gravel pit and the drainage ditch of a fruit orchard, dichlorvos was very rapidly degraded to CO_2. After 16 days incubation, 76 and 69% of the applied 1.0 mg ^{14}C-dichlorvos/l was mineralized to $^{14}CO_2$ in the two

systems, respectively. Unchanged parent compound could be detected until day 7 (0.5%) and day 3 (3.1%), respectively. The following dichlorvos metabolites occurred as intermediary products: phosphoric acid, mono(2,2-dichloroethyl) monomethyl ester, sodium salt, demethyl-dichlorvos, 2,2-dichloroethanol, 2,2-dichloroacetaldehyde and dichloroacetic acid. Contamination of surface waters by dichlorvos is unlikely owing to rapid and thorough metabolism.

The photolytic degradation of dichlorvos was studied in water and aqueous methanolic solutions at 20 °C. It was degraded with a half-life of about 6 hours in water but was stable in methanolic solution.

Dichlorvos was applied to soil at a rate corresponding to l kg ai/ha and aged for 0, 2, 8 and 12 days. In a column leaching study 35%, 10%, 2% and <0.1% of the applied radioactivity was detected in the leachate respectively. Up to 15% of the radioactivity in the leachate was dissolved $^{14}CO_2$. 2,2-dichloroethanol and demethyl-dichlorvos corresponded to about 10% and 1% respectively. Parent dichlorvos was rapidly mineralized in the soil, and it was not detectable in any leachates. Within 2 days of ageing, 60-65% of the parent compound was detected as $^{14}CO_2$.

Dichlorvos was very rapidly degraded to the final mineralization product CO_2 in non-sterile standard soil 2.1 of the BBA and in a natural biologically active soil. After an incubation period of 2 days, 1.2% of the unchanged parent compound could be detected in soil 2.1 and none in the second system. During the same period 60-61% of the radioactivity applied as the parent compound was measured as $^{14}CO_2$. The decomposition of the active ingredient was slower in sterile standard soil 2.1. The half-life was 8.7 days. Less than 1% $^{14}CO_2$ was formed.

Dichlorvos was converted to dichloroethanol, dichloroacetic acid and ethyl dichloroacetate by a microbial enrichment derived from sewage.

The persistence of dichlorvos in stored commodities is strongly dependent on the temperature and moisture content or relative humidity (RH). A moisture content of 12% in wheat is roughly equivalent to 60-65% relative humidity. Reported half-lives are 10 days at 25°C and 12% moisture content, 25 days at 21°C and 9.3% moisture content, and 1.8 days at 35°C and 13.7%. The Australian Grain Industry uses an estimated half-life of 7 days at 30°C and 50% RH, and 28 days at 20°C and 50% RH.

Stored wheat lots treated with 6, 12 and 20 mg/kg dichlorvos were processed and the residues were analysed in milling fractions and baked products. The results indicate that the loss in processing may be largely attributable to the scouring and conditioning process. The ratios of dichlorvos residues in bran, germ and flour to wheat were on average 1.5, 1.0 and 0.1, respectively. The residues (mg/kg) detected were as follows: in white bread <0.02-0.2, in wholemeal bread and steamed bread 0.2-0.3, and in Arabic flat bread 0.3-0.6. In calculating the reduction in residue in the cooked products the differences in moisture content were taken into account by the following factors: 1.5 for white, wholemeal and steamed bread, 1.14 for flat bread, and 1.0 for noodles. This gives a loss of 75% of the dichlorvos residue in the production of pan breads, about 65% in the case of Arabic flat bread, which tends to retain a higher residue owing to the short (30 second) heat treatment, and 55% in white noodles. There is a 100% loss in yellow noodles owing to the alkali treatment (1% sodium carbonate by flour weight). There were no detectable residues in any cooked products produced from wheat stored for 3 months after treatment even at an application rate of 20 g/tonne.

In cacao beans about 99% of the residue was lost after roasting. Cacao butter contained 1.3-3.3% of the residues detected in the un-roasted cacao beans.

Washing removed 97%, 24% and 6% of the initial dichlorvos residues from potatoes, lettuce and endive. Cooking endive resulted in an 84% loss of residues.

Whole soya beans containing 0.92-1.5 mg/kg residues were processed into hulls, toasted hulls, flakes, crude oil and refined oil. Residues were 5.4 - 6.0 mg/kg, <0.02 mg/kg, 0.2 mg/kg, 0.55 mg/kg and <0.02 mg/kg respectively.

Storage stability tests of dichlorvos in wheat samples with moisture contents ranging between 13% and 17% indicated that 2 months after treatment 62.5% of the initial concentration (20 mg/kg) was lost at -15°C. When stored at 5°C, 50% and 80% was lost after seven and thirty days respectively. In another study, 50 mg/kg dichlorvos was added to wheat samples of 9.3-13.7% moisture content and stored at -15°C for 11 months. The losses were between only 2% and 22% at different moisture levels.

Although these two experiments showed two different levels of loss, they indicated that the breakdown of dichlorvos cannot be completely prevented even under cold storage conditions.

Dichlorvos can be determined by many published multi-residue procedures.

The samples from supervised trials before 1972 were analysed by an automated cholinesterase-inhibition method described in the 1970 Evaluations. Since then all samples have been analysed by gas chromatography using phosphorus-specific flame-photometric detectors.

FURTHER WORK OR INFORMATION

Desirable

1. Storage stability tests carried out on major commodities at or below -18°C.

2. Residue data on milled products of cereals other than wheat.

3. An animal transfer study on poultry.

4.14 DIQUAT (031)

TOXICOLOGY

Diquat was previously evaluated by the Joint Meeting in 1970, 1972, and 1977. An ADI of 0-0.008 mg diquat ion/kg bw was allocated in 1977.

When administered orally, ^{14}C-diquat was poorly absorbed from the gastrointestinal tract of rats, cows and goats and mainly eliminated via the faeces during the first 24 hours, the small part absorbed being principally eliminated via the urine. The total percentages of the administered doses eliminated via the faeces were 94, 91 and 94 for the rat, cow and goat respectively; 3.1% and 0.4% were eliminated in the urine of rats and cows, respectively, and very small percentages of radioactivity were found in the milk of cows and goats (0.004% and 0.0175% respectively).

After oral administration of ^{14}C-diquat to rats (45 mg ion/kg bw) the major excreted product was diquat in both urine (5% of dose) and faeces (>57% of dose): diquat monopyridone was the main metabolite in the faeces (5% of dose), but a minor one in the urine. In another oral study in rats (100 mg ion/kg bw), small amounts of diquat dipyridone and picolinic acid were found in addition to the monopyridone. After subcutaneous injection (10 mg ion/kg bw) in the rat, 75% of the dose was present in the urine as diquat, about 3% as the monopyridone and 6% as the dipyridone.

Unlike paraquat, diquat is not actively taken up by lung slices and lung toxicity is not characteristic of diquat poisoning.

The acute oral toxicity of diquat varies with species, but is between 125 and 250 mg ion/kg bw in rodents. It is classified by WHO as moderately hazardous.

In a 90-day feeding study in rats, using dietary concentrations of 0, 20, 100 or 500 ppm, the NOAEL was 100 ppm, equal to 8.5 mg ion/kg bw/day, based upon reduction in body-weight gain, food consumption and plasma protein at the next higher dose.

In a one-year feeding study in dogs, doses of 0, 0.5, 2.5 or 12.5 mg/kg bw/day were added to the feed. The NOAEL was 0.5 mg ion/kg bw/day, based upon lens opacity in females at the next higher dose.

Two long-term toxicity/carcinogenicity studies were conducted in mice. The first (80 weeks) used dietary concentrations of diquat ion of 0, 30, 150 or 500 ppm. The NOAEL was 30 ppm, equivalent to 4.5 mg ion/kg bw/day, based upon reduced growth rates at the next higher dose together with hepatic vacuolation in males. In a 2-year study in mice, in which dietary concentrations of 0, 30, 100 and 300 ppm were used, the NOAEL was 30 ppm, equal to 3.6 mg ion/kg bw/day, based on reduction in body-weight gain and increased relative kidney weights at the next higher dose. There was no evidence of carcinogenicity in mice.

Two two-year feeding studies have been conducted in rats. In the first, diquat dibromide was administered in the diet at concentrations of 0, 5, 15, 75 or 375 ppm. The NOAEL was 5 ppm, equal to 0.2 mg ion/kg bw/day, based upon cataract formation in the 15 ppm group. In the second study, dietary concentrations of 0, 15, 25 or 75 ppm diquat ion were used. The NOAEL was 25 ppm (equivalent to 1.3 mg ion/kg bw/day), based on cataract formation at the next higher dose. There was no evidence of carcinogenicity in rats.

Numerous teratogenicity studies have been conducted. NOAELs could not be determined in two mouse studies. There were three teratogenicity studies in rats; in the first study dietary concentrations of 0, 125 or 500 ppm diquat ion were used. A dose-related increase in subcutaneous fetal haemorrhages compared to the controls was observed. An NOAEL could not be derived from this study. In the second study, diquat was administered at oral doses of 0, 4, 12, 24 or 40 mg ion/kg bw/day. For fetal toxicity, the NOAEL was 24 mg ion/kg bw/day but maternal toxicity was observed in all test groups (reduced weight gain and food consumption). In the third study, diquat was administered by gavage at doses of 0, 4, 12 or 40 mg ion/kg bw/day. The NOAEL for both maternal and fetal toxicity was 12 mg ion/kg bw/day, based in the case of the dams on reduced body weight and food consumption and in the case of the fetuses on reduced fetal weight and defects in fetal ossification at the highest dose.

In a study in rabbits, diquat was given orally at doses of 0, 1.25, 2.5 or 5.0 mg ion/kg bw/day. There was no evidence of any effects on embryonic or fetal development. The NOAEL was 2.5 mg ion/kg bw/day, based on mild maternal toxicity at the highest dose. In a second study in rabbits, doses of 0, 1, 3, 7 or 10 mg ion/kg bw/day were administered by gavage. Doses of 3 mg ion/kg bw/day or above were associated with maternal toxicity as manifested by weight loss or reduced weight gain and reduced food intake. No evidence of fetotoxicity was observed. The NOAEL was 1 mg ion/kg bw/day, based upon maternal toxicity. In a third study in rabbits, doses of 0, 1, 3 or 10 mg ion/kg bw/day diquat were given by gavage. The NOAEL was 1 mg ion/kg bw/day, based upon maternal toxicity (reduced weight gain and food consumption) and skeletal effects in the fetuses at doses of 3 mg ion/kg bw/day.

Two multigeneration reproduction studies were conducted in rats. In the first study, diquat was given at dietary concentrations of 0, 125 or 500 ppm. This study did not exhibit an NOAEL, since there was decreased weight gain in F_0 and F_1 animals at the lowest dose, but the effects

observed at this dose (125 ppm, equivalent to 6.3 mg ion/kg bw/day) were trivial. In the second study, rats were fed diquat at dietary concentrations of 0, 16, 80 or 400 ppm. The NOAEL was 16 ppm (equivalent to 0.8 mg/kg bw/day), based upon a low incidence of partial cataract formation at 80 ppm.

Diquat has been adequately tested in a series of genotoxicity assays *in vitro* and *in vivo*. Chromosomal aberrations were induced *in vitro* but there was no other evidence of genotoxicity. The Meeting concluded that diquat was not genotoxic.

An ADI of 0-0.002 mg/kg bw was established, based upon an NOAEL OF 0.19 mg ion/kg bw/day identified in a two-year study in rats, using a safety factor of 100.

A toxicological monograph summarizing the data received since the previous evaluation and incorporating relevant sections from the previous monograph and monograph addenda was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effects

Mouse: 30 ppm, equal to 3.6 mg ion/kg bw/day (two-year study)

Rat: 5 ppm, equal to 0.2 mg ion/kg bw/day (two-year study)
12 mg ion/kg bw/day (teratogenicity study)
16 ppm, equivalent to 0.8 mg ion/kg bw/day (multigeneration reproduction study)

Rabbit: 1 mg ion/kg bw/day (teratogenicity study)

Dog: 0.5 mg ion/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.002 mg ion/kg bw

Studies which will provide information in the continued evaluation of the compound

Observations in humans.

4.15 DITHIOCARBAMATES (105)

TOXICOLOGY

Based on data on the individual compounds, ADIs of 0-0.05 mg/kg bw could have been established for mancozeb and maneb and an ADI of 0-0.03 mg/kg bw could have been established for metiram. The Meeting concluded that the data base for zineb was inadequate to determine its own ADI.

Analytical methods for the determination of parent residues are non-specific. Residues are measured by the evolution of carbon disulphide, which is currently the only suitable regulatory method of analysis. Therefore, no distinction can be made as to the identification of the specific parent compound. Since no differentiation can be made between the parent EBDC residues of maneb, mancozeb, zineb and metiram the Joint Meeting established a group ADI of 0-0.03 mg/kg bw for these EBDCs, which was based on the lowest value within the group,

the ADI for metiram. Given the similarity of the chemical structure of zineb with the other EBDCs, and the comparable toxicological profiles of the EBDCs based on the toxic effects of ethylenethiourea (ETU), the Meeting included zineb in the group ADI. See the separate sections on ETU, mancozeb, maneb, metiram and zineb.

A separate ADI was established for ETU, the major common metabolite, degradation product and contaminant of all the EBDCs, based on its well-documented ability to inhibit thyroid function in rats, generally considered to be the most sensitive species.

The Meeting established an ADI of 0-0.007 mg/kg bw for propineb and a temporary ADI of 0-0.0002 mg/kg bw for propylenethiourea (PTU). The ADI for propineb is considerably lower than that allocated for the EBDCs, a consequence of which is discussed in Section 3.2.

RESIDUE AND ANALYTICAL ASPECTS

Mancozeb, maneb, propineb and their derivatives ethylenethiourea and propylenethiourea were scheduled for periodic re-evaluations at the 1993 JMPR (ALINORM 93/24A, para 133).

Extensive information on mancozeb, maneb and propineb was made available to the Meeting, and has been reviewed under those headings. Because the uses of the dithiocarbamates lead to a common residue, measured and expressed as CS_2, recommendations for MRLs are consolidated under DITHIOCARBAMATES (105), and listed in Annex I.

Information and recommendations on ethylenethiourea (ETU) are summarized under that heading.

4.16 ENDOSULFAN (032)

RESIDUE AND ANALYTICAL ASPECTS

Endosulfan has been reviewed by the JMPR eight times since 1967, including a major re-evaluation in 1989. At the 24th (1992) Session of the CCPR it was pointed out (ALINORM 93/24, paras 81-86) that the MRLs for head cabbages, Savoy cabbage and cauliflower did not reflect the residues expected from GAP in the USA. MRLs for broccoli, Brussels sprouts, head cabbage and Savoy cabbage were therefore held at Step 7B pending review by the present Meeting. The proposed deletion of the general MRLs for "fruit" and "vegetables, except as otherwise listed", as recommended by the 1989 JMPR, was also delayed until after this review.

Information on the current GAP of 21 countries was made available to the Meeting by the manufacturer, including full details from the USA. A large quantity of residue data that had not previously been submitted for review was also provided.

Residue data from supervised trials on many fruits, vegetables, cereals, oilseeds and beverage seeds which had not been reviewed previously were also provided and are recorded in the monograph on this compound. The Meeting confirmed that the data emphasised the desirability of withdrawing the current general MRLs for fruit and vegetables and replacing them with MRLS for individual commodities, usually at a lower level. It was also possible to make recommendations for MRLs on some additional crops.

The residue data on oranges were adequate to allow an MRL of 0.5 mg/kg to be recommended but the data on clementines and lemons were only in summary form and thus not sufficient to extend the MRL to the citrus fruit group.

Residues from trials on apples, cherries and plums were within the current MRLs of 1 mg/kg. Data for peach residues supported a similar MRL of 1 mg/kg. Residue data on grapes also allowed an MRL of 1 mg/kg to be recommended but the strawberry data were only summaries and were thus inadequate.

A dip treatment of pineapples with endosulfan is required in Australia for export quarantine purposes. The resultant residues are up to 2 mg/kg, within the CXL for "Fruits", and so an MRL of 2 mg/kg was recommended to cover this post-harvest use.

Unfortunately, the only residue data on brassica crops treated in the USA concerned two trials on Brussels sprouts that were carried out in 1964 and had been reported previously; at a 14-day PHI a maximum residue of 1.2 mg/kg was observed. In one trial on Brussels sprouts in the UK in 1976, 0.1 mg/kg was found after 14 days and 0.06 mg/kg after 21 days but the data were not adequate to support an MRL recommendation. Data from other countries under their GAP conditions were available for broccoli, head cabbage, Savoy cabbage and cauliflower; these results were consistent with the existing draft MRLs of 0.5, 1, 2 and 0.5 mg/kg, respectively.

For some other vegetables, currently covered by the CXL for "Vegetables, except as otherwise listed", the data presented were sufficient to allow recommendations to be made for broad bean, cucumber, melons except watermelon, summer squash and tomato, all at 0.5 mg/kg, and for soya bean at 1 mg/kg. Data for sweet peppers were inadequate.

Residues on celery (2 mg/kg), common bean (0.5 mg/kg), head lettuce (1 mg/kg) and potato (0.2 mg/kg) were within the respective CXLs.

For cereals, residue data were presented for maize and wheat, allowing recommendations of 0.1 mg/kg and 0.2 mg/kg, respectively, to be made.

Trials on some oilseeds gave sufficient residue data for MRLs to be recommended for cotton seed (1 mg/kg), rape seed (0.5 mg/kg) and sunflower seed (1 mg/kg).

New residue data were also available which allowed recommendations to be made for MRLs on cacao beans and coffee beans, both at 0.1 mg/kg.

Processing data were available for apples (juice and pomace), grapes (wine and must) and common beans (washing and cooking).

4.17 ETHEPHON (106)

TOXICOLOGY

Ethephon was evaluated at the 1978 JMPR, but an ADI was not allocated since the available toxicological data were insufficient. It is a plant growth regulator that acts by release of ethylene, influencing directly several physiological processes such as ripening and maturation and stimulating the production of endogenous ethylene. Since the compound in high concentration (>87%) is a waxy solid and difficult to handle, a technical product that contains 71% ethephon and 21% water is marketed and also used for most toxicological studies. Although ethephon is a dibasic phosphonic acid, its commercial formulation exhibits some anticholinesterase activity.

Following the oral administration of ethephon to rats, about 90% of the administered radioactivity was recovered, principally in urine (50%), expired air (19%), and faeces (6%) during 120 h after dosing. Most of the dose was recovered within 24 h.

After oral administration of ethephon to dogs, radioactivity was found in urine (40%),

expired air (30%) and faeces (5%). Total body retention was 1%. Peak plasma and red blood cell concentrations were observed 2 h after dosing. Only traces were observed after 22 h.

After oral administration to rats, ethephon was excreted in urine and faeces as the mono- and disodium salts and some unidentified metabolites, and metabolized to ethylene and eliminated in the expired air. In dogs, ethephon is partly metabolized to ethylene and eliminated in expired air and also excreted unchanged in the urine.

In dogs dosed orally with ethephon, plasma cholinesterase activity was inhibited at 2 h with recovery starting within a few hours. Erythrocyte cholinesterase levels responded more slowly with signs of recovery at 72 h.

Ethephon has a low oral acute toxicity in mice, rats, and rabbits. WHO has classified ethephon as unlikely to present acute hazard in normal use. Ethephon is corrosive to the skin of rabbits.

In a four-week study in mice at dietary concentrations of 0, 30, 100, 300, 1000 or 3000 ppm, the NOAEL was 300 ppm (equal to 51 mg/kg bw/day), based on inhibition of erythrocyte cholinesterase activity.

In a four-week study in rats at dietary concentrations of 0, 625, 1250, 2500, 5000 or 10000 ppm, the NOAEL was 625 ppm (equal to 52 mg/kg bw/day), based on inhibition of erythrocyte cholinesterase activity.

In a one-year study in dogs at dietary concentrations of 0, 100, 300, 1000 or 2000 ppm, the NOAEL was 1000 ppm (equal to 27 mg/kg bw/day), based on soft stools and changes in body and spleen weight. However, cholinesterase activities were not determined.

In a two-year study in dogs at dietary concentrations of 0, 30, 300, or 1500 ppm, the NOAEL was 30 ppm (equal to 0.86 mg/kg bw/day), based on inhibition of erythrocyte cholinesterase activity and smooth muscle hypertrophy in the stomach and small intestine.

In two 78-week studies in mice at dietary concentrations of 0, 30, 100, 300, 1000 or 10000 ppm, the NOAEL was 100 ppm (equal to 14 mg/kg bw/day), based on inhibition of erythrocyte cholinesterase activity. There was no evidence of carcinogenicity.

In two 104-week studies in rats at dietary concentrations of 0, 30, 300, 3000, 10000 or 30000 ppm, the NOAEL was 30 ppm (equal to 1.2 mg/kg bw/day), based on inhibition of erythrocyte cholinesterase activity. There was no evidence of carcinogenicity.

Brain cholinesterase was not depressed in any studies.

In a two-generation reproduction study in rats at dietary concentrations of 0, 300, 3000 or 30000 ppm, the NOAEL for maternal and filial toxicity was 300 ppm (equal to 22 mg/kg bw/day), based on reduced food intake, body weight and weight gain. There was no adverse effect on reproduction.

In two studies in hens for delayed neurotoxicity, no evidence of delayed neurotoxicity was observed.

In two oral teratogenicity studies in rats at dose levels of 0, 125, 200, 250, 500, 600, or 1800 mg/kg bw/day, the NOAEL was 600 mg/kg bw/day, based on maternal toxicity. There were no teratogenic effects.

In two teratogenicity studies in rabbits at oral dose levels of 0, 50, 62.5, 100, 125, or 250 mg/kg bw/day, the NOAEL was 50 mg/kg bw/day, based on maternal and embryo/fetotoxicity.

There were no teratogenic effects.

After reviewing the *in vitro* and *in vivo* genotoxicity data, the Meeting concluded that there was no evidence of genotoxicity.

In 16 male and female human volunteers treated orally with 3 x 40 mg/day of ethephon (approximately 1.5 and 2.2 mg/kg bw/day in males and females, respectively) for 28 consecutive days, no significant inhibitory effect on human plasma or erythrocyte cholinesterase activity was observed. Subjective complaints of urinary urgency, diarrhoea of sudden onset, effect on appetite and dyspepsia were recorded. An NOAEL could not be determined on the basis of the clinical symptoms.

In 30 male and female human volunteers treated orally with 0.5 mg/kg bw/day of ethephon (divided into 3 doses) for 16 consecutive days, plasma cholinesterase activity was inhibited but returned to its initial activity within the recovery period of 29 days. The NOAEL was 0.5 mg/kg bw/day, based on the lack of inhibition of erythrocyte cholinesterase.

In 20 male and female human volunteers receiving 0.17 or 0.33 mg/kg bw/day of ethephon orally (divided into 3 doses) for 22 consecutive days, plasma cholinesterase activity was inhibited and did not return within the recovery period of 14 days. An NOAEL of 0.33 mg/kg bw/day in both males and females was determined based upon the lack of inhibition of erythrocyte cholinesterase.

An ADI of 0-0.05 mg/kg bw was established, based on the NOAEL in the 16-day study in humans of 0.5 mg/kg bw/day, using a 10-fold safety factor.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 100 ppm, equal to 14 mg/kg bw/day (78-week study)

Rat: 30 ppm, equal to 1.2 mg/kg bw/day (104-week study)

Dog: 30 ppm, equal to 0.86 mg/kg bw/day (two-year study)

Human: 0.5 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.05 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. The Meeting noted that ethephon is a dibasic phosphonic acid and therefore not able to phosphorylate hydrolases at the serine residue. However, *in vivo* data showed inhibition of plasma and erythrocyte, but not brain, cholinesterase. Neither data with the pure compound nor *in vitro* studies were available. The Meeting considered that these effects on cholinesterases need clarification and recommended re-evaluation of the compound in 1995.

2. Further observations in humans.

4.18 ETHYLENETHIOUREA (ETU) (108)

TOXICOLOGY

Ethylenethiourea (ETU) was reviewed in conjunction with the ethylenebis(dithiocarbamate)s (EBDCs) by the Joint Meeting in 1963, 1965, 1967, 1970, 1974, 1977, 1980, 1986 and 1988. In 1988 the Joint Meeting extended the temporary ADI of 0-0.002 mg/kg bw pending the submission of additional data. ETU is also of interest because it forms part of the terminal residue to which consumers of produce treated with the EBDCs are exposed and because the levels of ETU in treated produce generally increase during food processing as the levels of the EBDC parent compounds decrease.

Following oral administration to mice essentially all of the ETU was recovered in the excreta within 48 hours; none was recovered as carbon dioxide. Approximately 50% of the administered dose was found in urine as unchanged ETU.

After the oral administration of radiolabelled ETU, its concentration in both pregnant mice and rats peaked at about the same time (1.4 hours), with concentrations in maternal and fetal tissues similar at 3 hours. The half-life of elimination from mice and rats was 5.5 hours and 9.4 hours respectively. Approximately 70% of the ETU was found in the urine in both species at 48 hours.

Mice metabolize ETU primarily by the flavin-monooxygenase (FMO) system and rats by the P-450 system of enzymes.

ETU is slightly toxic after acute oral administration, with the (LD_{50}) ranging from 545 mg/kg bw in pregnant rats to 4000 mg/kg bw in adult mice.

In a 13-week study in mice at dietary concentrations of 0, 125, 250, 500, 1000 or 2000 ppm the NOAEL was 250 ppm (equivalent to 38 mg/kg bw/day). Diffuse follicular cell hyperplasia of the thyroid and hepatocellular cytomegaly were observed at 500 ppm.

In a three-month study in mice at dietary concentrations of 0, 1, 10, 100 or 1000 ppm the NOAEL was 10 ppm, equal to 1.7 mg/kg bw/day. ETU produced thyroid follicular cell hyperplasia and decreased colloid density at 100 ppm.

The NOAEL in a study in which rats were fed dietary concentrations of ETU at 0, 0.63, 1.25, 2.5, 5.0 or 25 ppm for 8 weeks 25 ppm (equal to 2.6 mg/kg bw/day), the highest dose tested.

In a 13-week study in rats ETU was administered in the diet at concentrations of 0, 60, 125, 250, 500 or 750 ppm. The NOAEL was less than 60 ppm (equal to 3.0 mg/kg bw/day), based on histopathological findings of diffuse follicular cell hyperplasia in the thyroid.

In a 90-day study in rats ETU was administered in the diet at concentrations of 0, 1, 5, 25, 125 or 625 ppm. The NOAEL was 25 ppm (equal to 1.7 mg/kg bw/day), based on hyperaemia of the thyroids with and without enlargement, thyroid follicular cell hyperplasia, increased thyroid-to-brain-weight ratio, decreased ^{125}I thyroid uptake, decreased T_3 and decreased thyroxine at 125 ppm.

In a four-week feeding study in dogs at dietary concentrations of 0, 200, 980 or 4900 ppm, the NOAEL was 200 ppm, equal to 6.7 mg/kg bw/day. Decreased body-weight gain, decreased thyroxine and T_3 levels and enlarged thyroids were observed at 980 ppm.

In a 13-week feeding study in dogs at dietary concentrations of 0, 10, 150 or 2000 ppm the NOAEL was 10 ppm, equal to 0.39 mg/kg bw/day. At 150 ppm haemoglobin, packed cell volume, and red blood cell count were decreased, and cholesterol was increased. Effects on the thyroid were found only at 2000 ppm.

In a 52-week feeding study in dogs at dietary concentrations of 0, 5, 50, or 500 ppm, the NOAEL was 5 ppm, equal to 0.18 mg/kg bw/day. At 50 ppm a reduction in body-weight gain, hypertrophy of the thyroid with colloid retention, a slight increase in thyroid weight and pigment accumulation in the liver were observed.

Male and female mice received perinatal (F_0) and adult (F_1) exposure to ETU at the following dietary concentrations (F_0,F_1); 0,0; 0,330; 0,1000; 330,0; 330,330; 330,1000; 110,330; or 33,100 ppm. Mice receiving perinatal exposure only (330,0 ppm) showed no effect on the incidences of neoplasms after 2 years. Cytoplasmic vacuolization of follicular cells of the thyroid was evident in males and females at 33,100 ppm, but no increases in neoplasms of the liver, pituitary or thyroid were observed. T_4 values were significantly decreased in both sexes and TSH was slightly elevated. Animals receiving 330 ppm during adulthood showed tumours of either the liver, pituitary or thyroid. Increasing perinatal exposure from 0 to 330 ppm was associated with an increased incidence of thyroid and pituitary lesions in female mice receiving adult exposure to 330 ppm, but there were no enhancing effects of perinatal exposure in mice receiving adult exposures of 1000 ppm when compared to adults in the 0,1000 ppm group.

Rats were fed dietary concentrations of ETU at levels of 0, 5, 25, 125, 250 or 500 ppm for 2 years. The NOAEL was 5 ppm, equivalent to 0.25 mg/kg bw/day. Vascularity and hyperplasia of the thyroid were seen at 25 ppm.

In a two-year feeding study in rats using dietary concentrations of 0, 0.5, 2.5, 5 or 125 ppm the NOAEL was 5 ppm (equal to 0.37 mg/kg bw/day), based on changes in clinical chemistry, increased T_3, decreased T_4, increased thyroid weight, increased liver weight and an increased incidence and severity of diffuse thyroid follicular cell hyperplasia at 125 ppm.

In a two-year carcinogenicity study in rats using dietary concentrations of 0, 175 or 350 ppm, thyroid carcinomas and hyperplastic goitres were observed in both sexes at 175 ppm (equivalent to 8.8 mg/kg bw/day).

Male and female rats received perinatal (F_0) and adult (F_1) exposure to ETU at the following dietary concentrations (F_0,F_1); 0,0; 0,83; 0,250; 90,0; 90,83; 90,250; 30,83; or 9,25 ppm. Rats receiving perinatal and adult exposure of 9,25 ppm showed no increase in tumours and no apparent biologically meaningful changes in thyroid hormone function at two years when compared to 0,0 ppm controls. Thyroid hyperplasia was evident in both sexes. At 9 months, animals given 9,25 ppm manifested decreased T_3 and T_4 values and increased TSH without evidence of thyroid follicular cell hyperplasia. Males and females receiving a dose of 90,0 ppm showed no hormonal changes and no tumours at 2 years. Thyroid follicular cell hyperplasia was, however, evident. Animals receiving adult exposure showed a significant increase in thyroid follicular cell tumours at 83 and 250 ppm (males) and 250 ppm (females). Males and females showed no significant differences in the number of tumours between dose groups of 0,83; 30,83; and 90,83 ppm. Males and females receiving 90,250 ppm showed increases in thyroid follicular cell tumours when compared to 0,250 ppm. At the end of 2 years males and females receiving 0,83 or 0,250 manifested increased numbers of thyroid tumours when compared to 0,0 ppm controls.

In a two-generation reproduction study in rats at dietary concentrations of 0, 2.5, 25 or 125 ppm the NOAEL was 2.5 ppm, equal to a range of 0.16-0.38 mg/kg bw/day, based on thyroid gland follicular cell hyperplasia and hypertrophy at 25 ppm.

An oral teratogenicity study conducted in rats at dose levels of 0, 5, 10, 20, 40 or 80 mg/kg bw/day indicated no maternal toxicity at 40 mg/kg bw/day (NOAEL). Maternal lethality was observed at 80 mg/kg bw/day. The NOAEL for embryo/fetotoxicity effects was 5.0 mg/kg bw/day, based on teratogenic effects observed at 10 mg/kg bw/day.

An oral teratogenicity study in rats at dose levels of 0, 15, 25 or 35 mg/kg bw/day was conducted. No maternal toxicity was observed at 35 mg/kg bw/day (NOAEL). The NOAEL for embryo/fetotoxicity and teratogenicity was 15 mg/kg bw/day, based on higher incidences of dilated brain ventricles at 25 mg/kg bw/day.

Oral teratogenicity studies in rats (0, 10, 20, 30, 40 or 50 mg/kg bw/day), mice (0, 200, 400 or 800 mg/kg bw/day) and hamsters (0, 90, 270 or 810 mg/kg bw/day) revealed no maternal toxicity at the doses tested. The NOAEL for embryo/fetotoxicity in the rat was 10 mg/kg bw/day, based on dilation of the lateral or fourth ventricle at 20 mg/kg bw/day. The NOAEL for embryo/fetotoxicity in the hamster was 90 mg/kg bw/day, based on a decrease in fetal body weight at 270 mg/kg bw/day. The NOAEL for mice was higher than 800 mg/kg bw/day.

In an oral teratogenicity study, rabbits received 0, 5, 10, 20, 40 or 80 mg/kg bw/day of ETU. The NOAEL for maternal toxicity was 80 mg/kg bw/day. The NOAEL for embryo/fetotoxicity was 40 mg/kg bw/day, based on an increase in resorption sites, decreased brain weight and a degeneration of the proximal convoluted tubules in the kidneys of fetuses at 80 mg/kg bw/day. Malformations were not observed at the highest dose.

A study with pregnant rats administered ETU, T_3/T_4 and sodium iodide in combination indicated a reduction in some of the teratogenic responses when compared with groups administered ETU alone. These results indicate that the teratogenic potential of ETU may in part be secondary to the thyroid toxicity of ETU.

ETU has been the subject of many *in vitro* and *in vivo* studies for genotoxicity. It induces mutations in bacteria at very high doses but variable responses have been obtained in other types of mutation assays. Acceptable assays for other genotoxicity endpoints *in vitro* were generally negative, while all *in vivo* assays were negative. The Meeting concluded that ethylenethiourea was not genotoxic.

The ADI is based upon an NOAEL of 0.39 mg/kg bw/day in the 13-week dog study since this dose level is between the NOAEL of 5 ppm (equal to 0.18 mg/kg bw/day) and the middle dose (effect level) of 50 ppm (equal to 1.79 mg/kg bw/day) of the 52-week dog study. A 100-fold safety factor was applied.

A toxicological monograph was prepared, summarizing the data that have been received since the previous evaluation and incorporating the previous monograph and monograph addenda on ETU.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effects

Mouse: 10 ppm, equal to 1.7 mg/kg bw/day (3-month study)

Rat: 5 ppm, equal to 0.37 mg/kg bw/day (two-year study)
2.5 ppm, equal to a range of 0.16-0.38 mg/kg bw/day (reproduction study)

Dog: 10 ppm, equal to 0.39 mg/kg bw/day (13-week study)

5 ppm, equal to 0.18 mg/kg bw/day (52-week study)

Estimate of acceptable daily intake for humans

0-0.004 mg/kg bw.

Studies which will provide valuable information in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Ethylenethiourea (ETU) is a metabolite and decomposition product of the ethylenebis(dithiocarbamate) (EBDC) fungicides. MRLs have been established to reflect maximum residue levels in raw agricultural commodities at harvest. ETU was scheduled (ALINORM 93/24A, Appendix IV, Annex I) for periodic (toxicological and residue) re-evaluation by the 1993 JMPR.

Extensive data were made available to the Meeting on ETU residues in raw agricultural commodities from supervised trials, in processed foods from supervised trials, and in raw and processed commodities in trade, and on the production of ETU in the plant and animal metabolism of mancozeb and maneb.

ETU residues in raw agricultural commodities were generally low (0.1 mg/kg or less) or undetectable (LOD mostly 0.01-0.02 mg/kg). Some reported ETU residues could be an artefact of the analysis, because a small percentage of the ethylenebis(dithiocarbamate) residues can be converted to ETU during the determination.

Animal metabolism and animal transfer studies with mancozeb and maneb on lactating dairy cows, lactating goats and laying hens showed that ETU was a minor metabolite and that ETU residues in milk, eggs and tissues arising from ethylenebis(dithiocarbamate) (EBDC) feed residues would normally be very low or undetectable.

ETU was either undetectable or a minor residue in plant metabolism studies with applied mancozeb or maneb. Where ETU was detected, it was mostly in surface rinsings.

ETU was generally short-lived when applied to plant leaves or soil. It was rapidly degraded by UV light.

Ethylenebis(dithiocarbamate) residues are readily converted in part to ETU if processing includes a heating step. Levels of ETU in processed products bear no relationship to the ETU levels in the raw commodities. ETU levels in processed commodities depend on the levels of EBDC which are present at crucial stages where heating takes place and the duration and temperature of that heating.

Under a US Food and Drug Administration monitoring programme (1990-1991) a variety of baby foods (864 samples) were monitored for pesticide residues. ETU residues were detected in 65 samples; the highest levels detected were 0.06 mg/kg. In 1989-90 in the USA a large survey of food items (approximately 300 samples each of 19 different raw and processed commodities) was conducted for dithiocarbamate and ETU residues. No measurable residues of ETU (LOD 0.001 mg/kg) were found in 82% of the samples. All ETU residue levels were less than 0.1 mg/kg. ETU was not detected (LOD 0.005 mg/kg) in any of 100 commercial grape juice samples in the USA taken from producers using grapes from areas where dithiocarbamate fungicides were used.

The Meeting agreed that MRLs for ETU did not assist in deciding whether GAP in the use of EBDCs was being followed. The Meeting agreed to recommend the withdrawal of all MRLs for ETU.

Normally the regulation of a residue in the raw agricultural commodity sets a limit on the levels in processed food because some or all of the residue is lost during the process. The levels of ETU in the processed commodity bear no relation to the levels in the raw agricultural commodity. ETU is more likely to occur in processed food where it can be generated by the heating of EBDC residues during the process.

Processing trials demonstrate that under some conditions considerable conversion of EBDCs to ETU can occur. Processing studies available to the Meeting showed that an initial commercial washing and cleaning of the raw agricultural commodity removes much of the EBDC, which is a surface residue, and reduces the potential for ETU formation.

The extensive food surveys in the USA, which have included many processed foods, have generally found only low levels of ETU (less than 0.1 mg/kg) and only in a minority of samples (fewer than 20%). The data suggest that, if good processing practices are followed, ETU residues in processed food would rarely exceed 0.1 mg/kg.

The 1990 JMPR reported results of the monitoring of food in commerce or at consumption for ETU in Canada for 1975-1985. Residues in a number of processed products were all below the limit of detection (0.05 mg/kg). Limited 1989-1990 data from Canada on a variety of fruit juices and drinks showed residues to be below 1 µg/kg.

4.19 ETOFENPROX (184)

2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether

The compound was considered for the first time by the present Meeting.

Etofenprox is an insecticide with an action similar to the pyrethroids. It is active against a wide range of insect pests and is effective against strains of rice green leafhopper and planthoppers resistant to organophosphorus and carbamate insecticides.

Etofenprox is mostly formulated as 20% wettable powders or 20% emulsifiable concentrates.

TOXICOLOGY

After oral administration to rats, total excretion was 85-90% in faeces and 7-9% in urine. Excretion in bile was found to be 10 to 30%. Unchanged etofenprox was not found in the bile. Total retention in the body after 5 days was 3-4%. In the gastrointestinal tract from 48 to 93% was absorbed. Absorption tended to be dose-dependent. Tissue concentrations were highest in fat; this residue was present as unchanged parent compound. Etofenprox was excreted (as the unchanged compound) in milk. The major biotransformation routes involve *O*-de-ethylation of the ethylphenyl moiety and hydroxylation of the phenoxybenzyl moiety followed by conjugation with glucuronide or sulphate. Oxidation of the á-CH_2 group followed by hydrolysis represents an additional route. The available results for dogs indicate a lower gastrointestinal absorption rate than in rats. The major biotransformation routes were the same as in rats.

Etofenprox has a low acute oral toxicity in mice, rats and dogs. WHO has classified etofenprox as unlikely to present acute hazard in normal use.

In a 13-week study in mice, using dietary concentrations of 0, 50, 500, 3000 or 15000 ppm, the NOAEL was 500 ppm, equal to 60 mg/kg bw/day. The main effects seen were mortality, growth retardation, increased weights of liver (with enlarged hepatocytes) and kidneys (with tubular basophilia and dilatation) and decreases in red blood cell counts and haemoglobin concentration.

In a 13-week study in rats using dietary concentrations of 0, 50, 300, 1800 or 10800 ppm, the NOAEL was 300 ppm, equal to 20 mg/kg bw/day, based on effects on growth and the liver. In addition, increased thyroid weight with increased incidence of microfollicles in this organ was observed.

In a 52-week study in dogs using dietary concentrations of 0, 100, 1000 or 10,000 ppm, the NOAEL was 1000 ppm (equal to 32 mg/kg bw/day), based on decreased red blood cell counts, haemoglobin concentration and packed cell volume, increased serum alkaline phosphatase and increased liver weight (with swelling of hepatocytes).

In a two-year toxicity/carcinogenicity study in mice using dietary concentrations of 0, 30, 100, 700 or 4900 ppm, the NOAEL was 30 ppm (equal to 3.1 mg/kg bw/day), based on an increased incidence of tubular lesions in the kidneys at ≥100 ppm. There was no evidence of carcinogenicity.

A two-year toxicity/carcinogenicity study in rats also used dietary concentrations of 0, 30, 100, 700 or 4900 ppm. The NOAEL was 100 ppm (equal to 3.7 mg/kg bw/day), based on increased weights of thyroid and kidneys and microscopic liver changes at ≥700 ppm. The incidence of cystic follicles in the thyroid was increased only at 4900 ppm. There was an increased incidence of thyroid follicular adenomas among the 4900 ppm animals, which was statistically significantly increased only in females. The absence of genotoxicity of etofenprox (see below) in combination with the observed activation of the thyroid gland, which might be related to the effects on the liver (the latter probably leading to increased breakdown of thyroid hormones), is a strong indication for a non-genotoxic mechanism of induction of the thyroid tumours.

In a two-generation study in rats using dietary concentrations of 0, 100, 700 or 4900 ppm, the NOAEL was 100 ppm (equivalent to 5 mg/kg bw/day). No effects on reproduction were observed. The main effects seen in parents as well as young were decreased growth and effects on the weights and histopathology of liver and kidneys. The effects on the offspring were consistent with exposure to unchanged etofenprox via milk.

Embryo/fetotoxicity and teratogenicity were studied in rats (3 studies, segment I, II & III, respectively) and rabbits (1 study). In the three studies in the rat, etofenprox was administered by gavage at dose levels of 0, 12.5, 250 or 5000 mg/kg bw/day. In each of the studies, dose-related maternal toxicity (clinical signs, growth retardation) was observed at 5000 mg/kg bw/day. In the two studies in rats with dosing before or during pregnancy, no effects on offspring/fetuses were seen. In the study in rats with dosing during lactation (segment III), toxic effects developed in the offspring, most likely as a result of exposure to etofenprox via milk. In none of the studies in rats were irreversible structural malformations found. The NOAEL for maternal or parental toxicity in each of these studies was 250 mg/kg bw/day. For fetotoxicity, the NOAEL was 5000 mg/kg bw/day in the segment I and II studies. The NOAEL for neonatal effects in the segment III study was 250 mg/kg bw/day. In the study in rabbits the NOAEL for maternal toxicity was 10 mg/kg bw/day, based on decreased growth at 50 and 250 mg/kg bw/day. Incidences of late abortions and early-embryonal mortality were increased only at 250 mg/kg bw/day. The NOAEL for embryo/fetotoxicity was 50 mg/kg bw/day. No irreversible structural malformations were noted in this study.

On the basis of the results of the available *in vitro* and *in vivo* genotoxicity data there was no evidence that etofenprox is genotoxic.

The most sensitive species in the animal studies presently available appear to be rodents, with NOAELs of 3.1 and 3.7 mg/kg bw/day for mice and rats, respectively, in the long-term studies. The ADI was based on the long-term study in mice, using a 100-fold safety factor.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effects

Mouse: 30 ppm, equal to 3.1 mg/kg bw/day (long-term toxicity/carcinogenicity study).

Rat: 100 ppm, equal to 3.7 mg/kg bw/day (long-term toxicity/carcinogenicity study).

Rabbit: 10 mg/kg bw/day (maternal toxicity in a teratogenicity study).

Dog: 1000 ppm, equal to 32 mg/kg bw/day (52-week study).

Estimate of acceptable daily intake for humans.

0 - 0.03 mg/kg bw.

Studies which will provide information valuable in the continued evaluation of the compound.

1. Clarification of the dose-response relation for thyroid effects in the rat, including evaluation of T_3, T_4, TSH and other relevant parameters.

2. Observations in humans with adequate information on exposure levels.

RESIDUE AND ANALYTICAL ASPECTS

Degradation studies were carried out on etofenprox in plants (beans and rice) and soil. Metabolic studies were also carried out in animals (rats and dogs), but information about these was only available to the Meeting in a summarized form.

The metabolism of etofenprox in bean and rice plants was examined by applying á-^{14}C-benzyl-labelled and 1-^{14}C-propyl-labelled etofenprox to leaves of the plants under laboratory conditions. There was very limited translocation of the parent compound and its metabolites to other parts of the plants, including the seeds in rice. Etofenprox was gradually decomposed on and in the treated leaves and was reduced to approximately 50% after 3 weeks. The main metabolite from the oxidization of etofenprox was 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate. Residues of other metabolites, mainly 3-phenoxybenzoic acid and 2-(4-ethoxyphenyl)-2-methylpropan-1-ol, were also present but in small quantities. The half-life of etofenprox on beans was determined to be 3 weeks for both labelled forms. At that time the main metabolite accounted for 11-15% and unrecovered compounds for 14-18% of the radioactivity applied. Experiments have shown that all metabolites observed on the bean leaves, except conjugates, were very similar to products formed by photodegradation, implying that the metabolism on plant leaves is affected by light.

Degradation studies on etofenprox in soil were carried out with three different soil types using the same two ^{14}C-labelled forms as in the experiments on plants. The half-life of etofenprox in soil was determined to be 6-9 days and largely independent of the soil types and labelled forms used. The main products formed after oxidation were 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate and 2-(4-ethoxyphenyl)-2-methylpropyl 3-hydroxybenzyl eth-

er. The liberation of $^{14}CO_2$ from the degradation of ^{14}C-labelled etofenprox was examined. After 2 and 8 weeks the radioactivity originating from CO_2 was 8-12 and 32-44%, respectively. The degradation of etofenprox in soil was evidently caused by micro-organisms as no degradation occurred in sterilized soil.

Field studies were carried out to examine the rate of degradation of etofenprox in paddy and upland soils. The half-lives in the two paddy soil types examined were 79 and 62 days, while the half-lives in the two upland soils were 39 and 9 days. Etofenprox is strongly adsorbed to soil, and little leaching takes place. No residues of the parent compound and only small quantities of metabolites were detectable in the effluents from three soil types after 2 weeks of leaching.

Supervised trials were carried out on several kinds of fruits and vegetables in Japan, on apples and potatoes in Hungary, and on potatoes and rape in Poland. In Japan trials were also carried out on rice, wheat, corn and tea. The application rates were different in the three countries. In Japan the rates were generally of the order of 0.5-1.5 kg/ha, while the highest rate in Hungary was 0.15 kg ai/ha and in Poland 0.09 kg ai/ha. Residues in apples were 0.4-0.8 mg/kg in Japan and 0.1-0.2 mg/kg in Hungary. Residues in potatoes were below the limit of determination in all the trials, including those in Japan at the highest dose rate.

Residues were determined in animal products after feeding experiments on dairy cows. Cows were fed with etofenprox at levels of 10, 30 and 1000 mg/animal/day, where 1000 mg/day represents a considerably higher level of intake than would occur in practice. After a feeding period of 28 days residues in milk from cows fed with 10 and 30 mg/day were at or below the limit of determination (0.05 mg/kg), but residues from 1000 mg/day were up to 2 mg/kg. Residues in tissues were also examined after the feeding period. Residues in liver, kidney and skeletal muscle from 10 and 30 mg/day were at or below the limit of determination, but in the peritoneal and subcutaneous fat were quite high and up to 0.84 mg/kg. For cows fed with 1000 mg/day, residues were up to 14 mg/kg in peritoneal fat and up to 3.5 mg/kg in subcutaneous fat, and were also present in kidney, liver and muscle.

Residues of etofenprox in plant material and soil are determined by gas chromatography with an electron capture detector after extraction with acetone and clean-up by partitioning with water/n-hexane and by column chromatography on Florisil or alumina/silica gel. For most crops and soil the purified extract is reacted with trimethylsilyl iodide to form 3-phenoxybenzyl iodide. The limit of determination is 0.01 mg/kg. For milk and animal tissues the method is similar, but ethyl acetate/hexane is used for the extraction and a silica sep-pak is used for the chromatographic clean-up. The limit of determination for residues in animal products is 0.05 mg/kg.

The manufacturer informed the Meeting that the analytical methods described, including the chromatographic clean-up step, are specific for the parent compound etofenprox and do not determine other compounds containing the 3-phenoxybenzyl moiety.

Supervised trials for most crops were carried out in only one country, Japan, and although they were at two sites they took place within the same year. The Meeting was therefore able to propose maximum residue limits for etofenprox in only two crops.

FURTHER WORK OR INFORMATION

Desirable

1. Submission of documentation for the specificity of the analytical methods for the determination of etofenprox.

2. Supervised trials on crops from more than one year and trials carried out in more than one country.

3. Studies on the processing of crops containing residues of etofenprox

4. Residues in straw from wheat and other crops used as animal feedingstuffs.

4.20 FENBUTATIN OXIDE (109)

RESIDUE AND ANALYTICAL ASPECTS

Fenbutatin oxide, a miticide registered for use on many crops world-wide, was first reviewed by the 1977 JMPR for both toxicology and residues. A toxicological re-evaluation in the periodic review programme of the CCPR was conducted in 1992, but the corresponding residue review was postponed to 1993 owing to the late arrival of data. Although the present Meeting reviewed over 250 individual reports or studies containing residue data and GAP information, little or no information was provided on some critical supporting studies (e.g. plant, goat and hen metabolism studies, processing studies for tomatoes, freezer storage stability of analytical samples, analytical methods, etc.). The Meeting received processing studies for apples, grapes and citrus and, on request, cow metabolism and transfer studies as well as a chicken feeding study. The Meeting was informed that rat, hen and goat metabolism studies had been submitted to WHO and could be submitted to FAO for future review. A proposed LC analytical method for fenbutatin was also reviewed.

GAP and summary residue data received from Spain and The Netherlands for a number of commodities were received too late for full consideration. The GAP information has been added to the 1993 Monograph. Most if not all of the summary residue information appears to have been included in earlier submissions for 1993 review and has therefore been considered.

There was still a lack of critical supporting information, with the exception of the cow and chicken feeding studies and processing studies provided. Accordingly, the Meeting limited this periodic review primarily to evaluating supervised trials data and/or evaluating data in the context of the available information on current GAP.

Supervised trials data show fenbutatin oxide residues in general to be primarily on the surface or in the peel. Residues in banana pulp are 1-2% of the level in the whole banana; peeled cucumber residues are $\leq$33% of whole cucumber residues; citrus pulp residues are <5% of the whole fruit residues. In nuts residues in the shell are typically 25 times those in the nut meat, although in a few cases only 3 to 4 times. In almonds the hull residues were of the order of 60 times the level in nut meat.

Processing information was provided on a number of commodities. Washing may remove 20 to 40% of the residues on fruits and an even higher proportion in some cases on citrus fruits. Concentration occurs in some processed fractions, with concentration factors of 1.7 in wet apple pomace, 6 in dry apple pomace, 5 in dry citrus pulp, 6.7 in citrus oil, 4.3 in wet grape pomace, 18 in dry grape pomace, 4.3 in dried grapes, 2.4 in dried prunes, and up to 9 in dried peaches. Residues from GAP applications to grapes are $\leq$0.02 mg/kg in wine or grape juice.

In a number of studies samples were also analysed for residues of the metabolites dihydroxybis(2-methyl-2-phenylpropyl)stannane (SD31723) and 2-methyl-2-phenylpropylstannoic acid (SD33608). The former is with few exceptions $\leq$10% of the fenbutatin oxide residue and the latter usually $\leq$1/2 the level of the SD31723. There is some evidence that the canning process may reduce residues near the MRL to non-detectable levels, at least in stone fruit.

Avocado. There is no MRL for avocado. Because data were available only for the flesh and no GAP was available for the countries in which trials were conducted, the Meeting concluded that information was insufficient to support a limit.

Banana. There is currently no MRL for bananas. Maximum residues reflecting GAP were 6.3 mg/kg at 7 days, 3.4 mg/kg at 2 days and 5.7 mg/kg at 0 days. The GAP PHI is 1 day. Approximately 1-8% of the whole fruit residue has been found in the pulp (maximum level 0.14 mg/kg), although ≤2% is likely to be a more reliable estimate taking into account analytical factors. Although few of the results were exactly at the GAP PHI, residues show little decline over 7 days from application, and the Meeting concluded that data over this period were relevant to estimating a maximum residue level. Because results were available from only one country, the Meeting considered additional data reflecting the GAP of other countries desirable. However, because results were available from three locations in three different years, the Meeting concluded that they were sufficient to estimate a 10 mg/kg limit.

Beans. There is no MRL for beans. Residues in green beans from a single application in a single trial in one country were 0.5 mg/kg after 3 days. Data were available from another country at a slightly exaggerated application rate (75 g ai/hl instead of 50 g ai/hl) from a formulation which is not recognised as GAP. The plot size was only 12 M^2. The Meeting could not recommend a limit for green beans.

Residues in French beans from 2 applications at GAP rates under glasshouse conditions in one country resulted in maximum residues of 0.4 mg/kg after 6 days compared to a GAP PHI of 7 days. At twice the 25 g ai/hl GAP rate residues were 0.15 mg/kg after 7 days. The Meeting concluded that the data were insufficient to support a limit for beans.

Citrus. The CXL for citrus fruits is 5 mg/kg. Although 43 trials were conducted in 5 countries, 3/4 of these were in one country and only 12 of the trials represented current GAP (6 on oranges, 2 on grapefruit, 3 on lemons and one on mandarins). Maximum residues resulting from GAP were 1.5 mg/kg in grapefruit, 2.4 mg/kg in mandarins, 3.3 mg/kg in oranges and 4 mg/kg in lemons, the last at a 21-day PHI compared to the GAP 7 day PHI. Other trials at GAP application rates, but at twice the GAP number of applications resulted in residues up to 14 mg/kg, but generally less than 10 mg/kg. Residues of the metabolite SD31723 were typically 2-10% of the parent compound in whole oranges and in all the fruits the residue of SD33608 tends to be about half that of SD31723.

While additional data reflecting GAP for oranges, grapefruit and mandarins are desirable, the Meeting concluded that the available results were marginally sufficient in a mutually supportive way to confirm the existing 5 mg/kg citrus group CXL for these individual citrus fruits. This does not apply to lemons or limes, because relatively few trials representing GAP were available for lemons. As noted, the highest GAP residue (4 mg/kg) in lemons was at a 21-day PHI compared to a GAP 7-day PHI, and the next highest residue of 2.4 mg/kg was from only single applications whereas two are permitted. The Meeting concluded that additional data reflecting current GAP for lemons and/or limes with the minimum PHI and maximum application rates would be required before a limit could be recommended for lemons or limes or for citrus fruits as a group. Additional data reflecting GAP for oranges, grapefruit and mandarins are also desirable.

The available information from the simulated commercial processing of oranges with field-incurred residues indicates that residues in dry orange pulp are 2-4.6 times those in whole unwashed oranges. Assuming a fivefold concentration and a residue at the 5 mg/kg MRL level in the unprocessed fruit, the maximum dry pulp residue would be 25 mg/kg compared to the current 7 mg/kg limit. Although there is currently no Codex MRL for citrus oil, the 6.6 concentration factor from whole unwashed oranges indicates that an MRL of 30 mg/kg would be needed.

Cucumbers. The CXL for cucumbers is 1 mg/kg. Data were available from 4 European countries (open and glasshouse) and the USA (open), although the US data do not correspond to current GAP. While application rates in the US trials were higher and PHI intervals shorter than required by GAP in Europe, the data are useful for illustrating the dependence of residues on the application rate and giving some indication of differences in residues between 2 and 3 applications. Residues from single applications representing European GAP ranged from 0.03 to 0.3 mg/kg. The Meeting concluded that a 0.5 mg/kg limit was supported.

Egg plant. The CXL for egg plant is 1 mg/kg. Because data were available from only a single glasshouse trial in one country, because no GAP information was provided for that country and because the trials did not conform to GAP application rates or PHIs of neighbouring countries the Meeting concluded that the information was insufficient to support the limit, and recommended its withdrawal.

Gherkins. The CXL for gherkins is 1 mg/kg. Because only summary information from a single glasshouse trial was available, the Meeting concluded that it was insufficient to support the limit, and recommended its withdrawal.

Grapes. The CXL for grapes is 5 mg/kg. Data were available from over 60 supervised trials in 5 countries. Maximum residues of approximately 2 mg/kg resulted from European GAP and 4 mg/kg from US GAP. While US GAP is comparable to that of several European countries, many more US trials were available. The Meeting confirmed the existing 5 mg/kg limit. Currently there is no Codex limit for processed grape products. Because the concentration of residues from grapes to raisins is approximately fourfold, the Meeting concluded that an MRL of 20 mg/kg for raisins would be appropriate, based on 5 mg/kg in the whole fruit. Similarly, concentration of the order of 18 times in dry pomace (or stem waste) supports a limit of 100 mg/kg for dry pomace.

Hops. No MRL is proposed for fenbutatin oxide in hops. Supervised trials data reflecting GAP were available from a single trial in one country, resulting in residues of the order of 5 mg/kg. The Meeting concluded that these data were inadequate for estimating a maximum residue level.

Melons. Currently there is a 1 mg/kg CXL for melons, except watermelons. Although no residues (<0.01 mg/kg) resulted 7 or 14 days after applications at GAP rates in a single trial in one country whose GAP PHI is 3 days, the Meeting concluded that the data were insufficient to support the limit, and recommended its withdrawal.

Nuts. No MRL is established for nuts. Maximum residues of fenbutatin oxide in the nut meats of almonds, pecans, walnuts and filberts from treatments at US GAP application rates, PHIs and number of applications included residues of $\leq$0.02, 0.04, 0.05, 0.13, 0.16, and 0.3 mg/kg (the last at a 1.5-fold application rate). Appreciably more data were provided which were at GAP application rates and PHI, but with 3 applications instead of the maximum 2 per season which is GAP. These included residues of $\leq$0.02 (10); 0.03 (4); 0.04 (2); 0.05; 0.07; 0.08; 0.1; 0.2 (3) and 0.3 mg/kg.

Although there were no side-by-side comparisons, the overall data suggest similar residues from 2 or 3 applications at GAP rates. The Meeting therefore concluded that a 0.5 mg/kg limit could be supported for almonds, pecans, and walnuts. Residues were observed up to 56 mg/kg in almond hulls (an animal feed item).

Data were too limited to support a limit for filberts, for which no GAP information was provided.

Data were also available for metabolites SD31723 and SD33608 with levels of <0.02 mg/kg in nut meats.

Peppers. The CXL for peppers (sweet) is 1 mg/kg. Data were available from two supervised trials. The single application (2 are permitted) in the Belgian trial was outdoors, although the provided Belgian GAP was for glasshouse uses. The Netherlands glasshouse trial was at 0.5 kg ai/ha, which could not be related to the GAP rate of 25 g ai/hl. Although residues in two supervised trials (1 and 0.6 mg/kg after the 3-day PHIs) suggest that residues may not exceed 1 mg/kg from GAP, the Meeting did not consider two data points reflecting GAP sufficient to support the MRL, and recommended its withdrawal.

Pome fruit. The CXLs are 5 mg/kg for apples and pears and 20 mg/kg for dry apple pomace. The data base for pome fruit included 103 supervised trials for apples and 17 for pears. In many trials residues decreased little during 2-3 weeks after application. Maximum residues in apples were 2.9 mg/kg from GAP applications in non-US trials. In US trials the highest residues from GAP applications were 4.3 mg/kg from dilute sprays, 9.6 mg/kg from concentrated SC sprays and 12 mg/kg from concentrated WP sprays, although only three of the many trials on apples were with concentrated sprays at GAP application rates. The two apple trials which resulted in the higher residues were on a different variety from those in other trials, but it could not be concluded that the variety influenced the residue. While the trial plot was a single tree, this was also true of other trials. Higher residues from concentrated spray applications are also suggested by pear trials where maximum residues reflecting US GAP were 2.3 mg/kg for dilute sprays and 5.6 and 3 mg/kg for WP and SC concentrated spray applications respectively. These dilute and concentrated spray applications were all on the same variety of pear.

While the Meeting concluded that the current 5 mg/kg Codex limit is adequate for dilute spray applications, it would not accommodate the USA concentrated spray uses. The Meeting concluded that additional data reflecting GAP would be needed to accommodate these.

The Codex limit for dry apple pomace is 20 mg/kg to accommodate the current 5 mg/kg limit on apples (fourfold concentration factor). Concentration and reduction factors in apple processed products estimated from studies provided to this Meeting varied, depending on the study: juice (unclarified) 0.6 times, wet pulp 1.7-3.5 times, and dry pulp 6-12 times. Clearly the fourfold factor previously used by the JMPR is too low in view of this information. Putting greater weight on the most comprehensive processing study provided, the Meeting concluded that for estimating maximum residue levels a factor of 7 would be reasonable for whole fruit to dry pomace. With an MRL of 5 mg/kg and a concentration factor of 7 a 40 mg/kg limit can be recommended for dry apple pomace.

Raspberries. No MRL exists. Supervised trials information was available for only one country, for which no GAP information was provided and the GAP of other countries could not be used. The Meeting concluded that insufficient information was available to estimate a maximum residue level.

Soya beans. Because residue results (<0.01 mg/kg) were available from only three supervised trials in a single country 67-80 days after application compared to the GAP 7-day PHI, and because analytical recoveries by analytical method SAMS 345-1 were highly variable at a 0.2 mg/kg fortification level (50-110%), the Meeting concluded that data reflective of GAP were insufficient to support a limit.

Stone fruit

Forty-seven studies from 8 countries were available for stone fruit, representing 76 supervised trials. Most of the results referred to de-stoned fruit. No attempt was made to calculate residue in the whole fruit including stone, since average stone weights were only about 6% of the whole fruit weight.

Cherries. The CXL is 5 mg/kg. Maximum residues reflecting approximate GAP in Germany were 0.6 mg/kg and in the USA 5.1 mg/kg (whether results were adjusted for 69% recoveries was not stated). If not corrected, a maximum residue of 7.4 mg/kg would be indicated. Other US data also did not indicate whether corrections had been made for low recoveries. If not, other residues when adjusted for recoveries would be of the order of 7 mg/kg. Results from The Netherlands data did not reflect the national 42-day PHI. However, the residues up to 1.2 mg/kg were from applications consistent with German or Italian GAP PHIs, although German GAP was reported to be due to expire in 1993. Maximum residues of SD31723 were 0.9 mg/kg and SD33608 0.04 mg/kg from GAP. The former was ≤25% of the fenbutatin oxide residue and SD33608 is usually less than half of the level of SD31723.

The Meeting was particularly concerned at the lack of information on whether results from several US studies (the major portion of the data base) were corrected for analytical recoveries less than 70% (58% in one case), and at the information that German reregistration is to expire in 1993 (the German GAP is relevant to other European trials for which no GAP was provided). The Meeting concluded that a 10 mg/kg limit could be supported for cherries.

Peaches, nectarines. The CXL is 7 mg/kg. Maximum residues in peaches reflecting approximate GAP in Australia were 2.5 mg/kg, and in the USA 8 mg/kg from a 1.5-fold rate (5.3 mg/kg adjusted to the GAP rate) and up to 5.8 mg/kg from approximate GAP rates, but with 3 instead of the permitted 2 applications. Residues were up to 3.5 mg/kg in two US trials reflecting GAP on nectarines. Maximum peach residues were 0.8 mg/kg in Canada at US GAP rates; 1.3 mg/kg in France at German GAP rates; and 3.3 mg/kg in Germany. Three trials in South Africa also resulted in residues up to 3.1 mg/kg after 10 days and 4 mg/kg after 13 days (14 day-PHIs are common in other countries) at application rates which are GAP in other countries, although GAP information for South Africa was not provided. Residues were up to 6 and 7.8 mg/kg after 13 and 10 days respectively at higher application rates. The Meeting concluded that the data supported the current 7 mg/kg limit for peaches and in a mutually supportive way could support a limit at the same level for nectarines.

Plums. The CXL is 3 mg/kg. Maximum residues approximating GAP were: German trials 0.7 mg/kg; United States trials 2.1 mg/kg; Netherlands trials <0.1 mg/kg. No GAP information was available for South Africa. Residues were 0.9 and 1 mg/kg after 14 days. From GAP applications, maximum residues of SD31723 were 0.07 mg/kg and of SD33608 0.04 mg/kg. SD31723 is usually <5% of the fenbutatin oxide residue and SD33608 is similar to or lower than SD31723. Control values for fenbutatin oxide range from <0.01 to 0.1 mg/kg, depending on the analytical method used.

Although recoveries in some US trials were below 70% and no information was provided on whether the results were corrected, recoveries were acceptable in the trial with the highest GAP residue (2.1 mg/kg). Furthermore, assuming that the results in the trials with low recoveries are uncorrected, maximum residues would be about 2.2 mg/kg. The Meeting concluded that the data were sufficient to support the CXL for plums.

There is no MRL for prunes (dried plums). Data provided indicate that fenbutatin oxide residues are concentrated in drying plums by a factor as high as 2.5. Applying this to the 3 mg/kg limit for fresh plums would imply an MRL of 7.5 or 10 mg/kg for dried prunes.

Residue levels in dried plums from trees treated in accordance with GAP were provided, although no data were included for the fresh fruit from which a concentration factor could be estimated. Maximum residues were 3.1 mg/kg. Analytical recoveries for this study were only 55% and it was not indicated whether the result had been corrected for the low recovery. If not, a residue of 5.7 mg/kg would be indicated. This would be consistent with the theoretical 7.5 mg/kg estimated above.

Strawberries. The CXL is 3 mg/kg. Twenty-seven reports were available from 7 countries

representing 47 supervised trials (32 from the USA). Data from two countries could not be related to the available GAP. Maximum residues approximating GAP were 1.3 mg/kg from Australian trials, 0.4 mg/kg from French trials, 0.5 mg/kg from UK trials, and 7 mg/kg from Mexican trials (based on US GAP). The more numerous US trials resulted in a fairly continuous distribution of residues, except for two values, up to 9.9 mg/kg (the last from a 1.2-fold application rate). The exceptions were at one site with residues of 12 and 18 mg/kg. Because information on the project history for these trials was in question and because the residues (especially 18 mg/kg) were not consistent with those found in numerous other similar trials, even at exaggerated rates, the Meeting gave little weight to these two values.

Maximum residues from GAP of the metabolites SD31723 and SD33608 were respectively 0.1 and 0.05 mg/kg after 1 day. Generally residues of SD31723 were ≤5% of fenbutatin oxide residues and SD33608 residues were about half or less of the SD31723 residues (after one day). The Meeting concluded that the data supported an increase in the current 3 mg/kg CXL to 10 mg/kg.

Tomato. The CXL is 1 mg/kg. Four of the 12 supervised trials were according to GAP, and the maximum residues in these: Denmark 0.4 mg/kg (glasshouse); Italy 0.3 mg/kg (field); the UK 0.3 mg/kg (glasshouse). Although results were available from 3 additional countries, they could not be related to the GAP information provided. Residues were up to 0.8 mg/kg after 3 or 4 days in two trials that could not be confirmed to reflect GAP. No tomato processing data were provided. No residues (<0.1 mg/kg) of metabolite SD31723 were found in the two trials in which it was determined.

The Meeting concluded that the data were adequate to confirm the current limit for tomatoes, but only for glasshouse uses.

Animals. Feeding studies with labelled fenbutatin oxide at 34 ppm dietary feeding levels indicate that the greatest potential for residues is in the kidney and liver of cattle, with possible low residues in muscle. Conventional feeding studies were also conducted at 11 or 96 ppm in the cattle diet for 21 or 22 days. No residues (<0.02 mg/kg) were found in milk, cream or tissues from the lower feeding level. Residues of fenbutatin oxide were found in all cream and tissue samples from the higher feeding level, while SD 31723 was found only in the liver and kidney. SD 33608 was not detected in any sample (<0.02 mg/kg).

Depending on the assumptions used, a dietary intake of the order of 20 ppm could be estimated, about twice the level in the lower feeding level trial. Adjusting data from the highest feeding level trial to a 20 ppm dietary burden results in maximum fenbutatin oxide residues in liver of 0.02, kidney 0.05, fat of meat 0.01, muscle 0.01 and milk fat 0.05 mg/kg.

Again depending on what assumptions are made, a case could be made for a slight lowering of the previously estimated 0.2 mg/kg limits for liver and kidney, but since the levels are not much greater than the validated limits of determination for these organs, and because more than one of the feed items could be fed at one time, the Meeting concluded that the liver and kidney limits previously estimated for cattle, goats, pigs, horses and sheep could be confirmed. They have been combined under a new proposal at the same level for edible offal.

The Meeting had some reservations about the previous estimates for cattle meat and milk of 0.02 mg/kg at the limit of determination. There was no evidence that the levels would be exceeded in practice, but the analytical method had not been validated below 0.1 mg/kg for any animal matrix in studies provided to the Meeting. For this reason the Meeting recommended increasing the stated limits of determination and hence the MRLs for these commodities to 0.05 mg/kg and limits for the meat of cattle, dogs, horses and sheep have been combined at the same level as a new proposal for meat.

The Meeting also observed that residues of SD 31723 can be about twice those of

fenbutatin oxide in cattle liver. Because residues of fenbutatin oxide are found in liver and because it is the only matrix in which SD 31723 exceeds fenbutatin oxide, the Meeting concluded that definition of the residue solely as fenbutatin oxide is satisfactory.

Residues in skim milk and cream indicate a propensity for fenbutatin oxide to accumulate in lipid rather than aqueous media, but levels in muscle do not differ from those in mesenteric or subcutaneous fat sufficiently to regard fenbutatin oxide as a fat-soluble pesticide.

Feeding chickens at 5 ppm dietary levels produced no residues of fenbutatin oxide or its two metabolites in tissues or eggs, except 0.02 mg/kg fenbutatin oxide in two whole egg samples. From the 25 ppm dietary feeding level the maximum residues of fenbutatin oxide were 0.04 mg/kg in liver, 0.03 mg/kg in kidney and 0.12 mg/kg in whole eggs. These decreased to <0.02 mg/kg in liver and kidney 3 days after cessation of feeding, but the decrease was slower in whole eggs. No residues of either parent compound or metabolites were found in other tissues or organs. As in the case of cattle, residues of SD 13723 were greater than those of fenbutatin oxide in liver (3 to 5 times as high in this case) and residues of SD 33608 were generally comparable to those of the parent compound.

If it is assumed that the greatest dietary intake from feed items for which there are MRLs would be from dry grape pomace (100 mg/kg MRL) and that it is fed at a maximum of 5% of the diet, a dietary intake of approximately 5 ppm can be estimated. Maximum fenbutatin oxide residues of 0.02 mg/kg in whole egg from the 5 mg/kg feeding level and 0.12 mg/kg from the 25 ppm level support 0.02 mg/kg as a maximum residue level for whole eggs. While SD 317243 might occur near 0.02 mg/kg in liver (0.12 mg/kg from 25 ppm feeding), residues of fenbutatin oxide *per se* would not be expected to be above 0.02 mg/kg. Although residues would be likely not to exceed 0.02 mg/kg in whole eggs, kidney or liver, the same considerations as those mentioned above regarding the levels of method validation for cattle products led the Meeting to conclude that a limit of 0.05 mg/kg (not a limit of determination, because residues around 0.02 mg/kg may occur) would be more appropriate in whole eggs and 0.05 mg/kg (as a limit of determination) in liver and kidney. There would be no compelling need for a limit in poultry meat or fat. Because limits are proposed for eggs and chicken edible offal, 0.05 mg/kg is recommended for chicken meat as a limit of determination level.

Only one of the two analytical methods used in the supervised trials was provided, although the principles were summarized and recoveries and limits of detection were usually provided with field trials data. The two basic methods were both described in earlier monographs. The first is based on chloro-derivatization in a solvent containing HCl followed by GLC determination. The second (e.g. method MMS-R-494-1 provided to the Meeting) includes methylation of fenbutatin oxide, SD 31723 and SD 33608 with methyllithium and determination by GLC with flame-photometric detection of tin. In general determination at 0.02 to 0.05 mg/kg of each compound in cream, 0.1 mg/kg of each in cow liver, and 0.1 to 0.2 mg/kg SD 31723, 0.05 mg/kg SD 33608 and probably $\geq$0.1 mg/kg parent compound in grapes appears to be supported by sample chromatograms. Recoveries from the various substrates were generally $\geq$80%, but at near MRL levels, especially for fenbutatin oxide.

The submitted method may be adequate for regulatory analysis at proposed MRL levels, although submission of all of the analytical methods with sufficient information to permit estimation of the limits of determination and of any information on multi-residue methods suitable for enforcement is desirable.

A proposed liquid chromatographic procedure was also provided, but it was not validated sufficiently for the Meeting to recommend its use.

FURTHER WORK OR INFORMATION

Desirable

1. Information on whether residues in US stone fruit trials in 1993 Monograph Table 8 references 5,6,7,9 (cherries), 21, 23, 24, (plums), and 29, 30 (peaches), were corrected for analytical recoveries.

2. Information on South African GAP for the use of fenbutatin oxide on peaches.

3. Submission of the analytical methods used in the supervised field trials and in the cow feeding study TIR-26-119-73, with validation information.

4. Current information on analytical methods suitable for enforcement for both plant and animal foods, including multi-residue methods.

5. Current information on the stability of residues in stored analytical samples.

6. Current information on the fate of residues in poultry, plants, soil and water/sediment systems. Metabolism studies on rats, goats and hens reportedly submitted to WHO are specifically requested .

7. Information on residues in food in commerce or at consumption.

8. Information on the interval between the last feeding and slaughter in cow feeding study TIR-26-119-73 (Koos, 1973).

9. Submission of Report 22-112-74 (on the fate of residues), referenced in Potter and Nugent (1978), as the basis for analyses of animal products for fenbutatin oxide, SD 31723 and SD 33608.

10. Additional pome fruit data reflecting US concentrated spray GAP.

11. Tomato processing information.

4.21 FENPROPATHRIN (185)

(*RS*)-á-Cyano-3-phenoxybenzyl-2,2,3,3-tetramethylcyclopropanecarboxylate

Fenpropathrin was considered for the first time by the present Meeting. It is an ingestion and contact synthetic pyrethroid insecticide and acaricide formulated as an EC and used against various species of Acari, Aleyrodidae, Aphididae and Lepidoptera on cotton, grapes, ornamentals, fruits, vegetables and other field crops. Most countries approve a range of application rates (e.g. apple: 0.06 kg ai/ha, 2 applications in Hungary - 0.45 kg ai/ha, 8 applications in the USA). Normally, the effects of a treatment last for 3 -4 weeks.

TOXICOLOGY

After oral administration of fenpropathrin to rats, the compound was almost completely absorbed and eliminated in urine and in faeces. The major biotransformation reactions consist of oxidation at the methyl groups of the acid moiety and at the 2′- and 4′- positions of the alcohol moiety, and cleavage of the ester linkage followed by glucuronide, sulphate or glycine conjugation.

Fenpropathrin has been tested for acute toxicity and it has been classified as moderately hazardous by WHO.

In a short-term feeding study in rats conducted at dietary concentration levels of 0, 3, 30, 100, 300 or 600 ppm over thirteen weeks, the NOAEL was 300 ppm, equal to 17 mg/kg bw/day, based on reduced body-weight gain and the appearance of clinical signs at higher dose levels. In a second 13-week rat study the NOAEL was 150 ppm, equal to 8 mg/kg bw/day, based on depression of body-weight gain at higher dose levels.

A one-year study in dogs conducted at dose levels of 0, 100, 250 or 750 ppm revealed an NOAEL of 100 ppm, equal to 3 mg/kg bw/day, based upon reduced body weight gain and clinical signs (emesis, tremors) at 250 ppm.

A long-term toxicity/carcinogenicity study was performed in mice over 104 weeks at 0, 40, 150 or 600 ppm. The NOAEL was 600 ppm the highest dose tested, 600 ppm, equal to 56 mg/kg bw/day. There was no evidence of carcinogenicity.

In a long-term toxicity/carcinogenicity study in rats conducted at dietary concentrations of 0, 1, 5, 25, 125 or 500 ppm over two years, the NOAEL was 125 ppm, equal to 5 mg/kg bw/day, based on depression in body-weight gain at 500 ppm. There was no evidence of carcinogenicity.

A second long-term toxicity/carcinogenicity study in rats performed at dietary concentrations of 0, 50, 150, 450 or 600 ppm over two years revealed an NOAEL of 150 ppm, equal to 7 mg/kg bw/day, based on the appearance of clinical signs at higher doses. There was no evidence of carcinogenicity.

In a multigeneration reproduction study in rats fenpropathrin was administered at dietary levels of 0, 5, 25 or 250 ppm. The NOAEL was 25 ppm, equal to 1.6 mg/kg bw/day, based on decreased pup weights in the F_{3A} generation at 250 ppm.

In a second multigeneration reproduction study conducted at dose levels of 0, 40, 120 or 360 ppm, the NOAEL was 40 ppm, equal to 3 mg/kg bw/day, based on depression of body-weight gain, increased mortality in females and the occurrence of tremors in pups at 120 ppm and above.

Two oral teratogenicity studies in rats were performed at dose levels of 0, 0.4, 2 or 10 mg/kg bw/day and 0, 0.4, 1.5, 2, 3, 6 or 10 mg/kg bw/day. The NOAELs were 2 and 3 mg/kg bw/day in the two studies, respectively, with respect to maternotoxic effects and 10 mg/kg bw/day in both for embryotoxicity and teratogenicity.

In an oral teratogenicity study in rabbits at dose levels of 0, 1.5, 3 or 6 mg/kg bw/day, the NOAEL was 6 mg/kg bw/day. In a second study with oral doses of 0, 4, 12 or 36 mg/kg bw/day the NOAEL was 4 mg/kg bw/day with respect to maternal toxicity.

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

On the basis of studies in hens and rats, fenpropathrin exhibited no potential for delayed neurotoxicity.

Data on observations in humans were not suitable for the estimation of an acceptable daily intake.

An ADI of 0-0.03 mg/kg bw was established, based upon an NOAEL of 3 mg/kg bw/day in

the multigeneration reproduction study in rats, the teratogenicity studies in rats and the one-year feeding study in dogs, using a safety factor of 100.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels causing no toxicological effect

Mouse: 600 ppm, equal to 56 mg/kg bw/day (104-week study)

Rat: 150 ppm, equal to 7 mg/kg bw/day (104-week study)
40 ppm, equal to 3 mg/kg bw/day (reproduction study)
3 mg/kg bw/day (maternal toxicity in teratogenicity study)

Rabbit: 4 mg/kg bw/day (maternal toxicity in teratogenicity study)

Dog: 100 ppm, equal to 3 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Residue data from supervised trials on apples, cotton seed, gherkins, grapes, pears and tomatoes were supplied to the Meeting. No data on cucumber were received.

The major biotransformation reactions of fenpropathrin in animals consist in oxidation at the methyl groups of the acid moiety and at the 2_ and 4_ positions of the alcohol moiety, cleavage of the ester linkage and conjugation of the resultant carboxylic acids and alcohols with glucuronic acid, sulphuric acid and glycine.

Studies in plants with radio-labelled fenpropathrin demonstrate that in fruit fenpropathrin itself is the primary component of the residues, whereas in leaves degradation products constitute the greater part of the residues. The major metabolic reaction of fenpropathrin in plants has been found to be the rupture of the ester linkage followed by oxidation to produce 3-phenoxybenzoic acid (PB acid) and the corresponding alcohol and aldehyde. From the acid side of the molecule, the main metabolite is 2,2,3,3-tetra-methylcyclopropanecarboxylic acid (TMPA) and this compound can give rise to 2-hydroxymethyl-2,3,3-trimethyl-cyclopropanecarboxylic acid (TMPA-CH_2OH) and 5-hydroxymethyl-6,6-dimethyl 3-oxabicyclo-[3.1.0]hexan-2-one (TMPA-CH_2OH lactone) by subsequent hydroxylation. Also PB acid can be hydroxylated at the 4′ position and the parent molecule at the 2′ or 4′ position. The hydroxylated derivatives exist in both free and conjugated forms. Breakdown products in plants did not differ greatly from those in animals. The residues of the main metabolites PB acid and TMPA in samples from supervised field trials constituted only a negligible proportion of the total residues. It is therefore considered appropriate to define the residue in crops as the parent compound.

The fate of fenpropathrin in the soil will be influenced by a combination of photo degradation and microbiological processes. It is unlikely that fenpropathrin will remain in the soil long

enough for residues to survive and affect succeeding crops. Metabolites do not accumulate in soil. Fenpropathrin is strongly adsorbed by soils, and when used as recommended will not contaminate ground water. Examination of plants grown on treated soils showed only extremely small uptake of radioactivity.

The residue data from supervised trials were evaluated as follows.

Apple. Results of 19 US trials with a maximum application rate of 0.45 kg ai/ha, a 14-day PHI and a maximum of 8 applications showed that the residues were below 5 mg/kg in whole fruit (minimum 0.06 mg/kg, maximum 4.5 mg/kg, estimated maximum residue level 5 mg/kg).

Pear. The maximum level observed in pears treated according to anticipated approved uses was 3.2 mg/kg in whole fruit in the State of Washington, USA, where the spray concentration was 0.024%, the application rate 0.9 kg ai/ha, the PHI 14 days and the crops were subjected to a total of 6 applications. In 15 supervised US trials within GAP based on 0.45 kg ai/ha, 0.012%, a 14-day PHI and 8 applications all residues were below 5 mg/kg (minimum 0.58 mg/kg, maximum 2.9 mg/kg; estimated maximum residue level 5 mg/kg).

Grapes. The maximum GAP was in US trials. There were 4 trials within GAP (0.45 kg ai/ha, a 21-day PHI and 4 applications; minimum 0.84 mg/kg, maximum 2.6 mg/kg; estimated maximum residue level 5 mg/kg) and 18 trials using 0.22 kg ai/ha, with a PHI of 21 days and also 4 applications. It is considered that residue levels from applications based on accepted use recommendations would normally fall below 5 mg/kg.

Gherkin. Residues in samples from 4 supervised German trials using an application rate of 0.08 kg ai/ha , a 3-day PHI and 3 applications did not exceed 0.1 mg/kg (minimum <0.01 mg/kg, maximum 0.1 mg/kg; estimated maximum residue level 0.2 mg/kg).

Peppers, Sweet. Residues from outdoors supervised trials based on 3 applications of 0.01% and a 0-1-day PHI in Japan and Spain ranged from 0.2 mg/kg to 1.2 mg/kg (estimated maximum residue level 1 mg/kg). Spanish residues (indoors, 7-day PHI) ranged from 0.04 to 0.38 mg/kg and for a 2-day PHI from 0.34 to 0.52 mg/kg.

Tomato. The highest levels were seen in four Japanese studies, because GAP in Japan allows an application rate of 0.25 kg ai/ha and a one-day PHI. One figure exceeded 1 mg/kg. Residue results of 5 outdoor and 8 indoor supervised trials in Germany with a lower application rate of 0.08 kg ai/ha show that 3 days after the last application residues were all below 0.6 mg/kg. (Outdoors: minimum <0.01 mg/kg, maximum 0.37 mg/kg. Indoors: minimum <0.01 mg/kg, maximum 0.46 mg/kg; estimated maximum residue level 1 mg/kg).

Egg plant. Residues from 4 Japanese trials based on 3 - 5 applications of 0.01% and a 1-day PHI were low (minimum 0.12 mg/kg, maximum 0.19 mg/kg; estimated maximum residue level 0.2 mg/kg).

Cotton seed. A well-known factor that can influence the level of residues in cotton seed is whether an appreciable number of bolls have opened at the time of the last application. If not, residues in the seed are usually very low but if there is direct contact between the insecticide spray and the seed, residues can reach measurable levels. In considering the MRL needed it is important that it should be high enough to include cases where the last application was to plants with a comparatively high proportion of open bolls. It was possible to use 26 trials with an application rate of 0.22 kg ai/ha, 8 - 11 applications and a PHI of 18 - 22 days (minimum residues <0.01 mg/kg, maximum 1 mg/kg; estimated maximum residue level 1 mg/kg).

Residues in food of animal origin

Cattle. Residues in whole milk when a plateau level had been reached were approximately

0.15% of the level in the feed. If cows were fed on a diet consisting entirely of dried apple pomace at the postulated maximum residue level of 45 mg/kg (see processing of apples, below), it could be argued that the maximum level in milk would be 0.07 mg/l. Assuming that these residues would all be present in the fat and that the fat content of the milk would be 4%, such a level would be equivalent to 1.8 mg/kg in the milk fat. An animal transfer study showed levels in body fat to be approximately 1.4% of the level in the feed. Using the apple pomace figure of 45 mg/kg, it is reasonable to conclude that residues in meat fat would not exceed 0.6 mg/kg. Based on similar arguments and the data from the same studies, residues in meat (muscle) were about 0.08% of the feed level so that animals fed on apple pomace at 45 mg/kg would not be expected to have more than 0.05 mg/kg in muscle, kidney or liver.

Poultry. Poultry are unlikely to receive dietary items containing appreciable residues of fenpropathrin with the possible exception of cotton seed meal. With a maximum level of 1 mg/kg in raw cotton seed, it is unlikely that residues in meal would exceed 0.1 mg/kg. With a total feed level of 2.5 mg/kg, the level in fat reached only 0.02 mg/kg so that measurable residues would not be expected in the eggs, meat or edible offal of poultry fed on cotton seed meal.

In processing

In fruits the residues are essentially surface residues. As would be expected juice extraction leaves the great majority of the residues in the solids. In the case of dry apple pomace the data suggest a maximum concentration factor of 9, so that residues in dry apple pomace would not be expected to exceed 45 mg/kg on the basis of a maximum residue level in whole apples of 5 mg/kg.

As would be expected, raisins have higher residues than the raw grapes. The highest concentration factor in the trials is about 3. Using this factor and assuming that residues in raw grapes will not exceed 5 mg/kg, it would seem reasonable to estimate that residues in raisins would not exceed 15 mg/kg.

Dry grape pomace contained between 2 and 7 times the residue level in the original grapes. If the highest level in raw grapes is 5 mg/kg, the highest level to be expected in dry grape pomace would be 35 mg/kg.

Processing grape juice into wine appears to reduce residue levels still further and although strictly comparable data are only rarely available, residues of fenpropathrin have not been found above the limit of determination in wine, whereas in juice the highest level found was 0.06 mg/kg, which disappeared during vinification. In this particular case residues in the raw grapes were up to 5.6 mg/kg, so that even at this high level measurable residues did not survive in the wine.

As would be expected from the lipophilic nature of fenpropathrin, residues in oil obtained from cotton seed are higher than in the raw seed by roughly the inverse proportion of oil weight to seed weight. The residues in the meal ranged from 0.01 to 0.09 mg/kg. Residues in soapstock were about twice the level in the raw seed and residues in the refined oil were in the region of three times the seed level. Assuming a maximum level in raw cotton seed of 1 mg/kg, it can reasonably be concluded that residues in soapstock will not exceed 2 mg/kg and in oil 3 mg/kg.

Stability of stored analytical samples

In stability studies carried out on apples, pears, grapes, oranges, cotton seed, eggs and kidney of cattle over periods from 3-12 months there was no evidence of a decline in residue levels of fenpropathrin during storage at -20^{o}C.

Methods of residue analysis

Methods of analysis used GLC with an EC detector after solvent extraction of the substrate and clean-up by either silica gel or Florisil column chromatography. The limit of determination in most crop samples is between 0.005 and 0.01 mg/kg.

4.22 FENTIN (040)

RESIDUE AND ANALYTICAL ASPECTS

Fentin was last evaluated in 1991. The proposed limit of 1 mg/kg for dry hops was discussed at the 1993 CCPR (ALINORM 93/24A) and the delegation of France promised to send written comments which were considered by the Meeting.

The Meeting's attention was drawn to some printing errors in Table 7 (1991 Evaluations p.346) where the residue in dry hops was shown as <1.01 mg/kg instead of <0.01 mg/kg for reports A23619 and A23616, and <1.0 mg/kg instead of 10 mg/kg for the two trials from 1989 (Report No. A44068).

As the compound is applied before flowering according to GAP no residue would be expected in green hops at harvest. The Meeting therefore considered that the levels of 10 mg/kg of report A44068 were inconsistent with the other data. On the basis of the corrected residues in dry hops the Meeting concluded that a level of 0.5 mg/kg should not be exceeded when the compound is used in accordance with GAP.

4.23 FLUCYTHRINATE (152)

RESIDUE AND ANALYTICAL ASPECTS

Flucythrinate was reviewed for residues by the 1985, 1987, 1988, 1989 and 1990 Meetings. The 1985 JMPR listed additional data for a number of crops and information regarding likely residues in animal products as desirable. MRLs for these commodities have been retained at step 7, as have limits for maize forage and fodder. The 1990 JMPR required full documentation of data which were submitted only in summary form for citrus, cucumber, green beans and peppers. That Meeting did not evaluate summary information submitted on residues in animal products in the absence of the full reports. The present Meeting reviewed submissions made in response to the 1990 requirements, additional data for crops with and without current or proposed MRLs, and a re-submission of summary information on animal residues.

Green beans. Submission, as requested, of detailed reports on green bean trials provided only in summary to the 1990 JMPR reveals that the data are the same as the Egyptian data reviewed by the 1985 JMPR. The two values of 0.14 and 0.22 mg/kg after 3 days are consistent with reported Spanish GAP, but the Meeting concluded (as apparently did the 1985 JMPR) that the data were insufficient to support an MRL for green beans.

Brassica vegetables. There are no outstanding issues concerning the CXLs of 0.5 mg/kg for head cabbages and 0.2 mg/kg for flowerhead brassicas (broccoli, cauliflower). The Meeting received data on broccoli and Brussels sprouts which were reviewed by the 1985 JMPR and which did not need further review. New data were also received for red, white and Savoy cabbages. With maximum residues of 0.37 mg/kg from applications within Spanish GAP, no change in the current limits was required.

Citrus. Data reviewed by the 1985 JMPR from trials in Egypt (not GAP) and Japan were re-

submitted, together with additional detail and GAP information for Japan and Spain. While the data suggest that residues are unlikely to exceed 2 mg/kg from GAP, the Meeting concluded (as implicitly did the 1985 JMPR) that data reflecting GAP in additional countries are needed to support an MRL for a major crop such as citrus. Processing studies would also be needed.

Cotton seed. Summary data reported from supervised trials in the United States and apparently not previously reviewed by the JMPR indicate residues well below the 0.1 mg/kg CXL. The Meeting concluded that there was no need to request the complete studies nor to revise previous estimates.

Cucumber. Submission of detailed reports as requested by the 1990 Meeting reveals that the data are the same as the Egyptian data reviewed by the 1985 JMPR. While the detailed reports indicate that the maximum residues of <0.05 mg/kg are consistent with reported Spanish GAP (3-day PHI) for cucurbits, the manufacturer could not confirm that the use is GAP on cucumbers anywhere. The Meeting concluded (as apparently did the 1985 JMPR) that the data were too limited to support an MRL.

Peppers. Submission, as requested by the 1990 JMPR, of detailed reports indicate that the summary data provided to that Meeting are the same as the Italian data reviewed by the 1985 JMPR. While the detailed reports indicate that the 0.14 and 0.13 mg/kg values after 4 days should be within Spanish GAP, the Meeting concluded (as apparently did the 1985 JMPR) that the data were too limited for estimating MRLs.

Tomatoes. There were no questions on the 0.2 mg/kg CXL recommended by the 1985 JMPR. The re-submitted studies had been previously reviewed.

Cattle meat and milk; goat meat. The current 0.5 mg/kg limits for the meat of cattle and goats and the 0.1 mg/kg limit for cattle milk have been retained at Step 7 by the CCPR pending submission of adequate animal feeding studies representative of feeding levels likely to occur in practice. Government comments provided to the Meeting proposed deletion of these limits with the view that available information was based on feeding levels irrelevant to actual animal intakes. The manufacturers again submitted discussion points and summary information previously provided to the 1990 JMPR, which required submission of the detailed reports from which the summary information was taken. This information was not available to the Meeting.

The Meeting considered likely levels in commodities which could be used as animal feed items and agreed that the maximum dietary intake for cattle was unlikely to exceed 5 mg/kg, and in practice would probably be lower. Assuming this level, using the available feeding data summary, and assuming that residues in the animal products vary linearly with their levels in the feed from the 13 to 100 ppm levels fed experimentally down to the postulated 5 ppm, maximum residues of the order of 0.08 mg/kg in the fat of meat of cattle and goats and 0.1 mg/kg in milk could be estimated. This would suggest that the previously estimated levels of 0.5 mg/kg in the fat of meat and 0.1 mg/kg in milk would be adequate.

The summary information and comments provided to the Meeting provide greater insight into likely residues in animal products. However in the absence of the detailed reports from which the transfer data were summarized, and in view of the fact that the fat-solubility of flucythrinate leaves the potential for residues in animal tissues and milk, the Meeting recommended that the temporary limits for the meat and milk of cattle and goat meat should be withdrawn.

4.24 FLUSILAZOLE (165)

RESIDUE AND ANALYTICAL ASPECTS

Flusilazole was previously reviewed for residues by the 1989, 1990 and 1991 Meetings. The present Meeting reviewed information provided in response to the 1991 JMPR requirement for additional GAP and residue data to confirm the 0.1 mg/kg temporary estimate for peaches and nectarines, and information listed as desirable on grapes, details of wheat grain freezer storage studies, stability of metabolites in freezer-stored grain samples, hen metabolism, metabolites in grain processed fractions and soil studies. Additional residue data on pome fruit, grapes and cereals (although there were no outstanding residue data requirements on these commodities) and new data on sugar cane were also provided.

Fate of residues in animals. Several reports on hen metabolism were provided. Some had been submitted before and some, including the requested study by Smyser, were new. Only the Smyser report included data in need of review by the Meeting.

The report basically combines and summarizes information in two previously reviewed reports and provides further clarification of the residues of metabolites, especially in terms of the percentage of the total radioactivity in poultry tissues and eggs, for both the phenyl and triazole labels. It confirms previous JMPR conclusions that bis(4-fluorophenyl)(methyl)silanol (IN-F7321, the methyl silanol) and 4-fluorophenyl(methyl)silanediol are the predominant residues in poultry tissues and eggs arising from the phenyllabelled compound and that triazole is the main residue from the triazole label, except in fat where flusilazole is the primary residue from the triazole label.

The report does not effectively answer questions raised by the 1989 and 1991 Meetings concerning differences in residues found between ruminant and poultry metabolism and feeding studies. The Meeting noted and agreed with the 1991 JMPR conclusion that these differences probably result largely from the more detailed residue characterization and identification in the poultry studies than in the ruminant studies. The Meeting also agreed with the 1991 JMPR that although all questions have not been completely answered, the nature of the residue in animal products can be considered to be reasonably well understood in view of the low residues expected (especially for flusilazole) in animal products.

Soil dissipation. The Meeting reviewed the final report of a 3-year soil dissipation study (4 applications per year) for which an interim report was reviewed by the 1989 JMPR. It confirms the 1989 observations that over 92% of the radioactivity is confined to the top 8 cm of soil over the test period, and that the predominant residues in this segment are flusilazole and its silanol metabolite IN-F7321. The author cites statistical evaluation of the data to support the view that residues will reach a steady level at 57% of yearly application levels after repeated application levels under worst-case conditions.

The report cites the steady-state conclusion, the strong adsorption to the top layers of soil, the lack of residues exceeding 0.01 mg/kg in the 24-36 cm soil depths and the weak leaching potential indicated in other studies as evidence that residues in ground water were unlikely. While the data indicate that over 92% of the radioactivity remains in the top 8 cm of the silt loam soil investigated, and indeed that residue levels are extremely low in the 24-36 cm depths, it also shows an increasing penetration by low levels of radioactivity over the test period in this soil type. The identity of these residues in the deeper soil segments was not indicated.

While the adsorption of this persistent pesticide to soil is strong, the 1989 JMPR had noted that uptake of low residue levels can occur in rotational crops and that the leaching potential would be less for silt loams (as in this study) than for more sandy soils. Because the silt loam study was under worst-case conditions (bare ground, repeated applications) and was consistent with reassuring findings of a number of other relevant studies, the Meeting accepted that ground water residues from silt loam soils were unlikely.

Freezer storage stability. Instead of details of a previous 36.5-month study for the parent

compound only, the Meeting was provided with a new 11-month freezer storage study of flusilazole and its metabolites in wheat grain and straw. While the results suggest that about 30% of 0.3 mg/kg residues of the parent compound and its phenyl metabolites in grain and straw are lost after various storage intervals up to 11 months, the variability in the recoveries of freshly fortified samples indicates that the apparent losses are probably as much the result of analytical variability as actual storage losses. The Meeting concluded that the data demonstrated adequate stability of flusilazole and the metabolites IN-7321, 1,1,3,3-tetrakis(4-fluorophenyl)-1,3-dimethyldisiloxane (IN-G7072), 2-fluoro-5-[(4-fluorophenyl)(methyl)(1-*H*-1,2,4-triazol-1-ylmethyl)silyl]phenol (IN-37722) and 2-fluoro-5-[(4-fluorophenyl)(hydroxy)(methyl)silyl]phenol (IN-37738) (presumably unconjugated) over 11 months under the conditions of the study.

The 11-month storage interval compares with sampling-to-laboratory-receipt intervals ranging from 2 to 15 months in cereal grain trials from which data were reviewed by the 1989 JMPR. The Meeting did not know the actual sampling-to-analysis intervals for the data reviewed in 1989, although according to the 1989 monograph all samples were generally stored at -20°C.

Cereals. The original 1989 JMPR estimates of maximum residue levels of 0.1 and 2 mg/kg respectively for cereal grains and straws or fodders (dry) were based on maximum residues of 0.07 mg/kg in grain and 1.7 mg/kg in straw. Although there were no outstanding requirements for additional supervised trials data, the Meeting received extensive additional cereal grain, plant, forage and straw data from Europe and North America. Because no need for MRL revisions was indicated, the Meeting only briefly summarized the submitted data on grain and straw. It concluded that there was no need to revise the recently adopted limits of 0.1 mg/kg in the grains and 2 mg/kg in the straws and fodders (dry) of barley, rye and wheat at present. This conclusion may need to be reconsidered at a future Meeting in the light of future GAP information.

Cereal grain processing. The 1991 JMPR reviewed a wheat processing study submitted in response to a 1989 requirement. While no concentration in milled fractions was observed, samples were not analysed for metabolites (especially IN-F7321) and such analysis had been recorded as desirable. A barley grain processing study provided to the Meeting confirmed that no concentration of flusilazole or the major metabolite IN-F7321 occurred in milling fractions.

Grapes. Limited additional information on GAP in Europe and Australia and additional grape data submitted in response to the 1991 requests showed maximum residues reflecting GAP of 0.22 mg/kg compared to the recently adopted CXL of 0.5 mg/kg. A delegation to the CCPR had suggested that a 0.2 mg/kg limit was sufficient. The Meeting confirmed the 1989 JMPR conclusion that residues were unlikely to exceed 0.3 mg/kg.

Pome fruit. Additional GAP information and residue data did not require a revision of the current 0.2 mg/kg limit.

Stone fruit. The 0.1 mg/kg limit for peaches and nectarines recommended by the 1991 JMPR was temporary pending the submission of additional GAP and residue data. It had been based on data from New Zealand and France and GAP from New Zealand and Spain. The Meeting received information on current GAP from Spain, France, Greece (pending) and Italy, and residue data on nectarines from France and on peaches from Australia, Italy, Greece, and the United States. French apricot data were also provided as supporting information. No GAP information was available for Australia or the United States. One to 4 applications at 3-4 g ai/hl and a PHI of 7 to 10 days appears to be usual for countries with established GAP, although in two cases the maximum number of permitted applications was not indicated.

At a 7-day PHI, the new French data or those summarized by the 1991 JMPR which reflect GAP rates showed maximum residues of flusilazole *per se* in peaches of 0.09 mg/kg (1991) or

0.08 mg/kg (1993), except in one trial in the 1993 submission where a residue of 0.55 mg/kg after 8 days was reported from 9 applications at GAP rates. Maximum apricot residues reflecting GAP rates were 0.08 mg/kg after 7 days. Maximum residues in the US trials were 0.09 mg/kg at a 2.4 g ai/hl spray concentration after 7 or 14 days (0.2 mg/kg after 5 days) and 0.3 mg/kg at a 4.8 g ai/hl rate after 12 days. At a pending GAP rate, maximum residues after 7 days in the Greek trials were 0.09 mg/kg. Residues were not detected in the Australian or Italian trials (<0.05 mg/kg and <0.01 mg/kg respectively), but that is not unexpected in view of the long PHIs and the type of application. The Meeting concluded that a 0.5 mg/kg limit was supported for peaches. Observing that GAP for apricots and nectarines is similar to that for peaches, the Meeting concluded that the available data could also mutually support 0.5 mg/kg limits for apricots and nectarines at a 7-day PHI.

Limited data for plums and cherries were insufficient to recommend MRLs.

Sugar cane. No residues (<0.02 mg/kg) were detected in the juice from plants grown after dip treatments of sugar cane sets at fivefold application rates. No stalks were analysed. The Meeting concluded that the data were inadequate to support a limit for sugar cane.

FURTHER WORK OR INFORMATION

Desirable

1. Submission of analytical method AMR-115-85 cited in Du Pont, 1993, Vol. 1, exhibit 6. Submission of validation information to permit estimation of limits of determination is desirable.

2. On completion, submission of the soil dissipation report AMR-791-87 (Fujinari, 1988). The interim report was reviewed by the 1989 JMPR.

4.25 FOLPET (041)

TOXICOLOGY

Folpet was evaluated for acceptable daily intake by the Joint Meeting in 1969, 1973, 1982, 1984, 1986 and 1990. A temporary ADI of 0-0.01 mg/kg bw was established in 1986, which was extended in 1990 pending submission of the following studies for review in 1993:

- Results of further investigation of the relevance of metabolic data in animals for humans.

- Further studies to elucidate the mechanism for the induction of gastrointestinal tract tumours in mice.

- Studies designed to establish an NOAEL in mice.

The data that were reviewed at the present Meeting included a DNA-binding study in mice with the analogue, captan; an acute inhalation toxicity study in rats; a delayed cutaneous hypersensitivity study in guinea-pigs; and carcinogenicity studies in both $B_6C_3F_1$ mice (study designed to focus on the mechanism of tumour induction) and CD-1 mice (interim report: 0-42/60 weeks).

These data did not satisfy the above request but since relevant studies are known to be in progress, the Meeting extended the temporary ADI of 0-0.01 mg/kg bw to 1995, with submission of data to WHO by 1994.

A toxicological monograph was not prepared.

RESIDUE AND ANALYTICAL ASPECTS

Folpet was evaluated first in 1969, and several times since. The 1987 JMPR recommended that a detailed review of all aspects of the use of folpet be carried out at the 1989 Meeting or as soon as possible. At the 23rd (1991) Session of the CCPR it was decided (ALINORM 91/24A, para 95) to maintain CXLs for apple, cherries, cucumbers, grapes, bulb onions and strawberries, regarding them as temporary until 1992 when the results of current and planned supervised trials could be reviewed.

The 25th (1993) Session of the CCPR was informed that the manufacturer had provided information for all commodities with temporary MRLs except cherries and onions (ALINORM 93/24A, para 66).

The Meeting received information on registered uses of folpet and data from supervised trials on fruit and vegetables. MRLs for bulb onions and cherries will not be supported by new supervised field trials. Residue data from supervised trials on the following crops were reviewed:

mandarins (*Spain*), oranges (*Israel, Spain*), apples (*Chile, France, Israel, Portugal*), grapes (*Argentina, Chile, France, Israel, Italy, Spain*), strawberries (*Brazil, Hungary, Israel, Spain, Uruguay*).

melons (*France, Israel*), squash (*Greece*), lettuce (*Brazil, France, Israel*), potatoes (*Denmark, Israel, Netherlands, UK, Uruguay*), tomatoes (*France, Hungary, Israel*).

The Meeting was informed that the proposed GAP for folpet in Israel would probably become official in the near future. Only current official GAP is used in the evaluation of residue data.

There are no current registered uses for folpet on citrus, so the Meeting could not estimate a maximum residue level for citrus fruits. If the proposed use in Israel becomes registered, supervised trials data from Israel and Spain would suggest an MRL of 2 mg/kg.

The registered use of folpet on apples in Portugal requires a spray concentration of 0.13 kg ai/hl and a PHI of 21 days. Trials in Portugal and Israel conformed with this use pattern; the highest residues of folpet were 1.4 and 1.8 mg/kg. The Meeting was also aware of supervised trials on apples in France currently awaiting a final report. Because of the limited number of trials currently available within GAP the Meeting recommended withdrawal of the temporary MRL for apples.

Folpet is registered for use on grapes in Argentina, France, Italy and Spain. Supervised trials data were available from these countries. Trials were also available from Israel and were evaluated against GAP for grapes in Portugal and Spain. Residues arising from use according to GAP commonly fall in the 0.5-1 mg/kg range but residues of 1.3 and 2.0 mg/kg were recorded in a Spanish trial. The Meeting estimated a maximum residue level of 2 mg/kg for folpet in grapes.

Residue trial data on strawberries were provided from Brazil, Hungary, Israel, Spain and Uruguay, but there was no GAP for Hungary, Israel or Uruguay. Most of the residues in the Brazilian trials within GAP were in the 1-2 mg/kg range. The highest folpet residue in the Spanish trial within GAP was 1.1 mg/kg.

A folpet trial on strawberries in Israel (where registration is proposed) was evaluated against Portuguese GAP. Residues were consistently in the 2-5 mg/kg range, and were quite persistent. The highest residues were 4.7 and 4.8 mg/kg. The Hungarian trial was evaluated against Netherlands GAP; the highest folpet residue was 0.78 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg for folpet in strawberries.

No folpet was detected (<0.01 mg/kg) in melons from a French trial where an exaggerated spray concentration, approximately threefold, had been used. The laboratory had reported some problems with folpet recoveries when the sample was spiked before chopping. The fact that no residues were detected on samples taken the same day as the final application also throws doubt on the validity of the trial results.

No residues were detected (<0.02 mg/kg) in the pulp of melons in the Spanish trial. Data are required on a whole fruit-basis for MRL purposes. Trial data from the melon trials in Israel could not be evaluated because there is, as yet, no registered use in Israel.

The Meeting was unable to estimate a maximum residue level for folpet residues in winter squash because the data were too limited. The Meeting was informed that cucumber trial data would become available in the future from Turkey, Israel and Cyprus.

Folpet residues in lettuce treated according to Brazilian GAP ranged up to 1.4 mg/kg. Trial data on lettuce from Israel could not be evaluated because there is no registered use of folpet on lettuce in Israel, although it is proposed. The Meeting was also aware of supervised trials on lettuce in France currently awaiting a final report. Because of the limited number of trials available at present within GAP the Meeting recommended withdrawal of the temporary MRL for lettuce.

Supervised trials data for folpet on potatoes were available from Denmark, Israel, The Netherlands, the UK and Uruguay. The only country in this list which has registered uses for folpet on potatoes is Uruguay. Folpet residues in the trials from these countries were mostly not detectable (<0.01, <0.02 mg/kg). The pattern of residues expected for potatoes from the foliar use of a non-systemic pesticide is the occasional detection where a tuber has been directly exposed, but with no residues in most tubers. This pattern would not be much affected by the rate of application. The highest residue detected was 0.49 mg/kg in one plot in the Uruguay trial.

The Meeting noted that residues were generally undetectable in potatoes from application rates of 1.3 to 4.0 kg ai/ha in a number of different countries. The Meeting estimated a maximum residue level of 0.02* mg/kg for folpet in potatoes.

The maximum application rate for folpet on tomatoes in France is 1 kg ai/ha, but the rates used in the supervised trials were 1.5 and 3.0 kg ai/ha, so the data could not be used to estimate maximum residue levels. Folpet is not registered for use on tomatoes in Israel (although there is a proposed registration) so the data from trials in Israel could not be used. Folpet residues in tomatoes in Hungary treated according to GAP were not detectable (<0.02 mg/kg) 14 days after the final application. The Meeting considered the data were insufficient to estimate a maximum residue level for tomatoes.

Phthalimide residue data were also provided for most of the supervised trials. Phthalimide is the major primary metabolite of folpet. In many cases phthalimide residues were not detected in the trials, but in some cases they were of the same order as those of folpet, or even exceeded them. Phthalimide levels were generally not well related to the use of folpet and should not be included in the residue definition as an indicator of compliance with GAP.

The stability of folpet and phthalimide residues in stored analytical samples (lettuce, potato,

tomato, melon), separately fortified with each compound at 1 mg/kg, was tested at -18°C. About 10-20% of the residues were lost during 6 months freezer storage.

In the analytical methods used for many of the trials, samples were chopped and extracted with ethyl acetate, then cleaned up on a Florisil column for folpet, or by solvent partition (hexane, phosphate buffer) for phthalimide. Gas-liquid chromatography on a megabore column with a ^{63}Ni electron-capture detector for folpet and with a thermionic nitrogen-specific detector for phthalimide was used for the final determination. No interference was caused by 25 common pesticides which might occur in crop samples. The limits of determination were 0.05 mg/kg for folpet and 0.2 mg/kg for phthalimide. Limits of detection were lower by factors of 2-2.5.

The Meeting received information on national MRLs for folpet from Canada, the EEC, Hungary, The Netherlands and the USA.

FURTHER WORK OR INFORMATION

Desirable

1. Full details and results of the French trials on apples and lettuce now awaiting final reports, together with full details of the relevant French GAP.

4.26 HEPTACHLOR (043)

RESIDUE AND ANALYSIS ASPECTS

Information on use patterns of heptachlor was supplied to the 1991 JMPR, but only in a summarized form and no registered or recommended uses on vegetables were available. Residue data from monitoring heptachlor and heptachlor epoxide in fruits and vegetables and animal products were also reported. The 1991 Meeting recommended that the existing Extraneous Residue Limits for heptachlor in carrots, tomatoes and other vegetables should be converted to temporary limits until more information was available on the possible occurrence of residues in food in commerce or at consumption.

Monitoring data were received by the present Meeting from The Netherlands, Sweden and the USA.

Residues in fruit and vegetables occurred only to a very limited extent. In 15,300 samples of fruit, vegetables and cereal grains examined in The Netherlands residues were present in only 13 samples. In Sweden residues occurred in only 3 of about 9000 samples analysed, including many samples of carrots and tomatoes. In the USA residues of heptachlor were present in 18 of 14,800 samples of fruit and vegetables and 5 of 573 samples of cereal grains. The monitoring in the USA as well as in Sweden included the analysis of carrots and tomatoes. No residues were present in any of about 700 samples of carrots and 2200 samples of tomatoes analysed. The limit of determination in the three countries was 0.01-0.02 mg/kg.

In animals heptachlor is metabolised to heptachlor epoxide. This compound was not present in the animal products examined, with a few exceptions. No residues were detected in about 800 samples of domestic animal products examined in The Netherlands. In the USA no residues were found in milk, eggs or imported meat. Residues occurred at a level of 0.03-0.13 mg/kg in only three samples of domestic pigs and at 0.04 and 0.06 mg/kg in two samples of geese.

With this very low incidence of heptachlor in carrots, sugar beets, tomatoes and other

vegetables the Meeting was of the opinion that there is no further need for ERLs for heptachlor in vegetables.

4.27 HEXACONAZOLE (170)

RESIDUE AND ANALYTICAL ASPECTS

The 1990 JMPR recommended that MRLs for wheat and wheat straw and fodder be temporary pending receipt of data on residues in animal products resulting from feeding grain and/or straw, together with a method of analysis for hexaconazole in products of animal origin suitable for regulatory purposes, by 1993. Data on the fate of residues during the processing of grain were also required.

The Panel considered these requirements in view of the guidance for animal transfer studies discussed elsewhere in this report (Section 2.7). On the basis of the goat metabolism study with radio-labelled hexaconazole (1990 JMPR) and estimates of dietary intake, no detectable residues of hexaconazole would be expected in animal tissues or milk; total radioactive residues would be expected to be low (of the order of 0.01 mg/kg). It was agreed that in view of this a livestock feeding study and an analytical method for animal tissues would no longer be required. It was noted that while there may be some concentration in wheat processed fractions, in view of the low residues in the wheat grain and the character of the active ingredient, this information was no longer required but was desirable.

The Meeting recommended MRLs for wheat (0.1 mg/kg) and wheat straw and fodder (0.5 mg/kg) to replace previous temporary limits.

FURTHER WORK OR INFORMATION

Desirable

Data on the fate of residues during the processing of grain.

4.28 MANCOZEB (050)

TOXICOLOGY

Mancozeb was evaluated by the Joint Meeting in 1967, 1970, 1974, 1977 and 1980. An ADI of 0-0.05 mg/kg bw was established at the 1980 Meeting for mancozeb or the sum of maneb, mancozeb and zineb, of which not more than 0.002 mg/kg bw may be present as ethylenethiourea (ETU).

In pharmacokinetic studies conducted in male and female mice, orally administered ^{14}C-labelled mancozeb was rapidly absorbed, peaking in whole blood between 1 and 2 hours, extensively metabolized, and rapidly excreted (90%) within 24 hours. ETU was the major metabolite.

Rats given single oral doses of ^{14}C-labelled mancozeb absorbed about 50% of the dose within 3-6 hours. Most of the dose was excreted in 24 hours with half eliminated in the urine and half in the faeces. Less than 4% was found in the tissues, with the thyroid containing the highest residue level. Most of the ^{14}C dose in the faeces was unabsorbed, since only 2-8% of the dose was found in bile. ETU was the major metabolite. The half-life of ETU elimination was 4-5 hours. The estimated bioavailability of ETU in rats was about 6.8% on a weight/weight

basis and 20% on a mole/mole basis.

The acute oral, dermal and inhalation toxicity of mancozeb technical is low. WHO has classified mancozeb as unlikely to present acute hazard in normal use.

In a 13-week study in rats, mancozeb was administered in dietary concentrations of 0, 30, 60, 125, 250 or 1000 ppm. The NOAEL was 125 ppm (equal to 7.4 mg/kg bw/day), based on increased serum TSH and decreased T_4 values at the next higher dose.

Dogs administered 0, 10, 100, 1000 or 5000 ppm of mancozeb in the diet for three months demonstrated an NOAEL of 100 ppm, equal to 3.0 mg/kg bw/day. At the next higher dose, decreased body-weight gains and decreased erythrocyte count, packed cell volume and haemoglobin were observed.

In a 52-week study in dogs, mancozeb was administered in the diet at concentrations of 0, 50, 200, 800 or 1600 ppm. The NOAEL was 200 ppm, equal to 7.0 mg/kg bw/day, based on decreases in body-weight gain, increased cholesterol and decreased haemoglobin and packed cell volume at 800 ppm.

The NOAEL for dogs given mancozeb technical for 52 weeks, 7 days a week, by gelatin capsule was 2.3 mg/kg bw/day, based on decreased body weight, food consumption and thyroxine levels at 23 mg/kg bw/day.

In a 78-week carcinogenicity study in mice at dietary concentrations of 0, 25, 100 or 1000 ppm, there was no evidence of carcinogenicity. The NOAEL was 100 ppm, equal to 17 mg/kg bw/day, based on decreased body-weight gain at 1000 ppm.

In a second 78-week carcinogenicity study in mice at dietary concentrations of 0, 30, 100 or 1000 ppm in the diet, there was no evidence of carcinogenicity. The NOAEL was 100 ppm, equal to 13 mg/kg bw/day, based on decreased body weight and decreased T_3 and T_4 values at 1000 ppm.

The overall NOAEL in the two 78-week studies in mice was 17 mg/kg bw/day.

In a two-year toxicity/carcinogenicity feeding study in rats at dietary concentrations of 0, 20, 60, 125 or 750 ppm, the NOAEL was 125 ppm (equal to 4.8 mg/kg bw/day), based on decreased body-weight gain, decreased T_3 and T_4 values, increased TSH values, increased absolute and relative thyroid weight, thyroid follicular cell hypertrophy, hyperplasia, and nodular hyperplasia at 750 ppm. Tumorigenic effects were noted in both sexes in the form of thyroid follicular cell adenomas and/or carcinomas at the highest dose level.

Mancozeb technical when administered in the diet to rats for two years at dose levels of 0, 28, 113 or 454 ppm was not tumorigenic. The NOAEL was 113 ppm (equal to 4.0 mg/kg bw/day), based on decreased body-weight gain, decreased thyroxine levels, an increase in the height of the thyroid follicular epithelium and an increase in prominent microfollicles at 450 ppm.

The overall NOAEL in the two 2-year studies in rats was 4.8 mg/kg bw/day.

In a two-generation reproduction study in rats at dietary concentrations of 0, 25, 150 or 1100 ppm, the NOAEL was 25 ppm (equal to 1.7 mg/kg bw/day), based on decreased body weight at 150 ppm.

In a second two-generation reproduction study in rats at dietary concentrations of 0, 30, 120 or 1200 ppm, the NOAEL was 120 ppm, equal to 7.0 mg/kg bw/day, based on microscopic changes in the thyroid, kidney and pituitary, increased relative weights of the liver, kidney and thyroid, increased absolute thyroid weight, decreased body weight and feed consumption of

females during gestation and lactation, and decreased pre-mating body weight and feed consumption, at 1200 ppm.

The overall NOAEL in both reproduction studies was 7.0 mg/kg bw/day.

In a 90-day (neuropathology) study conducted in rats at dietary concentrations of 0, 20, 125, 750 or 5000 ppm, the NOAEL was 125 ppm, equal to 8.2 mg/kg bw/day, based on decreased food consumption and neurohistopathological changes at 750 ppm.

An oral teratogenicity study in rats at dose levels of 0, 2, 8, 32, 128 or 512 mg/kg bw/day produced no maternal effects at 32 mg/kg bw/day (NOAEL) and no teratogenic effects at 128 mg/kg bw/day (NOAEL). Maternal effects in the form of decreased body-weight gain and decreased food consumption were seen at 128 mg/kg bw/day. Teratogenic effects seen at 512 mg/kg bw/day included agnathia, cleft palate, meningoencephalocele and dilated brain ventricles.

A second oral teratogenicity study in rats at dose levels of 0, 10, 60 or 360 mg/kg bw/day showed no maternal or embryo/fetotoxic effects at 60 mg/kg bw/day (NOAEL). Maternal toxicity at 360 mg/kg bw/day was seen as "reeling gait", hind limb paralysis, and decreased body-weight gain and food consumption. Embryo/fetotoxicity at the highest dose was seen as reduction in the degree of ossification of the intraparietal bone, a marginal increase in the size of the anterior fontanelle and incomplete ossification of the thoracic vertebrae centra.

The NOEL in an oral teratogenicity study in rabbits given 0, 5, 30, 55, or 100 mg/kg bw/day was 55 mg/kg bw/day for maternal effects and greater than 100 mg/kg bw/day for embryo/fetotoxic effects. An increase in abortions, body-weight loss, and decreased food consumption were observed at 100 mg/kg bw/day.

The NOEL in an oral teratogenicity study in rabbits given 0, 10, 30 or 80 mg/kg bw/day was 30 mg/kg bw/day for maternal toxicity. The NOAEL for embryo/fetotoxic effects was greater than 80 mg/kg bw/day. Maternal toxicity at 80 mg/kg bw/day was based on an increase in aborted fetuses, decreased number of litters produced, decreased body-weight gain and food consumption, an increase in clinical signs and death.

Mancozeb has been tested in a series of *in vitro* and *in vivo* genotoxicity assays. Chromosomal aberrations were induced *in vitro*, whereas conflicting data were obtained with *in vivo* assays. There was no evidence for the induction of gene mutations or cell transformations. The Meeting concluded that the data on mancozeb were equivocal for genotoxicity. A number of available studies were not considered either because DMSO was used as a solvent in which mancozeb is very unstable or because of important omissions from the reports.

The data on mancozeb would support an ADI of 0-0.05 mg/kg bw, based on the NOAEL of 4.8 mg/kg bw/day for thyroid effects in rats, using a 100-fold safety factor. However, the Meeting established a group ADI of 0-0.03 mg/kg bw for mancozeb, alone or in combination with maneb, metiram and/or zineb, because of the similarity of the chemical structures of the EBDCs, the comparable toxicological profiles of the EBDCs based on the toxic effects of ETU, and the fact that parent EBDC residues cannot be differentiated using presently-available regulatory analytical procedures (see Section 4.15 - dithiocarbamates).

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and containing relevant summaries from previous monographs and monograph addenda on mancozeb.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effects

Mouse: 100 ppm in the diet, equal to 17 mg/kg bw/day (78-week studies)

Rat: 125 ppm in the diet, equal to 4.8 mg/kg bw/day (two-year studies)
120 ppm in the diet, equal to 7.0 mg/kg bw/day (reproduction studies)
125 ppm in the diet, equal to 8.2 mg/kg bw/day (90-day neuropathology study)

Dog: 200 ppm in the diet, equal to 7.0 mg/kg bw/day (52-week study)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw (group ADI with maneb, metiram, and zineb)

Studies which will provide valuable information in the continued evaluation of the compound

1. Clarification of genotoxicity potential.

2. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Mancozeb, evaluated in 1967 and several times since, was scheduled for review in 1993 in the CCPR periodic review programme (ALINORM 93/24A, para 71).

The Meeting received extensive information on GAP, supervised residue trials, animal transfer studies, metabolic fate in farm animals and crops, fate during processing and storage, residues in food in commerce and at consumption, and methods of residue analysis.

When lactating goats were dosed with [^{14}C]mancozeb ([^{14}C]ethylenediamine) in the feed, most of the ^{14}C was excreted in the faeces and urine. Excretion levels reached a plateau by day 2. The concentration of ^{14}C in milk reached a plateau by day 3 at all dosing levels. Concentrations of ^{14}C were higher in liver and kidney than in the other tissues or organs, most of it being incorporated into natural products. The main metabolites identified in the kidney were glycine, *N*-formylglycine, ethylenediamine, *N*-acetylethyl-enediamine, ethyleneurea, ethylenethiourea (ETU) and ethylenebisisothiocyanate sulphide.

When laying hens were dosed with [^{14}C]mancozeb in the feed, most of the ^{14}C was excreted in the faeces. ^{14}C levels in whole eggs were still increasing at the end of the 7-day dosing period, but declined rapidly in eggs from a group of hens in which dosing was discontinued. Ethyleneurea was the identified metabolite present at highest levels in eggs and tissues. ^{14}C was present at higher levels in liver and kidney than in other organs or tissues. In the highest dosed group (equivalent to 36 ppm mancozeb in the feed) dithiocarbamate levels (as CS_2) by direct chemical analysis were: muscle 0.02-0.04 mg/kg, liver 0.09 mg/kg, and eggs 0.007-0.02 mg/kg. ETU levels in the tissues of this group were either at or below the level of detection (0.007 mg/kg), and in eggs were 0.06 mg/kg. ETU levels in eggs were not detectable (<0.007 mg/kg) in the group dosed at the equivalent of 14 ppm.

Most of the ^{14}C was incorporated into the carbon pool, appearing in a range of natural products, when a tomato crop was treated with [^{14}C]mancozeb. Ethyleneurea was the major primary metabolite identified.

When a soya bean crop was treated with [^{14}C]mancozeb the primary metabolites identified in soya bean pods were 1-(2-imidazolin-2-yl)-2-imidazolidinethione, ethyleneurea, hydantoin and ethylenebisisothiocyanate sulphide. Much of the ^{14}C was incorporated into protein, lignin

and oil.

In a sugar beet crop treated with [^{14}C]mancozeb, 1-(2-imidazolin-2-yl)-2-imidazolidinethione was the major primary metabolite to be identified. The total ^{14}C label was distributed 77% in the leaf and stem, and 23% in the root.

The primary metabolites identified in wheat which had received foliar applications of [^{14}C]mancozeb were ethyleneurea, ethylenediamine, ethylenebisisothiocyanate sulphide, 2-imidazoline and 1-(2-imidazolin-2-yl)-2-imidazolidinethione. Much of the ^{14}C was incorporated into carbohydrates.

Mancozeb is registered as a protective fungicide for use on citrus fruits, pome fruits, stone fruits, berries and other small fruits, tropical and subtropical fruits, bulb vegetables, root and tuber vegetables, Brassica vegetables, leafy vegetables, stalk and stem vegetables, fruiting vegetables, legume vegetables, cereals, tree nuts, oilseeds and miscellaneous crops in very many countries.

Typical spray concentrations for high-volume application of mancozeb were 0.15-0.20 kg ai/hl to a wide variety of crops in many countries, but higher concentrations were recommended in some cases. The application rate for high-volume application depended on the volume of spray per hectare required for the particular crop and the typical spray concentration.

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

grapefruit (*USA*), lemons (*Spain, USA*), limes (*USA*), mandarins (*Japan, Spain*), oranges (*Australia, Brazil, Spain, USA*);

apples (*Australia, Austria, Belgium, Brazil, France, Germany, Hungary, Italy, Japan, Netherlands, UK, USA*), pears (*Australia, Brazil, France, Germany, Italy, Japan, USA*);

apricots (*Australia*), peaches (*Australia, Brazil*), plums (*Brazil, France*);

black currants (*UK*), cranberries (*USA*), grapes (*Australia, Brazil, France, Hungary, Italy, Japan, Portugal*), strawberries (*Japan, Spain*);

avocados (*Brazil*), bananas (*Australia, Brazil, Honduras, USA*), figs (*Brazil*), mangoes (*Australia, Brazil*), papayas (*USA*), passion fruit (*Australia*), persimmons (*Japan*);

garlic (*Brazil, France, Japan*), leeks (*France, Japan*), onions (*Australia, Brazil, Finland, Japan, Netherlands, USA*);

broccoli (*Brazil*), cabbage (*Brazil, Germany, Japan*), cauliflower (*Brazil, Spain*), Chinese cabbage (*Japan, Spain*);

cantaloupes (*USA*); cucumbers (*Australia, Brazil, France, Germany, Japan, Spain, USA*), gherkins (*Germany*), melons (*France, Germany, Japan*), pumpkins (*Australia, Brazil*), squash (*France, Japan*), summer squash (*Australia, France, USA*), watermelons (*Australia, Japan, USA*), winter squash (*USA*);

egg plants (*Brazil*), peppers (*Brazil, Spain*), sweet corn (*USA*), tomatoes (*Brazil, France, Germany, Italy, Japan, Netherlands, Portugal, Spain, USA*);

kale (*Brazil*), lettuce (*Spain*);

azduki beans (*Japan*), beans (*Australia, Brazil, France, Netherlands, Spain*), French beans (*Brazil*), kidney beans (*Japan*), peas (*Brazil, France*);

beet (*Brazil*), carrots (*Australia, Brazil, France, Germany, USA*), lotus (*Japan*), potatoes (*Australia, Brazil, Finland, France, Germany, Italy, Japan, Netherlands, UK, USA*), sugar beet (*France, Italy, Japan*), yams (*Japan*);

asparagus (*France, USA*), celery (*USA*), chard (*Australia*), witloof (*France, Netherlands*);

barley (*Brazil, Netherlands, USA*), maize (*USA*), rice (*Brazil*), summer wheat (*Germany*), wheat (*Brazil, Canada, France, Spain, USA*), winter wheat (*Germany, Netherlands, UK*);

hops (*Germany*);

peanuts (*Australia, USA*), rape seed (*France, Netherlands*);

almonds (*USA*), cocoa (*Brazil*), coffee (*Brazil*),

barley straw (*Netherlands, USA*), maize fodder (*USA*), wheat straw (*Canada, France, Germany, Netherlands, UK, USA*);

almond hulls (*USA*), bean pods and foliage (*Australia*), bean straw (*Australia*), peanut foliage (*Australia*), peanut hay (*USA*), sugar beet leaves (*Italy, Japan, USA*).

Dithiocarbamate residues are expressed as mg CS_2 /kg throughout.

Mancozeb is used as a cover fungicide, often with the same spray concentrations for high-volume application, on a wide range of crops. Because the residue is on the surface and there is no translocation from foliage to fruits, residue levels are often similar on fruits of a similar size.

Mancozeb use patterns are common across the citrus fruits in each country. Spanish trials on mandarins (GAP spray concentration 0.32 kg ai/hl, PHI 15 days) produced dithiocarbamate residues up to 4.7 and 6.6 mg/kg at 14 days. For a similar use pattern on oranges, residues of dithiocarbamates were mostly less than 1 mg/kg (highest 1.3 mg/kg). Japanese trials showed that most of the residues are in the peel while the Spanish trials confirmed that washing the fruit generally removes 90% or more of the residue. The Meeting estimated maximum residue levels of 10 mg/kg and 2 mg/kg for mandarins and oranges respectively, based on mancozeb uses.

US trials on lemons, limes and oranges demonstrated that most residues of both dithiocarbamates and ETU were on the peel with little in the pulp. US data on citrus could not be evaluated because there was no US GAP.

Residue data and mancozeb GAP for apples were available from many countries. The mancozeb spray concentrations used in high-volume applications were quite similar in most countries (0.15-0.2 kg ai/hl). GAP information from France did not include a PHI so French data were evaluated according to the German GAP for pome fruit. Residues in apples above 1 mg/kg were recorded in trials in Australia, Austria, Brazil, Germany, Italy and the UK when mancozeb was used within GAP. The highest recorded residue exceeded 4 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg for apples.

Use patterns on pears were the same as on apples, with the highest recorded residue being 2.2 mg/kg. The Meeting recommended an MRL for pome fruit of 5 mg/kg for dithiocarbamates, based on mancozeb uses.

The number of trials on apricots, peaches and plums was inadequate to recommend MRLs. No data were available for cherries. The Meeting agreed to withdraw the MRL recommendations for cherries, peaches and plums.

Grape residue data were supplied from many countries. The highest residues from the main population of data were in the 2.1-2.8 mg/kg range (Italy) suggesting an MRL of 5 mg/kg. Australian trials produced residues higher than 20 mg/kg when mancozeb was used according to GAP, and residues seemed somewhat anomalous when compared with similar uses elsewhere. The Australian use pattern is currently under review; Australian residue data were not included in the current evaluation.

The number of trials on strawberries was inadequate to permit the estimation of a maximum residue level. The Meeting recommended the withdrawal of the strawberry MRL.

A consistent series of mancozeb trials on cranberries in the USA in 1985 and 1988 suggested an MRL of 5 mg/kg.

The highest residues in black currants from UK mancozeb trials exceeded 5 mg/kg (5.1, 5.4 mg/kg). The Meeting estimated an MRL of 10 mg/kg for currants.

Residue data on bananas and mangoes are mutually supportive with similar uses leading to a similar range of residues. The Meeting estimated a maximum residue level of 2 mg/kg for banana and mango. Data on papayas, where the use pattern permits harvest on the same day as application, suggested an MRL of 5 mg/kg. The number of trials for avocados, figs and passion fruit was too limited for recommendations.

Residue data on garlic were made available from trials in Brazil, France and Japan. Generally, residues were not detectable (<0.05 mg/kg and lower) as would be expected from a foliar-applied non-systemic fungicide. However, residues were detected in a control sample at 0.1 mg/kg, and the possibility should not be excluded that some varieties of garlic or some conditions of production and storage could generate endogenous CS_2 as in onions. Mancozeb trials on leeks in France and Japan were made available for evaluation. The highest residue of 0.30 mg/kg and the possibility of endogenous CS_2 (a control sample registered 0.21 mg/kg of CS_2) suggested a maximum residue level of 0.5 mg/kg for garlic and leeks.

Onion trials in Brazil, Japan, The Netherlands and the USA showed residues up to 0.17 mg/kg, with control samples in Japan at 0.12 mg/kg. The highest residues in onions were in an Australian trial at 1.7 mg/kg but appeared to be an order of magnitude higher than others and difficult to explain for an immobile residue such as mancozeb. The Meeting agreed to evaluate bulb onions, garlic and leeks as a group, and estimated a maximum residue level of 0.5 mg/kg for onions resulting from mancozeb use.

Residue data from trials on broccoli and cauliflower in Brazil in 1989 according to GAP were mutually supportive, and suggested a maximum residue of 0.2 mg/kg. Broccoli has, however, been shown to contain endogenous CS_2. In a US study 8 samples of broccoli (6 varieties, 6 sites in the USA) certified to be untreated with dithiocarbamates, on analysis contained CS_2 residues ranging from undetectable (<0.01 mg/kg) to 0.79 mg/kg, median 0.32 mg/kg. The Meeting had no information on endogenous CS_2 levels in cauliflower. It did not estimate a maximum residue level for broccoli or cauliflower because of the limited number of trials. The Meeting drew attention to the endogenous CS_2 levels in broccoli and possible endogenous CS_2 in related crops.

The highest residue in cabbages from trials according to GAP in Brazil and Japan was 0.22 mg/kg. Chinese cabbage from trials in Japan contained residues of 0.1 mg/kg in the untreated control, again suggesting endogenous CS_2 in the various Brassica vegetables. The Meeting was unable to recommend MRLs for cabbage or Chinese cabbage because of the limited data.

Cucumber residue data from trials according to GAP were supplied from Australia, Brazil, France, Japan and the USA, with residues up to 0.3 mg/kg in US trials. The Meeting estimated a maximum residue level of 0.5 mg/kg for cucumbers, based on mancozeb uses.

Residues in melons from the same use patterns were generally in the same range as in cucumbers. The Meeting recommended an MRL of 0.5 mg/kg for melons except watermelon.

There were only two trials on pumpkins according to GAP, one from Australia and one from Brazil, but residues were generally consistent with those in other cucurbits. The Meeting estimated a maximum residue level of 0.2 mg/kg for pumpkins.

Summer squash in trials in Australia, France and the USA showed residues from undetectable levels to 0.83 mg/kg, the last in a US trial where the harvest took place on day 4 after the last application. Residues would have been higher than on day 5 (the recommended PHI), but the level on day 10 was still 0.65 mg/kg. The Meeting estimated an MRL of 1 mg/kg for summer squash.

US data on winter squash could not be evaluated because no US GAP was available. Residues in squash in trials in France and Japan were quite similar, even though there was quite a difference in the use patterns, with PHIs of 3 and 30 days in France and Japan respectively. The Meeting estimated an MRL of 0.1 mg/kg for winter squash.

A US watermelon trial with mancozeb used 12 applications, but this would probably have little influence on the residues since US GAP allows a maximum of 8. The residue level on day 5 after the final treatment was 0.38 mg/kg. In the Australian trials residues were not detected (<0.1 mg/kg), and in the Japanese trials residues were measured on the watermelon pulp rather than the whole fruit. Residues in the pulp were at quite low levels, 0.01-0.02 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg, based on mancozeb uses on watermelon.

When mancozeb was used according to GAP on peppers in Brazil and Spain the highest residues were in the 0.5-0.6 mg/kg range. The Meeting recommended an MRL of 1 mg/kg for sweet peppers.

Sixty-eight trials with mancozeb on tomatoes were available from many countries. Many of the measured residue levels were in the 0.1-1 mg/kg range, but residues up to 4.1 mg/kg were recorded in the US trials. The Meeting recommended an MRL of 5 mg/kg for tomatoes.

US trials on sweet corn showed that dithiocarbamate residues were on the husk rather than in the kernels. Residues were not detected (<0.03 mg/kg) in the cob + kernels. Additional data were available from US processing studies where application of mancozeb at the recommended US rate produced undetectable residues (<0.03 mg/kg) in cob + kernels. The residue level was 0.03 mg/kg when mancozeb was used at 5 times the recommended rate. Mancozeb, an immobile residue, would not be expected in the cob and kernels, which are protected by the husk from direct application. The Meeting recommended an MRL for sweet corn of 0.1* mg/kg as being a practical limit of quantification.

In supervised mancozeb residue trials on kale in Brazil dithiocarbamate residues 14 days after the last application were 0.95 and 1.0 mg/kg for label rate and double label rate of application, but the number of trials was too limited to allow the estimation of a maximum residue level.

When lettuce was sprayed with mancozeb at 0.16 kg ai/hl in trials in Spain and harvested 14 days after the final application residues in the 3-10 mg/kg range were found. The Meeting estimated a maximum residue level of 10 mg/kg for mancozeb use on head lettuce.

Trials in Japan on adzuki beans and kidney beans, and in Brazil on beans and French beans generally demonstrated undetectable or low residues on bean seeds, but the LOD for some of the older results was too high to be useful. The Meeting was unable to recommend an MRL for dry beans because of the limited data. It was not completely clear whether the commodity analysed in the Brazilian trials on peas included peas + pods, or peas only. The Meeting did not recommend an MRL for beans or peas.

Information on mancozeb residues in beetroot from trials in Brazil was made available, but the number of trials was insufficient to recommend an MRL.

Most residue levels in carrots arising from approved uses of mancozeb were less than 0.2 mg/kg, but a number of values were found in the 0.5-1 mg/kg range in the Brazilian trials. The Meeting estimated a maximum residue level of 1 mg/kg for carrots.

Dithiocarbamate residues were not detected (<0.02 mg/kg) in East Indian lotus in two trials from Japan, but the data were insufficient to estimate a maximum residue level.

One hundred and seventeen mancozeb potato trials, but many not within GAP, were available from 9 countries for review. Residues were mostly undetectable even when mancozeb had been used at exaggerated application rates. Residues were sometimes detected, and the residues are more likely to depend on the inadvertent spraying of exposed potatoes than on the application rates or pre-harvest intervals. The highest residues were found in a French trial at 0.32 mg/kg and a German trial at 0.26 mg/kg, but they appeared exceptional when compared with all the other results. The Meeting estimated a maximum residue level of 0.2 mg/kg for uses of mancozeb on potatoes.

Dithiocarbamate residues from sugar beet trials in France, Italy and the USA were mostly around 0.1 mg/kg or lower, but residues in the 0.2-0.4 mg/kg range were recorded in US trials. The Meeting recommended a maximum residue level of 0.5 mg/kg for mancozeb use on sugar beet.

The US use pattern for mancozeb on asparagus requires a long PHI, 120 days in some states and 180 days in others. As expected, residues were low after this interval in the US trials. The French trials on asparagus could not be evaluated because no information on the French PHI was available. The Meeting recommended a maximum residue level of 0.1 mg/kg for asparagus.

No US GAP for mancozeb uses on celery was available to permit evaluation of US trials. Only one trial on chard according to GAP was available, from Australia, and this was insufficient in the absence of data from other similar vegetables which could have provided mutual support. Witloof trial data from France and The Netherlands could not be evaluated in the absence of GAP information.

Results of barley trials in Brazil, The Netherlands and the USA were made available to the Meeting. Dithiocarbamate residues up to 0.55 mg/kg were recorded in the US trials, and an MRL of 1 mg/kg for barley is recommended.

Results of a large number of mancozeb trials on wheat were supplied from 8 countries. The highest dithiocarbamate residues were recorded from trials in France (0.26 mg/kg), Germany (0.4 mg/kg), The Netherlands (0.82, 0.75 and 0.49 mg/kg) and the UK (0.42, 0.5 mg/kg), but in many of the trials residues were not detected. The Meeting estimated a maximum residue level of 1 mg/kg for mancozeb uses on wheat.

The PHI for the use of mancozeb on maize in the USA is 40 days; most of the residue data in the supervised trials were from shorter treatment-to-harvest intervals, and so could not be

evaluated. In two trials where the longer interval was observed the commodity analysed was the "ear". Presumably this is the cob + grain. The appropriate commodity for a maize MRL is the grain.

Data from two supervised trials on rice according to the conditions of Brazilian GAP were made available to the Meeting. The data suggest a maximum residue level of 2 mg/kg, but trials covering a wider range of conditions are desirable for such an important crop. Also, if dithiocarbamate residues in this range or higher are likely, information on their fate during milling and cooking is desirable.

Two German trials with mancozeb on hops led to dithiocarbamate levels in dry hops of 2.2 and <1 mg/kg, but the information was too limited to permit the estimation of a maximum residue level.

Dithiocarbamate residues were not detected (<0.1, <0.03 mg/kg) in peanuts in Australian and US trials even when exaggerated application rates were employed. An MRL of 0.1* mg/kg was recommended.

Residues were detected in almonds in an Australian trial at the recommended application rate, but not at twice this rate. Because mancozeb is a surface residue only it is likely that any residues detected in the kernel were physically transferred during the cracking process. In the US trials dithiocarbamate residues were present in the almond hulls at 3 mg/kg, but no residues were detected (<0.03 mg/kg) in the almonds. The Meeting estimated a maximum residue level of 0.1* mg/kg for the use of mancozeb on almonds.

Mancozeb trials on cocoa and coffee in Brazil were insufficient for the Meeting to estimate maximum residue levels for cacao beans or coffee beans.

Residue data were available for wheat straw and fodder harvested at the same time as the wheat in the previously mentioned trials. Data on barley straw from trials in The Netherlands were also included for evaluation. Many of the residues were in the 2-5 mg/kg range but residues ranged up to 18 mg/kg. Two additional trials on barley with an identical use pattern were available from the USA, with residues of 24 mg/kg on barley straw from one of them. Wheat straw and barley straw should be assessed together for the same use pattern. The Meeting estimated maximum residue levels of 25 mg/kg for both. This level is compatible with animal commodity MRLs recommended on the basis of animal transfer studies.

Dithiocarbamate residues of 1.2 and 1.4 mg/kg were found in maize plants in two US trials 39 and 40 days after the final application of mancozeb. The Meeting estimated a maximum residue level of 2 mg/kg for maize fodder.

Dithiocarbamate residues up to 3.3 mg/kg on peanut foliage from previously mentioned Australian trials permitted the Meeting to estimate a maximum residue level of 5 mg/kg for peanut fodder. Data on almond hulls and peanut hay from US trials could not be evaluated because no US GAP was available for almonds and application rates on the peanuts were in excess of recommended rates.

When mancozeb was used on sugar beet crops according to US GAP, dithiocarbamate residues up to 17 mg/kg were found on sugar beet leaves. The Meeting estimated a maximum residue level of 20 mg/kg for sugar beet leaves or tops from mancozeb use.

Animal transfer studies with lactating dairy cows and laying hens were made available to the Meeting.

When dairy cows were fed a diet containing aged mancozeb residues equivalent to 5, 15 and 45 ppm mancozeb for 28 days dithiocarbamate residues were not detected (<0.04 mg/kg

as CS_2) in the milk from any group. In the highest feeding group residues were not detected (<0.02 mg/kg,as CS_2) in muscle, while residues in the kidney and liver were 0.04 and 0.1 mg/kg respectively. The Meeting estimated maximum residue levels of 0.05*, 0.02* and 0.1 mg/kg for milks, meat and edible mammalian offal, respectively. These levels should accommodate animals eating 45 ppm mancozeb (25 ppm as CS_2) in the diet.

ETU residues were not detected (<0.01 mg/kg) in milk from the highest feeding group, but were detected in the thyroids of all the animals, with the highest doses causing the highest levels. ETU was detectable in muscle, liver and kidney of the highest feeding group, but had disappeared from the tissues of an animal returned to a residue-free diet for 7 days.

When laying hens were fed aged mancozeb residues (5, 15 and 45 ppm as mancozeb) for 28 days, dithiocarbamate residues were not detected (<0.04 mg/kg as CS_2) in the eggs from any feeding group. In the middle and highest feeding groups residues were 0.08 and 0.09 mg/kg (as CS_2) in muscle, while residues in the liver were 0.03 mg/kg. Measured residues in control samples were also around 0.03 mg/kg. The Meeting estimated maximum residue levels of 0.05*, 0.1 and 0.1 mg/kg for eggs, poultry meat and poultry edible offal, respectively.

ETU residues were detected in some eggs from the highest feeding group (0.01-0.02 mg/kg), but were not detected in tissues.

Processing studies were made available to the Meeting on apples, grapes, sweet corn, tomatoes, potatoes, sugar beet, barley, wheat, maize and peanuts.

In general, mancozeb residues (which are on the surface) can be substantially diminished by vigorous washing. The remaining residues tend to remain with the insoluble fractions, so that clear juices are unlikely to contain them. The remaining mancozeb residues may, however, be converted to ETU if processing includes a heating step.

In the commercial processing of apples, washing removed 30-50% of the residue, the remainder being carried through the process into the pomace. Neither mancozeb nor ETU residues were detectable in clarified apple juice.

De-stemming and cleaning removed about 70% of the mancozeb residues from bunches of grapes. Dithiocarbamate residues were not detectable in clear grape juice, but were present in the thick juice. ETU was generated in the production of the grape juices and jelly.

Less than 1% of the dithiocarbamate residues in mancozeb-treated grapes entered red and white wines produced from them. Approximately 7% conversion to ETU occurred during the wine production.

In one study mancozeb residue levels in dried raisins were on average 3 times as high as in the raw grapes, while in another study levels in the raisins were 20-50% of the levels in the grapes. No ETU was generated in raisin production.

Mancozeb residues in frozen corn and canned corn were less than 10% of the levels in the raw sweet corn whole ears; ETU was not generated in the process.

The commercial washing of tomatoes removed more than 90% of the mancozeb residues. Dithiocarbamate residues in the tomato juice and pomace produced from the washed tomatoes were undetectable. ETU residue levels in the juice were of the same order as the dithiocarbamate levels in the washed tomatoes.

Dithiocarbamate residues were essentially undetectable (<0.1 mg/kg) in potatoes field-treated with mancozeb at an exaggerated rate, and in the processed potato products. ETU was present in potato granules (0.08 mg/kg) and potato flakes (0.23 mg/kg).

Dithiocarbamate and ETU residues were not detected (<0.03 and <0.01 mg/kg respectively) in white sugar produced from mancozeb-treated sugar beet containing dithiocarbamate residues of 0.15 mg/kg.

The cleaning of barley grain prior to milling reduced residue levels by 70%. Mancozeb residues were not detectable in bran or flour.

Milling and baking trials on wheat harvested after foliar mancozeb applications showed that dithiocarbamate residues in the bread were either undetectable or, on average, 30% of the levels in the grain. ETU was not detectable (<0.01 mg/kg) in the bread.

Maize was field-treated with mancozeb and harvested for processing into meal, flour, germ, grits, crude oil, refined oil and soapstock. Neither dithiocarbamates nor ETU were detected in the maize kernels or any of the products (<0.03 and <0.01 mg/kg respectively).

A peanut crop was field-treated with mancozeb and harvested for processing into meal, crude oil, refined oil and soapstock. Neither dithiocarbamates nor ETU were detected in the raw peanuts or any of the products (same limits as above).

The ETU level was 0.04 mg/kg in beer produced from mancozeb-treated hops (dithiocarbamates 2.2 mg/kg as CS_2).

Typical consumer practices were shown to reduce mancozeb residue levels in potatoes, tomatoes, apples and onions. Residues in potatoes subjected to washing, brushing, drying and peeling were reduced by 97%. Residues in tomatoes and apples subjected to washing and drying were reduced by 80% and 65% respectively. Residues in onions were reduced by 95% on peeling.

Mancozeb residues were stable (>70% remaining) in homogenised samples of apples, tomatoes and wheat stored for 2 years at -20°C. ETU residues were more labile; more than 70% of the ETU remained in tomato and wheat matrices after 12 months storage, but not after two years. ETU residues in an apple matrix had declined to less than 70% after 6 months storage and to less than 50% after 12 months.

Mancozeb residues were shown to be stable at -20 ± 5°C in stored analytical samples of dry beans, corn, lettuce, meat, milk, raw potato (marginal stability), and tomato. ETU residues were shown to be stable at -20 ± 5°C in stored analytical samples of dry beans, corn, lettuce (marginal stability), meat, milk, raw potato (marginal stability), and tomato.

Under a US Food and Drug Administration monitoring programme a variety of baby foods (864 samples) were monitored for pesticide residues. ETU residues were detected in 65 samples; the highest levels detected were 0.06 mg/kg.

In 1989-90 in the USA a large survey of food items (approximately 300 samples each of 19 different raw and processed commodities) was conducted for dithiocarbamate and ETU residues. Most of the samples (91% of 5241 samples) did not contain measurable dithiocarbamate residues (<0.003 mg/kg as CS_2); broccoli and onions were excluded because of endogenous CS_2 generation. No measurable residues of ETU (LOD 0.001 mg/kg) were found in 82% of the samples.

Grape juice samples (100), from major grape juice producers in the USA using grapes from districts where dithiocarbamates had been used on the 1990 crop, contained no detectable ETU residues (LOD 0.005 mg/kg). Dithiocarbamates were detected in 92 of the samples (median value approximately 0.022 mg/kg as CS_2). If the dithiocarbamates were ethylenebis(dithiocarbamate)s, ETU should also have been detected because the production

of grape juice involves several heating steps. There was a suggestion that ferbam, a dithiocarbamate fungicide but not an ethylene-bis(dithiocarbamate), may have been the source of some of the dithiocarbamate residues.

In an Australian study in 1991, ETU residues were not detected (<0.1 mg/kg) in tomatoes, commercially produced tomato paste or thin pulp (41 samples).

Analytical methods for dithiocarbamates rely on the generation of CS_2, which can be measured by GLC or by colorimetry.

Reaction with hydrochloric acid + stannous chloride at 100°C is needed for quantitative conversion to CS_2, which can be analysed by head-space GLC. Alternatively, the evolved CS_2 can be swept by a current of air into an ethanol trap maintained at dry ice/acetone temperature, and the ethanol solution then analysed by GLC. In the colorimetric approach the evolved CS_2 is swept into a trap of cupric acetate/diethanolamine reagent. Some types of sample can give a false response by generating a false colour in the reagent.

A UK Panel on the Determination of Dithiocarbamate Residues (1981) drew attention to the loss of dithiocarbamate residues which can occur between commencement of cutting of the sample and insertion into the reaction bottle. Vegetables and fruits must be analysed for residues as soon as possible after cutting or picking, and any further cutting or dicing of the whole commodity should be carried out immediately before placing in the reaction flask, and should be kept to a minimum. Foodstuffs should be frozen whole, when this becomes necessary, and chopped and mixed in the frozen state immediately before taking the analytical samples.

ETU methods rely on HPLC or GLC for final analysis. Samples are typically extracted with aqueous ammonia (pH 11-12) + methanol or ethanol and the extract cleaned up on an alumina column. ETU is easily oxidised or lost during the analysis; precautions are needed, such as the use of silanized glassware. Precautions must also be taken to prevent ethylenebisdithiocarbamate residues from being converted to ETU during the analysis.

The Meeting was aware of national MRLs established in Australia, Canada, Germany, Mexico, Spain and the USA.

FURTHER WORK OR INFORMATION

Desirable

1. Supervised trials on rice covering a wider range of conditions.

2. Fate of mancozeb residues during the milling and cooking of rice.

4.29 MANEB (dithiocarbamates, 105)

TOXICOLOGY

Maneb was evaluated by the Joint Meeting in 1963, 1965, 1967, 1970, 1974, 1977 and 1980. An ADI of 0-0.05 mg/kg bw was established at the 1980 Meeting for maneb or the sum of any combination of maneb, mancozeb, and zineb, of which not more than 0.002 mg/kg bw may be present as ethylenethiourea (ETU).

Male and female rats given 25 mg/kg bw/day of ^{14}C labelled maneb orally showed no differences between sexes with regard to excretion patterns. More than 90% of the absorbed

^{14}C was eliminated in urine by 24 hours. Less than 1% was eliminated as carbon dioxide. The average ^{14}C concentration as a percentage of the dose per g tissue was greatest for the thyroid, followed by the kidney and liver. The percentage of ^{14}C present in urine at 12 hours on a mole/mole basis was 21-30% as ETU and less than 0.4% as maneb.

The acute oral, dermal and inhalation toxicity of maneb technical and maneb 75% dust is low. WHO has classified maneb as unlikely to present acute hazard in normal use.

Rats were fed dietary concentrations of 0, 80, 400 or 1300 ppm maneb technical for 13 weeks. The NOAEL was 80 ppm (equal to 5.0 mg/kg bw/day), based on an increase in absolute thyroid weight and thyroid follicular cell hyperplasia at 400 ppm.

In dogs fed dietary concentrations of maneb technical at 0, 100, 400 or 1600 ppm for 13 weeks, the NOAEL was 100 ppm (equal to 3.7 mg/kg bw/day), based on thyroid follicular cell hyperplasia at 400 ppm.

In a 52-week study in dogs, maneb was administered at dietary concentrations of 0, 50, 200, 1000 or 2200 ppm. The NOAEL was 200 ppm (equal to 6.4 mg/kg bw/day), based on thyroid enlargement and thickening and thyroid follicular cell hyperplasia at 1000 ppm.

The overall NOAEL in dogs, based on the evaluation of all of the data on this species, was 6.4 mg/kg bw/day.

In a six-month study in monkeys, maneb was administered at dietary concentrations of 0, 100, 300 or 3000 ppm. The NOAEL was 100 ppm (equal to 7.3 mg/kg bw/day), based on an increase in thyroid weight at 300 ppm.

In a 79-week carcinogenicity study in mice at dietary concentrations of 0, 60, 240 or 2400 ppm, the NOAEL was 60 ppm (equal to 11 mg/kg bw/day), based on decreased body weight and decreased thyroxine levels at 240 ppm. Hepatocellular adenomas were observed at 2400 ppm in both sexes.

In a 31-month toxicity/carcinogenicity study in rats at dietary concentrations of 0, 30, 100, 300 or 1000 ppm, the NOAEL was 300 ppm (equal to 20 mg/kg bw/day), based on decreased body weight, an increase in the half-life retention time of ^{131}I in the thyroid, decreased T_4 values and an increased absolute thyroid weight at 1000 ppm. There was no evidence of carcinogenicity.

In a two-generation reproduction study in rats at dietary concentrations of 0, 75, 300 or 1200 ppm, the NOAEL was 75 ppm (equal to 5.6 mg/kg bw/day), based on increased organ-to-body-weight ratios for liver and kidney, and thyroid follicular cell hyperplasia at 300 ppm.

An oral teratogenicity study in rats was conducted at dose levels of 0, 20, 100 or 500 mg/kg bw/day. An NOAEL of 20 mg/kg bw/day for maternal toxicity and embryo/fetotoxicity was established. Maternal toxicity was seen at 100 mg/kg bw/day as decreased body weight and decreased food consumption. Embryo/fetotoxicity was observed as increased (early) resorptions, increased post-implantation losses and a decrease in viable fetuses at 100 mg/kg bw/day. No teratogenicity was observed.

In a second oral teratogenicity study in rats conducted at dose levels of 0, 20, 100 or 500 mg/kg bw/day the NOAEL for maternal toxicity and embryo/fetotoxic and teratogenic effects was 100 mg/kg bw/day. Maternal toxicity was seen at the highest dose as decreased body weight and clinical signs. Embryo/fetotoxicity and teratogenicity were seen at the highest dose as decreased fetal body weight and body length, and an increase in the number of anomalous litters and fetuses for all malformations combined and for all variations and retardations combined.

An oral teratogenicity study was conducted in rabbits at dose levels of 0, 5, 20 or 80 mg/kg bw/day. Owing to study deficiencies, an NOAEL could not be determined.

Maneb has been adequately tested in a series of *in vitro* and *in vivo* genotoxicity assays. The Meeting concluded that maneb is not genotoxic. A number of available studies were not considered, either because DMSO was used as a solvent in which maneb is very unstable or because of important omissions from the reports.

The data on maneb would support an ADI of 0-0.05 mg/kg bw, based on the NOAEL of 5.0 mg/kg bw/day for thyroid effects in rats, using a 100-fold safety factor. However, the Meeting established a group ADI of 0-0.03 mg/kg bw for maneb, alone or in combination with mancozeb, metiram and/or zineb, because of the similarity of the chemical structures of the EBDCs, the comparable toxicological profiles of the EBDCs based on the toxic effects of ETU, and the fact that parent EBDC residues cannot be differentiated using presently-available regulatory analytical procedures (see Section 4.15 - dithiocarbamates).

A toxicological monograph summarizing the data received since the previous evaluation and containing relevant summaries from previous monographs and monograph addenda on maneb was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 60 ppm in the diet, equal to 11 mg/kg bw/day (79-week study)

Rat: 80 ppm in the diet, equal to 5.0 mg/kg bw/day (13-week study)
300 ppm in the diet, equal to 20 mg/kg bw/day (31-month study)
75 ppm in the diet, equal to 5.6 mg/kg bw/day (reproduction study)

Dog: 200 ppm in the diet, equal to 6.4 mg/kg bw/day (52-week study)

Monkey: 100 ppm in the diet, equal to 7.3 mg/kg bw/day (six-month study)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw (group ADI with mancozeb, metiram, and zineb)

Studies which will provide valuable information in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Maneb, first evaluated in 1967, was scheduled for periodic re-evaluation at the 1993 JMPR (ALINORM 93/24A, para 133).

The Meeting received extensive information on GAP, supervised residue trials, metabolic fate in farm animals and crops, fate during processing, residues in food in commerce and at consumption, and methods of residue analysis.

When [^{14}C]maneb ([^{14}C]ethylenediamine) was fed to lactating goats for 5 days at the equivalent of 50 ppm maneb in the feed, the total ^{14}C residues in milk were close to a steady-state concentration by days 3 and 4. The levels in the morning milk samples, collected just

before the daily dose, were always considerably lower than in the evening samples, which suggested that levels in milk would decrease rapidly when dosing ceased. Total ^{14}C residues were distributed among the tissues and milk, with the highest levels in the liver and kidney. Ethyleneurea, 1-(2-imidazolin-2-yl)-2-imidazolidinethione and ethylenethiourea (ETU) were identified in all the tissues and milk. The main primary metabolite was Jaffe's base (1-(2-imidazolin-2-yl)-2-imidazolidinethione). Much of the ^{14}C had been incorporated into natural products.

ETU was identified in the goat tissues and milk. The levels of ETU by direct chemical analysis were: liver 0.075 mg/kg, kidney 0.050 mg/kg, muscle 0.035 mg/kg, fat <0.01 mg/kg, milk 0.037 mg/kg.

When [^{14}C]maneb ([^{14}C]ethylenediamine) was fed to laying hens for 7 days at the equivalent of 51 ppm maneb in the feed, the total ^{14}C residues in egg whites had reached a plateau by days 5-6 while the total ^{14}C in egg yolk was still increasing at the end of the study. Total ^{14}C was distributed among the tissues, but the highest levels were in the liver and kidney. Ethyleneurea was the main metabolite. Ethyleneurea, 1-(2-imidazolin-2-yl)-2-imidazolidinethione and ethylenediamine were identified in all of the tissues, egg white and egg yolk. Much of the ^{14}C had been incorporated into natural products.

ETU was identified in all of the tissues (except skin) and eggs. ETU levels in tissues and eggs by direct chemical analysis were: liver 0.14 mg/kg, breast muscle 0.044 mg/kg, egg white 0.098 mg/kg, and egg yolk 0.039 mg/kg.

Lettuce plants treated with foliar sprays of [^{14}C]maneb were harvested and surface-rinsed with an EDTA solution to identify the components of the dislodgable residue. Surface residues included mainly maneb and the primary metabolites ethylenebisisothiocyanate sulphide, ethyleneurea and ethylenethiourea. The identified metabolites in the lettuce tissue included ethylenebisisothiocyanate sulphide, ethyleneurea, ethylenethiourea, ethylenediamine and *N*-acetylethylenediamine. Amino acids and protein were found to contain ^{14}C, which demonstrated that metabolites had been incorporated into the natural carbon pool. ETU accounted for 7% of the total ^{14}C residues in lettuce + rinsings, or 2.8% of the total ^{14}C in the rinsed lettuce.

Most of the ^{14}C residues were in the foliage, with less than 0.3% in the tubers, of potatoes harvested 17 days after the final foliar application of [^{14}C]maneb. The primary metabolites constituted only a minor part, less than 9%, of the residues in the tuber. ETU identified in the potato peel, but not in the body of the tuber, (0.02 mg/kg tuber, by direct chemical analysis) was thought to be the result of contamination rather than of metabolism. The metabolism may be interpreted in terms of a relatively rapid conversion of the primary metabolites to a common plant metabolite such as glycine, which provides the mechanism for the ^{14}C to be incorporated widely into natural products.

In a metabolism study tomato plants were treated with foliar sprays of [^{14}C]maneb and harvested 24 days after the final application for metabolite identification and analysis. Much of the ^{14}C residue (49-63%) was dislodgable and was removed from harvested tomatoes when they were washed with a 1% EDTA solution. Maneb and EBIS (ethylenebisisothiocyanate sulphide) constituted the major part of the dislodgable residue; most of the ETU residue in the whole tomatoes was dislodgable. EBIS was the major metabolite identified in the whole tomato. The processes in tomato metabolism are similar to those in the other crops studied. The ^{14}C enters the metabolic carbon pool probably via glycine, from which it is incorporated into natural products.

Maneb is registered as a protective fungicide for use on pome fruits, stone fruits, berries and other small fruits, tropical and subtropical fruits, bulb vegetables, root and tuber vegetables, Brassica vegetables, leafy vegetables, stalk and stem vegetables, fruiting vegetables, legume vegetables, cereals, and tree nuts in many countries.

Typical spray concentrations for high-volume application are 0.15-0.3 kg ai/hl, and typical application rates for a wide range of crops are 1.3-3 kg ai/ha.

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

apples (*Netherlands, USA*), peaches (*USA*), grapes (*USA*);

onions (*USA, Netherlands*), broccoli (*USA*), cabbage (*USA*), cucumbers (*USA*), watermelons (*USA*), endive (*Canada*), kale *(USA*), lettuce (*Canada, USA*), beans (*USA*), peppers (*USA*), sweet corn (*USA*), tomatoes (*Netherlands, USA*), potatoes (*Netherlands, UK, USA*), sugar beet (*USA*), celery (*USA*);

barley (*Netherlands*), wheat (*Netherlands, UK, USA*), almonds (*USA*);

barley straw (*Netherlands*), maize forage (*USA*), wheat straw (*Netherlands, UK*) bean vines (*USA*), almond hulls (*USA*), sugar beet tops (*USA*).

Dithiocarbamate residues are expressed as mg CS_2/kg throughout.

The residue data on apples from The Netherlands could not be evaluated because the recommended use pattern was expressed in terms of spray concentration while the trial use pattern was expressed in terms of application rate. The US apple trials did not meet GAP conditions because the longest treatment-to-sampling interval in the trials was 30 days, but the US recommended use pattern requires a 77-day PHI.

Peach trials in the USA could not be evaluated because GAP information was not available.

The highest residues in grapes were 1.8 and 1.9 mg/kg in US trials where maneb was used within GAP conditions. The Meeting estimated a maximum residue level of 2 mg/kg for maneb uses on grapes.

Maneb use on green onions according to US GAP resulted in residues up to 7.4 mg/kg. The Meeting noted that analysis of a control sample of green onions produced 0.5 mg/kg as CS_2, probably resulting from endogenous CS_2. The Meeting estimated a maximum residue level of 10 mg/kg for spring onions.

The maneb application rate to bulb onions in Netherlands trials was 2.4 kg ai/ha, which is higher than the Netherlands recommended rate of 1.6 kg ai/ha. Residues in bulb onions are likely to arise from inadvertent spraying of exposed onions; the application rate will not be so influential on the residues. Dithiocarbamate residues in onions from the Netherlands trials were low (0.1 mg/kg and lower).

The recommended PHI in the USA for bulb onions is 7 days, but in the trials onions were harvested on the same day as the final spray and the results could not be evaluated against the recommended use pattern. The Meeting noted the repeated detection of CS_2 in control samples at levels up to 0.13 mg/kg.

Broccoli in US trials was sampled 3 and 4 days after the final maneb application, but US GAP specifies a PHI of 7 days. The Meeting noted the detection of CS_2 in control samples at levels up to 0.55 mg/kg, which was consistent with other analyses on control broccoli (up to 0.79 mg/kg as CS_2). The Meeting did not estimate a maximum residue level for broccoli because of the limited number of trials. It drew attention to the endogenous CS_2 levels in broccoli and possible endogenous CS_2 in related crops.

The highest residue in untrimmed cabbage from US maneb trials in 1987 was 10 mg/kg, but residues in that trial seemed much higher than the others. These trials and four others in 1989 and 1990 also included analyses of trimmed cabbages; removal of the wrapper leaves reduced maneb residue levels by an average of 30%. The highest residue in a control sample was 0.59 mg/kg, suggesting that endogenous CS_2 levels could be similar to those reported for broccoli. The Meeting estimated a maximum residue level of 5 mg/kg for maneb uses on cabbage and noted that the correct portion of the sample for analysis included the wrapper leaves unless obviously withered or decayed.

Dithiocarbamate residues in cucumbers exceeded 1 mg/kg in one trial when maneb was used according to GAP in a series of trials in the USA in 1987 and 1989. The Meeting estimated a maximum residue level of 2 mg/kg for maneb uses on cucumber.

The highest dithiocarbamate residue in watermelons was 0.57 mg/kg when maneb was used according to US GAP. An experiment in one trial demonstrated that residues existed exclusively on the peel and not in the pulp. The Meeting estimated a maximum residue level of

1 mg/kg for maneb uses on watermelon.

Residues in kale from a series of supervised trials in the USA during 1987 were typically in the 4-8 mg/kg range, but the highest were 14 and 28 mg/kg. The questionable aspect of this trial was that residues on day 10 after the final application were somewhat higher than on day 7. The distribution of the results suggested that residues up to 15 mg/kg would be possible. The Meeting estimated a maximum residue level of 15 mg/kg for maneb uses on kale.

Supervised trials data from Canada and the USA were made available for uses of maneb on lettuce, leaf lettuce and cos lettuce. The commodity described as lettuce was taken to be head lettuce. The highest residues in the US trials on lettuce were in the 5-7 mg/kg range. The highest residues in cos lettuce from the Canadian trials were in the 6-9 mg/kg range. Only one trial was specified as leaf lettuce and residues were just under 1 mg/kg. The Meeting estimated maximum residue levels of 10 mg/kg for uses of maneb on cos lettuce and head lettuce.

Samples from the US trials on lettuce were analysed with and without wrapper leaves. Removal of the wrapper leaves reduced residue levels by an average of 87%.

US maneb trials on spinach could not be evaluated because no US GAP was available. The trials demonstrated that maneb residue levels in washed spinach were about 25% lower than in unwashed spinach.

The official PHI for maneb use on beans in the USA is 30 days; the PHI in the trials was 4 days so no MRL could be recommended. Washing the beans did not significantly affect the dithiocarbamate residue levels.

The use of maneb on sweet peppers in US trials in 1987-89 typically produced residues in the 0.2-1 mg/kg range. The Meeting estimated a maximum residue level of 1 mg/kg for maneb uses on sweet peppers.

For sweet corn in the USA the registered application rate and PHI are 1.3 kg ai/ha and 7 days. The use pattern in the trials was 1.8 kg ai/ha with 4- and 5-day PHIs; consequently, a maximum residue level could not be estimated.

The highest dithiocarbamate residue in tomatoes arising from maneb use within US GAP was 2.0 mg/kg. Most commonly, residues were in the 0.1-0.5 mg/kg range. The Meeting estimated a maximum residue level of 2 mg/kg for the use of maneb on tomatoes.

Potato trials from The Netherlands could not be evaluated because application rates were double the official rate, 1.6 kg ai/ha, and because Netherlands GAP did not specify a PHI. Residues in potatoes in UK trials were undetectable (<0.01 mg/kg) with application at recommended rates and double recommended rates.

In 8 of the 9 US maneb trials on potatoes residues were not detected (<0.03 mg/kg), and in the other trial residues of 0.23 mg/kg were recorded for one plot. Maneb residues are generally immobile in the plant and residues on the tuber are only likely to arise if tubers are exposed above the soil during spraying. The Meeting estimated a maximum residue level of 0.2 mg/kg for maneb uses on potatoes.

In one sugar beet trial in the USA residues were much higher than in the remaining trials. Residues in the sugar beet tops up to 76 and 88 mg/kg seemed excessive for an application rate of 1.8 kg ai/ha. The Meeting was unable to estimate maximum residue levels for sugar beet or sugar beet leaves and tops because the number of trials was too small.

Supervised maneb trials on celery in the USA and barley in The Netherlands could not be evaluated because no relevant GAP was available.

When maneb was used within GAP on wheat in The Netherlands and the UK dithiocarbamate residues were mostly undetectable or in the 0.01-0.05 mg/kg range. The highest residue (0.65 mg/kg) from one plot of a trial in The Netherlands appeared to be anomalous; residues in wheat from the other plot in the same trial were undetectable (<0.01 mg/kg). The Meeting estimated a maximum residue level of 0.2 mg/kg for the use of maneb on wheat.

Residues in almonds from maneb trials in the USA were mostly undetected (<0.03 mg/kg). The Meeting estimated a maximum residue level of 0.05 mg/kg for almonds from the use of maneb.

Residues in wheat straw from The Netherlands and the UK ranged up to 2.1 mg/kg for registered uses of maneb. The Meeting estimated a maximum residue level of 5 mg/kg for wheat straw and fodder, resulting from maneb uses.

GAP information was not available for maize forage or bean vines, so trials data could not be evaluated for MRL purposes. Barley straw data from Netherlands trials evaluated against registered wheat uses supported the estimated maximum residue level in wheat straw and fodder resulting from maneb uses.

Many of the residues in almond hulls were in the 3-10 mg/kg range in US maneb trials on almonds, but the distribution of results suggested that residues in the 10 to 20 mg/kg would be likely from use according to GAP. The Meeting estimated a maximum residue level of 20 mg/kg for almond hulls.

Processing studies were made available to the Meeting on apples, beans, grapes, sugar beet, sweet corn and tomatoes.

Maneb residues in apple juice were approximately 20-50% of the levels in apples when no washing step was included in the process. Maneb residues were retained in the pomace fraction. ETU residue levels in the juice were lower than in the raw commodity.

Beans field-treated with maneb were passed through a simulated commercial process to produce canned beans, frozen beans and pureed beans (baby food). Dithiocarbamate residue levels were much reduced in frozen beans and were at very low levels in canned beans and not detectable in baby food. Heat was used in the production of these commodities; consequently ETU was produced in all of them.

In the processing of maneb-treated grapes dithiocarbamate residue levels in wet pomace and thick grape juice were approximately 60% and 7% respectively of the level in the raw grapes. Juice was heated at 82-85°C before being separated into thick juice and clear juice. The heating caused substantial conversion to ETU, the level in the thick juice being 5 mg/kg.

Dithiocarbamate and ETU residues were not detectable (<0.03, <0.01 mg/kg respectively) in white sugar produced from sugar beet field treated with exaggerated application rates (tenfold) of maneb in the USA.

Dithiocarbamate and ETU residues were not detectable (<0.03, <0.01 mg/kg respectively) in sweet corn (cut, washed and blanched) produced in a commercial process from sweet corn field-treated with a fivefold application rate of maneb in the USA.

Dithiocarbamate and ETU residues were at or about limits of quantification (0.03 and 0.01 mg/kg respectively) in canned whole tomatoes, tomato puree, tomato ketchup and tomato juice commercially produced from tomatoes field-sprayed with maneb at twice the recommended application rate in the USA. It is likely that the first step, commercial washing, reduced residue

levels substantially.

No freezer storage stability studies for maneb were available. Because of the nature of the residue the Meeting agreed that the results of the storage stability studies for mancozeb would also apply to maneb.

Information on dithiocarbamate surveys of food items is included in Section 4.28 - mancozeb.

Analytical methods for maneb residues rely on conversion by acid hydrolysis to CS_2, which is then measured colorimetrically or by GLC. Information on methods for dithiocarbamates and ETU is included under mancozeb (4.28).

4.30 METIRAM (186)

TOXICOLOGY

zinc ammoniate ethylenebis(dithiocarbamate) - poly(ethylenethiuram disulphide)
Note: metiram appears to be a mixture rather than a complex.

Metiram was considered for the first time by the present Joint Meeting.

Metiram was incompletely absorbed when administered orally to rats. Elimination was primarily via the faeces, with minimal biliary excretion. Comparatively higher urinary excretion at low doses suggested that metiram may be more poorly absorbed at higher doses. The highest residual tissue levels were found in the thyroid and kidney, with slightly higher concentrations present in females than in males. Comparison of tissue residues after single or multiple doses suggested slight accumulation in the body with multiple dosing.

The metabolism of metiram has not been completely elucidated. In the rat, the predominant urinary components were polar and were identified as ethylenediamine, *N*-acetylethylenediamine, ethanolamine, oxalic acid and glycine. Major, less polar components were ethyleneurea, ethylenethiourea (ETU) and ethylenebisisothiocyanato sulphide.

Metiram was practically non-toxic upon acute oral, dermal and inhalation administration to rats. The WHO has classified metiram as unlikely to present acute hazard in normal use.

The principal target organ upon repeated dietary exposure to metiram was the thyroid.

Mice treated with metiram for three months at 0, 300, 1000, 3000 or 7500 ppm in the diet revealed minimal to slight hypertrophy and vacuolation of the thyroid follicular epithelium in both sexes at levels of 3000 ppm and above. An NOAEL of 300 ppm (equal to 84 mg/kg bw/day) was based on decreased serum T_4 levels in both sexes at levels of 1000 ppm and above.

Thirteen-week dietary administration of metiram to SD CFY rats at 0, 50, 100, 300 or 900 ppm revealed an NOAEL of 100 ppm (equal to 6 mg/kg bw/day), based on decreased serum T_4 levels and increased thyroid weights at dietary levels of 300 and 900 ppm. Slight to minimal hyperplasia of the thyroid was observed at 900 ppm. Although reduced iodine uptake by the thyroid was observed at all dietary levels, these changes were shown to be reversible following the cessation of treatment. At the lowest dietary levels of 50 and 100 ppm, the effects on iodine uptake were not correlated with changes in thyroid hormone levels or any overt morphological alterations of the thyroid gland, thus rendering the toxicological significance of this finding doubtful.

In a recently conducted three-month study with Wistar rats receiving metiram at 0, 5, 80, 320 or 960 ppm in the diet, decreased serum T_4 levels and increased thyroid weights were observed at 960 ppm. Slight evidence of anaemia was observed at 320 ppm, indicating an NOAEL of 80 ppm (equal to 5.8 mg/kg bw/day).

Other effects of treatment in the diet with metiram in the rat were manifest as hind limb paralysis with corresponding atrophy of muscle fibres. In the 13-week study with SD CFY rats, microscopic changes in muscle fibres at levels of 300 ppm (equal to 20 mg/kg bw/day) and above were still prevalent in previously treated rats after the 6-week recovery period. Muscular atrophy was observed in a long-term study in SD CD rats treated at the highest level of 320 ppm (see below). General muscle weakness/ataxia and reduced grip strength of the limbs with no histopathological consequences were observed in the 3-month study with Wistar rats fed metiram at the highest level of 960 ppm.

A 52-week study in dogs at dietary levels of 0, 30, 80, 1000 or 3000 ppm yielded an NOAEL of 80 ppm (equal to 2.5 mg/kg bw/day), based on thyroid follicular hyperplasia with increased size, thickening and weight of this organ, in conjunction with decreased serum T_4 levels at dietary levels of 1000 ppm and above. Other effects recorded at 1000 ppm and above were a dose-related increased incidence of focal hepatic lipofuscin pigment deposition, slight evidence of anaemia, diarrhoea and changes in blood biochemical parameters. A preliminary 4-week study in dogs uncovered an increased frequency of microfollicles in the thyroid, in association with colloid depletion and minimal hyperplasia in both sexes treated at the highest level of 900 ppm (equal to 41 mg/kg bw/day).

Metiram given by gavage to rhesus monkeys at dose levels of 0, 5, 15 or 75 mg/kg bw/day for a period of 26 weeks indicated an NOAEL of 5 mg/kg bw/day, based on significantly decreased serum T_3 and T_4 levels, increased thyroid weights and minimal thyroid follicular hyperplasia at 15 and 75 mg/kg bw/day. Morphological changes of the thyroid were still apparent after a 15-week recovery period. In the absence of any correlation between thyroid hormone levels and morphological alterations, no significance was attributed to fluctuations in iodine uptake by the thyroid recorded at 5 mg/kg bw/day.

Long-term dietary treatment of mice with metiram at 0, 100, 300 or 1000 ppm resulted in an NOAEL of 300 ppm (equal to 24 mg/kg bw/day), based on decreased body weights recorded at 1000 ppm. Chronic dietary administration of metiram to SD CD rats at 0, 5, 20, 80 or 320 ppm revealed muscular atrophy at 320 ppm (equal to 12 mg/kg bw/day), with an NOAEL of 80 ppm (equal to 3.1 mg/kg bw/day).

Metiram was not carcinogenic when fed to mice or rats at dietary levels of up to 1000 and 320 ppm, respectively.

A three-generation, two litter per generation reproduction study in rats treated at 0, 5, 40 or 320 ppm in the diet failed to reveal any adverse effects on reproductive parameters. The NOAEL was 40 ppm (equal to 1.8 mg/kg bw/day), based on decreased parental body weight and food consumption recorded in the F_0 and F_1 generations treated at 320 ppm.

Metiram when administered to pregnant rats at 0, 40, 80 or 160 mg/kg bw/day or rabbits at 0, 10, 40 or 120 mg/kg bw/day during critical periods of organogenesis was not teratogenic at any dose. The NOAEL for maternal toxicity in the rat was 80 mg/kg bw/day, based on decreased body-weight gain and in the rabbit the NOAEL was 10 mg/kg bw/day, based on increased abortions, decreased body weights and decreased food consumption. The NOAELs for embryo/fetotoxicity were 80 mg/kg bw/day in the rat, based on slight decreases in litter size and weight, and 40 mg/kg bw/day in the rabbit, based on decreases in mean fetal weights.

Metiram has been tested in a series of *in vitro* and *in vivo* genotoxicity assays. The Meeting concluded that metiram is not genotoxic.

The Meeting allocated an ADI of 0-0.03 mg/kg bw, based on an NOAEL of 2.5 mg/kg bw/day in the 52-week study in dogs, using a 100-fold safety factor. This ADI is supported by the NOAEL of 3.1 mg/kg bw/day observed in the long-term study in rats. This ADI served as the basis for a group ADI that was established for metiram, alone or in combination with mancozeb, maneb, and/or zineb (see Section 4.15 - dithiocarbamates).

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

TOXICOLOGICAL EVALUATION

Level(s) causing no toxicological effect

Mouse: 300 ppm, equal to 24 mg/kg bw/day (88-week study)

Rat: 80 ppm, equal to 3.1 mg/kg bw/day (111-week study)
40 ppm, equal to 1.8 mg/kg bw/day (reproduction study)

Rabbit: 10 mg/kg bw/day (teratogenicity study)

Dog: 80 ppm, equal to 2.5 mg/kg bw/day (52-week study)

Monkey: 5 mg/kg bw/day (26-week study)

Estimate of acceptable daily intake for humans

0 - 0.03 mg/kg bw (group ADI with mancozeb, maneb, and zineb)

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

4.31 MONOCROTOPHOS (054)

TOXICOLOGY

Monocrotophos was evaluated by the Joint Meeting in 1972, 1975, and 1991. In 1991 the ADI was changed to 0-0.00005 mg/kg bw, based on an NOAEL of 0.005 mg/kg bw/day in a two-year study in rats. The Meeting identified (1) genotoxicity studies, known to exist, with commercial and purified monocrotophos and (2) historical control data on the incidence of brain malformations in rats at the laboratory that performed a recent teratogenicity study in rats, as being studies which would provide information valuable in the continued evaluation of the compound. Information relevant to these issues (new teratogenicity studies in rats and rabbits) was considered at the present Meeting. In addition, a human volunteer study that was reviewed at the 1975 Joint Meeting was re-evaluated together with all other available human data.

Monocrotophos is rapidly excreted without evidence of significant accumulation in the body.

In a new teratogenicity study in rats, no evidence of teratogenicity or embryo/fetotoxicity was observed at any doses tested (up to 2 mg/kg bw/day by gavage). Malformations of the brain were not observed. The NOAEL for maternal toxicity was 0.3 mg/kg bw/day.

Upon re-evaluation of the teratogenicity study in rats reviewed by the 1991 Joint Meeting

and of additional information provided, the Meeting concluded that the previously described brain malformations were artifacts due to incorrect tissue sampling and handling. This conclusion is also supported by the lack of a clear dose-response relationship and by the new negative teratogenicity study.

In a teratogenicity study in rabbits, monocrotophos was not teratogenic at doses up to 6 mg/kg bw/day, which was lethal to the mothers. Embryo/fetotoxicity was observed at this dose. The NOAEL for maternal toxicity was found to be 1 mg/kg bw/day.

Commercial formulations containing monocrotophos are genotoxic *in vitro*. In addition, *in vivo* results suggest that these formulations may cause chromosomal damage and sperm abnormalities in rodents. High-purity monocrotophos has not been adequately tested for genotoxicity.

Carcinogenicity studies in mice and rats evaluated by the 1991 Joint Meeting were negative.

In a human volunteer study (6 males), an oral dose of 0.0059 mg/kg bw/day for 30 days caused up to 28% plasma cholinesterase depression without erythrocyte cholinesterase depression.

The Meeting allocated an ADI of 0-0.0006 mg/kg bw on the basis of the 30-day human volunteer study with an NOAEL of 0.006 mg/kg bw/day based on the absence of erythrocyte cholinesterase inhibition, using a 10-fold safety factor.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: <1 ppm in the diet, equivalent to <0.15 mg/kg bw/day (two-year study) (1991 JMPR)

Rat: 0.1 ppm in the diet, equivalent to 0.005 mg/kg bw/day (two-year study) (1991 JMPR)

Human: 0.006 mg/kg bw/day (30-day study)

Estimate of acceptable daily intake for humans

0-0.0006 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Further observations in humans.

2. Genotoxicity studies with high-purity monocrotophos.

4.32 PHORATE (112)

RESIDUE AND ANALYTICAL ASPECTS

New information on use patterns and data on residues in carrots resulting from supervised trials were evaluated. The MRL proposed for carrots (0.5 mg/kg) by the 1977 Joint Meeting has been the subject of much discussion at the CCPR as it would appear that the use is limited to

the United Kingdom and Australia. GAP in the United Kingdom will result in residues that are unlikely to exceed 0.2 mg/kg. The residue data available were inadequate to permit an effective assessment of the residues likely to result from Australian GAP.

4.33 PHOSALONE (060)

TOXICOLOGY

Phosalone was previously evaluated by the Joint Meeting in 1972, when an ADI of 0-0.006 mg/kg bw/day was allocated.

After oral administration, phosalone was moderately well absorbed, 15-25% appearing in the faeces. It was extensively metabolized to phosphorothioates, phosphorodithioates and 3-methylthiomethyl-6-chlorobenzoxazolone, the last of which is subsequently metabolized ultimately to 3-methylsulphonylmethyl-6-chlorobenzoxazolone.

Pure phosalone is almost certainly not a cholinesterase inhibitor, but acquires inhibitory activity after conversion to phosalone oxon *in vivo*.

The acute oral toxicity varies with species, but is in the region of 100-200 mg/kg bw in rodents. Phosalone has been classified as moderately hazardous by WHO.

There were two short-term studies in rats which could be used to give NOAELs. In a five-week oral gavage study at doses of 0, 7.5 or 15 mg/kg bw/day, the NOAEL was 7.5 mg/kg bw/day, based on brain cholinesterase inhibition. In an eight-week study in rats using dietary concentrations of 0, 10, 100, 300, 600 or 1200 ppm, the NOAEL was 10 ppm (equal to 0.87 mg/kg bw/day), based on brain cholinesterase inhibition. It is possible that NOAELs could have been established at 100 or 300 ppm, but the dose rates for those groups were increased to 2,400 and 4,800 ppm, respectively, after 5 weeks to establish a maximum tolerated dose.

Five studies were carried out in dogs. In a one-month oral dosing study, an NOAEL could not be determined as plasma and erythrocyte cholinesterase depression were seen at the lowest dose (7.5 mg/kg bw/day). In another one-month study using dietary concentrations of 0, 12.5, 25 or 37.5 ppm, the NOAEL was at the highest level, which was equal to 0.81 mg/kg bw/day; although plasma cholinesterase depression was seen in the study, neither erythrocyte nor brain cholinesterase activity was depressed. In a 6-month study using dietary concentrations of 0, 10 or 25 ppm, although plasma and erythrocyte cholinesterase were depressed the brain enzyme was not, so the NOAEL was the highest dose (equivalent to 0.63 mg/kg bw/day). In a two-year study in beagle dogs, males and females were fed phosalone in the diet at concentrations of 0, 100, 200 or 1000 ppm. The NOAEL was 200 ppm, equivalent to 5 mg/kg bw/day, based on brain cholinesterase depression, body-weight loss and elevated alanine aminotransferase at the highest dose. In a more recent one-year study in dogs using dietary concentrations of 0, 5, 25 or 300 ppm phosalone, the NOAEL was 25 ppm (equal to 0.89 mg/kg bw/day), based on brain cholinesterase depression at 300 ppm. The overall NOAEL for dogs was considered to be 200 ppm, in view of the spacing of the doses in the most recent study.

In a lifetime carcinogenicity study in mice, phosalone was given at dietary concentrations of 0, 15, 50 or 150 ppm. The NOAEL was 150 ppm, equal to 23 mg/kg bw/day, based on the lack of depression of brain cholinesterase activity, although plasma and red blood cell cholinesterase depression were seen at this level. There was no evidence of carcinogenicity.

In a two-year study in rats using concentrations of 0, 25, 50 or 250 ppm phosalone in the diet, the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day, based on brain cholinesterase depression at the highest dose. In a second 2-year study in rats, dietary concentrations of 0,

5, 50 or 1000 ppm were used, the highest dose being reduced to 500 ppm later in the study. There was a statistically significant increase in the prevalence of testicular atrophy and reduction in testicular weight in both the high and mid-dose groups and a dose-response relation across all groups for both effects. The Meeting concluded that the NOAEL was ≤5 ppm, ≤0.2 mg/kg bw/day.

In a teratogenicity study in rats at doses of 0, 2, 10 or 20 mg/kg bw/day, the NOAEL was 10 mg/kg bw/day for both maternal toxicity and fetotoxicity. In a study in rabbits, using doses of 0, 2, 6 or 18 mg/kg bw/day, the NOAEL was the highest dose. In another study in rabbits, using doses of 0, 1, 10 or 20 mg/kg bw/day, the NOAEL was 10 mg/kg bw/day, based on maternal toxicity. Phosalone was not teratogenic in either the rat or rabbit.

Two multigeneration reproduction studies in rats were reviewed. In the first study, using dietary concentrations of phosalone of 25 or 50 ppm, no adverse effects were observed. The NOAEL was ≥ 50 ppm, equivalent to 2.5 mg/kg bw/day. In the second study, in which phosalone was administered at dietary concentrations of 0, 10, 50 or 400 ppm, the NOAEL was 50 ppm (equivalent to 2.5 mg/kg bw/day), based on retarded pup growth and plasma and erythrocyte cholinesterase depression.

Phosalone has been adequately tested in a series of *in vitro* and *in vivo* genotoxicity assays. The Meeting concluded that phosalone was not genotoxic.

There is no evidence that phosalone has the potential to cause delayed neuropathy.

Pralidoxime salts and obidoxime are both effective in experimental phosalone poisoning.

No human study was available from which an NOAEL could be derived.

An ADI of 0-0.001 mg/kg bw was established, based on the lowest dose (0.2 mg/kg bw/day) in the recent two-year study in rats. A 200-fold safety factor was used because of concerns that the trend for the occurrence of testicular atrophy and reduction in testis weight existed across all groups.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 150 ppm, equal to 23 mg/kg bw/day (two-year study)

Rat: <5 ppm, equal to 0.2 mg/kg bw/day (two-year study)
50 ppm, equivalent to 2.5 mg/kg bw/day (multigeneration reproduction study)

Rabbit: 10 mg/kg bw/day (teratology study)

Dog: 200 ppm, equivalent to 5 mg/kg bw/day (several studies)

Estimate of acceptable daily intake for humans

0-0.001 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Explanation of the testicular atrophy seen in the recent study in rats.

2. Observations in humans.

4.34 PROCYMIDONE (136)

RESIDUE AND ANALYTICAL ASPECTS

Procymidone was reviewed by the Joint Meeting in 1981, 1989 and 1990. The 1992 CCPR retained all MRLs at step 7B in view of the need to ensure that the residue data which were reviewed in 1981 reflected current GAP.

Residue data for common beans, cucumbers, grapes, lettuce, bulb onions and tomatoes were required together with information on current GAP.

In response to the request of the CCPR extensive information was provided by the manufacturer and some member countries on use patterns, together with some residue data from supervised field trials and monitoring.

In order to estimate maximum residue levels, the residues resulting from supervised trials published in the previous evaluations which accorded with current use patterns (GAP) were also taken into consideration.

Apples. GAP was reported from Japan and the Lebanon. Two trials reported from Japan in 1981 do not reflect GAP in either country. The previous recommendation (5 mg/kg) is withdrawn.

Cherries. GAP was reported from 6 countries. The maximum dosage rate is 0.75 kg ai/ha with a PHI of 14-28 days. A single trial in Hungary corresponds to current GAP. However the initial residues (0.8 mg/kg) are much lower than in the Australian trials (2.1-6.2 mg/kg) reflecting GAP which were reported in 1990. The previous recommendation (5 mg/kg) is replaced by 10 mg/kg.

Beans. GAP was reported from 6 countries with PHIs ranging between 2 and 21 days. Residues, reported in 1981, 1989 and 1993, deriving from corresponding national GAP (7-14 days, maximum 0.75 kg ai/ha) range from 0.1 to 0.8 mg/kg. The current GAP leads to lower residues, consequently the recommended limit is 1 mg/kg.

Cucumbers and gherkins. GAP was reported from 12 countries with PHIs ranging between 1 and 15 days. Trials reported in 1981 from Japan which reflect current GAP showed residues of 0.33-1.2 mg/kg at day 1. The previous recommendation (2 mg/kg) is maintained.

Currants. GAP was reported from one country where procymidone is used for stock treatment. Two trials reported in 1981 involved foliar applications to black currants. The residue limit established previously is not supported by current GAP, so the recommendation (10 mg/kg) is withdrawn.

Egg plants. GAP was reported from 6 countries with PHIs of 1-3 days. Residues from a trial in Poland ranged from 0.6 to 0.93 mg/kg at days 1 and 3. A trial reported from France in 1981 showed a residue level of 1.5 mg/kg at 14 days. The data are insufficient to estimate a maximum residue level, so the recommendation (2 mg/kg) is withdrawn.

Grapes. GAP was reported from 27 countries with PHIs of 1-28 days, 1-4 applications at 0.25-1.0 kg ai/ha. An extensive trial programme was conducted in seven wine-growing regions of Europe. Dosage and pre-harvest intervals were selected according to the relevant national GAP which cover the world-wide uses. Residues deriving from recommended uses ranged from 0.34 mg/kg to 4.6 mg/kg. They are in the same range as those obtained in earlier trials. The present limit (5 mg/kg) is reaffirmed and it should no longer be temporary.

Kiwifruit. GAP was reported from Italy. The trial conditions reported from New Zealand in 1981 reflect the current Italian GAP, but there was no information on the comparability of climatic conditions and cultural practices. Consequently the previous recommendation (7 mg/kg) is withdrawn.

Lettuce. GAP was reported from 16 countries with PHIs of 2-35 days. The number of applications is from 1 to 10, and the rates are between 0.28 and 2 kg ai/ha. Residues reported from France (indoor and outdoor) and Spain were in the range of 0.07 to 3.4 mg/kg 21-22 days after the last application. The residues derived from glass-house applications were about 2 to 4 times those from trials conducted outdoors. The previous recommendation (5 mg/kg) is reaffirmed.

Melons. GAP was reported from 4 countries. Trials reported in 1981 reflect the current use patterns, but no residues were reported in the whole commodity. The data base is considered inadequate for estimating a maximum residue level. The previous recommendation (1 mg/kg) is withdrawn.

Onions. GAP was reported from 14 countries with PHIs of 1-28 days. Trial conditions reported in 1981 are within the current recommended uses and lead to residues in the range of 0.01-0.14 mg/kg which support the present limit (0.2 mg/kg).

Peaches and nectarines. GAP for foliar and post-harvest applications was reported from 15 countries with PHIs of 1-14 days and maximum rates of 0.37-1.0 kg ai/ha applied 2-5 times. The trial conditions reported from Australia and New Zealand in 1981 and 1990 are in line with present use recommendations. The previous recommendation (10 mg/kg) is reaffirmed.

Peppers. GAP was reported from 11 countries on sweet, green and chilli peppers with PHIs of 1-7 days. The trials reported from Japan in 1981 reflect the current use and lead to residues up to 3.8 mg/kg one day after the last application. The present limit (5 mg/kg) is reaffirmed.

Potatoes. GAP was reported from 5 countries with PHIs of 3-35 days. In two Japanese trials, carried out in 1977 but reported in 1981 and again in 1993, the residues were 0.02, 0.03, 0.05 and 0.08 mg/kg in potatoes 19-28 days after the last application. The data base was considered inadequate to estimate a maximum residue level. The previous recommendation (0.1 mg/kg) is withdrawn.

Raspberries. GAP was reported from 3 countries with PHIs of 7-14 days. In German trials reported in 1989 residues ranged from 0.59 to 6.9 mg/kg at 14 days after applications according to current GAP. Trials in France in 1989 and in Hungary and Poland in 1992 resulted in lower residues, but the combined data support the present limit (10 mg/kg).

Rice. GAP was reported from Thailand where the application is repeated every 7-10 days. Results reported in 1981 were from samples taken 19-22 days after the last application with about 2.5 times the rate registered in Thailand. The trial conditions cannot be related to GAP, so the recommendations (rice, husked: 3 mg/kg and rice, polished: 1 mg/kg) are withdrawn.

Strawberries. GAP was reported from 27 countries with PHIs of 2-21 days and application rates of 0.23-1.0 kg ai/ha. Residues from field trials in France, Germany, The Netherlands and Poland in 1981 ranged from 0.4 to 5.1 mg/kg. Following glasshouse application in Japan, the residues were between 0.9 and 8.0 mg/kg. Residues reported from Spain in 1993 were in the range of 1.3-4.24 mg/kg. The previous recommendation (10 mg/kg) is maintained.

Sunflower seed. GAP was reported from 6 countries with PHIs of 14-42 days. Residues deriving from treatments with recommended and double rates were in the range of 0.02 to 0.12 mg/kg 14-28 days after the last application. The Meeting considered the results of a single trial leading to high residues atypical and estimated a maximum residue level of 0.2 mg/kg which

replaces the previous recommendation (2 mg/kg).

Tomatoes. GAP was reported from 25 countries with PHIs of 1-21 days and maximum rates of 0.5-1.8 kg ai/ha. Residues reported from France, Japan and New Zealand in 1981, from New Zealand in 1990 and from Italy in 1993 ranged from 0.1 to 2.1 mg/kg with a residue of 2.5 mg/kg at day 1 from a glasshouse trial in Japan. The previous recommendation (5 mg/kg) is maintained.

The fate of residues in wine processing was extensively studied. Grapes were harvested from 42 separately treated test plots and fermented into wine. The vinification procedure used for grapes from a given site was chosen to match the procedure used locally in the country or region of origin. The use of different procedures, each typical of the locale in which the grapes originated, allows a realistic estimation of residues expected in commercially-produced wine.

In addition to procymidone, 3,5-dichloroaniline (DCA), which may be formed during or just after vinification, was also determined in the wine.

When grapes were treated according to GAP, the wine contained procymidone residues between 0.04 and 0.59 mg/kg. The level of DCA ranged from <0.01 to 0.07 mg/kg in the same samples.

The results indicate that procymidone residues remaining in or on grapes after treatment show no tendency to concentrate in the wine. The average wine/grape ratio for procymidone ranged between 0.07 and 0.27, with an overall average of 0.16. DCA amounted to a maximum of 20% of the procymidone concentration in wine.

Sunflower seeds, containing residues of 0.04-0.12 mg/kg, were processed to oil. The crude and refined oil samples contained residues of 0.1-0.34 mg/kg and 0.08-0.14 mg/kg respectively. The concentration factors were between 2 and 3 for seed to crude oil, and between 1 and 2 for seed to refined oil.

A survey of procymidone residues in fresh fruits and vegetables imported by Finland gave positive results in 16 commodities. The maximum values were below the recommended limits in all cases. The commodities in which the positive results exceeded 10% were the following: broccoli 28%, cucumber 47%, pear 65%, sweet pepper 26%, strawberry 32%, tomato 15%. It is to be noted that maximum residue levels have not been estimated by previous Meetings for broccoli or pears. Furthermore, information on current GAP indicates that the compound is registered for pears only in Italy and not at all for broccoli.

4.35 PROPINEB

TOXICOLOGY

Propineb was first evaluated by the Joint Meeting in 1977, when a temporary ADI of 0-0.005 mg/kg bw/day was established. The temporary ADI was extended in 1980 and 1983. At the 1985 Joint Meeting, the temporary ADI was not extended in view of the carcinogenic response in the liver of mice to propylenethiourea (PTU) and the lack of NOAELs for thyroid effects of propineb and PTU.

Orally administered propineb in rats is rapidly absorbed and excreted largely via urine and faeces. Although there was some evidence of excretion by exhalation, the available metabolic studies (which detected PTU and propyleneurea as the main urinary metabolites together with propylenediamine and a small amount of 4-methylimidazoline) found no metabolites which could be considered as potential intermediates for degradation to CO_2. The study results indicated that a proportion of the administered dose accumulates temporarily in the thyroid.

Although most of the elimination occurred within 4 days of dosing, the half-life of elimination for the proportion remaining was relatively long. This could be due to incorporation of portions of the molecule into endogenous substances following metabolism, which would also account for the radioactivity eliminated with exhaled air.

Propineb has moderate to low acute toxicity in mice, rats, hamsters, cats and sheep. WHO has classified propineb as unlikely to present acute hazard in normal use.

The results of toxicity studies clearly indicate that propineb has a goitrogenic effect in rats, although no similar finding was noted in rabbits or dogs. In a 62-day study in male rats using dietary levels of 0, 2, 10, 50 or 250 ppm, the NOAEL was 10 ppm (equal to 0.74 mg/kg bw/day), based on changes in thyroxine concentration and increased thyroid weight at higher doses. Although in a later 63-day study using dietary levels of 0, 0.2, 0.6, 2 or 10 ppm slight hyperplasia was seen in the thyroid in 2 rats of 10 treated with 10 ppm, this finding was considered not to be a permanent adverse effect in rats.

In a comparative study of the effects of propineb, PTU, ETU, zineb and methylthiouracil on thyroid weight, propineb had only a moderate effect compared to methylthiouracil, whereas PTU had an equivalent effect to that of methylthiouracil and was somewhat stronger than ETU. These results suggest that the effects of propineb on the thyroid in rats may be caused primarily by the metabolite PTU. Dogs tolerated much higher doses of propineb, dietary administration of 3000 ppm, equivalent to 75 mg/kg bw/day, causing no adverse effects over 2 years.

In long-term studies, treatment-related alterations in tumour incidence were seen in rats and mice. In mice treated with 0, 50, 200 or 800 ppm, an increase in hepatocellular adenomas was seen only in males at the highest dose tested, but there was no increase in the incidence of hepatic carcinomas and no similar effect in females. The NOAEL was 200 ppm, equal to 26 mg/kg bw/day, based on this change in hepatic tumour incidence. In rats there were two studies, using dietary levels of 0, 1, 10, 100, 1000, 2000 or 8000 ppm in the first and 0, 5, 10, 25, 50 or 100 ppm in the second. The overall NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day, based on increased kidney and liver weight (without histological correlation) and increased thyroid weight at 100 ppm and above. An increase in TSH-related thyroid tumours and skeletal muscle degeneration was seen in rats at dietary levels of 1000 ppm and above, but these doses were accompanied by increased mortality.

In a three-generation reproduction study in rats using dietary levels of 0, 20, 60, 200 or 600 ppm the NOAEL was 60 ppm, equivalent to 3 mg/kg bw/day, with adverse effects on maternal health and impaired reproductive performance seen at higher doses.

Teratogenicity studies indicated that propineb has teratogenic potential in rats, but no evidence of teratogenicity was seen in rabbits even in the presence of maternal toxicity. In rats, using dose levels of 0, 3, 10, 30 or 100 mg/kg bw/day, the NOAELs were 10 and 30 mg/kg bw/day for maternal and embryo/fetotoxicity, respectively, with evidence of teratogenicity at 100 mg/kg bw/day. In rabbits, using dose levels of 0, 10, 30 or 100 mg/kg bw/day, the NOAEL for maternal toxicity was 10 mg/kg bw/day, while there was no evidence of teratogenicity or embryo/fetotoxicity at 100 mg/kg bw/day, the highest dose used.

Propineb has been adequately tested in a series of genotoxicity assays from which the Meeting concluded that it is not genotoxic.

An ADI for propineb was based on the NOAEL from the short-term thyroid function study in rats (10 ppm, equal to 0.74 mg/kg bw/day) using a safety factor of 100 (see Section 4.15 - Dithiocarbamates).

A toxicological monograph summarizing the data received since the previous evaluation

and incorporating relevant studies from the previous monograph on propineb was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 200 ppm in the diet, equal to 26 mg/kg bw/day (long-term study)

Rat: 10 ppm in the diet, equal to 0.74 mg/kg bw/day (62-day thyroid function study)
50 ppm, equivalent to 2.5 mg/kg bw/day (long-term study)

Dog: 3000 ppm in the diet, equivalent to 75 mg/kg bw/day (2-year study)

Estimate of acceptable daily intake for humans

0-0.007 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS (propineb and PTU)

Propineb was evaluated in 1977, 1984 and 1985. The temporary ADI was withdrawn by the 1985 JMPR, but the CCPR maintained the Guideline Levels for propylenethiourea (PTU). The compounds are included in the CCPR periodic review programme.

Propineb is currently registered on a large number of crops in several countries around the world, but the Meeting was informed that its actual use is restricted to a few crops. The results of numerous supervised field trials and processing studies were provided by the principal manufacturer only for grapes, tomatoes, potatoes, pome fruits, onions and melons. The use of the compound will still be recommended on these crops and on bell peppers, but the use recommendations for other crops are due to be withdrawn.

The metabolism in plants has been sufficiently presented in the 1984 Evaluations. The laboratory animal metabolism studies are discussed in the Toxicological Evaluations. The metabolic pathways in plants and animals are essentially the same. Propylenediamine and 4-methylimidazoline identified in animals were present in the form of *N*-formylpropylendiamine and 2-methoxy-4-methylimidazoline, respectively. No information was available on metabolism by farm animals or on animal transfer studies.

In the supervised trials, propineb residues were determined and expressed as mg/kg CS_2, and propylenethiourea (PTU) residues were determined and expressed as mg/kg PTU throughout.

In apples and pears, the residues of propineb ranged from <0.05 mg/kg to 0.96 mg/kg 14-21 days after the last treatment. For the main metabolite, PTU, the results were in the range of <0.02 mg/kg to 0.08 mg/kg. If propineb were used alone the estimated maximum residue levels on apples and pears would be 2 mg/kg propineb and 0.1 mg/kg PTU.

In grapes, at pre-harvest intervals ranging from 49 to 69 days, residues of propineb and PTU were between <0.05 and 1.2 mg/kg, and <0.01 and 0.08 mg/kg respectively, except in

one trial where 2.1 mg/kg propineb and 0.15 mg/kg PTU were measured. Following a different application schedule, the residues of propineb were more or less in the same range. The variety of grape did not influence the residue levels. If propineb were used alone the estimated maximum residue levels on grapes would be 2 mg/kg propineb and 0.1 mg/kg PTU.

In onions, 14 days after the last treatment, no residues of propineb were found above the limit of determination (0.2 mg/kg) in Australia. PTU was not determined. In Japanese trials seven days after the last treatment the residues of propylenediamine (PDA) were <0.05 mg/kg in four samples and 0.05 and 0.08 mg/kg in two samples, while the residues of PTU were below the limit of determination (<0.01 mg/kg). Propineb was not determined. The data are not sufficient to estimate a maximum residue level for the use of propineb on onions.

In melons, 7 to 21 days after the last treatment the residues of propineb and PTU were below the limits of determination (0.01-0.2 and 0.01 mg/kg respectively) in all samples, while PDA ranged between 0.06 and 0.72 mg/kg. If propineb were used alone the estimated maximum residue levels in melons would be 0.2 mg/kg propineb and 0.05 mg/kg PTU, both levels being at or about the limit of determination.

In tomatoes treated according to German GAP, seven days after the last application residues of propineb ranged from 0.08 to 0.55 mg/kg and residues of PTU were at or below the limit of determination of 0.02 mg/kg. If propineb were used alone the estimated maximum residue levels in tomatoes would be 1 mg/kg for propineb and 0.05 mg/kg for PTU.

In potatoes no residues of propineb or PTU were found above the limits of determination (0.2 mg/kg and 0.01 mg/kg respectively) within 8 to 69 days after the last treatment. These residue trials do not completely correspond to the current registered uses but they cover present good agricultural practice as the application rate was higher. All trials showed that in spite of the great variations in pre-harvest interval no residues of propineb or the major metabolite PTU could be detected in potatoes. If propineb were used alone the estimated maximum residue levels in potatoes would be 0.2 mg/kg propineb and 0.05 mg/kg PTU (the limits of determination).

The effects of processing on the residues were extensively studied on apples, cherries, grapes, hops and tomatoes. These studies showed that the concentration of propineb residues was reduced to non-detectable (<0.02 mg/kg) in the case of apple juice and puree, wine, beer, and tomato juice and ketchup, while in cherry juice and jam the average propineb residue was 40% of that in the fruits. The residue level of PTU in processed products is primarily influenced by the level of propineb and the mode of processing. The ratio of PTU in the processed product to propineb in the raw commodity was 0.04 for apple puree, 0.003 for beer, 0.2 for cherry juice, 0.1 for cherry jam, 0.2 for must and wine, 0.1 for tomato juice and 0.2 for ketchup. The residue levels of PTU were higher in products where the processing involves extensive contact with the peel of the harvested crop as in red wine and tomato ketchup.

The freezer storage stability of the residues in samples has not been studied systematically. However the Meeting was informed that the repeated analyses of samples analysed when taken and after prolonged freezer storage did not show any difference in the residue levels. Samples were always frozen whole before storage and homogenized deep-frozen before analysis in order to eliminate decomposition of the residues. The Meeting noted that this information provided on propineb residues was consistent with the results of frozen storage stability studies on mancozeb reported under that heading. It was also considered likely that the results of frozen storage stability studies on ETU would apply to PTU.

No information was reported on PTU levels in food moving in commerce or at

consumption.

Residue analytical methods are available to determine propineb residues as CS_2, using colorimetric or GLC detection, and PTU residues by HPLC. These methods are suitable for regulatory purposes with limits of determination of 0.1-0.2 mg/kg for CS_2 and 0.05 mg/kg for PTU. The propineb residues can be qualitatively distinguished from the other dithiocarbamates by converting them to propylenediamine which can be determined by gas chromatography after derivatization.

FURTHER WORK OR INFORMATION

Desirable

1. Residue data from supervised trials on bell peppers.

2. Freezer storage stability studies on propineb and PTU residues in representative commodities.

3. Metabolism study on farm animals.

4. Residue transfer study on farm animals.

5. Monitoring data on PTU in food in commerce and consumption.

4.36 PROPYLENETHIOUREA (PTU) (150)

TOXICOLOGY

Propylenethiourea (PTU) is a plant and animal metabolite and a degradation product of propineb. Results of the toxicological evaluation of propineb indicate that the effects of propineb on the rat thyroid may be caused primarily by PTU. PTU is also of interest because it forms part of the terminal residue to which consumers of produce treated with propineb are exposed and because the levels of PTU in treated produce generally increase during food processing as the levels of propineb decrease.

Following oral administration to rats, PTU was rapidly absorbed and eliminated in the urine and faeces. Less than 0.2% of the administered dose was detected in the exhaled air and after 10 days only 1-2% remained in the body. Biliary excretion was also observed, as was evidence for enterohepatic recirculation. Distribution in body tissues was essentially uniform, with the exception of the thyroid which had about 12 times the level found in other tissues.

The results of toxicity studies clearly indicate that PTU has a goitrogenic effect in rats. In a 21-day comparative study of the effects of propineb, PTU, ETU, zineb and methylthiouracil on thyroid weight, PTU had an equivalent effect to that of methylthiouracil, and was somewhat more potent than ETU. The thyroid enlargement was partially reversible during a 28-day withdrawal period and the results suggested that the effects of propineb on the thyroid in rats may be caused primarily by the metabolite PTU. In a 63-day study in male rats, in which PTU was administered in the drinking water at levels of 0, 0.1, 0.3, 1 or 10 ppm, no consistent effects on thyroid function were seen at doses up to 10 ppm, the highest dose tested, which was equal to 1 mg/kg bw/day. In a 24-month study on thyroid function, using dietary levels of 0, 1, 10, 100 or 1000 ppm, the NOAEL (based on increased thyroid weight at higher doses) was 10 ppm in the diet, equivalent to 0.5 mg/kg bw/day.

In long-term studies, treatment-related alterations in tumour incidences were seen in rats

and mice. In a long-term study in mice, using dietary levels of 0, 1, 10, 100 or 1000 ppm, it was considered not possible to establish an NOAEL, since the incidence of liver tumours in all treated groups was higher than in the controls. However, there was evidence of a dose-response relationship and the lowest dose level (equal to 0.2 mg/kg bw/day) was considered to be a marginal effect level. Thyroid tumour incidence was not affected by treatment of mice with PTU. In a long-term study in rats, also using dietary levels of 0, 1, 10, 100 or 1000 ppm, the NOAEL was 10 ppm in the diet, equal to 0.6 mg/kg bw/day. Treatment-related thyroid tumours were seen at 1000 ppm. This dietary level was accompanied by increased mortality, while non-neoplastic thyroid changes and reduced body-weight gain were seen at 100 ppm.

A published article indicated that PTU showed teratogenic effects in rats at 45 and 90 mg/kg bw/day, doses which showed slight maternal toxicity. Results were not, however, reported in sufficient detail to fully evaluate this study. No information was available to the Meeting regarding special studies with PTU on embryo/fetotoxicity in species other than rats.

PTU is not mutagenic in bacteria and does not cause damage to mouse DNA *in vivo*. The Meeting could not reach any conclusion regarding the genotoxicity of PTU because of the limited data.

A temporary ADI for PTU was based on the marginal effect level in the long-term study in mice (1 ppm in the diet, equal to 0.2 mg/kg bw/day). The Meeting felt reassured that, in view of the metabolic conversion of propineb to PTU, the long-term study in mice with PTU identified the same target organ as the long-term study in mice with propineb. However, in view of the overall inadequacy of the toxicological data for PTU, the Meeting concluded that a 1000-fold safety factor was necessary (see also Section 4.15 - dithiocar-bamates.

A toxicological monograph summarizing the data received since the previous evaluation and incorporating relevant studies on PTU from the previous monograph on propineb was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 1 ppm in the diet, equal to 0.2 mg/kg bw/day (marginal effect level in long-term study)

Rat: 10 ppm in the diet, equivalent to 0.5 mg/kg bw/day (long-term thyroid function study)
10 ppm in the diet, equal to 0.6 mg/kg bw/day (long-term study)

Estimate of temporary acceptable daily intake for humans

0-0.0002 mg/kg bw

Studies without which the determination of a full ADI is impracticable

Results to be submitted to WHO by 1998:

1. Long-term carcinogenicity study in mice, identifying an NOAEL.

2. Clarification of the genotoxic potential of PTU.

3. Clarification of the embryo/fetotoxic and teratogenic potential of PTU in rodents.

RESIDUE AND ANALYTICAL ASPECTS

See 4.35 - propineb.

4.37 PYRAZOPHOS (153)

RESIDUE AND ANALYTICAL ASPECTS

Owing to the late submission of GAP information, evaluation of the residue data for pyrazophos was postponed from the 1992 Meeting, at which an ADI was estimated and the existing Guideline Levels became MRLs. Full GAP information has now been recorded and some previously unreported data on residues resulting from supervised trials on fruits, vegetables and cereals have been evaluated, together with those included in the 1985 and 1987 reviews. In general, these additional data served only to reinforce the conclusions reached earlier. There were insufficient new data to support any recommendations on new crops, other than on barley and wheat straw.

For apples, the additional data were deemed adequate to support a recommendation to increase the MRL from 0.5 to 1 mg/kg. Data for strawberries, Brussels sprouts, cucumbers, barley and wheat supported the recommendations previously made for those crops. MRLs could also now be recommended for barley and wheat straw, based mainly on the ample trials data on wheat treatments. No additional data were received for carrots and hops,but a review of the data previously reported led to confirmation of the existing recommendations.

Data on residues in a few crops for which MRLs had not previously been recommended, namely nectarine, peach, summer squash, watermelon, egg plant, peppers, tomato, beetroot and Witloof chicory, were mostly only in summary form and, in any event, they were deemed insufficient as a basis for any MRL recommendation.

Some limited data on residue changes during the processing of barley and wheat were made available in response to previous requests. These showed that residues of pyrazophos were unlikely to be found in beer or bread produced from crops treated according to GAP. Residues in pressed apple juice and in a cooked mash from treated apples were below 0.01 mg/kg. Data on residues in animal products and the identities of plant metabolites were still not available.

FURTHER WORK OR INFORMATION

Desirable

1. Information on residues in meat and milk from cattle, meat from pigs, and meat and eggs from poultry fed on a diet containing pyrazophos.

2. Additional information on the identities and quantities of metabolites in plants after treatment with pyrazophos.

3. Full reports of the residue trials supplied in summary form by Spain and The Netherlands.

4.38 TRIAZOPHOS (143)

TOXICOLOGY

In 1991 the temporary ADI of 0-0.0002 mg/kg bw was extended in view of the uncertainty

regarding the potential for triazophos to cause delayed neurotoxicity. The 1991 Meeting also noted that previous investigations of the effects of antidotes to acute triazophos intoxication were inadequate.

Re-examination of sections of spinal cord and peripheral nerve from a 90-day study in hens (which the 1991 JMPR meeting had found difficult to interpret) revealed that lesions previously considered to be due to treatment with triazophos were in fact probably variations in background pathology and were not consistent with delayed neurotoxicity. In a new acute delayed neurotoxicity study in hens, there was no indication that treatment with triazophos was associated with any induction of delayed neurotoxicity. However the Meeting criticized the study design, in that higher doses could have been used in order to maximize the potential exposure of the nervous system to triazophos.

In an investigation of antidote treatment to triazophos intoxication in rats the expected results were obtained, a combination of atropine and oxime proving to be efficient antidotes.

The Meeting concluded that, despite shortcomings in the design of the neurotoxicity studies, the total available data indicated that triazophos does not have the potential to cause delayed neurotoxicity following dietary exposure. An ADI was allocated using the NOAEL from the human volunteer study reviewed in 1982 and 1991, using a 10-fold safety factor. This ADI was supported by the NOAEL from a 52-week study in dogs, using a 100-fold safety factor.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 30 ppm in the diet, equal to 4.5 mg/kg bw/day (2-year study) (1991 JMPR)

Rat: 3 ppm in the diet, equal to 0.17 mg/kg bw/day (2-year study) (1991 JMPR)
27 ppm in the diet, equal to 2-3 mg/kg bw/day (multigeneration reproduction study) (1991 JMPR)

Dog: 4 ppm in the diet, equal to 0.12 mg/kg bw/day (1-year study) (1991 JMPR)

Human: 0.0125 mg/kg bw/day (3-week study) (1982 and 1991 JMPR)

Estimate of acceptable daily intake for humans

0-0.001 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Triazophos was evaluated in 1982 and several times since then, most recently in 1991. Maximum residue levels were estimated for a number of commodities and recommended as TMRLs because the ADI was temporary. At the 23rd and 24th Sessions of the CCPR (1991-92) the proposed TMRLs for citrus fruits, bananas, Brussels sprouts, head cabbages, common beans and cauliflower were held at step 7b and referred back to the JMPR. Written comments were received from France, Germany and The Netherlands on citrus fruits, bananas, Brussels sprouts and head cabbages. The manufacturer submitted new residue data from supervised trials on carrots, strawberries and soya beans.

At the same Sessions of the CCPR it was proposed to lower the limit of determination from 0.05 mg/kg to 0.01 mg/kg for residues of triazophos in cereal grains, potatoes, bulb onions and sugar beet.

The Meeting took note of the observations made by France, Germany and The Netherlands, who stated that the data base was insufficient to set residue limits for citrus fruits and bananas. The Meeting examined the data and proposed to withdraw the TMRL of 1 mg/kg for bananas, as the limit is based on residue data from only two trials. It was also difficult to link the summarized data for citrus fruits to the information on GAP in the 1983 Evaluation. The Meeting was informed that new information on GAP for triazophos and residue data from a number of trials on citrus fruits would be available in the near future, and therefore recommended that the limit for triazophos in citrus fruits should be made temporary, irrespective of the status of the ADI, until the new data were evaluated.

In 1986 the JMPR had already re-evaluated and confirmed the proposed limits for residues in Brussels sprouts and head cabbages. No new data were available. The Meeting reaffirmed the recommendation.

The Meeting considered the limit of determination of 0.05 mg/kg for triazophos in cereal grains, potatoes, bulb onions and sugar beets. The residues in these crops reported to the 1983 and 1990 Meetings were below the limit of determination, which ranged from 0.001 to 0.07 mg/kg. Although most residues were below 0.02 mg/kg, the Meeting proposed to maintain the limit of determination of 0.05 mg/kg as a realistic limit of determination for the purpose of enforcement.

Supervised trials on carrots were carried out in the UK, all except two in accordance with recommended use. The highest residue in samples from two trials 28 days after the last treatment was 0.23 mg/kg. In addition to the trials a survey was carried out in the UK in which many samples of carrots with a known pesticide treatment history were analysed, all applications being in accordance with label recommendations. Residues were from <0.02 mg/kg to 0.94 mg/kg with a mean value of 0.17 mg/kg, and the 90th percentile was approximately 0.4 mg/kg. The Meeting recommended a maximum residue limit of 0.5 mg/kg for carrots.

Supervised trials were also carried out on strawberries in Germany. Residues were very low and except for the PHI of 11 days all residues were below 0.05 mg/kg. No information on GAP on in Germany was available, but GAP in The Netherlands would give rise to even lower residues. The Meeting estimated a maximum residue level at the limit of determination for strawberries (0.05 mg/kg).

Residues in seeds from trials on soya beans in Brazil with application in accordance with Brazilian GAP were also below the limit of determination, and a maximum residue limit was proposed at the limit of determination (0.05 mg/kg).

FURTHER WORK OR INFORMATION

Required (by 1994).

Information on GAP for triazophos on citrus fruits and residue data from trials in accordance with GAP.

4.39 ZINEB (dithiocarbamates, 105)

TOXICOLOGY

Zineb was previously evaluated by the Joint Meeting in 1963, 1965, 1967, 1970, 1974, 1977 and 1980. An ADI of 0-0.05 mg/kg bw, of which not more than 0.002 mg/kg bw may be present as ETU, was allocated at the 1980 Meeting for zineb or the sum of maneb, mancozeb, and zineb. Little new information on zineb has become available since the previous evaluation.

Zineb was poorly absorbed when administered orally to mice. The extent to which enterohepatic circulation may have been involved in the species studied, namely the mouse, rat and marmoset, has not been investigated. Absorption, as measured by urinary excretion in the rat, was highly variable and the reasons for this variability are not known. In the marmoset the majority of the administered dose was excreted in the urine, with lesser amounts in the faeces. The principal routes of excretion were via the faeces and urine, with negligible amounts in expired CO_2.

The metabolic pathway of zineb has not been clearly delineated. Characterization of urinary components in the mouse, rat and marmoset have revealed the presence of ethylenethiourea (ETU), ethyleneurea and polar components.

Zineb was practically non-toxic upon acute oral administration to rats and guinea pigs, when given subcutaneously to rats, or when given by intraperitoneal injection to mice. WHO has classified zineb as unlikely to present acute hazard in normal use.

Dietary administration of zineb to rats for six weeks at 0, 500 or 5000 ppm indicated an NOAEL of 500 ppm (equivalent to 25 mg/kg bw/day), based on morphological changes of the thyroid gland and reduced uptake of ^{124}iodine at 5000 ppm. Rats treated with zineb orally by gavage for four weeks (5 days/week) at 0, 15, 60, 250 or 1000 mg/kg bw/day exhibited slight hyperplasia of the thyroid at a dose level of 1000 mg/kg bw/day, resulting in an NOAEL of 250 mg/kg bw/day. There were no significant changes in the thyroid noted in rats previously treated at 1000 mg/kg bw/day following a two week recovery period. Rats administered zineb at doses of 490 or 2450 mg/kg bw, twice weekly for four months, developed paresis of the hind limbs, which progressed to complete paralysis. Similar treatment-related effects on the hind limbs were not confirmed in a two-year study in rats (see below) at the highest dietary level of 10,000 ppm, equivalent to 500 mg/kg bw/day.

In a limited one-year study, dogs treated with zineb at dietary levels of 20, 2000 or 10,000 ppm revealed thyroid hyperplasia at 10,000 ppm, resulting in an NOAEL of 2000 ppm (equivalent to 50 mg/kg bw/day).

Zineb was not carcinogenic when given to mice at 460 mg/kg bw/day from postnatal day 7 until weaning followed thereafter by dietary administration of 1300 ppm until 18 months of age. A two-year study in which rats (10/sex/group) were fed zineb at dietary levels of 500, 1000, 2500, 5000 or 10,000 ppm revealed goitrogenic effects at all doses. Treatment-related effects were manifest at or above 1000 ppm as renal congestion, nephritis and nephrosis, increased mortality and diminished growth rate. There was no evidence of carcinogenic potential. It

should be recognized, however, that neither of these long-term studies was judged to have adequately studied the carcinogenic potential of zineb.

Treatment of rats with zineb at doses of 50 to 960 mg/kg bw/day suggested adverse effects on reproduction, depicted as sterility, decreased fertility and resorption of fetuses. From the limited data available, a dose level of 50 mg/kg bw/day appeared to be without significant adverse reproductive effect.

Treatment of mice with zineb at dose levels of 0, 200, 630 or 2000 mg/kg bw/day during critical periods of organogenesis did not induce any maternal toxicity, embryo/fetotoxicity or teratogenicity at any of the dose levels studied.

An oral teratogenicity study in rats at doses of 0, 200, 630 or 2000 mg/kg bw/day revealed that zineb was teratogenic at the maternally toxic dose level of 2000 mg/kg bw/day. Treatment with zineb resulted in a significant increase in hydrocephalus, skeletal anomalies (enlarged frontal and occipital fontanelles, split centra and incomplete ossification of the supraocciput), and a higher incidence of abnormalities of the tail.

Zineb has been adequately tested in a series of *in vivo* genotoxicity assays. Positive responses were obtained in a *Drosophila* study and in a study for chromosomal aberrations in cultured mammalian cells. Other assays were negative. The Meeting concluded that zineb was not likely to be a significant genotoxic hazard.

The Meeting concluded that the toxicological data specifically generated for zineb were inadequate to estimate an ADI. However, because of the similarity of the chemical structure of zineb to that of the other ethylenebis(dithiocarbamate)s (EBDCs), the comparable toxicological profile of the EBDCs based on the toxic effects of ETU, and the fact that parent EBDC residues cannot be differentiated using presently-available regulatory analytical methods, zineb was included in the group ADI of 0-0.03 mg/kg bw for the EBDC group evaluated at this Meeting (mancozeb, maneb, metiram). (See also Section 4.15 - dithiocarbamates).

A toxicological monograph was prepared summarizing the data that were reviewed at the present Meeting, including relevant data that were summarized in the previous monograph and monograph addenda on zineb.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 460 mg/kg bw/day (18-month study: did not adequately study long-term toxicity or carcinogenic potential)
2000 mg/kg bw/day (teratogenicity study)

Rat: 500 ppm, equivalent to 25 mg/kg bw/day (six-week study)
<500 ppm, equivalent to <25 mg/kg bw/day (two-year study: did not adequately study long-term toxicity or carcinogenic potential)
50 mg/kg bw/day (reproduction study: did not adequately study potential for adverse effects on reproduction)
630 mg/kg bw/day (teratogenicity study)

Dog: 2000 ppm, equivalent to 50 mg/kg bw/day (one-year study: did not adequately study potential for toxicity in a non-rodent species)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw (Group ADI with mancozeb, maneb and metiram)

Studies which will provide information valuable in the continued evaluation of the compound.

1. Further elucidation of absorption/distribution/excretion patterns and metabolic pathways.
2. Reproduction study.
3. Long-term toxicity/carcinogenicity studies in two appropriate species.
4. Short-term repeated exposure studies in a rodent and non-rodent species to determine NOAELs with respect to effects on the thyroid and potential for neurotoxicity.
5. Observations in humans.

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 The Meeting recommended (Section 2.2) that:

(1) the Codex working paper, "Risk Assessment Procedures Used by the Codex Alimentarius Commission and its Subsidiary and Advisory bodies" (ALINORM 93/37), should not be published or distributed further in its present form,

(2) a revised paper be prepared that would take into account new developments in the dynamic field of risk assessment and recent Codex developments, and

(3) the revised paper should be circulated to national and international organisations to give them the opportunity to comment before publication or wider distribution.

5.3 The Meeting recommended (Section 2.3) that governments conduct appropriate dietary surveys, especially for population groups of special concern such as infants and children.

5.4 Regarding concomitant pesticide and veterinary uses of chemicals, the Meeting recommended (Section 2.5) that:

(1) the Codex Alimentarius Commission and the FAO/WHO Secretariats of the expert committees develop procedures to ensure consistency and appropriate exchange of information among the involved committees,

(2) the Joint Secretaries of the JMPR and JECFA obtain and make available to their respective meetings, and in advance to data reviewers, copies of pertinent evaluations,

(3) the Codex Secretariat arrange distribution of the pertinent evaluations to country Codex contact points, and

(4) for periodic review compounds the submission to the FAO Panel should include full information on approved veterinary uses, data from trials in accordance with those uses, and metabolism data for plants and animals.

5.5 Regarding the mode of action, mechanism of toxicity and toxicological evaluation of pesticides, the Meeting recommended (Section 2.10) that, where known, information on the mode of pesticidal action as well as on the mechanism of toxicity in non-target species should be made available to the Joint Meeting.

5.6 The Meetng recommended (Section 3.2) that the development of additional regulatory analytical methods to differentiate propineb residues from those arising from the use of ethylenebis(dithiocarbamate)s (EBDCs) should be aggressively pursued.

5.7 With the expectation that residues of DDT as an environmental contaminant will decrease as production ceases, the Meeting recommended (Section 4.11) that monitoring data should again be evaluated in 1998 with a view to the possible lowering of ERLs.

6. FUTURE WORK

The following items should be considered at the 1994 or 1995 Meeting. Compounds recommended for priority attention by the 25th or earlier Sessions of the CCPR which have not yet been evaluated are marked with an asterisk (*), and compounds scheduled for re-evaluation in the CCPR periodic review programme with a double asterisk.

6.1 1994 Meeting (tentative)

Toxicological Evaluation

Abamectin
Azocyclotin
Carbofuran
Chlorfenvinphos **
Chlormequat **
Clethodim *
Cyhexatin
Fenpropimorph *
Parathion **
Parathion-methyl **
Phorate
Phosmet **
Tebuconazole *
Tecnazene **
Teflubenzuron *
Tolclofos-methyl *

Residue Evaluation

Abamectin
Acephate
Aldicarb **
Bentazone
Captan
Chlorfenvinphos **
Chlormequat **
Clethodim *
Diazinon
Disulfoton
Fenpropimorph *
Glufosinate-ammonium
Hexythiazox
Imazalil
Methamidophos
Metiram *
Monocrotophos
Parathion-methyl **
2-Phenylphenol **
Phosalone **
Phosmet **
Pirimiphos-methyl
Profenofos
Pyrazophos
Tebuconazole *
Tecnazene **
Teflubenzuron *
Thiram **
Tolclofos-methyl *
Triazophos

6.2 1995 Meeting (tentative)

Toxicological Evaluation

Benomyl **
Captan
Carbendazim **
Cartap **
Chlorpropham *
Fenarimol *
Fenpyroximate *
Fenthion **
Folpet
Haloxyfop *
Malathion **
Piperonyl butoxide **
Quintozene **
Thiometon **
Thiophanate-methyl **
Trichlorfon **
Vinclozolin

Residue Evaluation

Buprofezin
Cartap **
Chlorpropham *
Fenarimol *
Fenpyroximate *
Fenthion **
Folpet
Haloxyfop *
Malathion **
Parathion
Quintozene **
Thiometon **
Trichlorfon **

7. REFERENCES

PREVIOUS FAO AND WHO DOCUMENTS

1. FAO/WHO. 1962 Principles governing consumer safety in relation to pesticide residues. Report of a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture. FAO Plant Production and Protection Division Report, No. PL/1961/11; WHO Technical Report Series, No. 240.

2. FAO/WHO. 1964 Evaluations of the toxicity of pesticide residues in food. Report of a Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues. FAO Meeting Report, No. PL/1963/13; WHO/Food Add./23.

3. FAO/WHO. 1965a Evaluations of the toxicity of pesticide residues in food. Report of the Second Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues. FAO Meeting Report, No. PL/1965/10; WHO/Food Add./26.65.

4. FAO/WHO. 1965b Evaluations of the toxicity of pesticide residues in food. FAO Meeting Report, No. PL/1965/10/1; WHO/Food Add./27.65.

5. FAO/WHO. 1965c Evaluation of the hazards to consumers resulting from the use of fumigants in the protection of food. FAO Meeting Report, No. PL/1965/10/2; WHO/Food Add./28.65.

6. FAO/WHO. 1967a Pesticide residues in food. Joint report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 73; WHO Technical Report Series, No. 370.

7. FAO/WHO. 1967b Evaluation of some pesticide residues in food. FAO/PL:CP/15; WHO/Food Add./67.32.

8. FAO/WHO. 1968a Pesticide residues. Report of the 1967 Joint Meeting of the FAO Working Party and the WHO Expert Committee. FAO Meeting Report, No. PL:1967/M/11; WHO Technical Report Series, No. 391.

9. FAO/WHO. 1968b 1967 Evaluations of some pesticide residues in food. FAO/PL:1967/M/11/1; WHO/Food Add./68.30.

10. FAO/WHO. 1969a Pesticide residues in food. Report of the 1968 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricul-tural Studies, No. 78; WHO Technical Report Series, No. 417.

11. FAO/WHO. 1969b 1968 Evaluation of some pesticide residues in food. FAO/PL:1968/M/9/1; WHO/Food Add./69.35.

12. FAO/WHO. 1970a Pesticide residues in food. Report of the 1969 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 84; WHO Technical Report Series, No. 458.

13. FAO/WHO. 1970b 1969 Evaluation of some pesticide residues in food. FAO/PL:1969/M/17/1; WHO/Food Add./70.38

14. FAO/WHO. 1971a Pesticide residues in food. Report of the 1970 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 87; WHO Technical Report Series, No. 474.

15. FAO/WHO. 1971b 1970 Evaluation of some pesticide residues in food. AGP:1970/M/12/1; WHO/Food Add./71.42.

16. FAO/WHO. 1972a Pesticide residues in food. Report of the 1971 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 88; WHO Technical Report Series, No. 502.

17. FAO/WHO. 1972b 1971 Evaluation of some pesticide residues in food. AGP:1971/M/9/1; WHO Pesticide Residues Series, No. 1.

18. FAO/WHO. 1973a Pesticide residues in food. Report of the 1972 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 90; WHO Technical Report Series, No. 525.

19. FAO/WHO. 1973b 1972 Evaluation of some pesticide residues in food. AGP:1972/M/9/1; WHO Pesticide Residues Series, No. 2.

20. FAO/WHO. 1974a Pesticide residues in food. Report of the 1973 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 92; WHO Technical Report Series, No. 545.

21. FAO/WHO. 1974b 1973 Evaluation of some pesticide residues in food. FAO/AGP/1973/M/9/1; WHO Pesticide Residues Series, No.3.

22. FAO/WHO. 1975a Pesticide residues in food. Report of the 1974 Joint Meeting of the FAO Working Party of experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 97; WHO Technical Report Series, No. 574.

23. FAO/WHO. 1975b 1974 Evaluation of some pesticide residues in food. FAO/AGP/1974/M/9/11; WHO Pesticide Residues Series, No.4.

24. FAO/WHO. 1976a Pesticide residues in food. Report of the 1975 Joint Meeting 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.

25. FAO/WHO. 1976b 1975 Evaluation of some pesticide residues in food. AGP:1975/M/13; WHO Pesticide Residues Series, No. 5.

26. FAO/WHO. 1977a Pesticide residues in food. Report of the 1976 Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues.
FAO Food and Nutrition Series, No. 9; FAO Plant Production and Protection Series, No. 8; WHO Technical Report Series, No. 612.

27. FAO/WHO. 1977b 1976 Evaluation of some pesticide residues in food.
AGP:1976/M/14.

28. FAO/WHO. 1978a Pesticide residues in food - 1977. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues.
FAO Plant Production and Protection Paper 10 Rev.

29. FAO/WHO. 1978b Pesticide residues in food: 1977 evaluations.
FAO Plant Production and Protection Paper 10 Sup.

30. FAO/WHO. 1979a Pesticide residues in food - 1978. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues.
FAO Plant Production and Protection Paper 15.

31. FAO/WHO. 1979b Pesticide residues in food: 1978 evaluations.
FAO Plant Production and Protection Paper 15 Sup.

32. FAO/WHO. 1980a Pesticide residues in food - 1979. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 20.

33. FAO/WHO. 1980b Pesticide residues in food: 1979 evaluations.
FAO Plant Production and Protection Paper 20 Sup.

34. FAO/WHO. 1981a Pesticide residues in food - 1980. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 26.

35. FAO/WHO. 1981b Pesticide residues in food: 1980 evaluations.
FAO Plant Production and Protection Paper 26 Sup.

36. FAO/WHO. 1982a Pesticide residues in food - 1981. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 37.

37. FAO/WHO. 1982b Pesticide residues in food: 1981 evaluations.
FAO Plant Production and Protection Paper 42.

38. FAO/WHO. 1983a Pesticide residues in food - 1982. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 46.

39. FAO/WHO. Pesticide residues in food: 1982 evaluations.

1983b FAO Plant Production and Protection Paper 49.

40. FAO/WHO. 1984 Pesticide residues in food - 1983. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 56.

41. FAO/WHO. 1985a Pesticide residues in food: 1983 evaluations. FAO Plant Production and Protection Paper 61.

42. FAO/WHO. 1985b Pesticide residues in food - 1984. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 62.

43. FAO/WHO. 1985c Pesticide residues in food: 1984 evaluations. FAO Plant Production and Protection Paper 67.

44. FAO/WHO. 1986a Pesticide residues in food - 1985. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 68.

45. FAO/WHO. 1986b Pesticide residues in food: 1985 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 72/1.

46. FAO/WHO. 1986c Pesticide residues in food: 1985 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 72/2.

47. FAO/WHO. 1986d Pesticide residues in food - 1986. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 77.

48. FAO/WHO. 1986e Pesticide residues in food: 1986 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 78.

49. FAO/WHO. 1987a Pesticide residues in food: 1986 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 78/2.

50. FAO/WHO. 1987b Pesticide residues in food - 1987. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 84.

51. FAO/WHO. 1988a Pesticide residues in food: 1987 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 86/1.

52. FAO/WHO. 1988b Pesticide residues in food: 1987 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 86/2.

53. FAO/WHO. 1988c Pesticide residues in food - 1988. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 92.

54. FAO/WHO. 1988d Pesticide residues in food: 1988 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 93/1.

55. FAO/WHO. 1989a Pesticide residues in food: 1988 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 93/2.

56. FAO/WHO. 1989b Pesticide residues in food - 1989. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 99.

57. FAO/WHO. 1990a Pesticide residues in food: 1989 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 100.

58. FAO/WHO. 1990b Pesticide residues in food: 1989 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 100/2.

59. FAO/WHO. 1990c Pesticide residues in food - 1990. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 102.

60. FAO/WHO. 1991a Pesticide residues in food: 1990 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 103/1.

61. FAO/WHO. 1991b Pesticide residues in food: 1990 evaluations - Toxicology. WHO/PCS/91.47.

62. FAO/WHO. 1991c Pesticide residues in food - 1991. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 111.

63. FAO/WHO. 1991d Pesticide residues in food: 1991 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 113/1.

64. FAO/WHO. 1992 Pesticide residues in food: 1991 evaluations - Part II - Toxicology. WHO/PCS/92.52.

65. FAO/WHO. 1993a Pesticide residues in food - 1992. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 116.

66. FAO/WHO. 1993b Pesticide residues in food: 1992 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 118.

67. FAO/WHO. 1993c Pesticide residues in food: 1992 evaluations - Part II - Toxicology. WHO/PCS/93.34.

CORRECTIONS TO REPORT OF 1992 JMPR

Additions and changes are shown **bold**. Minor typographical errors are not included.

P.13, para 4, l.5: Change "...were 0.05 mg/kg bw/day in the teratogenicity study in rats" to **"...was 0.05 mg/kg bw/day in the teratogenicity study in mice (CF1 strain)**".

P.19, para 4, ll.5&6: Change "4-12 mg/l" to "**4-12 µg/l**" and "400 mg/l" to "**400 µg/l**".

P.20, Entry 8: Under the heading "dosages", **underline 1.67** instead of 0.47.
Under the heading "NOAEL", change 0.12 to **0.47**.

P.29, last para, l.2: Change "1970 Joint Meeting" to "**1974 Joint Meeting**"

P.31, "Level causing no toxicological effect, mouse":
Change "...reviewed by 1990 JMPR" to"...**reviewed by 1987 JMPR**".

P.46, para 3, l.7: Change "1 mg/kg bw/day" to "**10 mg/kg bw/day**"

P.63, "Level causing no toxicological effect":
Move "dog" to the last line, **before "100 ppm, equal to..."**

P.78, para 2, l.3: Change "10 mg/kg bw/day" to "**2 mg/kg bw/day**".

P.79, "Level causing no toxicological effect, dog":
Change "10 mg/kg bw/day" to "**2 mg/kg bw/day**".

P.104, para 7, l.1: Change - 1977 to - 197**8**

P.105, para 9, l.2: Change 1986b to 1986**e**

P.106, para 5, l.2: Change 1990d to 1990**c**

P.106, para 9, l.3: Change 1113/1 to **113/1**

Annex I, p.123. In the new MRL for triadimenol in Milks, change 0.0^{*1,2} to 0.0**5***^{1,2}. (The error has been corrected in the evaluations.)

Annex III, p.134. In para 1, line 1, change 1966-91 to 1966-9**2**.

p.138. Insert in alphabetical position:

FAO Panel of JMPR, Manual on preparation of documents by 92-2.9

p.140. Under **Maximum residue level(s)**
Estimation of, add the ref. shown:
FAO Guide on.....91-2.5**; 92-2.7**

p.143. Under **Pesticide residue(s):**
Data on:
Evaluation of:, add the ref. shown:
FAO Guide on.....91-2.5**; 92-2.7**

ANNEX I

ACCEPTABLE DAILY INTAKES AND RESIDUE LIMITS PROPOSED AT THE 1993 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 Annexes to 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.

*	At or about the limit of determination
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 neat)	The recommendation applies to the fat of 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.

Commodities are listed in alphabetical order. This is a change from previous 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.)	Max. ADI (mg/ kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
Aldicarb (117)	0.003	VB 0402	Brussels sprouts	0.1	0.05 T
		Residue:	sum of aldicarb, its sulphoxide and its sulphone, expressed as aldicarb		
Amitrole [1] (079)	0.0005 T (1997)	Note	TADI increased from 0.00003 mg/kg bw, conditional		
Azinphos-methyl (002)	0.005	AS 0654	Wheat straw and fodder, dry	W	1 T
		Residue:	azinphos-methyl		
Benalaxyl (155)	0.05	VR 0589	Potato	0.02*	0.01*
		Residue:	benalaxyl		
Bromopropylate [1] (070)	0.03	FP 0226	Apple	W	5
		FI 0327	Banana	W	5
		VP 0526	Common bean (pods and/or immature seeds)	3	-
		FS 0013	Cherries	W	5
		FC 0001	Citrus fruits	2	5
		SO 0691	Cotton seed	W	1
		VC 0424	Cucumber	0.5	-
		FB 0269	Grapes	2	5
		DH 1100	Hops, dry	W	5
		VC 0046	Melons, except Watermelon	0.5	-
		FS 0245	Nectarine	W	5
		FS 0247	Peach	W	5
		FP 0230	Pear	W	5
		FS 0014	Plums (including prunes)	2	5
		FP 0009	Pome fruits	2	-
		VC 0431	Squash, Summer	0.5	-
		FB 0275	Strawberry	2	5
		DT 1114	Tea, Green, Black	W	5
			Vegetables	W	1
		Residue:	bromopropylate		
		Note	ADI increased from 0.008 mg/kg bw		
Carbofuran (096)	0.01	FC 0001	Citrus fruits	W	2 T
		Residue:	sum of carbofuran and 3-hydroxycarbofuran		

[1] Re-evaluation in periodic review programme

Pesticide (Codex Ref. No.)	Max. ADI (mg/ kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
Carbosulfan (145)	0.01	FC 0001	Citrus fruits	W	2 T
		Residue:	carbosulfan		
Chlorothalonil [1] (081)	0.03	FI 0327	Banana	W	0.2
		GC 0640	Barley	0.1	0.2 (cereals)
		AS 0640	Barley straw and fodder, dry	20	-
		FB 0264	Blackberries	W	10
		VB 0400	Broccoli	W	5
		VB 0402	Brussels sprouts	5	5
		VB 0041	Cabbages, Head	1	5
		VR 0577	Carrot	1	1
		VB 0404	Cauliflower	1	5
		VS 0624	Celery	10	15
		GC 0080	Cereal grains	W	0.2
		FS 0013	Cherries	0.5	10
		FC 0001	Citrus fruits	W	5
		VP 0526	Common bean (pods and/or immature seeds)	5	5
		FB 0265	Cranberry	5	5
		VC 0424	Cucumber	5	5
		FB 0021	Currants, Black, Red, White	W	25
		VL 0476	Endive	W	10
		FB 0269	Grapes	0.5	10
		VL 0480	Kale	W	10
		VL 0482	Lettuce, Head	W	10
		VD 0534	Lima bean (dry)	W	0.5
		VC 0046	Melons, except Watermelon	2	5
		VA 0385	Onion, Bulb	0.5	5
		FS 0247	Peach	1	25
		SO 0697	Peanut	0.05	0.1
		SO 0703	Peanut, whole	W	0.5
		VO 0051	Peppers	W	10
		VR 0589	Potato	0.2	0.1
		VC 0429	Pumpkins	W	5
		FB 0272	Raspberries, Red, Black	W	10
		VC 0431	Squash, Summer	5	5
		VR 0596	Sugar beet	0.2	1
		AV 0596	Sugar beet leaves or tops	20	-
		VO 0447	Sweet corn (corn-on the-cob)	W	1
		VO 0448	Tomato	5	5
		GC 0654	Wheat	0.1	0.2 (cereals)
		AS 0654	Wheat straw and fodder, dry	20	-
		VC 0433	Winter squash	5	5
		VS 0469	Witloof chicory (sprouts)	W	10
Chlorpyrifos-methyl (090)	0.01	SO 0495	Rape seed	W	10 Po T
		Residue:	chlorpyrifos-methyl		
Cycloxydim (179)	0.07	VD 0071	Beans (dry)	2	-
		VB 0040	Brassica vegetables	2	-
		VR 0577	Carrot	0.5	-

[1] Re-evaluation in periodic review programme

		VP 0526	Common bean (pods and/or immature seeds)	1	-
Cycloxydim (contd.)		FB 0269	Grapes	0.5	-
		VA 0384	Leek	0.2	-
		VL 0482	Lettuce, Head	0.2	-
		VL 0483	Lettuce, Leaf	0.2	-
		VP 0063	Peas	1	-
		VP 0064	Peas, shelled	2	-
		VR 0589	Potato	2	-
		SO 0495	Rape seed	2	-
		VD 0541	Soya bean (dry)	2	-
		FB 0275	Strawberry	0.5	-
		VR 0596	Sugar beet	0.2	-
		AV 0596	Sugar beet tops or leaves	1	-
		Residue: sum of 3-thian-3-ylglutaric acid (TME) and 3-hydroxy-3-thian-3-expressed as cycloxydim			
DDT (021)	0.02	VR 0577	Carrots	0.2 E	-
		PE 0112	Eggs	0.1 E	0.5 E T
		MM 0095	Meat	1 (fat) E	5 (fat) E T
		ML 0106	Milks	0.02 F E	0.05 F E T
		Residue: Sum of p,p_-DDT, o,p_-DDT, p,p_-DDE and p,p_-TDE (DDD) (fat-			
Diazinon [1] (022)	0.002		Almond, hull	5	-
		TN 0660	Almonds	0.05	0.1
		GC 0640	Barley	W	0.1
		FB 0264	Blackberries	0.1	0.5[1]
		FB 4079	Boysenberry	0.1	0.5[1]
		VB 0400	Broccoli	0.5	0.5[2]
		VB 0041	Cabbages, Head	2	0.5[2]
		VC 4199	Cantaloupe	0.2	0.5[2]
		VR 0577	Carrot	0.5	0.5[2]
		FS 0013	Cherries	1	0.5[1]
		VL 0467	Chinese cabbage	0.05	0.7[3]
		FC 0001	Citrus fruits	W	0.7
		VP 0526	Common bean (pods and/or immature seeds)	0.2	0.5[2]
		SO 0691	Cotton seed	W	0.1
		VC 0424	Cucumber	0.1	0.5[2]
		FB 0021	Currants, Black, Red, White	0.2	0.5[1]
			Fruits (except as otherwise listed)	W	0.5
		VP 0529	Garden pea, shelled	0.2	0.5[2]
		TN 0666	Hazelnuts	W	0.1
		VL 0480	Kale	0.05	0.7[3]
		FI 0341	Kiwifruit	0.2	0.5[1]
		VB 0405	Kohlrabi	0.2	0.5[2]
Diazinon (contd.)		VL 0053	Leafy vegetables	W	0.7
		VL 0482	Lettuce, Head	0.5	0.7[3]
		VL 0483	Lettuce, Leaf	0.5	0.7[3]
		AF 0645	Maize forage	10	-
		GC 0645	Maize	0.02*	-
		MM 0097	Meat of cattle, pigs and sheep	W	0.7 (fat) V
		ML 0106	Milks	W	0.02 F V
		OC 0305	Olive oil, virgin	W	2
		FT 0305	Olives	W	2
		VA 0385	Onion, Bulb	0.05	0.5[2]

[1] Re-evaluation in periodic review programme

		FS 0247	Peach	0.2	0.7
		SO 0697	Peanut	W	0.1
		TN 0672	Pecan	W	0.1
		VO 0445	Peppers, Sweet	0.05	0.5[2]
		FI 0353	Pineapple	0.1	0.5[1]
		FS 0014	Plums (including Prunes)	1	0.5[1]
		FP 0009	Pome fruits	2	0.5[1]
		VR 0589	Potato	0.01*	0.5[2]
		DF 0014	Prunes	2	0.5[1]
		VR 0494	Radish	0.1	0.5[2]
		FB 0272	Raspberries, Red, Black	0.2	0.5[1]
		CM 1205	Rice, polished	W	0.1
		SO 0699	Safflower seed	W	0.1
		VL 0502	Spinach	0.5	0.7[3]
		VA 0389	Spring onion	1	0.5[2]
		VC 0431	Squash, Summer	0.05	0.5[2]
		FB 0275	Strawberry	0.1	0.5[1]
		AV 0596	Sugar beet leaves or tops	5	-
		VR 0596	Sugar beet	0.1	0.5[2]
		SO 0702	Sunflower seed	W	0.1
		VO 0447	Sweet corn (corn-on-the-cob)	0.02	0.7
		VO 0448	Tomato	0.5	0.5[2]
			Vegetables (except as otherwise listed)	W	0.5
		TN 0678	Walnuts	0.01*	0.1
		GC 0654	Wheat	W	0.1
			Residue: diazinon (fat-soluble)		
		Notes	ADI confirmed		
			[1] Fruits (except as otherwise listed) [2] Vegetables (except as otherwise listed) [3] Leafy vegetables		
Dichlorvos [1] (025)	0.004	VP 0061	Beans, except broad bean and soya bean	W	0.5 for Vegetables...
		SB 0715	Cacao beans	W	5
		GC 0080	Cereal grains	5 (Po)	2
		SB 0716	Coffee beans	W	2
Dichlorvos (contd.)		PE 0112	Eggs	W	0.05
			Fruits	W	0.1
		MM 0814	Goat meat	W	0.05
		VD 0533	Lentil (dry)	W	2
		VL 0482	Lettuce, Head	W	1
		MM 0097	Meat of cattle, pigs & sheep	W	0.05
		MM 0095	Meat	0.05*	
		ML 0106	Milks	0.02*	0.02
		VD 0541	Soya bean (dry)	W	2 Po
			Vegetables (except as otherwise listed)	W	0.5
		CM 0654	Wheat bran, unprocessed	10	-
		CF 1211	Wheat flour	1	-
		CF 1210	Wheat germ	10	-
		CF 1212	Wheat wholemeal	2	-
		Residue:	dichlorvos		

[1] Re-evaluation in periodic review programme

		Note	ADI confirmed		
Diquat (031)	0.002	Note	ADI is for diquat ion. Lowered from 0.008 mg/kg bw		
Dithiocarbamates [1]	See		Almond hulls	20	-
(105)	Note	TN 0660	Almonds	0.1*	-
		VS 0621	Asparagus	0.1	-
		FI 0327	Banana	2	1
		GC 0640	Barley	1	-
		AS 0640	Barley straw and fodder, dry	25	-
		VB 0041	Cabbages, Head	5	-
		VR 0577	Carrot	1	0.5
		VS 0624	Celery	W	5
		FS 0013	Cherries	W	1
		VP 0526	Common bean (pods and/or immature seeds)	W	0.5
		VL 0510	Cos lettuce	10	-
		FB 0265	Cranberry	5	-
		VC 0424	Cucumber	2	0.5
		FB 0021	Currants, Black, Red, White	10	5
		MO 0105	Edible offal (Mammalian)	0.1	-
		PE 0112	Eggs	0.05*	-
		VA 0381	Garlic	0.5	-
		FB 0269	Grapes	5	5
		VL 0480	Kale	15	-
		VA 0384	Leek	0.5	-
		VL 0482	Lettuce, Head	10	5
		AS 0645	Maize fodder	2	-
		FC 0003	Mandarins	10	-
		MM 0095	Meat	0.02*	-
		VC 0046	Melons, except Watermelon	0.5	1
		ML 0106	Milks	0.05*	-
		VA 0385	Onion, Bulb	0.5	-
		FC 0004	Oranges, Sweet, Sour	2	-
		FI 0350	Papaya	5	-
		FS 0247	Peach	W	3
		SO 0697	Peanut	0.1*	-
		AL 0697	Peanut fodder	5	-
		VO 0445	Peppers, Sweet	1	-
		FS 0014	Plums (including Prunes)	W	1
		FP 0009	Pome fruits	5	Apple 3 Pear 3
		VR 0589	Potato	0.2	0.1
		PM 0111	Poultry, Edible offal of	0.1	-
		PO 0110	Poultry meat	0.1	-
		VC 0429	Pumpkins	0.2	-
		VA 0389	Spring onion	10	-
		FB 0275	Strawberry	W	3
		VR 0596	Sugar beet	0.5	-
		AV 0596	Sugar beet leaves or tops	20	-
		VC 0431	Squash, Summer	1	-
		VO 0447	Sweet corn (corn-on-the-cob)	0.1*	-
		VO 0448	Tomato	5	3
		VC 0432	Watermelon	1	-
		GC 0654	Wheat	1	0.2
		AS 0654	Wheat straw and fodder, dry	25	-
		VC 0433	Winter squash	0.1	-

[1] Re-evaluation in periodic review programme

		Residue: CS_2 Notes 1. Group ADI for ethylenebis(dithiocarbamate)s (EBDCs) - mancozeb, 0-0.03 mg/kg bw, alone or in any combination. ADIs for mancozeb, maneb and zineb See also ethylenethiourea, propineb and propylenethi-ourea. 2. Recommendations for MRLs apply to total residues arising s of dithiocarbamates.			
Endosulfan (032)	0.006	VP 0522	Broad bean (green pods and immature seeds)	0.5	2[1]
		SB 0715	Cacao beans	0.1	-
		SB 0716	Coffee beans	0.1	-
		VC 0424	Cucumber	0.5	2[1]
			Fruits	W	2
		FB 0269	Grapes	1	2[2]
		GC 0645	Maize	0.1	-
		VC 0046	Melons, except Watermelon	0.5	2[1]
		FC 0004	Oranges, Sweet, Sour	0.5	2[2]
		FS 0247	Peach	1	2[2]
		FI 0353	Pineapple	2 Po	2[2]
		SO 0495	Rape seed	0.5	-
		VD 0541	Soya bean (dry)	1	2[1]
		VC 0431	Squash, Summer	0.5	2[1]
		SO 0702	Sunflower seed	1	-
		VO 0448	Tomato	0.5	2[1]
			Vegetables, except as otherwise listed	W	2
		GC 0654	Wheat	0.2	-
		Residue: sum of alpha- and beta-endosulfan and endosulfan sulphate (fat-soluble) Notes [1] Vegetables, except as otherwise listed [2] Fruits			
Ethephon (106)	0.05	Note As an ADI has now been allocated, previous GLs would normally be nce ethephon is now scheduled for residue evalu-ation in 1984 however, adoption of esent recommended			
Ethylenethiourea [1] (ETU, 108)	0.004	VR 0577	Carrot	W	0.01*
		VS 0624	Celery	W	0.01*
		VL 0482	Lettuce, Head	W	0.01*
		VR 0589	Potato	W	0.01*
		Residue: ethylenethiourea Note ADI increased from TADI of 0.002 mg/kg bw. There are no other TMRLs			
Etofenprox [2] (184)	0.03	FP 0009	Pome fruits	1	-
		VR 0589	Potato	0.01*	-
		Residue: etofenprox (fat-soluble)			
Fenbutatin oxide [1] (109)	0.03	TN 0660	Almonds	0.5	-
		FP 0226	Apple	W[1]	5
		AB 0226	Apple pomace, dry	40	20
		FI 0327	Banana	10	-
		FS 0013	Cherries	10	5
		PO 0840	Chicken, Edible offal of	0.05*	-
		PM 0840	Chicken meat	0.05*	-

[1] Re-evaluation in periodic review programme

		FC 0001	Citrus fruits	W[2]	5
		AB 0001	Citrus pulp, dry	25	7
		VC 0424	Cucumber	0.5	1
		MO 0105	Edible offal (Mammalian)	0.2	-
		VO 0440	Egg plant	W	1
		PE 0112	Eggs	0.05	-
		VC 0425	Gherkin	W	1
		FB 0269	Grapes	5	5
		FC 0203	Grapefruit	5	5 (citrus)
		AB 0269	Grape pomace, dry	100	-
		MO 1292	Horse, kidney	W[3]	0.2
		MO 1293	Horse, liver	W[3]	0.2
		MO 0098	Kidney of cattle, goats, pigs, and sheep	W[3]	0.2
		MO 0099	Liver of cattle, goats, pigs and sheep	W[3]	0.2
		FC 0206	Mandarin	5	5 (citrus)
		MM 0095	Meat	0.05*	-
		MM 0096	Meat of cattle, goats, horses, pigs and sheep	W[4]	0.02*
		VC 0046	Melons, except Watermelon	W	1
		ML 0106	Milks	0.05*	0.02*
		FC 0208	Orange, Sweet	5	5 (citrus)
		FS 0247	Peaches	7	7
		FP 0230	Pear	W[1]	5
		TN 0672	Pecans	0.5	-
		VO 0445	Peppers, Sweet	W	1
		FS 0014	Plums (including Prunes)	3	3
		FP 0009	Pome fruits	5	Apple 5 Pear 5
		DF 0014	Prunes [dried plums]	10	-
		DF 5263	Raisins	20	-
		FB 0275	Strawberry	10	3
		VO 0448	Tomato	1	1
		TN 0678	Walnuts	0.5	-
		Residue: fenbutatin oxide			
		Notes [1] Replaced by limit for Pome fruit [2] Replaced by separate limits for Grapefruit, Mandarin, and Orange, Sweet [3] Replaced by Edible offal (mammalian) [4] Replaced by revised limit for Meat			
Fenpropathrin [2] (185)	0.03	MO 0812	Cattle, Edible offal of	0.05	-
		MM 0812	Cattle meat	0.5 (fat)	-
		ML 0812	Cattle milk	0.1 F	-
		SO 0691	Cotton seed	1	-
		OC 0691	Cotton seed oil, crude	3	-
		PE 0112	Eggs	0.01*	-
		VO 0440	Egg plant	0.2	-
		VC 0425	Gherkin	0.2	-
		FB 0269	Grapes	5	-
		VO 0445	Peppers, Sweet	1	-
		FP 0009	Pome fruits	5	-
		PO 0111	Poultry, Edible offal of	0.01*	-
		PM 0111	Poultry meat	0.02 (fat)	-
		VO 0448	Tomato	1	-

[1] Re-evaluation in periodic review programme

		Residue:	fenpropathrin (fat-soluble)		
Fentin (040)	0.0005	DH 1100	Hops, dry	0.5	1
		Residue:	fentin, excluding inorganic tin and di- and mono-phenyltin		
Flucythrinate (152)	0.02	MM 0812	Cattle meat	W	0.5 (fat) T
		ML 0812	Cattle milk	W	0.1 F T
		MM 0814	Goat meat	W	0.5 (fat) T
		Residue:	flucythrinate (fat-soluble)		
Flusilazole (165)	0.001	FS 0240	Apricot	0.5	-
		FS 0245	Nectarine	0.5	0.1 T
		FS 0247	Peach	0.5	0.1 T
		Residue:	flusilazole		
Folpet (041)	0.01 T (1995)	FP 0226	Apple	W	10 T
		FS 0013	Cherries	W	15 T
		FC 0001	Citrus fruits	W	10 T
		VC 0424	Cucumber	W	2 T
		FB 0269	Grapes	2	25 T
		VL 0482	Lettuce, Head	W	15 T
		VC 0046	Melons, except Watermelon	W	2 T
		VA 0385	Onion, Bulb	W	2 T
		FB 0275	Strawberry	5	20 T
		VR 0589	Potato	0.02*	-
		VO 0448	Tomato	W	5 T
		Residue:	folpet		
		Note	Existing TADI extended until 1995		
Heptachlor (043)	0.0001	VR 0577	Carrots	W	0.2 E T
		VR 0596	Sugar beets	W	0.05 E
		VO 0448	Tomato	W	0.02 E T
			Vegetables	W	0.05 E T
		Residue:	sum of heptachlor and heptachlor epoxide (fat-soluble)		
Hexaconazole (170)	0.005	GC 0654	Wheat	0.1	0.1 T
		AS 0654	Wheat straw and fodder, dry	0.5	0.5 T
Mancozeb [1] (050)	0.03	Notes	1. ADI is group ADI for EBDCs: see Dithiocarbamates. Previous ADI 0-0.05 mg/kg bw 2. See Dithiocarbamates for recommended MRLs		
Maneb [1] (Dithiocarbamates, 105)	0.03	Notes	1. ADI is group ADI for EBDCs: see Dithiocarbamates. Previous ADI 0-0.05 mg/kg bw 2. See Dithiocarbamates for recommended MRLs		
Metiram [2] (186)	0.03	Note	ADI is group ADI for EBDCs: see Dithiocarbamates.		
Monocrotophos (054)	0.0006	Note	ADI increased from 0.00005 mg/kg bw		
(112)	0.0002	VR 0577	Carrot	0.2	0.5
		Residue:	sum of phorate, its oxygen analogue, and their sulphoxides and orate		
Phosalone (060)	0.001	Note	ADI lowered from 0.006 mg/kg bw		

[1] Re-evaluation in periodic review programme

Procymidone (136)	0.1	FP 0226	Apple	W	5
		FS 0013	Cherries	10	5
		VP 0526	Common bean (pods and/or immature seeds)	1	2
		FB 0021	Currants, Black, Red, White	W	10
		VO 0440	Egg plant	W	2
		FB 0269	Grapes	5	5 T
		FI 0341	Kiwifruit	W	7
		VC 0046	Melons, except Watermelon	W	1
		VA 0385	Onion, Bulb	0.2	0.2
		VR 0589	Potato	W	0.1
		CM 0649	Rice, husked	W	3
		CM 1205	Rice, polished	W	1
		SO 0702	Sunflower seed	0.2	2
		OR 0702	Sunflower seed oil, edible	0.5	-
Propineb [1]	0.007	Notes	1. previous TADI of 0.005 mg/kg bw was withdrawn in 1985 2. See Dithiocarbamates for recommended MRLs		
Propylenethiourea (PTU) (150)	0.0002 T (1999)	Note	As a TADI has now been allocated, GIs for propylenethiourea would as TMRLs, but the Meeting did not consider the GIs in this context		
Pyrazophos (153)	0.004	FP 0226	Apple	1	0.5
		AS 0640	Barley straw and fodder, dry	5	-
		VC 0424	Cucumber	0.1	0.1
		VC 0046	Melons, except Watermelon	0.1	0.1
		AS 0654	Wheat straw and fodder, dry	5	-
		Residue:	pyrazophos		
Triazophos (143)	0.001	FI 0327	Banana	W	1
		VR 0577	Carrot	0.5	0.1
		FC 0001	Citrus fruits	2 T	2
		VD 0541	Soya bean (dry)	0.05*	-
		FB 0275	Strawberry	0.05*	-
		Residue:	triazophos		
		Note	ADI increased from TADI of 0.0002 mg/kg bw. All previous TMRLs become MRLs		
Zineb [1] (Dithiocarbamates, 105)	0.03	Note	ADI is group ADI for EBDCs: see Dithiocarbamates. Previous ADI 0-0.05		

17

[1] Re-evaluation in periodic review programme

[1] Re-evaluation in periodic review programme

[1] Re-evaluation in periodic review programme

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

	(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)
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)
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)
CARBOFURAN (096)	1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R)
CARBON DISULPHIDE (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)
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)
CHLORMEQUAT (015)	1970 (T,R), 1972 (T,R), 1976 (R), 1985 (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)
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)
CHLORTHION	1965 (T)
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)
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)
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-METHYLSULPHON (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)
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)
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)
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)
DISULFOTON (074)	1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I)
DITHIANON (180)	1992 (T,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)
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)
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)
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[7]), 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)
FENBUTATIN OXIDE (109)	1977 (T,R), 1979 (R), 1992 (T), 1993 (R)

[7]R evaluation omitted. Published 1986.

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)
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)
FENTIN COMPOUNDS (040)	1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R), 1993 (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)
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)
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)
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)
GLYPHOSATE (158)	1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R))
GUAZATINE (114)	1978 (T.R), 1980 (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)
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)
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)

IPRODIONE (111)	1977 (T,R), 1980 (R), 1992 (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)
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[8]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R)
METHIDATHION (051)	1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,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,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)
MYCLOBUTANIL (181)	1992 (T,R)

[8]R evaluation omitted. Published 1989.

NABAM	see dithiocarbamates, 1965 (T), 1976 (T,R)
NITROFEN (140)	1983 (T,R)

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 sulphoxide), 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)
PARATHION-METHYL (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)
PENCONAZOLE (182)	1992 (T,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 (R)
PHOSALONE (060)	1972 (T,R), 1975 (R), 1976 (R), 1993 (T)
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)
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)
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)
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)
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)
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)
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)

2,4,5-T (121)	1970 (T,R), 1979 (T,R), 1981 (T)
TECNAZENE (115)	1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R)
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)
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)
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)
TRIADIMENOL (168)	1989 (T,R), 1992 (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)

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 of pesticides on the agenda of the Joint Meeting, based on the methods described in *Guidelines for Predicting Dietary Intake of Pesticide Residues*[v].

Detailed EMDI (Estimated Maximum Daily Intake) calculations were not performed on those pesticides for which the TMDI (Theoretical Maximum Daily Intake), based upon global diets, exceeded the ADI, because there was insufficient opportunity at the Joint Meeting to review the detailed processing data that had been supplied on the compounds of interest. The results of EMDI calculations will be made available to the Twenty-sixth Session of the Codex Committee on Pesticide Residues (CCPR) in April 1994.

The TMDI calculations were based on 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:

aldicarb, benalaxyl, bromopropylate, carbofuran, chlorothalonil, cycloxydim, diazinon, DDT, dithiocarbamates (mancozeb and maneb), endosulfan, etofenprox, fenbutatin oxide, fenpropathrin, fentin, flucythrinate, flusilazole, folpet, hexaconazole, procymidone, propineb, and pyrazophos.

The TMDI exceeded the ADI for the following compounds (information on processing factors must be reviewed before EMDIs can be calculated):

azinphos-methyl, chlorpyrifos-methyl, dichlorvos, diquat, heptachlor, monocrotophos, phorate, phosalone and triazophos.

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:

amitrole, carbosulfan, ethephon, ethylenethiourea, metiram, propylenethiourea and zineb.

The TMDIs calculated grossly over-estimate the true pesticide 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, EMDI and, if necessary, EDI (Estimated Daily Intake), calculations should be performed.

[i] *Principles for the toxicological assessment of pesticide residues in food*. WHO Environmental Health Criteria, No. 104. Geneva, World Health Organization, 1990.

[ii] *Pesticides in the diets of infants and children*. National Academy of Sciences. Washington, National Academy Press, 1993.

[iii] *Guidelines for Predicting Dietary Intake of Pesticide Residues*. Geneva, World Health Organization, 1989.

[iv] T = Toxicology

R = Residue and analytical aspects

[v.] *Guidelines for Predicting Dietary Intake of Pesticide Residues*, World Health Organization, Geneva 1989.