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[1] T = Toxicology   *New compound
R = Residue and analytical aspects   **Evaluation in CCPR periodic review programme
E = Evaluation of effects on the environment

4.9 DINOCAP (087)

TOXICOLOGY

Dinocap was evaluated by the JMPR in 1969, 1974, and 1989. An ADI of 0-0.001 mg/kg bw was allocated in 1989 on the basis of a NOAEL of 0.5 mg/kg bw per day in a study of developmental toxicity in rabbits and a safety factor of 500. At the present Meeting recent data on material of greater purity than that tested previously were evaluated. Dinocap consists of 2,4- and 2,6-dinitro-octylphenyl crotonates in which the octyl moiety is either 1-methylheptyl, 1-ethylhexyl, or 1-propylpentyl. A number of the studies that were reviewed were performed with the methylheptyl isomer used as a model for dinocap.

WHO has classified dinocap as "slightly hazardous".

Dinocap is well absorbed after oral exposure. A proportion (5-25%) is absorbed after dermal exposure, varying with species and concentration. No conclusions were drawn about the degree of dermal absorption in humans from the results of a study in which mouse and human skin were compared; however, human skin is generally regarded as being less permeable to toxicants than that of mice.

The urinary metabolites of the methylheptyl isomer in rats and mice have been extensively characterized; characterization of the faecal metabolites was reported by the 1989 JMPR, which concluded that the pattern of metabolites in faeces seen by thin-layer chromatography was similar to that observed in squash and cucumbers.

The new data confirmed the generally low degree of acute toxicity of dinocap in rats; mice, however, appear to be more sensitive than rats to both acute and developmental effects. Dinocap is a skin irritant and sensitizer. The available studies did not address the uncoupling of oxidative phosphorylation, identified by the 1989 JMPR as a potentially significant mode of action.

In a carcinogenicity study in mice at 0, 15, 100 or 200 ppm no evidence of carcinogenicity was found. The NOAEL was 15 ppm, equal to 2.7 mg/kg bw per day. The lack of carcinogenicity in mice is consistent with the absence of carcinogenicity in rats reported by the 1989 JMPR. A multigeneration study of reproductive toxicity at dietary concentrations of 0, 40, 200 or 1000 ppm in rats showed no specific effect on any reproductive parameters; the NOAEL was 200 ppm equal to 13 mg/kg/day. The results of tests for genotoxicity (on the less pure form of dinocap) were negative.

In a study of developmental toxicity in mice dosed by gavage at 0, 4, 10 or 25 mg/kg bw per day, impaired otolith formation was seen at 25 mg/kg/bw per day. A dose-related increase in open eyelids and cleft palate extended down to 10 mg/kg bw per day in the absence of maternal toxicity. The NOAEL was 4 mg/kg bw per day. Dermal application of 50, 80 or 100 mg/kg bw per day to mice proved excessive for the evaluation of developmental toxicity. A further dermal study in mice at 0, 1, 4, 10 or 25 mg/kg bw per day showed malformations including impaired otolith formation at 25 mg/kg bw per day in the absence of maternal toxicity. The NOAEL for

developmental toxicity following dermal application to mice was 10 mg/kg bw per day. The results of these recent studies of developmental toxicity confirmed the teratogenic potential of purified dinocap in mice, even when applied dermally. Impaired otolith development, characteristic of dinocap teratogenicity in mice, was also seen in hamsters at doses that cause maternal toxicity. Less specific malformations were seen in rabbits at maternally toxic doses. The present Meeting concluded that the NOAEL in the studies in rabbits described by the 1989 JMPR was 3 mg/kg bw per day rather than 0.5 mg/kg bw per day, since the findings on which the putative effect level was established do not appear to be repeatable or clearly dose-related. The methylheptyl isomer has been shown not to be teratogenic to mice. The reason for the species difference in the teratogenicity of dinocap in rats and mice therefore cannot be deduced from the data on the metabolism of the methylheptyl isomer.

The 2-year study in dogs that was evaluated at the 1989 Joint Meeting was also reassessed on the basis that the critical effect (retinal atrophy) was secondary to effects on the tapetum lucidum. Since the tapetum lucidum is not present in humans, or in rats or mice in which no retinal effect was seen, the Meeting concluded that it would be inappropriate to base the evaluation on this effect. The NOAEL was 60 ppm, equivalent to 1.5 mg/kg bw per day.

Teratogenic effects in mice were considered to be the toxicological end-point of greatest concern. Since dinocap was shown to be teratogenic in mice after either oral or dermal administration and since malformations were seen in at least three species, the Meeting considered a high safety factor to be appropriate. An ADI of 0-0.008 mg/kg bw was established on the basis of the NOAEL of 4 mg/kg bw per day in the developmental toxicity study in mice and a safety factor of 500.

Establishment of an acute RfD was considered to be appropriate since teratogenicity may occur after a single exposure. An acute RfD was established on the basis of the NOAEL of 4 mg/kg bw per day for teratogenicity in mice and a safety factor of 500, to give an acute RfD of 0-0.008 mg/kg bw, which is appropriate for women of child-bearing age.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxicological effect

Mouse: 15 ppm, equal to 2.7 mg/kg bw per day (toxicity in a study of carcinogenicity)
4 mg/kg bw per day (developmental toxicity)
10 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rat: 200 ppm, equal to 6.4 mg/kg bw per day (toxicity in a study of carcinogenicity)

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

Rabbit: 3 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 60 ppm, equivalent to 1.5 mg/kg bw per day (study of toxicity)

Estimate of acceptable daily intake for humans

    0-0.008 mg/kg bw

Estimate of acute reference dose

    0.008 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Further observations in humans

List of end points for setting guidance values for dietary & non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	60-69% absorbed, max. concentration at 2-6 hours
Dermal absorption:	5%-25%
Distribution	Widely distributed
Potential for accumulation:	Limited (<0.3% in tissue after 7 days)
Rate and extent of excretion:	Biphasic; $T_{1/2}$=3 h for 1st phase, 44 h for 2nd phase, oral administration, rabbit
Metabolism in animals	Extensive; >96% metabolized
Toxicologically significant compounds (animals, plants and environment)	Metabolites assumed to be of similar toxicity to parent

Acute toxicity

Rat LD_{50} oral	3100 mg/kg bw
Rat LD_{50} dermal	> 5000 mg/kg bw
Rat LC_{50} inhalation	3 mg/L
Skin irritation	Irritating
Eye irritation	Irritating
Skin sensitization	Sensitizing

Short term toxicity

Target / critical effect	General toxicity (dog 2-year study)

Lowest relevant oral NOAEL	1.5 mg/kg bw per day
Lowest relevant dermal NOAEL	10 mg/kg bw per day (mouse, teratogenicity)
Lowest relevant inhalation NOAEL	No data

Genotoxicity

| Not genotoxic in an adequate battery of tests |

Long term toxicity and carcinogenicity

Target/critical effect:	Impaired weight gain
Lowest relevant NOAEL	2.7 mg/kg bw per day (mouse, carcinogenicity)
Carcinogenicity	Not carcinogenic

Reproductive toxicity

Reproduction target / critical effect	No effect on fertility or ability to rear young
Lowest relevant reproductive NOAEL	13 mg/kg bw per day (rat, multigeneration study)
Developmental target / critical effect	Malformations in mouse
Lowest relevant developmental NOAEL	4 mg/kg bw per day

Neurotoxicity / Delayed neurotoxicity

| No data, but no concern raised in other studies |

Other toxicological studies

| Inhibits oxidative phosphorylation; methylheptyl isomer not teratogenic |

Medical data

| No significant dinocap-related effects reported |

Summary	Value	Study	Safety factor
ADI	0-0.008 mg/kg bw	Mouse, developmental toxicity (4 mg/kg bw per day)	500
Acute reference dose	0.008 mg/kg bw	Mouse developmental toxicity (4 mg/kg bw per day)	500

1998 JOINT MEETING OF THE FAO PANEL OF EXPERTS ON PESTICIDE RESIDUES IN FOOD AND THE ENVIRONMENT AND THE WHO CORE ASSESSMENT GROUP

Rome, 21-30 September 1998

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ABBREVIATIONS WHICH MAY BE USED
(Well-known abbreviations in general use are not included)

Ache	acetylcholinesterase
ADI	acceptable daily intake
AFI(D)	alkali flame-ionization (detector)
ai	active ingredient
ALAT	alanine aminotransferase
AR	applied radioactivity
ASAT	aspartate aminotransferase
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
Bw	body weight
BOD	biological oxygen demand
CA	Chemical Abstracts
CAS	Chemical Abstracts Services
CCN	Codex Classification Number (this may refer to classification numbers for compounds or for commodities).
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residue of Veterinary Drugs in Food
ChE	cholinesterase
CI	chemical ionization
CNS	central nervous system
cv	coefficient of variation
CXL	Codex Maximum Residue Limit (Codex MRL). See MRL.
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-)
DP	dustable powder
DS	powder for dry seed treatment
DT-50	time for 50% decomposition (i.e. half-life)
DT-90	time for 90% decomposition
EBDC	ethylenebis(dithiocarbamate)
EC	(1) emulsifiable concentrate
	(2) electron-capture [chromatographic detector]
ECD	electron-capture detector
EI	electron-impact
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
FI(D)	flame-ionization (detector)
FP(D)	flame-photometric (detector)

g (not gm)	gram
μg	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography - mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
G.I.	gastrointestinal
GL	guideline level
GLC	gas-liquid chromatography
GLP	good laboratory practice
GPC	gel-permeation chromatograph or chromatography
GSH	glutathione

h (not hr)	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography - mass spectrometry

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 the WHO Core Assessment Group)
LC	liquid chromatography
LC_{50}	lethal concentration, 50%
LC-MS	liquid chromatography - mass spectrometry
LD_{50}	lethal dose, median
LOAEL	lowest observed adverse effect level
LOD	limit of determination (see also "*" at the end of the Table)
LSC	liquid scintillation counting or counter

M	molar
μm	micrometre (micron)
MFO	mixed function oxidase
min (no stop)	minute(s)
MLD	minimum lethal dose
mo (not mth.)	month(s)

MRL   Maximum Residue Limit. MRLs include <u>draft</u> MRLs and <u>Codex</u> MRLs (CXLs). The MRLs recommended by the JMPR on the basis of its estimates of maximum residue levels enter the Codex procedure as draft MRLs. They become Codex MRLs when they have passed through the procedure and have been adopted by the Codex Alimentarius Commission.

MS   mass spectrometry
MSD   mass-selective detection or detector
MTD   maximum tolerated dose

n (not *n*) normal (defining isomeric configuration)
NCI   National Cancer Institute (USA)
NMR   nuclear magnetic resonance
NOAEL   no-observed-adverse-effect level
NOEL   no-observed-effect level
NP(D)   nitrogen-phosphorus (detector)
NTE   neuropathy target esterase

OECD   Organization for Economic Co-operation and Development
OP   organophosphorus pesticide

PHI   pre-harvest interval
ppm   parts per million. (Used only with reference to the concentration of a pesticide in an experimental diet. In all other contexts the terms mg/kg or mg/l are used).
PT   prothrombin time
PTDI   provisional tolerable daily intake. (See 1994 report, Section 2.3, for explanation)
PTT   partial thromboplastin time
PTU   propylenethiourea

RBC   red blood cell
r.d.   relative density. (Formerly called specific gravity)

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)
SPE   solid-phase extraction
STMR   supervised trials median residue

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
TSH	thyroid-stimulating hormone (thyrotropin)
UDMH	1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine)
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet
WG	water-dispersible granule
WHO	World Health Organization
WP	wettable powder
$<$	less than
$\leq$	less than or equal to
$>$	greater than
$\geq$	greater than or equal to

USE OF JMPR REPORTS AND EVALUATIONS BY REGISTRATION AUTHORITIES

The summaries and evaluations contained in this book are, in most cases, based on unpublished proprietary data submitted for the purpose of the JMPR assessment. A registration authority should not grant a registration on the basis of an evaluation unless it has first received authorization for such use from the owner who submitted the data for JMPR review or has received the data on which the summaries are based, either from the owner of the data or from a second party that has obtained permission from the owner of the data for this purpose.

PESTICIDE RESIDUES IN FOOD

REPORT OF THE 1998 JOINT FAO/WHO MEETING OF EXPERTS

1. INTRODUCTION

A Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR) was held at FAO, Rome (Italy), from 21 to 30 September 1998. The FAO Panel of Experts had met in preparatory sessions from 16 to 20 September.

The Meeting was opened by Dr. Mahmud A. Duwayri, Director of the FAO Plant Production and Protection Division, on behalf of the Directors General of FAO and WHO. Dr. Duwayri emphasized the growing importance of the work of the JMPR for the establishment of international standards, as maximum residue limits (MRLs) for pesticide residues in food set by the Codex Alimentarius Commission had been incorporated into the Agreement on Sanitary and Phytosanitary measures of the World Trade organization (WTO). He underlined the significance of a transparent review and evaluation process to support the confidence in, and acceptance of, those MRLs by the consumer,

The meeting was marked by the introduction of two new features: (i) for the first time data from a national toxicological review were used for the allocation of an acceptable daily intake (ADI), for the insecticide endosulfan, and (ii) dietary risk assessments were made for the residues in food of the pesticides evaluated.

The Meeting was held in pursuance of recommendations made by previous Meetings and accepted by the governing bodies of FAO and WHO that studies should be undertaken jointly by experts to evaluate possible hazards to humans arising from the occurrence of residues of pesticides in foods. The reports of previous Joints Meetings (see References, Section 7) contain information on ADIs, MRLs and general principles for the evaluation of pesticides that have been evaluated. The supporting documents (Residue and Toxicological Evaluations) contain detailed monographs on these pesticides and include evaluations of analytical methods.

During the Meeting, the FAO Panel of Experts was responsible for reviewing residue and analytical aspects of the pesticides under consideration, including data on their metabolism, fate in the environment and use patterns, and for estimating the maximum residue levels that might occur as a result of the use of the pesticides according to good agricultural practices. The WHO Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides.

The Meeting evaluated 28 pesticides, including one new compound and 18 complete re-evaluations, for toxicology or residues or both, within the Periodic Review Programme of the Codex Committee on Pesticide Residues (CCPR).

The Meeting allocated ADIs and Acute Reference Doses (Acute RfDs), estimated maximum residue levels which it recommended for use as MRLs by the CCPR, and estimated Supervised Trials Median Residue (STMR) levels as a basis for the estimation of dietary intakes.

The Meeting devoted particular attention to the estimation of the dietary intakes of the pesticides reviewed in relation to their ADIs. In particular, in the case of compounds undergoing a complete evaluation or re-evaluation it distinguished between those whose estimated intakes were below their ADIs from those whose intakes might exceed their ADIs by designating the MRLs recommended for the latter as MRLMs (Maximum Residue Limits for Monitoring). A proposal to make this distinction and its rationale are described in detail in the report of the 1997 JMPR[1] (Section 2.3).

The Meeting was chaired by Mr. Denis Hamilton from Australia, who also took over the chairmanship of the FAO Panel of Experts from Mr. Fred Ives, USA. The Meeting expressed its appreciation of the time and effort Mr. Ives had devoted to the work of this Panel for many years and thanked him for his guidance and leadership.

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[1] *Pesticide residues in food - 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues.* FAO Plant Production and Protection Paper 145.

2. GENERAL CONSIDERATIONS

2.1 THE CAPACITY OF THE JMPR TO UNDERTAKE PERIODIC REVIEWS

The increasing amount of data on pesticides and the desire for more transparency, both of which require the preparation of increasingly comprehensive reports and evaluations, put severe strain on the JMPR. Assessments of dietary risk that incorporate estimates of intake, which were included in the report for the first time at the present Meeting, necessitate the estimation of STMR [and STMR-P] levels for processed items, which require more detailed reviews of residue trials, animal feeding studies, and food processing procedures than are needed for the estimation of MRLs alone. In addition, the complexity of the evaluations is increased when pesticides are re-evaluated under the CCPR Periodic Review Programme because data have been produced over many years according to different guidelines, often with technical products that meet changing specifications, differing residue definitions, and considerable changes in GAP.

Participants in the JMPR are subject to severe time constraints both during the preparation of their draft evaluations and during the Meeting itself. In many cases the preparatory work is done in their own time because their employers (usually national regulatory authorities) do not provide time for this work during office hours. Related to this, their work is sometimes not recognized as being important for the support of decisions on national registrations and for establishing international food standards. International peer reviews of national assessments substantially enhance the efficiency and quality of the JMPR evaluations, clearly demonstrating the mutual benefits of active participation in the Joint Meeting to both JMPR and the national authority.

To respond adequately to these constraints, better coordination and additional resources are needed. For efficient coordination between the CCPR and the JMPR Joint Secretaries, information is required from national delegations to the CCPR on their review schedules. The setting of priorities should take into account the amount of information to be evaluated for each compound, which will help the Secretariat to distribute the workload equally among the reviewers.

2.2 USE OF DATA FROM BIOMEDICAL TESTING INVOLVING HUMAN SUBJECTS IN HAZARD EVALUATION

From time to time, data on toxicity in humans are made available for consideration in the hazard identification and dose-response assessment phases of the risk assessment process. In certain cases, such human data are useful in characterizing the hazard of the pesticide under evaluation. Because data on intentional and deliberate exposures are not developed in response to specific requests or requirements of any regulatory authorities, no standard protocol exists for the design and conduct of such studies. As a consequence, questions often arise as to their adequacy, e.g. whether the numbers and diversity of subjects are sufficient. In addition, concern has been expressed as to whether such studies have been conducted in accordance with the ethical standards expected and/or required of other kinds of human studies.

The Meeting reached the following conclusions.

I. In order for human studies to be considered in the hazard evaluation of a pesticide, it must be shown that they have been conducted in accordance with principles such as those expressed in the Declaration of Helsinki (1964; amended most recently in 1996[1]) or equivalent statements prepared for use by national and/or multinational authorities. These principles embody the concepts of protection of the life and health of the subject, freely-given informed consent, use of an independent review board (i.e. ethical committee) and other factors. The components of the Declaration of Helsinki that are applicable to this discussion are reproduced below.

BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

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[1]*World Medical Association - Declaration of Helskinki: Recommendations guiding medical doctors in biomedical research involving human subjects*. Journal of the American Medical Association **277**:925-926, 1997.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained fromthe legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or whenthe subject is a minor, permission from the responsible relative replaces that ofthe subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

II. The results of human studies may be used to identify the potential hazard to, and to estimate acceptable levels of exposure of, human populations possessing a wide diversity of biological

and physiological characteristics. If such studies are conducted, they should be designed with sufficient rigour and robustness to ensure their applicability to these diverse populations. To that end, the study design should incorporate the following components as a *minimum.*

There should be sufficient numbers of subjects, usually of each sex.

The numbers of subjects in the study should be determined, in part, on the basis of the effects to be evaluated, to account for inherent normal variability and to ensure adequate statistical rigour.

The subjects should be adults, and any females should not be pregnant.

III. In order to ensure the greatest measure of protection of the human subjects in a study of toxicity, the entire standard toxicological database in the appropriate animal species needed to establish an ADI should be available.

IV. When appropriate and allowable , comparisons should be made of the pharmacokinetics in humans and rats (i.e. data on absorption, distribution, metabolism, excretion and kinetics).

The Joint Meeting will continue to make use of the results of biomedical tests involving human subjects when they are properly designed and when they meet appropriate ethical guidelines. Any studies conducted in the future must be shown to have adhered to the ethical principles articulated for the country in which the study is conducted. This discussion should not be construed as an argument in support of the injudicious development of human data following deliberate and intentional exposure. Vigorous efforts should continue to be made for the development of better animal models, *in vitro* and other short term tests, including those using human cells and tissues.

Sufficient time was not available at the present Meeting for a full discussion of all relevant aspects of the design and statistical robustness of studies of human toxicity. The Meeting therefore recommended that additional consideration should be given to this matter at future Joint Meetings.

2.3 ISSUES RELATED TO AGGREGATE AND CUMULATIVE RISK ASSESSMENT

The Meeting noted the request by the CCPR at its 30th Session (ALINORM 99/24 para 33) that consideration be given to issues related to the determination of the aggregate risk associated with human exposure to pesticides from multiple sources, including residues in food commodities. The Meeting also addressed the issue of cumulative risk, which results from multiple exposure to pesticides which have a common mechanism of action or which combine to produce similar adverse effects.

The Meeting also noted that these are matters of some concern in a number of countries. In the USA the Food Quality and Protection Act of 1996 makes aggregate and cumulative risk assessments mandatory.

The Meeting considered some of the issues which could have an impact on aggregate and cumulative risk assessment. These include:

- the development of appropriate methods for categorizing chemicals with a common mechanism of action, including the number of factors that must be in concordance before chemicals could be considered for clustering in such an analysis. Such factors could include: whether there are common target organs for toxicity; whether a common toxic intermediary metabolite is formed; whether the biotransformation and biodistribution characteristics are sufficiently similar; and whether the effects are common among different species or strains of animals.

- how to consider cumulative risk when there is uncertainty about the relevant mechanism(s) or when there are significant gaps in the mechanistic database for some of the chemicals under consideration in a cluster.

- what measures (e.g. toxicity equivalence factors; percentages of the ADI) would best serve to quantify the contributions of individual chemicals in the cluster to the overall risk.

- possible additive, synergistic, or antagonistic interactions.

- how exposure other than dietary intake could be determined (the CCPR considered that such data may be available only to national authorities)

- whether probabilistic (e.g. Monte Carlo) or deterministic (point estimate) models would be more appropriate, given that multiple pesticide residues are unlikely to occur in many samples of the same food commodities, and that over time a range of exposures is more likely to occur than constant exposure to fixed amounts of residues.

It was recognized that a particular problem for the JMPR is the extent of the database available to make aggregate and cumulative risk assessments. The JMPR database includes only those compounds which have been reviewed when data have been submitted in support of MRLs needed for food commodities in international trade. It would not be as extensive as the databases available to some national authorities. This could limit the ability of the JMPR to include all compounds that might need to be considered in conducting a cumulative risk assessment. Similar limitations to the database could also make an aggregate risk assessment more difficult.

The Meeting concluded that a number of these matters need to be resolved before aggregate and cumulative risk assessments could form part of the JMPR evaluation process.

2.4 INTERNATIONAL ESTIMATED SHORT-TERM INTAKE (IESTI)

The Meeting noted the recommendations relating to estimates of short-term dietary intake of the joint FAO/WHO Consultation on "Food Consumption and risk assessment of chemicals"[1] held in Geneva on 10-14 February 1997. In particular, the recommendation on the procedures developed for short-term dietary intake estimates should be considered for use at the international level for pesticide residues.

The Meeting also noted that the CCPR in a circular letter[2] had requested information from member governments on large portion weights i.e. single-day consumption data (eaters only) at the 97.5th percentile for the general population and also for children aged 6 and under. Data on typical commodity unit weights were also requested. The Meeting urged governments to respond to this request where data are available, since these data are required before short-term dietary intakes can be estimated by the JMPR.

The Meeting was also informed that international activities in this area were in progress and that their outcome would be reported to the 31st session of the CCPR (1999).

The Meeting concluded that it would be premature to attempt to estimate short-term dietary intakes at present but considered that the 1999 Meeting should be in a better position to undertake this work.

2.5 THE ESTIMATION OF STMRS AND MAXIMUM RESIDUE LEVELS FOR COMMODITIES OF ANIMAL ORIGIN - WORKED EXAMPLES

Introduction

The 1997 JMPR[3] recommended a procedure for estimating MRLs and STMRs for products of animal origin and further recommended that worked examples should be developed for the 1998 Meeting. The current Meeting prepared as an example the estimation of the intake of 2,4-D by dairy cattle to represent the case where a compound reaches a plateau rapidly in the milk. Since no example was available of a compound which reaches a plateau slowly, the Meeting agreed that a further worked example should be presented at a future Meeting.

Transfer studies

Groups of three cows were dosed at four dose levels (50.6, 99, 189 and 276 mg/kg bw/day, equal to 1446, 2890, 5779 and 8585 ppm 2,4-D ai in the diet on a dry weight basis) for 28 to 30 consecutive days.

The highest residues in all four groups were in the kidneys, followed in decreasing order by liver, fat, muscle and milk. The residue levels were generally dose-dependent.

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[1] Joint FAO/WHO Consultation on *Food Consumption and risk assessment of chemicals.* Report of a FAO/WHO Consultation, Geneva, Switzerland. 10-14 February 1997.

[2] Circular letter CL 1998/29 – PR. Information requested on acute hazard exposure assessments.

[3] Report of the Joint Meeting of the FAO Panel of experts on Pesticide Residues in Food and the Environment and the WHO Core assessment Group on Pesticide Residues. Lyons, France. 22 September - 1 October 1997.

The residues of 2,4-D in the milk reached a plateau after 7 days of treatment, so the plateau can be considered to be reached rapidly and therefore maximum residue levels should be used to estimate the dietary burden.

Dietary intake

The highest exposure to 2,4-D residues will arise from the use of the herbicide on pasture, where the highest residues were 358 mg/kg in grass forage. With the assumption that the maximum daily feed consumption of a dairy cow (body weight 550 kg) is 20 kg on a dry matter basis, of which 60% is grass forage containing 25% dry matter, the intake may be calculated as follows.

- 358 mg/kg on a wet weight basis is equivalent to 1432 mg/kg on a dry matter basis (358 ÷ 0.25).
- Grass forage forms 60% of the diet and therefore contributes 859.2 ppm total feed on a dry matter basis (1432 x 0.6).

The dietary intake is therefore 859.2 x 20/550 = 31 mg/kg bw/day.

Estimation of MRLs and STMRs for animal products

The lowest dose in the feeding study was 50.6 mg/kg bw/day but, as the relation between dose and residue level was nearly linear and its graph passed through the origin, the Meeting concluded that extrapolation downwards to the estimated actual intake was justified. The following table shows the highest and the mean actual and extrapolated residues used for the estimation of the maximum residue level and STMR respectively.

Dose, mg/kg bw/day (Actual) Extrapolated	Residues, mg/kg							
	Milk		Liver		Kidney		Muscle	
	highest	mean	highest	mean	highest	mean	highest	mean
(50.6) 31	(0.07) 0.043	(0.04) 0.025	(0.2) 0.12	(0.12) 0.074	(6.5) 3.98	(3.8) 2.33	(0.24) 0.15	(0.21) 0.13
(99) 31	(0.18) 0.056	(0.12) 0.038	(2.4) 0.75	(1.9) 0.59	(18) 5.64	(14) 4.38	(0.51) 0.16	(0.41) 0.13
(189) 31	(0.59) 0.097	(0.29) 0.048	(3.5) 0.57	(3.0) 0.49	(29) 4.76	(17) 2.79	(1.1) 0.18	(0.76) 0.12
(276) 31	(0.87) 0.098	(0.47) 0.053	(3.8) 0.43	(3.1) 0.35	(24) 2.7	(24) 2.7	(1.0) 0.11	(1.0) 0.11

2,4-D residues in the feeding study are in parentheses

The Meeting estimated a maximum residue level and STMR for edible offal based on the residues in kidneys, rather than making separate estimates for kidney and liver. The Meeting estimated maximum residue levels of 0.1 mg/kg for milk, 5 mg/kg for edible offal and 0.2 mg/kg for meat, and STMRs (medians of the 4 extrapolated means for each commodity) of 0.043 mg/kg for milk, 2.745 mg/kg for edible offal and 0.125 mg/kg for meat.The Meeting withdrew its previous recommendations for milk and milk products (0.05* mg/kg).

2.6 OECD GUIDANCE DOCUMENTS

The Meeting recognized the work of the OECD Pesticide Forum and welcomed efforts that would enhance the quality and presentation of the scientific data package which the JMPR receives and upon which the evaluations are based. In particular, two guidance documents were noted:

> Guidelines and Criteria for the Evaluation of Dossiers and for the Preparation of Reports by Regulatory Authorities in OECD Countries Relating to the Evaluation of Active Substances, the Registration of Plant Protection Products and the Establishment of Maximum Residue Limits (MRLs) and Import Tolerances

Guidelines and Criteria for Industry for the Preparation of Complete Dossiers and of Summary Dossiers for Plant Protection Products and their Active Substances in Support of Regulatory Decisions in OECD Countries

The JMPR publishes evaluations of the toxicology and residue aspects of pesticides which are transparent and comprehensive, and is committed to moving towards an internationally harmonized reporting format as this becomes more firmly established. JMPR reports should therefore become increasingly useful to national governments in supporting their registration and registration review activities.

2.7 THE DEVELOPMENT OF MINIMUM RESIDUE DATA REQUIREMENTS THROUGH THE OECD PESTICIDE FORUM

In 1994 the JMPR recommended that "the attention of international organizations should be drawn to the need to develop internationally recognized minimum residue data requirements for establishing maximum residue limits (minimum data requirements for supervised residues data)".

The FAO manual[1] provides useful guidance on the submission and evaluation of pesticide residues data in the context of the estimation of maximum residue levels, but does not provide details of data requirements for other aspects of residue evaluation, which the Meeting considers are more appropriately dealt with by other international organizations.

The Meeting was informed that the UK is coordinating approaches through the OECD Pesticide Forum to the development of minimum data requirements in the following areas.

- Criteria for the minimum number of residue trials.
- Guidance on geographical and climatic regions in which residue trials should be conducted.
- Guidance on the extrapolation of trials data to related crops and on the use of data from related crops to provide mutual support for the estimation of maximum residue levels.

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[1] *FAO Manual on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed*. Food and Agricultural Organization of the United Nations, Rome, 1997.

The Meeting welcomed this initiative, which should facilitate the international acceptance of Codex MRLs.

2.8 DATA REQUIREMENTS FOR THE VALIDATION OF ANALYTICAL PROCEDURES

The requirements for the quality and reliability of analytical data have increased substantially during the last few years. In order to satisfy the WTO SPS agreements, compliance with Codex MRLs has to be confirmed by accredited laboratories applying validated methods. At its last (30th) Session the CCPR supported the revision of the current list of Recommended Methods of Analysis and the preparation a List of Suitable Methods of Analysis (ALINORM 99/24, para 94.).

As part of the evaluation process the JMPR regularly assesses the suitability of analytical methods for regulatory purposes, and when possible concludes that specific methods used in supervised trials can be adapted for use in regulatory and monitoring analysis. Information on the efficiency of extraction of the regulatory method is not normally available however.

The JMPR fully supports the requirement for the validation of extraction efficiency, which may significantly influence the accuracy of the analytical results, especially because it cannot be checked by traditional recovery studies carried out with samples fortified shortly before analysis. The rigorous validation of the efficient extraction of all residues included in the residue definition can only be performed with samples that have incurred the analyte(s) through the route by which they would normally reach the sample. This is generally the case in metabolism studies, where the efficiency of extraction can be determined by means of radiolabelled analytes.

The use of metabolism studies for directly assessing the efficiency of extraction procedures used in regulatory monitoring methods is rarely possible, because the extraction procedures in such studies are usually much more rigorous than those which are generally used for monitoring purposes. Consequently, comparative extraction efficiency studies including the frequently used extraction solvents, such as acetone/water, ethyl, acetate, and acetonitrile should be carried out on samples from metabolism studies for the compounds which are expected to be included in the residue definition(s).

The JMPR draws the attention of Member States to the lack of this important information in many cases, and recommends that information on the efficiency of extraction be included in registration requirements and considered as part of the evaluation process, as it has already been by some national governments.

The JMPR considers it essential that information on the efficiency of extraction procedures be provided. Henceforth, information should be supplied to the JMPR on the efficiency of extraction with the solvents used in relevant regulatory methods.

2.9 RESIDUE DATA REFLECTING THE GAP OF DEVELOPING COUNTRIES

The JMPR welcomed the decision of the CCPR (ALINORM 99/24, para 108) relating to the general use by developing countries of the JMPR criteria on data requirements to generate the necessary information for submission to the JMPR to support the elaboration of Codex MRLs.

The Meeting recognised the limitations in expertise and resources prevailing in many developing countries. It concluded that, within a relatively short period of time, reliable residue data could be generated in several developing countries having appropriate laboratory capacity by providing assistance for the introduction and implementation of quality control and quality assurance principles in their laboratories, and for the execution of supervised field trials in compliance with GLP. The major part of this assistance would be related to the transfer of accumulated knowledge and experience and interested countries should explore their possibilities of obtaining the necessary support. For theoretical and practical training in this subject the Meeting recommends the use of the recently established FAO/IAEA Training and Reference Centre, for which FAO and other organisations could provide the necessary assistance if interested countries request it.

2.10 FORMAT FOR SUMMARIZING TOXICOLOGICAL DATA

Since the 1995 Joint Meeting, toxicological data derived from various routes of exposure have been tabulated in the reports. The purpose of the tables is to draw attention to the crucial toxicological results relevant to human exposure via various routes.

The present Meeting reviewed a format developed by the OECD that lists end points that may have a bearing on human health. The Meeting concluded that this format provided a clear presentation of data that highlighted the toxicological profile of the pesticide. It will therefore now be used in place of the format used previously.

2.11 DEFINITION OF INDEPENDENT SUPERVISED RESIDUE TRIALS

The estimation of STMRs relies on the selection of residue data from trials according to GAP, with one residue value (the highest residue from replicate plots; the mean result from replicate analyses of a single field sample) selected from each trial. A sufficient number of trials is needed to cover variations in site locations and cultural practices.

Judgement is needed on whether trials should be considered sufficiently independent to be treated separately.

The following trial conditions are usually recorded and are taken into consideration.

- Geographical location and site.
- Dates of planting (annual crops) and treatments.
- Crop varieties – differences between varieties may be sufficient to influence the residue.
- Formulations – trials with different formulations are generally counted as separate trials.
- Application rates and spray concentrations – trials at significantly different application rates and spray concentrations are counted as separate trials.

- Types of treatment, e.g. foliar, seed treatment, directed application – different types of treatment on different plots at the same site are considered as separate trials.
- Treatment operations – trials at the same site with treatment in the same spray operation are not counted as separate trials.
- Application equipment – trials at the same site in which different equipment is used, other things being equal, are not counted as separate trials.
- Addition of surfactants –the addition of surfactant may constitute a sufficient difference for the trial to be treated as independent.

Trials at different geographical locations are considered to be independent.

The set of trials should be examined for its overall suitability in representing the variability which may occur in farming practice. For example, two trials with different commercial formulations (otherwise essentially the same) at one site may be considered sufficiently independent to be useful, but three or more trials at the same site with different formulations add little further information.

For trials at the same location to be considered independent there should be convincing evidence that the additional trials are providing further independent information about the influence of the range of farming practices on residue levels.

2.12 FRAMEWORK FOR THE ASSESSMENT OF CARCINOGENICITY

The Meeting considered a document "Framework for evaluating a postulated carcinogenic mode of action"[1], which had been developed as part of the IPCS Programme on Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

A key objective of the document was the promotion of greater transparency in the process by which decisions are made about the relevance to the assessment of human risk of certain findings of neoplasia observed in human epidemiological studies and/or long-term bioassays in laboratory animals. The document outlines a structured approach to listing and organizing those factors that could shed light on possible mechanisms by which a carcinogenic response, or responses, may have occurred. The elements included descriptions of the nature of the dose-response and temporal relationships, comments on the strength, consistency, and specificity of associations, and comments on the biological plausibility and coherence of the postulated mechanism(s).

The document was accompanied by an illustrative analysis of one of the pesticides under consideration at the current Meeting.

The Meeting noted the approach recommended in the document and considered that it could facilitate understanding of the decision-making logic and render the basis for decisions more transparent. The Meeting recommended that the document, together with some suitable examples of its application, be referred to authors of working papers at future Joint Meetings, to

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[1] International Programme on Chemical Safety. Harmonization of approaches to the assessment of risk from exposure to chemicals, Third meeting of the Steering Committee, Geneva, 7-8 September, 1998. SC3/Room doc. 1

provide guidance on the framing of the discussion of the carcinogenic potential of the chemicals under consideration.

2.13 PROCEDURES FOR ESTIMATING AN ACUTE REFERENCE DOSE

The Meeting was informed that the CCPR (ALINORM 99/24, para 24) had invited WHO to prepare a guidance document on procedures for estimating an acute RfD for consideration by both the JMPR and the CCPR.

Acute reference dose

The acute reference dose of a chemical is an estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation. It is usually expressed in milligrams of the chemical per kilogram of body weight[1].

It has been suggested that the ADI may not be the appropriate toxicological estimate of the amount of a substance that can be ingested without appreciable health risk during excursions of exposure that exceed the ADI. The definition of an ADI allows occasional exposure on individual days to levels above the ADI. Such excesses are generally considered to be of no toxicological concern provided that the ADI is not exceeded over the long term. Certain pesticides might present an acute hazard, however, so that such excesses are of toxicological concern. For these pesticides, an acute RfD should be established to set an upper limit on such short-term excursions. For certain acutely toxic compounds (e.g. aldicarb), the acute RfD may have the same numerical value as the ADI. In this case, fluctuations above the ADI should not occur.

General considerations

A compound may have different effects at different doses. It follows that the dose-effect curve for each compound may vary according to the dosing regimen. Well-known examples of such dose-effect curves are those of certain organophophorus insecticides, which cause delayed polyneuropathy at doses much higher than those that inhibit cholinesterases. Anticholinesterase organophosphorus compounds provide another example of the way in which the dose-effect curve may change according to the dosing regimen. Assuming that soon after a single dose of an irreversible acetylcholinesterase inhibitor, inhibition of the erythrocyte enzyme is equal to that of the brain enzyme, given the different rates of resynthesis (erythrocyte acetylcholinesterase<<brain acetylcholinesterase), the inhibition obtained after repeated dosing with the same compound will be greater in erythrocytes than in the brain (i.e. a higher dose is required to obtain the same inhibition of brain acetylcholinesterase).

The dose-response curve may also depend on the dosing regimen. For example, administration of anticholinesterase compounds by gavage to fasted animals results in a higher

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[1]*Food Consumption and Risk Assessment of Chemicals*. Report of a FAO/WHO Consultation, Geneva, Switzerland, 10-14 February 1997 (WHO/FSF/FOS/97.5).

peak of acetylcholinesterase inhibition than that seen when the same dose is administered in the diet during the day (especially with reversible inhibitors such as the carbamates).

From these considerations it is evident that there are no general rules for establishing an acute RfD. It is difficult to identify *a priori* the appropriate studies for a specific compound, since the value can be derived only in a stepwise manner.

Current situation

Most acute RfD values have been set for well-studied compounds on the basis of the results of repeat-dose studies from standard databases, since investigations of LD_{50} and short-term studies were not adequate. The values obtained were therefore generally conservative. The main exceptions are some anticholinesterase agents for which acute toxicity studies with measurement of adequate toxicological end-points were available and compounds inducing developmental effects.

Identification of the toxicological end-point of concern

Analysis of the toxicokinetic and toxicodynamic profile of a compound should allow identification of the end-point to be used in setting the acute RfD. This end-point might differ from that used to set the ADI. Sometimes, as with anticholinesterase agents, knowledge of the mechanism of action helps to identify the relevant end-point, although other toxic effects should not be discounted. For compounds that are toxic to key systems (e.g. the nervous system) or functions (e.g. compounds that cause developmental effects), the end-point for establishing an acute RfD might be easy to identify, while its identification might be more difficult for compounds that have mild and/or questionable effects.

Identification of type of study

a) Standard studies

i) Acute oral toxicity (LD_{50}) studies

In such studies death is usually the only end-point assessed, and other clinical and pathological observations are limited or absent. Moreover, the compound is usually administered by gavage to fasted animals, which results in quicker absorption. This is not normally appropriate for mimicking human exposure to residues, although it might be relevant for compounds such as carbamates which inhibit acetylcholinesterase in a reversible manner.

ii) Short-term studies of toxicity

In these studies clinical, haematological, clinical chemical and pathological examinations are performed, and the results might be used for compounds of low toxicity. Conservative values will be obtained.

iii) Studies of developmental toxicity

It is assumed that developmental toxicity can be induced by a single dose administered at a certain point in development. Other effects might also be considered relevant to the assessment of an acute RfD, given the short duration of exposure.

iv) Studies of reproductive toxicity

These are the only studies in which animals are investigated from weaning onwards, which might be relevant for assessing evidence of increased susceptibility in this age group.

v) Long-term studies of toxicity and carcinogenicity

The results of such studies are generally used to establish the ADI and are of little or no use for establishing the acute RfD.

b) Other studies

i) Range-finding studies

The results of range-finding studies might be used if relevant end-points have been investigated.

ii) Human data

The results of studies with volunteers might be available for compounds which have a known mechanism of toxicity. If the relevant end-points have been assessed these studies are the most appropriate for setting the acute RfD. Data from human poisoning incidents might be useful in identifying the relevant toxicological end-points.

iii) Mechanistic studies

Studies of effects on enzymes and/or hormones, with examination of the temporal pattern of such effects, would be relevant in setting an acute RfD.

Proposed approach

The above indicates that decisions must be made on a case-by-case basis; however, more specific indication are given below.

A) Carbamates and organophosphorus compounds

If acetylcholinesterase inhibition is the relevant effect, any study in which brain or, as a surrogate, erythrocyte acetylcholinesterase has been measured minutes to hours after dosing is

appropriate. Dietary studies might be more appropriate than those in which fasted animals are treated by gavage.

B) Neurotoxic compounds

An acute neurotoxicity study is required, unless short-term studies include a detailed neurotoxicological assessment.

C) Compounds that cause developmental effects

The acute RfD will be based on the NOAEL for developmental effects, in the absence of other relevant effects at lower doses.

D) Compounds for which it is not normally necessary to allocate an acute RfD

It seems reasonable to attempt to identify categories of pesticides for which an acute RfD would not normally be necessary. Sufficient time was not available at the present Meeting for a full discussion of this aspect. It was therefore recommended that additional consideration be given to this issue at future Joint Meetings.

Conclusions

The possibility of establishing an acute RfD will be considered for all pesticides. If, on the basis of its toxicological profile, a pesticide is considered unlikely to present an acute hazard, an acute RfD will not be established. When it has been determined that an acute RfD should be established but data do not permit establishment of an accurate value, it will be allocated on the basis of the available information with an indication of the type of study(ies) considered to be necessary to refine the estimate. Refinement may not be necessary when it has been determined that the intake does not exceed the current acute RfD.

As the ADI provides a reference point for the dietary intake over a lifetime, a single end-point (the most sensitive) is chosen. Effects occurring after acute exposure might be different or occur at different doses in different population subgroups, such as women of child-bearing age, infants, and children. The Meeting will routinely set the acute RfD on the basis of the most sensitive end-point in the most sensitive subgroup, and this will be clearly identified in the report. An acute RfD for less sensitive subgroup(s) will be established when intake data indicate its usefulness.

2.14 INTERPRETATION OF CHOLINESTERASE INHIBITION

The Meeting considered the report of a Consultation on Interpretation of Inhibition of Acetylcholinesterase Activity, which was held in January 1998 (IPCS Document No. PCS/98.7) at the request of the 1997 JMPR. The Consultation made recommendations on several issues, as outlined below, which were adopted by the present Meeting.

Assessment of effects on peripheral nervous tissues

The JMPR considers the inhibition of brain acetylcholinesterase activity and clinical signs to be the primary end-points of concern in toxicological studies on compounds that inhibit acetylcholinesterases. Inhibition of erythrocyte acetylcholinesterase activity is also considered to be an adverse effect, insofar as it is used as a surrogate for brain and perpherial nerve acetylcholinesterase inhibition, when data on the brain enzyme are not available. It is sometimes difficult to distinguish central from peripheral anticholinesterase effects, and a few anticholinesterases which do not pass the blood-brain barrier to an appreciable extent cause peripheral cholinergic signs, associated with the inhibition of erythrocyte but not brain acetylcholinesterase activity. The Meeting was therefore concerned that possible effects on the peripheral nervous system or neuromuscular junctions might not be adequately addressed. The Meeting considered that, unless data on acetylcholinesterase activity in peripheral target tissues are available, the use of erythrocyte acetylcholinesterase inhibition as a surrogate for peripheral effects is justified for acute exposures resulting in greater acetylcholinesterase inhibition in erythrocytes than in the brain. Reliance on inhibition of erythrocytic enzyme in studies of repeated doses might result in an overestimate of inhibition in peripheral tissues, because of the lower rate of resynthesis of the enzyme in erythrocytes than in the nervous system. In these cases, comparison of the dose-response curves for erythrocyte acetylcholinesterase and brain acetylcholinesterase inhibition and the occurrence of clinical signs may aid in the establishment of a NOAEL.

The Meeting was also concerned that mild clinical effects might not be observed because of the relative insensitivity of the clinical assessment of experimental animals, although it was recognized that the situation was improving because of the more widespread conduct of studies of acute neurotoxicity. The Meeting noted that the toxicological end-point in studies of neurotoxic agents other than cholinesterase inhibitors had normally been the observation of clinical signs.

Methods

A number of factors can influence the accurate measurement of inhibition of cholinesterase activity. These factors include the timing of sampling, sample storage conditions, and, especially in the case of erythrocytes, the conditions of the assay. The Meeting recognized that only limited information is available on the protocols used in assaying cholinesterase activity in many older studies and that assumptions might have to be made about the acceptability of such studies. Although lack of information or non-compliance with modern protocols do not necessarily invalidate the results of an assay, in some circumstances the quality of the assay and its reliability may be called into question. Further information, over and above that in the database supplied by the sponsoring company, may be sought by people preparing monographs, although such information is just not available in many old studies. This is most often the case for brain acetylcholinesterase when the time between slaughter and assay and the storage conditions of the tissue are not recorded, because the problem of ex-vivo reactivation of organophosphorus-inhibited cholinesterase, which, although incomplete, is fairly rapid in the case of dimethyl organophosphates, was not appreciated until fairly recently.

Toxicological significance of cholinesterase inhibition

Butyrylcholinesterase

The JMPR has consistently considered that the inhibition of plasma and brain butyrylcholinesterase is not a toxicologically significant effect for the purpose of establishing the ADI. The reason for this is that there is no evidence that butyrylcholinesterase inhibition has any adverse effect. It can be used as an indicator of absorption of the inhibitor, and, as such, it is still a useful tool for monitoring occupational exposure. Data on statistically significant inhibition of butyrylcholinesterase activity should therefore always be included.

Brain and erythrocyte acetylcholinesterase

Regulatory agencies have traditionally used various thresholds, such as 10% inhibition, 20% inhibition, or any statistically significant inhibition, in defining biologically significant depression of enzyme activity. The Meeting considered that statistically significant inhibition by 20% or more represents a clear toxicological effect and any decision to dismiss such findings should be justified. The Meeting also agreed that statistically significant inhibition of less than 20% or statistically insignificant inhibition above 20% indicate that a more detailed analysis of the data should be undertaken. The toxicological significance of these findings should be determined on a case-by-case basis. Considerations affecting such determinations include *inter alia* the shape or slope of the dose-response curve, assay variability, and correlation with clinical signs.

Conclusion

The Meeting considered and essentially reaffirmed the previous approach of the JMPR to the evaluation of the inhibition of cholinesterase activity, with some clarification.

3. DIETARY RISK ASSESSMENT FOR PESTICIDE RESIDUES IN FOOD

Introduction

The 1997 Joint Meeting[1] recommended that MRLs recommended for new or periodic review chemicals whose ADIs might be exceeded should be distinguished from MRLs for other pesticides by designation as MRLMs (Maximum Residue Limits for Monitoring). The 1997 Meeting also recommended that the information needed for the JMPR to refine its estimates of dietary intakes should be clearly stated in the JMPR reports and evaluations. In view of these recommendations, the present Meeting agreed that full details of the risk assessments carried out by the JMPR should be included in the report of the Meeting.

The Meeting estimated STMRs for the new compound kresoxim-methyl and for all those undergoing periodic review that were on the agenda of the FAO Panel. However for compounds re-evaluated outside the Periodic Review Programme STMRs were not available for those commodities which were not considered at the Meeting. In these cases MRLs were used instead of STMRs. The Meeting agreed that dietary intakes estimated from a combination of MRLs and STMRs were neither full Theoretical Maximum Daily Intakes (TMDIs) nor full International Estimated Daily Intakes (IEDIs). The equations for the calculation of TMDIs and IEDIs are given in Chapter 3 of the revised guidelines for predicting dietary intakes[2].

The Meeting wished to draw attention to the fact that only the recommendations of the JMPR have been used in the intake calculations. For example, Codex MRLs whose withdrawal has been recommended by the JMPR have not been included in the dietary intake estimates carried out by the Meeting.

The dietary intakes have been calculated in accordance with the revised guidelines by multiplying the residue concentrations (STMRs or recommended MRLs) by the average daily per capita consumption estimated for each food commodity on the basis of the GEMS/Food Middle Eastern, Far Eastern, African, Latin American, and European diets and then summing the intakes from the individual commodities:

Dietary Intake = Σ Food Chemical Concentration x Consumption[3]

The ratio of the estimated dietary intake to the corresponding Acceptable Daily Intake (ADI) for a 60-kg person is then expressed as a percentage.

Even when STMRs and other correction factors are available, the estimate still overestimates the true dietary intake since at the international level dietary intake estimates assume that 100% of the crop is treated and that all treatments have been according to

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[1] 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 Toxicology. Lyons, France. 22 September – 1 October 1997

[2] WHO 1997a. *Guidelines for predicting dietary intake of pesticide residues*, 2nd revised edition, GEMS/Food Document WHO/FSF/FOS/97.7, World Health Organization, Geneva (1997)

[3] WHO 1997b. *Food consumption and exposure assessment of chemicals.* Report of a FAO/WHO Consultation. Geneva, Switzerland, 10-14 February 1997. World Health Organization,

maximum GAP (i.e. maximum number of treatments, minimum pre-harvest intervals). At the national level further refinements of the dietary intake calculations are therefore possible. National Estimates of Dietary Intake (NEDIs) take into account several correction factors which are only available at the national level. NEDI calculations should be based on more detailed information on food consumption, monitoring and surveillance data, total diet data or reliable data on the percentage of crop treated/percentage of crop imported. These factors are considered further in the revised guidelines.

A summary of the dietary intake estimates is given below. Dietary intakes are expressed as percentages of the relevant ADIs established by the JMPR and rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100%. The detailed dietary intake calculations are given in Annex III.

Estimated dietary intakes for the 1998 JMPR evaluations.

Code	Name	ADI (mg/kg bw)	Dietary intake, % of ADI[1]	Notes
122	Amitraz	0.01	2 - 20	TMDI
079	Amitrole	0.002	0	IEDI
069	Benomyl	0.1		IEDI[2]
172	Bentazone	0.1	0-1	TMDI
144	Bitertanol	0.01	8-30	IEDI
072	Carbendazim	0.03	1-6	IEDI[2]
020	2,4-D	0.01	0	IEDI
073	Demeton-S-methyl	0.0003[3]	1 - 8	IEDI[4]
083	Dicloran	0.01	0-20	STMRs & MRLs
027	Dimethoate	0.002[5]	10 - 140	IEDI[6]
087	Dinocap	0.001	0 - 10	IEDI
030	Diphenylamine	0.08	0 - 4	TMDI
074	Disulfoton	0.0003	160-920	STMRs & MRLs
032	Endosulfan	0.006	20 - 120	TMDI
035	Ethoxyquin	0.005	0 - 50	TMDI
041	Folpet	0.1	-	No estimate[7]
042	Formothion	No ADI	-	
175	Glufosinate-ammonium	0.02	3-10	STMRs & MRLs
176	Hexythiazox	0,03	0-5	STMRs & MRLs
199	Kresoxim-methyl	0.4	0	IEDI
102	Maleic hydrazide	0.3	1 - 8	IEDI
132	Methiocarb	0.02	1 - 30	TMDI
181	Myclobutanil	0.03	0 - 4	STMRs & MRLs
055	Omethoate	No ADI[8]	10 -140	IEDI[6]
166	Oxydemeton-methyl	0.0003[3]	10 - 90	IEDI[4]
103	Phosmet	0.01	0 -40	IEDI
136	Procymidone	0.1	1 - 10	STMRs & MRLs
064	Quintozene	0.01	0 -1	IEDI
077	Thiophanate-methyl	0.08	1-6	IEDI[2]
044	Hexachlorobenzene	0.00016[9]	0-1	IEDI[10]

[1]Range of rounded values from calculations based on the five GEMS/Food regional diets

[2] Intakes of residues of benomyl, carbendazim and thiophanate-methyl are considered together under carbendazim and compared to the ADI for carbendazim

[3]For demeton-S-methyl and related compounds, alone or in combination

[4] Intakes of residues of demeton-S-methyl and oxydemeton-methyl are considered together

[5]For sum of dimethoate and omethoate expressed as dimethoate

[6]Intakes of residues of dimethoate and omethoate are considered together

[7]All MRLs proposed for withdrawal

[8]The 1996 JMPR withdrew the ADI for omethoate of 0.003 mg/kg bw. However, the 1998 JMPR considered it an appropriate reference for dietary intake purposes

[9Tolerable] Daily Intake based on 1997 WHO evaluation: *Hexachlorobenzene - Environmental Health Criteria 195*, WHO, Geneva (1997)

[10]Residues of hexachlorobenzene arising from the use of quintozene

4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE FOR HUMANS, MAXIMUM RESIDUE LEVELS, AND STMR LEVELS

4.1 AMITRAZ (122)

TOXICOLOGY

Amitraz was evaluated by the Joint Meeting in 1980, 1984, and 1990. A temporary ADI of 0-0.0005 mg/kg bw was allocated in 1980, and an ADI of 0-0.003 mg/kg bw was established in 1984. The 1990 Meeting reviewed the compound at the request of a WHO Member State, which asked for a re-consideration of the ADI in view of the acute nature of the reported toxicological effects and the potential dietary exposure. The ADI of 0-0.003 mg/kg bw was maintained. Since that Meeting, studies have become available on absorption, distribution, excretion, biotransformation, effects on liver enzymes and the oestrus cycle, long-term toxicity, dermal and ocular irritation, and dermal sensitization. The compound was reviewed by the present Meeting within the CCPR periodic review programme.

WHO (1996) has classified amitraz as slightly hazardous.

Amitraz was well absorbed, extensively metabolized, and rapidly excreted, mainly in the urine, after oral administration to mice, rats, dogs, pigs, hens, cows, baboons, and humans. After oral treatment of mice with [^{14}C]amitraz, 86% of the radiolabelled dose was excreted, 62% in the urine, within the first 24 h. All of it had been excreted by 96 h, with 73% in the urine of animals of each sex. The concentrations of residues were highest in liver, adrenal glands, and eyes. After oral administration of [^{14}C]amitraz to rats 94% of the dose was recovered within three days with 82% in urine and 12% in faeces. After oral administration of [^{14}C]amitraz to two humans, 77-87% was recovered within three days. Amitraz is hydrolysed to two components, *N*-methyl-*N'*-(2,4-xylyl)formamidine and form-2',4'-xylidide. The former is the pharmacologically active compound and accounted for 5-30% of the total urinary excretion in mice and rats; it was further metabolized to 4-amino-*m*-toluic acid and the acetyl and formyl conjugates, 4-acetamido- and 4-formamido-*m*-toluic acids. These five metabolites were also found in plants.

Amitraz has low acute oral toxicity in rats but is more toxic in dogs. The LD$_{50}$ values ranged from 100 mg/kg bw in dogs to >1600 mg/kg bw in mice, indicating that dogs are the most sensitive species. The toxic signs after oral administration to mice and rats were hyperexcitability, ataxia, tremor, and ptosis. Amitraz had no sensitizing potential in guinea-pigs, and no local irritation was found in rabbits after a single application to skin or eyes. There was evidence of delayed contact hypersensitivity after application of amitraz either topically or intradermally.

In a 13-week study in which mice were fed diets providing 0, 100, 200, 400, 600, or 800 ppm, the NOAEL was 100 ppm, equal to 17 mg/kg bw per day, on the basis of reduced overall body-weight gain (by 34%).

In a 90-day study, rats were given amitraz at doses of 0, 3, or 12 mg/kg bw per day by gavage. The NOAEL was 3 mg/kg bw per day, on the basis of reduced terminal body-weight gain, absolute liver weight, and relative liver weight.

In a 90-day study in dogs, amitraz was administered at doses of 0, 0.25, 1, or 4 mg/kg per day in gelatin capsules. The NOAEL was 0.25 mg/kg bw per day, on the basis of central nervous system depression and reductions in rectal temperature and pulse rate.

In a two-year study, dogs were given amitraz at doses of 0, 0.1, 0.25, or 1 mg/kg bw per day in gelatin capsules. The NOAEL was 0.25 mg/kg bw per day, on the basis of central nervous system depression.

In two 90-day studies, the amitraz metabolite N-methyl-N'-(2,4-xylyl)formamidine was administered to rats at doses of 0, 0.25, 1, 3, or 12 mg/kg bw per day by gastric intubation or to dogs at 0, 0.1, 0.25, or 1 mg/kg bw per day by gelatine capsules. The NOAEL was 1 mg/kg bw per day in rats, on the basis of reduced body-weight gain and increased organ weights, and 0.1 mg/kg bw per day in dogs, on the basis of central nervous system depression and lowered body temperature.

In a 21-day study in rats and a 90-day study in dogs, the amitraz metabolite 4-amino-m-toluic acid was given at doses of 0, 40, 100, or 250 mg/kg bw per day by gastric intubation to rats or 0, 16, 40, or 100 mg/kg bw per day by gelatin capsules to dogs. The NOAEL was 250 mg/kg bw per day in rats and 100 mg/kg bw per day in dogs, (the highest doses).

In an 80-week study, mice were fed diets containing 0, 25, 100, or 400 ppm, equivalent to 0, 3.8, 15, and 60 mg/kg bw per day (wrongly given as 25, 100, or 400 mg/kg bw per day in the 1980 JMPR report). The NOAEL for carcinogenicity was 100 ppm, equivalent to 15 mg/kg bw per day, on the basis of an increased incidence of lymphoreticular tumours in females at 400 ppm.

In a two-year study in which mice were fed diets providing 0, 25, 100, or 400 ppm, the NOAEL for carcinogenicity was 100 ppm, equal to 11 mg/kg bw per day, on the basis of the occurrence of hepatocellular carcinoma in females at 400 ppm. This dose was considered to be greater than the conventional maximum tolerated dose. The NOAEL for toxicity was 25 ppm, equal to 2.3 mg/kg bw per day, on the basis of generalized toxic effects.

In a two-year study, rats were fed diets containing 0, 15, 50, or 200 ppm. The NOAEL for toxicity was 50 ppm, equal to 2.5 mg/kg bw per day, on the basis of effects on the central nervous system and reduced overall body-weight gain in males. There was no evidence of carcinogenicity.

The genotoxic potential of amitraz has been adequately evaluated in a range of assays *in vitro* and *in vivo*. The Meeting concluded that amitraz is not genotoxic.

In view of the lack of genotoxicity and the finding of tumours only in mice and only at concentrations at which severe toxicity was observed, the Meeting concluded that amitraz is not likely to pose a carcinogenic risk to humans.

In a three-generation study of reproductive toxicity in rats at dietary concentrations of 0, 15, 50, or 200 ppm, the NOAEL was 50 ppm, equal to 4.4 mg/kg bw per day, for maternal toxicity and 15 ppm, equal to 1.3 mg/kg bw per day for developmental toxicity. No teratogenic effect was observed.

In two studies of developmental toxicity, pregnant rats were given amitraz at 0, 1, 3, or 12 mg/kg bw per day by gavage on days 8-20 of gestation or 0, 7.5, 15 or 30 mg/kg bw per day by gavage on days 6-15. The NOAEL for maternal toxicity was 7.5-12 mg/kg bw per day, and that for developmental toxicity was 3-7.5 mg/kg bw per day.

In two studies of developmental toxicity in rabbits, amitraz was given at doses of 0, 1, 5, or 25 mg/kg bw per day by gavage on days 6-18 of gestation or 0, 3, 6, or 12 mg/kg bw per day by gavage on days 7-19. The NOAEL for maternal toxicity was 25 mg/kg bw per day in one study, but a NOAEL was not identified in the other because all of the treated animals died. The NOAEL for developmental toxicity was 3-6 mg/kg bw per day.

The effect of amitraz on the estrus cycle and hormone levels was evaluated in mice fed diets containing 0, 25, 100, or 400 ppm for 28 weeks and in rats fed diets containing 0 or 200 ppm for 18 weeks. In mice, pro-estrus was prolonged at 400 ppm, and blood levels of progesterone were reduced and of dehydroepiandrosterone increased at 100 and 400 ppm. The NOAEL was 25 ppm, equivalent to 3.8 mg/kg bw per day, on the basis of the changed hormone levels. The estrus cycles were longer in treated than in control rats, with no NOAEL.

In a double-blind, randomized, cross-over study of tolerance, six healthy adult male volunteers received sequential single oral doses of 0, 0.063, and 0.13 mg/kg bw amitraz, two to three weeks apart. The NOAEL was 0.13 mg/kg bw, the highest dose tested.

Two human volunteers who received single oral doses of 0.25 mg/kg bw [^{14}C]amitraz showed effects including drowsiness, disorientation, slurred speech, and decreased pulse rate and blood pressure.

In a double-blind cross-over study of tolerance, six adult volunteers received two single doses of placebo or 2 mg (about 0.03 mg/kg bw) of the amitraz metabolite *N*-methyl-*N*=(2,4-xylyl)formamidine one week apart. The NOAEL was 0.03 mg/kg bw, the highest dose tested.

The Meeting established an ADI of 0-0.01 mg/kg bw on the basis of the NOAEL of 1.3 mg/kg bw per day in the study of reproductive toxicity in rats and a safety factor of 100. The pharmacological effects on the central nervous system seen in dogs, with a NOAEL of 0.25 mg/kg bw per day, were considered not to be relevant for setting the ADI because they were reversible and the dogs became tolerant. Moreover, a NOAEL of 0.13 mg/kg bw per day was seen for such effects in humans.

The Meeting established an acute RfD of 0.01 mg/kg bw, on the basis of the NOAEL of 0.13 mg/kg bw per day in the study in humans and a safety factor of 10.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 25 ppm, equal to 2.3 mg/kg bw per day (toxicity in a two-
                      year study of carcinogenicity)

Rat: 3 mg/kg bw per day (toxicity in a 90-day study of
                      toxicity)
                      50 ppm, equal to 2.5 mg/kg bw per day (toxicity in a two-year study of
                      toxicity and carcinogenicity)
                      50 ppm, equal to 4.4 mg/kg bw per day (maternal toxicity in a three-
                      generation study of reproductive toxicity)
                      15 ppm, equal to 1.3 mg/kg bw per day (developmental toxicity in a three-
                      generation study of reproductive toxicity)
                      12 mg/kg bw per day (maternal toxicity in a study of developmental
                      toxicity)
                      3 mg/kg bw per day (developmental toxicity)

Rabbit: 25 mg/kg bw per day (maternal toxicity in a study of
                      developmental toxicity)
                      5 mg/kg bw per day (developmental toxicity)

Dog: 0.25 mg/kg bw per day (toxicity in a two-year study of
                      toxicity)

Human: 0.13 mg/kg bw (toxicity after single oral doses)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Estimate of acute reference dose

0.01 mg/kg bw

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

1.   Studies to further characterize the effects on the reproductive system of female rodents

2.   Further observations in humans

List of end-points relevant for setting guidance values for dietary and non-dietary exposure

  Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid/complete
Distribution:	Liver, adrenals, eyes
Rate and extent of excretion:	Rapid/complete, 80-100% in 96 h
Metabolism in animals	Metabolites same in rodents, dogs, humans
Toxicologically significant compounds (animals, plants and environment)	N-methyl-N^1-(2,4-xylyl)formamidine

Acute toxicity

LD_{50} oral	600 mg/kg bw, rat
LD_{50} dermal	>200 mg/kg bw, rabbit
LC_{50} inhalation	65 mg/l, rat
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization	Not sensitizing (Buehler test)

Short-term toxicity

Target/critical effect	CNS depression, dog
Lowest relevant oral NOAEL	0.25 mg/kg bw per day
Lowest relevant dermal NOAEL	50 mg/kg bw per day, rabbit
Lowest relevant inhalation NOAEL	0.01 mg/l air, rats

Genotoxicity

| | Unlikely to be genotoxic |

Long-term toxicity and carcinogenicity

Target/critical effect:	Lymphoreticular tumours, hepatocellular carcinomas
Lowest relevant NOAEL	11 mg/kg bw per day (80-week and 2-year mouse)
Carcinogenicity	Unlikely to be carcinogenic

Reproductive toxicity

Reproduction target / critical effect	Decrease in number of young alive at 21 days
Lowest relevant reproductive NOAEL	1.3 mg/kg bw per day (developmental toxicity)
Developmental target / critical effect	Reduced fetal weight
Lowest relevant developmental NOAEL	3 mg/kg bw per day (developmental toxicity)

Neurotoxicity / Delayed neurotoxicity

Acute CNS depression

Other toxicological studies
Oestrus cycles and hormone levels

Prolongation of estrus cycles and reduction of blood level of progesterone

Medical data
Clinical studies

CNS depression in two human volunteers after a single oral dose of 0.25 mg/kg bw

Summary	Value	Study	Safety factor
ADI	0-0.01 mg/kg bw	Reproductive toxicity, rat	100
Acute reference dose	0.01 mg/kg bw (single oral dose in six human volunteers)		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 2 to 20% of the ADI. The Meeting concluded that the intake of residues of amitraz resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.2 AMITROLE [079]

RESIDUE AND ANALYTICAL ASPECTS

Amitrole was first considered by the JMPR in 1974. It was re-evaluated in 1993 within the CCPR Periodic Review Programme, and a temporary ADI was allocated. A full ADI was allocated in 1997. No MRLs have been established, but it is stated that uses of amitrole should be restricted to those where residues in food would not be expected to occur. The 1993 Meeting recommended a further note that "A realistic limit of determination for the general monitoring of amitrole would be 0.05 mg/kg". This evaluation is within the CCPR Periodic Review Programme. New data on metabolism in rats and environmental fate, in addition to residue trials on apples, pears, peaches and grapes were reported by the manufacturer. The governments of The Netherlands and Poland provided information on analytical methods and national MRLs.

In addition to studies submitted previously to the JMPR, two recent studies (1995 and 1996) on metabolism in mice and rats were submitted. When [5-^{14}C]amitrole was administered orally to rats, absorption from the gastrointestinal tract was rapid and the peak plasma level was reached after 40 to 60 minutes in both dose groups (1 and 500 mg/kg bw). When the animals were killed 48 hours after administration, radioactivity was detected mainly in the liver and to a small extent in the kidney cortex and nasal mucosa. Biotransformation to volatile metabolites including carbon dioxide was negligible. More than 97% of the recovered radioactivity was excreted within 48 or 72 hours after oral administration. The major route of elimination (91 to 98%) was renal. The half-life of elimination was shorter after intravenous than after oral

administration. Amitrole accounted for more than 86% of the identified radioactivity and for about 66% or more of the administered dose. Small amounts of 7 metabolites were detected. The proposed pathway of biotransformation, mainly in the liver, is *via* substitution at C-5 by *N*-acetylcysteine to form 3-amino-1,2,4-triazolyl-*5*-mercapturic acid, which is hydrolysed to 3-amino-5-mercapto-1,2,4-triazole and excreted either directly or after methylation to 3-amino-5-methylthio-1,2,4-triazole.

Amitrole is a fast-acting herbicide which is taken up predominantly through the leaves. The only significant difference between the metabolism of amitrole in rats and in plants is the production of triazolylalanine (3-(1,2,4-triazol-l-yl)-2-aminopropionic acid) in plants. In a study on apples, triazolylalanine was the major metabolite (22-24%), occurring in the free form and as conjugates. This compound is also produced by the metabolism of other triazole pesticides and was therefore reviewed by the 1989 JMPR, which concluded that residues of triazolylalanine do not present a toxicological hazard. The ^{14}C balance at harvest after 5 months showed 1.11% in the tree, 0.07% in the harvested fruit, 0.16% in the roots and 42% remaining in the soil.

No metabolism studies were reported on farm animals.

In addition to studies which have been evaluated previously by the JMPR, new studies on the environmental fate in soil, water and sediment were reported. In soils, amitrole is rapidly degraded to NH_3 and CO_2, in addition to cyanamide and urea. In laboratory studies, the half-life of amitrole ranged from 2 to 26 days at ambient temperature in different soils. Adsorption-desorption studies showed significant adsorption and desorption, with K_{OC} values varying with the soil type from 20 to 120. It therefore appears that amitrole would readily be leached, but in leaching studies of soil with fresh or aged residues, as well in the lysimeter studies, leaching was not observed. This can be attributed to adsorption to the soil which, although reversible, gives time for breakdown to occur and prevents the compound from being leached to groundwater. This was confirmed by a field study in which amitrole was rarely detected below 15 cm. Therefore under practical conditions there is little risk that amitrole would reach the groundwater level.

The aerobic degradation of amitrole was investigated in 2 water-sediment systems, freshly sampled from fields in The Netherlands. mineralization amounted to 19 and 10% after 91 days and the half-lives were 95 and 76 days. Triazole and urea, both <3%, were the only identified products and at least 4 other polar compounds were observed at levels of about 4-5%. Unextractable residues increased with time, but it was shown by reverse isotope dilution analysis that approximately 50% of the unextractable fraction was still unchanged amitrole. In another study under anaerobic conditions at 22°C amitrole was also the major component present, accounting for about 71-87% of the applied radioactivity, after 52 weeks.

In a method of analysis for the determination of amitrole residues in various plants and plant products cold extraction with ethanol/water is followed by partition with dichloromethane and acetylation of the amitrole. The derivative is cleaned up by gel permeation and silica gel chromatography. The limit of determination is 0.01 mg/kg and recoveries ranged from 76 to 98%. The same method can be applied to soil, with a limit of determination of 0.01 mg/kg and recoveries of 82-91%. A method for blackberries using HPLC with fluorescence detection after conversion to a complex with fluorescamine was reported by the government of The Netherlands. The LOD is 0.02 mg/kg and recoveries range from 103 to 127%.

In an HPLC method with EC detection for the determination of amitrole residues in water, the sample is applied directly to a cation exchange column which is eluted with ammonia solution, and the eluate is further cleaned up on an aluminium oxide column. The limit of determination is 0.1 µg/l with recoveries in the range 86-102%. HPLC with electrochemical detection can also be used for samples of animal origin, after extraction with water/acetone, partition with dichloromethane and clean-up on ion-exchange and aluminium oxide columns. Mean recoveries at fortification levels of 0.01 to 0.1 mg/kg varied from 74% for milk to 87% for muscle.

A method in which extraction with acetone/water is followed by partitioning with dichloromethane was validated for grapes over the range 0.005-0.5 mg/kg. After acidification, a portion of the aqueous extract is cleaned up by solid-phase extraction, the eluate is evaporated to dryness, the residue is re-suspended in pyridine and the amitrole is derivatized with bis(trimethylsilyl)trifluor-oacetamide/trimethylchlorosilane (BSTFA/TMCS) before determination by GC-MS. The overall mean recovery was 83%.

The stability of residues in stored analytical samples was determined in grapes and apples at -20°C, after spiking with amitrole at levels from 0.05 to 1 mg/kg. The residues after 16 to 24 months were 60 to 75% of the initial levels.

On the basis of the animal and plant metabolism studies, the definition of the residue for both enforcement and the estimation of dietary intake should be amitrole.

Residues resulting from supervised trials

In eighteen trials on <u>apples</u> at the GAP rate (no specified PHI) in France, fourteen trials above the GAP rate (60 days PHI) in Germany, and two trials in Portugal where there is no GAP, the residues in the fruit from day 4 to day 171 were below the LOD (0.01 or 0.02 mg/kg). In one trial with <u>pears</u> in Portugal (no GAP) and three in Germany at a higher rate than recommended GAP, the residues after 60 to 120 days were similar. In four trials with <u>peaches</u> in Spain at twice the GAP rate (no PHI), the residues in the fruit without stones were <0.01 mg/kg at PHIs from 42 to 105 days.

As the reported GAP covers stone and pome fruits and the residues were determined over a wide range of PHIs, the Meeting estimated a maximum residue level at a practical limit of determination of 0.05 mg/kg and an STMR of 0 for amitrole in pome fruits and stone fruits. The residues of amitrole in fruit below the LOD are consistent with the results of the metabolism studies on apples.

In twenty four trials on grapes in France according to GAP (no PHI) the residues were <<u>0.02</u> (20), 0.03 (3) and 0.087 mg/kg. The high value of 0.087 mg/kg was reported to be due to contamination from an adjacent trial and was ignored. Sixteen trials in Germany at a higher rate than the recommended GAP (60 days PHI) yielded residues in fruit after 15-189 days below the LOD (0.02 mg/kg).

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.02 mg/kg for amitrole in grapes.

DIETARY RISK ASSESSMENT

STMRs were estimated for amitrole in pome fruits, stone fruits and grapes. As no other MRLs or STMRs have been previously established for amitrole these were the only ones used in the estimates of dietary intake. The International Estimated Daily Intakes for the five GEMS/Food regional diets were 0% of the ADI. The Meeting concluded that the intake of residues of amitrole resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.3 BENOMYL [069] / CARBENDAZIM [072]/THIOPHANATE-METHYL [077]

RESIDUE AND ANALYTICAL ASPECTS

Benomyl, carbendazim and thiophanate-methyl are benzimidazole fungicides with extensive use on fruit, vegetables and cereals in many countries. Carbendazim and benomyl were first evaluated in 1973 and most recently in 1994 (residues) and 1995 (toxicology). They were proposed for re-evaluation within the Periodic Review Programme in 1998 by the 1995 CCPR. The 1996 CCPR postponed discussion on individual MRLs not recommended for deletion, awaiting the evaluation by the 1998 JMPR. It noted that the residue definition would be reconsidered on the basis of information provided by the UK and that a risk assessment would be required in relation to any new definition (ALINORM 97/24, para 51). Information on use patterns, national MRLs and analytical methods was provided by the main manufacturers and the governments of The Netherlands, Poland and Australia. This section discusses data on metabolism, environmental fate and analytical methods for benomyl and carbendazim, and residue trials on all three compounds. The metabolism, environmental fate and methods of determination thiophanate-methyl are dealt with in the separate item on that compound (4.25).

The metabolism of benomyl and carbendazim was studied in rats, mice, ruminants, hens and plants. In rats, benomyl and carbendazim are rapidly absorbed after oral administration; the bioavailability is up to 85% and is dependent to a great extent on the route of administration (less after incorporation in the diet than after administration by gavage). Excretion is rapid and takes place almost entirely in the urine. After the oral administration of 3 mg/kg bw of labelled carbendazim, the maximum blood level of 1.0 μg/ml was reached after 15 to 40 minutes, and up to 63% of the administered radioactivity was found in the urine after 6 hours. Excretion in the faeces accounted for a maximum of 1%. At higher doses (300 mg/kg bw) peak blood levels were less than proportionately higher and were reached later (after 0.4 to 4 hours). Repeated doses showed no indications of a cumulative effect. Minor amounts of the labelled substance or its metabolites were found for a short time in the excretory organs, liver and kidney, but with no accumulation.

The metabolic conversion of carbendazim in rats and mice occurs mainly by hydroxylation and hydrolysis. The main metabolite in rats is methyl 5-hydroxybenzimidazol-2-ylcarbamate (5-HBC), and other hydroxylated metabolites are also found to a minor extent. They are usually excreted as sulfates or glucuronides. Metabolites may also be present in the faeces after higher doses.

Benomyl and carbendazim are metabolized in a similar manner in both ruminants (cows and goats) and laying hens. Reported data indicate that the initial metabolism of benomyl occurs by loss of the butylcarbamoyl group to form carbendazim. It is hyphothesized that carbendazim is oxidized to an epoxide, which can undergo a number of transformations to the identified compounds. These include hydrolysis to a dihydrodiol, reduction to methyl 4-hydroxybenzimidazol-2-ylcarbamate (4-HBC) and 5-HBC, and sulfide conjugation. Sulfide conjugation is proposed as the source of the unextractable residues in the livers of goats, cows, and poultry, which can only be released by reductive cleavage using Raney nickel as a catalyst. In two cow and two goat metabolism studies, with either [2-^{14}C]benomyl or [2-^{14}C]carbendazim, the majority of the dosed ^{14}C was excreted in the urine (57-85%) and faeces (14-18%), with only a small fraction in the tissues (0.09 to 0.45% in the kidneys and 2.6 to 4.1% in the liver) or milk (0.37 to 2.2%). In the carbendazim-dosed cows 4,5-DDBC (methyl 4,5-dihydro-4,5-dihydroxybenzimidazol-2-ylcarbamate), ADDB (2-amino-4,5-dihydro-4,5-dihydroxy-benzimidazole), DHBC-G (the monoglucuronide of 5,6-dihydroxy-cabenazim), 4-HBC and 5-HBC occurred in urine, while 4-HBC (3%), 5-HBC (41%), 4,5-DDBC, and DHBC-G were the major residues in the kidneys. In the liver, 4,5-DHHBC-G (*S*-[4,5-dihydro-5-hydroxy-2-(methoxycarbonylamino)-1*H*-benzimidazol-4-yl]glutathione) and other sulfur-linked dihydrohydroxy-carbendazim conjugates (15.2%) predominated, with smaller amounts of 4,5-DDBC and ADDB (0.8%), and 5-HBC (2.7%). 4,5-DDBC (<0.06 mg/kg, <25%) was found in the milk in addition to 4-HBC (0.05 mg/kg, 21%) and 5-HBC (0.11 mg/kg, 42%). The metabolites seen in benomyl-treated cows were similar, indicating the loss of the butylcarbamoyl group before further metabolism occurs.

Benomyl is metabolized in plants mainly to carbendazim. Benomyl itself accounted for 48, 60, 77, 53 and 62% of the total benomyl plus carbendazim residue on the leaves of apple, cucumber, banana, orange and grape plants respectively, 21-23 days after treatment. In orange and apple peel the proportions of benomyl were 61 and 34% respectively after 15-16 days, and in rice and peaches 19.8 and 33% respectively. To determine the amount of benomyl remaining in or on plant tissues, the sample was subjected to reflux under caustic conditions to convert any remaining benomyl to the stable derivative BUB (*N*-(1*H*-benzimidazol-2-yl)-*N'*-butylurea); carbendazim under these conditions is converted to 2-aminobenzimidazole (2-AB).

In soya beans treated with benomyl, 2-AB was found to be a major metabolite in addition to carbendazim. After the plants were treated twice at the early pod stage, the major residues in the mature beans after 35 days were 2-AB (0.42 mg/kg), benomyl (0.05 mg/kg) and carbendazim (0.14 mg/kg). Unextractable residues accounted for 13% of the total radioactivity. In all the other plants tested, 2-AB was always below 10%.

Crop rotation studies with lettuce, radishes, beet, cabbage, barley, beans, maize, carrots, tomatoes, alfalfa and ryegrass showed little or no uptake of benomyl or its major soil degradation product carbendazim into succeeding crops. The residues in plants grown in soil treated with carbendazim or benomyl at 1 to 3.4 kg ai/ha and aged for 30 to 224 days were <0.1 mg/kg.

Studies of <u>environmental fate</u> with carbendazim and benomyl were conducted in soil, water and air. Benomyl is rapidly converted to carbendazim in the environment, with half-lives of 2 and 19 hours in water and soil respectively. Carbendazim decomposes in the environment with half-lives of 6 to 12 months on bare soil, 3 to 6 months on turf, and 2 and 25 months in water under aerobic and anaerobic conditions respectively. In degradation studies with [*phenyl*-^{14}C]benomyl, [2-^{14}C]benomyl or [2-^{14}C]carbendazim, incubated with soil or sediment under

aerobic or anaerobic conditions, carbendazim was the major compound (34 to 57% of the applied radioactivity), followed by STB (3-butyl-1,3,5-perhydrotriazino[1,2-*a*]benzimidazole-2-4-dione) or BUB (up to 7.6%) and 2-AB (up to 1.5%). No formation of CO_2 (<0.1%) from benomyl was observed in sterilized aerobic soil or under strictly anaerobic conditions, but, 9.2% of the applied ^{14}C was evolved as CO_2 after 1 year of incubation under non-sterile aerobic conditions.

Adsorption/desorption experiments showed carbendazim desorption coefficients higher than adsorption coefficients (9 to 51 and 1.6 to 6.6 respectively), and a K_{oc} between 200 and 246. Column and container leaching studies showed that the leachate contained <2% of the applied radioactivity. In leaching experiments with benomyl in water-saturated silty clay loam soils, 94% of the applied radioactivity was found in the top soil segment (0-0.5 cm). Benomyl was well adsorbed to soils (K_a 6.1-90) but desorption occurred slowly (K_d 2.4-2.5), and the compound did not move significantly from the site of application (0.1-0.7% of the TRR was detected in the run-off water).

The hydrolytic, photochemical and biological degradation of carbendazim in aquatic systems at pH 5 to 9, under aerobic or anaerobic conditions and temperatures of 20-70°C, showed that 2-AB was the main degradation product, accounting for <3 to 30% of the total radioactivity. The half-life ranged from <0.125 days (aerobic, 20°C) to 457 days (pH 5, 22°C). There is little or no photolysis of benomyl. In an aerobic degradation study of [*phenyl*-^{14}C]benomyl in pond water and sediment the carbendazim formed had a half-life of 61 days under non-sterile conditions. After 30 days, 22% of the applied radioactivity was bound to the sediments and <1% was evolved as carbon dioxide.

The volatilization of carbendazim from bare soil and bean leaves was tested under outdoor conditions. After 6 hours from 76 to 117% of the applied compound remained in the soil and 83-100% on the leaves.

In the residue analysis for benomyl and carbendazim in plants, soil and water, the samples are homogenized with ethyl acetate or acetone under acidic condition to convert any benomyl present to carbendazim. The extracts are cleaned up by liquid-liquid partition and/or solid-phase extraction and carbendazim is determined by HPLC with UV, fluorescence or mass spectrometric detection, or by GLC with an ECD. In one study on pineapples, recoveries were 67-120% for benomyl (as carbendazim), 68-114% for carbendazim and 73-124% for 2-AB. The limit of determination ranged from 0.01 to 0.1 mg/kg. An ELISA immunoassay was developed for benomyl, as carbendazim, in water, with a linear range from 0.1 to 5 μg/l, a recovery of 100% and limit of determination of 0.65 μg/l.

Carbendazim and the metabolites 5-HBC and 4-HBC can be determined in animal products after hydrolysis and liquid-liquid extraction by HPLC with UV detection, with limits of determination of 0.01- 0.02 mg/kg in milk, 0.05-0.1 mg/kg in tissues and faeces, 0.1 mg/kg in urine and 0.05 mg/kg in eggs. Recoveries ranged from 50 to 100%.

Carbendazim residues in analytical samples were shown to be stable at -20°C for 18 months in apples and processed fractions, 26 months in peaches and processed fractions, 30 months in tomatoes and green beans, 24 months in wheat grain, wheat straw and soya beans and 9 months in soil, with the remaining residue ranging from 79 to 107% of the initial residue. 2-AB was shown to be stable for 24 months in tomatoes and for 9 months in soya beans.

Definition of the residue

The current residue definition to be used for enforcement for benomyl, carbendazim and thiophanate-methyl is carbendazim. The Meeting noted however that an appreciable proportion of the residue in crops arising from the use of benomyl was likely to be benomyl for compliance with MRLs (which would be determined as carbendazim), and concluded that the definition of residues of benomyl should be "the sum of benomyl and carbendazim expressed as carbendazim". Since the ADI of benomyl is five times that of carbendazim, the same definition would avoid under-estimating the dietary risk from benomyl and would therefore be appropriate for the estimation of STMRS.

The definition of residues arising from the use of carbendazim should continue to be "carbendazim" (both for compliance with MRLs and for the estimation of dietary intake), with the addition of a note that maximum residue levels and STMRs cover carbendazim residues arising as a result of the use of benomyl or thiophanate-methyl (occurring as a metabolite and/or hydrolysis product during analysis) or from the direct use of carbendazim.

Residues resulting from supervised trials

All the residues are expressed as carbendazim. Trials with benomyl, carbendazim and thiophanate-methyl are evaluated together for each crop. STMRs for benomyl, carbendazim or thiophanate-methyl have been estimated when there were enough trials according to GAP with each compound.

Citrus fruit, Oranges. Two trials with benomyl in the USA according to GAP yielded residues in the fruit, as carbendazim, of 0.29 and 0.43 mg/kg at a PHI of 2 days. Eleven other trials were at higher rates and/or longer PHIs. Four trials in Brazil at the GAP rate gave residues of 0.13, 0.14, 0.36 and 0.63 mg/kg at a 1-day PHI. Two other trials were at twice the GAP rate. The residues from treatments according to GAP were, in rank order, 0.13, 0.14, 0.29, 0.36, 0.43 and 0.63 mg/kg.

Two post-harvest trials were conducted with carbendazim in France, where no GAP was reported. One pre-harvest trial in South Africa at the GAP rate gave residues of 0.07 and 1.6 mg/kg in the pulp and fruit respectively, at 15 days. Another trial was at twice the GAP rate.

Two trials with thiophanate-methyl in Japan were according to GAP, giving residues in the pulp of 0.11 and 0.16 mg/kg at a 1-day PHI. The residues in the fruit, calculated from the peel/pulp ratio, were 0.16 and 0.23 mg/kg.

On the basis of the benomyl data the Meeting estimated a maximum residue level of 1 mg/kg, as carbendazim, in oranges. As there were not enough data on residues in the pulp from trials according to GAP, the Meeting estimated an STMR from the residues in the fruit of 0.325 mg/kg for benomyl, as carbendazim.

Other citrus fruit. Two trials were conducted with benomyl on grapefruit in the USA, according to GAP for citrus, giving residues in the fruit at a PHI of 2 days of 0.08 and 0.09 mg/kg. Four other trials on grapefruit and one trial on limes were at higher or lower rates or PHIs.

Two trials with thiophanate-methyl on Chinese citron were at a higher rate than the recommended GAP.

There were insufficient data from trials according to GAP to estimate a maximum residue level for grapefruit, Chinese citron or limes.

Pome fruit, Apples. Eleven trials with benomyl in France according to GAP gave residues in the fruit, as carbendazim, at PHIs of about 7 days of <0.05 (2), 0.11, 0.15, 0.19 (2), 0.28, 0.49, 0.60, 0.81 and 1.75 mg/kg. Three other trials were carried out in France at shorter PHIs and three in Germany at a higher rate than the recommended GAP. Nine trials in the UK (where there is no GAP) did not comply with any GAP in the northern part of Europe. Of 39 trials carried out in the USA 23 were according to GAP, giving residues at 14 days PHI of <0.01, 0.16, 0.18, 0.20, 0.27, 0.28, 0.36, 0.37, 0.38, 0.51, 0.54, 0.60, 0.65, 0.72, 0.78 (2), 0.98, 1.0 (2), 1.2, 1.4 and 1.6 (2) mg/kg.

Eight trials with carbendazim in Germany according to UK GAP gave residues at 7 days PHI of 0.30, 0.35, 0.36, 0.42, 0.49, 0.70, 0.84 and 0.90 mg/kg.

Two trials with thiophanate-methyl in France according to GAP gave residues as carbendazim at a 1-day PHI of 0.57 and 0.31 mg/kg. Sixteen post-harvest trials could not be evaluated as there was no GAP. Two trials in Japan at the GAP rate gave residues at a 1-day PHI of 0.25 and 1.0 mg/kg. Sixteen other trials in the UK and one in Denmark were at higher rates or longer or shorter PHIs than the recommended GAP.

Pears. Three trials with benomyl in the UK did not match any reported GAP. In eight trials in the USA according to GAP the residues at a PHI of 14 days were 0.52, 0.65, 0.72 (2), 0.85, 1.1, 1.3 and 2.4 mg/kg. Another trial was at a higher rate.

Two trials with thiophanate-methyl in Japan at the GAP rate gave residues at a 1-day PHI of 0.54 and 0.94 mg/kg. Four trials in the UK were at longer or shorter PHIs than the recommended GAP.

As the residue populations and the recommended uses on apples and pears are similar, the Meeting agreed to combine the residues in the two commodities and estimate a maximum residue level for pome fruits. The combined results are listed below.

Benomyl (as carbendazim): <0.01, <0.05 (2), 0.11, 0.15, 0.16, 0.18, 0.19 (2), 0.20, 0.27, 0.28 (2), 0.36, 0.37, 0.38, 0.46, 0.51, 0.52, 0.54, 0.60 (2), 0.65 (2), 0.72 (3), 0.78 (2), 0.81, 0.85, 0.98, 1.0 (2), 1.1, 1.2, 1.3, 1.4, 1.6 (2) 1.8 and 2.4 mg/kg.

Carbendazim: 0.30, 0.35, 0.36, 0.42, 0.49, 0.70, 0.84 and 0.90 mg/kg.

Thiophanate-methyl (as carbendazim): 0.31, 0.54, 0.57 and 0.94 mg/kg.

On the basis of the benomyl data the Meeting estimated a maximum residue level of 3 mg/kg as carbendazim in pome fruit, and STMRs for benomyl, carbendazim and thiophanate-methyl of 0.60, 0.455 and 0.555 mg/kg respectively.

<u>Apricots and nectarines</u>. One trial was conducted with benomyl on apricots in Switzerland, but no GAP was reported. Two trials in the USA on apricots and four on nectarines were at lower rates than the recommended GAP.

Eight trials were conducted with thiophanate-methyl on apricots in Italy, but the spray concentration was not reported.

As there were no data which could be related to approved GAP the Meeting could not estimate maximum residue levels and recommended the withdrawal of the existing draft MRLs for apricot and nectarine.

<u>Cherries</u>. Two trials with benomyl in Italy according to French GAP gave residues, as carbendazim, at a PHI of 7 days of 0.24 and 0.65 mg/kg. Forty one trials in the USA were at lower or higher rates than the recommended GAP.

Six residue trials with carbendazim in Germany did not match any reported GAP.

The treatment in one trial with thiophanate-methyl in France was below the recommended rate. One trial in the UK according to French GAP and another in France according to Belgian GAP gave residues, as carbendazim, of 0.17 mg/kg at day 0 and 0.22 mg/kg at 13 days respectively.

The Meeting concluded that there were insufficient data from trials according to GAP to estimate a maximum residue level for cherries, and recommended the withdrawal of the draft MRL.

<u>Peaches</u>. Four trials with benomyl in France according to GAP gave residues in fruit, as carbendazim, of 0.07, 0.09, 0.12 and 0.15 mg/kg at a PHI of 7 days. Trials in Portugal and Spain according to Portuguese GAP gave residues at a PHI of 7 days of 0.08, 0.09 and 0.56 mg/kg. Seven trials in the USA according to GAP gave residues at a PHI of 3 days of 0.21, 0.30, 0.51, 0.61, 0.72, 1.0 (2) mg/kg. Three other trials in the USA were at twice the GAP rate. The trials according to GAP gave residues, in rank order, of 0.07, 0.08, 0.09 (2), 0.12, 0.15, <u>0.21</u>, <u>0.30</u>, 0.51, 0.56, 0.61, 0.72 and 1.0 (2) mg/kg.

In 12 trials with carbendazim in Europe, where recommended PHIs are 14-15 days, the samples were harvested after 40 days or more.

In three trials with thiophanate-methyl in France at the GAP rate (no PHI specified) samples were harvested after 12 or 19 days. Two other trials were at a lower rate. Thirteen trials in Italy did not match GAP in Italy or a neighbouring country. In two trials in Japan at the GAP rate the residues in the pulp, as carbendazim, at a PHI of 1 day were 0.41 and 0.22 mg/kg.

On the basis of the benomyl data, the Meeting confirmed the draft MRL of 2 mg/kg for peach and estimated an STMR of 0.255 mg/kg for benomyl, as carbendazim.

<u>Plums</u>. In seven trials in France and Italy with benomyl according to French GAP, the residues in the fruit at a PHI of 7 days were <0.05(2), 0.05, 0.06, 0.08, 0.10 and 0.34 mg/kg. Two trials in Spain according to Portuguese GAP gave residues of 0.07 and 0.05 mg/kg after 7 days. In four trials in the USA according to GAP the residues at a PHI of 3 days were 0.02, 0.06, 0.21 and

0.24 mg/kg in the fruit. Another eight trials in the USA were at lower or higher rates. In rank order, the trials according to GAP gave residue of <0.05(2), 0.02, 0.05 (2), 0.06 (2), 0.07, 0.08, 0.10, 0.21, 0.24 and 0.34 mg/kg.

In three trials with thiophanate-methyl in France according to GAP (no PHI specified) none of the samples were taken at day 0. Four other trials were at a lower rate. In five trials in Italy the application concentration was not reported.

The Meeting confirmed the draft MRL of 0.5 mg/kg for plums and estimated an STMR of 0.06 mg/kg for benomyl as carbendazim.

Berries and small fruits, Grapes. In four trials with benomyl in France and Italy according to French GAP and two in Greece, one in Portugal and two in Spain according to the national GAP, the residues as carbendazim were 0.30, 0.36, 0.45, 0.46, 0.84, 0.86 and 1.0 (3) mg/kg at a PHI of 14 days. Two trials in Germany (no GAP) were at higher rates than reported European GAP.

Ten trials carried out with carbendazim on grapes in France and two in Spain did not match any reported GAP. Nine trials in Germany and two in Italy were at higher rates than the recommended GAP.

Of twenty trials with thiophanate-methyl in Italy, five which complied with Portuguese or Spanish GAP gave residues as carbendazim after 22 or 28 days of 0.21, 0.36, 0.56, 0.87 and 1.9 mg/kg. Two trials in Portugal according to GAP gave residues of 1.1 and 1.3 mg/kg at the GAP PHI of 28 days. Two trials in Japan were at the GAP rate, but at a longer PHI. The trials according to GAP gave residues of 0.21, 0.36, 0.56, 0.87, 1.1, 1.3 and 1.9 mg/kg.

On the basis of the trials with benomyl and thiophanate-methyl the Meeting estimated a maximum residue level of 3 mg/kg as carbendazim, and STMRs for benomyl and thiophanate-methyl, as carbendazim, of 0.84 and 0.87 mg/kg respectively.

Strawberries. One trial with benomyl in Canada and eighteen in the USA were at lower or higher rates or PHIs than the recommended GAP.

Two trials with carbendazim in the UK and one in Finland according to GAP in The Netherlands gave residues at a PHI of 15 days of 0.30, 1.2 and 2.0 mg/kg. Six other trials in Germany and one in Italy could not be evaluated because no GAP was reported.

One trial with thiophanate-methyl in Denmark was at a higher rate than the recommended GAP and two trials in The Netherlands and 7 in the UK did not comply with any reported GAP.

The Meeting concluded that there were insufficient data from trials according to GAP to recommend an MRL or estimate an STMR for strawberries.

Other berries. Three trials with benomyl on blackberries and blueberries in the USA according to GAP gave residues at PHIs of 3 days (blackberries) or 21 days (blueberries) of 0.42, 1.6 and 1.7 mg/kg. Ten other trials were at lower or higher rates.

Twenty one trials in the UK with thiophanate-methyl did not match any reported GAP.

The Meeting concluded that there were insufficient data from trials according to GAP and recommended the withdrawal of the draft MRL for berries and other small fruits.

Avocados. In two trials with benomyl in the USA according to GAP, the residues were 0.22 and <0.06 mg/kg at 30 days PHI. Eight other trials were carried out at higher rates.

There were too few trials according to GAP. The Meeting recommended the withdrawal of the CXL for avocado.

Bananas. Fourteen trials were conducted with benomyl in Central America (no PHI) and Brazil (3 days PHI) according to GAP, with residues of <0.03 (7), 0.05, 0.06 (3) and 0.11 mg/kg in whole fruit and <0.03 (10), <0.06 (2), 0.10 and 0.44 mg/kg in the pulp.

The Meeting estimated a maximum residue level of 0.2 mg/kg to replace the existing CXL of 1 mg/kg. On the basis of the residues in pulp the Meeting estimated an STMR of 0.03 mg/kg for benomyl, as carbendazim.

Kiwifruit. Two trials in Japan with thiophanate-methyl according to GAP gave residues of 0.20 and 0.61 mg/kg in the pulp.

There were too few trials to estimate a maximum residue level.

Mangoes. Nineteen trials with benomyl in the USA were at lower or higher rates than the recommended GAP. The Meeting recommended the withdrawal of the CXL for mango.

Persimmons. One trial was conducted with thiophanate-methyl in Italy, but no GAP was reported. The Meeting could not estimate a maximum residue level.

Pineapples. Eight trials with benomyl in Costa Rica complied with Mexican GAP, giving residues at a 0-day PHI of 1.9, 2.0, 2.1, 2.3, 2.5, 2.7, 2.9 and 3.3 mg/kg in the whole fruit and <0.03 mg/kg in all trials in the pulp.

The Meeting estimated a maximum residue level of 5 mg/kg for pineapple and an STMR of 0.03 mg/kg for benomyl, as carbendazim, in pineapples.

Onions. Two trials with thiophanate-methyl in Japan at the GAP rate gave residues of <0.02 and 0.04 mg/kg at a PHI of 1 day. One trial in The Netherlands and 7 trials in the UK with a seed dressing and/or foliar treatment could not be evaluated as there was no information on GAP.

The Meeting concluded that there were insufficient data from trials according to GAP and recommended the withdrawal of the CXL for bulb onion.

Brussels sprouts. Six trials with benomyl in the UK which complied with GAP (21 days PHI) gave residues, as carbendazim, of 0.04, <0.05, 0.05, 0.08, 0.16 and 0.27 mg/kg, and two in the USA according to GAP gave residues of 2.4 and 2.9 mg/kg (7 days PHI).

Two trials with thiophanate-methyl in The Netherlands could not be evaluated as there was no reported GAP.

The Meeting concluded that the benomyl residues were from two different populations and on the basis of the UK data confirmed the CXL of 0.5 mg/kg for Brussels sprouts. It estimated an STMR of 0.065 mg/kg for benomyl as carbendazim.

Fruiting vegetables, Cucumbers and gherkins. Two trials with benomyl in Canada and six in the USA were at a lower or higher rate than the recommended GAP. Two trials in Germany with a soil drench and three indoor trials in the UK could not be evaluated in the absence of information on GAP. One trial in the USA in 1967 according to GAP gave a residue, as carbendazim, of <0.06 mg/kg. In two trials in Portugal, two in Greece and four in Spain, according to the recommended rate in Spain, where the PHI is 14 days, the residues after 7 days were <0.03 (7) and 0.05 mg/kg.

In four trials with carbendazim in Belgium and The Netherlands above the GAP rate only the peel and washed commodities were analysed. In ten trials on gherkins in Germany according to GAP in Belgium or The Netherlands the residues were <0.05 mg/kg at 3 days.

In one trial with thiophanate-methyl in Denmark and 3 trials in The Netherlands the treatments were below or above recommended rate in The Netherlands. Five trials in the UK were below the GAP rate or with drench treatments for which no GAP was reported.

On the basis of the carbendazim trials with support from the benomyl trials at 7 days PHI, the Meeting estimated maximum residue levels at the limit of determination of 0.05* mg/kg for cucumbers and gherkins to replace the previous recommendations of 0.5 mg/kg for cucumber and 2 mg/kg for gherkins. The Meeting estimated STMRs of 0.03 and 0.05 mg/kg for benomyl and carbendazim respectively in both cucumbers and gherkins.

Melons. Two trials with benomyl in Canada were at a higher rate and a shorter PHI than the recommended GAP. In two trials in France according to GAP for cucurbits, the residues at a PHI of 7 days were <0.05 and 0.19 mg/kg.

One trial with thiophanate-methyl in Italy according to Spanish GAP gave a residue of 0.11 mg/kg at a PHI of 21 days.

The Meeting concluded that there were insufficient data from trials according to GAP and recommended the withdrawal of the CXL for melons, except watermelon.

Tomatoes. Two trials with benomyl in Greece were at a higher rate than the recommended GAP, and five in the UK did not match any reported GAP. In six trials in Portugal and Spain according to Portuguese GAP the residues at 3 days PHI were <0.03, 0.03(2), 0.06, 0.08 and 0.12 mg/kg. In three trials in the USA according to GAP the residues at 1 day were 0.15, 0.56 and 0.98 mg/kg. Sixteen other trials in the USA were at lower or higher rates. The European and US trials represent two different populations and the results cannot be combined.

A total of ten trials were carried out with carbendazim in Finland, France, Italy and Spain, but no relevant GAP was reported. Seven of 10 trials in The Netherlands were according to GAP and yielded residues at a PHI of 3 days of <0.1 mg/kg in the pulp and of 0.08, 0.11, 0.12, 0.16, 0.17, 0.18 and 0.22 mg/kg in the whole fruit. The other trials at higher rates gave similar results.

Two trials with thiophanate-methyl in Italy and eight trials with drench or foliar treatments in the UK could not be evaluated because no relevant GAP was reported. Two trials in Japan according to GAP gave residues at 1 day of 0.59 and 0.73 mg/kg. Two other trials at a higher spray concentration gave residues of 0.69 and 0.31 mg/kg.

On the basis of the carbendazim data, the Meeting estimated a maximum residue level of 0.5 mg/kg for tomato to replace the draft MRL of 0.1 mg/kg, and an STMR of 0.16 mg/kg for carbendazim. The Meeting estimated an STMR of 0.045 mg/kg for benomyl, as carbendazim, on the basis of the European trials with benomyl.

Other fruiting vegetables. In the USA, four trials were conducted with benomyl on watermelons (no GAP reported) and four trials on summer squash at a higher rate than the recommended GAP.

One trial with thiophanate-methyl on egg plants and two on peppers in Italy, and ten trials on mushrooms in The Netherlands, could not be evaluated because information was incomplete or no GAP was reported.

As there were no data from trials according to GAP, the Meeting could not estimate a maximum residue level for watermelon and recommended the withdrawal of the draft MRLs for carbendazim in mushrooms and peppers, and the CXLs for egg plant and summer squash. No trials on winter squash were reported so the Meeting recommended the withdrawal of the CXL.

Lettuce. Seven trials were conducted with thiophanate-methyl in the UK in the field and in glasshouses, but no relevant GAP was reported. The Meeting recommended the withdrawal of the draft MRL for carbendazim in head lettuce.

Common beans. One trial was conducted with benomyl in France, but no GAP was reported. In four trials on green beans in the USA according to GAP, residues in the whole commodity were <0.06 (2), 0.03 and 0.14 mg/kg at a PHI of 28 days.

In three trials with carbendazim on dwarf beans in the UK according to GAP, residues at 22 days were all <0.1 mg/kg. Another three trials were at higher or lower rates or PHIs.

In one trial on dwarf beans and one on runner beans with thiophanate-methyl in the UK according to GAP and seven other trials on dwarf, broad and French beans at higher rates or PHIs, only the beans were analysed.

The Meeting concluded that there were insufficient data from trials according to GAP and recommended the withdrawal of the CXLs for common bean and broad bean.

Dry beans. Seven trials with benomyl in Canada and the UK and 32 trials in the USA did not comply with GAP.

Seven trials with carbendazim on field beans in the UK were at the GAP rate or higher, but there was not enough information to decide whether the trials were according to GAP.

Two trials with thiophanate-methyl in Japan on kidney beans according to the GAP rate for adzuki beans gave residues of 0.09 and 0.39 mg/kg in the beans. Four other trials on adzuki

and kidney beans were at higher rates. In six trials with field beans in the UK at the GAP rate, the residues in the beans were 0.06, 0.09, 0.13, <0.2 (2) and 0.21 mg/kg after 6 to 19 days. The eight trials according to GAP gave residues in the beans of 0.06, 0.09 (2), <u>0.13</u>, <u><0.2</u> (2), 0.21 and 0.39 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg in dry beans, on the basis of the thiophanate-methyl data, to replace the CXL of 2 mg/kg, and an STMR of 0.165 mg/kg for thiophanate-methyl.

Peas. Two trials were conducted with benomyl in the UK at the recommended rate but with a shorter PHI.

Two trials with thiophanate-methyl in Japan were at a longer PHI, and nine in France were at a lower rate than recommended GAP. In four trials in the UK at GAP rates the residues in shelled peas, as carbendazim, were <0.01 (2) and 0.01 (2) mg/kg at 21 days PHI. Two other trials at shorter PHIs and two at longer PHIs gave similar results.

On the basis of the thiophanate-methyl trials according to GAP supported by two other trials at a shorter PHI, the Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR of 0.01 mg/kg for thiophanate-methyl, as carbendazim, in garden pea, shelled.

Soya beans. In four trials with benomyl in the USA according to GAP, residues in the beans at a PHI of 35 days were <0.03 (2), 0.03 and 0.04 mg/kg. Four other trials were at higher rates or longer PHIs.

The Meeting concluded that there were insufficient data from trials according to GAP and recommended the withdrawal of the existing CXLs for soya bean (dry) and soya bean fodder.

Carrots. Twenty one trials with benomyl on carrots in the USA according to GAP yielded residues of <0.01, 0.01, 0.02 (3), <0.03 (3), <u>0.04</u> (3), 0.05 (4), 0.06, 0.10, 0.11, 0.12, 0.13 and 0.14 mg/kg at a PHI of 4 days. Eight other trials carried out at higher rates or a longer PHI gave similar results.

The Meeting estimated a maximum residue level of 0.2 mg/kg for carrot and an STMR of 0.05 mg/kg for benomyl, as carbendazim, in carrots.

Sugar beet. No GAP was reported to evaluate one trial in France and twelve in the USA with benomyl or six trials in France and nine in Germany with carbendazim. In one trial in Germany according to Belgian GAP, the residue at a PHI of 28 days was <0.05 mg/kg. Residues were similar in five other trials at higher or lower rates, and in all but one trial at a 0-day PHI.

Two trials with thiophanate-methyl in Japan according to GAP gave residues of <0.04 mg/kg at a PHI of 7 days.

The Meeting concluded that there were insufficient data from trials according to GAP to estimate a maximum residue level for sugar beet or sugar beet leaves or tops, and recommended the withdrawal of the existing CXL and draft MRL.

Celery. Two trials were conducted with thiophanate-methyl in The Netherlands, but no GAP was reported.

As no data from trials according to approved GAP were submitted, the Meeting recommended the withdrawal of the CXL.

Cereals, Barley grain. In three trials with carbendazim in Germany according to GAP, residues in the grain at a PHI of 56 days were <0.02, 0.03 and 0.05 mg/kg. In five other trials at higher rates and/or shorter PHIs the residues were in the same range. Fourteen other trials in Germany, France, Italy and Spain were at lower rates or longer PHIs than the recommended GAP. In the UK, two trials according to GAP (the PHI is "up to and including grain watery ripe") yielded residues at 42-45 days PHI of <0.05 and 0.29 mg/kg. In rank order, the residues in the grain were <0.02, 0.03, <0.05, 0.05 and 0.29 mg/kg.

In fourteen trials with thiophanate-methyl in the UK (1973-1974) at up to 3 times the GAP rate (no PHI specified), the residues in the grain were <0.1 (13) and <0.2 mg/kg after 72 to 121 days. Fourteen trials with a seed dressing treatment (no GAP reported) gave similar results.

On the basis of the carbendazim trials complying with GAP (5 results), supported by the trials at a higher rate and/or shorter PHI (5 results), the Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.05 mg/kg for carbendazim in barley grain.

Barley straw. In six trials with carbendazim in Germany and two in the UK according to GAP, the residues in rank order were <0.05, 0.20 (2), 0.49, 0.77 and 0.98 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg (the existing CXL) and an STMR of 0.345 mg/kg for carbendazim in barley straw and fodder, dry.

Maize. In three trials with carbendazim in France in 1988 at the GAP rate and three at a lower rate the residues in the kernels after 10-31 days were <0.05 mg/kg.

The Meeting concluded that the data from trials according to GAP were insufficient to estimate a maximum residue level for maize.

Rice, grain. In seventeen trials with benomyl in the USA according to GAP, residues at 21 days, as carbendazim, were <0.03 (7), 0.04, 0.05, <0.07, <0.08, 0.16, 0.20, 0.26, 0.36, 0.70 and 1.6 mg/kg in the grain.

Three trials with thiophanate-methyl in Japan were at a higher rate than the recommended GAP.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.05 mg/kg for benomyl as carbendazim in rice, husked

Straw. In fifteen trials with benomyl in the USA according to GAP the residues, as carbendazim, were 0.25, 0.41, 0.65 (2), 0.98, 1.3, 1.4, 2.5 (2), 4.3 (2), 5.9 (2), 8.5 and 11 mg/kg in straw at a 21-day PHI.

The Meeting confirmed the CXL of 15 mg/kg for rice straw and fodder, dry, and estimated an STMR of 2.5 mg/kg for benomyl as carbendazim.

Wheat, grain. In two trials with benomyl in The Netherlands according to GAP the residues, as carbendazim, were <0.04 mg/kg at a PHI of 34/35 days. Two other trials at twice the rate and PHI gave similar results. In four trials in the USA according to GAP the residues at a PHI of 21 days were <0.03 mg/kg. Three other trials were at shorter PHIs than the recommended GAP. The residues in rank order from the trials according to GAP were <u><0.03</u> (4) and <u><0.04</u> (2) mg/kg.

In 30 trials with carbendazim in Germany the rates were higher than the recommended GAP and/or samples were not taken at the recommended PHI. In the UK, one trial according to GAP showed residues at a PHI of 42 days of <0.05 mg/kg. Seven trials in France, three in Italy, one in Spain and one in the UK were at higher or lower rates than allowed by GAP.

In two trials with thiophanate-methyl in Japan at the GAP rate the residues in husked grain after 14 or 30 days were <0.02 or 0.03 mg/kg. Seven trials in the UK which complied with GAP gave residues in the grain after 46 to 83 days of <0.01 (3), <u>0.01</u> and <0.03 (3) mg/kg. Another 15 trials at higher rates gave similar results. Four trials in The Netherlands with treatments up to four times the German GAP rate showed similar residues in the grain.

On the basis of the trials with thiophanate-methyl supported by those with benomyl, the Meeting estimated a maximum residue level in wheat grain 0.05* mg/kg as a practical limit of determination, and estimated STMRs of 0.03 and 0.01 mg/kg for benomyl and thiophanate-methyl, as carbendazim respectively.

Straw. In two trials with benomyl in The Netherlands and three in the USA according to GAP, residues, as carbendazim, were 0.05, <u><0.1</u> (2), 0.18 and 0.72 mg/kg.

In six trials with carbendazim in Germany and one in the UK according to GAP the residues were <u><0.03</u> (4), <0.05, 0.2 and 0.66 mg/kg, at PHIs of 42 or 56 days.

On the basis of the benomyl and carbendazim data, the Meeting estimated a maximum residue level of 1 mg/kg to replace the CXL of 5 mg/kg and STMRs of 0.1 mg/kg for benomyl as carbendazim and 0.03 mg/kg for carbendazim in wheat straw and fodder, dry.

Rye. Six trials with carbendazim in Germany at the GAP rate or higher gave residues in the grain below the LOD (0.01 or 0.05 mg/kg) at a longer PHI than the recommended GAP (56 days). In two trials the residues in stalks at 56 days were 0.33 and <0.05 mg/kg.

In the UK there is no GAP for the use of thiophanate-methyl on rye, so the estimated maximum residue level for wheat cannot be extended to rye.

As there were no data from trials according to GAP were submitted, the Meeting could not estimate a maximum residue level for rye, and recommended the withdrawal of the existing draft MRL.

Tree nuts. Fourteen trials with benomyl in the USA in almonds or macadamia nuts were at the GAP rate or higher, but the samples were taken much later than the recommended PHI. Six trials were conducted on pecans, but no GAP was reported.

As there were no data from trials according to GAP, the Meeting could not estimate a maximum residue level in tree nuts and recommended the withdrawal of the existing CXL.

Rape seed. Residues in ten trials with carbendazim in Germany according to GAP were <0.02 mg/kg in the pods and seeds at about 56 days PHI. In three other trials at higher rates and in five trials in France at or below the GAP rate and longer PHIs than recommended, residues in the seeds and pods were again below the LOD (0.05 or 0.02 mg/kg).

Four trials were carried out with thiophanate-methyl in France, but no GAP was reported.

On the basis of the carbendazim trials, the Meeting estimated a maximum residue level of 0.05* mg/kg to replace the existing CXL of 0.1 mg/kg. As trials with applications above the recommended rate also yielded residues below the LOD, the Meeting estimated an STMR of 0 for carbendazim in rape seed.

Hops. Four trials with carbendazim on hops in Germany were with 2 applications of 0.225 or 0.38 kg ai/ha. The residues at PHIs of 17 or 26 days were 16, 18, 29 and 49 mg/kg. As no GAP was reported, the Meeting recommended the withdrawal of the existing CXL.

Peanuts. Ten trials with benomyl in the USA with applications above the recommended GAP rate gave residues in the kernels of <0.06 mg/kg 11 to 86 days after the last application.

As no data from trials according to GAP were submitted, the Meeting recommended the withdrawal of the CXLs for carbendazim in peanut and peanut fodder.

Coffee. In one trial with carbendazim in Brazil with a higher application rate than the recommended GAP and in six trials in Kenya (no GAP) the residues in the beans after 44-81 days were <0.1 mg/kg.

As no data from trials according to GAP were reported, the Meeting recommended the withdrawal of the CXL for carbendazim in coffee beans.

Tea. In six trials with thiophanate-methyl in Japan at a lower rate than the recommended GAP, the residues were 1.1-1.8 mg/kg after 7-21 days.

As there were no data from trials according to GAP, the Meeting could not recommend an MRL.

Processing studies

In two processing studies with benomyl on oranges in Brazil and one in the USA which simulated commercial practices, the processing factors (PF) for juice were 0.016, 0.36 and 0.83, with an average of 0.40. In the US study the PF was 1.36 in orange oil and ranged from 0.012 in finisher pulp to 0.88 in dried peel.

On the basis of an STMR for benomyl in oranges of 0.325 mg/kg and the calculated processing factors, the Meeting estimated STMRs of 0.13 and 0.442 mg/kg for benomyl, as carbendazim, in orange juice and orange oil respectively.

Two processing studies were carried out in the USA with benomyl on apples, one simulating household and commercial preparation and the other industrial processing. Washing and packing normally decreased the residues on apples, with PFs ranging from 0.26 to 1.2 (mean 0.55 ± 0.28) and from 0.36 to 1.0 (0.68 ± 0.29) respectively. Residues in peeled and unpeeled apples decreased after cooking, with PFs of 0.80 and 0.24 respectively. Residues in peeled and cored apple slices were decreased by factors of 0.23-0.38 (0.24 ± 0.10). Canned apple slices, apple sauce and gradeout fruit had PFs of 0.14, 0.13 and 0.57 respectively, and the average PF for apple purée was 0.47. Residues in juice decreased by factors of 0.26 and 0.23.

On the basis of an STMR for benomyl in pome fruits of 0.60 mg/kg and the calculated processing factors, the Meeting estimated STMRs of 0.147, 0.282 and 0.078 mg/kg for benomyl, as carbendazim, in apple juice, apple purée and apple sauce respectively.

In two separate studies on peaches in the USA, washing and peeling processing factors were 0.18 and 0.37, and 0.02 and 0.12 respectively. The PFs for sliced and puréed peaches were <0.01 and 0.06 respectively. In seven studies on plums in California, the processing factors for prunes ranged from 0.08 to 0.83, with an average of 0.24 ± 0.27 (n = 25).

In four processing studies on grapes in Switzerland and two in the USA, the processing factors for wine averaged 0.53 (n = 4), for raisins 1.3 (n = 2) and for raisin waste 4.1 (n = 2).

On the basis of an STMR for benomyl in grapes of 0.84 mg/kg and the calculated processing factors, the Meeting estimated STMRs of 0.445, 1.09 and 3.44 mg/kg for benomyl, as carbendazim, in wine, raisins and raisin waste respectively.

A single processing study on tomatoes treated with benomyl was conducted in the USA in a pilot-scale plant, with processing factors of 0.29, 0.48, 0.27, 0.66, and 0.62 for wet tomato pomace, dry tomato pomace, juice, purée and ketchup respectively. The Meeting estimated corresponding STMRs of 0.013, 0.022, 0.012, 0.023, 0.030 and 0.028 mg/kg from the STMR of 0.045 mg/kg for benomyl in tomatoes.

In two processing studies in the USA with soya beans, the processing factors were 0.71, 1.9, <0.1, 0.23, 3.3 and 19.2 in meal, hulls, refined oil, crude oil, soap stock and aspirated fractions (assortment of seeds, stems, leaves, straw, hay, hulls, mill, sand and dirt) respectively, but there was no STMR for soya beans.

Two processing studies on rice in the USA in a pilot-scale plant closely simulated commercial practice. Processing factors from whole grain were 0.01, 0.31 and 2.3 in white rice, rice bran and rice hulls.

When benomyl was added to whole milk at a level of 1 mg/kg it appeared to be degraded during the production of commercial sterile evaporated canned milk (PFs of 0.64 and 0.43 for whole and skimmed milk respectively), but pasteurization did not affect residue levels. Residues tended to concentrate in mother liquor (PF=5.2) and cream (PF = 1.5 and 1.7).

As the STMR for benomyl in milk is 0, the STMR for cream is also 0.

Food of animal origin

Livestock feeding studies were conducted with benomyl or carbendazim at concentrations (in benomyl equivalents) ranging from 5 to 450 ppm in poultry and from 2 to 75 ppm in cattle. In two studies with cows at feeding levels above 10 ppm, residues in the milk of 4-HBC and 5-HBC ranged from <0.007 mg/kg after 7 days depuration to 0.09 mg/kg after 28 days of exposure. In four studies on poultry the residues of carbendazim, 4-HBC and 5HBC in the tissues and eggs were at or below the LOD (0.02 to 0.05 mg/kg) from levels of 5 ppm in the diet. A separate study showed that benomyl residues in liver reached a plateau within two weeks.

The STMRs for raisin waste and dry tomato pomace were equivalent to 5.2 and 0.033 mg/kg benomyl respectively, and the STMRs in barley, rice and wheat grain corresponded to 0.076, 0.076 and 0.045 mg/kg benomyl. On the basis of these estimates of the STMRs for animal feed items, the Meeting concluded that the levels used in the feeding studies were adequate to estimate maximum residue levels in animal commodities.

The Meeting recommended the withdrawal of the CXLs for milks, cattle meat, chicken fat, poultry meat and eggs and estimated maximum residue levels of 0.05* mg/kg to replace them. As the lowest feeding levels used in the animal studies were much higher than the estimated dietary burdens, the Meeting estimated STMRs of 0 for cattle and poultry commodities (meat, milks, edible offal, chicken fat and eggs).

Residues in food in commerce or at consumption

Monitoring or surveillance data for carbendazim residues generated in the UK during 1995 and 1996 from samples of fruits, vegetables, cereals and processed products of UK or imported origin were submitted. In 1995, 1135 samples were analysed, of which 62 samples (55%) of apples, apple juice, fruit-based infant food, plums, strawberries, lettuce and blackcurrants had detectable levels of carbendazim (0.1 to 0.9 mg/kg). Of the 1375 samples analysed in 1996, 16 samples or 1.2% (apples, celery, dessert grapes and pears) had levels above the limit of determination, ranging from 0.1 to 1.1 mg/kg.

Monitoring data generated by the food industry in the UK were also reported. Residues of carbendazim were above the limit of determination in 36 samples. It was not clear from the report how many samples were analysed. Bananas had the highest frequency of positive samples (20%). Residues in bananas, apples, grapes, fruit conserve, oranges, pineapples and cabbages ranged from 0.2 to 1.5 mg/kg.

DIETARY RISK ASSESSMENT

The residues of benomyl, carbendazim and thiophanate-methyl are all expressed as carbendazim, which has the lowest ADI of the three compounds. A total of 34 STMRs were estimated for benomyl, 8 for carbendazim and 5 for thiophanate-methyl. If STMRs were estimated for more than one compound in a commodity, the highest STMR was used for the calculation. No MRLs were used.

International Estimated Daily Intakes of benomyl, carbendazim and thiophanate-methyl for the five GEMS/Food regional diets were in the range of 1 to 6% of the carbendazim ADI.

The Meeting concluded that the intake of residues of benomyl, carbendazim and/or thiophanate-methyl resulting from their uses that have been considered by the JMPR is unlikely to present a public health concern.

4.4 BENTAZONE (172)

TOXICOLOGY

Bentazone was first evaluated by the Joint Meeting in 1991, when an ADI of 0-0.1 mg/kg bw was allocated on the basis of a NOAEL of 9 mg/kg bw per day in a long-term study of toxicity in rats and a safety factor of 100. Further observations in humans, a 90-day feeding study in rats with 6-hydroxybentazone, and studies of genotoxicity with 6-hydroxybentazone were identified as valuable in the continued evaluation of the compound.

WHO has classified bentazone as slightly hazardous.

After oral administration to rats, [*phenyl*-U-^{14}C]-bentazone was extensively absorbed and rapidly excreted in the urine. In rats given a single dose, 83-94% appeared in the urine by 24 h, and 90-97% of the dose was recovered in urine by 120 h after dosing, with less than 0.7% in the residual carcase. Biliary excretion of the compound amounted to less than 2% of the dose. Bentazone undergoes very limited biotransformation in rats. Bentazone was the major compound identified in the urine, representing 81-91% of the dose in males and 77-89% in females. 6-Hydroxybentazone was present in amounts up to 6.3% of the dose, and isomeric 8-hydroxybentazone was present in trace amounts (0-0.23% of the dose). There were no major differences among the groups. Glucuronide or sulfate conjugation was either negligible or non-existent; 6- and 8-hydroxybentazone are also metabolites of bentazone in plants.

Bentazone is more acutely toxic to rats than are its two hydroxylated metabolites when given by the oral route. The acute oral LD$_{50}$ of technical-grade bentazone was estimated to be 1800 mg/kg bw in males and 1500 mg/kg bw in females. The acute oral LD$_{50}$ values for 6- and 8-hydroxybentazone were ∃5000 mg/kg bw.

The two studies described below indicate that 8-hydroxybentazone does not have the anticoagulant and diuretic effects of bentazone at the doses tested and has less systemic toxicity than the parent compound under the test conditions. No data were available on the short-term toxicity of 6-hydroxybentazone.

Rats received technical-grade bentazone in the diet at concentrations of 0, 400, 1200, or 3600 ppm for 13 weeks. The body weights of females were decreased and were statistically significantly different from those of controls at 3600 ppm from week 10 onward. Examination of haematological parameters indicated statistically significant increases in prothrombin time and partial thromboplastin time in males at 3600 ppm in comparison with controls. Bentazone had a diuretic effect in animals of each sex, reaching statistical significance at 3600 ppm. The NOAEL for systemic toxicity was 1200 ppm (equal to 78 mg/kg bw per day) on the basis of statistically significant decreased body weights in females throughout the latter part of the treatment, increased prothrombin time and partial thromboplastin time in males, increased output of urine with decreased specific gravity in animals of each sex, and some degree of kidney hypertrophy in both males and females at 3600 ppm, equal to 240 mg/kg bw per day.

Rats received 8-hydroxybentazone in the diet at concentrations of 0, 400, 1200, or 3600 ppm for three months. No compound-related effects were observed on body weights, clinical signs, food consumption, haematological, clinical chemical, or urinary parameters, clotting time, organ weights, or gross or histopathological appearance. The NOAEL was 3600 ppm (equal to 260 mg/kg bw per day), the highest dose tested.

The following two studies of developmental toxicity indicate that bentazone has effects at doses below a maternally toxic dose, whereas 8-hydroxybentazone had no developmental or maternal toxicity at any of the doses tested.

Pregnant rats received technical-grade bentazone by gavage at 0, 40, 100, or 250 mg/kg bw per day on days 6-15 of gestation. The NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested. The NOAEL for developmental toxicity was 100 mg/kg bw per day on the basis of significantly decreased mean fetal weights and delays in tissue ossification, which reached statistical significance on a litter basis at the highest dose.

No developmental toxicity was observed in pregnant rats that received 8-hydroxybentazone by gavage at 0, 40, 100, or 250 mg/kg bw per day on days 6-15 of gestation. The NOAEL for developmental toxicity was 250 mg/kg bw per day, the highest dose tested.

Bentazone, 6-hydroxybentazone, and 8-hydroxybentazone did not induce reverse mutation in bacteria, and 8-hydroxybentazone did not induce gene mutation in mammalian cells or micronucleus formation in mice *in vivo*. The Meeting concluded that neither bentazone nor its metabolites are genotoxic.

8-Hydroxybentazone was less toxic than the parent compound, and, on the basis of the structural similarities between the 6- and 8-hydroxy isomers, the Meeting concluded that the 6-hydroxy isomer is also less toxic than the parent. Therefore, the Meeting maintained the ADI of 0-0.1 mg/kg bw for bentazone.

Because this was a limited review, data were not evaluated that would permit the establishment of an acute reference dose.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Bentazone

Mouse: 100 ppm, equal to 12 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)

Rat: 200 ppm, equal to 9 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)
1200 ppm, equal to 78 mg/kg bw per day (13-week study of toxicity)
250 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

100 mg/kg bw per day (developmental toxicity)

Dog: 400 ppm, equal to 13 mg/kg bw per day (one-year study of   toxicity)

*8-Hydroxybentazon*e

Rat: 3600 ppm, equal to 260 mg/kg bw per day (three-month study   of toxicity)

250 mg/kg bw per day (maternal and developmental toxicity in study of developmental toxicity)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw

Estimate of acute reference dose

Not considered

List of end-points relevant for comparing toxicities of bentazone, 6-hydroxybentazone and 8-hydroxybentazone

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	83-94% rapidly absorbed (bentazone)
Dermal absorption:	No data
Distribution:	Extensive
Potential for accumulation:	Little or none for bentazoneazone. No data on
Rate and extent of excretion:	Rapid excretion: 83-94% of the dose excreted in urine in 24 h (bentazone)
Metabolism in animals	Very little biotransformation: 81-91% of the dose excreted untransformed. Metabolites are 6-hydroxybentazone (6.3% of the dose) and 8-hydroxybentazone (0-0.23% of the dose)
Toxicologically significant compounds (animals, plants and environment)	Bentazone

Acute toxicity

Rat LD$_{50}$ oral	Bentazone: 1500 mg/kg bw 6-Hydroxybentazone: >5000 mg/kg bw 8-Hydroxybentazone: μ5000 mg/kg bw

Short-term toxicity

Target / critical effect	Bentazone: decreased body weights in females, increased clotting times (PT and PTT), and increased output of urine with decreased specific gravity.6-Hydroxybentazone: no data8-Hydroxybentazone: no effect up to the highest dose tested
Lowest relevant oral NOAEL	Bentazone: 90 days, rat: 78 mg/kg bw per day6-Hydroxybentazone: no data8-Hydroxybentazone: 260 mg/kg bw per day, the highest dose tested
Lowest relevant dermal NOAEL	Bentazone: 1000 mg/kg bw/day (the highest dose).No data for 6-hydroxybentazone or 8-hydroxybentazone
Lowest relevant inhalation NOAEL	No data

Genotoxicity

Bentazone and its metabolites are not genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect:	No data
Lowest relevant NOAEL	No data
Carcinogenicity	Bentazone: no carcinogenicity. 6-Hydroxybentazone: no data8-Hydroxybentazone: no data

Reproductive toxicity

Reproduction target / critical effect	No data
Lowest relevant reproductive NOAEL	No data
Developmental target / critical effect	Bentazone: developmental effects (decreased fetal weights and delayed ossification) below maternally toxic dose.6-Hydroxybentazone: no data8-Hydroxybentazone: no developmental toxicity at highest dose tested
Lowest relevant developmental NOAEL	Bentazone: rat, 100 mg/kg bw per day6-Hydroxybentazone: no data8-Hydroxybentazone: rat, 250 mg/kg bw per day

Neurotoxicity / Delayed neurotoxicity

No data

Other toxicological studies

No data

Medical data

No data

Summary	Value	Study	Safety factor
ADI	0-0.1 mg/kg bw	Long-term toxicity, rats	100
Acute reference dose	Not considered		

RESIDUE AND ANALYTICAL ASPECTS

Bentazone was originally evaluated in 1991 and subsequently in 1994 and 1995. The 29th (1997) Session of the CCPR requested the JMPR to consider revising the residue definition for plant commodities.

In order to respond to the CCPR request the Meeting considered the information provided in the 1991, 1994 and 1995 JMPR evaluations and that submitted by the manufacturer, which included summaries of new studies on plant metabolism and environmental fate, analytical methods and reports of supervised trials.

Metabolism studies in rats showed that bentazone is poorly metabolized. The parent compound was the predominant metabolite, with 6-hydroxy-bentazone identified as a minor metabolite and 8-hydroxy-bentazone found in trace amounts.

Metabolism studies in lactating goats and hens showed that the major residue component in meat, milk and eggs was the parent bentazone with small amounts of 6- or 8-hydroxy-bentazone and their glucuronide and sulfate conjugates.

New metabolism studies on soya beans, rice, maize, green beans and potatoes showed that the main residues in plants were bentazone and one or both of its conjugated metabolites, 6-

and 8-hydroxy-bentazone, depending whether a monocotyledonous or dicotyledonous crop was treated. The nature of residues in succeeding crops was also investigated, but residues in replanted crops were all below the LOD. Details of these studies were not provided since bentazone was not scheduled for a full re-evaluation.

Multi-residue analytical methods do not determine residues of bentazone and its hydroxy metabolites. In a specialized analytical method suitable for the determination of bentazone and conjugated 6- and 8-hydroxy-bentazone, each of the residue components can be determined with an LOD of 0.02 mg/kg. The 1995 JMPR recommended a practical limit of determination of 0.05 mg/kg for regulatory purposes for each component.

Residue definitions for national MRLs include bentazone alone and the sum of bentazone and its metabolites.

In most of the supervised trials, residues of the metabolites were below the LOD. Residues of 8-hydroxy-bentazone above the LOD were found in three samples of maize fodder and one of linseed in trials evaluated in 1991. Residues of 6-hydroxy-bentazone were found at higher concentrations than bentazone in some samples of field peas (dry) (1 of 31), potatoes (2 of 31), wheat (1 of 15), maize (3 of 12), maize fodder (3 of 5), linseed (1 of 5) and alfalfa (3 of 3).

The Meeting noted that existing and proposed MRLs are based in the sum of bentazone and its hydroxy metabolites, agreed that it was necessary to review all the studies on metabolism before taking a decision and recommended that the definition of the residue should be considered at the next periodic review.

DIETARY RISK ASSESSMENT

Although no maximum residue levels were estimated, a risk assessment was carried out because the compound was on the agenda of the FAO Panel. The International Estimated Daily Intakes for the five GEMS/Food regional diets were in the range of 0 to 1% of the ADI. The Meeting concluded that the intake of residues of bentazone resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4. 5 BITERTANOL (144)

TOXICOLOGY

Bitertanol was previously evaluated toxicologically by the Joint Meeting in 1983, 1987, and 1988. The 1983 JMPR allocated a temporary ADI of 0-0.005 mg/kg bw and requested studies on metabolism in order to clarify the metabolic pathway of bitertanol, a study of toxicity in dogs treated orally for a minimum of one year, and a long-term study of toxicity and carcinogenicity in rats at appropriate doses. Relevant data were submitted for evaluation by the 1987 JMPR, when an ADI of 0-0.003 mg/kg bw was established on the basis of a NOAEL of 10 ppm in a one-year study in dogs. In 1988, the Meeting concluded that, upon further consideration of the data from two-year and one-year studies of toxicity in dogs, the NOAEL was 25 ppm (equal to 1 mg/kg bw per day). Therefore, an ADI of 0-0.01 mg/kg bw was allocated using a safety factor of 100. The compound was reviewed at the present Meeting within the CCPR Periodic Review Programme.

Bitertanol has been classified by WHO as unlikely to present an acute hazard in normal use.

After oral administration bitertanol is rapidly and extensively absorbed (about 84%) and distributed. Excretion is also rapid (rats, almost complete within 72 h) and occurs mainly in the faeces (about 90%) by the biliary excretion, owing to the lipophilic nature of the parent substance. The liver and kidneys are the main sites of tissue accumulation in both male and female rats. Although some statistically significant sex-related differences were seen, they were of minor physiological importance. The substance has a relatively low rate of dermal penetration. The metabolic profile was similar at the various doses tested. The main metabolic pathways are hydroxylation of the phenyl ring in the *para* position and oxidation of the *tert*-butyl moiety, leading to bitertanol alcohol and the corresponding carboxylic acid; metabolites derived from the two pathways combined were also observed. The metabolites occur in both free and conjugated forms. The parent compound was not detected in urine or bile. There was no toxicological concern with regard to the metabolic profile in plants.

Bitertanol had very low acute toxicity in rats, mice, and dogs when given orally and after dermal application or by inhalation. It was of moderate to low toxicity in rats and mice after intraperitoneal injection. Females appeared to be slightly more sensitive than males, but only in some studies. This was perhaps due to slightly different absorption characteristics in animals of the two sexes, as seen after oral administration. In view of the toxic signs (including respiratory disturbances, sedation, spasms, and tremor) and the findings of the pharmacological screening tests, it may be inferred that bitertanol has central nervous system activity; however, no specific pharmacological effects, such as potentiation of amphetamine action, antagonism of reserpine ptosis, or an effect on hexobarbital anaesthesia were observed.

Bitertanol induces no, or only very slight, dermal irritation. It induces slight to moderate reactions of the ocular mucosa but has no effect on the cornea or iris. No evidence for a sensitizing effect was observed in any study

In medium- and long-term tests for toxicity, the liver is regarded as the main toxicological target organ in dogs and rats at doses of 1.2 and 28 mg/kg bw per day and above, respectively. Liver weight was found to be the most sensitive indicator. Corresponding patterns of disruption of liver function were observed in rats and dogs. Activities of the transaminases, alkaline phosphatase, and glutamate dehydrogenase in the serum were increased. In addition, a rise in cholesterol level was observed in several studies in rats at doses of 61 mg/kg bw per day and above. The ability of bitertanol to induce mixed-function oxidases was verified in both species. It is therefore likely that the effect on weight is essentially due to hypertrophy of the endoplasmic reticulum in hepatocytes at doses of 100 mg/kg bw per day and above. Morphological changes in the liver were seen only at relatively high doses and consisted of hepatocytic swelling, bile-duct proliferation, perilobular fatty degeneration, eosinophilic foci, and fibrous structures. The induced effects corresponded to toxic liver damage with bile-duct involvement.

Evidence for haemotoxicity was found at doses of 28 mg/kg bw per day and above in rats; this may be classified as an effect on the peripheral red blood cell population. The decreases in erythrocyte count, haemoglobin concentration, and packed cell volume and the compensatory rise in the reticulocyte count argue for this interpretation. No evidence was found for damage to the haematogenic organs.

Slight increases in the leukocyte count were also seen in a few studies in rats at doses of 61 mg/kg bw per day and above. The increased leukocyte counts are probably attributable to inflammatory processes, since the increase occurred in studies and at doses at which inflammatory processes were also observed. Hyperkeratosis of the esophageal epithelium and glandular stomach and/or erosions of the glandular stomach as well as parakeratosis of the stomach wall were observed in rats. The histopathological picture included distended epithelial cells, slight inward growth of the papillary body, and cellular infiltration of the epithelial and subepithelial layers in the affected animals. These changes are probably attributable to irritation of the mucous membranes by the active ingredient.

Effects on the skin were observed in dogs, sheep and rats. The effects in dogs at doses of 5 mg/kg bw per day and above consisted of reddening, with localized inflammation, desquamation, and hair loss, and increased reddening and slight inflammatory phenomena in the mucous membranes of the oral cavity and eyes. Histological examination showed broadening of the epithelial layer, enhanced cornification, and minor erosions. The dermal effects were apparently accompanied by pruritus. The keratitis observed in dogs was considered to be secondary to conjunctivitis. Hair loss was also observed in rats and sheep, which occurred after administration of bitertanol by capsule or gavage at doses of 300 mg/kg per day and above; this was considered to be a systemic effect.

Pathological changes were seen in the adrenals of dogs and rats at 1.2 and 81 mg/kg bw per day and above, respectively, consisting of swelling and fatty degeneration of the adrenal cortical cells, particularly in the zona reticularis and zona fasciculata. These alterations were considered to be due to inhibition of sterol biosynthesis by triazole derivatives. It is highly probable that this effect, which also represents the biological, antimycotic action of the substance, leads to an effect on corticoid metabolism with corresponding morphological effects in the cells of the adrenal cortex.

In feeding studies in dogs, lenticular opacity seen at doses of 4.9 mg/kg bw per day and above were considered to be related to treatment. No lenticular alterations attributable to administration of bitertanol were seen in any other study or species. The exact mechanism of the cataractogenesis resulting from long-term administration of triazole fungicides is presently unknown. The ocular lens undertakes its own *de novo* synthesis of cholesterol, which is isolated from lipoproteins circulating in the blood; other substances that inhibit cholesterol synthesis can induce cataracts.

No evidence for any carcinogenic potential of bitertanol was found in long-term studies of toxicity and carcinogenicity in rats and mice treated in the diet. The highest doses tested were 130 mg/kg bw per day in mice and 26 mg/kg bw per day in rats.

In a series of studies, bitertanol had no genotoxic potential in lower organisms or in mammalian cells or systems *in vitro* or *in vivo*.

In a three-generation study of reproductive toxicity in rats, adverse effects on the pups (reductions in survival rates during the four-week lactation period, reduced weight at birth, and retarded growth) were observed at parentally toxic doses of 100 or 500 ppm, equivalent to 5 or 25 mg/kg bw per day. The NOAEL was 1 mg/kg bw per day.

In studies of developmental toxicity, treatment with bitertanol led to several embryotoxic and teratogenic effects, depending on the animal species, route of administration, and dose. In rats, an oral dose of 10 mg/kg bw per day was tolerated with no observed effect. Doses of 25 mg/kg bw per day and above led to retardations and variations (e.g. increased incidence of the 14th rib). Malformations were observed at an oral dose of 100 mg/kg bw per day, which was clearly maternally toxic. Exposure of pregnant rats to concentrations of 27 mg/m^3 air and above by inhalation resulted in retardation effects; no malformations were observed. In rabbits, doses of 50 mg/kg bw per day and above were maternally toxic; fetotoxic effects were seen at doses of 100 mg/kg bw per day and above. Teratogenic effects were observed in Himalayan rabbits at 100 mg/kg bw per day, while in the second strain tested (Chinchilla), even a dose of 250 mg/kg bw per day did not lead to malformations.

The ADI established at the 1988 Meeting of 0-0.01 mg/kg bw, based on a combined NOAEL of 1 mg/kg bw per day from the two-year and the one-year study in dogs, was maintained. The ADI is supported by the NOAEL of 20 ppm (equivalent to 1 mg/kg bw per day) in a three-generation study in rats.

An acute RfD was not allocated because bitertanol has been classified by WHO as unlikely to present an acute hazard in normal use and it has not shown any specific adverse effects (teratogenicity, neurotoxicity) after single doses 100 times the lowest relevant NOAEL in long- and short-term studies that were used to establish the ADI. Therefore, the Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effects

Mouse: 100 ppm, equal to 25 mg/kg bw per day (toxicity in a
      two-year study of toxicity and carcinogenicity)

Rat: 100 ppm, equal to 4.9 mg/kg bw per day (toxicity in a
      two-year study oftoxicity and carcinogenicity)
                20 ppm, equivalent to 1 mg/kg bw per day (reproductiveand
                  parentaltoxicity in a three-generation study)
                10 mg/kg bw per day (maternal and developmental toxicity in a study of
                  developmental toxicity)

Dog: 1 mg/kg bw per day (overall NOAEL in one-year and two-year   studies
of toxicity)

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

Estimate of acceptable daily intake for humans
0 - 0.01 mg/kg bw

Estimate of acute reference dose
Not allocated (unnecessary)

Studies that would provide information useful for the continued evaluation of the compound
Further observations in humans

List of end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion, and metabolism in mammals

Rate and extent of oral absorption	Commenced immediately, about 84% absorbed
Dermal absorption	About 10%
Distribution	Highest concentrations in liver and kidneys
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	About 90% excreted with bile, 10% with urine
Metabolism in animals	No parent compound in bile or faeces; extensively metabolized to 14 metabolites (ring monohydroxylation, ring dihydroxylation, aryl O-methylation, aliphatic hydroxylation, aliphatic oxidation to carboxylic acids, and ether cleavage)
Toxicologically significant compounds (animals, plants and environment)	Parent compound

Acute toxicity

Rat LD_{50}, oral	> 5000 mg/kg bw
Rat LD_{50}, dermal	> 5000 mg/kg bw
Rat LC_{50}, inhalation	> 550 mg/m³ (4 h)
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization	Not a sensitizer (Magnussen & Kligman test)

Short-term toxicity

Target/critical effect	Liver, red blood cells, adrenals, digestive tract
Lowest relevant oral NOAEL	90 days, dog: 1 mg/kg bw per day
Lowest relevant dermal NOAEL	3 weeks, rabbit; 250 mg/kg per day
Lowest relevant inhalation NOAEL	3 weeks, rat: 63 mg/m³

Genotoxicity

No genotoxic or mutagenic potential

Long-term toxicity and carcinogenicity

Target/critical effect	Liver
Lowest relevant NOAEL	1 year and 2 years, dog: 1 mg/kg bw per day
Carcinogenicity	No evidence of carcinogenic potential

Reproductive toxicity

Reproductive target/critical effect	Reproductive effects (reduced litter size, pup growth rate, and pup survival) at parentally toxic doses
Lowest relevant reproductive NOAEL	1 mg/kg bw per day
Developmental target/critical effect	Fetotoxic and teratogenic effects at maternally toxic doses
Lowest relevant developmental NOAEL	Rat: 10 mg/kg bw per day

Neurotoxicity/Delayed neurotoxicity

No relevant effects

Other toxicological studies

Induction of hepatic microsomal activity

Medical data

No health impairments observed in employees subjected to regular medical examinations

Summary	Value	Study	Safety factor
ADI	0-0.01 mg/kg bw	1- and 2-years in dogs	100
Acute reference dose	None allocated (unnecessary)		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 8 to 30% of the ADI. The Meeting concluded that intake of residues of bitertanol resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.6 2,4-D (020)

RESIDUE AND ANALYTICAL ASPECTS

2,4-D, 2,4-dichlorophenoxyacetic acid was evaluated for residues at several Joint Meetings between 1970 and 1987, when MRLs were recommended for a number of commodities, and for its effects on the environment in 1997. The compound was evaluated by the present Meeting in the CCPR Periodic Review Programme.

The Meeting received information on animal and plant metabolism, environmental fate, analytical methods, updated GAP, supervised residue trials on crops, animal feeding studies, and residues after processing.

2,4-D is formulated as salts (diethanolamine, DEA; dimethylamine, DMA; tri-isopropanolamine, TIPA; isopropylamine, IPA) or esters (2-butoxyethyl, BEE; isopropyl, IPE; 2-ethylhexyl, EHE). It is a selective, systemic foliar-applied hormone herbicide, readily absorbed by leaves and roots, which acts as a growth regulator to control broad-leaved weeds.

The absorption, distribution, metabolism and excretion of $[^{14}C]$2,4-D have been studied in mice, rats, a goat, hens and fish.

Studies on rats and mice show that the absorption of 2,4-D after oral administration is rapid and almost complete: peak plasma levels were reached about 4 hours after dosing.

After oral administration of the 2-ethylhexyl ester to rats the test substance could not be detected in blood, indicating that it was rapidly hydrolyzed to 2,4-D acid whose concentration peaked in plasma 2 to 4 hours after administration and then decreased with an apparent half-life of about 9 hours.

When rats were dosed orally with 1 or 100 mg/kg bw of $[^{14}C]$2,4-D the excretion of radioactivity was rapid: over 94% of the administered dose was recovered by 48 hours after dosing and the half-life for urinary excretion was about 5 hours. Urine was the main route of excretion (85-94%), while faeces represented a minor excretory pathway (2-11%). At the high dose of 100 mg/kg bw 2,4-D elimination was saturated during the first hours after dosing. Its rapid clearance from plasma and rapid excretion in the urine show that its potential to accumulate is low.

In rats, $[^{14}C]$2,4-D was eliminated primarily unchanged in the urine (>97%). Two minor metabolites, probably 2,4-D conjugates, were detected.

The 2-ethylhexyl ester was rapidly absorbed and hydrolysed to 2,4-D and 2-ethylhexanol. No 2,4-D 2-ethylhexyl ester was found in the blood, urine or faeces 72 hours after oral administration. The 2,4-D acid produced was rapidly excreted unchanged in the urine, and the 2-ethylhexanol was further metabolized to 2-ethyl-hexanoic acid, 2-ethyl-1,6-hexanedioic acid, 2-ethyl-5-oxohexanoic acid, 2-ethyl-5-hydroxyhexanoic acid, 2-heptanone and 4-heptanone, which were and rapidly excreted in the urine, faeces and expired air.

The distribution pattern of the ^{14}C in the organs, tissues milk and urine of a lactating goat dosed orally with [^{14}C]2,4-D showed that the kidney (which contained 0.45% of the dose) is the main target organ. Lower proportions were found in the liver (0.07 %), milk (0.06%), fat (0.03 %) and muscle (0.01 %), whereas the total ^{14}C in the urine was 99.4 % (97.9% identified as 2,4-D). The metabolites found at lower levels were 2- or 4-chlorophenoxyacetic acid (2- or 4-CPAA) and 2,4-dichlorophenol (2,4-DCP).

In hens dosed orally with [^{14}C]2,4-D, about 90% of the dose was recovered from the excreta. The edible tissues and eggs each contained <0.1% of the total dose.

Bluegill sunfish were exposed to 11 mg/l [^{14}C]2,4-D in their water under static conditions for four consecutive days. The total ^{14}C (as 2,4-D) in the day-4 viscera (inedible) and fillet (edible) represented 1.9 and 0.41 mg/kg respectively. 2,4-D (80% of the ^{14}C, 0.33 mg/kg) and 2,4-DCP (7.9% of the total ^{14}C, 0.03 mg/kg) were present in the edible portion.

Information on the metabolism of 2,4-D in plants was provided for apples, lemons, potatoes and wheat.

After application of the 2-ethylhexyl ester to a potato crop at a rate of 0.35 kg acid equivalent per hectare (ae/ha), the residues in the tubers were 0.24 mg/kg 2,4-D (42% of the total ^{14}C), 0.15 mg/kg 4-CPAA (26% of the total ^{14}C) and 0.09 mg/kg 4-hydroxy-2,5-D (15.5% of the total ^{14}C).

In apples after the spray application of [^{14}C]2,4-D to the turf beneath the canopy of a dwarf apple tree according to label instructions, the residues were too low to be identified (total ^{14}C 0.009 mg/kg as 2,4-D).

In the forage and straw of wheat treated with 2,4-D-EME 74 and 70% of the total ^{14}C was recovered as free or conjugated 2,4-D. The rest consisted of a large number of distinct metabolites, of which 4-hydroxy-2,5-D was the major compound (8% of the total ^{14}C). In wheat grain about half the total ^{14}C was associated with natural products (protein, starch and cellulose). The remainder consisted mainly of unidentified polar and unextractable compounds. 2,4-D accounted for 6% of the total ^{14}C and was the only component identified.

[^{14}C]2,4-D IPE applied to lemons post-harvest resulted in residues of 2.4 mg/kg as 2,4-D. The fruits were stored at 5-6°C up to 16 weeks. Most of the total ^{14}C was found in the peel, with very small amounts in the pulp and juice. Lemon peel at 20 weeks contained 93.5% of the total ^{14}C (2.1 mg/kg). These residues were mainly free and conjugated forms of 2,4-D (64% of the total ^{14}C, 1.5 mg/kg). Other compounds found in minor quantities were free and bound 2,4-D IPE (0.73 % of the total ^{14}C, 0.017 mg/kg), 4-hydroxy-2,3-D or 5-hydroxy-2,4-D (0.58%, 0.013 mg/kg), 4-hydroxy-2,5-D (0.44%, 0.01 mg/kg) and 2,4-DCP (0.72%, 0.016 mg/kg). The main

metabolites found in the pulp and juice were also free and conjugated 2,4-D (2.9% of the total ^{14}C, 0.07 mg/kg in the pulp; 0.99% of the total ^{14}C, 0.023 mg/kg in the juice).

The degradation of 2,4-D does not lead to environmentally significant levels of degradation products in soil or water.

Under aerobic incubation conditions, 2,4-D is rapidly degraded in soil (half-life in silty clay soil 1.7 days at 25°C). The final degradation products are CO_2 and soil-bound residues, which are mostly distributed in the fulvic acid and huminic acid fractions of the soil.

Further information was received on the fate of the 2-ethylhexyl and isopropyl moieties of the 2,4-D esters and the dimethylamine and diethanolamine of the salts.

The K_{OC} values of $[^{14}C]$2,4-D ranged from 59 to 117, indicating a fairly high potential for 2,4-D to be leached through the tested soils (Arizona clay loam, Mississippi loam, California sandy loam, Plainfield sand), whereas the leaching potential of the degradation products 2,4-dichloroanisole (K_{OC}: 436-1442) and 2,4-dichlorophenol (K_{OC}: 368-1204) is medium to low. In contrast to that, the results of two field lysimeter studies show that 2,4-D and its degradation products are not mobile in sandy soils (pH 5.7 in the first 30 cm, 4.8-5.0 in the next soil horizons). This indicates that 2,4-D, in spite of its high potential to be leached, is not expected to be found in groundwater (owing to its rapid degradation in the soil) when the product has been used in compliance with GAP.

Terrestrial field dissipation studies with the dimethylamine salt and 2-ethylhexyl ester over a 2-year period showed similar rates of dissipation of 2,4-D when applied as either the salt or ester because both formulations are converted rapidly to the same anionic form.

Residues in rotational crops were determined in radishes, lettuce and wheat planted 30 and 139 days after the treatment of the soil with $[^{14}C]$2,4-D at a rate of 2.2 kg ae/ha (acid equivalent/ha). The total radioactive residues in the 30-day crops were <0.001 mg/kg in wheat forage, 0.01 mg/kg in radish roots and 0.06 mg/kg in wheat straw. No ether-soluble residues from free or conjugated 2,4-D or its metabolites were present at levels above 0.01 mg/kg after a 30-day planting interval. The ^{14}C residues observed in the rotational crops planted after both 30 and 139 days were due to incorporation into natural products.

An aerobic aquatic degradation study of $[^{14}C]$2,4-D was conducted at a concentration of 5 mg/l for up to 46 days. 2,4-D acid was degraded slowly at first and represented ≤75% of the applied dose after 25 days. The rate of degradation then increased sharply and at day 46 2,4-D represented only 0.5% of the applied radioactivity. The major product was CO_2, which accounted for 64% of the applied ^{14}C at the end of the study period. The highest levels of the other identified residues (expressed as % of applied ^{14}C) were 1.1% 2,4-dichlorophenol at day 35, 1.1% 4-chlorophenoxyacetic acid at day 14 and 1.4 % 4-chlorophenol at day 20.

2,4-D is not likely to remain long in the environment under anaerobic aquatic conditions, in which it was degraded with a half-life of 41 days.

Further information was received on the aquatic field and pond dissipation of the dimethylamine salt and its major degradation products 2,4-D, 2,4-dichlorophenol, 2,4-dichloroanisole, 4-chlorophenoxyacetic acid and 4-chlorophenol.

The current residue analytical methods are based on extraction with a basic aqueous solution before clean-up by solid phase extraction on a C18-bonded silica cartridge and solvent partitioning. After methylation and further clean-up of the ester, the 2,4-D residues are determined as 2,4-D methyl ester by GLC with an ECD. The method was validated for plant and animal commodities with recoveries above 70%. The typical limits of determination in plant materials, milk and animal tissues are 0.01- 0.05 mg/kg. For most of the supervised trials the reported LOD was 0.01 mg/kg. Residues were determined in water, soil and sediment by GLC with mass-selective detection with LODs of 0.001 mg/l in water and 0.01 mg/kg in soil and sediment.

The analytical method provided by The Netherlands is based on similar extraction and clean-up procedures but the SPE extracts are further processed by column-switched HPLC on a pre-column packed with internal surface reversed-phase (ISRP) material and a bonded C-18 analytical column with UV detection at 118 nm. The LOD was reported to be 0.02 mg/kg for meat and 0.05-0.1 mg/kg for cereals and vegetables.

Information was submitted on the stability of 2,4-D residues in various stored analytical samples. The Meeting concluded that the compound was stable for the duration of the studies (at least two years in potatoes, cherries and cranberries and for one year in the raw agricultural commodities and processed products of cereal grains, fodder and forage, oil seed, sugar cane, grapes and pears, and for seven months in citrus fruits, plums and peaches).

The nature of the 2,4-D residues in plants is adequately understood from the apple, lemon, potato and wheat metabolism studies, and the residues in animals are known from the mouse, rat, goat, poultry and fish metabolism studies.

The Meeting concluded that the definition of the residue in plants and animals should be defined as 2,4-D *per se* for compliance with MRLs and for the estimation of the dietary intake.

The value of the partition coefficient of 2,4-D at natural pH values (log $P_{OW} = 0.18$ and -0.83 at pH 5 and 7 respectively) indicates that the compound is not fat-soluble.

Plant metabolism studies on wheat and potatoes treated with the 2-ethylhexyl ester and on lemon treated with the isopropyl ester indicate nearly complete hydrolysis of the esters by about 10 days after treatment with 2,4-D as the terminal residue of importance. Mammalian pharmacokinetic and metabolism studies in rats and mice indicate that the 2-ethylhexyl ester is rapidly converted to 2,4-D acid and its metabolism can be considered to be equivalent to that of 2,4-D. For these reasons, the definition of the residue arising from the application of the ethylhexyl ester or other esters should be the same as that for the residue from the free acid.

Supervised residue trials on numerous crops were carried out all in the USA and evaluated against US GAP. Because no significant difference was observed between the residues left by the acid, esters and salts, the trials in which 2,4-D acid, the ethylhexyl ester and 2,4-D dimethylamine salt were applied were combined for evaluation.

Citrus fruits. 2,4-D is used as a plant growth regulator pre-harvest on grapefruit and oranges (US GAP 1 x 0.0024 kg ae/hl, PHI 7 days), and post-harvest on lemons (US GAP 1 x 0.05 kg ae/hl).

The Meeting was informed that foliar spraying of grapefruit and oranges with 2,4-D is a minor use.

Two trials according to US GAP were carried out on grapefruit. Because one year passed between the first and the last application, the samples of mature fruits from 1994 and 1995 are used for evaluation. The residues in the whole fruit were <0.05 (2), 0.07 and 0.08 mg/kg. Two further trials complying with GAP on oranges both resulted in residues in the whole fruit below the LOD: <0.05 mg/kg. All the residues in rank order were <0.05 (4), 0.07 and 0.08 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg for grapefruit and oranges, and recommended withdrawal of the current CXL of 2 mg/kg for citrus fruit. As no residue data were submitted for the edible pulp the Meeting estimated an STMR of 0.05 mg/kg, based on the residues in the whole fruit.

Two supervised residue trials of post-harvest use on lemons were carried out in California. No decrease of the residue level during storage (0-112 days at 6-16°C) was observed (range from 0.29 to 0.61 mg/kg). The Meeting could not estimate a maximum residue level owing to the small number of trials.

Use as herbicide in orchards and vineyards

A further use of 2,4-D in fruits is for weed control with applications directed to the orchard or vineyard floor. The apple metabolism study indicates that no residues are to be expected in the fruits after application directed to the orchard floor and is supporting the interpretation of the supervised trial residue data.

Pome fruits. A number of trials on apples and pears in the USA complied with current GAP (2 x 2.2 kg ae/ha, directed application, PHI 14 days). The residues in the fruits from all the 10 trials available were below the LOD of 0.01 mg/kg at 13-15 days PHI. The Meeting estimated a maximum residue level for pome fruits of 0.01* mg/kg as being a practical limit of determination. Because the residues were below the LOD in all samples, including fruit from one trial at a fivefold rate, an STMR level of 0 was estimated.

Stone fruits. Three trials each on cherries, peaches and plums (one on fresh prunes) treated at rates up to the maximum US GAP (2 x 1.6 kg ae/ha, directed application, PHI 14 days) resulted in residues below the LODs of 0.05 mg/kg (cherries) or 0.01 mg/kg (peaches and plums) at 14 days PHI. The Meeting estimated a maximum residue level for stone fruits of 0.05* mg/kg as being a practical limit of determination. Because the residues were below the LOD in all samples including fruit from one trial at a fourfold rate an STMR level of 0 was estimated.

Berries and other small fruits. In four blueberry trials at rates of 2 x 1.6 kg ae/ha as a directed application which complies with GAP in the USA, residues up to 0.01 mg/kg were found about 30 days after the last application. The residues were <0.01 (2) and 0.01 (2) mg/kg.

In six residue trials on strawberries according to US GAP (1 x 1.7 kg ae/ha, before blossom), no residues (<0.05 mg/kg) were found 59-129 days after treatment.

Two US trials on cranberries with 3 x 4.5 kg ae/ha were reported. US GAP specifies 2 x 4.5 kg ae/ha, directed application. At a PHI of 30 days, no residues above the LOD of 0.02

mg/kg were found in samples from the first trial but up to 0.11 mg/kg in those from the second trial.

Only one trial was carried out on raspberries (1 x 1.6 + 1 x 3.1 kg ae/ha). No residues above the LOD of 0.05 mg/kg were found. No residue data were reported for blackberries.

Two residue trials were carried out on grapes according to current US GAP (1 x 1.6 kg ae/ha, directed application). No residues above the LOD of 0.05 mg/kg were found at the recommended PHI of 100 days.

All the residues from trials complying with US GAP for berries in rank order were <0.01 (2), 0.01 (2), <0.05 (9) and 0.11 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for berries and other small fruits (including grapes) and recommended withdrawal of the CXLs for blackberries, raspberries, and vaccinium berries (including bearberry).

The Meeting estimated an STMR of 0.05 mg/kg for berries except grapes, and an STMR of 0 mg/kg for grapes because of their special use pattern (100 days PHI and high phytotoxicity).

Use as herbicide on vegetables

2,4-D is directed to the ground for weed control in vegetables. Supervised trials on sweet corn, potatoes and asparagus were reported.

Sweet corn (corn-on-the-cob). Nine supervised trials at US application rates were reported. Only two of them included the recommended PHI of 21 days but the treatment in all the trials was carried out at the registered plant growth stage. The residues were at or below the LOD of 0.05 mg/kg in all samples of kernels plus cob with husks removed. The Meeting estimated a maximum residue level for sweet corn of 0.05* mg/kg as being a practical limit of determination, and an STMR of 0.05 mg/kg.

Potatoes. Eight of ten trials in the USA complied with US GAP (2 x 0.078 kg ae/ha). The treatments were carried out at the registered plant growth stage. At harvest, the residues were <0.05 (5), 0.08 (2) and 0.13 mg/kg. The Meeting confirmed the current CXL of 0.2 mg/kg and estimated an STMR of 0.05 mg/kg.

Asparagus. Four trials covering the US application rate were reported but only two included the specified PHI of 3 days (the residues were 0.1 and 3 mg/kg). Two trials are not enough to estimate a maximum residue level.

Use as herbicide on cereals

2,4-D is used world-wide for the pre- or post-emergence or pre-harvest treatment of winter and summer cereals.

Maize. After three applications of the dimethylamine salt (7 trials), 2-ethylhexyl ester (6 trials), or free acid (1 trial) totalling 3.4 kg ae/ha, the residues of 2,4-D in grain after 7 days (US GAP) or 14 days were <0.01, 0.01 (8), 0.015, 0.02 (2), 0.03 and 0.04 mg/kg (4 residues at 14 days were

higher than the corresponding 7-day residues). The Meeting estimated a maximum residue level of 0.05 mg/kg to replace the current CXL (0.05* mg/kg) and an STMR of 0.01 mg/kg.

Rice. Seven of ten supervised US trials complied with GAP (1 x 1.7 kg ae/ha, PHI 60 days). The residues in the rice grain without husk in rank order were <0.01(2), 0.01 (3), 0.03 and 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg for husked rice to replace the current CXL of 0.05* mg/kg for rice and an STMR of 0.01 mg/kg.

Wild rice. Only one overdosed trial (4 replicates) was reported. No residues were found after treatment with 0.56 kg ae/ha at day 53 or 64. One trial is not enough to estimate a maximum residue level.

Sorghum. 2,4-D is registered in the USA for applications of 0.56 kg ae/ha of esters or 1.1 kg ae/ha of the acid or salts. In a total of ten trials in four US states the recommended rates were applied at the registered plant growth stage.

No residues above the LOD of 0.01 mg/kg were found in the grain at harvest. The Meeting estimated a maximum residue level for sorghum of 0.01* mg/kg as being a practical limit of determination to replace the current CXL of 0.05* mg/kg, and an STMR of 0.01 mg/kg.

Wheat and rye. Many field trials were carried out on wheat in the USA, 24 of them according to US GAP (1.4 + 0.56 kg ae/ha, PHI 14 days). The residues in wheat grain in rank order were 0.11 (2), 0.12, 0.13, 0.16 (2), 0.17 (4), 0.21, 0.22 (2), 0.23, 0.24 (2), 0.31, 0.34, 0.46, 0.63, 0.87, 0.94, 0.95 and 1.4 mg/kg. The Meeting agreed to extrapolate the residue data from wheat to rye because GAP is identical and estimated maximum residue levels of 2 mg/kg to replace the current CXLs of 0.5 mg/kg with STMRs of 0.22 mg/kg.

Other cereals. 2,4-D is registered world-wide for use on barley, millet, oats and triticale. Although the US GAP for barley, oats and millet is the same as for wheat the Meeting agreed that extrapolation from wheat to barley, oats and millet could be recommended because the residue could be considerably higher from the use after blossom at the dough stage.

2,4-D is registered on triticale in Australia (1 x 1.6 kg ae/ha, PHI 7 days). Many US trials on wheat complied with Australian GAP but the Meeting did not support extrapolation of the US data as the climatic conditions are different.

The Meeting agreed to recommend the withdrawal of the current CXLs for barley and oats of 0.5 mg/kg and could not estimate a maximum residue level for millet or triticale.

Sugar cane. Eight US supervised trials according to GAP with one pre-emergence and one post-emergence treatment of 2.2 kg ae/ha were reported. The residues in mature cane at PHIs of 137-214 days were <0.01 (7) and 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg.

Tree nuts. Ten trials each on almonds and pecans were carried out in the USA, five with directed applications of the dimethylamine salt and five with the 2-ethylhexyl ester, according to US GAP (2 x 1.6 kg ae/ha, PHI 60 days).

Two trials with directed applications on pistachio nuts were also according to US GAP (2 x 1.6 kg ae/ha, PHI 50 days).

Three trials each with the dimethylamine salt and the 2-ethylhexyl ester complied with the critical US GAP on hazelnuts, where 4 x 0.12 kg ae/hl are used as a spray to the stems of suckers with a PHI of 45 days.

The residues were <0.05 (8), 0.08 and 0.16 mg/kg in almond kernels, below the LOD of 0.05 mg/kg in all the samples of pecans and pistachio nuts and <0.05 (2), 0.05 and 0.1 mg/kg in hazelnuts. All residues in rank order were <0.05 (22), 0.05, 0.08, 0.1 and 0.16 mg/kg.

The Meeting estimated a maximum residue level for tree nuts of 0.2 mg/kg and an STMR of 0.05 mg/kg.

Soya bean seed, fodder and forage. The use of 2,4-D is registered in the USA for pre-planting applications of 1 x 0.56 kg ae/ha of esters or 1 x 1.1 kg ae/ha of free acid or salts. Twenty seven supervised trials were reported, with treatments of 0.56, 1.4 or 3.2 kg ae/ha. The residues in all samples of beans were lower than the LOD of 0.01 mg/kg. The Meeting concluded that no detectable residue is likely to occur in soya beans, and estimated a maximum residue level of 0.01* mg/kg and an STMR of 0 mg/kg.

No residues were detected in any of the 27 samples of fresh forage.

The fodder samples were analysed after air-drying forage for 1.5-7 days after cutting. No residues above the LOD of 0.01 mg/kg were found in the nine trials according to GAP. Residues up to 0.04 mg/kg were found after the treatments at higher rates.

The Meeting concluded that no detectable residue is to be expected in soya bean forage (green) or fodder, and estimated maximum residue levels of 0.01* mg/kg as a practical limit of determination. STMRs of 0 for soya bean forage (green) and 0.01 mg/kg for fodder were estimated.

Animal feedstuffs

Forage, hay or fodder of grasses. Supervised trials according to US GAP (2 x 2.2 kg ae/ha) were reported on rangeland and pasture grass used for animal feed. The Meeting was informed that a PHI of 0 days has to taken into account for the estimation of a maximum residue level for rangeland. The residues in the forage on the day of treatment in rank order were 90, 92, 135, 153, 154, 162, 169, 172, 173, 177, 182, 183, 192, 194, 198, 223, 233, 236, 241, 258, 271, 280, 285, 31, 314 and 358 mg/kg. The Meeting estimated an STMR of 193 mg/kg for grass forage.

The highest residues from each trial on hay (PHI of fresh forage 7-30 days) were 19, 39, 40, 50, 61, 65, 68 (2), 74, 82, 86, 94, 96, 101, 103, 109, 126, 142, 145, 147, 149, 150, 155, 180, 182, 206, 216, 218, 231, 236, 279 and 330 mg/kg. The Meeting estimated a maximum residue level of 400 mg/kg and an STMR of 117.5 mg/kg for the hay or fodder (dry) of grasses.

Maize forage and fodder. US GAP allows pre-emergence application at 1.1 kg ae/ha, a directed post-emergence application at 0.56 kg ae/ha when the maize is 25-41 cm high, and a pre-harvest application at 1.7 kg ae/ha (PHI for grain 7 days).

After two applications of 2,4-D at rates totalling 1.7-2.2 kg ae/ha, the residues in rank order were 0.01, 0.03, 0.09, 0.25 (2), 0.33, 0.46, <u>0.61</u>, <u>0.69</u>, 0.88, 1.0 (2), 1.1, 2.7, 3.0 and 5.2 mg/kg in 16 forage samples collected at a 7-day PHI and <<u>0.01</u> (14), 0.01, 0.03 mg/kg in 16 samples for silage use collected after 54-89 days.

After three applications of 2,4-D totalling approximately 3.4 kg ae/ha, the residues in fodder were 3.6, 4.2, 4.4 (2), 5.7, <u>6.4</u> (2), 9.1, 9.9, 15, 20, 25 and 30 mg/kg at 7 or 14 days after treatment.

The Meeting estimated a maximum residue level of 10 mg/kg for maize forage and 40 mg/kg for maize fodder. STMRs of 0.65 and 6.4 mg/kg were estimated for maize forage and fodder respectively.

<u>Rice straw and fodder</u>. The residues of 2,4-D after treatments according to GAP at 61-66 days were 1.1, 1.5, 2.1, <u>3.1</u>, 5.4, 6.4 and 8.8 mg/kg. The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 3.1 mg/kg for rice straw and fodder, dry.

<u>Sorghum, straw and fodder</u>. The residues in the green forage in the 10 US trials described above in rank order were <0.01, 0.02 (2), <u>0.03</u> (2), <u>0.04</u>, 0.06, 0.08, 0.13 and 0.14 mg/kg 30 days after treatment. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.035 mg/kg for sorghum forage (green).

Fodder samples were harvested at maturity, approximately 82-112 days after treatment. The residues in the untreated control samples were of the same order as those in the supervised trials. The Meeting therefore concluded that the submitted data could not be used to estimate a maximum residue level for sorghum straw and fodder.

<u>Wheat forage, straw and fodder</u>. In the USA the first application of 2,4-D is recommended after the plant is fully tillered but before joints are formed in the stems, and the second when the grain is at the dough stage.

The wheat can be cut before the pre-harvest application and used as forage, so the forage samples were taken 7 days after the first treatment. The residues in rank order were 5, 6 (3), 6.3, 7, 8 (2), 8.5, 9 (2), 11, 14 (3), 15 (2), 16, 17, 18 (2), 19, <u>20</u> (2), 22 (2), 23 (2), 24, 25, 26, 29, 30 (2), 33 (3), 34, 35, 41, 42, 50, 54, 55, 58 and 112 mg/kg.

The residues in straw from treatments according to GAP were 2, 3, 4 (5), 5 (3), 6 (2), <u>7</u> (3), 8 (2), 11, 15 (4), 17, 18, 22, 41 and 85 mg/kg 13-15 days after pre-harvest treatment.

The Meeting estimated a maximum residue level of 100 mg/kg and an STMR of 7 mg/kg for wheat straw and fodder, dry, and an STMR of 20 mg/kg for wheat forage.

<u>Sugar cane forage</u>. After applying 2,4-D pre-emergence and post-emergence (at layby) to sugar cane at 2.2 kg ae/ha, the residues were <0.01(2), 0.01, <u>0.03</u>, 0.04, 0.08 and 0.14 mg/kg in forage samples collected 88-92 days after the second application. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.03 mg/kg.

<u>Animal transfer studies</u>

Groups of 3 cows were dosed at four dose levels equal to 1446, 2890, 5779 and 8585 ppm 2,4-D ae in the diet on a dry weight basis for 28 to 30 consecutive days. Two further groups were treated at the high dose level for 28 days and slaughtered 3 or 7 days after the last dose.

Residues of 2,4-D were detected in most of the milk samples analysed. The mean residue levels in the samples from the high-dose group reached a plateau after 7 days of treatment, showing a residue level of 0.47 mg/l throughout the remaining treatment period. The mean residues in the groups allowed 3 and 7 days of recovery decreased from the levels of 0.46 and 0.47 mg/kg at 28 days to 0.01 mg/l.

The residues in the milk from the medium-high dose groups also reached a plateau after 7 days at mean levels of 0.29 and 0.04 mg/kg respectively. The residues from the medium-low dose group became steady after the first day of treatment, having a mean level of 0.12 mg/kg throughout the remaining treatment period.

Residues of 2,4-D were also detected in most of the tissue samples analysed. The mean liver residue levels in the high, medium-high, medium-low and low dose groups were 3.1, 3.0, 1.9 and 0.12 mg/kg respectively, decreasing to 0.45 and 0.39 mg/kg after 3 and 7 days recovery respectively.

The mean residues in the kidneys from the four groups were 24, 17, 14 and 3.8 mg/kg respectively, decreasing to 0.06 and <0.05 mg/kg after 3 and 7 days recovery.

The mean residues in the muscles from the four groups were 1.0, 0.76, 0.41 and 0.21 mg/kg, decreasing to 0.06 and <0.05 mg/kg after 3 and 7 days recovery, and those in the fat were 2.2, 2.5, 0.59 and 0.42 (those in the medium-high group being highest), and were 0.07 and <0.05 mg/kg after 3- and 7-day recovery periods.

Thus the highest residues were in the kidneys, followed in decreasing order by liver, fat, muscle and milk. This relationship was generally consistent in all four dose groups. The residue levels were generally dose-dependent, except in fat where the mean residue in the high dose group was slightly lower than that in the medium-high group, indicating that a plateau level had been reached in fat.

The highest exposure to 2,4-D residues will arise from the use of the herbicide on pasture, where the highest residues were 358 mg/kg in grass forage. With the assumption that the maximum daily feed consumption of a dairy cow (body weight 550 kg) is 20 kg on a dry matter basis, of which 60% is grass forage containing 25% dry matter, the intake may be calculated as follows.

358 mg/kg on a wet weight basis is equivalent to 1432 mg/kg on a dry matter basis (358 + 0.25).

Grass forage forms 60% of the diet and therefore contributes 859.2 ppm total feed on dry matter basis (1432 x 0.6).

Hence the dietary intake is 859.2 x 20 / 550 = 31 mg/kg bw/day.

The lowest dose in the feeding study was 50.6 mg/kg bw/day but, as a nearly linear relation between dose and residue level with its graph passing through the origin was established,

the Meeting concluded that an extrapolation downwards to the estimated actual intake was justified in this case. The following Table shows the highest and the mean measured and extrapolated residues. Maximum residue levels were estimated from the highest extrapolated residue, and STMRs from the medians of the mean extrapolated residues for estimation of the maximum residue level and the STMR respectively.

Dose, group	Residues, mg/kg									
mg/kg bw/day	Milk		Liver		Kidney		Muscle		Fat	
	highest	mean	highest	mean	highest	mean	highest	mean	highest	mean
(50.6) Actual	(0.07)	(0.04)	(0.2)	(0.12)	(6.5)	(3.8)	(0.24)	(0.21)	(0.51)	(0.42)
31 Extrapolated	0.043	0.025	0.12	0.074	3.98	2.33	0.15	0.13	0.31	0.26
(99) Actual	(0.18)	(0.12)	(2.4)	(1.9)	(18)	(14)	(0.51)	(0.41)	(0.75)	(0.59)
31 Extrapolated	0.056	0.038	0.75	0.59	5.64	4.38	0.16	0.13	0.23	0.18
(189) Actual	(0.59)	(0.29)	(3.5)	(3.0)	(29)	(17)	(1.1)	(0.76)	(3.6)	(2.5)
31 Extrapolated	0.097	0.048	0.57	0.49	4.76	2.79	0.18	0.12	0.59	0.41
(276) Actual	(0.87)	(0.47)	(3.8)	(3.1)	(24)	(24)	(1.0)	(1.0)	(2.3)	(2.2)
31 Extrapolated	0.098	0.053	0.43	0.35	2.7	2.7	0.11	0.11	0.26	0.25

[1]Residues found in the feeding study are in parentheses

The Meeting considered that liver and kidney should by combined as "edible offal", with the residues found in kidney, and estimated maximum residue levels of 0.1 mg/kg for milk, 5 mg/kg for edible offal and 0.2 mg/kg for meat and STMRs of 0.043 mg/kg for milk, 2.745 mg/kg for edible offal and 0.125 mg/kg for meat, and recommended the withdrawal of the CXLs for milks and milk products (0.05* mg/kg). No maximum residue level or STMR was estimated for fat as the results appeared to be atypical.

A metabolism study in hens showed that about 90% of the dose was recovered in the excreta. The edible tissues and eggs contained <0.1% of the total dose. The highest exposure to 2,4-D residues will arise from wheat and rye grain in which the highest residue found in the supervised trials was 1.4 mg/kg and maximum residue levels of 2 mg/kg and STMRs of 0.22 mg/kg were estimated. With the assumption that the daily maximum feed consumption of a chicken (bw 1.9 kg) is 0.12 kg on a dry matter basis, consisting of 80% wheat grain (89% dry matter) and 20% rye grain (88% dry matter), an intake of 2.25 ppm can be calculated from the maximum residue level. Therefore, no residues higher than 0.002 mg/kg (0.1%) could be expected theoretically in edible tissues and eggs. The Meeting estimated STMRs of 0 for poultry meat, edible offal and eggs, and maximum residue levels for poultry meat and edible offal of 0.05* mg/kg as a practical limit of determination. The Meeting estimated a maximum residue level for eggs at the LOD of 0.01* mg/kg to replace the CXL of 0.05* mg/kg.

Processing

Studies have been carried out to determine the effect of processing on residues of 2,4-D in lemons, maize, rice, sorghum, wheat and sugar cane.

Lemons containing 0.51 mg/kg 2,4-D (median) were processed to juice, wet and dry pulp, molasses and oil, which contained median residues of 0.05, 0.45, 1.9, 2.0 and <0.5 mg/kg respectively. The corresponding mean processing factors were 0.1, 0.88, 4.7, 4.3 and <1. The Meeting applied these factors to the STMRs of 0.05 mg/kg for oranges and grapefruit, and estimated STMR-Ps of 0.005 mg/kg for juice, 0.044 mg/kg for wet pulp, 0.235 mg/kg for dried pulp, 0.215 mg/kg for molasses and 0.05 mg/kg for oil.

The processing data on maize indicate that residues of 2,4-D do not concentrate in any of its processed commodities used for food or feed. In grits, meal and flour, the 2,4-D residues (0.04, 0.05 and 0.05 mg/kg respectively) were of the same order as in the grain (0.06 mg/kg). In aspirated maize grain fractions the residues of 2,4-D were approximately 37 times those in the grain. In view of the chemical nature of the compound, the residues in maize oil would be lower than the LOD of 0.01 mg/kg.

Because an STMR of 0.01 mg/kg was estimated for maize grain and the residues in the processed commodities were similar to those in the raw commodity, the Meeting estimated STMR-Ps of 0.01 mg/kg for maize grits, meal and flour.

One processing study on rice was reported. Residues of 2,4-D were not concentrated in rice bran or milled white rice but were concentrated by a factor of 3 in rice hulls. No STMR-P could be estimated for milled white rice because no data were reported for the unprocessed commodity (rice with husk).

As residues of 2,4-D were not detectable in sorghum grain or its processed commodities the processing trials could not be evaluated.

Wheat was treated with excessive amounts of 2,4-D to obtain high residues (1.5 and 2.4 mg/kg) and processed to produce bran, flour, middlings and shorts. The residues were concentrated in the bran and reduced in the flour by mean processing factors of 3.65 and 0.11 respectively. From the STMR for wheat grain of 0.22 mg/kg and these factors the Meeting estimated STMR-Ps of 0.803 mg/kg and 0.024 mg/kg for wheat bran and flour respectively.

Residues from two supervised trials on sugar cane with treatment at four times the GAP rate were below the limit of determination (0.01 mg/kg). The cane from one trial was processed into molasses and sugar with residues of $\leq$0.01 mg/kg in molasses and <0.01 mg/kg in sugar. No STMR-Ps were estimated.

DIETARY RISK ASSESSMENT

The International Estimated Daily Intakes of 2,4-D, based on the STMRs estimated for 26 commodities, for the five GEMS/Food regional diets were in the range of 3 to 10% of the ADI. The Meeting concluded that the intake of residues of 2,4-D resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.7 DICLORAN (083)

TOXICOLOGY

Dicloran was evaluated for toxicological effects by the Joint Meetings in 1974 and 1977. A temporary ADI of 0-0.03 mg/kg bw was established in 1974 on the basis of the results of a two-year study in dogs and short- and long-term studies in rats. The 1977 Meeting established an ADI of 0-0.03 mg/kg bw on the basis of the above studies, after examination of further data on oculotoxicity in dogs, metabolism and pharmacokinetics in pigs, and elucidation of the effects of dicloran on liver microsomal enzymes, in compliance with the request of the 1974 Joint Meeting.

Dicloran was reviewed by the present Meeting within the CCPR periodic review programme. In addition to studies previously reviewed, newly available studies, including those on metabolism, short-term toxicity in mice and rats, carcinogenicity in mice, genotoxicity, reproductive toxicity in rats, and developmental toxicity in rabbits, were reviewed.

WHO has classified dicloran as unlikely to present an acute hazard in normal use.

Dicloran is rapidly absorbed, metabolized, and eliminated, mainly in the urine, after oral administration to rats, goats, and humans; it is also rapidly excreted by hens. Rats excreted most of the radiolabel (90-96%) within 24 h, with > 70% in the urine and an additional 13-22% in the faeces, depending on the dose. Elimination was essentially complete (91-97% of the administered dose) by 48 h, with total tissue residues accounting for 0.2-0.3%. The highest tissue concentrations were found in the liver (0.05-0.06 mg/kg) and kidneys (0.02 mg/kg). Unchanged parent compound was detected in the faeces of animals at the high dose only. The major urinary metabolites were the sulfate and glucuronide conjugates of 2,6-dichloro-4-hydroxyaniline, which accounted for 55-79% of the total administered radioactivity, and the major faecal metabolites were derivatives of glutathione conjugates. The parent compound and its glutathione conjugates were the major residues in plants. None of the metabolites were of toxicological concern. The rapid excretion of dicloran as a conjugate indicates that it is readily metabolized *in vivo.*

The major metabolite in rat urine (2,6-dichloro-4-hydroxyaniline) was not present in goat urine, which contained more polar conjugates that could not be hydrolysed by glucuronidase or sulfatase. In goats, dicloran is reduced to 4-amino-2,6-dichloro-aniline and acetylated to 4-amino-3,5-dichloro-acetanilide (4-6% in urine), which is rapidly metabolized and excreted in the urine and faeces, although a reactive intermediate is formed in goat liver and bound covalently to macromolecules. Species differences in dicloran metabolism were also apparent in dogs and mice, which partly explain the photosensitive oculotoxic effects observed in dogs and the methaemoglobinaemia noted in mice, which are not seen in other mammals. Preliminary studies suggested that the metabolites of dicloran in humans are similar to those in rats. Although recovery was considered complete, excretion was somewhat slower in humans than in rats, most of the material being excreted within 1.5 days.

Dicloran has low or slight toxicity when administered by the oral route, depending on species. It has low dermal toxicity, is not irritating to the skin, is a mild eye irritant, and is not a skin sensitizer.

The results of short-term toxicity studies in rabbits treated dermally and in mice and rats treated in the diet or by gavage, as well as of long-term toxicity studies in mice, rats, and dogs treated in the diet indicate that the liver is the primary target organ. Increased liver weights and centrilobular hepatic hypertrophy were observed consistently in all species treated orally, and increased splenic activity and splenic extramedullary haematopoiesis were noted in short- and long-term studies in mice.

When dicloran was fed to mice at 0, 300, 600, or 1200 ppm for 60 days, the NOAEL was 300 ppm (equal to 49 mg/kg per day), on the basis of hepatic lesions, splenic extramedullary haematopoiesis, and increased methaemoglobin at doses of 600 ppm and above.

In a 90-day study in mice treated by gavage with 0, 15, 45, 135, 400, or 600 mg/kg bw per day, the NOAEL was 15 mg/kg bw per day on the basis of significant polycythaemia in

males and hypercholesterolaemia and a significant increase in the incidence of splenic extramedullary haematopoiesis in females at 45 mg/kg bw per day and above.

A NOAEL was not identified in a 90-day study in rats fed diets containing, 0, 1000, 3000, or 5000 ppm dicloran because of significantly reduced body-weight gain in conjunction with effects on the liver and thyroid in all treated groups. In an eight-week study in which rats were given diets containing dicloran at doses of 0, 500, or 750 ppm, the NOAEL was 500 ppm (equal to 44 mg/kg bw per day) on the basis of reduced body-weight gain, decreased food consumption, and increased liver weights with associated hepatic histopathological manifestations at 750 ppm.

In a study in which dicloran was fed to rats for six months at 0, 30, 300, or 3000 ppm, the NOAEL was 300 ppm (equal to 22 mg/kg bw per day) on the basis of reduced body weights and increased liver and spleen weights at 3000 ppm.

In a four-week study in rats given doses of 0, 35, 140, or 350 mg/kg bw per day by gavage, the NOAEL was 35 mg/kg bw per day on the basis of growth depression and hepatic hypertrophy and vacuolation at 140 mg/kg bw per day.

In an 18-month study of carcinogenicity in mice at dietary concentrations of 0, 50, 175, or 600 ppm, the NOAEL was 175 ppm (equal to 25 mg/kg bw per day) on the basis of increased liver weights, centrilobular hepatocyte enlargement, centrilobular haemosiderosis, focal and single-cell liver necrosis, and vacuolation of centrilobular hepatocytes. There was no evidence of carcinogenicity in mice.

Two studies were conducted in rats to assess toxicity over a two-year period of exposure. Rats were fed diets containing dicloran at concentrations of 0, 20, 100, or 3000 ppm or 0 or 1000 ppm. The overall NOAEL was 1000 ppm (equal to 59 mg/kg bw per day), on the basis of changes in body-weight, food consumption, and haematological parameters, spleen pigmentation, increased liver weights, centrilobular hepatocyte enlargement, and thyroid hypertrophy at 3000 ppm. There was no evidence of carcinogenicity in these studies; but they were considered inadequate for complete evaluation of the carcinogenetic potential of dicloran.

Dogs fed dicloran at dietary concentrations of 0, 20, 100, or 3000 ppm for two years had treatment-related changes in haematological and clinical chemical parameters and significant increases in liver, spleen, and kidney weights, accompanied by histological changes at 3000 ppm that included irregular hepatic-cell size, moderate hepatic-cell hypertrophy, and increased pigmentation of the liver and spleen. The NOAEL was 100 ppm, equal to 1.7 mg/kg bw per day.

Dicloran was not mutagenic in most assays, although occasional positive responses were seen in more recent tests for reverse mutation and in a test for mitotic recombination. The results of an assay for sex-linked recessive mutation in *Drosophila* were equivocal. The Meeting concluded that dicloran is unlikely to be genotoxic.

Studies of reproductive and developmental toxicity indicated that dicloran is not a reproductive toxicant and is not teratogenic in rats or rabbits. Dicloran was embryotoxic at maternally toxic doses in rabbits, but an NOAEL for maternal or developmental toxicity was not identified in rats.

In a two-generation study of reproductive toxicity in rats (one litter/generation) at dietary concentrations of 0, 50, 250, or 1250 ppm, the NOAEL for systemic toxicity was 250 ppm (equal to 21 mg/kg bw per day) on the basis of reduced body-weight gains and increased liver weights at 1250 ppm. The NOAEL for reproductive and developmental toxicity was 250 ppm (equal to 21 mg/kg bw per day) on the basis of reduced weights of F_1 and F_2 pups at 1250 ppm.

In a study of developmental toxicity, dicloran was administered by gavage to rats on days 6-15 of gestation at doses of 0, 100, 200, or 400 mg/kg bw per day. Because of significantly reduced mean maternal body-weight gains and higher incidences of totally resorbed litters in all treated groups, NOAELs for maternal or developmental toxicity were not identified. Dicloran was not teratogenic in this study.

In a study of developmental toxicity in rabbits, dicloran was administered by gavage at doses of 0, 8, 20, or 50 mg/kg bw per day on days 6-18 of gestation. The NOAEL for maternal toxicity was 8 mg/kg bw per day, on the basis of reduced maternal body-weight gains early during treatment with 20 or 50 mg/kg bw per day. The NOAEL for developmental toxicity was 20 mg/kg bw per day on the basis of a slight increase in post-implantation losses, a slight increase in the incidence of minor anomalies of the gall-bladder, and delays in ossification of all limb epiphyseal sites in fetuses at 50 mg/kg bw per day.

Dogs have been shown to develop lesions in the cornea and lens after prolonged oral administration of dicloran. The 1977 Joint Meeting reviewed additional data requested by the 1974 Meeting and concluded that the photosensitive oculotoxic effects observed in dogs but not in other mammals were due partly to a species difference in the kinetics of dicloran. No oculotoxic effects were seen in any of the more recent studies, although no further studies have been conducted in dogs.

In a double-blind clinical study, 20 men were given 10 mg dicloran (equivalent to 0.14 mg/kg bw per day) and 10 received a placebo once daily for 90 days. The dose and duration were chosen on the basis of the maximum residues estimated to be derived from consumption of fruits and vegetables over one year. There was no indication that administration of dicloran at this dosage had any adverse effect.

An ADI of 0-0.01 mg/kg bw per day was established on the basis of the NOAEL of 1.7 mg/kg bw per day for hepatic and haematological effects in the two-year study in dogs and a 200-fold safety factor. A larger than normal safety factor was used because of the inadequacy of the long-term studies in rats for assessing the carcinogenic potential of dicloran and because of the lack of a NOAEL for maternal and developmental toxicity in rats.

An acute RfD was not allocated because dicloran has low or slight toxicity when administered orally or dermally and because acute effects occur only at very high doses, resulting in a 10 000-fold difference between the ADI and the LOAEL for maternal and developmental toxicity in rats. Therefore, the Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 49 mg/kg bw per day (lowest dose tested, eight-week study   of toxicity)
             15 mg/kg bw per day (13-week study of toxicity)
             25 mg/kg bw per day (18-month study of carcinogenicity)

Rat: 35 mg/kg bw per day (lowest dose tested, four-week study of
        toxicity)
             44 mg/kg bw per day (lowest dose tested, eight-week study of toxicity)
             22 mg/kg bw per day (six-month study of toxicity)
             59 mg/kg bw per day (2 two-year studies of toxicity)
             21 mg/kg bw per day (two-generation study of reproductive toxicity)

Rabbit: 8 mg/kg bw per day (maternal toxicity in a study of   developmental
toxicity)

             20 mg/kg bw per day (developmental toxicity)

Dog: 1.7 mg/kg bw per day (two-year study of toxicity)

Human: 0.14 mg/kg bw per day (90-day study of toxicity)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Estimate of an acute reference dose

Not allocated (unnecessary).

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

1.   Combined study of toxicity and carcinogenicity in rats.
2.   Study of developmental toxicity in rats at less than 100 mg/kg bw per day to establish clear NOAELs for maternal and developmental toxicity.
3.   Assays for genotoxicity in mammals *in vivo*, such as an assay for micronucleus formation
4.   Further observations in humans.

List of endpoints for setting guidance values for dietary & non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid/complete, >70% urinary excretion in 24h
Dermal absorption:	No data
Distribution:	Liver, kidney
Potential for accumulation:	Minimal
Rate and extent of excretion:	Rapid/complete, 90-96% in urine and faeces within 24 h
Metabolism in animals	Metabolites differ in rats and goats

Toxicologically significant compounds (animals, plants and environment)	Parent compound

Acute toxicity

Rat LD$_{50}$ oral	>4000 mg/kg bw
Rabbit LD$_{50}$ dermal	>2000 mg/kg bw
Rat LC$_{50}$ inhalation	No data
Skin irritation	Not irritating
Eye irritation	Minimally irritating
Skin sensitization	Non-sensitizer (Draize test)

Short term toxicity

Target/critical effect	Liver/centrilobular hepatotoxicity (mice, rats, dogs) Spleen/extramedullary haematopoiesis (mice)
Lowest relevant oral NOAEL	44 mg/kg bw/per day (diet); 15 mg/kg bw per day (gavage)
Lowest relevant dermal NOAEL	120 mg/kg bw per day
Lowest relevant inhalation NOAEL	Poor study: data on actual intake, particle size not provided.

Genotoxicity	Unlikely to be genotoxic No study of genotoxicity in mammals *in vivo*.

Long term toxicity and carcinogenicity

Target/critical effect	Liver/centrilobular hepatotoxicity (mice, rats, dogs)Spleen/extramedullary haematopoiesis (mice)
Lowest relevant NOAEL	1.7 mg/kg bw per day (2-year study in dogs)
Carcinogenicity	No evidence of carcinogenicity in mice. The study in rats was inadequate.

Reproductive toxicity

Reproduction target/critical effect	Increased ovary/testis weights (no histological findings)
Lowest relevant reproductive NOAEL	21 mg/kg bw per day (reduced body-weight gain, increased liver weight)
Developmental target/critical effect	Increased resorptions, delayed ossification, not teratogenic
Lowest relevant developmental NOAEL	20 mg/kg bw per day in rabbits; no NOAEL in rats. A 10 000-fold difference exists between the ADI and the LOAEL in rats.

Neurotoxicity/Delayed neurotoxicity

No data

Other toxicological studies
Cataractogenicity

Photosensitive oculotoxic effects observed in dogs are not seen in other mammals.

Medical data
Clinical Studies

No indication that administration of dicloran at 10 mg/day to men for 90 days had any adverse effect. Extensive examinations were made on one industrial worker occupationally exposed to dicloran over three years, with considerable inhalation and dermal exposure for about 60 days/year. No adverse effects were observed.

Summary

	Value	Study	Safety factor
ADI	0-0.01 mg/kg bw	2-year, dog	200
Acute reference dose	Not allocated (Unnecessary)		

RESIDUE AND ANALYTICAL ASPECTS

Dicloran was evaluated for toxicology and residues in 1974 and 1977. An ADI was established in 1977.

Dicloran is a protective fungicide used to control *Botrytis, Monilinia, Rhizopus, Sclerotinia and Sclerotium* spp. on fruits and vegetables during the growing stages and/or post-harvest. The compound was evaluated at the present Meeting within the CCPR Periodic Review Programme.

The Meeting received data on residues and information on GAP from the manufacturer and the governments of The Netherlands, Poland and Germany.

Animal metabolism

The following abbreviations for dicloran metabolites are used.

DCHA: 4-amino-3,5-dichlorophenol   DCPD: 4-amino-2,6-dichloroaniline
DCAA: 4-amino-3,5-dichloroacetoanilide   DCNP: 2,6-dichloro-4-nitrophenol
DCAP: 4-amino-2,6-dichlorophenol   DCNAP:3,5-dichloro-4-hydroxyacetanilide
HNCA: 2-chloro-6-hydroxy-4-nitroaniline   2,6-DCP: 2,6-dichlorophenol
2,6-DCA: 2,6-dichloroaniline

Animal metabolism was studied in rats, goats and hens with [^{14}C]dicloran. Dicloran metabolism in animals involves reduction of the nitro group to amino, deamination and hydroxylation to phenolic derivatives, and acetylation to form acetanilides.

Conjugation to form the glucuronide and/or sulfate at the *N* or *O* position and glutathione conjugation at the Cl position also apparently occurred.

The contribution of each of the metabolic reactions differs among the species examined. While DCHA and its conjugates were the predominant metabolites in rats, DCAA and DCNP were at higher levels than DCHA in goats and hens respectively.

Rat metabolism has been studied with [^{14}C]dicloran in several experiments (single doses of 1.5-500 mg/kg bw, repeated doses of 5 mg/kg bw). The total recoveries of radioactivity were >94% in the studies, and >90% of the radioactivity was excreted within 48 hours after dosing. Irrespective of the dosing regimen, most of the radioactivity (72.3-90.2%) was excreted in the urine. The faeces contained 7.9-22.4%.

The radioactivity in the expired air was monitored in the group dosed once with 5 mg/kg bw and no significant amounts of ^{14}C were detected in the carbon dioxide traps, indicating that the molecule was not completely broken down.

After repeated doses of 5 mg/kg bw for 7 days the tissue residues were highest in the liver (0.06 and 0.049 mg/kg as dicloran in males and females respectively) and kidneys (0.016 and 0.015 mg/kg in males and females respectively). All other residues in the tissues were at or below the limit of determination (0.01 mg/kg).

The major urinary metabolites were DCHA sulfate and DCHA glucuronide, together accounting for up to 79% of the total administered radioactivity. The metabolites DCHA, DCAP and DCNAP were also found.

The faeces from the animals dosed at 500 mg/kg contained a small amount of dicloran and many minor metabolites. Much of the radioactivity in the faeces was released only by acid hydrolysis and was thought to be from glutathione conjugates of several metabolites. Similar metabolic pathways were found after repeated low doses and single high doses of dicloran.

Metabolism in goats was studied in two experiments. In one, female goats were given single doses of 1.5 or 10 mg/kg bw of [^{14}C]dicloran and slaughtered after 72 hours. In the other study a lactating goat was dosed with [^{14}C]dicloran for 5 consecutive days at an average level of 613 mg/day (12 mg/kg bw), equivalent to 359 ppm of dicloran in the diet based on the measured feed consumption during the treatment period. The goat was killed 22 hours after the final dose. The total recoveries of radioactivity were 77.9% after the single dose of 1.5 mg/kg bw, 113.6% after the single 10 mg/kg bw dose, and 88.7% after the last of the repeated doses of 12 mg/kg bw/day. Overall, the radioactivity excreted in the urine ranged from 33.0% to 68.9% and the faeces contained 43.3-44.9% of the dose. The highest tissue residues in all the animals were found in the livers.

Examination of the urine from the singly-dosed goats showed the metabolite DCAA and its conjugates after both high and low doses, with a range from 3.3% to 5.6% of the urinary radioactivity, but DCPD was not detected. After enzymatic hydrolysis, a small amount of DCHA (1.6% of the urinary ^{14}C) was detected in the urine from the low-dose goat.

The residues in the tissues and milk of the lactating goat given repeated doses of [^{14}C]dicloran were examined in detail. The extraction of ^{14}C from milk, liver, kidney, muscle and

fat ranged from 65.2% from muscle to 93.6% from fat and milk. Dicloran accounted for 80.7% of the total radioactive residues in fat, 19.6% in milk and 15.7% in muscle. DCAA was found in muscle (35.0% of the TRR), kidney (13.9%) and liver (11.9%). The metabolite DCAP was found in milk (25.7%). DCHA, DCPD and DCNP each constituted less than 5% of the radioactivity in the tissues or milk.

Two metabolites totalling 37% of the TRR were isolated from liver extracts and identified as methylated 2,6-dichloro-4-nitro-3-glutathionylaniline and 4-amino-3-chloro-5-glutathionylacetanilide. The radioactivity in the post-extraction solids from liver and muscle was not due to sulfate or glucuronide conjugates. Most of the remaining radioactivity in the liver and muscle was released by protease hydrolysis. DCHA, DCNP, DCAA, and the glutathione conjugates were detected. Less than 10% of the radioactivity in the tissues and milk remained unidentified.

Laying hens were dosed for 3 days at a level of 0.15 mg/bird/day (0.075 mg/kg bw/day) and killed 24 hours after the last dose. Lipid-rich tissues such as egg yolk and fat contained almost exclusively dicloran with no detectable metabolites. Egg white contained approximately equal amounts of dicloran and DCNP. Residues in the livers consisted mainly of dicloran (54.8% of the ^{14}C), DCAA (24.2%) and DCNP (21.0%).

In a further study laying hens were dosed by capsule for 5 consecutive days at levels equivalent to 3.1 and 50 ppm in the diet (0.24 and 3.8 mg/kg bw) and killed 22 hours after the last dose. The total recovery of radioactivity was 84.5% and 91.6% for the low-dose and high-dose groups respectively. Over 80% of the administered radioactivity was eliminated in the excreta, of which 3-11% was from the parent compound. The entire egg production contained less than 0.6% of the total radioactivity. Less than 2% of the total ^{14}C was retained in all the other tissues combined. In the high-dose group the concentration of radioactivity as dicloran was 6.64 mg/kg in abdominal fat, 2.98 mg/kg in liver and 0.36 mg/kg in muscle. Egg yolks contained up to 2.38 mg/kg and egg whites up to 0.19 mg/kg.

Dicloran was the major component in the fat (94%), egg yolk (>80%) and egg white (up to 72%). DCNP was found in liver (45-58%), egg white (28-33%) and muscle (11-14%) but constituted less than 3% of the residue in egg yolk and fat. DCAA constituted up to 29% of the residue in muscle and 12% in liver, and DCNAP up to 33% and 2% respectively. Minor metabolites (individually less than 10% of the residues in tissues and eggs) were DCHA, DCPD, DCAP, dicloran sulfate, dicloran N-acetylcysteine conjugate and 2-acetylthio-6-chloro-4-nitroaniline.

Plant metabolism
Studies were carried out with peaches, potatoes and lettuce. There were no significant differences between the metabolic profiles of these crops. In summary, the metabolism of dicloran in plants involves reduction and acetylation of the nitro group, and deamination and hydroxylation of the amino group. Glutathione conjugation with simultaneous removal of one or both chlorine atoms was also shown to occur.

The metabolism of dicloran in peaches was investigated under field and glasshouse conditions. The peaches were treated with [^{14}C]dicloran formulated as a WP at the GAP concentration of 130 g ai/hl with simulated commercial application. The fruit were treated 3

times at 7-day intervals. The field-grown peaches were treated with a total of 0.54 mg ai/peach and the glasshouse peaches at the higher level of 0.77 mg/peach to aid identification.

At the final-harvest, 14 days after the third application, a total residue of 1.65 mg/kg dicloran equivalents was found in the field-grown peaches, of which 71.7% was extractable with solvent (hexane/acetone, acetonitrile, or acetonitrile/water). The glasshouse peaches at the final harvest 18 days after the third treatment contained 14.07 mg/kg dicloran equivalents of which 56.6% was solvent-extractable. A further 37.5% was recovered by processing the peach fibre, which contained 43.4% of the ^{14}C. The fibre was treated with 6M sodium hydroxide, then soxhlet-extracted successively with acetonitrile, ethyl acetate, and water, and finally hydrolysed with 4M hydrochloric acid to leave only 5.9% of the residue still bound to the fibre. After extensive clean-up and purification over 50% of the residue in the glasshouse peach fibre was identified using TLC, HPLC and LC-MS.

Free and conjugated dicloran with its conjugate formed the principal component in the residue (31.7% for glasshouse peaches and 51.3% for field peaches). The remainder comprised free and conjugated DCHA (10.9% glasshouse, 4.1% field) and DCAA with its conjugate (7.9% glasshouse, 1.2% field), and conjugated DCPD (6.5% glasshouse, 2.2% field). In addition, DCAP (5.5%), 2,6-DCP (2.8%) and DCNP (1.2%) were isolated after hydrolysis of the glasshouse peach fibre. The remainder of the residue in both the field and glasshouse peaches comprised many minor components, none of which constituted more than 3.6% of the total residue. There was no significant difference between the metabolic profiles of the field and glasshouse peaches.

Potato seed pieces were planted under field conditions and broadcast-treated with eight applications of [^{14}C]dicloran at approximately 1.8 kg ai/ha, slightly above the maximum US label rate. Mature tubers, vines and roots were harvested 14 days after the final application at a typical stage for dicloran treatment. The radioactive residues were isolated by extracting with polar and non-polar solvents. Extracted samples were hydrolysed with hydrochloric acid followed by sodium hydroxide. The hydrolysates were partitioned with methylene chloride. A range from 26.9 to 37% of the radioactive residue in the tubers, vines and roots was extracted with acetonitrile. Most of the unextracted radiocarbon was released by acid and basic hydrolysis and the remaining bound radioactivity found in the fibre was 2.7, 10.8 and 16.2% for tubers, vines and roots respectively.

Dicloran was found in all the samples. The metabolites DCNAP, DCAA, DCHA and 2,6-DCA were also present in some fractions. Unknown 1, a polar component found in the acid and/or base hydrolysates, accounted for 30-40% of the TRR. Unknown 1 is a mixture and appeared to consist of the glutathione conjugates of several dicloran metabolites. Five other unidentified components were detected at levels of #0.03 mg/kg as dicloran.

Lettuce seeds were planted under field conditions and broadcast-treated with [^{14}C]dicloran at 4.9 kg ai/ha, 10% above the maximum US label use rate, at a typical stage for dicloran application. The plants were grown according to typical agricultural field practices. Mature lettuce were harvested 20 days after the final application, and the radioactive residues isolated by extracting with polar and non-polar solvents. Extracted samples were hydrolysed with hydrochloric acid followed by sodium hydroxide, and the hydrolysates were partitioned with methylene chloride.

Seventy three per cent of the radioactive residue was extracted by acetonitrile, about 9% of the radiocarbon was contained in each of the acid and base hydrolysates, and about 8% of the TRR remained bound.

Dicloran was the main residue in the solvent extracts; a small amount of DCAP was also present. None of the residue in the aqueous phases resulting from the partitioning the acid and base hydrolysates was identified. All of the identified metabolites were in the organic extract of the acid hydrolysate: DCAP, DCPD, DCNAP, DCAA, 2,6-DCP and 2,6-DCA. Ten unidentified components were detected in the aqueous and organic phases after partitioning of the acid and base hydrolysates. None of these individually represented more than 5% of the TRR in the hydrolysate, and their total in all the hydrolysate fractions accounted for 12% of the TRR. Of these, unknown 1 represented 6.48% of the TRR and was later determined to be a mixture.

Environmental fate

In a study of aerobic degradation in soil the main residue in the soil extracts was the parent compound, with <1% of DCAA and DCPD also present. Other unidentified polar compounds constituted less than 3% of the applied radioactivity.

These results were confirmed in a field soil dissipation study in California, USA. Dicloran was applied at the rate of 4.5 kg/ha and the soil was analysed for residues of the parent compound, DCAA, DCHA and DCPD for a period of 18 months. Dicloran dissipated rapidly during the first two months of the study and the half-life then stabilized at approximately 35 days. No degradation products were detected.

Dicloran is degraded rapidly in flooded soils. In laboratory studies with [^{14}C]dicloran the half-life was less than 30 days under flooded conditions. The principal degradation product, arising from reduction of the parent compound, was DCPD. This did not accumulate but was further degraded to unextractable bound residues and CO_2.

In another study [^{14}C]dicloran was incubated in flooded sediment under anaerobic conditions. The decline of dicloran was biphasic with half-lives of 0.45 days in the initial fast phase (0-12 hours) and 3 days in the following slow phase (up to 14 days). Small amounts of nine products, including DCHA, DCPD, DCAA, DCNAP and a polymeric material, were detected. The radioactivity became progressively more bound and was associated with the humic and fulvic acid fractions of the sediment.

Photolysis studies were conducted on soil and in aqueous solutions and half-lives were calculated as 132 hours on soil and 24-41 hours in aqueous solution.

Analytical methods

Historically residues of dicloran in food commodities were determined by colorimetric methods, which were mainly used in the supervised trials carried out in the early 1960s. After the mid-1960s, dicloran residues were determined by GLC, usually with microcoulometric detection. Current GLC methods commonly use capillary columns with an ECD.

Colorimetric methods

Plant samples are macerated with benzene and filtered. The extract is evaporated to dryness, and if necessary lipid is removed by partitioning with acetonitrile and hexane. The residue is dissolved in benzene and cleaned up on a Florisil column eluted with benzene. The eluate is evaporated to dryness and the residue dissolved in acetone. Aqueous KOH is added and the residual dicloran determined by measuring the optical density against a control sample solution at 464 nm. The detection limits were about 0.05 mg/kg with general recoveries of about 75%. The methods can be applied to fruits and vegetables.

Information on the selectivity of the colorimetric determination of dicloran and its metabolites was not available, but the Meeting concluded that the colorimetric method used in the supervised trials was acceptable since the sample extracts were cleaned up by column chromatography and the predominant plant metabolites lacked the nitro group which may affect the absorbance significantly.

Early GLC methods

Sample preparation was similar to that in the colorimetric methods described above. The detection limit was about 0.01-0.5 mg/kg, with recoveries generally above 70%.

Current GLC methods

Analytical methods have been developed to determine dicloran in plant material, eggs, milk and animal tissues.

Plant residues are extracted with acetone or chloroform and isolated by partition between acetonitrile and hexane or petroleum ether. If necessary, further clean-up can be achieved by evaporating the acetonitrile layer to dryness, dissolving the resulting residue in acetone, adding an excess of water and sorbing the dicloran on a solid-phase disposable C-18 column which is eluted with toluene. Capillary gas chromatography with electron capture detection can be used for quantitative determination of the analyte. Limits of determination are in the range 0.02-0.05 mg/kg. Recoveries exceed 79%.

Residues in milk and animal tissues are extracted by steam distillation with hexane from acidified samples. The hexane extract is evaporated to dryness and the residue dissolved in petroleum ether. Capillary gas chromatography with electron capture detection is used for quantitative determination. The limit of determination is 0.03 mg/kg with recoveries above 73%.

Sample preparation is modified for eggs and fat. Eggs are blended with acetonitrile and the acetonitrile is partitioned with hexane. The acetonitrile layer is taken to dryness, then steam-distilled from an acid solution. Fat is dissolved in hexane and partitioned with acetonitrile. The acetonitrile layer is evaporated to dryness, the residue is dissolved in hexane and cleaned up on a Florisil column eluted with hexane before capillary column chromatography. The limit of determination is 0.03 mg/kg. Recoveries are more than 90%.

Multi-residue methods

Dicloran residues in food commodities can be determined by multi-residue methods. A sophisticated method developed in The Netherlands depends upon a modular arrangement to cover a wide range of pesticide-sample combinations. Recoveries were satisfactory in various

types of sample. Determination limits depend on the clean-up procedure. The method is suitable for monitoring dicloran residues in a range of food commodities.

Stability of pesticide residues in stored analytical samples

Storage stability studies were carried out with fruit, vegetables and animal products. Residues of dicloran in macerated fruits and vegetables were stable for the duration of storage, about 1 year. Dicloran was shown to be stable for eighteen months in bovine muscle and eggs, and for 25 months in fat, but in fortified liver only 55% of the added amount was found after eighteen months.

Definition of the residue

The plant metabolism studies showed that dicloran will be degraded gradually by reduction and acetylation of the nitro group, and deamination and hydroxylation of the amino group. Glutathione conjugation at the chlorine atoms may also occur. However, 14-20 days after the final application, dicloran was still the main residue in all the crops examined except potato tubers.

The rate of decrease of dicloran was slower after post-harvest than after pre-harvest treatment. The Meeting took into consideration the rate of decrease of dicloran in or on crops and concluded that the present definition of the residue as dicloran was appropriate both for enforcement and the estimation of dietary intake. The animal metabolism studies showed dicloran to be concentrated in lipid-rich tissues or products. Taking into consideration the residues found in animals and the octanol/water partition coefficient log $P_{ow} = 2.8$, the Meeting concluded that residues of dicloran should be categorized as fat-soluble.

Residues from supervised trials

Most of the old trials data were provided in summary form and sometimes without necessary information such as data on recoveries. The Meeting agreed not to use trials data which did not include information on recoveries unless recovery data were reported for other trials from which samples were analysed in the same laboratory at about the same time.

Apple and pears. Twenty four post-harvest trials on apples and 22 on pears were carried out in Spain (1990-95), at nominal concentrations of 0.035, 0.04 and 0.08 kg/hl. The residues were not proportional to the intended concentration however. Because the information on recoveries and the actual concentration of dicloran in the treatment solution was not available the Meeting could not estimate maximum residue levels.

Apricots. Fourteen supervised trials were carried out in the USA (1961-64). Two supervised trials with an application rate of 0.09 kg/hl and a PHI of 11 days were comparable to US GAP (0.12 kg/hl, 10 days PHI). The residues were 0.05 and 0.59 mg/kg. Another trial with an application rate of 0.12 kg/hl and PHI of 7 days also approximated US GAP, but there were no recovery data. The other eleven trials were not according to any reported GAP. There were too few trials to estimate a maximum residue level.

<u>Cherries</u>. Five pre-harvest trials were carried out in the USA (1963-64) and two in Canada (1964) but no relevant GAP was reported and the analysis of the sample in one Canadian trial was unsatisfactory.

Eleven post-harvest trials were carried out in the USA (1964), but the sample in nine trials were analysed with stems. The Meeting agreed not to use these results for the evaluation.

Two adequately conducted trials at 0.09 kg/hl were comparable with Argentinian, US and Australian GAP. The residues were 1.3 and 1.4 mg/kg. There were too few adequate trials to estimate a maximum residue level for cherries.

<u>Citrus fruits</u>. Twenty post-harvest trials on oranges and 17 on mandarins were carried out in Spain (1987-1996) at treatment concentrations of 0.03-0.08 kg/hl. Four of the trials, at 0.075 kg/hl (1990-91) and 0.08 kg/hl (1996), complied with Spanish post-harvest GAP (0.03-0.1 kg/hl, dipping or drenching), but the residues from the two groups were in different populations although the treatments by drenching were essentially the same. Because information on recoveries and the actual concentrations of dicloran in the treatment solution was not available the Meeting could not estimate a maximum residue level.

<u>Grapes</u>. One Italian and 25 US trials were reported.

The Italian trial carried out in 1982 did not comply with any reported GAP and there were no recovery data.

Two US trials in 1967 and two in 1984 with a WP application at 2.2 kg/ha followed by 1-3 dust applications at 2.0 kg/ha with 1-2 days PHI were comparable with US GAP (1.7-3.9 kg/ha for WP/SC or 2.0 kg/ha for D, 1 day PHI). The residues were undetectable, 0.29, 0.62 and 7.34 mg/kg at 1 or 2 days PHI.

One US trial in 1995 with a WP application at 4.5 kg/ha approximated US GAP (1.7-3.9 kg/ha for WP/SC): the residue was 1.23 mg/kg.

Six US trials in 1967 with a WP or D application at 2.0-2.2 kg/ha and 12-142 days PHI complied with US application rates. The residues ranged from undetectable to 0.70 mg/kg.

The samples from 14 US trials in 1980 rotted because the freezer broke down. The results could not be used for evaluation.

The Meeting concluded that there were too few satisfactory trials and recommended withdrawal of the existing CXL (10 mg/kg Po).

<u>Kiwifruit</u>. Three supervised trials were carried out in the USA (1979), but no relevant GAP was reported. The Meeting could not estimate a maximum residue level.

<u>Nectarines</u>. Three pre-harvest trials were carried out in the USA (1968), but the conditions (0.12 kg/hl with WP or 3.4 kg/ha with D, 1-day PHI) were not comparable with any reported GAP.

Five post-harvest and five combined pre- and post-harvest trials were carried out in the USA (1968) with a post-harvest application rate of 0.24 kg/hl. The concentration in the treatment

solution accorded with US post-harvest GAP but in six trials the treatment solution did not contain wax, whereas US GAP specifies the use of wax. The Meeting considered that these trials were not according to GAP since the use of wax could have a significant influence on the residue level.

The pre-harvest conditions in the combined trials (0.12 kg/hl of WP or 3.4 kg/ha of D, 1 day PHI) did not comply with US pre-harvest GAP (0.12 kg/hl, 4 applications, 10 days PHI) but the Meeting considered that as the residue levels would depend mainly on the post-harvest treatments the deviation of the pre-harvest treatments from GAP could be ignored. The residues in the four valid trials were 0.4, 0.5, 4.4 and 6.2 mg/kg.

One combined pre- and post-harvest trial with a 0.34 kg/hl post-harvest application did not comply with any reported GAP.

One Australian post-harvest trial complied with Australian post-harvest GAP (0.075 kg/hl dip or spray for stone fruit) but only the surface residue was measured. The Meeting concluded that there were too few trials to estimate a maximum residue level.

Peaches. One trial in Canada (1964) and one the USA (1966) were reported but there was no information on relevant GAP.

Twenty six post-harvest and 22 combined pre- and post-harvest trials were carried out in the USA (1966, 1975, 1976, 1988 and 1996), but there were very high residues in several untreated samples (maximum 11 mg/kg) and many reports were summaries without recovery data. The Meeting concluded that the trials could not be evaluated.

Two US (1966) post-harvest trials at application rates of 0.054-0.06 kg/hl approximated Australian post-harvest GAP for stone fruit (0.075 kg/hl dip or spray). The residues were 1.93 and 2.71 mg/kg.

In eight US combined post- and pre-harvest trials (1988, 1996) the post-harvest rate of 0.09 kg/hl complied with post-harvest GAP in Argentina (0.09-0.11 kg/hl dip or spray), Chile (0.09 kg/hl dip), the USA (0.09 kg/hl) and Australia but in six trials the pre-harvest applications were made one day before harvest whereas US pre-harvest GAP requires 10 days. The Meeting concluded that these trials were not according to GAP. The residues from the two trials which complied with pre- and post-harvest US GAP were 6.5 and 6.7 mg/kg.

One US pre- and post-harvest trial at the post-harvest rate of 0.018 kg/hl was comparable with Israel post-harvest GAP (0.023 kg/hl dip or spray), but not pre-harvest. The Meeting concluded that the data could be used for the estimation of a maximum residue level, since the residue from the pre-harvest application was much lower than from the post-harvest treatment. The residue was 2.8 mg/kg. Other US post-harvest trials at 0.036 and 0.15 kg/hl were not according to reported GAP.

One Canadian post-harvest trial (1966) at 0.36 kg/hl did not comply with any reported GAP. Four post-harvest supervised trials in Australia (1971, 1973) were not adequately reported or not properly conducted. Four Spanish post-harvest trials (1995) were reported without recovery data and no relevant GAP was available.

The Meeting concluded that there were too few trials to estimate a maximum residue level and recommended the withdrawal of the CXL for peach (15 mg/kg).

Plums. One pre-harvest trial in the USA (1995) was not according to any reported GAP.

Three of four post-harvest trials in the USA (1986, 1995) at 0.24 kg/hl or 1.1 kg/hl complied with US post-harvest GAP (0.24 kg/hl, 113-190l/h, 1 kg ai/25000 kg of fruit, or 0.9-1.1 kg/hl, 19-30 l/h, 1 kg/56000-67000 kg of fruit). The residues were 2.4, 2.4 and 6.1 mg/kg.

Four post-harvest trials in Spain (1995) were not according to any reported GAP and recovery data were not reported.

There were too few trials to estimate a maximum residue level. The Meeting recommended the withdrawal of the existing CXL for plums (including prunes) of 10 mg/kg.

Strawberries. Eight supervised trials in Spain (1995) lacked recovery data. Twelve trials in the USA (1963) did not comply with reported GAP.

The Meeting could not estimate a maximum residue level and recommended withdrawal of the existing CXL for strawberry (10 mg/kg).

Carrots. Eight pre-harvest trials in the USA (1995) were not comparable with any reported GAP. Five post-harvest trials in the USA (1965) at 0.09 and 0.10 kg/hl complied with US post-harvest GAP (0.09 kg/hl dip). The residues were 4.92, 5.94, 6.11 and 10.84 (2) mg/kg.

In six pre- and six pre- and post-harvest trials in the USA (1983) the residues in untreated samples were unreasonably high. The Meeting concluded that they could not be evaluated.

Two Israel post-harvest trials were reported without recovery data and could not be used for evaluation.

The residues in the five relevant trials were 4.92, 5.94, 6.11 and 10.84 (2) mg/kg.

The Meeting estimated a maximum residue level of 15 mg/kg and an STMR of 6.11 mg/kg for carrot.

Cucumbers and gherkins. The conditions in three of five indoor trials on cucumbers in the USA in 1965 (0.09-0.15 kg/ha, 1 and 8-21 days PHI) were according to US GAP (0.12 kg/ha, 1 day PHI). The residue at the GAP PHI was 1.79 mg/kg and at 8-21 days 0.18 and 0.22 mg/kg.

Two supervised trials on gherkins in The Netherlands (1972) at 1.6 and 1.8 kg/ha, 3 days PHI complied with GAP (1.4 kg/ha, 5 applications, 3 days PHI) except in the number of applications. The Meeting concluded that the trials could be used for evaluation because the effect of repeated application would be offset by growth dilution.

The Meeting could not estimate a maximum residue level for cucumbers or gherkins because there were too few trials.

Lettuce. Eighteen glasshouse trials with foliar and/or soil treatments in the USA (1971) lacked necessary information such as formulation type and recovery data. The Meeting could not evaluate them.

One of three field trials in the USA (1964) at 3.4 kg/ha, 26 days PHI, complied with US GAP (0.84-4.5 kg/ha, 14 days PHI) and the residue was 0.13 mg/kg. The other two trials were not comparable with any reported GAP.

One trial was carried out in the UK (1972) but no relevant GAP was reported.

Four trials in Belgium (1975, 1977) and six in The Netherlands (1970-71) were reported without recovery data and could not be used for evaluation.

The Meeting could not estimate a maximum residue level as there was only one satisfactory trial, and recommended withdrawal of the CXL for head lettuce (10 mg/kg).

Onions. Four trials with spring planting and six with autumn planting were carried out in the USA (1962, 1963, 1983 and 1986). The application rate in three of the spring trials (11 kg/ha at planting) was slightly higher than Canadian GAP (5.1-8.3 kg/ha for spring planting) but the Meeting agreed that the data could be used for estimation of a maximum residue level because the residues were low: 0.02, 0.07 and 0.11 mg/kg. The other spring trial was at the excessive application rate of 34 kg/ha.

Four of the autumn trials (28-35 kg/ha at planting) complied with Canadian GAP (27-33 kg/ha at planting). The residues were <0.05, 0.06, 0.11 and 0.19 mg/kg. The other two autumn planting trials with 9 applications of 2.2 kg/ha, 7-8 days PHI, exceeded the total application limit of US GAP (1.3-2.2 kg/ha, up to 2.8 kg/ha per season, 14 days PHI) and the PHI was too short, but the Meeting concluded that the trials could be evaluated because the residues in both were below the limit of determination, <0.1 mg/kg.

One trial in Finland and two US post-harvest trials were reported but without relevant GAP.

The residues from the nine relevant trials were 0.02, <0.05, 0.06, 0.07,<0.1 (2) 0.11 (2) and 0.19 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.1 mg/kg for bulb onion.

Tomatoes. Three glasshouse trials were carried out in the USA (1962). One at 0.07 kg/hl, 10 days PHI, with a residue of 0.62 mg/kg complied with US glasshouse GAP (0.09 kg/hl, 0.84 kg/ha, 10 days PHI and another with a residue of 0.89 mg/kg (0.13 kg/hl, 5 days PHI) approximated Canadian glasshouse GAP (0.13 kg/hl, 1 day PHI).

One glasshouse fumigation trial in the UK in 1972 (1.3 kg/ha, 2 days PHI) complied with GAP in The Netherlands (1.4 kg/ha, 5 applications, 3 days PHI). The Meeting could only regard the trial as supplementary because only the surface residue was determined.

Twelve field trials and four post-harvest trials were carried out in the USA (1963) but no relevant GAP was reported.

There were too few suitable trials to estimate a maximum residue level and the Meeting recommended withdrawal of the CXL for tomato (0.5 mg/kg)

Common beans. Thirty supervised trials were carried out in the USA (1964, 1965). Four trials in 1964 at application rates of 3.4 and 3.6 kg/ha and 4-7 days PHI accorded with US GAP (3.4 kg/ha, 2 days PHI). The residues were 9.67-17.1 mg/kg.

Three of the trials in 1965 at 3.4 kg/ha and 2 days PHI which also complied with US GAP gave residues of 0.45, 4.90 and 9.8 mg/kg.

One trial with a bush variety at 3.4 kg/ha with a dust formulation and another at 1.7 kg/ha with a WP formulation accorded with US GAP for the bush variety (2.7 kg/ha for dust, 1.9 kg/ha for WP, 2 days PHI). The residues were 0.61-1.44 mg/kg.

Twenty one other trials were not in accord with reported GAP.

Four trials in Australia (1963,1971) were reported only in summary form without necessary information, and could not be used for the estimation of a maximum residue level.

The Meeting concluded that there were too few satisfactory trials to estimate a maximum residue level.

Processing studies

Processing studies were carried out on grapes, plums and tomatoes. Processing factors for grapes were 1.34, 1.1 and 0.47 to juice, 2.10 and 0.98 to wet pomace, <0.1 and <0.2 to raisin waste and <0.1, <0.2 and <0.04 to raisins.

The raisins in the processing trials were sun-dried. In view of the photodegradability of dicloran, it was assumed that the very low residue of dicloran in the raisin waste and raisins was mainly due to photodegradation. The Meeting considered that a processing factor of zero for raisin waste and raisins could apply only to sun-dried raisins.

The mean processing factors were 1.1 to juice, 1.5 to wet pomace and zero to sun-dried raisin waste and raisins.

The processing factor from plums to dried prunes was 1.8 and the processing factors for tomatoes were 1.9 to paste and 1.1 to purée.

DIETARY RISK ASSESSMENT

STMRs have been estimated for 2 commodities. The International Estimated Daily Intakes for the five GEMS/Food regional diets were in the range 0-20% of the ADI. The Meeting concluded that the intake of residues of dicloran resulting from its uses that have been considered by the JMPR   is   unlikely   to   present   a   public   health   concern.

4.8 DIMETHOATE (027)/OMETHOATE (055)/FORMOTHION (042)

RESIDUE AND ANALYTICAL ASPECTS

Dimethoate, *O,O*-dimethyl *S*-methylcarbamoylmethyl phosphorodithioate, is a contact and systemic insecticide typically applied as an emulsifiable concentrate (EC) diluted in water at 0.3 – 0.7 kg ai/ha. The toxicology was reviewed in 1996 and an ADI of 0.002 mg/kg bw was allocated to the sum of dimethoate and omethoate, expressed as dimethoate. Omethoate, *O,O*-dimethyl *S*-methylcarbamoylmethyl phosphorothioate, is a metabolite of dimethoate and a systemic pesticide. Since 1986, the JMPR has estimated separate maximum residue levels for dimethoate and omethoate. Formothion, *S*-[formyl(methyl)carbamoylmethyl] *O,O*-dimethyl phosphorodithioate, is metabolized by plants to dimethoate and omethoate. No Codex MRLs or draft MRLs exist for formothion. Its toxicology was last reviewed in 1969 but no ADI was allocated.

The three compounds are now re-evaluated within the CCPR Periodic Review Programme, but as no information on formothion was submitted the evaluation refers only to dimethoate and omethoate.

Animal metabolism

Metabolism studies were reported for rats, goats and chickens. In the rat studies, three metabolites were identified in urine: *O,O*-dimethyl hydrogen phosphorothioate (7%), *O,O*-dimethyl hydrogen phosphorodithoate (25%) and dimethoate carboxylic acid (36%).

Leghorn chickens were given oral doses (0.9 mg/kg bw/day) of [*methoxy*-^{14}C]dimethoate for 7 days. The radioactive residue levels in the liver, muscle, fat, egg yolk (last day) and egg white (last day) were 0.64, 0.09, 0.038, 0.34 and 0.15 mg/kg respectively. The liver residue (0.82 mg/kg as dimethoate) was shown to consist mainly of phosphorylated natural products (33% of the TRR), omethoate (10% of the TRR) and dimethoate carboxylic acid (16% of the TRR). Phosphorylated natural products were significant proportions of the residue in muscle (36-46% of the TRR), egg white (50%), and egg yolk (35%). Dimethoate was not found in any of the samples. Omethoate was absent from muscle and fat, but found in egg whites at 3% of the TRR (0.004 mg/kg) and liver after protease treatment.

Dimethoate labelled on the methoxy carbons was administered orally to goats once daily for 3 consecutive days at 1.6 mg/kg bw/day. The concentrations of ^{14}C as dimethoate were liver 1.2 mg/kg, kidney 0.15 mg/kg, muscle 0.07 mg/kg, fat 0.05 mg/kg, and milk (48–60 h) 0.23 mg/kg. Much of the residue was characterized as phosphorylated natural products, 35% of the TRR in the liver, 32% in the kidneys, 53% in the muscle, and 53% in the milk. Dimethoate was not found in any sample and omethoate was found only in the liver (0.12 mg, 10% of the TRR) after protease treatment of the extraction residue. Urine was shown to contain dimethoate carboxylic acid, dimethyl hydrogen phosphorothioate and dimethyl hydrogen phosphate. The metabolism in both poultry and ruminants is consistent with the formation of the sulfoxides of omethoate and dimethoate carboxylic acid. The sulfoxides would react with nucleophiles, leading to phosphorylated natural products.

The Meeting concluded that the metabolism of dimethoate and omethoate in animals is adequately understood.

Plant metabolism

The metabolism of [^{32}P]dimethoate in sugar beet, maize, cotton, peas, potatoes and beans has been reported. The reports were summaries which did not provide the customary detail. Generally, the main components of the radiolabelled residue were dimethoate, omethoate, dimethoate carboxylic acid, dimethyl hydrogen phosphate and *O,O*-dimethyl hydrogen phosphorodithioate, indicating oxidation to omethoate, omethoate carboxylic acid and dimethoate carboxylic acid, and cleavage of the P-S linkage either before or after oxidation. A difference from animal metabolism is that the sulfoxide is apparently not formed.

Dimethoate is water-soluble and considerable translocation of foliar dimethoate might be expected. The metabolism studies with maize, cotton, potatoes and peas indicated the extent of penetration of residues into the leaves, but no detailed study on residue translocation was reported.

The Meeting concluded that the plant metabolism studies were incomplete, both because a detailed study was not provided and because translocation was not adequately addressed.

Environmental fate

Studies were reported on confined rotational crops, degradation, dissipation and mobility in soil, adsorption and desorption, photodegradation on soil, and aquatic dissipation.

In the confined rotational crop study, soil was treated with [^{14}C]dimethoate at a rate of 0.56 kg ai/ha. Lettuce, turnips and wheat were planted after 30 and 120 days and grown to maturity. The radioactive residues were highest in the 30-day plantings, ranging from 0.008 mg/kg as dimethoate in turnip roots to 0.045 mg/kg in wheat straw. A substantial proportion of each crop sample (30-60% of the TRR) was characterized as polar compounds or polar hydroxy compounds. The crops planted after 120 days showed very low radioactive residues, ranging from 0.001 mg/kg in turnip roots to 0.02 mg/kg in wheat straw.

The Meeting concluded that inadvertent residues in rotational crops would not be significant, that the low residue levels consisted mainly of polar metabolites and that dimethoate and omethoate concentrations under field conditions would be below 0.01 mg/kg, a typical lower limit of quantification.

When the degradation of [^{14}C]dimethoate in soil under aerobic and anaerobic conditions was studied its half-life in sandy loam soil under aerobic conditions was 2.4 days, with two products identified: dimethyl hydrogen phosphorothioate and *O*-demethyl-dimethoate. Radioactive carbon dioxide accounted for 75% of the applied radioactivity after 180 days, indicating mineralization as the ultimate fate. The half-life of dimethoate under anaerobic conditions (after two days of aerobic conditioning) was 4 days. The same products were identified.

Soil dissipation studies in the UK and the USA showed that dimethoate does not migrate readily below the top 15 cm and that the half-life is 2–4 days. In other studies half-lives of

dimethoate in soil were 9.8 days in bean plots, 6.0 days in grape plots and 7.8 days in bare soil. A lysimeter test in Germany showed that radiolabelled dimethoate had little tendency to migrate downward through the soil, with 17% of the recovered radioactivity in the top 12 cm.

The Meeting concluded that dimethoate was degraded at a moderate rate in soil with a half-life of about 4 days, and that it migrates only slowly under normal agricultural conditions.

Leaching studies were reported with four types of soil. Dimethoate is readily leached, with the rate of leaching decreasing with increasing loam content of the soil, but leaching is offset by the short half-life in soil.

The half-lives of dimethoate in two water/sediment systems were 13 and 17 days. The only identified product was demethyl-dimethoate.

In a study of the photodegradation of dimethoate on soil the half-life in sunlight was 10 days, but the half-life in the dark was 8 days. The Meeting concluded that photodegradation was not significant.

Methods of residue analysis

Adequate methods exist for data collection, monitoring, and the enforcement of MRLs. The methods are similar and involve maceration of the substrate with solvent, typically acetone/water, and extraction of the (concentrated) macerate with chloroform or methylene chloride. Extracts are sometimes cleaned up on a column of celite or Florisil or by GPC. Some Australian methods use sweep co-distillation with ethyl acetate after the chloroform extraction, but this step destroys omethoate. The final extracts are analysed on a gas chromatograph equipped with a capillary column and a flame photometric detector (FPD). The typical lower limits of quantification are 0.01 mg/kg for both dimethoate and omethoate.

Extensive recovery data were presented for the most common methods.

Stability of stored analytical samples

The stabilities of dimethoate and omethoate on fortified analytical samples of tubers, oranges, sorghum grain, sorghum forage and cotton seed during frozen storage were determined. The Meeting concluded that dimethoate was stable on all these commodities for at least 1.7 years and that omethoate was also stable on all of them with the possible exception of cotton seed, from which a 20% loss may have occurred during the first 5 months with no subsequent decrease.

Definition of the residue

On the basis of the metabolism of dimethoate in plants and animals, the conclusions of the 1996 JMPR on the toxicology, the available analytical methods and the lack of significant data on omethoate *per se*, the Meeting concluded that the residue for compliance with MRLs should be defined as dimethoate. The MRLs for omethoate should be considered for withdrawal because no data were reported to support omethoate MRLs. For the estimation of dietary intake the residue is based on the sum of dimethoate and omethoate, each considered separately.

Residues resulting from supervised trials

Supervised trials were reported on oranges (post-harvest), apples, pears, cherries, plums, blueberries, strawberries, grapes, currants, avocados (post-harvest), litchis (post-harvest), chives, leeks, Brussels sprouts, cabbages, cauliflowers, broccoli, kohlrabi, cucumbers (post-harvest), zucchini (post-harvest), rockmelons (post-harvest), watermelons (post-harvest), tomatoes, sweet peppers, kale, spinach, chard, lettuce, peas, French beans, mung beans, potatoes, turnips, sugar beet, carrots, long radishes, asparagus, sorghum, barley, maize, wheat and witloof chicory.

Oranges. Post-harvest trials were reported from Australia. Only one residue was reported at the specified 0-day post-treatment holding period. The data were insufficient to estimate a maximum residue level or STMR. The Meeting recommended withdrawal of the existing CXLs for dimethoate and omethoate in citrus fruits.

Pome fruit (apples and pears). Supervised field trials on apples in The Netherlands and Germany were reported. Two trials in The Netherlands and 10 in Germany complied with GAP for apples and pears (3 x 0.02 kg ai/hl (0.30 kg ai/ha), 21-day PHI, and 3 x 0.04 kg ai/hl (0.6 kg ai/ha), 21-day PHI respectively). Two trials were reported with the use of omethoate on apples in The Netherlands, with residues as high as 0.1 mg/kg, but this is insufficient for the estimation of residues from the use of omethoate *per se*. Four supervised field trials in Germany with foliar application of dimethoate to pears complied with GAP. The residues of dimethoate in apples and pears in rank order were 0.01, 0.03, <0.05 (5), 0.06, 0.07, 0.08, 0.10, 0.14, 0.15, 0.16, 0.26 and 0.30 mg/kg. The residues of omethoate from the use of dimethoate were 0.04, <0.05 (6), 0.05 (2), 0.06 (2), 0.07, 0.08 and 0.13 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 0.5 mg/kg and an STMR of 0.065 mg/kg, and an STMR for omethoate of 0.05 mg/kg.

Cherries. In four supervised trials in the USA the application rate was about 7.7 times the GAP rate. Ten trials in Germany complied with GAP (3 x 0.04 kg ai/hl (0.6 kg ai/ha), 21-day PHI). The residues of dimethoate were <0.02, <0.05, <0.05, 0.03, 0.06, 0.06, 0.08, 0.13, 0.19 and 1.5 mg/kg, and those of omethoate were <0.01, 0.03, 0.05, 0.11, 0.27, 0.27, 0.28, 0.28, 0.28 and 0.46 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 2 mg/kg, and STMRs for dimethoate of 0.06 mg/kg and for omethoate of 0.27 mg /kg.

Plums. Four replicate trials in The Netherlands could not be used to estimate a maximum residue level because the PHI of 14 days was less than the GAP 21-day PHI and one of the trials showed a significant residue at 14 days. Twenty-three trials according to GAP (3 x 0.04 kg ai/hl (0.6 kg ai/ha), 14-day PHI) were reported from Germany, with residues of dimethoate of <0.02, <0.05 (6), 0.05, 0.06, 0.07, 0.09, 0.10, 0.11, 0.12 (2), 0.13 (2), 0.15, 0.24, 0.28, 0.36, 0.46 and 0.75 mg/kg and of omethoate of <0.02, <0.05 (10), 0.05 (3), 0.07, 0.08, 0.12 (2), 0.14, 0.17 and 0.22 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 1 mg/kg , an STMR for dimethoate of 0.10 mg/kg and an STMR for omethoate of 0.05 mg/kg.

Blueberries. Supervised field trials were reported from the USA. There is no current GAP.

Strawberries. Three varieties were treated at various rates in replicate plots in Australia, but the combined residue of dimethoate and omethoate was measured and only 3 residues were from GAP conditions (0.30 kg ai/ha, 1-day PHI). There were insufficient data to estimate a maximum residue limit or STMR and the Meeting recommended withdrawal of the CXL for strawberry.

Grapes. Supervised field trials were reported from France and Germany, but without corresponding GAP. GAP for The Netherlands is 3 x 0.02 kg ai/hl (0.24-0.30 kg ai/ha), 21- or 28-day PHI. GAP for Hungary is 0.04 kg ai/hl (0.32 kg ai/ha) with a 14-day PHI. Seven trials in France were close to these conditions. The residues were 0.11, 0.18, 0.21, <u>0.48</u>, 0.53, 0.89 and 1.2 mg/kg of dimethoate and <0.05, <0.05, 0.08, <u>0.11</u>, 0.11, 0.14, 0.19 mg/kg of omethoate. The Meeting estimated a maximum residue level for dimethoate of 2 mg/kg, and STMRs for dimethoate of 0.48 mg/kg and for omethoate of 0.11 mg/kg.

Currants. Supervised field trials were carried out in Germany but no GAP was reported. GAP for The Netherlands is 3 x 0.24 kg ai/ha, 21-day PHI, but none of the German trials complied with it. The Meeting recommended withdrawal of the existing CXL for currant, black.

Sub-tropical fruits with inedible peel. Two supervised trials each on avocados, mangoes and litchis, post-harvest dips or high-volume sprays, were reported from Australia. The residues belonged to different populations and could not be combined for evaluation. There were therefore insufficient data to estimate maximum residue levels or STMRs.

Leeks. One supervised trial in Germany complied with GAP for The Netherlands, assuming an application of 1000 l of spray solution per ha. One trial was inadequate to estimate a maximum residue level or STMR.

Onions. Seven supervised field trials according to GAP (2 x 0.24 kg ai/ha, 14-day PHI) were reported from Germany. The residues were <0.01, 0.01, <0.02, <u><0.02</u>, 0.04, <0.05 and <0.05 mg/kg of dimethoate and <0.01, <0.01, <0.02, <u><0.02</u>, <0.02, <0.05 and <0.05 mg/kg of omethoate. The Meeting estimated a maximum residue level of 0.05* mg/kg for dimethoate and STMRs of 0.02 mg/kg for both dimethoate and omethoate.

Cauliflowers. Nine field trials on cauliflowers in Germany were not according to GAP. Eight trials in the UK complied with UK GAP for brassica vegetables (6 x 0.40 kg ai/ha, 7-day PHI). The residues were 0.02, 0.02, 0.03, <u>0.04</u>, <u>0.09</u>, 0.09, 0.11 and 0.34 mg/kg of dimethoate and <<u>0.01</u> (8) and 0.01 mg/kg of omethoate. The Meeting estimated a maximum residue level of 0.5 mg/kg for dimethoate and STMRs of 0.065 mg/kg for dimethoate and 0.01 mg/kg for omethoate.

Broccoli. Only one supervised trial was reported, which did not comply with GAP. A maximum residue level or STMR could not be estimated.

Brussels sprouts. Four supervised field trials in Germany (GAP 0.24 and 0.36 kg ai/ha, 14-day PHI), three in The Netherlands (GAP 0.2 kg ai/ha repeated, 21-day PHI), one in the USA (GAP 6 x 1.12 kg ai/ha, 10-day PHI) and eight in the UK (GAP 6 x 0.40 kg ai/ha, 7-day PHI) complied with national GAP. The residue in the US trial (3.12 mg/kg) was an outlier and was not included. In one of the UK trials there was an unacceptable concentration of residue in the control. In the remaining trials the residues of dimethoate were 0.005, 0.009, 0.03, <0.05, <0.05, 0.05, <u>0.06</u>, <u>0.07</u>, 0.08, 0.10, 0.11, 0.17, 0.21 and 0.46 mg/kg, and those of omethoate were <0.01, <0.01, <0.01, 0.01, 0.02, 0.03, <u>0.03</u>, 0.04, 0.07, 0.08, 0.09, 0.16, 0.30 mg/kg (omethoate was not determined in one of the German trials). The Meeting estimated a maximum residue level of 1 mg/kg for dimethoate and STMRs of 0.065 mg/kg for dimethoate and 0.03 mg/kg for omethoate.

Cabbage. Twelve supervised field trials on cabbages in Germany (8 Savoy and 4 head) complied with GAP (0.4 kg ai/ha, 42-day PHI or 2 x 0.24 kg ai/ha, 14-day PHI), as did eight on head

cabbages in the UK (6 x 0.40 kg ai/ha, 7-day PHI) and two in The Netherlands (0.2 kg ai/ha repeated, 21-day PHI). The residues in head cabbages were in two population groups, those in Germany and The Netherlands ranging from <0.01 to 0.07 mg/kg dimethoate and <0.01 to 0.02 mg/kg omethoate and those in the UK ranging from 0.04 to 1.2 mg/kg dimethoate and <0.01 to 0.64 mg/kg omethoate. In the UK trials only one residue (of omethoate) was below the LOD. In the German and Dutch trials, 4 of 6 dimethoate residues and 4 of 5 omethoate residues were below the LOD. The residues of dimethoate in the population with highest residue levels (UK) were 0.04, 0.07, 0.14, 0.25, 0.67, 0.82, 0.99 and 1.2 mg/kg, and those of omethoate in the same population were <0.01, 0.02, 0.04, 0.05, 0.28, 0.35, 0.63 and 0.64 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for dimethoate and STMRs of 0.46 mg/kg for dimethoate and 0.165 mg/kg for omethoate on head cabbages except Savoy cabbage.

The residues of dimethoate on Savoy cabbages in Germany were <0.01 (2), <0.02 (4) and <0.05 (2) and of omethoate <0.01 (2), <0.02 (2), 0.13, 0.17, 0.31 and 0.66 mg/kg. The Meeting estimated maximum residue levels of 0.05* mg/kg for dimethoate and STMRs of 0.02 mg/kg for dimethoate and of 0.075 mg/kg for omethoate on Savoy cabbage.

Kohlrabi. Two supervised trials in Germany complied with UK GAP but were insufficient to estimate a maximum residue level or STMR.

Cucumbers, zucchini, cantaloupes. A single trial on each in Australia with post-harvest treatment was reported. One trial is insufficient for the estimation of a maximum residue level or STMR.

Watermelons. Two post-harvest trials in Australia at maximum GAP (400 mg/l dip, 0-day post-treatment interval) were inadequate for the estimation of a maximum residue level or STMR.

Tomatoes. Six post-harvest trials in Australia were according to GAP (400 mg dimethoate/l solution dip, 7-day post-treatment interval), but only dimethoate was determined. Fourteen trials in Germany complied with GAP (3 foliar applications, 0.24, 0.36, 0.48 kg ai/ha or 0.04 kg ai/hl, 3-day PHI). The 20 dimethoate residues in rank order were 0.01, 0.05 (2) 0.06 (2), 0.08, 0.12, 0.15, 0.19, 0.20, 0.22, 0.24, 0.26 (2), 0.31, 0.34, 0.41, 0.42, 0.80 and 1.3 mg/kg. The 14 omethoate residues were 0.01, 0.03 (3), 0.04, <0.05, 0.05 (3), 0.06, 0.09, 0.13, 0.14 and 0.32 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for dimethoate and STMRs of 0.21 mg/kg for dimethoate and 0.05 mg/kg for omethoate.

Sweet peppers. Three trials in Australia with post-harvest dip treatment of sweet peppers were according to the Queensland GAP of 0.04 kg dimethoate per 100 l of dipping solution with no specified holding period. The Meeting concluded that three trials were inadequate for the estimation of maximum residue levels or STMRs and recommended withdrawal of the existing CXL for peppers.

Kale. Eight supervised field trials were carried out in Germany, but no relevant GAP was reported. The Meeting could not evaluate the data and recommended withdrawal of the existing CXL.

Chard, leaf lettuce. One trial in Germany on each crop was reported but without relevant GAP. The data were inadequate.

Head lettuce. Twelve supervised trials reported from Germany complied with GAP (2 x 0.24 kg ai/ha, 21-day PHI). One trial was not evaluated because the total residues increased substantially from 7 to 14 days and the dimethoate/omethoate ratio at 14 and 21 days was quite different from that in the other trials. The residues of dimethoate were <u><0.02</u> (7), <0.05 (2), 0.09 and 0.24 mg/kg, and those of omethoate were <0.02 (3), 0.02, <u>0.03</u>, <u>0.03</u>, <0.05, <0.05, 0.05, 0.06 and 0.10 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg for dimethoate and STMRs of 0.02 mg/kg for dimethoate and 0.03 mg/kg for omethoate.

Spinach. Two of four supervised trials in Germany complied with the GAP of The Netherlands (0.20 kg ai/ha, 21-day PHI). The Meeting considered the data inadequate and recommended the withdrawal of the existing CXL.

Peas. Supervised trials according to GAP were reported from Denmark (2 trials; GAP 0.32 kg ai/ha, 14-day PHI); the UK (3 trials; GAP 6 x 0.34 kg ai/ha, 14-day PHI); Germany (3 trials according to UK GAP); The Netherlands (2 trials; GAP 3 x 0.20 kg ai/ha, 21-day PHI) and the USA (4 trials; GAP 0.19 kg ai/ha, 0-day PHI). The dimethoate residues were <0.01, 0.018, 0.026, 0.027, 0.03, 0.04, <u>0.04</u>, <u>0.09</u>, 0.19, 0.27, 0.36, 0.44, 0.50 and 0.64 mg/kg, and the omethoate residues <0.01, <0.01, 0.015, <u>0.02</u> (5), 0.022, 0.026, 0.03, 0.04, 0.052 and 0.20 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg for dimethoate and STMRs of 0.065 mg/kg for dimethoate and 0.02 mg/kg for omethoate.

Beans. Three trials on French beans in Germany were not according to GAP. A single trial on mung beans in the USA complied with GAP (0.56 kg ai/ha, 0-day PHI). The data on beans were inadequate.

Potatoes. Nine trials in Germany (GAP 0.24 kg ai/ha, 14-day PHI) and one each in the UK (GAP 2 x 0.34 kg ai/ha), The Netherlands (GAP 4 x 0.20 kg ai/ha, 21-day PHI) and Denmark (GAP 0.30–0.32 kg ai/ha, 14-day PHI) were according to national GAP. The residues of dimethoate were <u><0.01</u> (6), <u>0.01</u>, <0.02 (4) and 0.02 mg/kg and those of omethoate were <u><0.01</u> (6), <u>0.01</u>, <0.02 (4) and 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg for dimethoate and STMRs of 0.01 mg/kg each for dimethoate and omethoate.

Turnips, turnip greens. Seven trials in the USA complied with GAP (0.28 kg ai/ha, 14-day PHI). The residues of dimethoate and omethoate in the roots were <0.1 mg/kg in all the samples. The Meeting estimated a maximum residue level for dimethoate of 0.1 mg/kg and STMRs of 0.1 mg/kg each for dimethoate and omethoate in garden turnips.

The residues of dimethoate on the turnip tops (greens) were <u><0.1</u> (5), 0.25 and 0.55 mg/kg and those of omethoate were <u><0.1</u> (6) and 0.20 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg for dimethoate and STMRs of 0.1 mg/kg each for dimethoate and omethoate in turnips greens.

Sugar beet roots and tops. Two trials in the UK complied with UK GAP (2 x 0.40 kg ai/ha, before June 30) and one each in Denmark and The Netherlands with Dutch GAP (3 x 0.40 kg ai/ha, no PHI). Most of the six trials in Germany (GAP 0.16 kg ai/ha, 35-day PHI) were at about twice the GAP rate, but could be included in the evaluation because the residues were at the limit of quantification at the appropriate PHI. The residues of dimethoate in the roots were <u><0.01</u> (7), <0.02 (2) and <0.05 mg/kg, and those of omethoate were <u><0.01</u> (7), <0.02 and <0.05 mg/kg. The

Meeting estimated a maximum residue level for dimethoate of 0.05 mg/kg and STMRs for dimethoate and omethoate of 0.01 mg/kg each in sugar beet (roots).

The residues of dimethoate on the tops were <0.01 (2), <0.02, <u>≤0.05</u>, 0.06 and 0.10 mg/kg and those of omethoate <0.01 (2), <0.02, <u>≤0.05</u>, 0.05 (2), and 0.17 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 0.1 mg/kg and STMRs for dimethoate and omethoate of 0.05 mg/kg each for sugar beet leaves or tops.

<u>Carrots</u>. Only two of 14 trials in Germany complied with GAP (2 x 0.24 kg ai/ha, 14-day PHI). The Meeting recommended withdrawal of the existing CXL.

<u>Radishes</u>. Twenty trials were carried out in Germany, but no GAP was reported for Germany or any other country. The Meeting could not estimate a maximum residue level or STMR.

<u>Asparagus</u>. In four supervised field trials in the USA which were according to GAP (5 x 0.56 kg ai/ha, 180-day PHI) the residues of dimethoate were <u><0.02</u> (3) and <0.03 mg/kg, and those of omethoate were <u><0.02</u> (3) and <0.12 mg/kg. In three additional trials at twice the GAP rate the residues of dimethoate and omethoate were all below the LOD (<0.02 mg/kg). The Meeting estimated a maximum residue level for dimethoate of 0.05* mg/kg and STMRs for dimethoate and omethoate of 0.02 mg/kg each.

<u>Barley grain and straw</u>. Supervised field trials according to GAP were reported from Denmark (GAP 0.80 kg ai/ha; 1 trial), The Netherlands (GAP 0.20 kg ai/ha, 14-day PHI; 2 trials), Germany (2 trials according to Dutch GAP) and the UK (GAP 4 x 0.34 kg ai/ha, 14-day PHI; 3 trials). The residues of dimethoate in the grain were 0.03, 0.06, 0.07, <u>0.10</u>, <u>0.41</u>, 0.49, 0.73 and 1.43 mg/kg and those of omethoate <0.01 (2), <u>0.01</u> (2<u>)</u>, <u>0.02</u>, 0.03, 0.06 and 0.10 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 2 mg/kg and STMRs of 0.255 mg/kg for dimethoate and 0.015 mg/kg for omethoate in barley grain.

The residues of dimethoate on the straw were 0.09, 0.13, 0.20, <u>0.44</u>, <u>0.55</u>, 0.88, 1.59 and 2.81 mg/kg and those of omethoate <0.01, 0.01, <u>0.03</u> (3), 0.07 (2) and 0.11 mg/kg. The Meeting estimated STMRs for straw of 0.495 mg/kg for dimethoate and of 0.03 mg/kg for omethoate.

<u>Maize</u>. Two supervised field trials were reported from Denmark, but the PHIs were at least twice the GAP interval. The Meeting could not estimate a maximum residue level or STMR.

<u>Sorghum (grain, forage and hay)</u>. Six trials in the USA complied with GAP (3 x 0.56 kg ai/ha, 28-day PHI). All the residues of dimethoate and omethoate in the 5 samples of grain analysed were <0.01 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 0.01* mg/kg and STMRs of 0.01 mg/kg each for dimethoate and omethoate in sorghum grain.

The residues of dimethoate on the forage were <0.01 (4), 0.01 and 0.02 mg/kg and those of omethoate all <0.01 mg/kg. The residues of dimethoate on the hay were <0.01 (5) and 0.01 mg/kg and of omethoate all <0.01 mg/kg. The Meeting estimated STMRs for forage and hay of 0.01 mg/kg each for dimethoate and omethoate.

<u>Wheat grain and straw</u>. One trial each in The Netherlands, Denmark, the UK and Germany complied with UK GAP (4 x 0.68 kg ai/ha low volume, 4 x 0.34 kg ai/ha high volume, 14-day PHI) and three trials in Germany complied with German GAP (2 x 0.24 kg ai/ha, 21-day PHI).

The residues of dimethoate in the grain were <0.01, <0.02 , <0.05, 0.09, 0.10, 0.11 and 0.12 mg/kg, and those of omethoate were <0.01 (3), 0.01, 0.02 and <0.05 mg/kg. The Meeting estimated a maximum residue level for dimethoate of 0.2 mg/kg and STMRs of 0.09 mg/kg for dimethoate and 0.01 mg/kg for omethoate in wheat grain.

The residues of dimethoate in or on the straw were <0.02, <0.05, 0.12, 2.23, 2.37, 4.42 and 8.95 mg/kg, and of omethoate <0.02, 0.02, <0.05, 0.08, 0.12, 0.13 and 0.17 mg/kg. The Meeting estimated a maximum residue level of 10 mg/kg for dimethoate and STMRs of 2.23 mg/kg for dimethoate and 0.08 mg/kg for omethoate in wheat straw and fodder, dry.

<u>Chives</u>. Five supervised field trials were carried out in Germany, but no GAP was reported for any country. No maximum residue level or STMR could be estimated.

<u>Witloof chicory</u>. Five trials in The Netherlands did not comply with GAP (5.0 kg ai/ha, 21-day PHI) because the PHIs all exceeded 35 days. The Meeting recommended withdrawal of the existing CXL for witloof chicory (sprouts).

Feeding studies

No feeding studies were reported but the studies of metabolism in hens and goats indicated that dimethoate and omethoate are extensively metabolized. Dimethoate was undetectable in all the samples and omethoate was found only in hen and goat livers and egg whites after protease treatment of the residue from the solvent extractions.

Possible ruminant feed items include apple pomace, barley grain and straw, wheat grain and straw, potato culls, processed potato waste, sorghum grain, forage and hay, sugar beet tops, molasses and pulp, and turnip roots and tops. Poultry feed may include barley grain and sorghum grain. There was no information available on residues in apple pomace, potato waste and culls or sugar beet molasses and pulp and potential residues in these commodities could not be estimated.

The maximum residues found in supervised field trials with feed items, e.g. wheat straw at 2 mg/kg dimethoate and 0.2 mg/kg omethoate and barley grain at 2 mg/kg dimethoate and 0.1 mg/kg omethoate, indicate that a dairy cow would receive about 7 ppm dimethoate and 0.2 ppm omethoate in the diet and poultry about 1.7 ppm dimethoate and 0.2 ppm omethoate. The metabolism studies were at levels equivalent to 10 ppm dimethoate in the diet for poultry and 30 ppm for goats, or about 5 and 15 times the highest estimated dietary burdens. In the metabolism studies, omethoate was found in liver (0.12 mg/kg in goats, 0.082 mg/kg in hens) and egg whites (0.004 mg/kg). From the calculated dietary burdens, the maximum omethoate residues are estimated to be 0.008 mg/kg in ruminant liver, 0.016 mg/kg in poultry liver, and 0.0008 mg/kg in egg whites.

The Meeting estimated maximum residue levels for ruminant and poultry commodities at the limit of determination, 0.05* mg/kg, for dimethoate. The residues are likely to be much less than 0.05 mg/kg, but the Meeting considered 0.05 mg/kg to be the practical limit of quantification that can be routinely achieved in the laboratory. The Meeting also estimated STMRs of 0 mg/kg each for dimethoate and omethoate in the same commodities.

Processing studies

Processing studies were reported on oranges, tomatoes, potatoes, cotton seed, maize and wheat. The raw wheat and cotton seed contained no quantifiable residues and processing factors could not be determined for these crops. The processing factors and estimated STMRs for the other processed commodities were as follows.

Processed Commodity	Processing factor		Raw agricultural commodity STMR, mg/kg		Processed commodity STMR, mg/kg	
	Dimethoate	Omethoate	Dimethoate	Omethoate	Dimethoate	Omethoate
Orange juice	0.14	0.21	Not available	Not available		
Orange oil	0.19	0.07	Not available	Not available		
Tomato juice	0.11	0.17	0.21	0.05	0.03	0.009
Tomato purée	1.7	1	0.21	0.05	0.4	0.05
Tomato paste	2.9	1.4	0.21	0.05	0.6	0.07
Tomato ketchup	1.8	1	0.21	0.05	0.4	0.05
Potato granules (flakes)	0.12	-	0.01	0.01	0.002	0.002
Potato chips	0.12	-	0.01	0.01	0.002	0.002
Refined cotton seed oil	0.34	-	Not available	Not available		
Maize meal	0.34	-	Not available	Not available		
Maize grits	0.34	-	Not available	Not available		
Maize flour	0.34	-	Not available	Not available		
Maize starch	0.17	-	Not available	Not available		
Refined maize oil	0.17	-	Not available	Not available		

FURTHER WORK OR INFORMATION

Desirable

A plant metabolism study that provides detailed results and includes data on translocation is highly desirable. A root crop is suggested.

DIETARY RISK ASSESSMENT

The Meeting considered approaches to the dietary risk assessment of mixed residues of dimethoate and omethoate, resulting from the use of dimethoate. Noting that the ADI for omethoate had been withdrawn by the JMPR (Evaluations 1996, Part II – Toxicological), the Meeting considered that it would be inappropriate to rely on the previous omethoate ADI in the dietary risk assessment. However, the Meeting noted that the toxicity of omethoate was generally about ten times that of dimethoate across a range of toxic endpoints dependent upon cholinesterase inhibition, reflecting the fact that it is an active metabolite of dimethoate. The Meeting considered that it would be appropriately conservative to multiply the omethoate component of the residue by a tenfold factor, for comparison of the combined residues with the current dimethoate ADI.

STMRs for dimethoate derived from residues of dimethoate in or on commodities have been combined with STMRs for omethoate derived from residues of omethoate arising from the use of dimethoate multiplied by a factor of 10. Dietary intakes estimated from the combined adjusted STMRs were compared with the dimethoate ADI (0.002 mg/kg bw).

The International Estimated Daily Intakes for the GEMS/Food European diet was 140% of the ADI. International Estimated Daily Intakes for the other four GEMS/Food regional diets

were in the range of 10 to 80% of the ADI. The Meeting concluded that the combined dietary intakes of dimethoate and omethoate residues, expressed as described above, may exceed the ADI for dimethoate for the European diet. The recommended MRLs are therefore designated as MRLMs.

The Meeting identified wheat, tomatoes and potatoes as the main contributors to the dietary exposure.

4.9 DINOCAP (087)

RESIDUE AND ANALYTICAL ASPECTS

Dinocap is a contact fungicide used to control powdery mildew on many crops and is also used as a non-systemic acaricide. It has been evaluated several times by the JMPR. In 1992 the JMPR recommended withdrawal of the temporary MRLs and in 1993 the CAC agreed to delete dinocap from the Codex list. In the present evaluation dinocap is therefore considered as a new compound.

Dinocap is marketed as WP and EC formulations, and is also formulated with other fungicide such as myclobutanil and fenbuconazole.

Dinocap is composed of a mixture of six isomeric dinitrooctylphenyl crotonates, three isomers of 2,4-dinitro-6-octylphenyl crotonate (2,4-DNOPC) and three of 2,6-dinitro-4-octylphenyl crotonate (2,6-DNOPC), where "octyl" is a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups. The ratio of the 2,4-DNOPC to the 2,6-DNOPC isomers in technical dinocap is approximately 2:1, and that of the octyl isomers 1:1:1.

The metabolic degradation of dinocap has been studied in rats and mice with 2,4-DNOPC uniformly labelled with ^{14}C in the aromatic ring.

In an early feeding study with rats, radioactivity was rapidly excreted in the faeces and urine. Another study with male mice and rats showed different metabolite profiles in the two species and it was also observed that in mice but not in rats the proportion of the administered radioactivity excreted in the urine decreased with increasing dose. Metabolites in the faeces and urine samples were characterized by HPLC with UV detection.

In a study to characterize the urinary metabolites in rats and mice after the oral administration of labelled 2,4-DNOPC, the DNOPC was rapidly metabolized with the rats excreting approximately 30.9% and mice approximately 58.3% of the administered ^{14}C in the urine over a 4-day period: in both species, more than 90% of the total was excreted within 24 hours. Twelve metabolites in rats and 13 in mice were identified. In both species the pattern of metabolites was consistent with a metabolic pathway involving hydrolysis of the crotonate ester, β- or α-oxidation of the methylheptyl group and β-oxidation, followed in rats only by reduction of the nitro groups and N-acetylation. Although there were qualitative and quantitative differences in the metabolic profile in rats and mice, the main metabolites in the urine of both species were the same, namely 6-(4-carboxy-1-methylbutyl)-2,4-dinitrophenol and 6-(3-carboxy-1-methypropyl)-2,4-dinitrophenol.

In cows dosed with radiolabelled 2,4-DNOPC at levels equivalent to 0.1, 0.3 and 1 ppm in the diet the main route of elimination was in the faeces with small amounts in the urine. No radioactive residues were detectable in the milk or tissues at any dosing level.

Bluegill sunfish were exposed to concentrations of 1 or 0.2 μg/l of [^{14}C]2,4-DNOPC in water tanks for 28 days, followed by a depuration period of 14 days. Bioconcentration was observed with accumulation increasing during the first 3 days, after which a steady level was reached and maintained until the end of the exposure period. Loss of residue during depuration was rapid. At the end of the depuration period more than 90% of the radioactivity in whole fish had been eliminated. The half-lives calculated for the ^{14}C in whole fish were 0.6 and 0.9 days for the low and high dose respectively.

The fate of residues in plants was studied in apples, cucumbers and squash with radiolabelled 2,4-DNOPC. Studies on apples showed that more than 92% of the radioactivity in the fruit was associated with the peel. Two groups of compounds, the parent 2,4-DNOPC isomers and the corresponding phenols 2,4-DNOP, were identified in the fruit. The phenol metabolites represented 2-4% of the total radioactivity at all sampling intervals. The calculated half-life of 2,4-DNOPC was 5.2 days. The relatively constant concentration of the phenols throughout the sampling period showed that they did not accumulate. They appeared to be metabolized to more polar compounds.

In another study on apples, peel samples were extracted with methanol, partitioned with hexane and analysed by TLC, HPLC and GC-MS. Five minor unknown compounds were isolated from the peel, each of which accounted for less than 0.5% of the total residue. The results suggest that photolysis is a potential degradation pathway for 2,4-DNOPC.

In cucumbers, the metabolism of 2,4-DNOPC produced 28 metabolites, but only the parent mixture and 2,4-DNOP were identified. 2,4-DNOPC dissipated rapidly from cucumber leaves and stems.

In squash the residues in mature fruit were mainly associated with the peel. Six unidentified metabolites were found in the fruit and 10 in the leaves at low concentrations.

The half-lives of the total radioactive residues on cucumber and squash leaves were 11.8 and 8 days respectively.

Dinocap metabolites from squash and cucumber were very similar in their TLC behaviour and more similar to rat faecal metabolites than to urinary metabolites.

In summary, plant metabolism studies indicated that the metabolic pathways of dinocap in crops are complex, resulting in a large number of metabolites present at low concentrations. The isolation of sufficient quantities of most of the metabolites to allow identification was not possible. The only significant metabolite found was 2,4-DNOP. Residues are associated with the peel and it was found that dinocap is rapidly degraded on fruit and leaf surfaces, suggesting that photolysis is a significant pathway of degradation.

Four studies were carried out to determine the rate of dissipation of dinocap in different soils. A study with two standard soils and one agricultural soil showed that dinocap was slowly degraded in the standard soils but readily degraded to CO_2 in a typical agricultural soil. It can be

concluded that moisture and microbial activity play an important role in the degradation of dinocap in soil.

The route and rate of degradation of 2,4-DNOPC was also investigated in sandy loam, silty loamy sand, loamy sand and clay loam at two temperatures. 2,4-DNOPC was degraded rapidly in all the soils at rates which appear to be dependent on the soil pH rather than other characteristics, indicating that chemical hydrolysis to 2,4-DNOP is a major route of degradation. The half-life ranged from 4.1 days at pH 7.1 to 24 days at pH 4.8 at 20ºC.

The degradation of 2,4-DNOPC and 2,6-DNOPC was studied in a sandy loam soil (pH 5.8) in aerobic conditions. Both were degraded rapidly, the 2,6- isomers more rapidly than the 2,4-. Calculated half-lives were 10 and 4.5 days for 2,4- and 2,6-DNOPC respectively. The main degradation products were 2,4- and 2,6-DNOP. After 120 days of incubation significant mineralization was observed (22.4% of the applied 2,4-DNOPC and 36.7% of the 2,6-DNOPC).

A study of the adsorption and desorption of [^{14}C]2,4-DNOPC in four different agricultural soils showed that it was strongly adsorbed in the soils studied and could be classified as having very low mobility in soil.

The leaching behaviour of [^{14}C]dinocap was studied in five different fresh soils, in sandy loam soil after ageing for 30 days and in silt loam after ageing for 102 days before leaching. Radioactivity was detectable in the leachate from only two of the fresh soils (silt loam and clay loam). Between 74% and 99% of the applied radioactivity was recovered in the top layers of all the soils. It can be concluded that it is very unlikely that dinocap or its degradation products could be leached even under exaggerated laboratory conditions.

The octanol/water partition coefficient was determined for 2,4- and 2,6-DNOPC and their phenol metabolites. The coefficients showed that DNOPC isomers are fat-soluble (log P_{ow} 2,4-DNOPC 6.55, log P_{ow} 2,6-DNOPC 6.45).

The rates of hydrolysis of the isomeric forms of DNOPC and the corresponding phenols were determined in buffer solutions at pH 4, 7 and 9 at 20º and 30ºC. It was concluded that hydrolysis of the crotonates was highly dependent on pH and temperature, being more rapid at basic pH. Degradation of the phenols was found to be negligible at all pH values and temperatures.

The photolysis of 2,4-DNOPC was investigated in a pH 5 aqueous buffer solution irradiated with a xenon arc for 367 hours. Degradation was biphasic with initial and terminal half-lives equivalent to 4.9 and 57.2 hours of summer sunlight. The major degradation product was $^{14}CO_2$. The free phenol 2,4-DNOP was an important initial product. In another study the aqueous photolysis of the isomeric forms of DNOPC and DNOP was measured in sterile, aqueous buffer (50 µg/l, pH 4) irradiated with a xenon arc for up to 10 hours for DNOPC and 96.1 hours for DNOP. The half-life was 0.63 and 0.73 days for 2,4- and 2,6-DNOPC respectively and 8.7 and 20.8 days for 2,4- and 2,6-DNOP. The only photodegradation product of DNOP identified was CO_2. Other photodegradation products were not resolved by HPLC.

The aerobic aquatic degradation of [^{14}C]2,4-DNOPC was studied in two water/sediment systems from natural environment sites at 20ºC in the dark. There was rapid transfer of radioactivity from water to sediment and an apparent rapid degradation of DNOPC to DNOP,

which was further degraded to CO_2. At the end of the 100-day study 40.7% to 78.4% of the applied radioactivity was associated with sediments and 6.4 to 11.8% with the water phases.

Analytical methods for the determination of residues of dinocap have been developed for several crops and their processed products, and for soil and water. All the methods are similar. They include extraction with methanol, either by Soxhlet or maceration with the solvent. Juices and wine are simply diluted with methanol. The dinocap isomers are converted to the corresponding phenols by basic hydrolysis, and the extracts partially purified by partition into hexane. After solvent evaporation the residue is taken up in diethyl ether, methylated with diazomethane, and purified by silica gel column chromatography. The methylated phenols are determined by GLC with an ECD or NPD, the sum of the peak areas or heights being measured. The method was validated for many crops. The mean recoveries of dinocap from fruit were above 70% with reported LODs of 0.05 mg/kg. Crop samples were fortified with 2,4-DNOPC and 2,6-DNOPC and the analytical standards were the methyl esters of 2,4-DNOP and 2,6-DNOP.

In studies of the storage stability of residues in frozen analytical samples of apples and grapes stored for 24 months, the residues in grapes showed good stability, but there was a marked decrease of the dinocap residue during the storage of apples. In another study, the storage stability of dinocap at levels of 1 mg/kg was determined in cucumbers, tomatoes, peaches, apples and strawberries over a period of 9 months in the dark at approximately –20ºC. Dinocap residues were found to be stable in all the crops for at least 9 months. The analytical method for apples was modified slightly by increasing the volume of the extraction solvent. This modification improved the extraction efficiency. It was reported that studies on cucumbers, peaches, apples and strawberries would be continued for a total of 24 months.

The results of metabolism studies showed that the dinocap isomers are readily hydrolysed to the corresponding phenols. The analytical methods used in residue trials quantify residues of dinocap and their phenol metabolites as the methylated phenols and express the results as dinocap. The Meeting concluded that the residues should be defined as the sum of dinocap isomers and the dinocap phenols, expressed as dinocap.

Dinocap is fat-soluble but metabolism, feeding and bioaccumulation studies showed that residues do not accumulate in tissues. This is probably because dinocap is rapidly degraded and the metabolites that constitute the main residues are not fat-soluble.

Residues resulting from supervised trials

Data from trials on apples, grapes, strawberries, stone fruits and cucurbits in European countries were evaluated.

Residues of 2,4- and 2,6-DNOPC in the trials were calculated from the sum of 6 peak areas or heights. The residues of the two groups of isomers were generally recorded separately and their sum expressed as dinocap. If the calculated concentration of each isomeric group was <0.05 mg/kg the total dinocap residue was recorded as <0.05 mg/kg.

Apples. Trials in France, Greece, Italy and the UK were reported. In two trials in France and two in Greece according to GAP the residues were <0.05 mg/kg. Six trials according to Italian GAP yielded total residues between <0.04 and 0.09 mg/kg. In the UK, 18 trials complied with GAP, with residues from <0.05 to 0.08 mg/kg.

The dinocap residues in rank order (median underlined) were <0.04 (2), <u><0.05</u> (18), 0.05, 0.05, 0.06, 0.07, 0.08 (3) and 0.09 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.05 mg/kg for apples.

Grapes. Numerous field trials on vines in France, Germany, Greece, Italy and Portugal were reported to the Meeting. Ten of thirteen trials in France were according to GAP: the residues ranged from <0.05 to 0.59 mg/kg. Six field trials in Germany complied with French GAP, with residues from 0.22 to 0.67 mg/kg. In two field trials in Greece according to Italian GAP the residues were 0.1 and 0.2 mg/kg. In sixteen trials in Italy and three in Portugal complying with the national GAP the residues ranged from <0.04 to 0.3 mg/kg.

The residues of dinocap in rank order (median underlined) were <0.04 (7), <0.05 (7), 0.06, 0.08, 0.09, <u>0.1</u>, <u>0.11</u>, 0.14, 0.18, 0.2 (2), 0.22 (2), 0.26, 0.28, 0.3 (2), 0.35, 0.36, 0.42, 0.43, 0.46, 0.5, 0.59 and 0.66 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.105 mg/kg.

Strawberries. Trials were conducted in France, Italy, Spain and the UK. In four French trials complying with French GAP the residues were 0.05-0.33 mg/kg. Two Spanish trials complying with GAP gave residues below the LOD of 0.04 mg/kg. In ten trials in the UK according to GAP (5 applications, 0.49 kg ai/ha, 7 days PHI) the residues ranged from <0.05 to 0.33 mg/kg.

The dinocap residues in rank order (median underlined) were <0.04 (2), <0.05, 0.05, 0.05, <u>0.06</u> (4), 0.08, 0.09, 0.14, 0.21, 0.32 and 0.33(2) mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.06 mg/kg.

Stone fruits. A single trial in Italy on apricots according to GAP, with residues at 21 days PHI below the LOD (0.04 mg/kg) was insufficient to estimate a maximum residue level.

Residues in a trial on peaches in Greece complying with GAP were below the LOD (0.05 mg/kg). Six of nine trials in Italy complied with French GAP (0.018 kg ai/hl, 7 days PHI), giving residues from <0.04 to 0.09 mg/kg. In two trials in Spain according to GAP the residues were <0.04 and 0.05 mg/kg. The dinocap residues in peaches in rank order (median underlined) were <0.04 (5), <u><0.05</u> (3), 0.05 and 0.09 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.05 mg/kg.

Cucumbers. Two protected trials in France and three in Spain according to GAP gave residues below the LOD (0.05 and 0.04 mg/kg). The residues were <0.04 (3) and <0.05 (2).

Melons. Several field trials were carried out in France, Greece, Italy and Spain, and one indoor trial in Spain. In two trials in France at a higher spray concentration than the recommended GAP (0.18 kg ai/hl, 3 day PHI) the residues were below the LOD (0.04 mg/kg). In one trial in Greece, 6 trials in Italy and two in Spain according to GAP the residues were all <0.04 or <0.05 mg/kg.

In summary, dinocap residues in melons from 9 trials according to GAP and 2 at a higher rate were all below the LOD.

Summer squash. Residues in three trials in France, 4 in Italy and 2 in Spain according to national GAP were all below the LOD.

The use patterns on cucumbers, melons and summer squash are similar. The residues in all these crops were below the LOD, which is consistent with the results of metabolism studies. The Meeting therefore estimated a maximum residue level of 0.05[*] mg/kg and an STMR of 0.05 mg/kg for cucurbits.

Peppers. Eight protected trials carried out on peppers in Greece, Italy and Spain complied with Greek GAP (0.018 kg ai/hl, 7 days PHI). The residues in rank order (median underlined) were <0.05, 0.05, 0.06, 0.06, 0.06, 0.07, 0.11 and 0.12 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.06 mg/kg for peppers.

Tomatoes. Field and protected trials were conducted in Southern France, Italy and Spain. There is no GAP for tomatoes in France or Italy and all the trials were at much higher application rates than allowed by GAP in Spain (0.011 kg ai/hl, 7 days PHI) and shorter PHIs than GAP in Greece.

As no trials according to GAP were reported, the Meeting could not estimate a maximum residue level.

Processing studies

Apples. Unwashed apples from 2 trials in France with sprays of 6 x 0.021 kg ai/hl and 14 days PHI were processed to juice and purée. Residues were not detected in the processed commodities. In two studies in the UK apples treated according to GAP were processed according to commercial practice to juice, purée and pomace. Dinocap residues were not detected in the juice or purée and residues in the pomace were similar to those in the raw commodity.

The data indicated that there is no concentration of residues in apple juice. On the basis of the STMR of 0.05 mg/kg for apples, the Meeting estimated an STMR of 0.05 mg/kg for apple juice.

Grapes. Data from processing studies in France and Germany indicated that residues of dinocap decreased in wine and must and were below the LOD or not detected. Studies with higher residue levels in the raw grapes in Germany showed a processing factor of 0.07 for both must and wine. The Meeting therefore estimated STMRs for must and wine of 0.007 mg/kg, derived from the STMR for grapes of 0.105 mg/kg.

Peaches. Peaches treated according to GAP in two trials in Italy were processed into juice and preserves. Residues in the raw peaches were below the LOD and no concentration was detected in the processed commodities.

Tomatoes. Tomatoes from one supervised trial were processed into juice, purée, preserve and ketchup. Residues of total dinocap in the tomatoes were below the LOD (0.05 mg/kg) and residues were not detected in the processed commodities.

The Meeting could not calculate processing factors for peaches and tomatoes since the residues in the raw commodities were below the LOD.

Strawberries. Two processing trials in the UK showed that residues do not concentrate in strawberry jam or preserved strawberries. The average processing factor was 0.29 for both commodities. On the basis of an STMR of 0.06 mg/kg for strawberries, the Meeting estimated an STMR of 0.017 mg/kg for strawberry jam and preserved strawberries.

FURTHER WORK OR INFORMATION

Desirable

1. Processing studies with raw commodities containing dinocap residues at higher concentrations.

2. Animal feeding studies

3. Final report of the completed study of the storage stability of residues in analytical samples that was reported to be in progress.

DIETARY RISK ASSESSMENT

STMRs have been estimated for apples, grapes, strawberries, peaches, peppers and cucurbits. The International Estimated Daily Intakes of dinocap for the five GEMS/Food regional diets were in the range of 0 to 1% of ADI. The Meeting concluded that the intake of residues of dinocap resulting from its uses that had been considered by the JMPR is unlikely to present a public health concern.

4.10 DIPHENYLAMINE (030)

TOXICOLOGY

Diphenylamine was first evaluated by the JMPR in 1969, when an ADI of 0.025 mg/kg bw was established on the basis of a NOAEL of 2.5 mg/kg per day in a two-year study in dogs. Diphenylamine was re-evaluated in 1976, when an ADI of 0-0.02 mg/kg was allocated on the basis of a NOAEL of 1.5 mg/kg per day for Heinz-body formation reported in a six-month study in mice and a safety factor of 100. The 1982 JMPR considered impurities in commercial-grade diphenylamine and concluded that additional data on this aspect were desirable; the ADI was made temporary and the Meeting required additional data on teratogenicity, haematological effects, and mutagenicity. The 1984 JMPR established an ADI of 0-0.02 mg/kg bw for diphenylamine of 99.9% purity, based on the NOAEL of 1.5 mg/kg bw per day in mice.

WHO has not classified diphenylamine for acute toxicity.

After oral administration to rats, goats, or hens, [^{14}C]diphenylamine was extensively absorbed and rapidly excreted. In rats given a single dose, 45-72% appeared in the urine within 24 h and 68-89% by 168 h after dosing, with less than 0.4% of the dose in the residual carcase and less than 0.05% in any individual tissue. In goats treated with single daily doses for seven days, 85-91% of the daily dose was excreted in urine and 0.5-0.8% in milk; the concentrations of residues in milk reached a plateau after 24 h. When laying hens were treated with single daily oral doses for seven days, 84-98% of the daily dose was recovered in the excreta; the concentrations in egg yolk reached 0.31 mg/kg on day 7, but no residues were in egg whites. Diphenylamine underwent extensive biotransformation in rats, goats, and hens, with ring hydroxylation and formation of glucuronide and sulfate conjugates. In addition to untransformed diphenylamine (<3% of the dose), the following 12 metabolites were identified at all doses: 4,4'-dihydroxydiphenylamine (unconjugated and as the *O*-sulfate and the *O,O*-disulfate), 4-hydroxydiphenylamine (unconjugated and as the *O*-glucuronide, *N*-glucuronide, *O*-sulfate, and *O,N*-diglucuronide), indophenol (unconjugated and as the *O*-sulfate), 3-hydroxydiphenylamine, and 2-hydroxydiphenylamine. These metabolites accounted for about 80-90% of the dose and were excreted largely as their sulfate and glucuronide conjugates. There was no cleavage of the diphenylamine structure. Except for a polar oligomer of 4-hydroxydiphenylamine found only in the eggs and tissues of hens, all of the metabolites reported in hens and goats were detected in rats. Residues of a number of plant metabolites were identified in apple peel and pulp, but untransformed diphenylamine was the major contributor to the total residue 40 weeks after application. The major metabolite was 4-hydroxydiphenylamine, as the glucose conjugate. Other metabolites identified were 2-hydroxydiphenylamine, 3-hydroxydiphenylamine, and dihydroxydiphenylamine (possibly the 2,4- isomer). These compounds were either free or conjugated with mono- or oligosaccharides. Although all of the hydroxylated metabolites (aglycones) identified in plants were seen in rats, the conjugating species were generally different.

After acute oral administration to rats, diphenylamine (99.9% pure) was slightly toxic (LD$_{50}$ about 3000 mg/kg bw in one study, whereas in another study with super-refined diphenylamine 99.0-100.1% purity was essentially non-toxic (LD$_{50}$: >15 000 mg/kg bw).

In mice given diphenylamine at dietary concentrations of 0, 10, 520, 2600, or 5200 ppm for 90 days, dose-related changes in haematological parameters (decreased erythrocyte counts and packed cell volumes and increased reticulocyte counts) were observed. The mean corpuscular haemoglobin count was significantly increased at dietary levels of 520 ppm and above. Necropsy revealed dark, enlarged spleens with haemosiderosis and congestion at dietary levels of 520 ppm and above. Spleen haematopoiesis was increased in animals of each sex at 520 ppm. The NOAEL was 10 ppm (equal to 1.7 mg/kg bw per day) on the basis of changes in haematological parameters and findings at necropsy in animals at 520 ppm.

In rats that received diphenylamine in the diet at concentrations of 0, 150, 1500, 7500, or 15 000 ppm for 90 days, body weights and body-weight changes, although generally lower than the control values at 1500 ppm, were not significantly different from those of controls at doses below 7500 ppm. The cholesterol concentration increased with dose in females and was significantly different from that of controls at 1500 ppm. In females, the absolute and relative weights of the liver increased with dose, and the relative liver weights were significantly different from those of controls in animals at 1500 ppm and above. Histopathological examination revealed increased haematopoiesis and pigment in the liver, haematopoiesis,

haemosiderosis, and congestion in the spleen, and pigmented kidneys in animals of each sex at 7500 and 15 000 ppm. Additionally, the spleens of all females at 1500 ppm showed minimal or slight haematopoiesis and haemosiderosis. The NOAEL was 150 ppm (equal to 12 mg/kg bw per day) on the basis of changes in clinical chemical parameters, increased organ weights, and gross and histological changes in female rats at 1500 ppm.

Groups of rabbits were exposed dermally to diphenylamine in distilled water at doses of 0, 100, 500, or 1000 mg/kg bw per day for 6 h per day. No effects were observed. Gross necropsy revealed dark-red foci in the stomachs of rabbits at the intermediate and high doses, which increased in number with dose. The NOAEL for systemic effects was 100 mg/kg bw per day on the basis of effects on the stomach at 500 mg/kg bw per day in animals of each sex.

Groups of dogs received diphenylamine by gelatin capsule at doses of 0, 10, 25, or 50 mg/kg bw per day for 90 days. There were no treatment-related effects. The NOAEL was 50 mg/kg bw per day, the highest dose tested.

In a study of carcinogenicity, mice received diets containing diphenylamine at concentrations of 0, 520, 2625, or 5200 ppm for 78 weeks. At 520 ppm and above, decreased packed cell volumes were seen in females and spleen congestion and haemosiderosis in animals of each sex. At 2600 ppm and above, clear haematological effects, consistent with regenerative anaemia, were observed. The incidences of tumours were not increased when compared with those in controls. The NOAEL for toxicity was 520 ppm (equal to 73 mg/kg bw per day) on the basis of decreased body-weight gain, reduced survival, and significant alterations in haematological and gross and microscopic pathological parameters at higher levels. Examination of the incidence and severity of some haematological effects at 520 ppm suggested that this dose is close to the NOAEL/LOAEL threshold. There was no evidence of carcinogenicity.

In a combined study of toxicity and carcinogenicity, rats received diets containing diphenylamine at concentrations of 0, 200, 750, 3750, or 7500 ppm (males) and 0, 150, 500, 2500, or 5000 ppm (females). At 500 ppm and above, decreased erythrocyte count, haemoglobin, and packed cell volumes were observed in animals of each sex; these decreases reached statistical significance only sporadically during treatment in males at 750 ppm and in females at 500 ppm. Haematopoiesis was increased in the liver and spleen of males at 750 ppm and above. At 2625 ppm and above, clear haematological effects consistent with regenerative anaemia were observed. There was no significant increase in the incidence of tumours when compared with that in controls. The NOAEL was 150-200 ppm (equal to 7.5 mg/kg bw per day) based on haematological and histological effects at dietary levels equal to or greater than 500 ppm. This appeared to be close to the threshold dose, since body-weight gain was not depressed and only sporadic haematological changes were observed at 500-750 ppm. There was no evidence of carcinogenicity.

Dogs received diphenylamine by gelatin capsule at doses of 0, 10, 25, or 100 mg/kg bw per day for one year. Platelet counts in males and total bilirubin concentrations in animals of each sex were statistically significantly higher than those of controls. The NOAEL for toxicity was 10 mg/kg bw per day, and the LOAEL was 25 mg/kg bw per day, both based on haematological and clinical chemical changes.

In a two-generation study of reproductive toxicity, rats received diphenylamine in the diet at levels of 0, 500, 1500, or 5000 ppm during premating. A NOAEL for parental toxicity was not

observed; the LOAEL was 500 ppm (equal to 40 mg/kg bw per day) on the basis of enlarged spleens in F_1 females, increased spleen congestion and haemosiderosis in animals of each sex in all generations, and hepatocyte hypertrophy in F_0 females. The NOAEL for developmental toxicity was 500 ppm (equal to 46 mg/kg bw per day) on the basis of statistically significantly decreased mean body weight in F_2 pups at 1500 ppm and above. The NOAEL for reproductive toxicity was 1500 ppm (equal to 120 mg/kg bw per day). Although haemosiderin, congestion of the spleen, and hepatocyte hypertrophy were observed in parental animals at all doses, they occurred at appreciably lower incidence and intensity at the lower dose than at the higher doses, which suggested that the lower dose was close to the NOAEL/LOAEL threshold for parental toxicity.

In a study of developmental toxicity, rats received diphenylamine by gavage at doses of 0, 10, 50, or 100 mg/kg bw per day on days 6-15 of gestation. The NOAEL for maternal toxicity was 50 mg/kg bw per day on the basis of enlarged, blackish spleens with higher weights than controls at 100 mg/kg bw per day. The NOAEL for developmental toxicity was 100 mg/kg bw per day, the highest dose label.

In a study of developmental toxicity, rabbits received diphenylamine by gavage at doses of 0, 33, 100, or 300 mg/kg bw per day on days 7-19 of gestation. The NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of decreased body-weight gain and food consumption at 300 mg/kg bw per day. The NOAEL for developmental toxicity was 300 mg/kg bw per day, the highest dose tested.

Diphenylamine has been tested for genotoxicity in three assays. Negative results were obtained for mutation in bacteria and for induction of micronuclei in mouse bone marrow *in vivo*. A weakly positive response was observed only for mutation in mouse lymphoma cells *in vitro* at a dose range in which the toxicity was relatively high and the mutant frequency did not increase with dose. The Meeting concluded that, although diphenylamine has some genotoxic potential, it is unlikely to present a human genotoxic hazard.

An ADI of 0-0.08 mg/kg bw was established on the basis of the NOAEL of 150 ppm, equal to 7.5 mg/kg bw per day, in the two-year study of toxicity and carcinogenicity in rats and a 100-fold safety factor.

An acute RfD was not allocated because diphenylamine is of low acute toxicity. The Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

<u>Levels that cause no toxic effect</u>

Mouse: 520 ppm, equal to 73 mg/kg bw per day (78-week study of carcinogenicity)

Rat: 150-200 ppm, equal to 7.5 mg/kg bw per day (two-year study   of toxicity and carcinogenicity)

500 ppm, equal to 46 mg/kg bw per day (reproductive toxicity in a two-generation study of reproductive toxicity)
50 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
100 mg/kg bw per day (developmental toxicity)

Rabbit: 100 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
300 mg/kg bw per day (highest dose in a study of developmental toxicity)

Dog: 10 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.08 mg/kg bw

Estimate of acute reference dose

Not allocated (unnecessary)

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

Further observations in humans of end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	Rapid absorption: at least 68-89% of the dose
Dermal absorption:	No data
Distribution:	Extensive
Potential for accumulation:	Very little
Rate and extent of excretion:	At 24 h, 45-72% of dose found in urine
Metabolism in animals	Extensively metabolized. Parent <3%. Approximately 80-90% of the dose appeared as 12 metabolites: indophenol and various isomers of mono- and di-hydroxydiphenylamine excreted in urine as sulfate and glucuronide conjugates.
Toxicologically significant compounds (animals, plants, and environment)	Parent. Indophenol might be able to engage in electrophilic interactions

Acute toxicity

LD_{50} oral	3000 mg/kg bw, rat
LD_{50} dermal	>2000 mg/kg bw, rabbit
LC_{50} inhalation	No data
Skin irritation"	None to slight
Eye irritation	Slight to corrosive with corneal opacity
Skin sensitization	Not a sensitizer

Short term toxicity

Target / critical effect	Erythrocytes/anaemia

Lowest relevant oral NOAEL	1.7 mg/kg bw per day, 90-day, mouse
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEL	No data

Genotoxicity

	Unlikely to be a human genotoxic hazard

Long term toxicity and carcinogenicity

Target/critical effect:	Erythrocytes/haemolytic anaemia.
Lowest relevant NOAEL	7.5 mg/kg bw per day, rat
Carcinogenicity	No carcinogenicity

Reproductive toxicity

Reproduction target / critical effect	Decreased mean litter size in both generations and decreased mean body weights of F_2 pups at maternally toxic doses
Lowest relevant reproductive NOAEL	46 mg/kg bw per day
Developmental target / critical effect	No developmental toxicity, rat
Lowest relevant developmental NOAEL	100 mg/kg bw per day, highest dose tested

Neurotoxicity / Delayed neurotoxicity

	No data

Other toxicological studies

46 mg/kg bw per day in maternal animals	No data

Medical data

	No data

Summary	Value	Study	Safety factor
ADI	0-0.08 mg/kg bw	Long-term toxicity and carcinogenicity rats	100
Acute reference dose	Not allocated (unnecessary)		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 0 to 4% of the ADI. The Meeting concluded that the intake of residues of diphenylamine resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.11 DISULFOTON (074)

RESIDUE AND ANALYTICAL ASPECTS

Residue aspects of disulfoton were reviewed by the JMPR in 1973, 1975, 1979, 1981, 1984, 1991 and 1994. At the 1996 CCPR MRLs set "at or about the limit of determination" were amended from 0.01 to 0.02 mg/kg after a recommendation from the Ad Hoc Working Group On Methods of Analysis (ALINORM 97/24 para. 52). Several delegations expressed concern at the high levels of estimated intakes relative to the ADI and it was noted that processing data were not available for refinement of the estimation of intake. The Committee requested revised intake calculations and decided to keep all other proposals at step 7C (ALINORM 97/24, paras. 53 and 54).

In 1997, the CCPR was informed that additional data would be available for the 1998 JMPR and disulfoton MRLs were kept at Step 7B pending the 1998 evaluation. The present Meeting received new residue data on lima beans, cotton, lettuce and potatoes, as well as reports of recent processing studies on coffee, cotton seed, maize, sorghum and wheat. Processing data on potatoes were also submitted, although minimal information was provided on the field conditions and the analytical methods used. The Meeting received summaries of data reviewed in the previous monographs on disulfoton for the estimation of STMRs and refinement of the dietary intake calculations.

Plant metabolism

The metabolism of [^{14}C]disulfoton in lettuce, potatoes, wheat and soya beans was reported.

[^{14}C]disulfoton was applied to soil at a rate of 3.2 kg ai/ha before planting lettuce. Total radioactive residues of 3.7 mg/kg disulfoton equivalents were found in mature lettuce 49 days after treatment. Approximately 93% of the radioactivity was extracted with 1% trifluoroacetic acid in methanol (1%TFA/MeOH). Four major metabolites which were identified by HPLC accounted for a total of 60% of the radioactivity. The metabolites were disulfoton sulfone, disulfoton oxygen analogue sulfone, disulfoton oxygen analogue sulfoxide and disulfoton sulfoxide, which constituted 26, 23, 6 and 5% of the TRR respectively.

Potatoes were planted in soil treated with [^{14}C]disulfoton at a rate of 7.9 kg ai/ha. Two foliar sprays were applied 33 and 69 days after planting at a rate of 2.2 kg ai/ha. In tubers harvested 99 days after planting the total radioactive residues were 3.7 mg/kg as disulfoton. 1% TFA/MeOH extracted 91% of the total radioactivity in the tubers. The organophosphorus triesters (disulfoton sulfone and sulfoxide, disulfoton oxygen analogue sulfone and sulfoxide) constituted in total 2% of the TRR. Most of the radioactivity (69%) was incorporated into amino acid conjugates of 2-(ethylsulfonyl)ethylene which is formed from disulfoton oxygen analogue sulfone by hydrolysis and elimination of water.

Wheat was planted in soil treated with [^{14}C]disulfoton at a rate of 0.97 kg ai/ha. At 37 and 63 days after planting, two foliar sprays were applied at a rate of 0.85 kg ai/ha. Immature and mature plants were harvested 37 days (before the first foliar application) and 90 days after planting respectively. Straw and forage samples were collected 104 days after planting. The TRRs in grain, wheat forage and straw were 2.8, 36.2 and 40.2 mg/kg disulfoton equivalents respectively. Metabolites were identified and quantified by HPLC after extraction with 1% TFA/MeOH. The organophosphorus triesters in total were <4% of the TRR in grain, 23% in wheat forage and 20% in wheat straw.

Soya beans were planted in soil treated with [^{14}C]disulfoton at a rate of 1.8 kg ai/ha. Mature plants were harvested 85 days after planting and hay samples were collected 99 days after planting. The TRR in soya beans, forage and hay was 1.4, 27 and 43.7 mg/kg disulfoton equivalents respectively, of which 1% TFA/MeOH extracted 67, 93 and 85% respectively. The organophosphorus triesters constituted less than 4% of the TRR in all of the samples. After further extraction, 39% of the TRR in the beans and 22% in the forage was identified as 2-(ethylsulfonyl)acetic acid. Another 58% of the TRR in the forage was identified as 2-(ethylsulfonyl)ethanol.

In summary, the metabolism studies indicated that there were common processes involved in the transformation of disulfoton in lettuce, potatoes, wheat and soya beans. The metabolism of disulfoton before hydrolysis of the triesters was similar in all the crops. Cleavage of the triesters led to the formation of alkylsulfonyl and sulfonic acid products such as 2-(ethylsulfonyl)ethanol and its oxidation product 2-(ethylsulfonyl)acetic acid. Both of these compounds were identified in soya beans and potatoes. Neither disulfoton nor its oxygen analogue (demeton-S) were identified in any of the metabolism studies; the inclusion of demeton-S in the residue definition was therefore questioned.

The question of including demeton-S in the residue definition was raised at the 1994 Joint Meeting and was discussed at the present Meeting in relation to the new crop metabolism studies provided. The Meeting agreed that although the disulfoton oxygen analogue was not isolated in any of the new metabolism studies reviewed and it would be oxidized to the corresponding sulfone in any determination of the total residue, there was no reason to remove it from the definition. The definition of the residue for compliance and MRLs and the estimation of dietary intake is *sum of disulfoton, demeton-S and their sulfoxides and sulfones, expressed as disulfoton.*

Analytical methods

Disulfoton is included in a multi-residue method reported by the government of The Netherlands. Recoveries from lettuce and potatoes were reported.

The determination of disulfoton in a number of types of sample was included in a general method. A rapid screening method for alfalfa and wheat was also reported. Recoveries were determined with mixtures of disulfoton, disulfoton oxygen analogue and their sulfones and sulfoxides and all recoveries were within acceptable limits (71 to 100%).

Stability of residues in stored analytical samples

The storage stability of disulfoton and its metabolites in a number of crops and processed commodities was investigated for periods up to 36 months. A loss of 37% of disulfoton oxygen analogue sulfone and sulfoxide was found in cotton seed after 24 months. In peanut soapstock losses of 18% of disulfoton sulfone and sulfoxide and 37% of disulfoton oxygen analogue sulfone and sulfoxide were found after 30 months. The Meeting considered that the reported losses were acceptable for storage periods up to 36 months.

Supervised residue trials

The manufacturer provided summaries of data reviewed in previous monographs on disulfoton (1991 and 1994) to estimate STMRs. These were combined with data from currently reviewed

studies where appropriate. Only results from supervised trials conducted in accordance with GAP or current use patterns were used in the estimation of the STMRs.

Dry beans (Lima beans). The 1994 Meeting requested the provision of additional residue data reflecting GAP for beans. US GAP allows a maximum rate of 2.2 kg ai/ha to be applied as an in-furrow or side-dress application at planting. On registered US labels, a PHI of 60 days is indicated for beans. The 1994 monograph reported residues in lima beans and green vines of <0.01 and 0.06 mg/kg respectively, 92 days after a double side-dress application at 2.2 kg ai/ha. Data from the current evaluation were included in the estimation of a maximum residue level and an STMR for dry beans. Although samples were harvested 105 and 106 days after treatment, the data were considered to be reflective of GAP for dry beans.

In US trials reported in the 1991 monograph application rates ranged from 1.6 to 3.9 kg ai/ha. GAP in Japan allows a maximum rate of application of 2 kg ai/ha with a PHI of 60 days. Data from four Japanese trials on kidney beans reviewed in 1991 were from treatments at 2 and 4 kg ai/ha, The residues in the beans were all <0.01 mg/kg 62 and 68 days after both treatments.

Residues reflecting GAP in the USA ranged from <0.01 to 0.14 mg/kg at pre-harvest intervals ranging from 52 to 106 days after treatment. The residues from the US and Japanese trials used to estimate the STMR were in rank order <u>0.01</u> (15), 0.01, 0.02, 0.04, 0.06, 0.10, 0.11 (2) and 0.14 mg/kg. The data do not support the existing MRL of 0.05 mg/kg for dry beans (Step 7B). The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.01 mg/kg for dry beans.

Cotton seed. Data from eight trials in Greece in 1993 and 1994 were reported. GAP in Greece allows application of disulfoton at rates of 1–1.5 kg ai/ha at planting with a PHI of 60 days. Cotton seed was harvested 150 to 169 days after planting (normal harvest) and the residues were below the limits of determination in all the samples of cotton seed. The limits of determination were 0.06 and 0.12 mg/kg based on fortifications with the six components of the defined disulfoton residue.

GAP in the USA allows an in-furrow treatment at 1.1 kg ai/ha, a post-planting in-furrow application at 2.2 kg ai/ha and up to three foliar sprays at 0.63 kg ai/ha. PHIs vary from 28 to 90 days according to the treatment regime. No more than three applications (soil and foliar) may be made. Residues reflecting GAP in the USA (1991 and 1994 evaluations) ranged from <0.01 to <0.19 mg/kg.

Residues resulting from GAP in the USA and Greece used in the estimation of the STMR were in rank order <0.01 (20), <0.02, 0.02, <0.03 (2), <u>0.03</u> (3), 0.04 (2), <0.05 (2), 0.05 (3), <0.06 (6), 0.10 (2), 0.11, <0.12 (4), 0.12 (2) and <0.19 (4) mg/kg.

The Meeting confirmed the previous recommendation for the draft MRL (Step 7B) of 0.1 mg/kg for cotton seed on the basis of the Greek and US data and estimated an STMR of 0.03 mg/kg.

Lettuce. Data from six US trials on head and leaf lettuce in 1995-6 were submitted for evaluation. GAP in the USA dictates a soil treatment at planting at 1.2-2.2 kg ai/ha and a PHI of 60 days. In the residue trials, disulfoton was applied as a single side-dress application at sowing at a rate of 1.1 or 1.2 kg ai/ha. Samples of leaf lettuce were taken 60 to 90 days after planting and

head lettuce (with wrapper leaves) were sampled 62 to 116 days after planting. Residues in leaf lettuce ranged from <0.05 to 1.15 mg/kg and in head lettuce from <0.05 to 0.22 mg/kg. Five trials each on leaf and head lettuce in 1985 reported in the 1991 monograph were according to GAP and gave residues of <0.01-0.56 mg/kg in leaf and 0.01-0.64 mg/kg in head lettuce.

The residues resulting from US GAP from the 1985 and 1995-6 trials in rank order were leaf <0.03 (2), 0.06, 0.11, 0.56, 0.59 and 1.15 mg/kg; head <0.03, 0.04, <0.05 (2), 0.10, 0.44 and 0.64 mg/kg.

The Meeting confirmed the existing draft MRLs of 1 mg/kg for head lettuce and leaf lettuce and estimated STMRs of 0.11 and 0.05 mg/kg for leaf and head lettuce respectively.

Potatoes. Data were reported from two trials in The Netherlands (government submission). At planting, disulfoton was applied at a rate of 1.5 kg ai/ha and tubers were harvested after 113 days. There is no reported GAP for potatoes in The Netherlands. Field details were not reported although an analytical method was provided. The data could not be evaluated.

Data from the USA and Japan were evaluated in 1991. Residues from the US and Japanese trials used for the estimation of the STMR in rank order were <0.01 (3), 0.01, <0.02, 0.04, 0.06, 0.07 (3). 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.15, 0.16, 0.20, 0.23 and 0.31 mg/kg.

The Meeting confirmed the existing CXL of 0.5 mg/kg and estimated an STMR of 0.08 mg/kg for potatoes.

Processing studies

Processing studies on coffee, cotton seed, maize, potatoes and sorghum were reported.

In a coffee processing study, disulfoton was applied at a tenfold rate to the soil around coffee trees. Coffee beans were harvested and the initial preparation of the berries involved removal of the skin, pulp and endocarp to leave green beans. These were roasted and processed into instant coffee. Average residues in green coffee beans, roasted beans and instant coffee were 0.3, <0.1 and <0.1 mg/kg respectively. Processing factors for roasted coffee and instant coffee were both <0.3.

Cotton was treated at five times the maximum rate in a processing study with an in-furrow treatment at planting, a soil injection and three foliar sprays. The cotton was mechanically harvested and ginned. The resulting cotton seed was processed into meal, hulls and refined, bleached and deodorised (RBD) oil. The residues in the undelinted cotton seed, hulls, meal, and RBD oil were all <0.025 mg/kg. There was no concentration of disulfoton residues in any of the processed fractions. As residues were not detected in the raw agricultural commodity, processing factors could not be calculated.

Maize was treated with a band application at planting and a foliar spray 7 days before harvest at a total of approximately five times the recommended rate. Mature maize was mechanically harvested and processed into aspirated grain fractions (grain dust), starch, grits, meal, flour, and RBD oil produced by wet and dry milling. The average residues were 0.41 mg/kg in the grain, 4.24 mg/kg in aspirated grain fractions, and <0.1 mg/kg in grits, meal, flour,

and RBD oil produced by wet and dry milling. The processing factors were 10.3 for the aspirated grain fractions and <0.25 for all the other fractions.

Two processing studies in potatoes were reported. In one the details were inadequate and the Meeting requested additional information to allow the study to be used for refining dietary intake calculations. In the second study an in-furrow treatment plus three foliar sprays were applied at five times the maximum recommended rate in the USA. Potatoes were harvested and processed into granules, chips, wet peel and dry peel. The average disulfoton residues, with processing factors in parentheses, were potatoes 0.37 mg/kg, granules 0.52 mg/kg (1.4), chips 0.2 mg/kg (0.54) and wet peel 0.64 mg/kg (1.7). Residues were concentrated in the granules and wet peel.

In a processing study on sorghum an in-furrow treatment, a side-dress application and three foliar sprays were applied at three times the recommended US rate. Sorghum was harvested and processed into aspirated grain fractions. The average residues in the sorghum grain and aspirated fractions were 1.5 and 4.0 mg/kg respectively, giving a processing factor of 2.7.

Wheat treated at three times the maximum recommended rate in the USA was harvested and processed into bran, flour, germ, middlings, shorts and aspirated grain fractions. The average residues, with processing factors in parentheses, were grain 0.88 mg/kg, bran 0.83 mg/kg (0.94), flour 0.17 mg/kg (0.19), germ 1.87 mg/kg (2.1), middlings 0.36 mg/kg (0.41), shorts 0.98 mg/kg (1.1) and aspirated grain fractions 1.18 mg/kg (1.3). Disulfoton residues were concentrated in the germ and aspirated grain fractions.

Estimation of STMRs for refinement of dietary intake calculations
Data evaluated by the 1991 and 1994 Meetings were combined with data supplied to the present Meeting for the estimation of STMRs to refine the dietary intake calculations.

US and Canadian data on barley were evaluated in 1991 and 1994. The residues in trials according to GAP in rank order were <0.01 (7), 0.01 (2), <0.02 (3), 0.02 (2), 0.03, 0.04, 0.06, 0.09 and 0.1 (2) mg/kg. The Meeting estimated an STMR of 0.02 mg/kg for barley.

Trials on broccoli in accordance with US and Canadian GAP were reviewed in 1991. The residues in rank order were <0.02 (6), 0.03 (2), 0.05, 0.06, 0.09 and 0.11 mg/kg. The Meeting estimated an STMR of 0.025 mg/kg.

Trials on head cabbage in the USA and Japan in accordance with GAP gave residues in rank order of <0.02 (12), 0.02 (3), 0.03, 0.06, 0.07 (3), 0.08, 0.09, 0.12, 0.17(2), 0.23 and 0.32 mg/kg. The Meeting estimated an STMR of 0.02 mg/kg for head cabbages.

Trials on cauliflower were reviewed in 1991. Although GAP in the USA and Canada allows a maximum of two sprays but three sprays were applied in the trials, the data were considered to be acceptable as the applications were made at an early stage of crop growth (pre-emergent and post-emergent). The residues in rank order were <0.01 (6), 0.01 (3), 0.02, 0.03, 0.04, 0.05 and 0.31 mg/kg. The residue of 0.31 mg/kg was considered to be an outlier and was not used in estimating the STMR. The Meeting estimated an STMR of 0.01 mg/kg.

Three trials on <u>coffee</u> were reviewed in 1991. The rates of application were one, three and ten times the maximum recommended rate and the residues in the dry beans were 0.1-0.2 mg/kg. The Meeting could not estimate an STMR for coffee beans from only three results.

Residues in <u>green peas</u> and empty pods were reported in the 1991 and 1994 monographs. Data on Southern peas were not included in the estimation of the STMR as the trials were not compatible with current GAP in the USA. The residues in peas in six trials according to GAP were all <0.01 mg/kg and in the empty pods <0.01 (2), 0.02, 0.03 and 0.08 mg/kg. The Meeting estimated an STMR of 0.01 mg/kg for garden pea (shelled). As information on the weights of the whole pods in relation to the empty pods was not provided, an STMR for whole pods could not be estimated.

The 1994 Meeting considered the possibility of revising the maximum residue level of 0.01 mg/kg for <u>maize</u> estimated by the 1991 JMPR. The 1994 Meeting stated that the additional data provided since 1991 did not reflect GAP in the USA and that the MRL could not be set at 0.01* mg/kg as some residues had been determined at 0.01 mg/kg. Although GAP in the USA allows one soil treatment and a foliar spray, three sprays were applied in most of the trials reviewed in 1994. As the residues in most instances were below the limit of determination however, the present Meeting included the data from excessive treatments in estimating the maximum residue level and STMR. The residues in rank order were <0.01 (14), 0.01 and <0.02 (4) mg/kg. The Meeting estimated an STMR of 0.01 mg/kg and recommended a change in the existing MRL (Step 7B) from 0.01 mg/kg to 0.02* mg/kg.

Data on <u>oats</u> were reviewed in 1991. The results may be compared to Canadian GAP. Only three results may be strictly according to GAP, but as the treatment is either pre-emergent or early post-emergent, the data from all six trials could be considered for estimating an STMR. The Meeting concluded that on the basis of the recent studies of wheat metabolism where the four organophosphorus triesters constituted less than 4% of the TRR, and in view of the early application of the product, an STMR of 0 was appropriate.

Residues in <u>peanut</u> kernels were evaluated in 1991. The residues in four US trials reflecting GAP in rank order were <0.01 (2), 0.02 and 0.09 mg/kg. The Meeting estimated an STMR of 0.015 mg/kg for peanut.

Further information requested by the 1994 Meeting included additional residue data on <u>pecans</u> reflecting the higher aerial foliar application rates and data from soil applications according to GAP. The residues in trials reflecting GAP in rank order in the kernels were <0.01 (3), 0.01 and 0.02 mg/kg; and in whole nuts 0.08, 0.21 and 0.22 mg/kg. The Meeting concluded that there were enough trials reflecting GAP to estimate an STMR of 0.01 mg/kg for pecan kernels.

Data on <u>pineapples</u> from Martinique and Brazil were reviewed in 1991, in relation to GAP in France and Honduras. The residues in seven trials reflecting GAP were all <0.1 mg/kg at rates of 0.75 times to twice the maximum recommended rates. The Meeting estimated an STMR of 0 as the residues were below the limit of determination and were consistent with the results of recent metabolism studies.

Trials on <u>Japanese radishes</u> were reviewed in 1991. The residues in rank order were 0.004 (4), 0.008, 0.01, <u>0.02</u> (4), <u>0.03</u> (3), 0.06, 0.07, 0.10 (2), 0.12, 0.15 and 0.17 mg/kg. The Meeting estimated an STMR of 0.025 mg/kg for Japanese radish.

Data from the 1973 evaluation of disulfoton from Japan and the USA were submitted for the estimation of an STMR for <u>rice</u>. The Japanese data from only three trials. Twelve trials in the USA were reported but GAP was not identified and the residues were determined by a colorimetric method with a limit of quantification of 0.1 mg/kg. As recent GAP for the USA was not available and there were only three results from Japan, the Meeting could not estimate an STMR.

GAP for the treatment of <u>sorghum</u> in the USA allows a maximum of 2 soil treatments at 1.1 kg ai/ha followed by a maximum of three foliar applications at 0.56 kg ai/ha. The PHI for grain is 34 days after soil application and 7 days after foliar applications. Trials on sorghum were reviewed in 1991 and 1994. The residues resulting from excessive applications either at planting or post-planting were accepted for use in estimating an STMR, but those from excessive foliar treatments were not. As all the trials with foliar applications were either at twice the maximum recommended rate or with PHIs longer than 7 days, the foliar applications were not considered to reflect current GAP and the Meeting did not estimate an STMR for sorghum.

Trials on <u>sugar beet</u> reported in the 1991 monograph were with excessive treatment regimes. The data were originally evaluated against GAP from Chile, although the trials were conducted in the USA. The residues in rank order were <0.01 (3), 0.01 (4), <u>0.02</u> (2), <0.03, 0.03 (2), 0.04 and 0.06 (3) mg/kg. The Meeting considered that as recent GAP for sugar beet was not available and Chilean GAP could not be applied to the US trials, an STMR could not be estimated.

Residues in <u>tomatoes</u> were reported in 1991. The 1991 Meeting recommended an MRL of 0.1 mg/kg for tomatoes and the withdrawal of the MRL for vegetables. The residues in trials which reflect GAP in the USA and Japan were <0.01 (2), 0.02, 0.04 and 0.05 mg/kg. The Meeting considered that there were too few results to estimate an STMR.

Numerous trials on <u>wheat</u> were reviewed in 1991 and 1994. The residues in trials according to GAP in the USA and Canada in rank order were <0.01 (20), 0.01 (5), <<u>0.02</u> (10), 0.02 (5), 0.03 (2), 0.04 (2), <0.05 (2), 0.05 (3), <0.1, 0.11, 0.14, 0.16, 0.18, 0.19, 0.24 and 0.27 mg/kg. The Meeting reaffirmed the existing draft MRL of 0.2 mg/kg and estimated an STMR of 0.02 mg/kg for wheat.

FURTHER WORK OR INFORMATION

Desirable

Details of the potato processing study (Anon., 1968) for consideration in the refinement of dietary intake calculations.

Additional residues data for rice and sorghum to allow the estimation of an STMR for the calculation of dietary intake.

DIETARY RISK ASSESSMENT

In the current evaluation STMRs were estimated for 18 commodities. Where consumption data were available these STMRs were used in the estimates of dietary intake together with the existing MRLs and draft MRLs for 9 other food commodities.[1]

The estimated daily intake exceeds the ADI for the five GEMS/Food regional diets by the following percentages: Middle Eastern 190%, Far Eastern 920%, African 440%, Latin American 280% and European 160%.

The Meeting concluded that the dietary intake of disulfoton residues may exceed the ADI for all the GEMS/Food regional diets. Since the compound is neither new nor being evaluated in the CCPR Periodic Review Programme, the recommended MRLs are not designated as MRLMs.

Since the commodities which made a large contribution to the intake are rice and sorghum, further consideration should be given to these commodities to allow refinement of the dietary intake estimate at the international level.

4.12 ENDOSULFAN (032)

TOXICOLOGY

Endosulfan, an insecticide, has been evaluated toxicologically on several occasions by previous Joint Meetings, the latest being the 1990 JMPR when an ADI of 0-0.006 mg/kg bw was established. Endosulfan was reviewed by the present Meeting within the Periodic Review Programme of the Codex Committee on Pesticide Residues.

The present evaluation made full use of the national review of endosulfan prepared by the Australian National Registration Authority. The full document may be obtained at http://www.dpie.gov.au/nra/prsendo.html.

WHO has classified endosulfan as moderately hazardous.

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[1] The commodity garden peas (whole pods) was not included in the dietary estimate as a consumption figure for whole pods was not available.

More than 90% of an oral dose of endosulfan was absorbed in rats, with maximum plasma concentrations occurring after 3-8 h in males and about 18 h in females. Elimination occurs mainly in the faeces and to a lesser extent in the urine, more than 85% being excreted within 120 h. The highest tissue concentrations were in the kidneys. The metabolites of endosulfan include endosulfan sulfate, diol, hydroxy-ether, ether, and lactone but most of its metabolites are polar substances which have not yet been identified. Endosulfan would not be expected to accumulate significantly in human tissues. No data on plant metabolites were available to the Meeting.

A battery of tests for acute toxicity in several species with technical-grade endosulfan showed that it is highly toxic after oral or dermal administration, with respective LD_{50} values of 10-160 mg/kg bw and 45-135 mg/kg bw. The LC_{50} for rats in a single study was 13 mg/m^3 in females and 35 mg/m^3 in males. Endosulfan, administered by any route, is more toxic to female than to male rats. Clinical signs of acute intoxication include piloerection, salivation, hyperactivity, respiratory distress, diarrhoea, tremors, hunching, and convulsions.

The kidney is the target organ for toxicity. The renal effects include increased renal weights and granular pigment formation after short-term administration and progressive, chronic glomerulonephrosis or toxic nephropathy after long-term exposure, although the observation of progressive glomerulonephrosis is complicated by the fact that this is a common lesion in ageing laboratory rats and occurs at high incidence in control rats.

In a 90-day feeding study in rats, the cytoplasm of isolated cells in the renal proximal convoluted tubules had a yellowish colour, particularly in males, at all dietary concentrations from 10 ppm. The presence of this yellow pigmentation was largely reversible during a four-week recovery period, and it did not appear to indicate nephrotoxicity. A darker, more particulate, granular and/or clumped pigment was also observed, predominantly in cells of the straight portions and occasionally in the proximal convoluted tubules, at dietary concentrations of 30 ppm and above. This darker pigment was more persistent than the yellow one, and urinalysis revealed darker urine and marginally more ketones at doses from 60 ppm, and marginally more protein, particularly in males, indicating renal damage at doses of 360 ppm and above. Similar findings emerged from a multigeneration study but not from a two-year study of carcinogenicity in rats. The changes in pigmentation were considered to be due to the presence of endosulfan and/or its metabolites in the enlarged lysosomes. To test this hypothesis, a four-week feeding study was conducted in which male rats were given dietary concentrations of 360 or 720 ppm endosulfan. Light and electron microscopy of the kidneys of these animals clearly showed increases in the number of lysosomes and the size of cells in the convoluted tubule, probably as a result of accumulation of the test material and/or its metabolites. Lysosomal changes were not observed in either brain or liver, and the renal changes receded appreciably during a 30-day recovery period. Chemical analysis of the kidneys indicated the presence of α-endosulfan and, to a lesser extent β-endosulfan sulfate, and endosulfan lactone. The concentrations of the dominant α-endosulfan in the kidneys were about 50 times those in the liver. The concentrations in blood were usually below the level of detection. After the 30-day recovery period, renal α-endosulfan was detected only in traces and β-endosulfan not at all. Similar analysis of tissues from rats in the two-year study of toxicity and carcinogenicity did not reveal the presence of these substances in the kidney, although measurable α-endosulfan was found in the liver at 75 ppm. The yellow colour therefore indicates the presence of endosulfan and/or its metabolites, rather than either a stage in the pathogenesis of nephropathy or an independent expression of toxicity. It was

postulated that in longer studies its removal from lysosomes is accelerated by enzyme induction, which has not been investigated.

In a 78-week study, exposure of rats to endosulfan at a high dose of 20 mg/kg bw per day resulted in testicular atrophy, characterized by degeneration and necrosis of the germinal cells lining the seminiferous tubules. In addition, decreased sperm counts accompanied by an increased incidence of sperm abnormalities have been reported in mice, again at high doses of endosulfan. Reductions in the activities of some testicular xenobiotic-metabolizing enzymes and some hormones that are necessary for normal testicular function were also seen in a 30-day study in rats at 10, but not at 7.5 mg/kg bw per day. The functional significance of these findings was not clear, as studies of reproductive and developmental toxicity in rats and rabbits showed neither impaired fertility nor any increase in the incidence of defects or abnormalities in offspring. Given the high doses at which these testicular effects were observed, it would appear that they are of little human significance.

No genotoxic activity was observed in an adequate battery of tests for mutagenicity and clastogenicity *in vitro* and *in vivo*. The Meeting concluded that endosulfan is not genotoxic.

No carcinogenic effect was observed in mice at 18 ppm for 24 months, in female rats at 445 ppm for 78 weeks in one study or in male or female rats at 75 ppm or 100 ppm for two years in two other studies. The Meeting noted the differences in the dietary concentrations used in these studies, but non-neoplastic responses were seen even at the lower doses.

Endosulfan at dietary concentrations of 0, 3, 15, or 75 ppm did not affect reproductive performance or the growth or development of the offspring of rats over the course of a two-generation study. The NOAEL was 75 ppm, the highest dose tested, equal to 5 mg/kg bw per day for males and 6.2 mg/kg bw per day for females. The NOAEL for parental toxicity was 15 ppm, equal to 1 mg/kg bw per day for males and 1.2 mg/kg bw per day, on the basis of increased liver and kidney weights at 75 ppm.

In two studies of developmental toxicity in rats given oral doses of 0, 0.66, 2, or 6 mg/kg bw per day, the NOAEL for maternal toxicity was 0.66 mg/kg bw per day in one study and 2 mg/kg bw per day in the other. In the first case the basis was decreased body-weight gain at 2 mg/kg bw per day and decreased body-weight gain and clinical signs of toxicity at 6 mg/kg bw per day; in the second case, the basis was mortality, clinical signs of toxicity, and decreased body-weight gain at 6 mg/kg bw per day. In both studies the NOAEL for developmental toxicity was 2 mg/kg bw per day, in the first case on the basis of delayed development and a low incidence of skeletal variations seen at 6 mg/kg per day and in the second on the basis of an increased incidence of fragmented thoracic vertebral centra seen at 6 mg/kg bw per day. In neither study was there any treatment-related major malformation.

In a study of developmental toxicity in rabbits given oral doses of 0, 0.3, 0.7, or 1.8 mg/kg bw per day, the NOAEL for maternal toxicity was 0.7 mg/kg bw per day on the basis of clinical signs of toxicity at 1.8 mg/kg bw per day. The NOAEL for developmental toxicity was 1.8 mg/kg bw per day, the highest dose tested.

Several recent studies have shown that endosulfan, alone or in combination with other pesticides, may bind to estrogen receptors and may perturb the endocrine system. The available studies show only very weak binding to hormone receptors *in vitro*, and the evidence for their

relevance to adverse physiological effects *in vivo* is extremely limited. Long-term assays of toxicity and studies of reproductive and developmental toxicity in experimental mammals did not indicate that endosulfan induces functional aberrations that might result from loss of endocrine homeostasis.

The absence of immunotoxic effects in a large number of bioassays with endosulfan suggested that it does not have an adverse effect on the immune function of laboratory animals. However, in two studies, rats given endosulfan in the diet at 30 or 50 ppm for 6 weeks or 20 ppm for 22 weeks had reduced serum titres of tetanus toxoid antibody and reduced immunoglobulins G and M, and inhibition of migration of both leukocytes and macrophages. These findings have not been confirmed.

In a summary of case reports of human poisoning incidents, the lowest reported dose that caused death was 35 mg/kg bw. Higher doses caused death within 1 h. The clinical signs in these patients were dominated by tonic-clonic convulsions, consistent with the observations in experimental animals.

An ADI of 0-0.006 mg/kg bw was established on the basis of the NOAEL of 0.6 mg/kg bw per day in the two-year dietary study of toxicity in rats and a safety factor of 100. The ADI is supported by similar NOAELs in the 78-week dietary study of toxicity in mice, the one-year dietary study of toxicity in dogs, and the developmental toxicity study in rats.

An acute RfD of 0-0.02 mg/kg was established on the basis of the NOAEL of 2 mg/kg bw per day in the study of neurotoxicity in rats and a safety factor of 100.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 0.58 mg/kg bw per day (females in a 78-week study of toxicity)

Rat: 0.6 mg/kg bw per day (two-year dietary study of toxicity)
                6 mg/kg bw per day (reproductive toxicity)
                0.66 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
                2 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)

Rabbit: 0.7 mg/kg bw per day (study of developmental toxicity)

Dog: 0.57 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.006 mg/kg bw

Estimate of acute reference dose for humans

0.02 mg/kg bw

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

1.   Studies of immunotoxicity with standard test protocols
2.   Studies of the significant sex difference in acute toxicity, particularly in rats
3.   Further observations in humans

List of end points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion, and metabolism in mammals

Rate and extent of absorption:	Rat: oral, > 90% absorption; max. concentration at 3-8 h (m) 18 h (f)
Distribution:	Mainly in kidney and liver
Potential for accumulation:	Low
Rate and extent of excretion:	Biphasic; urinary t = 6h for first phase, 68h + 33-68h for 2nd phase; faecal t = 10 h and 30 h; >85% excretion in 120 h
Metabolism in animals	Oxidation & hydrolysis; unidentified polar metabolites
Toxicologically significant compounds (animals, plants and environment)	Parent No data on plant metobolites were available

Acute toxicity

Rat LD_{50} oral	10 mg/kg bw (f)
Rat LD_{50} dermal	500 mg/kg bw (f)
Rat LC_{50} inhalation	13 mg/m^3 4 h (f)
Skin irritation	Rabbit: not irritating
Eye irritation	Rabbit: not irritating
Skin sensitization	Guinea-pig: not sensitizing

Short-term toxicity

Target / critical effect	Reduced survival, convulsions, salivation
Lowest relevant oral NOAEL	0.64 mg/kg bw/day, rat, dietary
Lowest relevant dermal NOAEL	3 mg/kg bw/day, rat
Lowest relevant inhalation NOAEL	2 mg/m^3, rat, no effect (highest concentration)

Genotoxicity

Not genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect	Kidney
Lowest relevant NOAEL	0.6 mg/kg bw per day, rat 2-year study
Carcinogenicity	Not carcinogenic

Reproductive toxicity

Reproduction target / critical effect	none identified
Lowest relevant reproductive NOAEL	6 mg/kg bw per day, rat

Developmental target / critical effect	Fetoxicity at maternally toxic doses
Lowest relevant developmental NOAEL	2 mg/kg bw per day

Neurotoxicity / Delayed neurotoxicity

Rat: 1.5 mg/kg bw (f); 12.5 mg/kg bw (m) no effect

Other toxicological studies

1. Immunotoxicity in certain special assays, not confirmed in sensitization test or histologically. 2. Some conflicting evidence of interaction with oestrogen receptors *in vitro*; none *in vivo*

Medical data

lowest lethal dose: 35 mg/kg bw x 1, oral

Summary	Value	Study	Safety factor
ADI	0 - 0.006 mg/kg bw	several different species & end-points	100
Acute reference dose	0.02 mg/kg bw based on a NOAEL of 2 mg/kg bw per day in rats in a study of neurotoxicity and with a safety factor of 100		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on proposed or existing MRLs, were in the range of 20 to 120% of the ADI. Further refinements of dietary intake estimates will be undertaken during the periodic review of residues scheduled for 2000.

4.13 ETHOXYQUIN (035)

TOXICOLOGY

Ethoxyquin was previously evaluated by the Joint Meeting in 1969, when an ADI of 0-0.06 mg/kg bw was established on the basis of the NOAELs in a long-term feeding study in dogs and a study of reproductive toxicity in rats. The compound was reviewed at the present meeting within the CCPR Periodic Review Programme.

WHO has not classified ethoxyquin for acute toxicity.

Published studies show that ethoxyquin is rapidly absorbed from the gastrointestinal tract of rats and mice, with peak blood levels within 1 h. Liver, kidney, and adipose tissue have the highest tissue concentrations. Excretion occurs predominantly via the urine and is rapid, with more than 85% of doses up to 25 mg/kg bw being excreted within 24 h. At 250 mg/kg bw, absorption and excretion are slowed, which is attributed to reduced gastric emptying, and only 50% of the dose is excreted within 24 h. Repeated oral doses of 25 mg/kg bw per day resulted in an excretion profile similar to that for single doses, but repeated administration of 250 mg/kg bw

per day was reported to result in a profile similar to that for lower doses, indicating induction of metabolism, transport, and/or a return to normal gastric emptying. Biliary excretion and enterohepatic recirculation play a significant role in the toxicokinetics of ethoxyquin, more than 40% of an intravenous dose of 25 mg/kg bw being detected in the bile of bile-duct-cannulated rats. The metabolism of ethoxyquin involves *O*-deethylation or hydroxylation followed by conjugation as the sulfate or glucuronide. A proposed reaction scheme for the production of biliary metabolites involves epoxidation and the generation of reactive, electrophilic intermediates. No information on plant metabolites was available.

Ethoxyquin has low acute toxicity when administered orally (LD_{50} = 1700 mg/kg bw), dermally, or by inhalation. It is slightly irritating to the eyes and skin and had only very weak sensitizing potential when administered topically to guinea-pigs. Exposure to ethoxyquin in the workplace has been linked to allergic contact dermatitis, and the substance should be considered as a sensitizer in humans.

The main target organ after repeated administration of ethoxyquin to rats for 28 days or more at doses of 50-1000 mg/kg bw per day was the kidney. Mechanistic studies with dietary concentrations equivalent to 250 mg/kg bw per day showed that the precise effects were dependent on the age at first exposure, were progressive, more severe in males than in females, and not reversible after 24 weeks of exposure. Other effects seen in rats exposed to ethoxyquin for 28 or 90 days at doses $\geq$ 200 mg/kg bw per day were stained fur, brown urine, changes to haematological parameters, increased liver weights, and changes in clinical chemical parameters consistent with altered liver function. The overall NOAEL in the short-term studies in rats was 20 mg/kg bw per day.

In dogs given capsules containing ethoxyquin for 90 days at 0, 2, 4, 20, or 40 mg/kg bw per day, the liver was the primary target. Alterations in haematological parameters and clinical chemical changes indicative of altered liver function were seen at doses $\geq$ 4 mg/kg bw per day, together with hepatocellular necrosis, vacuolation, and pigment deposition. Although staining indicated that the pigment was haemosiderin, a specific investigation showed it to be protoporphyrin IX. The overall NOAEL in short-term studies in dogs was 2 mg/kg bw per day. This is consistent with the results of an older, one-year study in dogs in which a NOAEL of 3 mg/kg bw per day was established on the basis of findings suggestive of effects on the kidney and liver at 10 mg/kg bw per day.

No modern long-term studies of toxicity or carcinogenicity have been performed. In studies summarized by the 1969 Meeting in which ethoxyquin was administered to dogs at 0 or 300 ppm in the diet for 5 years or at 0, 3, 10, 50, or 100 mg/kg bw per day by gavage for 1 year. In these studies, effects were observed in the liver and kidneys at doses of 10 mg/kg bw per day and above. The NOAEL was 300 ppm, equivalent to 7.5 mg/kg bw per day. A two-year study in rats that received dietary concentrations of 0, 62, 125, 250, 500, 1000, 2000, or 4000 ppm, published in 1959, gave no indication of carcinogenicity, with an overall NOAEL of 125 ppm, equivalent to 6 mg/kg bw per day; lesions in the kidney, liver, and thyroid gland were seen at higher doses. Mechanistic studies on tumour induction and promotion show that ethoxyquin induces both phase-I and phase-II xenobiotic metabolism. Although its incorporation into the diet at 8000 ppm after treatment with an *N*-nitrosamine reduced the formation of preneoplastic foci in the liver, it increased the incidence of preneoplastic and neoplastic events in the kidney and urinary bladder. No significant increase in tumour incidence was seen after one year in mice that received four subcutaneous, near-lethal doses of ethoxyquin.

Published reports of studies of bacterial mutagenicity indicate that ethoxyquin is not mutagenic in prokaryotic systems, but only limited details of the protocols and results were provided. No data were available on other genotoxic end-points.

No modern study of reproductive toxicity has been performed in rodents. Three studies in which rats received 0, 125, 250, 375, 500, 1000, or 1125 ppm in the diet, all with non-standard protocols, which were summarized by the 1969 Meeting, gave slightly contradictory results. Two of the studies, including the most extensive, apparently showed no effects on the aspects of reproduction investigated at doses up to 1125 ppm in the diet (equivalent to 56 mg/kg bw per day), while the other showed an increased incidence of stillbirths at 1125 ppm and decreased litter size at 375 ppm, with a NOAEL of 125 ppm (equivalent to 6 mg/kg bw per day).

A modern two-generation study of reproductive toxicity in dogs given diets containing 0, 100, or 225 ppm showed that ethoxyquin had no effects on reproductive parameters at 225 ppm (equivalent to 5.6 mg/kg bw per day), the highest dose tested. The clinical signs observed included dehydration, excess lachrymation, and evidence of hepatic toxicity, especially in females. The effects were seen at both doses and were consistent with the results of the short-term studies in dogs. The findings in females may have been related to increased consumption during gestation and lactation. The lowest dose tested, 100 ppm, equivalent to 2.5 mg/kg bw per day, was considered to be a minimal effect level.

A study of developmental toxicity in rats at 0, 50, 150, or 350 mg/kg bw per day showed that ethoxyquin is not fetotoxic or teratogenic at doses up to 350 mg/kg bw per day. Maternal toxicity, stained fur, and reduced body-weight gain were seen at 150 and 350 mg/kg bw per day. No studies of developmental toxicity have been performed in other species.

An ADI of 0-0.005 mg/kg bw per day was established on the basis of the minimal-effect level of 2.5 mg/kg bw per day in the multigeneration study in dogs and a 500-fold safety factor to account for the lack of a NOAEL in this study and for the incompleteness of the database. The multigeneration study of reproductive toxicity was of longer duration and more recent than a 90-year study in dogs treated by gavage with a NOAEL of 2 mg/kg bw per day.

An acute RfD was not allocated because ethoxyquin is of low acute toxicity. The Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Rat: 125 ppm, equivalent to 6 mg/kg bw per day (two-year study of toxicity and
         carcinogenicity)
              500 ppm, equivalent to 25 mg/kg bw per day (two-generation study of
         reproductive toxicity)
              50 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
              350 mg/kg bw per day (developmental toxicity)

Dog: 2 mg/kg bw per day (general toxicity in a 90-day study of toxicity
              3 mg/kg bw per day (one-year study of toxicity)
              300 ppm, equivalent to 7.5 mg/kg bw per day (five-year study of toxicity)
              2.5 mg/kg bw per day (minimal effect level for general toxicity in a two-
         generation study of reproductive toxicity)
              5 mg/kg bw per day (reproductive performance; highest dose tested)

Estimate of acceptable daily intake for humans

0-0.005 mg/kg bw

Estimate of acute reference dose

Not allocated (unnecessary)

Studies that would provide information useful for the continued evaluation of the compound.
1.   Studies of genotoxicity in mammalian systems
2.   A long-term study of toxicity and carcinogenicity in rats that complies with modern
      guidelines
3.   Observations in humans

List of end points for setting guidance values for dietary & non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	Rapid absorption, >50%
Dermal absorption:	No relevant information
Distribution:	Widely distributed; liver, kidney, adipose tissue
Potential for accumulation: Potential for accoP	Slight evidence of bioaccumulation
Rate and extent of excretion:	>85% eliminated in 24 h
Metabolism in animals	Extensive; no parent compound detected in urine
Toxicologically significant compounds (animals, plants and environment)	Metabolites considered of equivalent toxicity to parent compound

Acute toxicity

Rat LD_{50} oral	1700 mg/kg bw
Rat LD_{50} dermal	>2000 mg/kg bw

Rat LC$_{50}$ inhalation	>2.0 mg/l (whole body exposure)
Skin irritation	Slightly irritating
Eye irritation	Slightly irritating
Skin sensitization	Sensitizing

Short-term toxicity

Target / critical effect	General toxicity in multigeneration study, dogs
Lowest relevant oral NOAEL	<2.5 mg/kg bw per day (dog, reproductive toxicity)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEL	No data

Genotoxicity

	No evidence of genotoxicity, but testing inadequate

Long term toxicity and carcinogenicity

Target/critical effect:	Inadequate data
Lowest relevant NOAEL	Inadequate data
Carcinogenicity	No evidence of carcinogenicity, but testing inadequate

Reproductive toxicity

Reproduction target / critical effect	No adverse effect on reproduction, dogs
Lowest relevant reproductive NOAEL	5 mg/kg per day, multigeneration study, dog
Developmental target / critical effect	No adverse effect on development, rats
Lowest relevant developmental NOAEL	350 mg/kg/bw per day (rats)

Neurotoxicity / Delayed neurotoxicity

	No data, but no concern from other studies

Other toxicological studies

	Not an initiator or promoter of rat liver tumoursPossible increase in urinary bladder pre-neoplastic and neoplastic changes

Medical data

	Contact allergic dermatitis reported in food handlers

Summary	Value	Study	Safety factor
ADI	0-0.005 mg/kg bw	Dog, multigeneration reproductive toxicity study	500
Acute reference dose	Not allocated (unnecessary)		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 0-50% of the ADI. The Meeting concluded that the intake of residues of ethoxyquin resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.14 FOLPET (041)

RESIDUE AND ANALYTICAL ASPECTS

Folpet was first evaluated in 1969 and has been reviewed several times since. It was listed by the 1997 CCPR (29th Session, ALINORM 97/24A, Appendix III) for periodic re-evaluation for residues by the 1998 JMPR. Residue aspects were reviewed in 1997, when it was agreed that the 1997 review would be included in the 1998 Periodic Review for completeness. The Meeting received information on metabolism, analytical methods, freezer storage stability, registered uses, data from supervised trials on fruit and vegetable crops and processing studies.

When a lactating goat was dosed orally with [*trichloromethyl*-^{14}C]folpet at 0.55 mg/kg bw (equivalent to 20 ppm in the feed) daily for 3 days, most of the dose was rapidly excreted in the faeces (42% of the dose) and in expired air (31%). ^{14}C levels in the milk were 0.23-0.38 mg/kg as folpet and accounted for 1% of the dose. The tissues contained ^{14}C at 0.8% of the dose with most in the liver and kidneys (0.34 and 0.26 mg/kg respectively, expressed as folpet).

When a lactating goat was dosed orally with [*benzene*-^{14}C]folpet at 0.34 mg/kg bw (equivalent to 14 ppm in the feed) daily for 6 days 93% of the ^{14}C was excreted in the urine and faeces. The ^{14}C in the tissues and milk constituted less than 0.1% of the dose. ^{14}C levels (expressed as folpet) in the milk, liver and kidneys were 0.004-0.006, 0.022 and 0.052 mg/kg respectively.

The metabolism studies showed that folpet is rapidly degraded in goats, initially by loss of the CCl$_3$ group. The carbon from the CCl$_3$ becomes incorporated into thiazolidine and natural products. The remainder of the molecule was metabolized to phthalimide and phthalamic acid.

When the roots of tomato plants were treated with [*carbonyl*-^{14}C]folpet the ^{14}C was rapidly absorbed into the plants (85% within 1 day). After 11 days 90% of the absorbed ^{14}C was in the tops. Folpet itself was a very minor part (<0.1-0.2%) of the residue within the plant. The main identified components were phthalimide, phthalamic acid and phthalic acid. Unidentified polar metabolites, possibly ring-hydroxylated phthalamic acid derivatives, accounted for 15-30% of the ^{14}C in the tops.

Levels of ^{14}C were lower in the roots than in the straw or grain of wheat treated with [*benzene*-^{14}C]folpet at a rate equivalent to 1.6 kg ai/ha and harvested 43 and 54 days after the second treatment. Folpet was the major component of the residue in or on the straw (4.7 mg/kg) and grain (9.3 mg/kg), with phthalic acid (4.3 mg/kg in straw and 6.4 mg/kg in grain) and phthalimide (1.5 mg/kg in straw and 3.1 mg/kg in grain) also prominent.

When Thomson Seedless grape vines were treated 3 times with [*benzene*-^{14}C]folpet at a rate equivalent to 1.5 kg ai/ha and the grapes harvested 25 days after the final treatment, surface rinsing removed 26% of the grape residue. Folpet itself constituted 27% of the residue in or on

the grapes, and phthalic acid and phthalimide 5.8% and 11% respectively. An unidentified compound in the water-soluble fraction accounted for 41% of the residue. It was very polar and yielded phthalic acid on hydrolysis, so was likely to be a conjugate or conjugates of phthalic acid.

A small avocado tree was treated with 3 foliar applications equivalent to 3.4 kg ai/ha of [*benzene*-^{14}C]folpet and fruit were harvested at maturity 97 days after the final application. Very little residue was removed by rinsing the fruit, but most was extractable with ethyl acetate from the peel and pulp. The residues in or on the fruit were folpet 0.026 mg/kg, phthalimide 0.22 mg/kg and phthalic acid 4.5 mg/kg. Polar and other unidentified residues amounted to about 0.7 mg/kg. Folpet and phthalimide residues were mainly on the peel, but most of the phthalic acid was in the pulp.

No information was provided on the environmental fate of folpet in soil or water/sediment systems. Such studies are needed for a periodic review (page 13 of *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed*). The Meeting was informed at a late stage that studies were available on aerobic and anaerobic degradation and photolysis in soil, field dissipation, adsorption, desorption and mobility in soil, leaching of aged residues and aqueous photolysis.

The Meeting agreed to withdraw its previous recommendations for MRLS and agreed that maximum residue levels estimated from the trials could not be recommended as suitable for establishing MRLs until these critical supporting studies had been evaluated.

The 1993 JMPR reviewed the Schlesinger analytical method for residues of folpet and phthalimide. The methods used in the supervised trials on apples, lettuce, melons, onions, strawberries and tomatoes were developed from the Schlesinger method. Folpet was determined in the cleaned up extract by GLC with an ECD. Methods were validated for all the above commodities and some others. The recovery of folpet from various fortified commodities was commonly 70-100%, but with some excursions outside this range. In a total of 340 recovery tests the mean and median were 87% and 86% respectively. The LOD was 0.05 mg/kg.

Care is needed that there is no opportunity for conversion of folpet to phthalimide during analysis because folpet is very susceptible to hydrolysis.

Cereal grains and straw in the UK trials were analysed by an HPLC method with an LOD of 0.05 mg/kg. Folpet residues were extracted with ethyl acetate and clean-up was effected by gel permeation chromatography. Separations were on a reversed-phase column with an acetonitrile-water mobile phase.

Folpet is included in an official multi-residue method of The Netherlands for pesticides amenable to gas chromatography. LODs for various matrices are 0.01-0.05 mg/kg.

Folpet residues were shown to be stable during frozen storage for the intervals tested in apple juice (30 days), wet apple pomace (35 days), apples (149 days), cranberries (176 days), cucumbers (29 days), grape juice (36 days), lettuce (90 days), onions (41 days), potatoes (55 days), tomato paste (30 days), tomato purée (31 days), tomatoes (136 days), chopped wheat grain (366 days) and chopped wheat straw (366 days).

The Meeting agreed that the current definition of the residue is suitable for enforcing compliance with MRLs and for estimation of dietary intake.

Definition of the residue for compliance with MRLs and for the estimation of dietary intake: *folpet*

Information was made available to the Meeting on registered uses of folpet and on supervised trials on apples, grapes, strawberries, onions, cucumbers, melons, tomatoes, lettuce, potatoes, barley, wheat, cereal fodder and cereal forage. Relevant data from the 1993 and 1994 monographs were also included where possible to support the evaluations.

Trials on <u>apples</u> were reported from Argentina, Canada, Chile, France, Hungary, Germany, Poland, Portugal, Spain, Switzerland and the USA. Six trials in Germany and one in Poland suggest that folpet residues on apples decrease quite slowly and that some latitude in the PHI can be accepted in evaluating the trials.

Folpet is registered in Argentina for use on apples with a spray concentration of 0.12 kg ai/hl and a PHI of 15 days. Residues in apples from 2 trials where the spray concentration accorded with GAP but the PHI was 10 days (sufficiently close for a persistent residue) were 1.4 and 2.6 mg/kg.

The Canadian trials were based on a PHI of 7 days, which was too remote from Canadian GAP (1 day) to be used. Trials in France, Germany and the USA were not evaluated because labels with relevant GAP were not available. No field report was available for the trial in Poland.

Two trials on apples in Chile where the trial conditions corresponded to the registered application rate (2.0 kg ai/ha), but the harvest was 7 days after the final application instead of the official 3 days, could not be evaluated because the difference in the PHI was too great .

In a Hungarian trial according to GAP (application at 1.6 kg ai/ha and a PHI of 10 days), the highest folpet residue on apples was 8.0 mg/kg. In a Swiss trial which complied with GAP (spray concentration of 0.10 kg ai/hl and a PHI of 21 days), the residue was 3.4 mg/kg, and in a Spanish trial complying with GAP (spray concentration of 0.16 kg ai/hl and a PHI of 10 days), the highest residue was 3.1 mg/kg.

Folpet may be sprayed at 0.13 kg ai/hl on apples in Portugal with the harvest 21 days after the final application. In a trial meeting these conditions the folpet residue on apples was 3.2 mg/kg. In a trial recorded in the 1993 Evaluations folpet was applied 10 times at a concentration of 0.13 kg ai/hl and the resulting residue 21 days after the final application was 1.8 mg/kg

In summary, the folpet residues in apples from trials according to GAP were Argentina 1.4 and 2.6 mg/kg, Chile 2.0 and 3.7 mg/kg, Hungary 8.0 mg/kg, Switzerland 3.4 mg/kg, Spain 3.1 mg/kg and Portugal 1.8 and 3.2 mg/kg. The residues in rank order (median underlined) in the 7 trials were 1.4, 1.8, 2.6, <u>3.1</u>, 3.2, 3.4 and 8.0 mg/kg.

The Meeting estimated a maximum residue level for folpet in apples of 10 mg/kg but could not recommend it as suitable for use as an MRL until the critical supporting studies on environmental fate have been evaluated.

The folpet residue in grapes was 1.6 mg/kg in a supervised trial that complied with GAP in Argentina (spray concentration 0.13 kg ai/hl and PHI 7 days).

Italian GAP permits application to table grapes at a spray concentration of 0.16 kg ai/hl with harvest 10 days after the final application. In an Italian trial under these conditions the folpet residue was 3.3 mg/kg. A second Italian trial could not be evaluated because the PHI of 41 days was too long.

Folpet may be used on grapes in France at 1.0-1.5 kg ai/ha (SC and WG formulations) or 1.0-1.8 kg ai/ha (WP formulations) with specified PHIs of 21 and 30 days for SC, 21 and 28 days for WG and 28 days for WP. Variations of rate and PHI may depend on other fungicides in the same formulation. Trials in France in 1992, 1994, 1995 and 1996 were accepted as complying with maximum GAP conditions where the application rate was within 30% of 1.5 kg ai/ha and the PHI was 16-28 days. The residues in grapes from 12 trials meeting these conditions in rank order (median underlined) were 1.6, 1.9, 1.9, 2.2, 2.4, 2.8, 3.1, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg.

Trials in Chile could not be evaluated because the interval between final application and harvest was 14 days whereas GAP specifies 3 days. Trials in Germany and Russia could not be evaluated because relevant GAP and registered labels were not available.

In summary, the folpet residues in grapes from trials according to GAP were Argentina 1.6 mg/kg, Italy 3.3 mg/kg and France 1.6, 1.9, 1.9, 2.2, 2.4, 2.8, 3.1, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg. The residues in rank order (median underlined) in the 14 trials were 1.6, 1.6, 1.9, 1.9, 2.2, 2.4, 2.8, 3.1, 3.3, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg

The Meeting estimated a maximum residue level for folpet on grapes of 10 mg/kg but could not recommend it as suitable for use as an MRL until the critical supporting studies on environmental fate have been evaluated.

Folpet is registered for use on strawberries in Spain at a spray concentration of 0.15 kg ai/hl with a PHI of 21 days. The residues in three trials in Italy according to Spanish GAP were <0.01, 0.04 and 0.09 mg/kg. Data from a fourth Italian trial could not be used because the longest interval between the final application and harvest was 14 days.

Mexican GAP permits the application of folpet to strawberries at 1.3 kg ai/ha with no restriction on the PHI (the label statement is "interval between final application and harvest – no limit"). The residues in 3 Mexican trials complying with GAP (the PHI of 2 days is sufficiently close to the label statement, which implies a 0-day PHI) were 1.6, 1.8 and 2.2 mg/kg.

In three trials on strawberries in plastic tunnels in The Netherlands which complied with glasshouse GAP (spray concentration 0.13 kg ai/hl and 14 days PHI) the folpet residues were 1.4, 1.6 and 1.9 mg/kg.

In summary, the folpet residues in strawberries from trials according to GAP were Italy <0.01, 0.04 and 0.09 mg/kg, Mexico 1.6, 1.8 and 2.2 mg/kg and The Netherlands 1.4, 1.6 and 1.9 mg/kg. The Meeting agreed that the data from Italy appeared to be in a different population from the others and should not be considered for the estimation of an STMR. The folpet residues in strawberries in rank order (median underlined) in the 6 trials were 1.4, 1.6, 1.6, 1.8, 1.9 and 2.2 mg/kg.

The Meeting estimated a maximum residue level for folpet on strawberries of 5 mg/kg but could not recommend it as suitable for use as an MRL until the critical supporting studies on environmental fate have been evaluated.

The folpet residues in onions from a trial in Chile complying with GAP (2 kg ai/ha and 7 days PHI) was 0.36 mg/kg. Portuguese GAP for onions allows a spray concentration of 0.13 kg ai/hl and a 7 days PHI. Folpet residues in a Portuguese and a Spanish trial which complied with GAP were 5.0 and 2.5 mg/kg respectively. (The PHI in Spain was 10 days).

Trials in Greece could not be evaluated because the PHIs were 20 days whereas Greek GAP does not specify the PHI, suggesting that 0 days is permissible. Similarly, Hungarian data could not be used because the PHIs in the trials were 14 days, while Hungarian GAP specifies 5 days. Mexican trials also could not be evaluated because the label does not limit the PHI, implying 0 days, while the interval in the trials was 7 days. No relevant GAP was available for the evaluation of trials in The Netherlands and Germany.

The Meeting could not estimate a maximum residue level for folpet in onions because there were too few trials (3) according to GAP.

Folpet may be used on cucumbers in Mexico at 1.8 kg ai/ha with no limit for the PHI, implying that harvest on the day of the final application is permissible. In the 4 trials in Mexico the PHI was 3 days, which was too far from 0 days to be considered as maximum GAP for such a rapidly growing crop as cucumbers. The single Canadian trial could not be used because the trial conditions did not correspond to GAP.

The Meeting agreed to withdraw the recommendation of the 1994 JMPR for folpet on cucumbers (0.5 mg/kg).

In Greece folpet is registered for use on melons with a spray concentration of 0.16 kg ai/hl and a PHI of 20 days. Folpet residues were below the LOD (<0.05 mg/kg) in melons from 2 Greek trials complying with GAP (0.12 kg ai/hl and 20 days PHI).

GAP in Honduras permits a spray concentration of 0.13 kg ai/hl with harvest 7 days after the final application. Melons were harvested 3 days after the final application in one trial in Guatemala and 2 trials in Honduras but the data could not be used because the interval was too short to be considered to comply with GAP for Honduras.

Mexican GAP permits application at 1.8 kg ai/ha with harvest on the day of the final application (the label does not limit the PHI). The three trials in Mexico could not be evaluated because the interval between the final application and harvest was 7 days, which is not sufficiently close to maximum GAP.

The Meeting agreed to withdraw the 1997 recommendation for folpet in melons (3 mg/kg) because there were too few trials (2) according to GAP.

Data were available from supervised trials on tomatoes in Chile, Hungary, Italy, Mexico, The Netherlands, Portugal, Spain and the USA. Trials in the USA and The Netherlands, and

trials in plastic greenhouses in Italy could not be evaluated because no relevant GAP was available.

The folpet residue in tomatoes from a trial in Chile complying with GAP (1.7 kg ai/ha and 7 days PHI) was 2.4 mg/kg. Mexican GAP permits application of folpet to tomatoes at 2.0 kg ai/ha and harvest without timing restriction. The residues in tomatoes in five Mexican trials complying with GAP (the PHI of 2 days is sufficiently close to the implied 0 days of GAP) were 0.45, 1.0, 1.3, 1.6 and 1.8 mg/kg.

In Hungary folpet is registered for use on tomatoes at a spray concentration of 0.13 kg ai/hl with harvest 14 days after the final application. In four Hungarian trials with conditions complying with GAP and in one recorded in the 1993 Evaluations complying with GAP, the residues were all below the LOD (<0.02 and <0.05 mg/kg (4)).

In two Portuguese trials (0.16 kg ai/hl and 7 days PHI) in compliance with Portuguese GAP (0.13 kg ai/hl and 7 days PHI) the residues were 0.34 and 0.58 mg/kg.

Folpet is registered for use on tomatoes in Spain at a spray concentration of 0.15 kg ai/hl with a 10 days PHI. The residues in two Spanish and four Italian trials substantially according to Spanish GAP were 1.2 and 1.3 mg/kg in Spain and 0.43, 0.60, 0.70 and 0.80 mg/kg in Italy.

In summary, the folpet residues in tomatoes from trials according to GAP were Chile 2.4 mg/kg, Mexico 0.45, 1.0, 1.3, 1.6 and 1.8 mg/kg, Hungary <0.02 and <0.05 4 mg/kg, Portugal 0.34 and 0.58 mg/kg, Spain 1.2 and 1.3 mg/kg and Italy 0.43, 0.60, 0.70 and 0.80 mg/kg. The residues in rank order in the 19 trials were <0.02, <0.05 (4), 0.34, 0.43, 0.45, 0.58, 0.6, 0.7, 0.80, 1.0, 1.2, 1.3, 1.3, 1.6, 1.8 and 2.4 mg/kg

The residues from the Hungarian trials appear to be in a different population from the others. The residues in the 14 trials in the other countries (median underlined) which were used to estimate an STMR for tomatoes were 0.34, 0.43, 0.45, 0.58, 0.6, 0.7, 0.80, 1.0, 1.2, 1.3, 1.3, 1.6, 1.8 and 2.4 mg/kg

The Meeting estimated a maximum residue level for folpet on tomatoes of 3 mg/kg but could not recommend it as suitable for use as an MRL until the critical supporting studies on environmental fate have been evaluated.

Portuguese GAP for the use of folpet on lettuce allows a 0.13 kg ai/hl spray with a 14 days PHI. The residue in head lettuce from a trial in Portugal complying with GAP was 4.3 mg/kg. A trial in Spain on leaf lettuce complied with Spanish GAP (0.13-0.15 kg ai/hl and 21 days PHI). The residue was undetectable (<0.05 mg/kg).

Trials in Greece could not be evaluated because the interval between the final application and harvest was 20 days whereas Greek GAP does not specify a PHI, implying that 0 days is permitted. Lettuce were harvested 7 days after the final application in Mexican trials, but again the registered use specifies no limit for the PHI, so the trial conditions were not sufficiently close to GAP. Trials in Hungary and Germany could not be evaluated because no relevant GAP was available.

The Meeting agreed that there were too few results to estimate a maximum residue level or STMR for lettuce.

Supervised trials on potatoes were carried out in Italy, Mexico, Poland, Russia and South Africa. Translocation to the tubers from foliar applications would not be expected from a compound with such low solubility in water as folpet. Occasional residues could occur if a tuber is exposed above the soil surface to direct spray.

Four Italian trials (0.13 kg ai/hl, 10 days PHI) complied with Spanish GAP (spray concentration 0.15 kg ai/hl and PHI 10 days). The residues were 0.08 and <0.01 (3) mg/kg.

No relevant GAP was available to evaluate the other trials.

There were too few results to estimate a maximum residue level or STMR. The Meeting recommended the withdrawal of the current CXL for folpet on potatoes (0.02* mg/kg).

Documented studies of numerous folpet trials in France and the UK on barley and wheat, which included extensive data on forage and fodder, were reported but could not be evaluated because no information on GAP supported by registered labels was made available. Field reports for many of the trials were lacking.

The Meeting noted that feeding studies on farm animals had not been reported. These would be needed before MRLs could be established for cereal grains, fodder and forage.

Studies of the effects of processing on folpet residues in apples, grapes and tomatoes were reported.

Field-treated apples were processed to juice and wet pomace by procedures simulating commercial practice as closely as possible. The process included an initial washing step which removed about 40% of the residue. The calculated processing factors for the production of wet pomace and apple juice from unwashed apples were 2.6 and 0.035 respectively.

Grapes were treated post-harvest by dipping bunches for 30 seconds into a vat containing folpet (1.25 kg ai/hl). The grapes were allowed to dry and then processed into raisins and juice. Because folpet residues are on the surface the treatment was considered valid.

The treated grapes were dried in the sun until the moisture level had reached 12-16%. After destemming, the dried grapes were rehydrated to 18-20% moisture in an incubator at 21°C to produce raisins. Juice was produced from treated grapes by crushing, enzyme treatment, heating and filtering.

Folpet residues were not detectable (<0.05 mg/kg) in the grape juice. The calculated processing factor for grapes to juice is 0 (<0.003). Folpet residues in the dried raisins and hydrated raisins were higher than in the original grapes, with processing factors of 3.2 and 1.9 respectively.

The Meeting estimated a maximum residue level for folpet residues in dried grapes or raisins of 40 mg/kg after rounding up, from the processing factor (3.2) and the estimated maximum residue level in grapes (10 mg/kg).

In ten trials in Germany in 1993 residues of folpet were measured in must and wine produced from folpet-treated grapes. The processing factors for must ranged from 0 to 0.97 (mean 0.29). Folpet was not detected (<0.05 mg/kg) in any wine sample, so the processing factor was 0. The metabolite phthalimide was consistently present in the must and wine at levels typically 25-50% of the folpet levels in the grapes. The metabolism study on grapes had shown the formation of a water-soluble conjugate of phthalic acid in grapes which also has the potential to reach the wine.

A tomato crop was treated five times with folpet (2.2 kg ai/ha) and harvested seven days after the final application for processing. Tomatoes were treated in 0.5% sodium hydroxide and then vigorously washed before being processed to juice, purée and paste. Purée was produced from juice by evaporation and adjustment of salt and water levels before heating and canning. Paste was produced similarly, but with a higher salt level.

Folpet residues were not detected (<0.05 mg/kg) in tomato purée or paste produced from tomatoes containing 1.8 mg/kg of folpet. It is likely that the initial vigorous cleaning of the tomatoes and the sodium hydroxide treatment completely removed or destroyed the folpet. The estimated processing factor for the transfer of folpet from tomatoes to purée and paste is therefore 0.

FURTHER WORK OR INFORMATION

<u>Desirable</u>

1. Expression of the residues found in forage and fodder on a dry-weight basis so that the results can be used in the estimation of maximum residue levels for animal commodities.

2. Studies on the environmental fate of folpet in soil and in water/sediment systems are needed before MRLs can be recommended for folpet (see page 13 of *Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed*).

DIETARY RISK ASSESSMENT

Recommendations for folpet MRLs have been withdrawn because critical supporting studies were not available for the periodic review. Consequently, no MRLs or STMRs are available for the estimation of dietary intake.

4.15 GLUFOSINATE-AMMONIUM (175)

RESIDUE AND ANALYTICAL ASPECTS

Glufosinate-ammonium was first evaluated for residues and toxicology by the 1991 JMPR and subsequently for residues in 1994. Glufosinate-tolerant crops have now been developed with new GAP and different residue patterns, requiring new MRLs.

The Meeting received information on metabolism and environmental fate, registered uses and supervised residue trials on tropical fruits, tree nuts and various genetically-modified field crops. Feeding and processing studies were also reported.

Studies on the metabolism of glufosinate-ammonium in genetically modified rape seed (canola), sugar beet, maize, soya beans and tomatoes showed that the tolerant crops rapidly converted the active glufosinate isomer (L–glufosinate) to *N*-acetyl-glufosinate (NAG). The main components of the residue in tolerant plants are the L–isomer of NAG and D-isomer of glufosinate.

The Meeting received information on animal metabolism studies on rats, lactating goats and laying hens.

When <u>rats</u> were dosed orally with L–[3,4-^{14}C]NAG some de-acetylation to glufosinate occurred and some glufosinate was bioavailable, but unchanged NAG was the main component (85-89%) of the TRR in the faecal extracts. Almost all of the administered ^{14}C was excreted in the faeces within 4 days.

When rats were dosed orally with [3,4-^{14}C]glufosinate-ammonium, 75-89% of the ^{14}C was excreted in the faeces and 8-11% in the urine within 48 hours. The main components in the faecal extracts were glufosinate (77% of administered ^{14}C), NAG (7.5%), 4-methylphosphinico-2-hydroxybutanoic acid or MHB (4.3%) and 3-methylphosphinicopropionic acid or MPP (1.3%). The main components in the urine were glufosinate (4.3%) and MPP (0.8%).

Very small amounts of the administered ^{14}C were found in the tissues (<0.1%) and milk (<0.02%) of a <u>lactating goat</u> dosed orally for 4 days with [3,4-^{14}C]glufosinate. Levels of ^{14}C reached a plateau in the milk by day 2. Levels of ^{14}C were higher in the kidneys and liver than in other tissues. Glufosinate and MPP constituted about 50% and 30% respectively of the residue in both kidneys and liver. Glufosinate accounted for 50% of the ^{14}C in the milk. When a lactating goat was dosed orally with L–[3,4-^{14}C]NAG the disposition of ^{14}C in the tissues and milk was similar to that after dosing with glufosinate. Glufosinate was the main residue in the kidneys, liver and milk with NAG and MPP forming a substantial part of the residue in the kidneys and liver.

Less than 0.02% of the administered ^{14}C was present in the edible tissues when <u>laying hens</u> were dosed orally for 14 days with [3,4-^{14}C]glufosinate-ammonium. MPP and glufosinate were the main residues identified in the liver and eggs respectively. After dosing orally for 14 days with L–[3,4-^{14}C]NAG less than 0.1% of the administered dose was present in the edible tissues and blood. NAG was the main residue identified in liver and egg yolks while glufosinate was the main residue in egg whites.

The Meeting received information on metabolism studies in rape seed, canola, sugar beet, maize, soya beans and tomatoes.

Genetically modified <u>rape</u> plants rapidly acetylated glufosinate. Cut rape plants were placed in a nutrient solution containing [3,4-^{14}C]glufosinate-ammonium for 6 days, by which time 57% of the ^{14}C in the plants was associated with NAG and 36% with glufosinate.

In glufosinate-tolerant <u>canola</u> plant tissues sampled 1 hour after treatment with [^{14}C]glufosinate, 73% and 18% of the ^{14}C was present as glufosinate and NAG respectively, demonstrating very rapid acetylation of glufosinate. After 21 days 60%, 21% and 7% of the ^{14}C corresponded to NAG, glufosinate and MPP respectively.

When glufosinate-tolerant <u>sugar beet</u> plants were sprayed with [3,4-^{14}C]glufosinate-ammonium the racemic isomer composition in the surface residue was unchanged, but in the absorbed residue L–glufosinate was metabolised to L–NAG.

Glufosinate was generally a minor component of the residue in treated tolerant <u>maize</u>. NAG was the main residue in the forage, silage and fodder, while MPP was the major component in grain, cobs and husks. The GLC enforcement analytical method for glufosinate, MPP and NAG was in reasonable agreement with a radiolabel method for the residues in the forage.

NAG was the main residue in the forage, straw, pods and beans of treated tolerant <u>soya bean</u> plants. MPP levels exceeded glufosinate levels in the pods and beans. The GLC enforcement method and an HPLC radiolabel method were in reasonable agreement in analyses of forage, straw, pods and beans at the higher residue levels, but at low levels the result from the enforcement method was less than from the ^{14}C measurement.

The translocation of [^{14}C]glufosinate-ammonium from treated leaves to shoots, other leaves and roots was approximately 4 times as fast in glufosinate-resistant <u>tomato</u> plants as in susceptible tomatoes. Most of the surface residue was glufosinate itself, but this was very rapidly converted to NAG once absorbed into the leaves. NAG constituted essentially all the residue in the ripe fruit harvested 60 or 74 days after the plants were treated.

The Meeting received information on the degradation and dissipation of glufosinate-ammonium in soil, residues in rotational crops and fate in water-sediment systems.

Glufosinate disappeared with a half-life of about 3-6 days during aerobic incubation with a sandy loam soil. MPP, the major product, reached its maximum after about 14 days incubation. MPA, 2-methylphosphinicoacetic acid, became the main residue after long intervals. Glufosinate suffered 62% and 31% mineralization during 120 days incubation with and without incorporation of plant material into the soil respectively.

In a dissipation study glufosinate-ammonium, applied 3 times to bare ground, dissipated quickly with calculated half-lives of 15, 7.2 and 2.7 days, the increased rates probably being related to increased soil moisture and temperature. The estimated half-lives for MPP after its residues peaked were 38, 14 and 16 days, and for MPA 25, 19 and 7 days. No residues were detected below a 45-60 cm depth section, but glufosinate and MPP reached a depth of 30-45 cm on several occasions during the study. Glufosinate and its degradation products have some mobility in soil but their rapid dissipation ensures that travel down the soil profile is limited.

When L–[3,4-^{14}C]NAG was incubated in a sandy loam soil it was very rapidly converted to L–glufosinate, which was then itself broken down and mineralized. The comparable rate of mineralization and production of unextractable residues suggests that the degradation pathway for NAG is through glufosinate. Further experiments showed that the half-life of NAG was only hours.

No important degradation products other than CO_2 were identified when $[2-^{14}C]$MPA was incubated in a sandy loam under aerobic conditions. Estimated decline and mineralization half-lives were 24 and 74 days respectively. Degradation in a loamy sand was much slower. When MPP was incubated under aerobic conditions in a sandy loam, MPA was the only significant product after 120 days.

After 3 days incubation of a sandy loam soil with tolerant tomato leaves containing residues, mainly of glufosinate and NAG, most of the residue had been converted to MPP, which itself was degraded more slowly to MPA and ultimately to CO_2.

Residues of degradation products of glufosinate should be undetectable or at very low levels in rotational crops. When radishes, lettuce and wheat were sown in a confined rotational crop study 28 days after glufosinate treatment of bare ground (to simulate re-sowing a failed crop) residues of MPP and MPA were present at low levels in the crops, demonstrating possible uptake of these compounds. The pattern of residues was similar in the three crops. When sowing was 119 days after treatment (to simulate a following crop) residues were not detectable in lettuce or radishes but MPP and MPA were detected by ^{14}C methods at very low levels in the wheat grain and straw.

The photolytic breakdown of glufosinate in natural waters was very slow.

MPP became the major component of the residue within a few days when $[3,4-^{14}C]$glufosinate-ammonium was incubated in a water-sediment system at 20°C. Glufosinate itself disappeared with a half-life of 3 days, but only 25% mineralization occurred during the 361 days of the study. In other experiments the rates of degradation were shown to be affected by the source of the water and the residue level of glufosinate (with faster disappearance at lower levels). In all cases most of the residue was in the water phase.

Methods of residue analysis

The main components of the residue in genetically modified tolerant crops are glufosinate, NAG and MPP. Analytical methods have been designed to measure the three components separately or, because glufosinate and NAG produce the same derivative in the analytical procedure, to measure glufosinate and NAG combined and MPP separately. Residues are extracted from the finely ground sample with water, and the extract is cleaned up on an anion exchange resin column. After solvent exchange, NAG and MPP are separated from glufosinate on a cation exchange column. The residues are taken up in glacial acetic acid and methylated, and glufosinate acetylated, with trimethyl orthoacetate in refluxing acetic acid. After solvent exchange and final clean-up on a silica gel cartridge the derivatized residues are determined by GLC with flame-photometric detection.

Modifications of the extraction and initial clean-up are needed for samples such as maize oil, fats and milk. A variation of the method dispenses with the cation exchange separation and determines glufosinate and NAG as a combined GLC peak because both compounds produce the same analytical derivative. The LOD for crop samples is typically 0.05 mg/kg for each analyte. Analytical recoveries have been extensively tested and found satisfactory on many substrates.

Analysts should be aware that transgenic glufosinate-tolerant soya beans plants can convert L–glufosinate to NAG very rapidly, giving apparently low analytical recoveries in spiked samples.

Glufosinate, NAG and MPP were shown to be stable during frozen storage for intervals of 12, 15 or 24 months in the following substrates: genetically modified maize and soya beans and their processed commodities, cow and chicken tissues, milk, eggs, susceptible maize grain, and transgenic rape seed and sugar beet roots. The 1994 JMPR reported that residues of glufosinate and MPP (described as Hoe 061517) in apples, oranges, kiwifruit, maize, soya beans and almonds were stable during frozen storage.

Some samples from the supervised trials were stored for 2 years, but the storage stability studies have demonstrated that the residues were still stable.

Definition of the residue

The current definition includes glufosinate and MPP and is based on the residues occurring in conventional crops. When glufosinate is used on glufosinate-tolerant crops NAG is produced. It should be included in the residue definition for enforcement because NAG is generally the main component of the residue and because the same derivative is produced in the analytical method from glufosinate itself and NAG, and in the simplified method both appear in the GLC peak from their common derivative. The revised residue definition is also suitable for commodities from conventional crops because if NAG is absent it will not contribute to the analytical result and if present at low levels it is necessarily included in the analytical result.

A suitable revised residue definition would be *Sum of glufosinate-ammonium, 3-(hydroxy(methyl)phosphinoyl)propionic acid and N-acetyl-glufosinate expressed as glufosinate (free acid)*, but the Meeting could not consider the adoption of this definition until the toxicological evaluation of NAG had been completed.

The residue reported in the supervised trials consists of three components, but is often reported with the glufosinate and NAG residue combined. The metabolism studies show that residues of the main component constitute 65-75% of the combined residue when all three components are at measurable levels. It follows that if all three components are below the LOD a reasonable assumption is that the combined residue is also below or close to the LOD. When one component is above and the others are below the LOD, the combined residue is assumed to be equal to the residue of the main component.

The method of calculating the total residue for various situations is illustrated by the following example.

Glufosinate	MPP	NAG	Total
<0.05	<0.05	<0.05	<0.05
<0.05	<0.05	0.06	0.06
0.05	<0.05	0.09	0.14

Information was made available on uses of glufosinate around fruit trees and nut trees. Limited information was provided on GAP for use of glufosinate on transgenic crops.

Glufosinate-ammonium is registered for use in Australia as a directed spray for weed control around avocados, bananas, feijoa, guava, kiwifruit, litchis, mangoes, papaya, passion fruit, pineapples and rambutans at 0.20-1.0 kg ai/ha. Malaysia has similar registered uses for glufosinate-ammonium as a directed herbicide spray around bananas, carambola, durians, guava, jack fruit and mangoes at 0.3-0.5 kg ai/ha. Residues in the fruit would generally not be expected from this type of use. Glufosinate itself is not taken up by roots but MPP, the main degradation product in soil, can be absorbed by the roots and translocated through the crop.

Supervised trials

Supervised trials were reported on tropical fruits, nut trees, maize, soya beans, rape, canola and sugar beet.

Residues were not detected in avocados in 3 Australian trials where glufosinate was used at 1.0, 1.2 and 2.0 kg ai/ha. In one trial at 1.2 kg ai/ha, glufosinate was detected at 0.06 mg/kg (presumably direct contamination during application) in 1 sample on day 0, but in no other samples. Residues were not detected in the fruit from 3 Australian trials on mangoes where the application rates were 1.0, 1.2 and 2.0 kg ai/ha or 1 trial on papayas at 1.2 kg ai/ha.

Residues were not detected in the fruit from Malaysian trials on carambola and guavas (2 trials at 0.5 kg ai/ha and 2 at 1 kg ai/ha on each fruit).

The Meeting agreed to consider these fruits together as "tropical fruits with inedible peel" but noted that a CXL of 0.2 mg/kg had already been established for banana, which would have to be excluded from the group. The residues in rank order from the 16 trials were <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, <0.05, 0.06, <0.1, <0.1, <0.1 and <0.1 mg/kg.

In view of the type of use and generally unquantifiable residues at 3-5 sampling intervals in all of the trials the Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for glufosinate in Assorted tropical and sub-tropical fruits – inedible peel (except banana).

The US registered use for glufosinate around almond, pecan and walnut trees permits a directed application at 1.7 kg ai/ha, with no more than 5.1 kg ai/ha total per year, and a 14-day PHI. MPP residues were 0.07 mg/kg in almonds from a US trial at the label rate and up to 0.22 mg/kg in a trial at twice the label rate. MPP is the main degradation product in soil, so its presence demonstrates the possibility of root uptake rather than contamination of foliage by spray. Residues were not detected in almonds from 3 other trials at the label rate or 3 trials at the double rate. The trials were in California in 1985.

Residues were not detected (<0.05 mg/kg) in nuts from 3 trials on pecans (USA, 1985) with glufosinate applied at 1.7 kg ai/ha and 3 at twice that rate. In 2 trials nuts were harvested 21 days after application rather than 14 days, but the use pattern is sufficiently close to GAP. Residues were not detected (<0.05 mg/kg) in nuts from 6 walnut trials at 1.7 kg ai/ha, 5 trials 3.4 kg/ha or 3 at other rates higher than GAP in the USA in 1985.

The Australian registration for glufosinate-ammonium permits 0.2-1.0 kg ai/ha as a directed spray around nut trees. Residues were not detected (<0.1, <0.05 mg/kg) in macadamia nuts in Australian trials from 1992 and 1995 at the label rate (2 trials) and double rate (2 trials).

Italian registration permits a directed application of 0.5-1.6 kg ai/ha (maximum 2.5 kg ai/ha per year) for weed control around hazelnuts. Residues were not detected (<0.05 mg/kg) in nuts from 5 hazelnut trials in Italy in 1985 according to GAP.

The Meeting considered the 4 almond, 6 pecan, 14 walnut, 4 macadamia and 5 hazelnut trials as a group. The residues in the 33 trials were <0.05 (30), 0.07 and <0.1 (2) mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR level of 0.05 mg/kg for glufosinate in tree nuts.

Glufosinate-ammonium is registered in Canada for use on transgenic maize at 0.30-0.50 kg ai/ha with final application at the 8-10 leaf stage. In Canadian trials in 1994-5 no residues (<0.05 mg/kg) were detected in 7 trials at 0.5 or 0.6 kg ai/ha or 3 trials at 1.0 kg/ha applied at growth stage GS 17-19 (7-9 leaves), or in 4 trials at 0.6 kg ai/ha at a later growth stage (GS 33, 3 nodes detectable).

Glufosinate-ammonium is registered in Portugal for use on transgenic maize at 0.40-0.80 kg ai/ha with the final application when the plant has no more than 8-10 leaves. In 7 Italian trials and 3 Spanish trials in 1996 according to Portuguese GAP no residues (<0.05 mg/kg) were detected in the harvested maize.

The German registration for glufosinate-ammonium on tolerant maize allows a single application of 0.9 kg ai/ha during the 3-8 leaf growth stage or 2 applications 6 weeks apart at 0.45 kg ai/ha with the final application at the 8-leaf stage. Residues were below the LOD (0.05 mg/kg) in 13 trials in Germany where the trial conditions (2 applications of 0.45-0.60 kg ai/ha, the second at GS 18 or GS 19, i.e. 8 or 9 leaves) were considered to comply with the registered use, 22 trials in France in accord with German GAP, and in 5 trials in Germany and 7 in France where glufosinate-ammonium was used at excessive rates (2 applications of 0.80 kg ai/ha).

Glufosinate-ammonium is registered for use in the USA on tolerant maize with 2 applications at 0.23-0.41 kg ai/ha, the second at a plant height of 60 cm with harvest 70 days later. Supervised trials on maize in the USA at rates of 0.40-0.50 kg ai/ha (1 or 2 applications) at the nominated growth stage were accepted as equivalent to the maximum GAP. The PHI (70 days) was considered secondary to the growth stage in deciding the timing of the applications. In many cases the grain was harvested 90-120 days after the final treatment. The residues (glufosinate + NAG + MPP expressed as glufosinate) in the 35 trials according to GAP were <0.05 (29), 0.05 (2) and 0.07 (4) mg/kg.

In summary, the residues of glufosinate + NAG + MPP expressed as glufosinate in tolerant maize were Canada <0.05 (14) mg/kg, Italy <0.05 (7) mg/kg, Spain <0.05 (3) mg/kg, Germany <0.05 (18) mg/kg, France <0.05 (29) mg/kg, the USA <0.05 (29), 0.05 (2) and 0.07 (4) mg/kg. The residues in rank order were <0.05 (100), 0.05 (2) and 0.07 (4) mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for glufosinate in maize and noted that this was equivalent to the existing CXL. The major residue in the glufosinate-tolerant crop is NAG, which is not included in the current residue definition. NAG was included

in the reported residues where the derivatization GLC procedure without an ion-exchange separation step was used, and was below the LOD when determined separately.

Glufosinate is registered for use on transgenic glufosinate-tolerant <u>canola</u> in Canada with 1 application at 0.60 kg ai/ha or 2 applications of 0.30-0.50 kg ai/ha, the final application at the early bolting growth stage. The label carries the instruction not to graze the treated crop or cut for hay. The Meeting was informed that the 10 leaves stage is very close to bolting. Only two supervised trials in Canada met the condition of final treatment at the 10-leaf stage, each with 1 application of 0.5 or 0.75 kg ai/ha. Residues were not detected (<0.05 mg/kg) in either of the trials, but 2 trials were insufficient to support a recommendation.

Glufosinate-ammonium is registered for use in the USA on tolerant soya beans with 2 applications at 0.23-0.41 kg ai/ha, the second application at bloom with harvest 70 days later. Supervised trials on soya beans in the USA with 2 applications of 0.40-0.50 kg ai/ha at the nominated growth stage were accepted as equivalent to the maximum GAP. The PHI (70 days) was considered as secondary to the growth stage in deciding the timing of the applications. In the trials the grain was harvested 62-102 days after the final treatment. The residues of glufosinate + NAG + MPP expressed as glufosinate in the 20 trials according to GAP in rank order (median underlined) were 0.32, 0.39, 0.43, 0.52, 0.56, 0.71, 0.72, 0.78, 0.81, <u>0.85</u>, <u>0.89</u>, 0.92, 0.96, 1.02, 1.24, 1.26, 1.33, 1.56, 1.64 and 1.88 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg for soya beans but could not recommend it as suitable for use as an MRL until the toxicological evaluation of NAG had been completed.

Residues in almond hulls from 3 trials on almonds at the label rate and 3 at twice that rate (see above) were all <0.5 mg/kg. Unfortunately, residues in the hulls were not determined in the 2 trials where MPP was detected in the almonds. However, the Meeting estimated a maximum residue level of 0.5 mg/kg for almond hulls, which is recommended for use as an MRL.

The registered use of glufosinate-ammonium on tolerant maize in the USA (see above) specifies pre-harvest intervals of 60 and 70 days for maize forage and fodder respectively. The supervised trials on maize in the USA described above, which complied with GAP, showed residues of glufosinate + NAG + MPP expressed as glufosinate in the forage or silage harvested 60-92 days after treatment (the residue is reasonably persistent) in rank order, median underlined, of 0.09, 0.12, 0.12, 0.13, 0.17, 0.2, 0.26, 0.28, 0.3, 0.32, 0.33, 0.33, 0.36, 0.4, 0.48, 0.53, 0.53, <u>0.54</u>, <u>0.54</u>, 0.68, 0.74, 0.78, 0.78, 0.79, 0.9, 1.07, 1.1, 1.19, 1.2, 1.45, 1.67, 1.7, 1.71, 1.76, 2.9 and 3.48 mg/kg.

The residues of glufosinate + NAG + MPP expressed as glufosinate in maize fodder harvested 84-122 days after treatment were 0.07, 0.08, 0.11, 0.12, 0.15, 0.22, 0.25, 0.25, 0.32, 0.33, 0.43, 0.5, 0.53, 0.58, 0.65, 0.68, 0.69, <u>0.72</u>, 0.8, 0.94, 0.95, 1.13, 1.19, 1.32, 1.42, 1.5, 1.69, 1.74, 1.76, 1.78, 1.96, 2.31, 2.65, 2.83 and 5.4 mg/kg.

The Meeting estimated maximum residue levels of 5 mg/kg in maize forage and 10 mg/kg in maize fodder but could not recommend them as suitable for use as MRLs until the toxicological evaluation of NAG had been completed.

Feeding studies on lactating dairy cows and laying hens were reported.

Lactating dairy cows were dosed with glufosinate-ammonium + NAG (15 + 85% to simulate the typical terminal residue) at rates equivalent to 9, 27 and 91 ppm glufosinate free acid equivalents in the diet for 28 days. Residues were not detected in the milk at the 9 ppm feeding level, but reached a plateau on day 3 at the 91 ppm level. Residues (glufosinate, NAG and MPP) in the tissues were below the LODs at the lower feeding levels; at 91 ppm they were detected in the kidneys and liver, but not in muscle or fat. MPP was the major residue in the liver.

Laying hens were dosed with glufosinate-ammonium + NAG (15 + 85) at levels equivalent to 0.36, 1.1 and 3.6 ppm glufosinate free acid equivalents in the diet for 28 days. Residues (glufosinate, NAG and MPP) were not detected in the tissues or eggs.

Studies on the fate of residues during the commercial food processing of sugar beet, maize, soya beans and canola were reported.

When tolerant sugar beet were treated with glufosinate-ammonium and processed, residues of glufosinate, NAG and MPP tended to remain in the juice and ultimately appear in the molasses. Residues were not detected (<0.05 mg/kg) in the raw sugar. The processing factors for glufosinate + NAG for raw sugar in 3 trials were nominally 0 (<0.17), 0 (<0.83) and 0 (<0.05) on the basis of the residues in the roots. The mean processing factor for molasses was 6.8, showing that glufosinate residues are concentrated in the molasses on evaporation of the water. In another study on sugar beet with fivefold application rates MPP was the main residue component and again no residues were detected in the raw sugar. The calculated processing factors were 0 (<0.08) for refined sugar and 6.4 for molasses.

In 2 processing trials (wet and dry milling) of glufosinate-tolerant maize treated with excessive rates of glufosinate-ammonium, only NAG was quantifiable in the grain from only one trial. In this trial no residues (<0.05 mg/kg) were detected in crude or refined oil from either process or in the starch and hulls from the wet milling process. The estimated processing factors were meal 1, grits 1, and hulls 2, all from dry milling.

Residues of glufosinate, NAG and MPP were not detected (<0.05 mg/kg) in refined or crude oil in a processing study with a transgenic soya bean crop treated with glufosinate-ammonium at a fivefold rate. The calculated factors for processing seed to meal and seed to crude or refined oil are 1.3 and 0 (<0.3) respectively.

Glufosinate itself was not detected in the seed or any processed fraction of a transgenic canola crop treated at a fourfold rate with glufosinate-ammonium. The main residue was NAG. The calculated processing factor for untoasted meal was 3.1 and for toasted meal 3.7. No residues (<0.05 mg/kg) were detected in the oils.

Information was made available to the Meeting on national MRLs. Governments have adopted a variety of residue definitions.

DIETARY RISK ASSESSMENT

Estimated STMRs for glufosinate-ammonium on tropical fruit and tree nuts have been added to the previous list of MRLs (21) for other commodities. The estimated dietary intakes of

glufosinate-ammonium expressed as glufosinate for the 5 GEMS/Food regional diets were in the range of 3 to 10% of the ADI. The Meeting concluded that the intake of residues of glufosinate-ammonium resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.16 HEXYTHIAZOX (176)

RESIDUE AND ANALYTICAL ASPECTS

Hexythiazox was first evaluated in 1991 and again in 1994. It was scheduled for evaluation by the 1998 JMPR because the 28th Session of the CCPR (1996) was informed that data on hops would be made available (ALINORM 97/24, para 75). The Meeting received information on methods of analysis, registered uses, supervised residue trials and processing studies on hops.

The analytical method used in the supervised trials and processing studies in Germany relies on solvent partition and column chromatography for clean-up. In the GLC determination the residue is injected into a hot injector (300°C) where hexythiazox and its metabolites are converted to 5-(4-chlorophenyl)-4-methylthiazolidin-2-one (PT 1-3) which becomes the analyte. The LODs were 0.05 mg/kg in beer and brewing wastes, 0.1 mg/kg in green hops, and 0.5 mg/kg in dry hops.

The 1991 JMPR reported that hexythiazox is the main residue in crops and its metabolites are present in negligible amounts. The residues determined by this "total residue" method may therefore be accepted as equivalent to residues of hexythiazox, the current definition of the residue.

The method was shown to be free of interference from 26 pesticides registered for use on hops in the USA.

Hexythiazox was hydrolysed with alkali to convert it to PT 1-3 in the analytical method used in the US trials on hops. An LOD of 0.1 mg/kg was achieved for dry hops.

A similar extraction and clean-up was used in the Japanese trials but there was no hydrolysis step and the hexythiazox was determined by HPLC as the parent compound. An LOD of 0.2 mg/kg was achieved.

Hexythiazox residues on green and dry hops were stable during a two-year study of freezer storage stability, but the residues in beer declined by approximately half during refrigerator storage at 4°C for two years.

Hexythiazox is not registered for use on hops in the USA so the US trials could not be evaluated.

GAP for hops in Japan permits 2 applications at 0.0033-0.005 kg ai/hl or 0.2-0.3 kg ai/ha with harvest 7 days after the final application. In two Japanese trials in 1985 where the trial conditions were close to GAP the residues in dry hops were 14 and 16 mg/kg 7 days after the second application.

Hexythiazox is registered for use on hops in Germany where it may be applied at spray concentrations of 0.003-0.0045 kg ai/hl with an application rate not exceeding 0.15 kg ai/ha. Two applications are permitted and a 28 days PHI is specified. Hexythiazox was applied to hops in 9 trials in Germany in 1992 and 1993 following the conditions of German GAP. Only one application was made instead of the possible 2, but the average half-life of the hexythiazox residues in the 1992 trials was 10 days, which suggests that an earlier application would contribute no more than 20% of the final residue and probably much less because the first application would be at an earlier growth stage. The residues in dry hops from the 9 German trials according to GAP in rank order (median underlined) were 0.61, 0.64, 0.71, 0.79, <u>0.79</u>, 0.88, 0.93, 1.3 and 1.5 mg/kg.

The residues in the Japanese trials (14 and 16 mg/kg) could not be combined with those in the German trials because they appeared to be from separate populations. The Meeting considered that 2 trials were insufficient to support an MRL, so the estimated maximum residue level was based on the highest data population with sufficient support, in this case the 9 German trials.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.88-1.5 mg/kg for hexythiazox in dry hops.

In 4 trials where beer was brewed from dry hops containing hexythiazox residues of 0.88-1.5 mg/kg, no residues (<0.05 mg/kg) were detected in the beer. The level of hexythiazox residues in dry spent hops was approximately half that in the initial dry hops. From 57% to 86% of the hexythiazox residues in the dry hops was accounted for in the spent hops and dregs from the process. Calculation showed that if all the remaining hexythiazox was in the beer, i.e. no losses occurred during boiling and fermentation, the level in the beer would be less than 0.0009 mg/l. The Meeting concluded that the STMR for hexythiazox residues in beer should be 0 mg/kg.

DIETARY RISK ASSESSMENT

A maximum residue level for hexythiazox in hops has been recommended for use as an MRL. A processing study has resulted in an estimated STMR level of 0 mg/kg for hexythiazox residues in beer. All the other in values used for the intake estimation are previously established CXLs.

Estimated daily intakes for hexythiazox for the 5 GEMS/Food regional diets are in the range of 0 to 5% of the ADI. The Meeting concluded that the intake of residues of hexythiazox resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.17. KRESOXIM-METHYL (199)

methyl (*E*)-methoxyimino[$\forall$-(*o*-tolyloxy)-*o*-tolyl]acetate

Kresoxim-methyl is a broad-spectrum fungicide and a member of the strobilurin family, a new class of biologically active compounds structurally related to Strobilurin A, a natural product of the wood-decaying fungus *Strobilurus tenacellus*. It is intended for use as an agricultural spray in the control and treatment of fungal infections on crops and fruits. Strobilurins are known to bind to the bcl complex (complex III), one of the oxide reductase proteins of the electron transport chain in mitochondria. The ester linkage in kresoxim-methyl is essential for its activity.

Kresoxim-methyl was evaluated for the first time by the present Meeting.

TOXICOLOGY

Who has not classified kresoxim-methyl for acute toxicity.

About 60% of an oral dose of 50 mg/kg bw and 25% of a dose of 500 mg/kg bw kresoxim-methyl was absorbed. It was excreted mainly in the faeces (70% of the low dose and 80% of the high dose), predominantly via the bile (about 40% of the low dose and 15% of the high dose within 48 h), with lesser amounts in urine (about 20% of the low dose and 10% of the high dose). Peak levels of the radiolabel in plasma were reached 0.5-1 h after the low dose and 8 h after the high dose. The plasma half-life was 17-19 h at the low dose and 22-31 h at the high dose. The highest residual concentrations were found in the liver, but the concentrations in all tissues, including the liver, were less than 0.1 g equivalent/g tissue after 120 h of treatment at the low dose.

After oral administration of kresoxim-methyl, a high proportion of the parent compound was found in the faeces, but none was detected in tissues or bile examined 4 h after dosing. In rats, 34 metabolites of kresoxim-methyl were identified. The proposed metabolic pathways are hydrolytic cleavage of the ester, the oxime ether, and the benzyl ether bonds, hydroxylation at the *para* position of the phenoxy ring, hydropyl of the aryl-methyl group and its subsequent oxidation to form the corresponding carboxylic acid, and conjugation of the resulting hydroxy groups with glucuronate or sulfate. The major metabolites identified in both rats and plants were the free acid, code number 490M1 ((*E*)-methoxyimino[$\forall$-(*o*-tolyloxy)-*o*-tolyl]acetic acid), the hydroxy derivative of this, 490M2 ($\forall$-(*o*-hydroxymethylphenoxy)-*o*-tolyl(methoxyimino)acetic acid) formed by hydroxylation of the aryl-methyl group, the *p*-hydroxytolyloxy product 490M9

(α-(p-hydroxy-o-tolyloxy)-o-tolyl(methoxyimino)acetic acid), and their conjugates. 490M1, 490M2 and 490M9 all had low acute toxicity and were not mutagenic.

In a range-finding study in B6C3F1 mice, kresoxim-methyl was administered in the diet at concentrations of 0, 500, 2000, or 8000 ppm for 28 days. The NOAEL was 8000 ppm, equal to 2100 mg/kg bw per day. In a three-month study, C57Bl/6N mice received kresoxim-methyl in the diet at concentrations of 0, 250, 1000, 4000, or 8000 ppm. The NOAEL was 8000 ppm, equal to 1900 mg/kg bw per day.

In a range-finding study in rats, kresoxim-methyl was administered in the diet at concentrations of 0, 1000, 4000, or 16 000 ppm for 28 days. The NOAEL was 4000 ppm in males, equal to 370 mg/kg bw per day, on the basis of increased activities of serum γ-glutamyl transferase at 16 000 ppm, equal to 1500 mg/kg bw per day. In a three-week study of toxicity in rats, kresoxim-methyl was administered in the diet at concentrations of 0, 10, 50, or 8000 ppm. The NOAEL was 50 ppm, equal to 3 mg/kg bw per day, on the basis of increased hepatic γ-glutamyl transferase activity in males at 8000 ppm. In a 90-day study of toxicity in rats, kresoxim-methyl (purity, 98.7%) was administered in the diet at concentrations of 0, 500, 2000, 8000, or 16 000 ppm. The NOAEL was 500 ppm in females, equal to 43 mg/kg bw per day, based on increased relative liver weight at 2000 ppm and above, and 2000 ppm in males, equal to 150 mg/kg bw per day, based on decreased body-weight gain and increased activity of serum γ-glutamyl transferase at 8000 ppm and above.

In a three-month study of toxicity in dogs, kresoxim-methyl was administered at dietary concentrations of 0, 1000, 5000, or 25 000 ppm. The NOAEL was 5000 ppm, equal to 140 mg/kg bw per day, on the basis of vomiting, diarrhoea, and reduced body-weight gain in animals of each sex at 25 000 ppm. In a 12-month study in dogs, kresoxim-methyl was administered at dietary concentrations of 0, 1000, 5000, or 25 000 ppm. The NOAEL was 5000 ppm, equal to 140 mg/kg bw per day, on the basis of a reduction in body weight in males at 25 000 ppm. No compound-related toxicity was observed in females.

In an assay for carcinogenicity in mice, kresoxim-methyl was administered at dietary concentrations of 0, 400, 2000, or 8000 ppm for 18 months. The NOAEL was 400 ppm, equal to 81 mg/kg bw per day, in females on the basis of reduction in body weight at 2000 ppm. The NOAEL in males was 2000 ppm, equal to 300 mg/kg bw per day, on the basis of decreased body weight and increased relative adrenal weight at 8000 ppm. At this dose, increased incidences of renal papillary necrosis and hepatic amyloidosis were observed in females. There was no evidence of carcinogenicity.

In a two-year study of toxicity in rats, kresoxim-methyl was administered at dietary concentrations of 0, 200, 800, 8000, or 16 000 ppm. The NOAEL was 800 ppm, equal to 36 mg/kg bw per day, on the basis of an increased incidence of hepatocellular carcinoma in animals of each sex, increased serum γ-glutamyl transferase activity, increased relative liver weight, an increased incidence and degree of severity of eosinophilic foci and mixed-cell foci in males, and a decrease in terminal body weight and body-weight gain in females at 8000 ppm and 16 000 ppm. There was also an increased incidence of biliary cysts and bile-duct proliferation.

In a study of carcinogenicity in rats, kresoxim-methyl was administered at dietary concentrations of 0, 200, 800, 8000, or 16 000 ppm for 24 months. Evidence of biliary alterations included increased incidences of biliary cysts and cholangiofibrosis in females at 16 000 ppm. At

this dose, increased relative liver weights and an increased incidence of hepatocellular hypertrophy were observed in males. The NOAEL was 800 ppm, equal to 36 mg/kg bw per day, on the basis of increased incidences of hepatocellular carcinoma, reductions in body weight and body-weight gain, and an increased incidence of eosinophilic foci and mixed-cell foci in animals of each sex at 8000 ppm and above. The overall NOAEL for neoplastic and non-neoplastic effects was 800 ppm, equal to 36 mg/kg bw per day.

It is generally recognized that the process of carcinogenesis is divided into three stages: initiation, promotion, and progression. A series of mechanistic studies was conducted with kresoxim-methyl, including tests for tumour initiating and promoting potential. In a study on tumour initiating activity, kresoxim-methyl did not increase the number of liver-cell foci in rats at a single dose of 2400 mg/kg bw. In a study on the promoting potential of kresoxim-methyl, rats received an initiating dose of N-nitrosodiethylamine and then a diet containing 0, 200, 800, 8000, or 16 000 ppm kresoxim-methyl for six weeks. Quantitative analysis of hepatic foci with a computer-assisted image analyser revealed significant, dose-dependent increases in the number and area of placental-type glutathione S-transferase-positive hepatocellular foci, indicating a promoting effect of kresoxim-methyl on hepatocarcinogenesis at 8000 ppm and above. The NOAEL for the promoting effect was 800 ppm, equal to 43 mg/kg bw per day.

Four studies were conducted to investigate the effect of kresoxim-methyl on hepatic-cell proliferation in rat liver by measuring bromodeoxyuridine incorporation into hepatocyte DNA during S-phase DNA synthesis. The results showed a selective cell proliferation effect of kresoxim-methyl on hepatocytes in the periportal zone. The NOAEL was 800 ppm, equal to 61 mg/kg bw per day, while animals treated with 8000 ppm and above showed a statistically significant increase in cell proliferation. There was no difference in the sensitivity of young and old rats.

The genotoxic potential of kresoxim-methyl was investigated in a series of tests, including assays for gene mutation in bacteria and mammalian cells, unscheduled DNA synthesis, and cytogenicity *in vitro,* an assay for micronucleus formation *in vivo*, and an assay for unscheduled DNA synthesis *ex vivo*. Kresoxim-methyl had moderate potential to induce chromosomal aberrations *in vitro* with exogenous metabolic activation, but positive effects were not observed in any other test, including the assay for micronuclei in rat bone marrow. The Meeting concluded that kresoxim-methyl is not genotoxic. The three major metabolites in rats did not induce reverse mutation in *Salmonella typhimurium in vitro*.

The increased incidence of liver tumours observed in rats at 8000 ppm and above was considered to be associated with increased cell proliferation. The mechanistic studies indicated that kresoxim-methyl has tumour promoting potential at 8000 ppm, which coincides with the lowest level at which increased liver-cell proliferation was observed. These results indicate a threshold for the neoplastic mode of action. The Meeting concluded that a level of 800 ppm kresoxim-methyl has no carcinogenic potential.

In a two-generation study of reproductive toxicity in rats, the NOAELs were 1000 ppm for parental animals of each sex, 100 mg/kg bw per day for F_0 offspring, and 88 mg/kg bw per day for F_1 offspring; these were based on reductions in body weight and body-weight gain and increased serum γ-glutamyl transferase activity and relative kidney weight at 4000 ppm and above. The NOAEL for pups was 1000 ppm, equal to 110 mg/kg bw per day for F_1 pups and 97

mg/kg bw per day for F_2 pups, on the basis of reductions in body weight and body-weight gain at 4000 ppm and above.

The NOAEL for embryo and fetotoxicity in a developmental toxicity study in rats was 400 mg/kg bw per day. No maternal toxicity or teratogenic effects were observed up to and including the highest dose of 1000 mg/kg bw per day. Kresoxim-methyl did not induce toxicity in a developmental toxicity study in rabbits up to and including the highest dose of 1000 mg/kg bw per day.

An ADI of 0-0.4 mg/kg bw was established on the basis of the NOAEL of 800 ppm, equal to 36 mg/kg bw per day, in the 24-month study of toxicity and carcinogenicity in rats, and a 100-fold safety factor.

An acute RfD was not allocated because kresoxim-methyl has low acute toxicity and did not exhibit developmental toxicity. The Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxicological effect

Mouse: 400 ppm, equal to 81 mg/kg bw per day (18-month study of toxicity)

Rat: 800 ppm, equal to 36 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
1000 ppm, equal to 88 mg/kg bw per day (two-generation study of reproductive toxicity)
400 mg/kg bw per day (embryo/fetotoxicity in a study of developmental toxicity)

Rabbit: 1000 mg/kg bw per day (developmental toxicity; highest dose tested)

Dog: 5000 ppm, equal to 140 mg/kg bw per day (12-month study of toxicity)

Estimate of acceptable daily intake for humans

0 - 0.4 mg/kg bw

Estimate of acute reference dose

Not allocated (unnecessary)

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

Observations in humans

List of end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion, and metabolism in mammals

Rate and extent of oral absorption:	Rapid, 25-60% absorbed
Dermal absorption:	No data
Distribution:	Minimum, highest levels in liver
Potential for accumulation:	Very little potential
Rate and extent of excretion:	Rapid/complete, 87-93% within 48 h
Metabolism in animals	Extensive. No parent compound in urine, bile, or tissues; 34 metabolites identified.
Toxicologically significant compounds (animals, plants and environment)	Parent compound in rat. Three major metabolites in plants.

Acute toxicity

LD$_{50}$ oral	>5000 mg/kg bw, rat
LD$_{50}$ dermal	>2000 mg/kg bw, rat
LC$_{50}$ inhalation	>5.6 mg/l rat
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization	Not a sensitizer

Short-term toxicity

Target / critical effect	Liver/increased relative liver weight (mouse, rat)
Lowest relevant oral NOAEL	28-day, rat, 43 mg/kg bw per day
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEL	No data

Genotoxicity

Not genotoxic

Long term toxicity and carcinogenicity

Target/critical effect:	Rat, hepatocellular carcinoma.
Lowest relevant NOAEL	2-year, rat, 36 mg/kg bw per day, diet
Carcinogenicity	Non-genotoxic carcinogen, tumour promotor

Reproductive toxicity

Reproduction target / critical effect	Reduction in F_0 body weight at parenterally toxic dose
Lowest relevant reproductive NOAEL	97 mg/kg bw per day, diet, rat
Developmental target / critical effect	None
Lowest relevant developmental NOAEL	1000 mg/kg bw per day, highest dose tested, rat

Neurotoxicity / Delayed neurotoxicity

No data

Other toxicological studies

No data

Medical data

No data

Summary	Value	Study	Safety factor
ADI	0-0.4 mg/kg bw	2-year, rat, toxicity and carcinogenicity	100
Acute reference dose	Not allocated (unnecessary)		

RESIDUE AND ANALYTICAL ASPECTS

Kresoxim-methyl was considered for the first time by the current Meeting. It is used as a broad spectrum fungicide structurally related to Strobilurin A, a natural product of the wood-decaying fungus *Strobilurus tenacellus*. It is a member of a new class of biologically active compounds, the strobilurins, and is formulated as an SC, WG or SE.

Pure kresoxim-methyl is a white crystalline solid with a melting point of *c.* 102°C and low volatility. It has limited solubility in water with medium-high solubility in certain organic solvents. The log octanol-water partition coefficient of 3.4 suggests bioaccumulation may occur. Kresoxim-methyl does not dissociate at neutral pH, but the acid dissociation constant of the free acid 490M1 (pKa 4.2) indicates dissociation at neutral pH.

The main metabolites are identified by code numbers as shown in the Table below.

Code	Chemical name
parent	methyl (*E*)-methoxyimino[∀-(*o*-tolyloxy)-*o*-tolyl]acetate
490M0	methyl (*Z*)-methoxyimino[∀-(*o*-tolyloxy)-*o*-tolyl]acetate
490M1	(*E*)-methoxyimino[∀-(*o*-tolyloxy)-*o*-tolyl]acetic acid
490M2	∀-[(*o*-hydroxymethyl)phenoxy]-*o*-tolyl(methoxyimino)acetic acid
490M4	∀-(*o*-carboxyphenoxy)-*o*-tolyl(methoxyimino)acetic acid
490M8	∀-[*p*-hydroxy-(*o*-hydroxy)methylphenoxy]-*o*-tolyl(methoxyimino)acetic acid
490M9	α-(*p*-hydroxy-*o*-tolyloxy)-*o*-tolyl(methoxyimino)acetic acid

490M15   methyl α-(*p*-hydroxy-*o*-tolyloxy)-*o*-tolyl(methoxyimino)acetate
490M48   methyl hydroxyimino[∀-(2-methoxyphenoxymethyl)phenyl]acetate

Animal metabolism and environmental fate

Animal metabolism

Metabolism of absorbed kresoxim-methyl in rats was rapid and produced a large number of metabolites of which 34, including conjugates, were identified in the tissues and/or excreta. Ester cleavage to form the free acid 490M1 is a fast and important initial reaction. Other reactions involve cleavage of the oxime and benzyl ether bonds, ring hydroxylation, side chain oxidation and several conjugation reactions.

Goats were given daily doses of radiolabelled kresoxim-methyl equivalent to 7.1 or 450 ppm diet for 5 or 8 days respectively. Most of the dose was excreted (59-69% in the urine, 18-24% in the faeces). Apart from the excreta, the highest residue levels were in the kidneys and bile. Transfer into the milk and other edible tissues was low. The total radioactive residue (TRR) from the low dose was below 0.01 mg/kg as kresoxim-methyl in the milk, muscle and fat: 0.038 mg/kg in the liver and 0.142 mg/kg in the kidneys. The main metabolites identified in the liver and kidney extracts were 490M9 (1.9 and 4.0 mg/kg respectively), 490M1 (0.8 and 2.9 mg/kg) and 490M2 (0.5 and 4.6 mg/kg). 490M6, 490M18 and 490M19 were minor products. Three metabolites in the goats had not been identified in rats, of which the minor metabolite 490M18 was at the highest concentration (0.12 mg/kg in the ethyl acetate extract of the liver from the high-dosed goat), but the Meeting agreed that in practice concentrations of 490M18 would be very low (<0.01 mg/kg) in commodities of animal origin. Kresoxim-methyl itself was detected only in the faeces and fat.

Hens were given radiolabelled kresoxim-methyl in six daily doses equivalent to 10 or 180 ppm in the diet. 71-82.6% of the radioactivity recovered from the low dose was excreted and the total radioactive residue levels in the skin, kidneys and liver were 0.009, 0.065 and 0.082 mg/kg kresoxim-methyl equivalents respectively. The ^{14}C in eggs sampled at the end of the study was equivalent to 0.012 mg/kg and 0.215 mg/kg from the low and high doses respectively and did not appear to have reached a plateau. Metabolites were identified only in the high-dose group. A number of metabolites were produced, of which 490M9 was the most prominent with residues of 1.35 mg/kg in the liver. Two major metabolites in goats were 490M2 and 490M9. 490M2 was not identified in hens and 490M9 was found only in the eggs at 0.005 mg/kg. The parent compound was identified in the eggs, skin, muscle and fat at 0.01, 0.08, 0.005 and 0.31 mg/kg respectively.

Apples were sprayed with [p*henyl*-^{14}C]kresoxim-methyl at (1) 6 x 0.4 kg/ha, PHI 14 days (2) 2 x 0.4 kg ai/ha, PHI 149 days, or (3) 2 x 0.8 kg/ha, PHI 14 days. The total radioactive residues (TRR) in or on the apples were 0.36 mg/kg from (1), 0.04 mg/kg from (2) and 0.84 mg/kg from (3). When trees were sprayed with fruit present the radioactivity remained mainly on the peel (89%-98% of the TRR) and translocation to the pulp was low after 14 days. Extracts from all three experiments showed similar patterns of metabolites, containing predominantly unchanged kresoxim-methyl (74%-93% of the TRR). The extracts from (1), in which the fruit was present at the time of treatment, contained kresoxim-methyl (78.3% of the TRR), 490M0 (3.3% of the TRR), the acid 490M1 (3.0%) and conjugates of the alcohol-acid 490M2 (1.8%) and phenol-acid 490M9 (2.1%). Kresoxim-methyl appeared to be translocated within the apple tree and to be persistent, since it was found in the fruit above the limit of determination 149 days after an early treatment when the fruit would not have been present. However, the Meeting concluded that this was not entirely consistent

with the low water-solubility and the relatively low residues of the parent compound in crops shortly after treatment, and drew attention to the possibility that the parent compound found in the fruit 149 days after treatment may have been the result of methylation of the metabolite 490M1 during methanol extraction of the samples.

The metabolism of [*phenyl*-^{14}C]kresoxim-methyl was investigated in <u>wheat</u> treated twice at 0.25 kg ai/ha at an interval of 56 days. The total radioactive residues were 0.06 mg/kg in the grain and 9.21 mg/kg in the straw 64 days after the second application, and 1.31 mg/kg in the forage 55 days after the first. 30-99% of the TRR could be extracted with methanol, the extractability from mature grain being low. Subsequent extraction with dilute aqueous ammonia released an additional 31% of the TRR from grain and 16% from straw. Unextractable residues were 0.27 mg/kg in straw (2.9% of the TRR) and 0.025 mg/kg in grain (38.8% of the TRR).

Most of the radioactivity was due to unchanged parent compound at levels of 5.9 mg/kg in the straw after both treatments and 0.98 mg/kg in the forage one day before second (-1 day forage). Other compounds identified in the straw and -1 day forage were 490M0, the acid 490M1 and conjugates of the alcohol-acid 490M2 and the phenol-acid 490M9. The grain extract contained 0.011 mg/kg kresoxim-methyl and a variety of other metabolites constituting 0.3-5.6% of the TRR. Enzymatic treatment of conjugate fractions yielded 0.03 mg/kg 490M2 and 0.103 mg/kg 490M9 in -1 day forage, and 0.39 mg/kg 490M2 and 1.04 mg/kg 490M9 in straw. Samples from a 1.25 kg ai/ha treatment contained higher relative and absolute amounts of the parent compound. No cleavage of the phenyl or phenoxy rings was observed. Kresoxim-methyl was apparently translocated within the plant since grain contained determinable residues of the parent compound after two treatments although the grain was not present at the time of the second treatment (growth stage 52). As with apples the Meeting noted the possibility that the residues of kresoxim-methyl found in the grain at harvest may have been the result of methylation of 490M1 during methanol extraction. No experimental clarification was reported.

<u>Grapes</u>. The metabolism of phenyl- and phenoxy-labelled kresoxim-methyl was investigated in grapes treated at rates equivalent to a total dose of 2.5 kg/ha. The total radioactive residues from the phenoxy and phenyl labels were equivalent to 3.8-4.0 mg/kg and 3.6-4.7 mg/kg respectively. Kresoxim-methyl was the main compound in the residue: 55-57% of the TRR, 2.2-2.7 mg/kg. Conjugated 490M2 accounted for 8.8-13.8% of the TRR. After treatment with β-glucosidase, 490 M9 accounted for 4.4-5.7% of the TRR and 490 M54 for 1.4-2.1%. Unextractable residues accounted for 4.0-4.1%. There were no major qualitative differences between the metabolism of the phenyl and the phenoxy labels and no ring cleavage was observed. The metabolite 490 M54 was not identified as a product of wheat, apple or rat metabolism. The Meeting concluded that in practice concentrations of 490 M54 would be very low (<0.01mg/kg) in grapes treated according to GAP.

In studies carried out to assess metabolism in rotational crops, phenyl-labelled kresoxim-methyl was applied to bare soils at a rate of 0.3 kg/ha. After being aged for 30 days, the soils were diluted with untreated soils at a ratio of 1:9 to simulate ploughing, and spring wheat, green beans, carrots and lettuce were planted. The highest total radioactive residues at harvest, expressed as mg/kg kresoxim-methyl, were 0.15 in wheat straw, 0.007 in wheat grain, 0.21 in bean forage, 0.009 in green beans, 0.006 in carrot roots, 0.047 in carrot foliage and 0.01 in lettuce leaves. In bean forage, carrot forage and lettuce, conjugates constituted the main radioactive residue, accounting for 0.071 mg/kg, 0.015 mg/kg and 0.012 mg/kg respectively. Enzymatic cleavage yielded mainly the aglycones 490M2 and 490M9. Lettuce contained 0.003 mg/kg kresoxim-methyl and carrot

forage 0.005 mg/kg 490M1. Wheat straw contained the free hydroxy metabolites 490M2 and 490M9 (together 0.011 mg/kg). Enzyme treatment of extracts of wheat straw produced 4.8% of the TRR as 490M2 and 10.4% as 490M9. No parent compound was detected in wheat, bean or carrot forage. Metabolites in grain extracts were not characterized. The results confirm the expectation that significant residues of kresoxim-methyl would not occur because of its rapid degradation in soil. (Half-lives in soils were 1-3 days for kresoxim-methyl and 38-131 days for 490M1, and DT90s for combined parent compound and 490M1 in the field were 18-25 days; see below).

Environmental fate in soil and water/sediment systems

Both aerobic and anaerobic degradation of kresoxim-methyl in soil produced 490M1 (the free acid) in amounts representing 66-84% of the applied radioactivity (AR). In aerobic conditions this was then degraded to CO_2 (27-43% of the AR in 180 days and 24% of the AR in 1 year in different experiments) or bound residues (a maximum of 36-47% of the AR) with 490M4 found in very small amounts as an intermediate. The bound radioactivity still unextractable after treatment with aqueous alkali was largely associated with the humin fraction.

In sterile conditions some degradation of kresoxim-methyl occurred but the rate was considerably slower than that in anaerobic or aerobic conditions. In anaerobic and sterile conditions the degradation of 490M1 was too slow to measure and levels of CO_2 and bound residues were considerably lower.

In aerobic conditions at 20°C and average moisture contents (usually 40% of the maximum water-holding capacity) the degradation of kresoxim-methyl, largely to 490M1, was extremely rapid with DT90 values of 2-3 days. The 490M1 was subsequently degraded with a half-life of 38-131 days.

In anaerobic conditions the DT90 for kresoxim-methyl was also <3 days. In photolysis studies degradation was more rapid in the dark controls than in the irradiated samples, which could have been caused by loss of moisture in the irradiated soil resulting in slower aerobic degradation.

In field studies undertaken in Germany in May, the DT50 values for the combined dissipation of kresoxim-methyl and 490M1 were 8-38 days and the DT90 values 18-125 days. The dissipation of 490M1 was mainly measured since substantial dissipation of kresoxim-methyl had already occurred in the samples taken on day 0 and no residues were determinable after 14 days.

The K_{oc} of kresoxim-methyl in four soils was found to be 219-372, indicating moderate mobility, although degradation to 490M1 occurred during the experiment. In a separate experiment the K_{oc} of 490M1 was found to be 17 and 24 in two soils, but sorption to two other soils was too low for quantification measurement. In column leaching studies with three standard soils up to 77% of the applied dose was leached as a mixture of kresoxim-methyl and 490M1. When the study was repeated with aged soil about 60% of the AR was found in the leachate and most of this was associated with 490M1.

Leaching was examined in more realistic conditions in a lysimeter study where a crop was planted and kresoxim-methyl was applied twice at 150 g ai/ha. No kresoxim-methyl was

found in the leachate during the two years of the study and the annual average concentrations of 490M1 were <0.01-0.04 µg/l.

In a study of aqueous hydrolysis half-lives assuming first-order kinetics were 875, 34 and 0.29 days at pH 5, 7 and 9.

Methods of residue analysis

Satisfactory validation data were submitted for analytical methods for a number of commodities of plant and animal origin. Determinations of kresoxim-methyl and the metabolites 490M2 and 490M9 in apples, cereal grain, straw, soil and water were usually by GLC with an ECD after extraction with a variety of solvents and clean-up by solid-phase extraction. Commodities of animal origin were analysed by HPLC with UV detection. Limits of determination were 0.01-0.05 mg/kg in plant commodities, 0.01 mg/kg in soil, 0.05 µg/l in water, 0.001-0.002 mg/kg in milk and 0.01 mg/kg in animal products.

Stability of residues stored analytical samples

Kresoxim-methyl residues in samples of wheat (immature plants, grain and straw) and apples stored at $-18^{o}C$ were stable for the duration of the studies, namely up to 214 days for grain, 91 days for straw, 168 days for forage and 295 days for apples. There was no marked change in the qualitative or quantitative composition of radioactive residues in wheat samples stored frozen for 21 months, apple samples for 14 months, grape samples for 8 months or poultry samples for 21 months.

Definition of the residue

On the basis of the metabolism in apples, wheat and grapes, the Meeting agreed that the definition of the residue for compliance with MRLs for plant commodities should be kresoxim-methyl since this is the major component of the residue in primary crops. In several of the residue trials the metabolites 490M2 and 490M9 were also found but the Meeting considered these metabolites to be of low toxicity.

In ruminants the metabolite 490M9 is a major component of the residue and the parent compound is present only at very low relative concentrations. In poultry 490M9 would also be a suitable indicator compound since it was the main compound found in the liver.

The Meeting agreed to recommend the following residue definitions for both compliance with MRLs and the estimation of dietary intake.

Commodities of plant origin: *kresoxim-methyl*
Commodities of animal origin: *α-(p-hydroxy-o-tolyloxy)-o-tolyl(methoxyimino)acetic acid, expressed as kresoxim-methyl*

Supervised trials

Pome fruit. GAP for apples was reported for Austria, Belgium, Brazil, Chile, France, Germany (pome fruit), Hungary, Israel, Italy, Japan, The Netherlands, New Zealand, Norway, Poland, Slovakia, South Africa, Spain, Sweden, Switzerland, the UK and Uruguay.

Four Italian, four French and two Spanish trials were considered to comply with French and Spanish GAP (max. 0.1 kg ai/ha, PHI 35 days). The residues in all ten trials were <0.05 mg/kg. Seven German, two Belgian, six UK and two Dutch trials complied with GAP for Austria, Belgium, Hungary, Poland and the UK (also 0.1 kg ai/ha, PHI 35 days) with residues of <0.05 (11), 0.05 (3), 0.06 and 0.11 (2) mg/kg. Two New Zealand trials complied with New Zealand GAP (0.1 kg ai/ha; PHI 14 days) with residues in both of 0.04 mg/kg. Three South African trials according to South African GAP (0.01 kg ai/hl; PHI 45 days) yielded residues of 0.06, 0.09 and 0.11 mg/kg. Other trials were reported from the USA and Canada which included determinations of the metabolites 490M2 and 490M9, but no GAP was reported for the North American continent. The Meeting agreed that all the results could be combined, as they were essentially from one population, to give residues of 0.04 (2), <0.05 (11), 0.05 (3), 0.06 (2), 0.09 and 0.11 (3) mg/kg.

GAP for pears was reported for Austria, Belgium, Chile, France, Germany, Hungary, Italy, Japan, The Netherlands, Norway, Poland, South Africa, Spain, Sweden, Switzerland and Uruguay. Separate GAP for "oriental pear" was reported for Japan.

Four Spanish trials were according to Spanish and French GAP (max. 0.1 kg ai/ha, PHI 35days) all with residues of <0.05 mg/kg. Two South African trials were reported, one of which complied with South African GAP for apples and the other with GAP for pears. The residues were 0.06 and 0.01 mg/kg respectively. The Meeting agreed that the data on pears and apples could be combined.

The combined residues in apples and pears were 0.01, 0.04 (2), <0.05 (15), 0.05 (3), 0.06 (3), 0.09 and 0.11 (3). The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.05 mg/kg for pome fruit.

Grapes. GAP was reported for Austria, Chile, Germany, Hungary, Israel, Japan, Slovakia, South Africa, Spain and Switzerland.

Seven Italian trials were according to Spanish GAP (max 0.015 kg ai/hl, PHI 35 days) with residues of <0.05 (6) and 0.15 mg/kg. Several French and German trials were reported at applications of 0.025-0.038 kg ai/hl which were higher than the German or Swiss GAP concentration of 0.0075 kg ai/hl and the Austrian concentration of 0.0125 kg ai/hl. Five French and seven German trials were considered to comply with the maximum Austrian GAP equivalent of 0.125 kg ai/ha however, with residues of 0.06, 0.09, 0.15, 0.17, 0.18, 0.20, 0.21, 0.23, 0.25, 0.36, 0.44 and 0.73 mg/kg. Three trials complied with South African GAP (0.023 kg ai/hl, PHI 14 days), with residues of 0.09, 0.14 and 0.27 mg/kg. Trials in the USA included analyses for the metabolites 490M2 and 490M9, but no GAP was reported for the North American continent. The Meeting agreed that the residues resulting from Austrian and South African GAP could be combined, since they appeared to be from the same population, to give 0.06, 0.09 (2), 0.14, 0.15, 0.17, 0.18, 0.20, 0.21, 0.23, 0.25, 0.27, 0.36, 0.44 and 0.73 mg/kg. The residues from the trials according to Spanish GAP were considered to be from a different population since six of the

seven results were below the limit of determination. The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.2 mg/kg.

<u>Onions</u>. GAP for onions was reported for Nicaragua and for Welsh onions for Japan, but as trials were reported only from Germany and The Netherlands there was no basis for an evaluation.

<u>Cucumbers</u>. GAP was reported for Brazil, Japan, Spain and Norway.

The residues in eight Spanish indoor trials which complied with Spanish GAP (0.01-0.015 kg ai/hl; PHI 3 days) were all <0.05 mg/kg, and in seven of the trials <0.05 mg/kg even on the day of application. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg.

<u>Melons</u>. No GAP was reported.

<u>Tomatoes, sweet peppers</u>. Eight indoor trials in Spain on each commodity complied with Spanish glasshouse GAP (max. 0.025 kg ai/hl; PHI 3 days), with residues of 0.09, 0.13, 0.14, 0.20, 0.23, 0.25, 0.27 and 0.31 mg/kg in tomatoes, and 0.10 (2), 0.15, 0.19, 0.21, 0.37, 0.39 and 0.44 mg/kg in peppers. As none of the trials were identified as complying with GAP until late in the Meeting however, neither maximum residue levels nor STMRs were estimated.

<u>Wheat</u>. GAP for wheat was reported for Belgium, Ireland, Luxembourg, The Netherlands, Poland, Slovakia and the UK, and for cereals for Germany and Japan.

The residues in winter and spring wheat were evaluated together because the levels were similar and the latest time of application was described as a pre-harvest interval not a growth stage. Seven German, three Belgian and five French trials accorded with Belgian, Polish, German, Dutch and Luxembourg GAP (0.105-0.150 kg ai/ha, PHI 35 days) with residues all <0.05 mg/kg in the grain or ears and <0.05, 0.05, 0.08, 0.09, 0.12, 0.13, 0.18, <u>0.19</u>, 0.26, 0.28, 0.50, 1.27, 1.45, 2.59 and 4.00 mg/kg in the straw or haulm. Residues of the metabolites 490M9 and 490M2 were also measured and the total residue calculated. The Meeting estimated maximum residue levels of 0.05* and 5 mg/kg and STMRs of 0.05 and 0.19 mg/kg for the grain and straw respectively.

<u>Barley</u>. GAP for barley was reported for Belgium, France, Germany, Luxembourg, Norway, Switzerland, Ireland, The Netherlands, Poland and the UK, and for cereals for Germany and Japan.

The trials on winter and spring barley were evaluated together for the reasons given above. Three Dutch, two French and six German trials complied with GAP in Belgium, France, Germany, Luxembourg, The Netherlands, Norway and Poland (max. rate 0.105 or 0.125 kg ai/ha, PHI 35 or 42 days) with residues of <u>0.05 </u>(9) and 0.06 (2) mg/kg in the grain or ears and 0.07, 0.08, 0.14 0.20, <u>0.22, 0.26</u>, 0.28, 0.45, 0.79 and 0.92 mg/kg in the straw or haulm. The Meeting estimated maximum residue levels of 0.1 and 2 mg/kg and STMRs of 0.05 and 0.24 mg/kg for grain and straw respectively.

<u>Rye</u>. GAP was reported for Belgium, France, Germany, Luxembourg, Poland, Switzerland and The Netherlands, with maximum application rates of 0.105 or 0.125 kg ai/ha and PHIs of 35 days.

Only two trials were reported, both in Germany and according to GAP, with residues of <0.05 mg/kg in the ears and 0.08 and 0.11 mg/kg in the haulms. The Meeting agreed that the data for wheat could be extrapolated to rye, giving combined residues of <u>0.05 (17) mg/kg in the grain and <0.05, 0.05, 0.08 (2), 0.09, 0.11, 0.12, 0.13, 0.18, 0.19, 0.26, 0.28, 0.50, 1.27, 1.45, 2.59 and 4.00 mg/kg in the straw or haulm. The Meeting estimated maximum residue levels of 0.05* and 5 mg/kg, and STMRs of 0.05 and 0.18 mg/kg for grain and straw respectively.

The Meeting agreed that it was appropriate to recommend a group MRL for cereal straws rather than separate MRLs for the individual straws. Accordingly the Meeting recommended an MRL of 5 mg/kg and estimated an STMR of 0.24 mg/kg for "straw and fodder (dry) of cereal grains" since these represented the highest estimates for any individual cereal.

<u>Pecans</u>. A number of trials in the USA were reported but the Meeting was informed that there was no current GAP for pecans.

Processing studies

Apples were processed to washed fruit, apple juice, wet pomace and apple sauce, and grapes to juice, must, wine, wet pomace, and raisins. The mean processing factors were <0.4, <1 and <0.4 for apple juice, wet apple pomace and apple sauce, and 0.1, 0.7, <0.2 and 1.6 for must, wet grape pomace, wine and raisins respectively.

From these factors the Meeting estimated a maximum residue level of 2 mg/kg for dried grapes and STMRs of 0.05, 0.02 and 0.02 mg/kg for wet apple pomace, apple sauce and apple juice and 0.14, 0.02, 0.04 and 0.32 mg/kg for wet grape pomace, grape must, wine and dried grapes respectively. A study of the effects of brewing on residues in barley was difficult to interpret since the residues were <0.05 mg/kg in the initial grain although the barley had been treated at twice the GAP rate.

Farm animal feeding studies

Dairy cows were dosed twice daily with kresoxim-methyl at rates equivalent to 6, 18 and 60 ppm in the feed for 28 or 29 days. Residues of 490M2 and 490M9 in whole milk, cream and skimmed milk were <0.002 mg/kg; 490M1 was not determined. Residues in the tissues of the low-dose group were all <0.01 mg/kg, except those of 490M1 which appeared in the kidneys at 0.021-0.028 mg/kg. In the high-dose group the highest residue concentrations were 490M1 in the kidneys (<0.01-0.29 mg/kg) and peritoneal fat (<0.01-0.091 mg/kg), and 490M9 in the liver (<0.01-0.024 mg/kg) and kidneys (<0.01-0.049 mg/kg).

The highest residue levels in the feed items were in wheat straw for which the Meeting estimated a maximum residue level of 5 mg/kg. This leads to a theoretical maximum dietary level of 2.5 ppm, based on a 50% level of straw in the diet. The Meeting concluded that no residues above the practical limits of determination (0.01 mg/kg for milk and 0.05 mg/kg for other animal products) would occur in animal commodities from this dietary level. The Meeting estimated maximum residue levels of 0.01* mg/kg for milks and 0.05* mg/kg for mammalian meat, edible offal and fats, and corresponding STMRs of 0.002 and 0.01 mg/kg. The STMRs are based on the validated limits of determination of the analytical methods for these commodities.

The only poultry feed item containing determinable residues was barley grain with residues in the trials of ≤0.06 mg/kg and an estimated maximum residue level of 0.1 mg/kg. The Meeting concluded that the intake for poultry would be ≤0.1ppm in the feed. In the poultry metabolism study TRRs were very low in the skin (0.009 mg/kg), kidneys (0.065 mg/kg) and liver (0.082 mg/kg) at doses equivalent to 10 ppm in the feed. The Meeting concluded that no residues above the practical limit of determination (0.05 mg/kg) would occur in edible poultry tissues, and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.01 mg/kg for poultry meat. The STMR is based on the validated limit of determination for the reported methods of analysis.

FURTHER WORK OR INFORMATION

<u>Desirable</u>

1. Information on residues in food in commerce or at consumption (monitoring or total diet data).

2. Experimental determination of whether (*E*)-methoxyimino[∀-(*o*-tolyloxy)-*o*-tolyl]acetic acid (490M1) is methylated to kresoxim-methyl when methanol is used as an extractant in metabolism studies or the analysis of samples from supervised trials.

DIETARY RISK ASSESSMENT

STMRs have been estimated for 18 commodities of which the 11 commodities for which there are consumption data have been used in the estimate of dietary intake.

The International Estimated Dietary intakes for the five GEMS/Food regional diets were 0% of the ADI. The Meeting concluded that the intake of residues of kresoxim-methyl resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.18 MALEIC HYDRAZIDE (102)

RESIDUE AND ANALYTICAL ASPECTS

Maleic hydrazide (6-hydroxy-2*H*-pyridazin-3-one) was first reviewed in 1976. At the request of the manufacturer, it was scheduled for the CCPR Periodic Review Programme. Its toxicology was evaluated in 1996 and it is now evaluated for residues.

The Meeting received information on animal and plant metabolism, environmental fate, analytical methods, updated GAP, supervised residue trials and the effect on residues of processing.

Maleic hydrazide is a plant growth regulator. It is formulated (as the potassium salt) as dispersible granules (SG, GR) and as liquid formulations (SL, SC). It main uses are for suppression of sprouting in stored potatoes and bulb vegetables, the control of suckers on tobacco and of volunteer potatoes in following crops and as a grass growth retardant in non-crop situations.

The absorption, distribution, metabolism and excretion of [^{14}C]maleic hydrazide has been studied in rats, rabbits, cows, a goat and hens.

Maleic hydrazide was well absorbed when administered orally to rats. Elimination was rapid and mainly via the urine (77-87% of the administered dose). Elimination via the faeces and expired CO_2 was less than 14% and 0.5% respectively. Very low levels of the test material were found in the carcase (<0.5% of the dose). No differences in the rate or route of elimination were noted between males and females. The major urinary component was maleic hydrazide (45-70%) and a minor metabolite was tentatively identified as its sulfate conjugate.

Maleic hydrazide was absorbed through rabbit skin at a rapid rate after a 4-hour topical exposure. The absorbed radioactivity was rapidly eliminated, almost entirely in the urine and in most cases during the first 24 hours after application. Approximately 90% of the urinary radioactivity excreted in the first 24 hours was identified as maleic hydrazide. The total dermal absorption of the radiolabelled material was calculated to be 26% of the total applied dose in males and 40% in females.

Most of the total radioactive residue (TRR) in cows dosed with [^{14}C]maleic hydrazide at 3 levels (0.45, 1.36, 4.5 mg/kg bw/day) was found in the kidneys. In milk, radioactive residues reached a plateau after 3-4 days of treatment, at a level of 0.02 mg/kg in the low-dose group. Radioactive residues in the low-dose animals were 0.34 mg/kg in the kidneys and ranged from <0.05 mg/kg in the fat and muscle to 0.08 mg/kg in the liver.

In a goat [^{14}C]maleic hydrazide was excreted in the urine (approximately 63% of the administered dose), faeces (23%) and milk (0.13%). Only 0.06% of the administered dose was recovered from the tissues (fat, muscle, kidneys, liver, blood and bile). Most of the radioactivity in the tissues and milk was in a conjugate, which was hydrolysed to maleic hydrazide and 2 relatively nonpolar compounds. One of these, observed in the liver, muscle and fat, co-chromatographed with fumaric acid. The residues of the parent before hydrolysis were 0.11 mg/kg in milk, 0.03 mg/kg in muscle and undetectable in the kidneys, liver and fat. More maleic hydrazide was identified after enzymatic hydrolysis in the milk (0.38 mg/kg) and after acid hydrolysis in the tissues (kidneys 0.96, liver 0.16, muscle 0.15 and fat 0.05 mg/kg).

Maleic hydrazide was rapidly metabolized by hens. Approximately 98% of the administered ^{14}C was recovered in the excreta within 24 hours after dosing laying hens for 3.5 days. Maleic hydrazide was the major component of egg yolk (0.18 mg/kg, 69% of the TRR) but was not present in muscle. An unidentified nonpolar metabolite was the major component of the residue in the liver (60% of the TRR) and was also present in the kidneys, muscle, egg white and egg yolk. Mass spectrometry of the nonpolar metabolite isolated from egg white indicated that it was a conjugate of a methylated maleic hydrazide. A polar compound was present in the kidneys and eggs. After acid treatment, the level of this compound in extracts decreased, with a corresponding increase in maleic hydrazide and some unidentified compounds.

Six hens were dosed daily for 28 days with [^{14}C]maleic hydrazide at 1, 3 and 10 mg/kg bw/day. The TRR reached a plateau in egg whites after 5 days of administration and in egg yolks after about 8 days. The plateau levels in egg whites and yolks were 0.01-0.02 mg/kg from the low dose, 0.05-0.07 mg/kg from the mid dose and 0.19-0.23 mg/kg from the high dose. The highest TRR was observed in the kidneys (0.06 mg/kg in the low-dose group) and the lowest in

abdominal fat (0.006 mg/kg in the low-dose group). Radioactive residues in muscle, liver and skin were 0.01 to 0.02 mg/kg from the low dose.

Information on the metabolism of maleic hydrazide in plants was provided for potatoes and onions. Maleic hydrazide is rapidly absorbed by foliage and translocated to growing shoots and roots.

Approximately 99% of the radioactivity in potato plants harvested 1 hour after treatment was in the vines. In plants harvested 8 weeks after treatment 61% was in the tubers. Most of the TRR in potato tubers consisted of maleic hydrazide (52-84%), with lower levels of a glucose conjugate (6.4-13%).

Leaves of onions harvested 1 hour after treatment contained approximately 87% of the total radioactivity. At 2 weeks after application, the levels of radioactivity in the bulbs were about 10 times those at the first harvest. The residues in the methanol-extractable fraction were identified as maleic hydrazide (no glucose conjugate was identified).

Maleic hydrazide is degraded rapidly in soil and is efficiently mineralized to CO_2 under aerobic conditions (half-life 11 hours). Degradation proceeds via the initial formation of maleamide resulting from the elimination of one of the nitrogens, followed by further conversion to maleamic acid, maleic and fumaric acids which will yield lactic acid and succinic acid and finally CO_2. Most of the radioactivity remaining in the soil is in the form of firmly bound residues. Maleic hydrazide has a high leaching potential but if it is allowed to age for a number of days after application it will be degraded rapidly and bind strongly to the soil, which will minimize leaching. The dissipation of maleic hydrazide in the environment is attributed to both aerobic and anaerobic degradation. Photolysis and hydrolysis may make limited contributions.

In a metabolism study on rotational crops wheat was planted 30 and 92 days after treatment of the soil with [^{14}C]maleic hydrazide in the field. Total radioactive residues in wheat forage, grain, chaff and straw ranged from 0.02 mg/kg to 0.29 mg/kg expressed as maleic hydrazide. The residues were too low to permit identification.

A further rotational wheat study showed that the residues in the grain are incorporated into glucose or associated with protein.

Analytical methods for total residues of maleic hydrazide in plants are based on reduction with zinc and hydrolysis in hot alkali to hydrazine. The hydrazine is isolated by distillation and determined colorimetrically as the azine by the addition of *p*-dimethylaminobenzaldehyde. These procedures are useful for determining total maleic hydrazide. The LOD for onions was 1 mg/kg.

Maleic hydrazide and its ß-D-glucoside can be determined by HPLC. Both maleic hydrazide and the glucoside are extracted from plant tissue with methanol and the extract is concentrated. Maleic hydrazide and the glucoside are cleaned up separately by passage through different cation-exchange columns. The glucoside is then hydrolysed with ß-glucosidase and maleic hydrazide is determined by HPLC with detection by light absorption at 313 nm. The average recovery of maleic hydrazide from beets, carrots, potatoes and turnips fortified at 1 to 50 mg/kg was 87%. The LOD was 1 mg/kg. The same average recovery of the glucoside was obtained at levels from 2 to 50 mg/kg.

A gas-chromatographic method involves oxidation of maleic hydrazide with aqueous lead dioxide to 3,6-pyridazinedione in the presence of cyclopentadiene. The reaction product is determined by GLC with an ECD. The mean recovery of maleic hydrazide (as the Diels-Alder adduct) from potato samples fortified at 0.1, 0.5, 1, 5 and 10 mg/kg was 92% and the coefficient of variation was 3.1%. The limit of determination was 0.1 mg/kg. This method quantifies free extractable maleic hydrazide but not its conjugates.

An enzyme immunoassay based on two monoclonal antibodies specific for maleic hydrazide has been developed but the method has not been validated for plant samples.

HPLC with electrochemical detection has been used for the determination of maleic hydrazide in soil and water. The LODs were 0.005 mg/kg for soil and 0.0001 mg/l for water.

Proteolytic enzymes have been employed to solubilize maleic hydrazide from its bound residues in animal products, which occur as glucuronide and sulphate conjugates. Both types of conjugate will release maleic hydrazide on acid hydrolysis, so methods for the analysis of maleic hydrazide are also suitable for some of its conjugates if these are first hydrolysed. In view of the susceptibility of both conjugates to hydrolysis, it was assumed that maleic hydrazide glucoside would serve as a standard for the validation of methods for the glucuronide and sulphate conjugates. The extracted maleic hydrazide was analysed by HPLC with UV detection. Recoveries at fortification levels of 0.2 mg/kg of maleic hydrazide and its glucose conjugate (expressed as maleic hydrazide) were 90-114% for cow milk, 72-94% for liver and 68-80% for eggs.

The Meeting noted that the method was validated by fortifying animal products with the glucoside conjugate of maleic hydrazide, a plant metabolite. Furthermore, metabolism in goats indicated that a large proportion of conjugated metabolites were not released by acid hydrolysis. The Meeting could not confirm the validity of the method, based on HCL/pepsin hydrolysis, for residues in animal products arising from residues in feed.

In a study of the storage stability of maleic hydrazide and its metabolites in milk at -20°C, 33 and 22% of the applied radioactivity was identified as 3-pyridazinone after 1 and 18 months storage respectively.

Information was submitted on the stability of maleic hydrazide residues in stored analytical samples of potatoes and onions. The Meeting concluded that the compound is stable for at least six months in potatoes and onions.

The metabolism studies with a root or tuber vegetable (potato) and a bulb vegetable (onion) showed that the metabolic pattern is similar in these crops. Maleic hydrazide is degraded slowly in plants and is the major residue identified in studies of plant metabolism. Maleic hydrazide glucoside was the main metabolite in potatoes (6-13% of the total ^{14}C) and did not occur in onions.

The Meeting concluded that the definition of the residue in plants for compliance with MRLs and for the estimation of dietary intake should be maleic hydrazide *per se.*

For animal products an appropriate definition would be the sum of free and conjugated maleic hydrazide, but metabolism in goats produced a large proportion of conjugated metabolites from which the exocons were not released by acid hydrolysis.

In a storage stability study of maleic hydrazide and its metabolites in milk, 3-pyridazinone accounted for 33 and 22% of the applied radioactivity after 1 and 18 months storage but the relevance of free and conjugated pyridazinone to the definition of the residue could not be estimated from the data submitted. Furthermore, no validated analytical method for the metabolites, including pyridazinone, is available. From the limited data reported the Meeting could not recommend a definition of the residue in animal products.

The octanol/water partition coefficient of maleic hydrazide at natural pH (log $P_{OW} = -0.68$ at pH 5 and -2.01 at pH 7) shows that the compound is hydrophilic. The Meeting concluded that the compound is not fat-soluble.

Information was made available to the Meeting on registered uses of maleic hydrazide and on supervised residue trials on garlic, shallots, onions and potatoes.

Garlic, shallots and bulb onions. The reported GAP is 1 x 2.3-3.0 kg ai/ha, with PHIs (days) of 4 or 7 in the UK, 10 in France, 15 in Greece and 28 in The Netherlands. Labels give the following directions.
Apply one or two weeks before harvest and not later than 50% necking.
Do not apply less than one week before harvesting.
Avoid spraying edible onions too early, if spraying is done earlier than two weeks before maturity, spongy bulbs may result.

One trial on garlic (1 x 2.4 kg ai/ha, PHI 10 days) approximated French GAP (1 x 2.4 kg ai/ha, PHI 10 days). The residues in duplicate samples were 2.4 and 2.7 mg/kg. In one further trial, residues of 5.0 to 7.0 mg/kg were determined after storage times of 30-90 days, but no information on the analytical method used was available.

Five trials on shallots in France were carried out at the registered application rate of 1 x 2.4 kg ai/ha. In two of them, the residues were 9.5 and 4.5 mg/kg after PHIs of 5 and 7 days. No information on the analytical method used was available for the other trials.

Seven residue trials on onions were carried out in the UK (1 x 2.1-3.6 kg ai/ha, PHI 7-25 days). Ten of 37 Dutch trials were at approximately the registered application rate (1 x 2.3 kg ai/ha), but the PHIs ranged from 16 to 39 days. Three French trials at 1 x 2.4-3.6 kg ai/ha were reported. Fifteen trials were conducted in the USA (1 x 2.2 kg ai/ha, PHI 10 days), but no GAP was reported.

In general, the residues after short and long PHIs were of the same order, as the decrease of the residues is offset by translocation of the compound from the onion tops to the bulbs and the uptake of residues by roots from the soil. No degradation of residues was observed after storing bulbs for 5-11 months after harvest.

Because the use pattern and growing conditions of bulb onions, garlic and shallots are alike, the Meeting agreed to extrapolate the residue data for onions (application 1 x 2.3-3 kg ai/ha) to garlic and shallots.

On the basis of the label recommendation that application should be at the earliest two and at the latest one week before harvest, the residues at PHIs from 5 to 17 days were used for the evaluation. In the case of replicates, only the highest result was selected. The residues in onions, shallots and garlic in rank order were 2.3, 2.4, 2.7, 3.7, 3.7, 4.5, 4.8, 5.5, 7.5 and 9.5 mg/kg. The Meeting estimated STMRs of 4.1 mg/kg and maximum residue levels of 15 mg/kg for garlic, bulb onions and shallots. The estimate of 15 mg/kg confirms the current CXL for onion, bulb.

Potatoes. The reported GAP is 1 x 2.6-3.1 kg ai/ha, with PHIs of 14 days in Denmark and 21 days in France and the UK. The label recommendation for application states:
> The last few flowers may still be apparent but most of blossom will already have fallen. A few of the lowest leaves may be turning yellow but the haulm must be predominately green and active growing.

The label recommendation indicates that the PHI could range from about 4 to 10 weeks. The metabolism studies on potatoes show that the residue level in the tubers depends on the time available for translocation of maleic hydrazide from the treated leaves to the tubers, so the critical GAP should not be linked to the registered PHIs of 14 or 21 days.

A total of 14 trials were carried out in the USA (1 x 2.9-3.5 kg ai/ha, PHI 21 days) but no GAP was reported. A number of trials from 1985 to1992 in the UK complied with GAP (1 x 3.0 kg ai/ha). The residues in the tubers at PHIs from 21 to 69 days were 3.9, 4.3, 4.8, 5.5, 5.7, 5.9, 6.5, 7.0, 8.0, 8.5, 8.7, 8.7, 8.9, 9.3, 9.5, 9.5, 10, 11, 11, 12, 13, 13, 14, 14, 14, 16 and 29 mg/kg. In the 1985 trials the residues were determined again after storage for about six months. The residues in the stored samples were 2.3, 3.0, 4.6, 7.0, 7.3, 9.5, 11, 12, 12, 15, 16, 19 and 36 mg/kg.

In six trials in the UK in 1982 residues were measured during the storage of field-treated potatoes for 180 days. The field treatment complied with UK GAP but the PHIs were not reported. The residues in rank order at the four sampling intervals 0 days 8.2, 10, 14, 17, 22 and 25 mg/kg, 30 days 8.6, 13, 15, 15, 29 and 34 mg/kg, 90 days 4.7, 6.8, 11, 13, 14 and 14 mg/kg and 180 days 7.2, 7.7, 7.9, 12, 13 and 17 mg/kg. The median values were 15.5, 15, 12 and 9.95 mg/kg for the 0, 30, 90 and 180 days storage periods respectively.

The Meeting based its evaluation on the highest data population, the residues in stored potatoes in the 1985 UK trials, and estimated an STMR of 11 mg/kg and a maximum residue level of 50 mg/kg.

No residue data were reported on carrots.

Animal feeding studies

The exposure of farm animals to maleic hydrazide residues will arise from its use on potatoes with a maximum residue level of 50 mg/kg and an STMR of 11 mg/kg.

Dairy and beef cattle. Because the residue could not be satisfactorily defined the Meeting could not estimate maximum residue levels for cattle milk, meat or edible offal.

Poultry. A 28-day feeding study with [^{14}C]maleic hydrazide at dose levels of 1, 3 and 10 mg/kg bw/day was submitted. As potatoes are a minor feedstuff (less than 10% of diet, according to US data), the Meeting concluded that further studies and the estimation of maximum residue levels for residues in poultry commodities resulting from feed were not necessary.

Processing studies were conducted on potatoes in the UK to determine the effect of washing, peeling, microwave baking, oven baking, boiling and frying on residues of maleic hydrazide. Mean processing factors were 0.52 for boiling, 1.2 for microwave baking, 1.35 for oven baking, 0.0265 for frying crisps and 0.92 for frying chips. A further study in the USA showed a mean processing factor for granules and chips of 3.5 and for dry peels of 3.25. A third study demonstrated that washing and peeling do not reduce the residues (processing factors were 1.4 or 1.3).

Since washing, peeling and microwave or oven baking do not change the residue content substantially, the Meeting estimated only STMRs of 5.7 mg/kg (0.52 x 11) for boiled potatoes and 0.29 mg/kg for crisps (0.0265 x 11). As fried potatoes may be prepared in widely varying ways with different processing factors (means 3.5 and 0.92 in the trials), the Meeting estimated STMRs for chips of 38.5 mg/kg (3.5 x 11) for US commercial practice and 10.12 (0.92 x 11) for UK commercial practice for the assessment of dietary intake.

FURTHER WORK OR INFORMATION

Desirable

Further information on the nature of the residues in farm animals.

DIETARY RISK ASSESSMENT

The International Estimated Dieatary Intakes of maleic hydrazide for the five GEMS/Food regional diets based on the STMRs for garlic, bulb onions, shallots and boiled potatoes, were in the range of 1 to 8% of the ADI. The Meeting concluded that the intake of residues of maleic hydrazide resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern

4.19 METHIOCARB

TOXICOLOGY

Methiocarb was evaluated for toxic effects by Joint Meetings in 1981, 1983, 1984, 1985, and 1987. An ADI of 0-0.001 mg/kg bw was allocated in 1981,which was extended at subsequent meetings. Methiocarb was evaluated by the present Meeting within the CCPR periodic review programme.

WHO has classified methiocarb as moderately hazardous.

Methiocarb appeared to have been well absorbed in a small study of absorption, distribution, metabolism, and excretion of the radiolabelled compound in rats. More than 70% of the administered radiolabel was excreted within 48 h, mostly in the urine. Methiocarb was extensively metabolized. The main route of metabolism in both animals and plants appears to be to methiocarb phenol, methiocarb phenol sulfoxide, and methiocarb phenol sulfone. In some studies, methiocarb sulfoxide was also found.

In single-dose and short-term studies in rats, methiocarb administered by gavage inhibited plasma and erythrocyte cholinesterase activity. In the short-term study, plasma, erythrocyte, and brain cholinesterase activities were depressed at 10 mg/kg bw per day; the NOAEL for this effect was 3 mg/kg bw per day. In a short-term study of the ability of methiocarb or its sulfoxide to inhibit cholinesterase activity in rats, the NOAEL for inhibition of erythrocyte acetylcholinesterase activity was 0.5 mg/kg bw per day for methiocarb, but a NOAEL was not identified for the sulfoxide. In a 29-day study in which dogs were given methiocarb or methiocarb sulfoxide in gelatine capsules at 0.05 or 0.5 mg/kg bw per day, both plasma and erythrocyte cholinesterase activities were inhibited by both treatments.

The acute toxicity of methiocarb given by a number of routes has been measured in a number of species. The oral LD_{50} in fasting rats ranged from 13 to 130 mg/kg bw. The oral LD_{50} values for methiocarb phenol, methiocarb phenol sulfoxide, and methiocarb phenol sulfone in rats are all greater than 1 g/kg bw, as is that of methiocarb sulfone, but that of methiocarb sulfoxide is between 6 and 43 mg/kg bw.

The short-term toxicity of methiocarb has been tested in rats, rabbits, cats, dogs, and chickens. Few of these studies were appropriate for identifying NOAELs and, of those that were, a study in rats was carried out by inhalation and that in rabbits by dermal application. In the study in rats, which were exposed by inhalation, for five days per week for three weeks, no findings related to treatment were seen on histopathological examination but depressed brain acetylcholinesterase activity was observed at the highest dose in animals of each sex and in males at the intermediate dose. Consequently, the NOAEL was 6 mg/m^3 per day. In a 21-day study of the dermal toxicity of methiocarb in rabbits, the substance was applied for 6 h/day at 0, 60, 150, or 375 mg/kg bw per day. Plasma cholinesterase activity was reduced in males at the highest dose, but no significant differences were seen between groups in the activities of erythrocyte and brain acetylcholinesterase. The NOAEL was 150 mg/kg bw per day on the basis of reduced food consumption at the highest dose.

In a long-term study of toxicity in mice, methiocarb was administered at dietary concentrations of 0, 67, 200, or 600 ppm. A NOAEL was not identified because haematological

changes were observed in all treated males at 12 months and in all treated females at 24 months. The LOAEL was 67 ppm, equal to 15 mg/kg bw per day, on the basis of minor haematological changes. Methiocarb was not carcinogenic in mice.

In a two-year study of toxicity, rats received methiocarb at dietary concentrations of 0, 67, 200, or 600 ppm. The NOAEL was 67 ppm, equal to 3.3 mg/kg bw per day, on the basis of haematological changes at 3, 6, and 12 months. Methiocarb was not carcinogenic.

In a two-year study of toxicity, dogs were fed methiocarb in the diet at 0, 5, 60, or 240 ppm. The NOAEL was 60 ppm, equivalent to 1.5 mg/kg bw per day, on the basis of reversible clinical signs at the next highest dose, which were not observed after 15 weeks.

Three studies of developmental toxicity were available, one in rats and two in rabbits. Fertilized rats received methiocarb by gavage on days 6-15 of gestation at 0, 1, 3, or 10 mg/kg bw per day. The NOAEL for maternal toxicity was 3 mg/kg bw per day on the basis of reduced body-weight gain at the highest dose. As no fetotoxicity was observed, the NOAEL for this end-point was 10 mg/kg bw per day, the highest dose tested. In a study of developmental toxicity in rabbits, pregnant animals received methiocarb at 0, 1, 3, or 10 mg/kg bw per day by gavage on days 6-18 of gestation. The NOAEL was 3 mg/kg bw per day for maternal toxicity on the basis of clinical effects and weight loss at the highest dose. As no fetotoxicity or teratogenicity was observed, the NOAEL for these end-points was 10 mg/kg bw per day, the highest dose tested. In a further study, rabbits received methiocarb by dermal application at 0, 10, 50, or 250 mg/kg bw per day for 6 h/day on days 6-18 of gestation. The NOAEL for both maternal and fetal toxicity was 50 mg/kg bw per day on the basis of reduced maternal food consumption and some decrease in mean fetal weight at the highest dose; slight retardation of fetal development was also observed. A multigeneration study of reproductive toxicity was undertaken in rats given methiocarb at dietary concentrations of 0, 30, 100, or 300 ppm. The NOAEL was 300 ppm, equivalent to 30 mg/kg bw per day, as no effect clearly related to treatment was observed. No teratogenic effect was observed in any of these studies.

Methiocarb has been tested for genotoxicity in an adequate battery of tests *in vitro* and *in vivo*. The Meeting concluded that methiocarb is not genotoxic.

Methiocarb did not cause skin sensitization in studies conducted by either the Magnusson and Kligman or the Beuhler technique.

In an early study of neurotoxicity in hens, methiocarb did not cause delayed polyneuropathy of the organophosphorus type. Atropine has consistently been shown to be an effective antidote for methiocarb, while the effects of pyridinium oximes were somewhat inconsistent.

The Meeting established an ADI of 0-0.02 mg/kg bw on the basis of the NOAEL of 1.5 mg/kg bw per day in the two-year study of toxicity in dogs and a safety factor of 100. This ADI results in a further safety factor of 10 on the LOAEL in the long-term study of toxicity in mice.

An acute RfD was allocated on the basis of the NOAEL of 1.5 mg/kg bw per day in the two-year study in dogs, because the signs observed were acute, and a safety factor of 100. Of the shorter studies in dogs, neither the 29-day nor the 12-week study was considered by the Meeting to be adequate for the purpose of establishing a NOAEL.

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

TOXICOLOGICAL EVALUATION

<u>Levels that cause no toxic effect</u>

Mouse: No NOAEL; LOAEL: 67 ppm, equal to 15 mg/kg bw per day
          (long-term study of toxicity)

Rat: 67 ppm, equal to 3.3 mg/kg bw per day (long-term study of toxicity)
          300 ppm, equivalent to 30 mg/kg bw per day (maternal and fetal toxicity in a study of reproductive toxicity)
          3 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
          10 mg/kg bw per day (developmental toxicity)

Rabbit: 3 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
          10 mg/kg bw per day (developmental toxicity)

Dog: 60 ppm, equivalent to 1.5 mg/kg bw per day (two-year study of toxicity)

<u>Estimate of acceptable daily intake for humans</u>

0-0.02 mg/kg bw

<u>Estimate of acute reference dose</u>

0.02 mg/kg bw

<u>Studies that would be useful for the continued evaluation of the compound</u>

1. A modern study of absorption, distribution, metabolism, and excretion
2. A modern multigeneration study of reproductive toxicity
3. Further observations in humans

<u>List of end points relevant for setting guidance values for dietary & non-dietary exposure</u>

Absorption, distribution, excretion, and metabolism in mammals

Rate and extent of oral absorption	No data
Dermal absorption	No data
Distribution	No data
Potential for accumulation	Not likely to accumulate
Rate and extent of excretion	73 to > 90% in 48 h
Metabolism in animals	Sulfoxidation and loss of carbamate side-chain
Toxicologically significant compounds (animals, plants and environment)	Parent compound and methiocarb sulfoxide

Acute toxicity

Rat LD$_{50}$, oral	13-135 mg/kg bw
Rat LD$_{50}$, dermal	350->5000 mg/kg bw
Rat LC$_{50}$, inhalation	>300 mg/m^3
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization	Not sensitizing

Short-term toxicity

Target/critical effect	Clinical signs
Lowest relevant oral NOAEL	1.5 mg/kg bw per day
Lowest relevant dermal NOAEL	150 mg/kg bw per day
Lowest relevant inhalation NOAEL	6 mg/m^3

Genotoxicity

Not genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect	Clinical signs
Lowest relevant NOAEL	1.5 mg/kg bw per day
Carcinogenicity	Not carcinogenic

Reproductive toxicity

Reproductive target/critical effect	No effect
Lowest relevant reproductive NOAEL	30 mg/kg bw per day
Developmental target/critical effect	Maternal toxicity: clinical signs: reduced weight gain; no fetotoxicity observed
Lowest relevant developmental NOAEL	3 mg/kg bw per day

Neurotoxicity/Delayed neurotoxicity

Does not cause delayed polyneuropathy

Other toxicological studies

No data

Medical data

No data

Summary	Value	Study	Safety factor
	0-0.02 mg/kg bw	Dog, 2 years	100
	0.02 mg/kg bw (dog, 2-year study)		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 2 to 5% of the ADI. The Meeting concluded that the intake

of residues of methiocarb resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.20 MYCLOBUTANIL (181)

RESIDUE AND ANALYTICAL ASPECTS

Myclobutanil was evaluated in 1992 and 1997. In 1997 the JMPR evaluated six field trials on hops conducted in the UK but the four trials which complied with GAP were considered insufficient to estimate a maximum residue level. Several post-harvest trials on bananas were according to proposed GAP, but since only proposed GAP was reported the 1997 Meeting could not estimate a maximum residue level. The present Meeting was informed that further trials in Germany were in progress which included processing studies, and that there was now registered GAP for bananas which would allow the recommendation of an MRL for banana.

The manufacturer requested the present Meeting to evaluate additional data on hops and re-evaluate of the data on bananas in the light of the recently established GAP.

The analytical methods for myclobutanil and its hydroxy metabolite RH-9090 used in the trials on hops and bananas reported in 1997 were described in the 1992 and 1997 monographs. The method used in the hop trials in Germany was described in the 1992 evaluation. The LODs for dried hops and beer were 0.5 and 0.01 mg/kg respectively. This method was validated for many plant commodities.

Four of the six UK trials reported in 1997 complied with GAP (6 applications, 0.0045 kg ai/hl, 10 days PHI). The residues of myclobutanil on hops (dried cones) ranged from 0.27 to 1.2 mg/kg. Eight supervised trials on hops were conducted in Germany in 1996 and 1997, four of which can be considered to comply with UK GAP. The residues of myclobutanil in dried hops in these trials ranged from <0.5 to 1.08 mg/kg.

The residues of myclobutanil in dried hops in the eight trials according to GAP in rank order (median underlined) were 0.27, 0.3, <0.5, 0.5, 0.53, 1.02, 1.08 and 1.2 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.515 mg/kg for dried hops.

Bananas. The trials evaluated by the 1997 JMPR showed myclobutanil residues in whole bananas treated according to Costa Rica GAP from 0.64 to 1.7 mg/kg. The residues in the edible pulp in rank order (median underlined) were 0.1, 0.17, 0.19, 0.2, 0.21, 0.22, 0.27, 0.35, 0.39 and 0.41 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg (whole fruit) and an STMR of 0.215 mg/kg for banana.

Processing studies. Dried hops from two supervised trials containing residues of 1.02 and 1.06 mg/kg were brewed into beer. The residues in the beer in both studies were below the LOD. The calculated processing factor for hops to beer is 0 (<0.009), and the estimated STMR for beer is 0 mg/kg.

DIETARY RISK ASSESSMENT

Recommendations for myclobutanil MRLs on bananas and hops have been added to the previous recommendations and STMRs have been estimated for these commodities. The other values used for the intake estimation were previously estimated STMRs for six commodities and CXLs established for ten commodities. The International Estimated Daily Intakes of myclobutanil for the five GEMS/Food regional diets were 0 to 4% of the ADI. The Meeting concluded that the intake of residues of myclobutanil resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.21 OXYDEMETON-METHYL (166)/DEMETON-S-METHYL (073)

RESIDUE AND ANALYTICAL ASPECTS

Oxydemeton-methyl (ODM), *S*-2-ethylsulfinylethyl *O,O*-dimethyl phosphorothioate, is a systemic and contact insecticide and is a metabolite (sulfoxide) of the insecticide demeton-S-methyl, *S*-2-ethylthioethyl *O,O*-dimethyl phosphorothioate. The 1992 JMPR carried out a complete re-evaluation of oxydemeton-methyl. The residue is currently defined as the sum of oxydemeton-methyl, demeton-S-methyl, and demeton-S-methylsulphon, expressed as oxydemeton-methyl.

The present evaluation is part of the Periodic Review Programme of the CCPR.

Extensive data and information were submitted for oxydemeton-methyl. No information was provided on demeton-S-methyl, except on its metabolism by wheat.

Animal metabolism

Metabolism studies were submitted on rats, poultry, and goats. Rats treated orally or intravenously with a single dose of [*ethylene*-^{14}C]ODM (20 mg/kg bw) eliminated at least 89% of the dose in the urine within 72 hours. In a composite 0–24 hour urine sample ODM accounted for about 50% of the administered radioactivity. The identified metabolites were 1-(ethylsulfinyl)-2-(methylsulfinyl)ethane and 1-(ethylsulfonyl)-2-(methylsulfinyl)ethane, each 16%, demethyl-ODM and demethyl-ODM sulfone, each 2–3%.

Lactating goats were dosed orally with [*ethylene*-^{14}C]ODM for three consecutive days at a rate of 7 mg ODM per kg body weight. Urine and milk were collected daily, the goats were slaughtered 2 hours after the final dose, and tissues were collected. Water extracted virtually all of the radioactive residues from all samples except fat, from which about 85% was extracted. Milk was centrifuged, and the supernatant was eluted from C-18 solid phase extraction cartridges. The eluate contained about 80% of the original ^{14}C in the milk. The total radioactive residue (TRR) concentrations, expressed as ODM, were kidneys 13 mg/kg, liver 4.2 mg/kg, muscle 4.0 mg/kg, fat 0.62 mg/kg, and milk 3.8 mg/kg. The only compounds identified were ODM and its sulfone, with the parent constituting 23–61% of the TRR and the sulfone 0.8–23%.

Laying hens dosed with [*ethylene*-^{14}C]ODM at 6.9 mg/kg body weight for three consecutive days were killed within four hours of the final dosing, and appropriate tissues were

collected and analysed. The total radioactive residues as ODM were breast 0.51 mg/kg, thigh 0.43 mg/kg, liver 0.60 mg/kg, kidney 1.4 mg/kg, skin 0.41 mg/kg, and eggs (day 3) 0.36 mg/kg. A mixture of acetone and methylene chloride extracted >80% of the TRR from all samples except eggs (70% extraction). Demethyl-ODM sulfone was the main compound in the breast (70% of the ^{14}C), thigh (80%), liver (48%), skin (100%) and eggs (100%). The main residue in the kidneys was a mixture of 2-(ethylsulfinyl)ethanesulfonic acid and 2-(ethylsulfonyl)ethanesulfonic acid (84%). These compounds also constituted a high proportion (42%) of the residue in the liver.

The results of the three metabolism studies indicate oxidation to the sulfone and cleavage of the P-S linkage. The Meeting concluded that the animal metabolism studies were adequate.

Plant metabolism

The metabolism of [*ethylene*-^{14}C]ODM in cabbage and sugar beet, of [*ethylene*-^{14}C]demeton-S-methyl in wheat , and of demeton-S-methylsulphon in apples were reported. The radioactive residues in cabbage were characterized only as highly polar and water-soluble. The radioactive residues in the foliage and roots of sugar beet were extracted and some of the major metabolites were identified by MS. ODM was a minor component on the foliage (2% of the TRR). The main metabolites were demethyl-ODM 14%, bis(2-ethylsulfinylethyl) disulfide 12%, 2-hydroxy-3-(2-ethylsulfinylethylthio)propionic acid 14%, 2-hydroxy-3-(2-ethylsulfonylethylthio)propionic acid 10%, and 2-hydroxy-3-(2-ethylsulfonylethylsulfinyl)propionic acid 11%. All except demethyl-ODM involve cleavage of the P-S bond.

The metabolism of [*ethylene*-^{14}C]demeton-*S*-methyl by wheat grown in a greenhouse again revealed cleavage of the P-S bond with the formation of sulfonic acids, disulfides, and ethanol derivatives: 2-(ethylsulfonyl)ethanesulfonic acid 8% of the TRR, 1-(ethylsulfinyl)-2-(methylsulfinyl)ethane 9%, 1-(ethylsulfinyl)-2-(methythio)ethane 4%, 2-ethylsulfinylethanol, 5%. ODM and ODM sulfone constituted 20% of the radioactive residue.

The metabolism of [*ethylene*-^{14}C]-demeton-S-methylsulphon by apples produced compounds formed by P-S bond cleavage, as well as demethyl- and didemethyl-demeton-S-methylsulphon (5-6% of the TRR). At day 27, demeton-S-methylsulphon (the test material) accounted for 24% of the applied radioactivity in both peel and pulp. The main metabolites were *S*-2-ethylsulfonylethyl *O*-methyl *O*-hydrogen phosphorothioate (demethylated parent) 3% in both pulp and peel, *S*-2-ethylsulfonylethyl *O*-*O*-dihydrogen phosphorothioate (didemethylated parent), 1% in pulp and 3% in peel, 2-ethylsulfonylethanesulfonic acid 3%, and 2-ethylsulfonylethanol 3% in pulp. The total of the identified compounds at 27 days accounted for less than 40% of the applied radioactivity.

The Meeting concluded that the plant metabolism studies were marginally acceptable. The details and raw data of the studies were not provided and therefore some results, particularly the quantitative results, could not be verified. Isolated metabolites were positively identified by mass spectrometry and comparison with authentic standards. The four studies indicate a common mechanism involving oxidation to the sulfone, formation of the demethyl and didemethyl derivatives, and cleavage of the P-S linkage.

Environmental fate

The Meeting received reports of studies on uptake by rotational crops, dissipation under field conditions, photolysis on soil, adsorption and desorption on four types of soil, leaching from clay, aerobic and anaerobic degradation on soil, and aerobic and anaerobic degradation in water/sediment systems.

The degradation of [*ethylene*-^{14}C]ODM on sandy loam soil was studied over a 12-month period. Volatile compounds accounted for only 9% of the applied radioactivity after 12 months. The major products were 2-ethylsulfinylethanesulfonic acid and 2-ethylsulfonylethanesulfonic acid, 20–30% of the applied radioactivity. The half-life of ODM, assuming first order kinetics, was 3.2 days. A similar degradation of ODM was observed under anaerobic conditions, but the data were not adequate to calculate a half-life. The Meeting concluded that ODM is degraded at a moderate rate under aerobic conditions in soil, with formation of the sulfonic acid after cleavage of the P-S bond.

For the rotational crop study, kale, wheat, and beetroot were planted in soil that had been treated with [*ethylene*-^{14}C]ODM at 3.4 kg ai/ha in Kansas, USA. The crops were planted at intervals of about 30, 180, and 300 days after treatment of the soil and harvested at normal maturity. Beet roots, beet tops and kale contained no residues after any planting interval. Immature wheat (boot stage) showed radioactivity equivalent to 0.02 mg/kg ODM from the 34-day planting. Wheat grain, straw and chaff contained low levels of radioactivity, 0.01–0.06 mg/kg, from the 34-day and 184-day plantings. These levels represent the sum of ODM and its metabolites, so ODM and demeton-S-methylsulphon are not expected to be quantifiable in crops planted at the intervals studied. The Meeting concluded that inadvertent residues in rotational crops were not a significant source of dietary exposure and need not be considered in estimating maximum residue levels.

[*Ethylene*-^{14}C]ODM applied to sandy loam soil was exposed to natural sunlight for 30 days. The rate of degradation was no more than in a dark control sample. A similar result was found for ODM in sterile buffer solution at pH 5 exposed to natural sunlight for 30 days. The Meeting concluded that photolysis was not a significant degradation pathway for ODM.

The adsorption and desorption of ODM was measured by a batch equilibrium procedure in four types of soil. ODM was not bound substantially to any of the soils.

The leaching of [*ethylene*-^{14}C]ODM through a sandy clay loam soil was studied. Aerobic ageing of the soil for 30 days before leaching caused a 50% loss of radioactivity as CO_2. Water (1.25 cm of simulated rainfall) was applied each day for 45 days to the aged soil. Over 80% of the radioactivity remained in the top 2.5 cm of the soil. A soil dissipation study under field conditions in California, USA, showed a half-life of ODM of about 2 days, with no tendency to migrate below 15 cm. The Meeting concluded that ODM is not leached through soil.

The degradation of [*ethylene*-^{14}C]ODM was studied in sterile buffer solution at 25°C. The half-life decreased dramatically with increasing pH, from 94 days at pH 5 to 2.5 days at pH 9. The identified products were demethyl-ODM and 2-ethylsulfinylethanethiol (34 and 13% respectively after 35 days at pH 7).

Water and sediment from an orchard drainage ditch and from a fish pond were treated in separate experiments with [*ethylene*-^{14}C]ODM at 0.5 mg ai/l. Samples were taken on days 1, 7, 20, 41, and 91. Volatile compounds accounted for about 25% of the applied radioactivity after 91

days. After 7 days, ODM accounted for about 10% of the applied ^{14}C in the waters and <1% in the sediments. The main products were demethyl-ODM, 2-ethylsulfinylethanesulfonic acid, 2-ethylsulfonylethanesulfonic acid, demethyl-ODM sulfone, and bis(2-ethylsulfinylethyl) disulfide. ODM sulfone accounted for <1% of the applied ^{14}C at all intervals in all fractions.

A water/sediment degradation study was also conducted under anaerobic conditions for a period of 12 months. [*Ethylene*-^{14}C]ODM represented only 3% of the applied radioactivity within 14 days. The main products were 1-(ethylsulfinyl)-2-(methylsulfinyl)ethane (18% of the applied ^{14}C in the surface water), 2-ethylsulfinylethanesulfonic acid (9% in the surface water), and 2-ethylsulfonylethanesulfonic acid (4% in the surface water).

The Meeting concluded that ODM is degraded rapidly in soil and in water via cleavage of the P-S bond.

Methods of residue analysis

Numerous similar methods were presented for enforcement and data collection. All determine the combined residue of demeton-S-methyl, oxydemeton methyl, and demeton-S-methylsulphon. The analyte measured is the sulfone. The crop sample is extracted with solvent, typically acetone/water, the extract is cleaned up (optionally) by gel permeation chromatography (GPC), oxidized with permanganate, cleaned up if necessary by solid-phase extraction (SPE), and analysed on a gas chromatograph equipped with a flame photometric detector. The oxidation step converts demeton-S-methyl and ODM to the sulfone. Extensive recovery data were presented. Typical lower limits of determination are 0.01 and 0.05 mg/kg as ODM.

The Meeting concluded that adequate methods exist for the determination of demeton-S-methyl and ODM in plant and animal commodities.

Stability of residues in stored analytical samples

Storage stability studies were reported for cabbage, maize forage, maize kernels, maize husks, lettuce, and papaya. ODM and demeton-S-methylsulphon were stable on cabbage stored frozen for 800 days. Demeton-S-methylsulphon was stable on maize forage stored frozen for 160 days, but ODM showed significant loss after 60 days. ODM was stable on lettuce and papaya stored frozen for 50 days and 13 days respectively. (The Meeting did not accept the apparent recovery from lettuce of 98% after 180 days as valid because it was the mean of 69% and 128%).

The Meeting concluded that the data were generally inadequate and contradictory, and that additional studies were highly desirable.

Definition of the residue

The residue is currently defined as the sum of oxydemeton-methyl, demeton-S-methyl and demeton-S-methylsulphon, expressed as oxydemeton-methyl. The analytical methods determine the combined residue as the sulfone. The pesticide demeton-S-methyl is metabolized to its sulfoxide, ODM. The Meeting confirmed the current definition, both for compliance with MRLs and for the estimation of dietary intake.

Residues resulting from supervised trials

Supervised field trials were reported for oranges, lemons, apples, pears, plums, grapes, cabbage, kale, kohlrabi, lettuce, peas, beans, potatoes, sugar beet, wheat, oats, barley, almonds, rape, sunflower, and cotton seed.

The Meeting was informed that instruction labels were being revised in Europe for some crops to include conditions aimed at yielding lower residues, such as reduced application rates and extended PHIs. Some labels may be awaiting approval by national governments. The Meeting based its recommendations on the available labels and did not consider pending or possible changes.

Oranges and lemons. Supervised field trials were conducted on oranges in Spain (6 trials, GAP for oranges 2 x 0.75 kg ai/ha, 30-day PHI) and Portugal (1 trial; GAP for citrus fruit 2 x 0.050 kg ai/hl (calculated 0.75 kg ai/ha), 84-day PHI). All the trials complied with GAP for Portugal and two of them with GAP for Spain, but the peel and pulp were analysed separately and their relative weights were not reported. The higher residues in the peel were used to estimate maximum residue levels, and the residues in the pulp to estimate STMRs. Two field trials on lemons in Spain and two in Italy complied with Portuguese GAP, and the Spanish trials also with Spanish GAP for oranges. The 11 trials on oranges and lemons may be combined for the estimation of maximum residue levels and STMRs to give rank orders of residues in the pulp of <0.01 (7), 0.01, 0.02 (2) and 0.04 mg/kg, and in the peel of <0.01 (5), 0.01 (2), 0.06, 0.09 and 0.13 (2) mg/kg. The Meeting estimated maximum residue levels of 0.2 mg/kg and STMRs of 0.01 mg/kg for oranges and lemons.

Apples and pears. Supervised field trials on apples in Germany (4 trials, GAP 1 x 0.025 kg ai/hl (0.40 kg ai/ha, 1500 l water/ha) before or directly after flowering, PHI about 60 days), Belgium (2 trials, no GAP reported), and France (3 trials, GAP 0.020 kg ai/hl, 60-day PHI) were reported. The trials in Belgium were at the higher rate of 0.083 kg ai/hl and did not comply with French or German GAP, and in two of the German trials application was apparently at a later growth stage. Two trials in Germany and three in France were according to GAP.

Field trials were also reported on pears: 2 in Germany, same GAP as apple; 1 in France, same GAP as apple, 2 in Italy according to Portuguese GAP (0.038 kg ai/hl, 56-day PHI) and 1 in Belgium, GAP not reported. All the trials were according to GAP except the Belgian trial with a longer PHI (100 days) than the 60 days of German GAP.

The five apple and five pear trials may be evaluated together: GAP for the two fruits is very similar and the residues are in one population. The residues in rank order were <0.01 (7), 0.03 and <0.04 (2) mg/kg. The Meeting estimated maximum residue levels of 0.05 mg/kg and STMRs of 0.01 mg/kg for apples and pears.

Plums. Four supervised field trials in Germany were according to GAP (1 x 0.025 kg ai./hl, before or directly after flowering, PHI about 60 days). The residues were 0.040, 0.014, 0.044 and 0.028 mg/kg). The Meeting concluded that 4 trials were insufficient for the estimation of a maximum residue level or an STMR and recommended withdrawal of the draft MRL.

Grapes. Supervised field trials were reported from Italy (2 trials, GAP 1 x 0.23 kg ai/ha, 40-day PHI) and Germany (3 trials, GAP 1 x 0.025 kg ai/hl applied from 2 leaves to developed

inflorescences, BBCH Code 57). The residues were <0.04 (4) and 0.06 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.04 mg/kg.

Cabbages (head). Sixteen supervised field trials in Germany were according to GAP (1 x 0.15 kg ai/ha (height under 50 cm), 21-day PHI). The residues in rank order were <0.01 (6), 0.02, <0.03 (3), <0.04, <0.05 (4) and <0.06 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.03 mg/kg for head cabbages, and recommended withdrawal of the draft MRL for Savoy cabbage.

Kale. Four trials in Germany were according to GAP (the same as for cabbages). All the residues were <0.01 mg/kg. The Meeting considered the four trials an adequate database for kale and estimated a maximum residue level of 0.01* mg/kg and an STMR of 0.01 mg/kg.

Kohlrabi. Four supervised field trials in Germany complied with GAP for kohlrabi (the same as for cabbages). The residues were <0.01 (2), 0.03 and <0.06 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.02 mg/kg .

Lettuce. Seven reported trials in Germany comprised one trial in triplicate (same location, time, and application) which complied with GAP (1 x 0.16 kg ai/ha, 21-day PHI) and two duplicate trials in which the PHIs were more than 33% below the GAP PHI and which displayed quantifiable residues. The Meeting concluded that one trial was not adequate for the estimation of a maximum residue level or STMR and recommended the withdrawal of the draft MRL for leaf lettuce.

Field peas and beans (dry). Three of five trials on field beans in Germany accorded with GAP (2 x 0.15 kg ai/ha (height under 50 cm) or 0.25 kg ai/ha (over 50 cm), 28-day PHI). The other two trials were apparently replicates of one of these. Three trials on field peas were conducted in Germany (GAP only for garden peas) and two in France (no GAP). GAP for Italy is 1 x 0.23 kg ai/ha, 21-day PHI, but the trials were at less than half this rate. All residues in the shelled dry peas were <0.01 mg/kg. The Meeting decided that the three trials on field beans, supplemented by the 5 trials on field peas whose rates and PHIs approximated GAP for field beans, provided an adequate data base for the estimation of a maximum residue level and STMR for beans but not peas. The residues in rank order were <0.01 (5), <0.04, 0.05 and 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.01 mg/kg for common bean (dry), and recommended withdrawal of the draft MRLs for beans (dry) and peas (dry).

Potatoes. Supervised trials were reported from Germany (14 trials, GAP 3 x 0.3 kg ai/ha, 21-day PHI), France (1 trial; no GAP reported), the UK (3 trials, no GAP reported), and The Netherlands (2 trials, no GAP reported). GAP for Ireland is 2-4 x 0.15 kg ai/ha (height under 50 cm) or 0.22 kg ai/ha (over 50 cm), 200 l water/ha, PHI 28 days. All the trials approximated German or Irish GAP but two German trials were discounted because they were replicates and not independent trials. In the 18 independent trials the residues in rank order were <0.01 (7), <0.02 (9) and <0.05 (2) mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.02 mg/kg.

Sugar beet (root). Supervised field trials were reported from Germany (9 trials + 2 on fodder beet, GAP 4 x 0.24 kg ai/ha, 28-day PHI) and France (2 trials, GAP 0.15 kg ai/ha, 28-day PHI). The two trials in France and two of the German trials were at excessive application rates. Seven trials on sugar beet and the two trials with fodder beat in Germany complied with GAP for sugar

beet. The residues in rank order in the sugar and fodder beets were <0.01 (4) and <0.04 (5) mg/kg. The residues in the four trials at excessive rates were all <0.04 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.04 mg/kg.

Sugar beet (tops). The residues in the leaves of the sugar and fodder beets treated according to GAP were 0.02 and <0.04 (8) mg/kg. The residues from the two German trials at excessive rates were also <0.04 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.04 mg/kg for sugar beet leaves or tops.

Wheat, barley and rye. Supervised field trials on wheat were reported from Germany (8 trials, GAP 2 x 0.12 kg ai/ha, 21-day PHI) and the UK (1 trial; no GAP reported; Irish GAP for wheat, rye and barley: 0.12 kg ai/ha, 200 l water/ha, 21-day PHI). Six trials in Germany were according to maximum GAP conditions and complied with Irish GAP. Three trials on barley were reported from Germany and one from the UK. Two German trials and the UK trial (according to Irish GAP) were at the maximum GAP conditions and gave residues of <0.04 (2) and <0.05 mg/kg in the grain. Two supervised field trials on oats (grain residues <0.01 and 0.05 mg/kg) were submitted from Germany, but no current GAP was available.

A total of 10 trials on wheat and barley complied with GAP. The results may be combined for the evaluation of these crops and rye. The residues in the grain in rank order were <0.04 (6), <0.05 (2) and 0.05 mg/kg. The Meeting estimated maximum residue levels of 0.05* mg/kg and STMRs of 0.04 mg/kg for wheat, barley and rye.

Wheat, barley and rye straw and fodder. The 10 trials according to GAP for wheat and barley described above yielded residues in or on the straw of <0.04 (4), <0.05, 0.06, 0.12, 0.18, 1.2 and 1.3 mg/kg. The Meeting estimated maximum residue levels of 2 mg/kg and STMRs of 0.06 mg/kg for the fodders and straws of wheat, barley and rye.

Almonds. In six supervised field trials on almonds in Spain (GAP 2 x 0.25 kg ai/ha, 30-day PHI) all the PHIs were 90 days. The Meeting concluded that there were no results from trials according to GAP and that no maximum residue level or STMR could be estimated.

Rape seed. Three supervised field trials in France (GAP 0.12 kg ai/ha, unspecified PHI) yielded residues in the seed of <0.05 mg/kg after application at 0.12 kg ai/ha and a 63- or 79-day PHI. The Meeting concluded that 3 trials were insufficient to estimate a maximum residue level or STMR.

Sunflower seed. Three trials in France (GAP 1 x 0.1 kg ai/ha, PHI unspecified) gave residues in the seeds of <0.01 mg/kg after a foliar treatment at 0.1 kg ai/ha and an 83–87-day PHI. The Meeting concluded that 3 field trials were inadequate for the estimation of a maximum residue level or STMR.

Cotton seed. Ten trials in Australia (no GAP reported), 4 in Brazil (Peruvian GAP 3 x 0.25 kg ai/ha, 14-day PHI), and 7 in the USA (GAP 3 x 0.84 kg ai/ha, 14-day PHI) were reported. Two of the trials in Brazil with residues of 0.03 and 0.02 mg/kg complied with GAP and six US trials approximated GAP. The status of the remaining trials could not be ascertained from the information provided. The residues in rank order were <0.01 (2), 0.01 (3), 0.02 and 0.03 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg.

Feeding studies

Animal feeding studies on lactating dairy cows and laying hens were reported. The cows received daily doses of ODM for 28 days at levels equivalent to 10, 30, or 100 ppm in the feed. The combined residue of ODM and ODM sulfone was <0.01 mg/kg in all milk samples and in the liver, kidneys, muscle and fat. The demonstrated lower limit of quantification was 0.01 mg/kg.

Three groups of ten hens each were fed ODM in the daily diet for 28 days at rates of 0.65, 1.95, or 6.5 ppm in the feed. The combined residue was <0.01 in all egg samples and in the tissues of the 6.5 ppm group. Tissues from the other groups were not analysed.

The potential animal feed items containing ODM and the relevant maximum residue levels are as follows: potato culls and processed waste (potatoes 0.05 mg/kg), sugar beet tops, pulp, and molasses (sugar beet 0.05 mg/kg), wheat and barley grain (0.05 mg/kg) and straw (2 mg/kg), cotton seed and cotton seed oil, meal and hulls (cotton seed 0.05 mg/kg). A dietary burden for dairy cattle can be calculated as follows: barley straw (2 mg/kg/0.89 dry matter) x 60% of the diet + cotton seed (0.05 mg/kg/0.88 dry matter) x 20% of the diet + sugar beet tops (0.05 mg/kg/0.23 dry matter) x 20% of the diet = 1.5 ppm. The dietary burden for poultry would be cotton seed meal (0.05 mg/kg/0.89 dry matter x 20% of the diet) + grain (0.05 mg/kg/0.88 dry matter x 50% of the diet) = 0.04 ppm. The cattle and hen feeding studies at maximum rates represent approximately 66 times (100/1.5) and 160 times (6.5/0.04) these levels respectively, and no residues were found. The Meeting concluded that quantifiable residues of demeton-S-methyl, ODM, and/or demeton-S-methylsulphon in commodities of animal origin (meat, milk, poultry and eggs) are unlikely and that MRLs could be set at the practical limits of quantification of 0.05* mg/kg for all commodities except milk and at 0.01* mg/kg for milk. The Meeting recommended these levels as MRLs, estimated STMRs of 0 mg/kg for all the commodities, and recommended withdrawal of the draft MRL for derived milk products.

Processing studies

Processing studies on apples and cotton seed were reported. The processing factor for apple juice was 0.5 and for sauce 1. The processing factor for refined cotton seed oil was 0.2, for meal 0.6, and for hulls 0.2. Limited information on processing was provided for sugar beet, kale, potatoes, rape, and wheat, but in all cases the raw agricultural commodity lacked quantifiable residues.

FURTHER WORK OR INFORMATION

<u>Desirable</u>

Data on the stability of stored analytical samples of raw agricultural commodities containing quantifiable residues of oxydemeton-methyl are highly desirable. The available information was not representative of the various crop groups, did not cover extended storage intervals, and suggested variable storage stability.

DIETARY RISK ASSESSMENT

STMRs have been estimated for oxydemeton-methyl in 30 commodities, of which five are processed commodities and seven are products of animal origin. Where consumption data were available, these STMRs were used in the estimate of dietary risk. No MRLs were used.

The International Estimated Daily Intakes for the five GEMS/Food regional diets ranged from 10 to 90% of the ADI. The Meeting concluded that the intake of residues of oxydemeton-methyl resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.22 PHOSMET (103)

TOXICOLOGY

The 1994 JMPR concluded that a two-year study of toxicity in dogs that was evaluated at that Meeting was inadequate for deriving a NOAEL, in view of the small group size (three animals of each sex per group) and the spacing of the dietary concentrations (0, 20, 40, and 400 ppm), and requested a new long-term toxicity study in dogs. The 1994 Meeting also considered that phosmet is not clastogenic but that its mutagenic potential was not clear. The submission of the results of studies of DNA binding *in vivo* were therefore requested. Furthermore, the 1994 Meeting considered that the doses of phosmet given to the hens in the studies of delayed polyneuropathy might have been insufficient to elicit neuropathic effects, and a study of delayed polyneuropathy in hens at adequate doses and with estimation of neuropathy target esterase was requested. The study of delayed polyneuropathy has now been supplied, together with a study of unscheduled DNA synthesis in rats *in vivo*. A new study in dogs was not available.

In the study of delayed polyneuropathy, a dose of 600 mg/kg bw was given to 24 hens, this dose being greater than the experimentally determined LD_{50}. There was no evidence that phosmet could produce clinical signs of delayed polyneuropathy or significantly inhibit neuropathy target esterase.

The ability of phosmet (96.4% pure) to induce unscheduled DNA synthesis in the liver of male rats *in vivo* was determined with doses of 32 or 50 mg/kg bw, the higher dose being the maximum tolerated dose of phosmet. Unscheduled DNA synthesis was not observed. The Meeting noted that the study on DNA binding had not been provided, but it concluded that no further characterization of mutagenicity was required. The Meeting considered that a further study in dogs would be unlikely to affect the overall evaluation.

The ADI of 0-0.01 mg/kg bw allocated by the 1994 JMPR, which was based on a NOAEL of 1.3 mg/kg bw per day in a multigeneration study in rats and a safety factor of 100, was confirmed.

An acute RfD of 0.02 mg/kg bw was allocated on the basis of a NOAEL of 2 mg/kg bw per day in a study of developmental toxicity in rabbits (fetotoxicity) and a safety factor of 100.

An addendum to the toxicology monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that have no toxic effect (from 1994 monograph)

Mouse: 25 ppm, equivalent to 4 mg/kg bw per day (two-year study of carcinogenicity)

Rat: 40 ppm, equal to 1.8 mg/kg bw per day (two-year study of toxicity and
        carcinogenicity)
                20 ppm, equal to 1.3 mg/kg bw per day (two-generation study of reproductive
                toxicity)
                5 mg/kg bw per day (maternal toxicity in study of developmental toxicity)
                15 mg/kg bw per day (developmental toxicity)

Rabbit: 5 mg/kg bw per day (maternal toxicity in study of developmental toxicity)
                2 mg/kg bw per day (developmental toxicity)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw

Studies that would be useful for continued evaluation of the compound

Further observations in humans.

DIETARY RISK ASSESSMENT

International Estimated Daily Intakes for the five GEMS/Food regional diets, based on existing STMRs, were in the range of 0 to 40% of the ADI. The Meeting concluded that the intake of residues of phosmet resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.23 PROCYMIDONE (136)

RESIDUE AND ANALYTICAL ASPECTS

Residue aspects of procymidone were reviewed by the JMPR in 1981, 1989, 1990 and 1993. At the 27th session of the CCPR (1995), draft MRLs for apples, currants (black, red, white), egg plant, kiwifruit, melons (except watermelon), potatoes and rice (polished and husked) were recommended for deletion. The Committee noted that residue data for peaches, plums, kiwifruit, peas and brassica vegetables would be made available for evaluation in 1998. In addition to these commodities, data on pears were also submitted. Information on analytical methods, stability of residues in stored analytical samples and current GAP in numerous countries was provided.

Validated methods for the determination of procymidone in pears, peaches, plums, cabbage and peas were provided. The limit of determination in all these crops was 0.02 mg/kg and validated recoveries ranged from 70 to 110%. The methods are almost identical to the

method reviewed in the 1981 monograph. The Netherlands government provided a multi-residue method for the determination of procymidone in fruits and vegetables. The limits of determination ranged from 0.01 to 0.1 mg/kg, with recoveries above 80%.

The storage stability of procymidone in strawberries, homogenised cherries, lettuce and haricot beans was reported. The Meeting concluded that procymidone residues were stable under frozen storage conditions for the duration of the 12 month studies in strawberries, lettuce and homogenised haricot beans, but some degradation was observed in homogenised cherry samples.

Supervised residue trials

Pears. GAP from Italy was reported, where registered use patterns indicate a maximum rate of 0.075 kg ai/hl using 25 SC, 50 WP or 75 WDG formulations. Procymidone may be applied from the end of flowering with repeated applications at intervals of 7 to 10 days depending on disease indications. A 14-day pre-harvest interval is recommended. In the reported trials 5 sprays were applied with a minimum re-treatment interval of 14 days. In two trials finite procymidone residues were found in untreated control samples; the result found in one of these was included in the estimation of the MRL and STMR as the residue in the control sample was comparable to the limit of quantification in the study.

The residues reflecting GAP ranged from 0.16 to 0.62 mg/kg 14 days after the fifth application. The residues used in the estimation of the STMR were in rank order 0.16, 0.35, 0.43, 0.43, 0.45, 0.58 and 0.62 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.43 mg/kg for procymidone in pears on the basis of GAP in Italy.

Peaches. Data from supervised trials in France and Italy were reported. Application rates were 0.075-0.11 kg ai/hl, with a maximum of 3 applications in the Italian trials. Registered labels in Italy allow a maximum of five applications. at appearance of flowering buds, when 25% of flowers have opened, at full flowering and at a lower rate at 4-5 and 2-3 weeks before harvest. In the French trials, two applications were made at the maximum rate of 0.75 kg ai/ha.

The residues resulting from treatments according to GAP in France and Italy ranged from 0.19 to 1.40 mg/kg 8–14 days after treatment. The residues in rank order were 0.19, 0.39, 0.44, 0.68, 0.72, 1.30, 1.33 and 1.40 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.70 mg/kg on the basis of GAP in France and Italy.

Plums. In France GAP allows a maximum rate of 0.75 kg ai/ha, with no indication of application timing or maximum number of sprays; a pre-harvest interval of 8 days is recommended. In Italy, 2–3 applications from the appearance of flowering buds to full flowering are recommended at rates from 1.1 to 1.8 or 1.5 to 2 kg ai/ha. A pre-harvest interval of 21 days is indicated.

Trials according to GAP were carried out in France and Italy. The residues in the French trials ranged from 0.19 to 1.20 mg/kg 7 or 8 days after 2 foliar applications at 0.75 kg ai/ha and in the 3 Italian trials were 0.74, 1.38 and 1.50 mg/kg 21 days after 3 sprays at 1.8 kg ai/ha.

The residues in rank order were 0.19, 0.31, 0.48, 0.52, 0.59, 0.60, 0.61, <u>0.74</u>, 0.77, 0.86, 0.90, 1.06, 1.20, 1.38 and 1.50 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.74 mg/kg for plums.

<u>Kiwifruit</u>. GAP was reported for Italy and France. The maximum label rate in France is 0.75 kg ai/ha; the labels did not indicate application timings or a maximum number of sprays. Italian labels for the 25 SC formulation indicate a maximum of 5 consecutive foliar applications at a maximum rate of 0.1 kg ai/hl, including a spray 14 days before harvest as a storage protection measure. For the 50 WP and 50 WDG formulations, 2–3 sprays are recommended followed by a post-harvest dip. A pre-harvest interval of 14 days and post-harvest storage period of 60 days are recommended.

Pre-harvest trials were reported from France and Italy, and post-harvest from Italy. The pre-harvest trials did not reflect GAP for foliar application in Italy or France. In some of them, single applications were made at various intervals before harvest and the residues were monitored for prolonged storage periods. Details of the storage conditions were not given, and analytical recoveries were not adequately reported. The post-harvest trials were in accordance with GAP and details of storage conditions were provided, but no analytical recoveries were reported. The data from post-harvest treatment and storage trials indicate that residues can decrease by as much as 50% of their initial levels, but without details of the storage conditions the results could not be evaluated.

On the basis of the minimal data provided, the Meeting could not estimate a maximum residue level in kiwifruit. Further information such as details of post-harvest storage conditions and analytical recoveries would be needed.

<u>Cabbages</u>. Trials on cabbages, cauliflowers, broccoli and Brussels sprouts were carried out in France, but GAP was reported only for cabbages. The application rate for cabbages in France is 0.75 kg ai/ha with a pre-harvest interval of 21 days; the maximum number of applications is not indicated on any product labels.

Procymidone residues in cabbages after two sprays at varying intervals ranged from <0.02 to 1.30 mg/kg 20 or 21 days after treatment. The results reflecting GAP were <0.02 (2), 0.03 (2), 0.17, <u>0.26</u>, 0.30, 0.32, 0.43, 0.44 and 1.40 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.26 mg/kg for head cabbages.

The trials on Brussels sprouts, broccoli and cauliflower could not be evaluated in the absence of appropriate registered labels.

<u>Peas</u>. Data were reported from supervised trials reflecting GAP in France, where a maximum of 2 sprays are permitted at 0.75 kg ai/ha, with a re-treatment interval of 20–21 days and a pre-harvest interval of 14 days. Residues were determined in whole plants with pods, whole pods, peas and empty pods. Re-treatment intervals were typically 14 to 19 days. The highest levels of procymidone were found in whole plants with pods, with residues of 16.5–25.1 and 10.3–19.6 mg/kg at early and late harvests respectively. Residues in empty pods were 0.6 to 3.23 mg/kg 13 to 15 days after treatment. The residues in peas ranged from 0.03 to 0.48 mg/kg. It was noted that

higher residues were found in peas harvested mechanically than in those which were hand-picked.

The residues in whole pods 13 to 15 days after treatment were in the range 0.26–0.83 mg/kg. In trials where the residue was higher after 21 days than after the GAP PHI the higher value was used in the estimation of the STMR. The residues at 13-21 days ranged from 0.26 to 2.1 mg/kg in whole pods and from 0.03 to 0.48 mg/kg in peas.

The residues reflecting GAP in the whole pods in rank order were 0.26, 0.28, 0.36, 0.49, 0.60, 0.83, 1.12, 1.50 and 2.1 mg/kg, and those in the shelled peas were 0.03, 0.07 (4), 0.08, 0.15, 0.17, 0.20, 0.27 and 0.48 mg/kg. The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.60 mg/kg for garden pea (young pods) and a maximum residue level of 1 mg/kg and an STMR of 0.08 mg/kg for garden pea (shelled).

The Meeting did not consider that the data on whole pea plants were adequate for estimating a maximum residue level for a leguminous animal feed commodity as appropriate GAP had not been reported.

DIETARY RISK ASSESSMENT

STMRs have been estimated for procymidone in six commodities. These have been used in estimating the dietary intake together with MRLs for 12 commodities. The International Estimated Daily Intakes for the five GEMS/Food regional diets were in the range 1 to 12% of the ADI. The Meeting concluded that the intake of residues of procymidone resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

FURTHER WORK OR INFORMATION

<u>Desirable</u>

Details of post-harvest storage conditions and analytical recoveries in relation to the reported supervised residue trials on kiwifruit.

4.24 QUINTOZENE (064)

RESIDUE AND ANALYTICAL ASPECTS

Quintozene was evaluated as a periodic review by the 1995 JMPR. That Meeting estimated a number of maximum residue levels but agreed not to recommend their use as MRLs, and recommended the withdrawal of existing MRLs, because of the lack of critical supporting data on environmental fate. Some of the processing studies could not be evaluated because of their uncertain validity.

Data on environmental fate, residues in rotational crops, supervised trials on lettuce and the effects of processing on residues in cotton seed, peanuts and potatoes have been made available to the present Meeting.

Environmental fate in soil

Quintozene is unstable in soil under photolytic conditions. In sandy loam soil exposed to simulated sunlight quintozene had a half-life of 28.5 days. Pentachloroaniline (PCA) was the only significant degradation product.

Quintozene in sandy loam soil under aerobic conditions had a half-life of 189 days. The major degradation product was pentachloroaniline (PCA). A secondary product, methyl pentachlorophenyl sulfide (pentachlorothioanisole, PCTA), was formed from PCA by deamination via nucleophilic displacement at the aromatic ring. Other degradation products were methyl pentachlorophenyl sulfone (PCTASO$_2$), methyl pentachlorophenyl sulfoxide (PCTASO) and pentachlorobenzene (PB). Soil-bound products and CO$_2$ were formed to a limited extent.

When quintozene was subjected to anaerobic conditions in the same soil after a period of 30 days under aerobic conditions, it was degraded significantly more quickly, with a half-life of 15 days. PCA was the major residue. Minor products such as PCTA and PB were also observed.

Quintozene is immobile to slightly mobile in soil (Freundlich adsorption constants in silt loam, sandy loam, clay loam and sand with about 1% organic matter were 24, 46, 89 and 31 respectively). The mobility of the major metabolite PCA was also investigated in the same soils: its Freundlich constants were even higher, indicating less mobility than the parent compound.

Field dissipation studies showed that the half-life of quintozene applied on soil surfaces was significantly shorter than when applied by incorporation.

The uptake of [*phenyl*-^{14}C]quintozene by rotational crops was investigated. Treated soil was allowed to age for periods of 30, 120 or 365 days (DAT) before planting turnips, lettuce and wheat. The soil treatments were at a low rate of 2.2 kg ai/ha (the US GAP rate for cotton), 11 kg ai/ha (the US rate for peanuts) and 34 kg ai/ha, which was used only for rotational wheat.

After the 11 kg ai/ha treatment the total radioactive residue (TRR) expressed as quintozene in turnip tops and roots was 1.12 and 0.21 mg/kg respectively at 365 DAT, in mature lettuce 0.15, 0.10 and 0.43 mg/kg at 30, 120 and 365 DAT, in wheat forage, grain and straw 3.0, 0.79 and 11 mg/kg respectively at 30 DAT, 3.4, 0.94 and 17 mg/kg at 120 DAT, and 0.64, 0.14 and 4.6 mg/kg at 365 DAT.

Residues of the parent compound were found only in lettuce (max. 0.032 mg/kg) and wheat straw (2.2 kg ai/ha, 120 DAT, 0.012 mg/kg). PCA was found in all three crops, at the highest levels of 0.11 mg/kg in turnip roots (365 DAT, 11 kg ai/ha), 0.065 mg/kg in immature lettuce (365 DAT, 11 kg ai/ha), 0.85 mg/kg in wheat straw (30 DAT, 34 kg ai/ha) and 0.11 mg/kg in wheat forage (30 DAT, 34 kg ai/ha). PB was found only in lettuce (30 DAT, 11 kg ai/ha) at less than 0.001 mg/kg.

In another field rotational crop study unlabelled quintozene was applied to bare soil at the maximum GAP rate for peanuts (11 kg ai/ha per season) at typical times of 15 or 45 days before peanut harvest. No residues above the LOD of 0.005 mg/kg of quintozene, PB, HCB, PCTA or PCTASO were found in the leaves, roots or grain of lettuce, turnips or wheat planted 365 days after the treatment. Residues of PCA and tetrachloroaniline (TCA) were found in the turnip roots at levels not exceeding 0.014 mg/kg, and PCA residues in two of eight mature wheat grain samples (0.007, 0.016 mg/kg).

Environmental fate in water

Quintozene is stable to hydrolysis. In buffered solutions at pH 5, 7 and 9, the half-life was longer than 180 days. However, aqueous photodegradation occurred in simulated natural sunlight (with a xenon arc lamp), with a half-life of less than two days in buffered water at pH 5.

Definition of the residue

The 1995 JMPR considered that for risk assessment purposes the residue in plant and animal commodities should be defined as the sum of quintozene, pentachloroaniline and methyl pentachlorophenyl sulfide, expressed as quintozene. This definition is also suitable for animal commodities for enforcement purposes since the parent quintozene is not an adequate indicator compound in such commodities. Quintozene alone is a suitable definition of the residue in crops for enforcement purposes. The residue is fat-soluble.

Residues of the impurity hexachlorobenzene (HCB) arising from the use of quintozene should also taken into account for risk assessment. Before 1988, the HCB content of the technical material was approximately 0.5%. In 1988 modifications to the manufacturing process reduced the level of HCB to 0.1% or less. An ADI of 0-0.01 mg/kg bw was established by the 1995 JMPR for quintozene containing less than 0.1% HCB.

New supervised residue trials

Lettuce. The 1995 JMPR recommended withdrawal of the existing CXL of 3 mg/kg because no residue data were submitted. The current Meeting received reports of two Japanese trials (1 x 60 kg ai/ha pre-transplanting, PHI 49 or 67 days) resulting in quintozene residues of 0.007 and 0.01 mg/kg. No metabolites or impurities were determined. Two German trials could not be evaluated as the application rates were not reported. The Meeting agreed that the data were insufficient to estimate a maximum residue level and confirmed the recommendation of the 1995 JMPR to withdraw the CXL of 3 mg/kg.

New processing studies

Potatoes. Potatoes treated with 1 x 28 kg ai/ha were analysed for quintozene, PCA, PCTA, HCB and PB. Analyses of whole tubers, peeled potatoes, and wet and dry peel showed that most of the residue is on the peel.

The residues of HCB were 0.0012 mg/kg in the unpeeled whole potatoes, 0.0007 mg/kg in the peeled tubers, 0.002 mg/kg in wet peel and 0.0028 mg/kg in dry peel.

Peanuts. After treatment at 112 kg ai/ha (10 times the US GAP rate) the maximum residues in whole peanuts of quintozene, PCA, PCTA, PB and HCB were 6.9, 1.8, 0.56, 0.34 and 0.083 mg/kg respectively. The mean quintozene residue was concentrated 2.5 times in the hulls but not in any other fractions. PB was concentrated 1.3 times in the hulls and crude oil and 1.7 times in the refined oil. HCB was concentrated in the kernels (x 1.7), soapstock (x 1.1), crude oil (x 3), and refined oil (x 3.9), and PCTA in the kernels (x 1.1), crude oil (x 1.6) and refined oil (x 2.1). PCA was concentrated slightly in the hulls (x 1.2) and refined oil (x 1.2).

Cotton seed. No residues of quintozene, PCA, PCTA or HCB above 0.0005 mg/kg or PB above 0.1 mg/kg were found in cotton seed after treatment at 6.7 kg ai/ha. No residues of quintozene or its metabolites or impurities were detected in crude or refined oil, or in the hulls above the LOD (0.0005 mg/kg). No residues of quintozene, PCTA or PB were detected above 0.1 mg/kg in soapstock, and no residues of HCB above 0.0005 mg/kg. Residues of PCA were detected in soapstock however (mean 0.0064 mg/kg). It cannot be concluded from the results whether quintozene or its metabolites or impurities become concentrated in the processed products of cotton seed. As quintozene is fat-soluble, it would be expected that residues in the seeds would be transferred to the oil. Since the processing procedure for the preparation of cotton seed oil is comparable to that for the preparation of peanut oil the results of the peanut processing study should be applicable to cotton seed and other oilseeds.

Recommendations for MRLs and estimation of STMR levels for commodities for which maximum residue levels were estimated by the 1995 JMPR

The evaluation of the residue data was described in the 1995 monograph and appraisal. If there were different populations of residues, the STMRs are derived from the highest population. In some commodities (sweet peppers, soya beans, soya bean forage and fodder, sugar beet, sugar beet leaves, barley straw and fodder) the residues of quintozene, PCTA and PCA were below the LOD in all the samples. The results of a rotational crop metabolism study indicated that residues could occur in succeeding crops. The main part of the total residue consisted of quintozene (about 60%), with about 30% of PCA and 10% of PCTA. The Meeting therefore estimated the

STMRs for commodities with no detectable residues of quintozene, PCTA or PCA on the basis of the LOD for quintozene only.

The present Meeting recommended the maximum residue levels estimated in 1995 for use as MRLs.

No HCB residues above the LOD were found in broccoli, head cabbages, sweet peppers, tomatoes, common beans (dry), peas (dry), soya beans (dry), sugar beet (roots and leaves), barley, maize, wheat, cotton seed, pea hay (dry), maize forage, soya bean fodder or soya bean forage, and rotational crop studies did not show residues of HCB in succeeding crops. The Meeting therefore estimated an STMR of 0 for HCB in these commodities.

Broccoli. On the basis of the 1995 evaluation, the Meeting recommended an MRL of 0.05 mg/kg.

The critical use was treatment of the soil after planting the seedlings and this resulted in total residues of 0.04, 0.046, 0.057, 0.06, 0.075 and 0.098 mg/kg. The Meeting estimated an STMR of 0.0585 mg/kg for broccoli, based on the sum of quintozene, PCTA and PCA expressed as quintozene.

Head cabbages. The Meeting recommended an MRL of 0.1 mg/kg, based on the residues in samples with wrapper leaves after transplant solution treatment (the soil was treated after the seedlings were planted). The STMR estimate was based on the residues of quintozene and PCA in the samples without wrapper leaves as the PCTA residues in all the samples without wrapper leaves were below the LOD (<0.002 mg/kg). The highest residue population of the samples without wrapper leaves resulted from GR broadcast treatment, with residues of 0.0042 (6), 0.0052, 0.0053, 0.0108, 0.0119, 0.0122, 0.0152 and 0.0182 mg/kg. The Meeting estimated an STMR of 0.0052 mg/kg for head cabbages, based on the sum of quintozene and PCA expressed as quintozene.

Sweet peppers. The Meeting recommended an MRL of 0.05* mg/kg as a practical limit of determination.

The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.05 mg/kg.

Tomatoes. The Meeting recommended an MRL of 0.02 mg/kg. The STMR was estimated on the basis of the quintozene residues (from the WP in-furrow treatment) as the PCA and PCTA residues were all below the LOD (<0.002 mg/kg). The quintozene residues in rank order were <0.002 (7), 0.003, 0.006 and 0.012 mg/kg. The Meeting estimated an STMR of 0.002 mg/kg.

Common beans and common beans (dry). The Meeting recommended an MRL of 0.02 mg/kg for common bean (dry). The EC treatment (1 x 1.7 kg ai/ha, 1993) was identified as giving rise to the population with the highest residues.

The residues in fresh beans, as the sum of quintozene, PCA and PCTA, in rank order were <0.002 (2), 0.0327, 0.0358, 0.0795 and 0.0925 mg/kg, expressed as quintozene. The Meeting estimated an STMR of 0.0342 mg/kg for common bean (pods and/or immature seeds).

The residues in dry beans (quintozene, PCA and PCTA) were <0.002 (4), 0.0168 and 0.0297 mg/kg, expressed as quintozene. The Meeting estimated an STMR of 0.002 mg/kg for common bean (dry).

Peas (dry). The Meeting recommended an MRL of 0.01 mg/kg. The STMR was estimated on the basis of the quintozene residues as no PCA or PCTA residues exceeded the LOD (0.005 mg/kg) in any of the samples. The quintozene residues were <0.005 (6), 0.005 and 0.007 mg/kg. The Meeting estimated an STMR of 0.005 mg/kg.

Soya beans (dry). The Meeting recommended an MRL of 0.01* mg/kg as a practical limit of determination. The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg.

Potatoes. The 1995 Meeting could not estimate a maximum residue level and recommended withdrawal of the CXL as no information on GAP was available. The present Meeting was informed that there is only a conditional time-limited registration for the use of quintozene on potatoes in the USA. The Meeting therefore confirmed the recommendation of the 1995 Meeting.

Sugar beet. The Meeting recommended an MRL of 0.01* mg/kg as a practical limit of determination. The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg.

Barley, maize. The Meeting recommended an MRL of 0.01* mg/kg as a practical limit of determination for both commodities. The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated STMRs of 0.005 mg/kg for barley and maize.

Wheat. The Meeting recommended an MRL of 0.01 mg/kg. The STMR was estimated on the basis of the quintozene residues as the PCA and PCTA residues were all below the LOD (<0.005 mg/kg). The quintozene residues were <0.005 (19) and 0.0061 mg/kg. The Meeting estimated an STMR of 0.005 mg/kg.

Cotton seed. The Meeting recommended an MRL of 0.01 mg/kg. The STMR was estimated on the basis of the 1988 trials with EC and FL treatments (1995 monograph, Table 19), which gave residues of <0.016 (24), 0.0188 (2), 0.0249 and 0.0284 mg/kg for the sum of quintozene, PCTA and PCA, expressed as quintozene. The Meeting estimated an STMR of 0.016 mg/kg.

Peanuts. The Meeting recommended an MRL of 0.5 mg/kg. The STMR was estimated on the basis of the 1994 trials (EC treatment). The residues were 0.099, 0.106, 0.324, 0.382, 0.436 and 0.446 mg/kg for the sum of quintozene, PCTA and PCA, expressed as quintozene. The Meeting estimated an STMR of 0.353 mg/kg.

The processing study showed that only PCTA moved into the oily fractions, with concentration factors exceeding 1.5 (1.6 for crude and 2.1 for refined oil). Because PCTA residues are only a third of the total, and no concentration of quintozene or PCA would be expected, no STMR was estimated for residues of quintozene or its metabolites.

On the basis of HCB residues of 0.0022, 0.0025, 0.0064, 0.008, 0.016 and 0.017 mg/kg in the 1994 trials, the Meeting estimated an STMR of 0.0072 mg/kg for HCB in peanuts.

Multiplication of the STMR by the processing factors for HCB gave derived STMRs of 0.0216 mg/kg in crude oil and 0.0281 mg/kg in refined oil.

Maize forage. The Meeting recommended an MRL of 0.01* mg/kg as a practical limit of determination. The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg.

Cereal straws and fodders. The Meeting recommended MRLs of 0.01* mg/kg (a practical limit of determination) for barley straw and fodder, dry, 0.01 mg/kg for maize fodder and 0.03 mg/kg for wheat straw and fodder, dry.

In barley straw, the residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg for barley straw and fodder, dry.

The STMRs for maize fodder and wheat straw were calculated on the basis of the quintozene residues as the PCA and PCTA residues were all below the LOD (<0.005 mg/kg). The quintozene residues were <0.005 (12) and 0.006 mg/kg in maize fodder and <0.005 (17), 0.006, 0.007 and 0.023 mg/kg in wheat straw. The Meeting estimated STMRs of 0.005 mg/kg for maize fodder and for wheat straw and fodder, dry.

In one of 20 wheat straw samples, the HCB residue was higher than the LOD (population: <0.005 (19) and 0.014 mg/kg). Because the supervised residue trials were carried out in 1987, the HCB content of the formulation could be as high as 0.5% and the trials were therefore not applicable to the current situation.

In view of the high persistence of HCB in the soil and the results of a rotational crop metabolism study indicating that it could be taken up from the soil by cereals, the Meeting could not estimate an STMR for HCB in cereal straws and fodders, dry.

Pea hay. The Meeting recommended an MRL of 0.05 mg/kg and an STMR of 0.021 mg/kg, based on residues of 0.0156 (3), 0.0166, 0.0255, 0.0268, 0.0305 and 0.0415 mg/kg, for the sum of quintozene, PCTA and PCA expressed as quintozene, in pea hay (dry).

Soya bean fodder and forage. The Meeting recommended an MRL of 0.01* mg/kg as a practical limit of determination for both commodities. In whole green plants, the residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg for soya bean forage.

No residues of quintozene, PCTA or PCA were found above the LOD in the hay or the whole plant at harvest except one PCA residue of 0.0154 mg/kg (expressed as quintozene). The residues in rank order were <0.0055 (29) and 0.0154 mg/kg. The Meeting estimated an STMR of 0.0055 mg/kg for soya bean fodder, based on the residues of PCA expressed as quintozene.

Sugar beet leaves. No maximum residue level was estimated for sugar beet leaves in 1995 but they could be used as a feed item. The residues of quintozene, PCTA and PCA in all the samples were below the LOD. The Meeting estimated an STMR of 0.005 mg/kg for sugar beet leaves.

Animal products

<u>Chickens</u>. The Meeting recommended MRLs of 0.03* mg/kg for eggs and 0.1* mg/kg for chicken meat (in the fat) and edible offal as practical limits of determination.

The residues of quintozene, PCTA and PCA in all the samples from feeding levels up to the equivalent of 5 ppm in the diet were below the LODs.

Since (1) the main part of the total residue in plants is quintozene, (2) the residues in feed items for poultry will be below 1 mg/kg, (3) no quintozene occurred in meat, liver or eggs at 1 ppm in the diet or in fat at 15 ppm, and (4) the residue is fat-soluble, the Meeting estimated STMRs of 0.01 mg/kg for eggs, 0.04 mg/kg for chicken meat (in the fat) and 0.03 mg/kg for edible offal, based on the LODs for quintozene.

No STMR was estimated for HCB as the feeding study was carried out with quintozene which contained 1.4% HCB.

DIETARY RISK ASSESSMENT

The International Estimated Daily Intakes of quintozene for the five GEMS/Food regional diets were in the range of 0 to 1% of the ADI. The Meeting concluded that the intake of residues of qiuntozene resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

The IEDIs of hexachlorobenzene arising from the use of quintozene were estimated on the basis of the STMRs for peanuts and refined peanut oil for comparison with a Tolerable Daily Intake (TDI) of 0.00016 mg/kg bw established by WHO[1].

The IEDIs for hexachlorobenzene arising from the use of quintozene were in the range 0 to 1% of the TDI. The Meeting concluded that the intake of residues of hexachlorobenzene resulting from uses of quintozene that have been considered by the JMPR is unlikely to present a public health concern.

FURTHER WORK OR INFORMATION

<u>Desirable</u>

Animal transfer studies on ruminants

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[1]Hexachlorobenzene - Environmental Health Criteria 195, WHO, Geneva (1997)

4.25 THIOPHANATE-METHYL (077)

TOXICOLOGY

Thiophanate-methyl was evaluated toxicologically by the Joint Meeting in 1973, 1975, 1977 and 1995. An ADI of 0-0.08 mg/kg bw was allocated in 1973, on the basis of a NOAEL of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and a safety factor of 100. This ADI was confirmed in 1975 and 1977. Additional data that became available were reviewed at the 1995 Joint Meeting within the CCPR Periodic Review Programme, at which time an ADI of 0-0.02 mg/kg bw was established on the basis of a NOAEL of 2 mg/kg bw per day in a study of developmental toxicity in rabbits and a safety factor of 100. New information on the metabolism of thiophanate-methyl and the results of a second study of developmental toxicity in rabbits have become available since the 1995 evaluation, and were reviewed at the present Meeting.

WHO has classified thiophanate-methyl as unlikely to present an acute hazard in normal use.

Thiophanate-methyl was rapidly absorbed in rats after oral administration. The extent of absorption may be dose-dependent, decreasing with increasing dose; a study of biliary excretion would be useful to confirm this hypothesis. The highest residual levels occurred in the liver, thyroid, and kidneys. The elimination of thiophanate-methyl was rapid, with more than 90% in the urine and faeces within 24 h of administration. There was a shift towards faecal elimination between the low and high doses and after repeated doses. There was no indication of potential bioaccumulation. The major urinary metabolite was 5-hydroxy-carbendazim sulfate (21-42%); 5-hydroxycarbendazim and 4-hydroxy-thiophanate-methyl each represented approximately 2% of the radiolabel. The major faecal metabolites were 4-hydroxy-thiophanate-methyl (6-10%) and 5-hydroxycarbendazim (2-5%); carbendazim (2-3%) was also found. Unchanged thiophanate-methyl accounted for approximately 20-24% and 50% of the administered radioactivity after repeated low and high doses respectively. In plants, unchanged thiophanate-methyl and carbendazim accounted for approximately 60 and 30% of the residue respectively, 7-14 days after treatment.

In a study of developmental toxicity in rabbits, thiophanate-methyl was administered by gavage at 0, 5, 10, 20, or 40 mg/kg bw per day. The NOAEL for maternal toxicity was 10 mg/kg bw per day, as doses at and above 20 mg/kg bw per day caused transient significant reductions in maternal body-weight gain and feed consumption. Additionally, faecal output was reduced at 40 mg/kg bw per day. The NOAEL for developmental toxicity was 20 mg/kg bw per day, as the incidence of supernumerary thoracic ribs was increased at 40 mg/kg bw per day, a variation that occurred only at the higher of two maternally toxic doses. Thiophanate-methyl did not affect embryonic or fetal viability, growth, or morphology and was not teratogenic.

In the study of developmental toxicity in rabbits reviewed by the 1995 Joint Meeting, the NOAEL for maternal and developmental toxicity was 2 mg/kg bw per day, on the basis of reduced maternal body-weight gain and treatment-related increased incidences of supernumerary ribs, ribs thickened at the costal cartilage, incomplete or asymmetric ossification of costal elements of sacral vertebrae, 27 presacral vertebrae, and asymmetric pelvises at 6 and 20 mg/kg bw per day. Because of reporting deficiencies, compromised maternal health, and an

unacceptably low number of litters available for analysis, the present Meeting concluded that the status of this study should be reduced to that of a range-finding study. The new study submitted to the present Meeting was considered to be more appropriate for the identification of the NOAEL for developmental toxicity in rabbits, as modern methods were used, the reporting was adequate, and the population of rabbits was larger and healthier.

A two-generation study of reproductive toxicity in rats was evaluated by the 1995 Joint Meeting, which considered 10 mg/kg bw per day to be the LOAEL for parental toxicity; however, after re-examining this study, the present Meeting concluded that 10 mg/kg bw per day should be considered the NOAEL. The effects in the liver observed in all treated groups were considered to be non-adverse at this dose, and the slight changes in the thyroid occurred in the absence of a measurable effect on thyroid hormones.

An ADI of 0-0.08 mg/kg bw per day was established on the basis of the NOAEL of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and in a one-year study in dogs, both of which were evaluated at earlier Meetings, and a safety factor of 100.

The Meeting concluded that an acute RfD was not required because thiophanate-methyl is of low acute toxicity when administered orally or dermally and is only slightly toxic when administered by inhalation. The Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

Although the toxicities of thiophanate-methyl and carbendazim are qualitatively different, carbendazim is an important metabolite in plants, but a minor metabolite in animals. The risk assessment for residues in plants and plant products should therefore include consideration of both thiophanate-methyl and carbendazim. The ADI for the latter, established by the 1995 JMPR, is 0-0.03 mg/kg bw.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 150 ppm, equal to 29 mg/kg bw per day (18-month study of toxicity and carcinogenicity)
1000 mg/kg bw per day (maternal toxicity and teratogenicity in study of reproductive toxicity)
500 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)

Rat: 200 ppm, equal to 9 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
160 ppm, equivalent to 8 mg/kg bw per day (study of reproductive toxicity)
1000 mg/kg bw per day (teratogenicity and fetotoxicity in a study of developmental toxicity)
300 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

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

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

Dog: 10 mg/kg bw per day (studies of toxicity of up to two years)

Estimate of acceptable daily intake for humans

0-0.08 mg/kg bw

Estimate of an acute reference dose

Not allocated (unnecessary)

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

1. Study of excretion in the bile
2. Further observations on humans

List of relevant end points for setting guidance values for dietary & non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid (~70% based on urinary excretion, 96 h)
Dermal absorption:	No data
Distribution:	Thyroid, liver, kidney
Potential for accumulation:	No indication of bioaccumulation
Rate and extent of excretion:	Rapid/complete, > 90% in 24 h
Metabolism in animals	Predominantly metabolized (71-88%)
Toxicologically significant compounds (animals, plants and environment)	Urine (rats): 5-hydroxy-carbendazim sulfate, 5-hydroxy-carbendazim and 4-hydroxy-thiophanate-methyl. Faeces (rats): 4-hydroxy-thiophanate-methyl and 5-hydroxy-carbendazim. Plants: unchanged thiophanate-methyl and carbendazim

Acute toxicity

Rat LD_{50} oral	7000 mg/kg bw
Rabbit LD_{50} dermal	> 10 000 mg/kg bw
Rat LC_{50} inhalation	1.8 mg/l air
Skin irritation	Not irritating
Eye irritation	Mildly irritating
Skin sensitization	Sensitizer (maximization test)Not a sensitizer (Buehler test)

Short term toxicity

Target/critical effect	Thyroid, liver/hypertrophy of the thyroid epithelium, increased thyroid & liver weight, (rats, dogs) Liver/increased liver weight (mice)
Lowest relevant oral NOAEL/NOEL	10 mg/kg bw per day (capsule, overall NOAEL, dog)
Lowest relevant dermal NOAEL/NOEL	No data
Lowest relevant inhalation NOAEL/NOEL	No data

Genotoxicity	Not mutagenic, weak aneugenic potential

Long term toxicity and carcinogenicity

Target/critical effect	Thyroid hyperplasia, increased TSH, decreased T4 (rats, dogs); thyroid adenoma in ratsHepatocellular adenoma in mice
Lowest relevant NOAEL/NOEL	8 mg/kg bw per day (1-year dog)
Carcinogenicity	Hepatocellular adenoma in mice; thyroid adenoma in rats at high doses

Reproductive toxicity

Reproduction target/critical effect	Increased ovary/testis weights (no histological findings)
Lowest relevant reproductive NOAEL/NOEL	8 mg/kg bw per day (decreased litter size, reduced pup body-weight gain in F_1, F_2, F_3)
Developmental target/critical effect	Supernumerary ribs (rabbit); not teratogenic in rat or rabbit
Lowest relevant developmental NOAEL/NOEL	20 mg/kg bw per day, rabbit

Neurotoxicity/Delayed neurotoxicity

	No data. No indication of neurotoxic potential in other studies.

Other toxicological studies

Mechanistic Studies	Inhibition of thyroid microsomal peroxidase involved in thyroid hormone synthesis

Medical data

Clinical Studies	No adverse effects on the health of personnel involved in the manufacturing process

Summary	Value	Study	Safety factor
ADI	0-0.08 mg/kg bw	3-generation, rat1-year, dog	100
Acute reference dose	Not allocated (unnecessary)		

RESIDUE AND ANALYTICAL ASPECTS

[See also BENOMYL (069)/CARBENDAZIM (072)/THIOPHANATE-METHYL (77)]

Thiophanate-methyl was first evaluated in 1973 and the most recent evaluations of residue aspects was in 1994. The 1994 evaluation listed as desirable data from supervised trials according to currently registered uses on residues in fruits and vegetables arising from post-harvest treatments, as well as on lettuce, peppers, tomatoes and sugar beet, and on crops for which CXLs were listed. The CCPR in 1994 noted that the data on residues were not complete (ALINORM 95/24, para 194). The scheduled periodic re-evaluation by the 1998 JMPR was confirmed by the 1997 CCPR. Data on metabolism and supervised residue trials were provided by the manufacturer. Additional residue trials carried out in the USA and Germany were reported but have not been evaluated because full study reports and/or labels were not provided.

Metabolism studies were conducted in mice, rats, dogs, poultry, livestock and plants. The metabolic pathways of thiophanate-methyl in animals and plants includes hydroxylation, hydrolysis to carbendazim with subsequent metabolism, oxidation of the thiocarbonyl group, and formation of sulfate conjugates. In mice, labelled thiophanate-methyl was mainly excreted in the urine (66-78%) and faeces (17.5-27%) within 96 hours. In rats dosed daily with [^{14}C]thiophanate-methyl, an average of 89.6% of the ^{14}C was excreted every day (54.27% in the urine and 35.38% in the faeces). The main metabolites in the faeces and urine after exposure to labelled thiophanate-methyl at various doses and with various regimes were methyl 5-hydroxy-benzimidazol-2-ylcarbamate (5-HBC, 2.0-40.2%), unchanged parent compound (2.9-52.4%), 4-hydroxy-thiophanate-methyl (5.1-10.6%), dimethyl 4,4´-(4-hydroxy-1,2-phenylene)bisallophanate (0.1-6.2%) and carbendazim (2-5.3%). In one experiment the sulfate conjugate of 5-HBC accounted for 19-36% of the administered ^{14}C.

In dogs dosed once, 74% of the total radiolabel was found in the urine and 14% in the faeces after 24 hours. In goats dosed for 5 days the cumulative percentages of ^{14}C were 56% in the urine and 14% in the faeces. The residues in the edible tissues (liver, kidney, muscle and fat) constituted 2.1% of the administered dose. Milk contained 1.5% of the total dose and reached 1.59 mg/kg as thiophanate-methyl at day 4.

In poultry, thiophanate-methyl was mainly eliminated in the excreta (up to 94%), with only a small percentage of the total dose found in the tissues and eggs. In the tissues the highest residues were in the liver (1.7 mg/kg) and kidneys (1.2 mg/kg).

On average, 64% of the applied thiophanate-methyl was found unchanged in soya bean pods and apples 7 or 14 days after treatment. When bean plants were grown in water containing thiophanate-methyl labelled with ^{14}C or ^{35}S the ^{14}C label was translocated through the roots more readily than the ^{35}S. Approximately 20% of the ^{14}C was translocated from the roots to the leaves within 14 days after application. The metabolites found in the pods and leaves of soya beans 14

days after the application of [*phenyl*-U-^{14}C]thiophanate-methyl were the parent compound (54.4-86.1%), carbendazim (9.4-37%), dimethyl 4,4′-(*o*-phenylene)bisallophanate (FH-432, up to 8.7%) and 1-(3-methoxycarbonylthioureido)-2-(3-methoxycarbonylureido)benzene (DX-105, up to 6.4%). Studies with young apple plants gave similar results.

Bean, apple and grape plants were treated by leaf dotting once with thiophanate-methyl labelled with ^{14}C or ^{35}S in the thioureido groups. After 14 days most of radioactivity remained in the treated leaves (64-72% in bean plants), and was recovered by washing in chloroform. The identified compounds were thiophanate-methyl, carbendazim and FH-432.

In studies of environmental fate [^{14}C]thioureido-, [^{14}C]methyl-, or [^{35}S]thioureido-labelled thiophanate-methyl was applied to sandy loam or silty loam soils which were kept in the dark at 23°C or 33°C for 60 days or exposed to sunlight for 28 days. Thiophanate-methyl disappeared completely within 7 days under dark conditions and had a half-life of 3.9 days in sunlight. In all cases the main degradation product was carbendazim.

When a series of thiophanate-methyl solutions (0-5000 mg/l) were incubated with sandy loam or silty loam soils at 30°C for 30 days the counts of microflora were not affected by the thiophanate-methyl.

Adsorption/desorption isotherms of labelled thiophanate-methyl and its metabolites were determined with four USA upland soils (sand, sandy loam, loamy sand and loam) and two USA paddy field soils (loam and clay loam). The Freundlich constants K ranged from 0.27 to 14.14 for thiophanate-methyl, 0.45 to 88.24 for carbendazim, 0.28 to 10.11 for FH-432 and 0.29 to 11.88 for DX-105. Sandy upland soils and clay loam paddy field soils had the lowest and highest values respectively. The adsorbed thiophanate-methyl was not easily desorbed.

In leaching studies with [*phenyl*-U-^{14}C]thiophanate-methyl in soil columns 54.5%, 43.4%, 22.0% and 0.4% of the applied ^{14}C was recovered in the leachates from sand, silt loam, sandy loam and clay loam respectively.

[*Phenyl*-U-^{14}C]thiophanate-methyl was degraded in sterile pH 5 aqueous buffer exposed to sunlight with a half-life of 2.17 days. Carbendazim was the main photoproduct and accounted for 50% of the initial ^{14}C at 5.5 days. Thiophanate-methyl in oxygen-saturated river water at pH 7, incubated under shaking and in the dark for 42 days at 0.1 mg/l and 52 days at 1.0 mg/l showed half-lives of about 15 and 25 days respectively. The major degradation product was carbendazim, which accounted for 72.2% of the initial ^{14}C at 42 days and 74.1% at 52 days.

In most residue analytical methods thiophanate-methyl and carbendazim are extracted and thiophanate-methyl is converted to carbendazim by refluxing in acidic or neutral conditions. The total carbendazim is determined by UV spectrophotometry, HPLC with UV detection, derivative spectrophotometry or LC-MS-MS. The detection limits are 0.02 mg/kg for UV, 0.02 mg/kg for HPLC, 0.05 mg/kg for derivative spectrophotometry and 0.003 mg/kg for LC-MS-MS. Limits of determination range from 0.02 to 0.2 mg/kg. In another method, thiophanate-methyl is partially converted to carbendazim during the analysis, which involves extraction of the compounds with acetone/dichloromethane/petroleum ether, clean-up by diol-bonded silica SPE and HPLC with UV-fluorescence detection. The LOD, as carbendazim, was 0.05 mg/kg and recoveries were >97.6%. In a method in which ethyl acetate extraction is followed by TLC with detection by a spray of fungal spores the reported LOD is 0.1 mg/kg with recovery >90%.

Two methods for animal products were reported. In one, which determines thiophanate-methyl, DX-15, 4-OH-TM, 4-OH-FH-432 and FH-432, the analytes are extracted with acetonitrile, cleaned up by solid-phase extraction (C-18 and NH$_2$) and determined by HPLC with UV or fluorescence detection. The second method was developed for the determination of carbendazim, 5-HBC, 5-HBC-S and 2-AB and involves acid extraction in acetone to hydrolyse the sulfate conjugate, ethyl acetate partition, and clean-up on an NH$_2$ cartridge. In both methods the limit of determination is 0.2 mg/kg.

The stability of thiophanate-methyl and/or carbendazim in stored analytical samples was studied in many crops. Residues in pears, persimmons, cabbages, soya beans and rape seed were stable at –30°C for 2 years, with 71-98% of the initial residues remaining in the crop at the end of the study. In apples stored for 6 months at –20°C, 42.3-68.4% of the initial thiophanate-methyl and 50-128% of the carbendazim remained at the end of the study. In potatoes thiophanate-methyl residues were 58.4 and 67.1% of the initial residue after 176 days at –20°C.

The current definition of the residue is "carbendazim". The Meeting noted however that about two-thirds of the residue in crops arising from the use of thiophanate-methyl was likely to be thiophanate-methyl (which would be determined as carbendazim), and concluded that the definition for compliance with MRLs should be *sum of thiophanate-methyl and carbendazim, expressed as carbendazim*. Since the ADI of thiophanate-methyl is nearly three times that of carbendazim, the same definition would avoid under-estimating the dietary risk and would therefore be appropriate for the estimation of STMRs.

Residues resulting from supervised trials

A number of residue trials were carried out on citrus fruit, apples, pears, apricots, cherries, peaches, plums, berries, grapes, strawberries, kiwifruit, persimmons, onions, Brussels sprouts, cucumbers and gherkins, mushrooms, tomatoes, egg plants, melons, peppers, lettuces, beans, peas, sugar beet, celery, barley, rice, wheat, rape and tea. As thiophanate-methyl residues are expressed as carbendazim, which can also occur from the use of benomyl or carbendazim, residue trials with thiophanate-methyl, benomyl and carbendazim were evaluated together and are described in Section 4.3.

DIETARY RISK ASSESSMENT

See Benomyl/carbendazim/thiophanate methyl, Section 4.3

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 <u>recommended</u> that Joint Meetings on Pesticide Residues should continue to be held annually.

5.2   The Meeting considered the question of the use of data from biomedical testing involving human subjects in hazard evaluation and <u>recommended</u> (Section 2.2) that additional consideration be given at future meetings of the JMPR to this item.

5.3   The Meeting <u>recommended</u> (Section 2.8) that information on the efficiency of extraction of residues from analytical samples should be included in national registration requirements and considered as part of the evaluation process, and that in future information should be supplied to the JMPR on the efficiency of extraction of residues with the solvents used in the relevant regulatory analytical methods.

5.4   The Meeting <u>recommended</u> (Section 2.9) the use of the recently established FAO/IAEA Training and Reference Centre for theoretical and practical training in the implementation of quality control and quality assurance principles for laboratory staff in developing countries.

5.5   The Meeting <u>recommended</u> (Section 2.10) that an OECD format for tabulating toxicological endpoints be used to summarize the toxicological profile of a pesticide in place of the table format used previously.

5.6   The Meeting <u>recommended</u> (Section 2.12) that the document "Framework for evaluating a postulated carcinogenic mode of action", which had been developed as part of the IPCS Programme on Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, together with some suitable examples of its application, be referred to authors of working papers at future Joint Meetings, to provide guidance on the framing of the discussion of the carcinogenic potential of the chemicals under consideration.

5.7   The Meeting <u>recommended</u> (Section 2.13) that additional consideration be given at future meetings of the JMPR to the issue of categories of pesticides for which an acute reference dose would normally not be necessary.

6. FUTURE WORK

The following items should be considered at the 1999 or 2000 Meeting.

The compounds listed include those recommended for priority attention by the 30th or earlier Sessions of the CCPR, as well as compounds scheduled for re-evaluation in the CCPR Periodic Review Programme.

6.1 1999 Meeting (tentative)

Toxicological evaluations	Residue evaluations
New compounds	**New compounds**
pyriproxyfen	pyriproxyfen
Periodic review compounds	**Periodic review compounds**
Chlorpyrifos (017)	bitertanol (144)
dimethipin (151)	ethoxyquin (035)
ethoprophos (149)	fenamiphos (085)
permethrin (120)	malathion (049)
2-phenylphenol (056)	methiocarb (132)
propargite (113)	2-phenylphenol (056)
pyrethrins (063)	
Other evaluations	**Other evaluations**
N-acetyl-glufosinate	buprofezin (173)
propylenethiourea (PTU, 150)	clethodim (187)
	diazinon (022)
	ethephon (106)
	fenpropimorph (188)
	fenpyroximate (193)
	folpet (041)
	phosalone (060)

6.2 2000 Meeting (tentative)

Toxicological evaluations   **Residue evaluations**

New compounds   New compounds

                                            fipronil

Periodic review compounds   Periodic review compounds

acephate (095)   amitraz (122)
deltamethrin (135)   captan (007)[1]
dodine (084)   chlorpyriphos (017)
fenitrothion (037)   cypermethrin (118)
imazalil (110)   diphenylamine (030)
methamidophos (100)   endosulfan (032)
thiodicarb (154)   parathion (058)
vamidothion (078)   parathion-methyl (059)
                                            piperonyl butoxide (062)
                                            pyrethrins (063)

Other evaluations   Other evaluations

DDT (021)   aldicarb (117)
fipronil   chlorfenvinphos (014)
                                            chlormequat (015)
                                            DDT (021)
                                            fenthion (039)
                                            methomyl (094) / thiodicarb (154)
                                            thiabendazole (065)

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[1]Availability of data to be confirmed

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CORRECTIONS TO REPORT OF 1997 JMPR

Changes are shown **bold**. Minor typographical errors are not included.

P. 172 (Section 4.24), para 1, line 2

Change "…ranged from 0.02 to 0.15…" to "…ranged from 0.0**3** to 0.15…".

P. 172 (Section 4.24), penultimate para, Hops line 2

Change "…ranged from 0.2 to 1.2…" to "…ranged from 0.**3** to 1.2…".

P. 221 (Annex I), Abamectin, Cattle kidney

Change CCN from 1289 to 128**0**.

P. 229 (Annex I), Tebuconazole

Change ADI from 0.003 to **0.03** mg/kg bw.

ANNEX I

**ADIs , ACUTE REFERENCE DOSES, RECOMMENDED MRLs AND MRLMs, AND
STMRs RECORDED BY THE 1998 MEETING**

The Table is in two parts. Part 1 includes maximum Acceptable Daily Intakes (ADIs), Acute Reference Doses (RfDs), recommendations for Maximum Residue Limits (MRLs), and Supervised Trials Median Residue (STMR) levels. In Part 2 recommendations are for Maximum Residue Limits for Monitoring (MRLMs) rather than for MRLs. MRLMs apply to compounds whose estimated dietary intakes might, on the basis of the available information, exceed their ADIs. A proposal to distinguish such compounds from those whose intakes are clearly below the corresponding ADIs was made at the 1997 Joint Meeting and its rationale is described in detail in the report (Section 2.3). It should be noted that the distinction between MRLs and MRLMs applies only to new compounds and those re-evaluated within the CCPR Periodic Review Programme.

STMR levels were introduced in 1996 in response to recommendations of a Joint FAO/WHO Consultation on Guidelines for Predicting the Dietary Intake of Pesticide Residues held in York, UK, in 1995.The 1996 JMPR report explains the reasons for their introduction and gives details of the procedures used in their calculation (Sections 2.2.1, 2.2.3, Annex IV and the introduction to Annex I).

In general, the MRLs recommended for compounds which have been reviewed previously are additional to, or amend, those recorded in the reports of earlier Meetings. If a recommended MRL is an amendment the previous value is also recorded. All recommendations for compounds re-evaluated in the CCPR periodic review programme are listed however (even if identical to existing CXLs or draft MRLs) because such re-evaluations replace the original evaluation rather than supplement it.

Some ADIs may be 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 Table includes the Codex reference numbers of the compounds and the Codex Classification Numbers (CCNs) of the commodities, to facilitate reference to the Guide to Codex Maximum Limits for Pesticide Residues and other Codex documents. Commodities are listed in alphabetical order.

Apart from the abbreviations indicated above, the following qualifications are used in the Table.

* following recommended MRL	At or about the limit of determination

* following name of pesticide	New compound
** following name of pesticide	Compound reviewed in CCPR Periodic Review Programme
Po	The recommendation accommodates post-harvest treatment of the commodity.
T	Temporary
W in place of a recommended MRL	The previous recommendation is withdrawn, or withdrawal of the recommended MRL or existing Codex or draft MRL is recommended

PART 1. ADIs, acute RfDs, recommended MRLs, and STMRs

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
Amitraz** (122)	0.01	Acute RfD 0.01 mg/kg bw Previous ADI 0-0.003 mg/kg bw Periodic review was for toxicology only				
Amitrole**	0.002	FP 0009	Pome fruits	0.05*		0
(079)		FS 0012	Stone fruits	0.05*		0
		FB 0269	Grapes	0.05		0.02
		Residue (for MRLs and STMRs): amitrole Periodic review was for residues only				
Benomyl**	0.1	Residues arising from the use of benomyl are covered by the recommendations for carbendazim				
(069)		Residue (for MRLs and STMRs): sum of benomyl and carbendazim, expressed as carbendazim Periodic review was for residues only				
Bentazone (172)	0.1	Acute RfD not considered ADI unchanged				
Bitertanol** (144)	0.01	Acute RfD unnecessary ADI unchanged Periodic review was for toxicology only				
Carbendazim**	0.03	JF 0226	Apple juice			0.147 (B)
(072)			Apple purée			0.282 (B)
			Apple sauce			0.078 (B)
		FS 0240	Apricot	W	0.1 (B)	
		VS 0621	Asparagus	W	0.1* (B)	
		FI 0326	Avocado	W	0.5 (B)	
		Fl 0327	Banana	0.2 (**B**)	1 Po (B,C,Th)	0.03 (B)
		GC 0640	Barley	0.5 (**C**)	0.1 (C,Th)	0.05 (C)
		AS 0640	Barley straw and fodder, dry	2 (**C**)	2 (B)	0.345 (C)
		VD 0071	Beans (dry)	0.5 (**Th**)	2 (B)	0.165 (Th)
		FB 0018	Berries and other small fruits	W	1 (B, Th)	

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		VP 0522	Broad bean (green pods and immatu seeds)	W	2 (Th)	
		VB 0402	Brussels sprouts	0.5 (**B**)	0.5 (B)	0.065 (B)
		VR 0577	Carrot	0.2 (**B**)	-	0.04 (B)
		MM 0812	Cattle meat	0.05* (**B**)	0.1* (B)	0 (B)
		VS 0624	Celery	W	2 (B, C)	
		GC 0080	Cereal grains	W	0.5[1] (B,C,Th)	
		FS 0013	Cherries	W	2 (Th)	
		PF 0840	Chicken fat	0.05* (**B**)	0.1* (Th)	0 (B)
		SB 0716	Coffee beans	W	0.1* (C)	
		VP 0526	Common bean (pods and/or mmature seeds)	W	2 (B, C Th)	
		VC 0424	Cucumber	0.05* (B, **C**)	0.5 (B,C,Th)	0.03 (B) 0.05 (C)
		MO 0105	Edible offal (Mammalian)	0.05* (**B**)	-	0 (B)
		VO 0440	Egg plant	W	0.5 (C)	
		PE 0112	Eggs	0.05* (**B**)	0.1* (B,Th)	0 (B)
		VP 0529	Garden pea, shelled (succulent seeds)	0.02 (**Th**)	-	0.01 (Th)
		VC 0425	Gherkin	0.05* (B,**C**)	2 (C,Th)	0.03 (B) 0.05 (C)
		FB 0269	Grapes	3 (B,**Th**)	1 (B,Th)	0.84 (B) 0.87 (Th)
		DH 1100	Hops, Dry	W	50 (C)	
		VL 0482	Lettuce, Head	W	5 (Th)	
		FI 0345	Mango	W	2 (B)	
		VC 0046	Melons, except Watermelon	W	2 Po (B,C)	
		ML 0106	Milks	0.05* (**B**)	0.1* (B)	0 (B)
			Milk cream			0 (B)
		VO 0450	Mushrooms	W	1 [2](Th)	
		FS 0245	Nectarine	W	2 (B)	
		GC 0647	Oats	W	0.1 (C)	
		VA 0385	Onion, Bulb	W	2 (C,Th)	
		FC 0004	Oranges, Sweet, Sour	1 (**B**)	-	0.325 (B)
		JF 0004	Orange juice			0.13 (B)
			Orange oil			0.442 (B)
		FS 0247	Peach	2 (**B**)	2 (B)	0.255 (B)
		SO 0697	Peanut	W	0.1* (B,C)	
		AL 0697	Peanut fodder	W	5 (B,C)	
		VO 0051	Peppers	W	0.1 (Th)	
		FI 0353	Pineapple	5 (**B**)	-	0.03 (B)
		FS 0014	Plums (including Prunes)	0.5 (**B**)	0.5 (Th)	0.06 (B)
		FP 0009	Pome fruits	3 (**B**,C,Th)	2 (B,C,Th)	0.60 (B) 0.455 (C) 0.555 (Th)
		VR 0589	Potato	W	3 Po (B,C)	
		PM 0110	Poultry meat	0.05* (**B**)	0.1* (B,Th)	0 (B)
		DF 5263	Raisins			1.09 (B)
			Raisin waste			3.44 (B)
		SO 0495	Rape seed	0.05* (**C**)	0.1* (C)	0 (C)
		CM 0649	Rice, husked	2 (**B**)	-	0.05 (B)

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		AS 0649	Rice straw and fodder, dry	15 (**B**)	15 (B,C,Th)	2.5 (B)
		GC 0650	Rye	W	0.1 (C,Th)	
		MM 0822	Sheep meat	W	0.1* (B)	
		VD 0541	Soya bean (dry)	W	0.2 (C)	
		AL 0541	Soya bean fodder	W	0.1* (C)	
		VC 0431	Squash, Summer	W	0.5 (B)	
		VR 0596	Sugar beet	W	0.1*(B,C,Th)	
		AV 0596	Sugar beet leaves or tops	W	5 (B,Th)	
		VR 0497	Swede	W	0.1* (C)	
		VR 0508	Sweet potato	W	1 (B)	
		VR 0505	Taro	W	0.1* (B)	
		VO 0448	Tomato	0.5 (B,**C**)	0.1 (Th)	0.16 (C) 0.045 (B)
		JF 0448	Tomato juice			0.012 (B)
			Tomato purée			0.030 (B)
			Tomato ketchup			0.028 (B)
			Tomato pomace, wet			0.013 (B)
			Tomato pomace, dry			0.022 (B)
		TN 0085	Tree nuts	W	0.1* (B)	
		GCO 654	Wheat	0.05* (B,**Th**)	0.1 (B,C,Th)	0.03 (B) 0.01(Th)
		AS 0654	Wheat straw and fodder, dry	1 (**B,C**)	5 (B)	0.1 (B) 0.03 (C)
			Wine			0.445 (B)
		VC 0433	Winter squash	W	0.5 (B)	

Residue (for MRLs and STMRs): carbendazim

[1]To be replaced by MRLs for barley, oats, rye and wheat (1994 JMPR)

[2] Group MRL for berries and other small fruits
Letters in parentheses in columns 5 and 6 indicate the compounds for which sufficient data from trials Complying with GAP were provided (B=benomyl; C= carbendazim; Th= thiophanate-methyl). Bold Letters indicate the source(s) of the data on which the recommendation is based.
Letters in parentheses in column 7 indicate the compound to which the STMR applies.
Recommendations cover carbendazim arising from the direct use of carbendazim or (as a metabolite And/or a hydrolysis product formed during analysis) from the use of benomyl or thiophanate-methyl.
Periodic review was for residues only

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
2,4-D**	0.01	GC 0640	Barley	W	0.5	
020		FB 0018	Berries and other small fruits	0.1	-	
			Berries, except grapes			0.05
		FB 0264	Blackberries	W[1]	0.1	
		FC 0001	Citrus fruits	W	2	
		MO 0105	Edible offal (Mammalian)	5	-	2.745
		PE 0112	Eggs	0.01*	0.05*	0
		FC 0203	Grapefruit	0.1	2[2]	0.05
		JF 0203	Grapefruit juice			0.005
			Grapefruit molasses			0.215
			Grapefruit oil			0.05
			Grapefruit pulp, dry			0.235
			Grapefruit pulp, wet			0.044
		FB 0269	Grapes			0
			Grass forage (green)			193
		AS 0162	Hay or fodder (dry) of grasses	400	-	117.5
		GC 0645	Maize	0.05	0.05*	0.01
		CF 1255	Maize flour			0.01
		AS 0645	Maize fodder	40	-	6.4

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		AF 0645	Maize forage	10	-	0.65
			Maize grits			0.01
		CF 0645	Maize meal			0.01
		MM 0095	Meat (from mammals other than marine mammals)	0.2	0.05*	0.125
			Milk products	W	0.05*	
		ML 0106	Milks	0.1	0.05*	0.043
		GC 0647	Oats	W	0.5	
		JF 0004	Orange juice			0.005
			Orange molasses			0.215
			Orange oil			0.05
			Orange pulp, dry			0.235
			Oranges pulp, wet			0.044
		FC 0004	Oranges, Sweet, Sour	0.1	2[2]	0.05
		FP 0009	Pome fruits	0.01*	-	0
		VR 0589	Potato	0.2	0.2	0.05
		PM 0110	Poultry meat	0.05*	-	0
		PO 0111	Poultry, Edible offal of	0.05*	-	0
		FB 0272	Raspberries, Red, Black	W[1]	0.1	
		GC 0649	Rice	W[3]	0.05*	
		CM 0649	Rice, husked	0.1	-	0.01
		AS 0649	Rice straw and fodder, dry	10	-	3.1
		GC 0650	Rye	2	0.5	0.22
		GC 0651	Sorghum	0.01*	0.05*	0.01
		AF 0651	Sorghum forage (green)	0.2	-	0.035
		VD 0541	Soya bean (dry)	0.01*	-	0
		AL 0541	Soya bean fodder	0.01*	-	0.01
		AL 1265	Soya bean forage (green)	0.01*	-	0
		FS 0012	Stone fruits	0.05*	-	0
		GS 0659	Sugar cane	0.05	-	0.01
		AV 0659	Sugar cane forage	0.2	-	0.03
		VO 0447	Sweet corn (corn-on-the-cob)	0.05*	-	0.05
		TN 0085	Tree nuts	0.2	-	0.05
		FB 0019	Vaccinium berries, including Bearberry	W[1]	0.1	
		GC 0654	Wheat	2	0.5	0.22
		CF 0654	Wheat bran, processed	-	-	0.803
		CF 1211	Wheat flour	-	-	0.024
			Wheat forage			20
		AS 0654	Wheat straw and fodder, dry	100	-	7

Residue (for MRLs and STMRs): 2,4-D

[1]Replaced by recommendation for berries and other small fruits

[2]Included in MRL for Citrus fruits

[3]Replaced by recommendation for Rice, husked

Periodic review was for residues only

Demeton-S-methyl**	0.0003[1]	Residues of demeton-S-methyl are covered by the recommendations for oxydemeton-methyl				
(073)		Residue: sum of demeton-S-methyl, oxydemeton-methyl, and demeton-S-methylsulphon, expressed as oxydemeton-methyl				
		[1]For demeton-S-methyl and related compounds, alone or in combination				
		Periodic review was for residues only				
Dicloran**	0.01	VR 0577	Carrot	15 Po	10 Po	6.11
(083)		FB 0269	Grapes	W	10 Po	

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		VL 0482	Lettuce, Head	W	10	
		VA 0385	Onion, Bulb	0.2	10 Po	0.1
		FS 0247	Peach	W	15 Po	
		FS 0014	Plums (including Prunes)	W	10 Po	
		FB 0275	Strawberry	W	10	
		VO 0448	Tomato	W	0.5	
		Residue (for MRLs and STMRs): dicloran				
		The residue is fat-soluble				
		Acute RfD unnecessary				
		Previous ADI 0-0.03 mg/kg bw				
Dimethoate**		See Part 2				
Dinocap	0.001	FP 0226	Apple	0.2	-	0.05
(087)		JF 0226	Apple juice	-	-	0.05
		VC 0045	Fruiting vegetables, Cucurbits	0.05*	-	0.05
		FB 0269	Grapes	1	-	0.105
			Grape must			0.007
		FB 0275	Strawberry	0.5	-	0.06
			Strawberry jam and preserved			0.017
		FS 0247	Peach	0.1	-	0.05
		VO 0051	Peppers	0.2	-	0.06
			Wine			0.007
		Residue (for MRLs and STMRs): sum of dinocap isomers and dinocap phenols, expressed as dinocap				
		Acute RfD 0.008 mg/kg bw				
		Previous ADI 0-0.001 mg/kg bw				
Diphenylamine* *	0.08	Acute RfD unnecessary				
(030)		Previous ADI 0-0.02 mg/kg bw				
		Periodic review was for toxicology only				
Disulfoton	0.0003	GC 0640	Barley	-	0.2	0.02
(074)		VD 0071	Beans (dry)	0.2	0.05	0.01
		VB 0400	Broccoli	-	0.1	0.025
		VB 0041	Cabbages, Head	-	0.2	0.02
		VB 0404	Cauliflower	-	0.05	0.01
		SO 0691	Cotton seed	0.1	0.1	0.03
		VP 0529	Garden pea, shelled (succulent seeds)	-	0.02*	0.01
		VL 0482	Lettuce, Head	1	1	0.05
		VL 0483	Lettuce, Leaf	1	1	0.11
		GC 0645	Maize	0.02*	0.01	0.01
		CF 1255	Maize flour			0.0025
		GC 0647	Oats	-	0.02*	0
		SO 0697	Peanut	-	0.1	0.015
		TN 0672	Pecan	-	0.1	0.01
		FI 0353	Pineapple	-	0.1	0
		VR 0589	Potato	0.5	0.5	0.08
		VR 0591	Radish, Japanese	-	0.2	0.025
		GC 0654	Wheat	-	0.2	0.02
		CM 0654	Wheat bran			0.019
		CF 1211	Wheat flour			0.004

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		CF 1210	Wheat germ			0.042
		Residue (for MRLs and STMRs): sum of disulfoton, demeton-S and their sulfoxides and sulfones, expressed as disulfoton				
Endosulfan** (032)	0.006	Acute RfD 0.02 mg/kg bw ADI unchanged Periodic review was for toxicology only				
Ethoxyquin** (035)	0.005	Acute RfD unnecessary Previous ADI 0-0.06 mg/kg bw Periodic review was for toxicology only				
Folpet**	0.1	FP 0226	Apple	W[1]	10	
(041)		VC 0424	Cucumber	W	0.5	
		DF 0269	Dried grapes (= currants, raisins and sultanas)	W[1]	40	
		FB 0269	Grapes	W[1]	10	
		VC 0046	Melons, except Watermelon	W	3	
		VR 0589	Potato	W	0.02*	
		FB 0275	Strawberry	W[1]	5	
		VO 0448	Tomato	W[1]	3	
		Residue (for MRLs and STMRs): folpet [1]The previous recommendation is withdrawn because critical supporting studies on the environmental fate of folpet were not provided for the 1998 Meeting Periodic review was for residues only				
Formothion** (042)		Formothion is metabolized by plants to dimethoate and omethoate. It is no longer used as a pesticide and no information was supplied. ADI withdrawn by 1996 JMPR				
Glufosinate-ammonium (175)	0.02	FI 0030	Assorted tropical and sub-tropical fruits - inedible peel[1]	0.05*	-	0.05
		FI 0341	Kiwifruit	W[2]	0.05*	
		TN 0085	Tree nuts	0.1	-	0.05
		AM 0660	Almond hulls	0.5	-	
		Residue (for MRLs and STMRs): Sum of glufosinate-ammonium and 3-[hydroxy(methyl)phosphinoyl]propionic acid calculated as glufosinate (free acid) [1]Except Banana [2]Replaced by recommendation for group MRL				
Hexythiazox	0.03	DH 1100	Hops, dry	2	-	0.79
(176)			Beer			0
		Residue (for MRLs and STMRs): hexythiazox				
Kresoxim-methyl*	0.4	JF 0226	Apple juice			0.02
(199)			Apple pomace, wet			0.05
		JF 0226	Apple sauce			0.02
		GC 0640	Barley	0.1		0.05
		VC 0424	Cucumber	0.05*		0.05
		DF 0269	Dried grapes (= currants, raisins and sultanas)	2		0.32
		MO 0105	Edible offal (Mammalian)	0.05*		0.01
			Grape must			0.02
			Grape pomace, wet			0.14
		FB 0269	Grapes	1		0.2
		MF 0100	Mammalian fats (except milk fats)	0.05*		0.01
		MM 0095	Meat (from mammals other than marine mammals)	0.05*		0.01
		ML 0106	Milks	0.01*		0.002
		FP 0009	Pome fruits	0.2		0.05
		PM 0110	Poultry meat	0.05*		0.01
		GC 0650	Rye	0.05*		0.05

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		AS 0081	Straw and fodder (dry) of cereal grains	5		0.24
		GC 0654	Wheat	0.05*		0.05
			Wine			0.04
		Residue (for MRLs and STMRs for plant commodities): kresoxim-methyl				
		(for MRLs and STMRs for animal commodities): α-(*p*-hydroxy-*o*-tolyloxy)-*o*-tolyl(methoxyimino)acetic acid, expressed as kresoxim-methyl				
		Acute RfD unnecessary				
Maleic hydrazide**	0.3	VA 0381	Garlic	15	-	4.1
(102)		VA 0385	Onion, Bulb	15	15	4.1
		VR 0589	Potato	50	50	11
			Potato crisps			0.29
			Potato chips			38.5[1] 10.12[2]
			Potato, boiled			5.7
		VA 0388	Shallot	15	-	4.1
		Residue (for MRLs and STMRs): maleic hydrazide [1]US commercial practice [2]UK commercial practice Note changed definition of residue Periodic review was for residues only				
Methiocarb**	0.02	Acute RfD 0.02 mg/kg bw				
(132)		Previous ADI 0-0.001 mg/kg bw				
		Periodic review was for toxicology only				
Myclobutanil	0.03	FI 0327	Banana	2	-	0.215
(181)			Beer			0
		DH 1100	Hops, dry	2	-	0.515
		Residue (for MRLs and STMRs): myclobutanil				
Omethoate**		See Part 2				
Oxydemeton-methyl**	0.0003[1]	AL 1020	Alfalfa fodder	W	5	
(166)		FP 0226	Apple	0.05	1	0.01
		JF 0226	Apple juice	-	-	0.005
			Apple sauce			0.01
		GC 0640	Barley	0.05*	0.2	0.04
		AS 0640	Barley straw and fodder, dry	2	-	0.055
		VD 0071	Beans (dry)	W	0.01*	
		VB 0400	Broccoli	W	1	
		VB 0402	Brussels sprouts	W	1	
		VB 0403	Cabbage, Savoy	W	0.01*	
		VB 0041	Cabbages, Head	0.05*	1	0.03
		MF 0812	Cattle fat	0.05*	0.05*	0
		VB 0404	Cauliflower	W	0.01*	
		FS 0013	Cherries	W	1	
		AL 1031	Clover hay or fodder	W	5	
		VD 0526	Common bean (dry)	0.1	-	0.01
		VP 0526	Common bean (pods and/or immature seeds)	W	0.2	
		SO 0691	Cotton seed	0.05	0.05	0.01
		OR 0691	Cotton seed oil, edible	-	-	0.002
			Cotton seed meal			0.006
			Cotton seed, hulls			0.002
		VC 0424	Cucumber	W	0.5	
		LD 0106	Derived milk products	W	0.05	

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		VO 0440	Egg plant	W	0.2	
		PE 0112	Eggs	0.05*	0.05*	0
		VP 0528	Garden pea (young pods)	W	0.1	
		FC 0203	Grapefruit	W	0.1	
		FB 0269	Grapes	0.1	0.5	0.04
		VL 0480	Kale	0.01*	0.05	0.01
		VB 0405	Kohlrabi	0.05	0.01*	0.02
		FC 0204	Lemon	0.2	1	0.01
		VL 0483	Lettuce, Leaf	W	2	
		VP 0534	Lima bean (young pods and/or immature beans)	W	0.2	
		GC 0645	Maize	W	0.2	
		AS 0645	Maize fodder	W	5	
		FC 0206	Mandarin	W	0.5	
		MM 0097	Meat of cattle, pigs and sheep	0.05*	0.05*	0
		ML 0106	Milks	0.01*	0.01*	0
		HH 0738	Mints	W	20	
		GC 0647	Oats	W	0.2	
		VA 0385	Onion, Bulb	W	0.05	
		FC 0004	Oranges, Sweet, Sour	0.2	0.5	0.01
		FS 0247	Peach	W	1	
		FP 0230	Pear	0.05	0.5	0.01
		VD 0072	Peas (dry)	W	0.01*	
		VO 0051	Peppers	W	1	
		MF 0818	Pig fat	0.05*	0.05*	0
		FS 0014	Plums (including Prunes)	W	0.5	
		VR 0589	Potato	0.05*	0.2	0.02
		PF 0111	Poultry fats	0.05*	0.05*	0
		PM 0110	Poultry meat	0.05*	0.05*	0
		VC 0429	Pumpkins	W	0.1*	
		GC 0650	Rye	0.05*	-	0.04
		AS 0650	Rye straw and fodder, dry	2	-	0.055
		SO 0699	Safflower seed	W	1	
		MF 0822	Sheep fat	0.05*	0.05*	0
		GC 0651	Sorghum	W	0.5	
		AF 0651	Sorghum forage (green)	W	1	
		AS 0651	Sorghum straw and fodder, dry	W	3	
		VC 0431	Squash, Summer	W	0.1*	
		FB 0275	Strawberry	W	0.5	
		VR 0596	Sugar beet	0.05*	0.05*	0.04
		AV 0596	Sugar beet leaves or tops	0.05*	0.5	0.04
		VO 0447	Sweet corn (corn-on-the-cob)	W	0.05	
		VO 1275	Sweet corn (kernels)	W	0.05	
		VO 0448	Tomato	W	0.5	
		TN 0085	Tree nuts	W	0.05*	
		VR 0506	Turnip, Garden	W	0.1*	
		AV 0506	Turnip leaves or tops	W	5 fresh wt	
		VC 0432	Watermelon	W	0.2	
		GC 0654	Wheat	0.05*	0.2	0.04
		AS 0654	Wheat straw and fodder, dry	2	-	0.055
		VC 0433	Winter squash	W	0.1*	

Pesticide	ADI, Mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		Residue (for MRLs and STMRs): sum of demeton-S-methyl, oxydemeton-methyl, and demeton-S-methylsulphon, expressed as oxydemeton-methyl [1]For demeton-S-methyl and related compounds, alone or in combination. All recommendations are based on the use of oxydemeton-methyl. No data were supplied for the use of demeton-S-methyl or demeton-S-methylsulphon. The residues will be the sum of oxydemeton-methyl and demeton-S-methylsuphon. Any inadvertent demeton-S-methyl would also be included. Previous recommendations are currently at Step 3 or Step 6 Periodic review was for residues only				
Phosmet (103)	0.01	Acute RfD 0.02 mg/kg bw ADI unchanged				
Procymidone (136)	0.1	VB 0041	Cabbages, Head	2	–	0.26
		VP 0528	Garden pea (young pods)	3	–	0.60
		VP 0529	Garden pea, shelled (succulent seeds)	1	–	0.08
		FS 0247	Peach	2	–	0.70
		FP 0230	Pear	1	–	0.43
		FS 0014	Plums (including Prunes)	2	–	0.74
		Residue (for MRLs and STMRs): procymidone				

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg	
(Codex ref. No.)		CCN	Name	New	Previous[1]	Quintozene	HCB
Quintozene (064)	0.01	GC 0640	Barley	0.01*	-	0.005	0
		AS 0640	Barley straw and fodder, dry	0.01*	-	0.005	
		VB 0400	Broccoli	0.05	0.02	0.0585	0
		VB 0041	Cabbages, Head	0.1	0.02	0.0052	0
		PO 0840	Chicken, Edible offal of	0.1*	-	0.03	
		PM 0840	Chicken meat	0.1* (in the fat)	-	0.04 (in the fat)	
		VD 0526	Common bean (dry)	0.02	0.2	0.002	0
		VP 0526	Common bean (pods and/or immature seeds)	0.1	0.01	0.0342	0
		SO 0691	Cotton seed	0.01	0.03	0.016	0
		PE 0112	Eggs	0.03*	-	0.01	
		VL 0482	Lettuce, Head	W[2]	3		
		GC 0645	Maize	0.01*	-	0.005	0
		AS 0645	Maize fodder	0.01	-	0.005	
		AF 0645	Maize forage	0.01*	-	0.005	0
		SO 0697	Peanut	0.5	2	0.353	0.0072
		OC 0697	Peanut oil, crude				0.0216
		OR 0697	Peanut oil, edible				0.0281
		VD 0072	Peas (dry)	0.01		0.005	0
		AL 0072	Pea hay or Pea fodder (dry)	0.05		0.021	0
		VO 0445	Peppers, Sweet	0.05*	0.01	0.05	0
		VR 0589	Potato	W[2]	0.2		
		VD 0541	Soya bean (dry)	0.01*		0.005	0
		AL 0541	Soya bean fodder	0.01*		0.0055	0
		AL 1265	Soya bean forage (green)	0.01*		0.005	0
		VR 0596	Sugar beet	0.01*		0.005	0
		AV 0596	Sugar beet leaves or tops			0.005	0
		VO 0448	Tomato	0.02	0.1	0.002	0
		GC 0654	Wheat	0.01		0.005	0
		AS 0654	Wheat straw and fodder, dry	0.03		0.005	

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg	
(Codex ref. No.)		CCN	Name	New	Previous[1]	Quintozene	HCB
		Residue for compliance with MRLs for plant commodities: quintozene. For compliance with MRLs for animal commodities: sum of quintozene, pentachloroaniline and methyl pentachlorophenyl sulfide, expressed as quintozene. For estimation of dietary intake for plant and animal commodities: sum of quintozene, pentachloroaniline and methyl pentachlorophenyl sulfide, expressed as quintozene. The compounds are fat-soluble. [1]Withdrawal of all previous MRLs (now CXLs) was recommended by 1995 JMPR owing to lack of supporting studies. 29th (1997) CCPR agreed to retain them for 4 years according to periodic review procedure [2]This confirms the recommendation of the 1995 Meeting to withdraw the CXL.					
Thiophanate-methyl**	0.08	Residues arising from the use of thiophanate methyl are covered by the MRLs for carbendazim.					
(077)		Residue (for MRLs and STMRs): sum of thiophanate-methyl and carbendazim, expressed as carbendazim. Acute RfD unnecessary Previous ADI 0-0.02 mg/kg bw Periodic review was for residues only					

PART 2: ADIs, recommended MRLMs and STMRs

Pesticide	ADI (mg/kg bw)	Commodity		Recommended MRLM (mg/kg)		STMR (mg/kg)
(Codex reference no.)		CCN	Name	New	Previous	
Dimethoate**	0.002[1]	FP 0226	Apple	W[2]	1	
(027)		VS 0621	Asparagus	0.05*	-	0.02
		FI 0327	Banana	W	1 Po	
		GC 0640	Barley	2	-	0.255
		AS 0640	Barley straw and fodder, dry	-	-	0.495
		VR 0574	Beetroot	W	0.2	
		VB 0402	Brussels sprouts	1	2	0.065
		VB 0041	Cabbages, Head[3]	2	2	0.46
		VB 0403	Cabbage, Savoy	0.05*	-	0.02
		VR 0577	Carrot	W	1	
		MO 0812	Cattle, Edible offal of	0.05*	-	0
		VB 0404	Cauliflower	0.5	-	0.065
		VS 0624	Celery	W	1	
		FS 0013	Cherries	2	2	0.06
		FC 0001	Citrus fruits	W	2	
		FB 0278	Currant, Black	W	2	
		PE 0112	Eggs	0.05*	-	0
		FB 0269	Grapes	2	1	0.48
		DH 1100	Hops, dry	W	3	
		VL 0480	Kale	W	0.5	
		VL 0482	Lettuce, Head	0.5	2	0.02
		MF 0100	Mammalian fats (except milk fats)	0.05*	-	0
		MM 0096	Meat of cattle, goats, horses, pigs and sheep	0.05*	-	0
		ML 0107	Milk of cattle, goats and sheep	0.05*	-	0
		OR 0305	Olive oil, refined	W	0.05*	
		FT 0305	Olives	W	1	
		DM 0305	Olives, processed	W	0.05*	
		VA 0385	Onion, Bulb	0.05*	0.2	0.02
		FS 0247	Peach	W	2	
		FP 0230	Pear	W[2]	1	
		VP 0063	Peas (pods and succulent =	1	0.5	0.065

Pesticide	ADI (mg/kg bw)	Commodity		Recommended MRLM (mg/kg)		STMR (mg/kg)
(Codex reference no.)		CCN	Name	New	Previous	
			immature seeds)			
		VO 0051	Peppers	W	1 Po	
		FS 0014	Plums (including Prunes)	1	0.5	0.1
		FP 0009	Pome fruits	0.5	-	0.065
		VR 0589	Potato	0.05	0.05	0.01
			Potato granules			0.002
			Potato chips			0.002
		PO 0111	Poultry, Edible offal of	0.05*	-	0
		PF 0111	Poultry fats	0.05*	-	0
		PM 0110	Poultry meat	0.05*	-	0
		MO 0822	Sheep, Edible offal of	0.05*	-	0
		GC 0651	Sorghum	0.01*	-	0.01
		AF 0651	Sorghum forage (green)	-	-	0.01
		AS 0651	Sorghum straw and fodder, dry	-	-	0.01
		VL 0502	Spinach	W	1	
		FB 0275	Strawberry	W	1	
		VR 0596	Sugar beet	0.05	0.05	0.01
		AV 0596	Sugar beet leaves or tops	0.1	1 T	0.05
		VO 0448	Tomato	2	1 Po	0.21
		JF 0448	Tomato juice			0.03
			Tomato purée			0.4
			Tomato paste			0.6
			Tomato ketchup			0.4
		VR 0506	Turnip, Garden	0.1	0.5	0.1
		VL 0506	Turnip greens	1	-	0.1
		GC 0654	Wheat	0.2	-	0.09
		AS 0654	Wheat straw and fodder, dry	10	-	2.23
		VS 0469	Witloof chicory (sprouts)	W	0.5	
		Residue (for MRLMs and STMRs): dimethoate [1]For sum of dimethoate and omethoate expressed as dimethoate [2]Replaced by recommendation for Pome fruits [3]Except Savoy cabbage Periodic review was for residues only				
Omethoate**	No ADI[1]	FP 0226	Apple	W	2	
(055)		FS 0240	Apricot	W	2	
		VS 0620	Artichoke, Globe	W	0.5	
		VS 0621	Asparagus	-	-	0.02
		FI 0327	Banana	W	0.2*	
		GC 0640	Barley	-	-	0.015
		AS 0640	Barley straw and fodder, dry	-	-	0.03
		VP 0061	Beans, except broad bean and soya bean	W	0.2	
		VB 0400	Broccoli	W	0.2	
		VB 0402	Brussels sprouts	W	0.2	0.03
		VB 0403	Cabbage, Savoy	-	-	0.075
		VB 0041	Cabbages, Head	W	0.5 T	0.165
		VR 0577	Carrot	W	0.05	
		VB 0404	Cauliflower	W	0.2	0.01
		VS 0624	Celery	W	0.1	
		GC 0080	Cereal grains	W	0.05	
		FS 0013	Cherries	W	2	0.27
		FC 0001	Citrus fruits	W	2	

Pesticide	ADI (mg/kg bw)	Commodity		Recommended MRLM (mg/kg)		STMR (mg/kg)
(Codex reference no.)		CCN	Name	New	Previous	
		VC 0424	Cucumber	W	0.2	
		FB 0278	Currant, Black	W	2	
		FB 0269	Grapes	W	2	0.11
		DH 1100	Hops, dry	W	3	
		VL 0480	Kale	W	0.2	
		VL 0482	Lettuce, Head	W	0.2	0.03
		VL 0483	Lettuce, Leaf	W	0.2	
		VA 0385	Onion, Bulb	W	0.5	0.02
		FS 0247	Peach	W	2	
		FP 0230	Pear	W	2	
		VP 0063	Peas (pods and succulent = immature seeds)	W	0.1	0.02
		VO 0051	Peppers	W	1	
		FS 0014	Plums (including Prunes)	W	1	0.05
		FP 0009	Pome fruits	-	-	0.05
		VR 0589	Potato	W	0.05	0.01
			Potato chips			0.002
			Potato granules			0.002
		GC 0651	Sorghum	-	-	0.01
		AF 0651	Sorghum forage (green)	-	-	0.01
		AS 0651	Sorghum straw and fodder, dry	-	-	0.01
		VL 0502	Spinach	W	0.1	
		FB 0275	Strawberry	W	1	
		VR 0596	Sugar beet	W	0.05	0.01
		AV 0596	Sugar beet leaves or tops	W	1T	0.05
		VO 0448	Tomato	W	0.5	0.05
		JF 0448	Tomato juice	-	-	0.009
			Tomato purée			0.05
			Tomato paste			0.07
			Tomato ketchup			0.05
		VR 0506	Turnip, Garden	W	0.2	0.1
		VL 0506	Turnip greens	-	-	0.1
		GC 0654	Wheat	-	-	0.01
		AS 0654	Wheat straw and fodder, dry	-	-	0.08
		VS 0469	Witloof chicory (sprouts)	W	0.5	
		Residue (for STMRs): omethoate [1]ADI was withdrawn in 1996 because the Meeting was informed that the primary manufacturer was no longer producing omethoate Periodic review was for residues only				

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

ABAMECTIN (177)   1992 (T,R)[1], 1994 (T,R), 1995 (T), 1997 (T,R)

ACEPHATE (095)   1976 (T,R), 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1996 (R)

ACRYLONITRILE   1965 (T,R)

ALDICARB (117)   1979 (T,R), 1982 (T,R), 1985 (R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1994 (R), 1996 (R)

ALDRIN (001)   1965 (T), 1966 (T,R), 1967 (R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)

ALLETHRIN   1965 (T,R)

AMINOCARB (134)   1978 (T,R), 1979 (T,R)

AMINOMETH-   1997 (T,R)
YLPHOSPHONIC
ACID (AMPA, 198)

AMITRAZ (122)   1980 (T,R), 1983 (R), 1984 (T,R), 1985 (R), 1986 (R), 1989 (R), 1990 (T,R), 1991 (R & corr. to 1990 R evaluation); 1998 (T)

AMITROLE (079)   1974 (T,R), 1977 (T), 1993 (T,R), 1997 (T); 1998 (R)

ANILAZINE (163)   1989 (T,R), 1992 (R)

AZINPHOS-ETHYL   1973 (T,R), 1983 (R)
    (068)

AZINPHOS-METHYL   1965 (T), 1968 (T,R), 1972 (R), 1973 (T), 1974 (R),
    (002)   1991 (T,R), 1992 (corr. to 1991 rpt), 1993 (R), 1995 (R)

AZOCYCLOTIN   1979 (R), 1981 (T), 1982 (R),1983 (R), 1985 (R), 1989 (T,R),
    (129)   1991 (R), 1994 (T)

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

BENALAXYL (155)   1986 (R), 1987 (T), 1988 (R), 1992 (R), 1993 (R)

BENDIOCARB (137)   1982 (T,R), 1984 (T,R), 1989 (R), 1990 (R)

BENOMYL (069)   1973 (T,R), 1975 (T,R), 1978 (T,R), 1983 (T,R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E), 1998 (R)

BENTAZONE (172)   1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1995 (R); 1998 (T,R)

BHC (technical)   1965 (T), 1968 (T,R), 1973 (T,R) (see also lindane)

BIFENTHRIN (178)   1992 (T,R), 1995 (R), 1996 (R), 1997 (R)

BINAPACRYL (003)   1969 (T,R), 1974 (R), 1982 (T), 1984 (R), 1985 (T,R)

BIORESMETHRIN (093)   1975 (R), 1976 (T,R), 1991 (T,R)

BIPHENYL   see diphenyl

BITERTANOL (144)   1983 (T), 1984 (R), 1986 (R), 1987 (T), 1988 (R), 1989 (R), 1991 (R); 1998 (T)

BROMIDE ION (047)   1968 (R), 1969 (T,R), 1971 (R), 1979 (R), 1981 (R), 1983 (R), 1988 (T,R), 1989 (R), 1992 (R)

BROMOMETHANE (052)   1965 (T,R), 1966 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R), 1992 (R)

BROMOPHOS (004)   1972 (T,R), 1975 (R), 1977 (T,R), 1982 (R), 1984 (R), 1985 (R)

BROMOPHOS-ETHYL (005)   1972 (T,R), 1975 (T,R), 1977 (R)

BROMOPROPYLATE (070)   1973 (T,R), 1993 (T,R)

BUTOCARBOXIM (139)   1983 (R), 1984 (T), 1985 (T), 1986 (R)

BUPROFEZIN (173)   1991 (T,R), 1995 (R), 1996 (corr.to 1995 rpt.)

sec-BUTYLAMINE (089)   1975 (T,R), 1977 (R), 1978 (T,R), 1979 (R), 1980 (R), 1981 (T), 1984 (T,R: withdrawal of TADI, but no evaluation)

CADUSAFOS (174)   1991 (T,R), 1992 (R), 1992 (R)

CAMPHECHLOR (071)   1968 (T,R), 1973 (T,R)

CAPTAFOL (006)   1969 (T,R), 1973 (T,R), 1974 (R), 1976 (R), 1977 (T,R), 1982 (T), 1985 (T,R), 1986 (corr. to 1985 rpt), 1990 (R)

CAPTAN (007)   1965 (T), 1969 (T,R), 1973 (T), 1974 (R), 1977 (T,R), 1978 (T,R), 1980 (R), 1982 (T), 1984 (T,R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1995 (T), 1997 (R)

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), 1996 (T)

CARBENDAZIM   1973 (T,R), 1976 (R), 1977 (T), 1978 (R), 1983 (T,R), 1985 (T,R),
    (072)   1987 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E); 1998 (T,R)

CARBOFURAN (096)   1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R), 1996 (T), 1997 (R)

CARBON   1965 (T,R), 1967 (R), 1968 (R), 1971 (R), 1985 (R)
DISULPHIDE (009)

CARBON   1965 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R),
TETRACHLORIDE   1985 (R)
    (010)

CARBOPHENO-   1972 (T,R), 1976 (T,R), 1977 (T,R), 1979 (T,R), 1980
THION (011)   (T,R), 1983 (R)

CARBOSULFAN   1984 (T,R), 1986 (T), 1991 (R), 1992 (corr. to 1991 rpt), 1993 (R),
    (145)   1997 (R)

CARTAP (097)   1976 (T,R), 1978 (T,R), 1995 (T,R)

CHINOMETHIONAT   1968 (T,R) (as oxythioquinox), 1974 (T,R), 1977 (T,R), 1981
    (080)   (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   1971 (T,R), 1975 (T,R), 1977 (T), 1978 (T,R), 1979(T), 1980(T),
    (013)   1985(T), 1986 (R), 1987 (T)

CHLORFENSON   1965 (T)

CHLORFENVINPHOS 1971 (T,R), 1984 (R), 1994 (T), 1996 (R)
    (014)

CHLORMEQUAT   1970 (T,R), 1972 (T,R), 1976 (R), 1985 (R), 1994 (T,R), 1997 (T)
  (015)

CHLOROBENZILATE   1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R),
  (016)   1980 (T)

CHLOROPICRIN   1965 (T,R)

CHLOROPRO-   1968 (T,R), 1972 (R)
PYLATE

CHLOROTHALONIL   1974 (T,R), 1977 (T,R), 1978 (R), 1979 (T,R), 1981 (T,R), 1983
  (081)   (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), 1997 (R)

CHLORPROPHAM   1965 (T)

CHLORPYRIFOS   1972 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1981 (R), 1982(T,R),
  (017)   1983 (R), 1989 (R), 1995 (R)

CHLORPYRIFOS-   1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990
METHYL (090)   (R), 1991 (T,R), 1992 (T) and corr. to 1991, 1993 (R), 1994 (R)

CHLORTHION   1965 (T)

CLETHODIM (187)   1994 (T,R), 1997 (R)

CLOFENTEZINE   1986 (T,R), 1987 (R), 1989 (R), 1990 (R), 1992 (R)
  (156)

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   1975 (T,R), 1978 (T: ADI extended, but no evaluation), 1980, (T),
  (091)   1982 (R), 1983 (T)

CYCLOXYDIM (179) 1992 (T,R), 1993 (R)

CYFLUTHRIN (157) 1986 (R), 1987 (T & corr. to 1986 rpt), 1989 (R), 1990 (R), 1992
                  (R)

CYHALOTHRIN   1984 (T,R), 1986 (R), 1988 (R)
  (146)

CYHEXATIN (TRICYCLO HEXYLTIN HYDROXIDE (067)

1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R), 1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T), 1989 (T), 1991 (T,R), 1992 (R), 1994 (T)

CYPERMETHRIN (118)

1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985(R), 1986 (R), 1987 (corr. to 1986 evaluation), 1988 (R), 1990 (R)

CYROMAZINE (169)   1990 (T,R), 1991 (corr. to 1990 R evaluation), 1992 (R)

2,4-D (020)

1970 (T,R), 1971 (T,R), 1974 (T,R), 1975 (T,R), 1980 (R), 1985, (R), 1986 (R), 1987 (corr. to 1986 rpt, Annex I), 1996 (T), 1997 (E); 1998 (R)

DAMINOZIDE (104)   1977 (T,R), 1983 (T), 1989 (T,R), 1991 (T)

DDT (021)

1965 (T), 1966 (T,R), 1967 (T,R),1968 (T,R), 1969 (T,R), 1978 (R), 1979 (T), 1980 (T), 1983 (T), 1984 (T), 1993 (R), 1994 (R), 1996 (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); 1998 (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), 1994 (R), 1996 (R)

1,2-DIBROMO ETHANE (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-DICHLORO ETHANE (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); 1998 (T,R)

DICOFOL (026)   1968 (T,R), 1970 (R), 1974 (R), 1992 (T,R), 1994 (R)

DIELDRIN (001)   1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (R), 1970, (T,R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)

DIFLUBENZURON   1981 (T,R), 1983 (R), 1984 (T,R), 1985 (T,R), 1988 (R)
    (130)

DIMETHIPIN (151)   1985 (T,R), 1987 (T,R), 1988 (T,R)

DIMETHOATE (027)   1965 (T), 1966 (T), 1967 (T,R), 1970 (R), 1973 (R in evaluation of formothion), 1977 (R), 1978 (R), 1983 (R) 1984 (T,R) 1986(R), 1987 (T,R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1994 (R), 1996 (T); 1998 (R)

DIMETHRIN   1965 (T)

DINOCAP (087)   1969 (T,R), 1974 (T,R), 1989 (T,R), 1992 (R); 1998 (R)

DIOXATHION (028)   1968 (T,R), 1972 (R)

DIPHENYL (029)   1966 (T,R), 1967 (T)

DIPHENYLAMINE   1969 (T,R), 1976 (T,R), 1979 (R), 1982 (T), 1984 (T,R); 1998 (T)
    (030)

DIQUAT (031)   1970 (T,R), 1972 (T,R), 1976 (R), 1977 (T,R), 1978 (R), 1994 (R)

DISULFOTON (074)   1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1996 (T); 1998 (R)

DITHIANON (180)   1992 (T,R), 1995 (R), 1996 (corr. to 1995 rpt.)

DITHIOCARB   1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R propineb, thiram),
AMATES   1984 (R propineb), 1985 (R), 1987 (T thiram), 1988 (R thiram),
    (105)   1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T thiram), 1993 (T,R), 1995 (R), 1996 (T,R ferbam, ziram; R thiram)

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); 1998 (T)

ENDRIN (033)   1965 (T), 1970 (T,R), 1974 (R), 1975 (R), 1990 (R), 1992 (R)

ETHEPHON (106)   1977 (T,R), 1978 (T,R), 1983 (R), 1985 (R), 1993 (T), 1994 (R),
                        1995 (T), 1997 (T)

ETHIOFENCARB   1977 (T,R), 1978 (R), 1981 (R), 1982 (T,R), 1983 (R)
    (107)

ETHION (034)   1968 (T,R), 1969 (R), 1970 (R), 1972 (T,R), 1975 (R), 1982 (T),
                        1983 (R), 1985 (T), 1986 (T), 1989 (T), 1990 (T), 1994 (R)

ETHOPROPHOS (149)   1983 (T), 1984 (R), 1987 (T)

ETHOXYQUIN (035)   1969 (T,R); 1998 (T)

ETHYLENE   see 1,2-dibromoethane
DIBROMIDE

ETHYLENE   see 1,2-dichloroethane
DICHLORIDE

ETHYLENE OXIDE   1965 (T,R), 1968 (T,R), 1971 (R)

ETHYLENETHIO   1974 (R), 1977 (T,R), 1986 (T,R), 1987 (R), 1988
UREA (ETU) (108)   (T,R), 1990 (R), 1993 (T,R)

ETOFENPROX (184)   1993 (T,R)

ETRIMFOS (123)   1980 (T,R), 1982 (T,R[2]), 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),
    1997 (T)

FENARIMOL (192)   1995 (T,R,E), 1996 (R & corr. to 1995 rpt.)

FENBUCONAZOLE   1997 (T,R)
    (197)

FENBUTATIN OXIDE   1977 (T,R), 1979 (R), 1992 (T), 1993 (R)
    (109)

FENCHLORPHOS   1968 (T,R), 1972 (R), 1983 (R)
    (036)

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[2]R evaluation omitted. Published 1986.

FENITROTHION (037)   1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R)

FENPROPATHRIN (185)   1993 (T,R)

FENPROPIMORPH (188)   1994 (T), 1995 (R)

FENPYROXIMATE (193)   1995 (T,R), 1996 (corr. to 1995 rpt.)

FENSULFOTHION (038)   1972 (T,R), 1982 (T), 1983 (R)

FENTHION (039)   1971 (T,R), 1975 (T,R), 1977 (R), 1978 (T,R), 1979 (T), 1980 (T), 1983 (R), 1989 (R), 1995 (T,R,E), 1996 (corr. to 1995 rpt.), 1997 (T)

FENTIN COMPOUNDS (040)   1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R), 1993 (R), 1994 (R)

FENVALERATE (119)   1979 (T,R), 1981 (T,R), 1982 (T), 1984 (T,R), 1985 (R), 1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)

FERBAM   see dithiocarbamates, 1965 (T), 1967 (T,R), 1996 (T,R)

FIPRONIL   1997 (T)

FIPRONIL-DESULFINYL   1997 (T)

FLUCYTHRINATE (152)   1985 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1993 (R)

FLUMETHRIN (195)   1996 (T,R)

FLUSILAZOLE (165)   1989 (T,R), 1990 (R), 1991 (R), 1993 (R), 1995 (T)

FOLPET (041)   1969 (T,R), 1973 (T), 1974 (R), 1982 (T), 1984 (T,R), 1986 (T), 1987 (R), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1993 (T,R), 1994 (R), 1995 (T), 1997 (R); 1998 (R)

FORMOTHION (042)   1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R); 1998 (R)

GLUFOSINATE-
AMMONIUM (175)

1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R); 1998 (R)

GLYPHOSATE (158)

1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1994 (R), 1997 (T,R)

GUAZATINE (114)

1978 (T.R), 1980 (R), 1997 (T,R)

HALOXYFOP (194)

1995 (T,R), 1996 (R & corr. to 1995 rpt.)

HEPTACHLOR (043)

1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R), 1974 (R), 1975 (R), 1977 (R), 1987 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1993 (R), 1994 (R)

HEXACHLORO
BENZENE (044)

1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)

HEXACONAZOLE
    (170)

1990 (T,R), 1991 (R and corr. to 1990 R evaluation), 1993 (R)

HEXYTHIAZOX
    (176)

1991 (T,R), 1994 (R); 1998 (R)

HYDROGEN
CYANIDE (045)

1965 (T,R)

HYDROGEN
PHOSPHIDE (046)

1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1971 (R)

IMAZALIL (110)

1977 (T,R), 1980 (T,R), 1984 (T,R), 1985 (T,R), 1986 (T), 1988 (R), 1989 (R), 1991 (T), 1994 (R)

IPRODIONE (111)

1977 (T,R), 1980 (R), 1992 (T), 1994 (R), 1995 (T)

ISOFENPHOS (131)

1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986 (T,R), 1988 (R), 1992 (R)

KRESOXIM-
METHYL (199)

1998 (T,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) (publ. as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R), 1997 (T)
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), 1997 (T)
MALEIC HYDRAZIDE (102)	1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R), 1996 (T); 1998 (R)
MANCOZEB (050)	1967 (T,R), 1970 (T,R), 1974 (R), 1977 (R), 1980 (T,R), 1993 (T,R)
MANEB	see dithiocarbamates, 1965 (T), 1967 (T,R), 1987 (T), 1993 (T,R)
MECARBAM (124)	1980 (T,R), 1983 (T,R), 1985 (T,R), 1986 (T,R), 1987 (R)
METALAXYL (138)	1982 (T,R), 1984 (R), 1985 (R), 1986 (R), 1987 (R), 1989 (R), 1990 (R), 1992 (R), 1995 (R)
METHACRIFOS (125)	1980 (T,R), 1982 (T), 1986 (T), 1988 (T), 1990 (T,R), 1992 (R)
METHAMIDOPHOS (100)	1976 (T,R), 1979 (R), 1981 (R), 1982 (T,R[3]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R), 1996 (R), 1997 (R)
METHIDATHION (051)	1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,R), 1994 (R), 1997 (T)
METHIOCARB (132)	1981 (T,R), 1983 (T,R), 1984 (T), 1985 (T), 1986 (R), 1987 (T,R), 1988 (R); 1998 (T)
METHOMYL (094)	1975 (R), 1976 (R), 1977 (R), 1978 (R), 1986 (T,R), 1987 (R), 1988 (R), 1989 (T,R), 1990 (R), 1991 (R)
METHOPRENE (147)	1984 (T,R), 1986 (R), 1987 (T and corr. to 1986 rpt), 1988 (R), 1989 (R)
METHOXYCHLOR	1965 (T), 1977 (T)
METHYL BROMIDE (052)	See bromomethane
METIRAM (186)	1993 (T), 1995 (R)
MEVINPHOS (053)	1965 (T), 1972 (T,R), 1996 (T), 1997 (E,R)
MGK 264	1967 (T,R)

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[3]R evaluation omitted. Published 1989.

MONOCROTOPHOS   1972 (T,R), 1975 (T,R), 1991 (T,R), 1993 (T), 1994 (R)
(054)

MYCLOBUTANIL   1992 (T,R), 1997 (R); 1998 (R)
(181)

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); 1998 (R)

ORGANOMERCURY   1965 (T), 1966 (T,R), 1967 (T,R)
COMPOUNDS

OXAMYL (126)   1980 (T,R), 1983 (R), 1984 (T), 1985 (T,R), 1986 (R)

OXYDEMETON-   1965 (T, as demeton-S-methyl sulphoxide), 1967 (T), 1968 (R),
METHYL (166)   1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R); 1998 (R)

OXYTHIOQUINOX   see chinomethionat

PACLOBUTRAZOL   1988 (T,R), 1989 (R)
(161)

PARAQUAT (057)   1970 (T,R), 1972 (T,R), 1976 (T,R), 1978(R), 1981 (R), 1982 (T),
1985 (T), 1986 (T)

PARATHION (058)   1965 (T), 1967 (T,R), 1969 (R), 1970 (R), 1984 (R), 1991 (R),
1995 (T,R), 1997 (R)

PARATHION-   1965 (T), 1968 (T,R), 1972 (R), 1975 (T,R), 1978 (T,R), 1979
METHYL (059)   (T), 1980 (T), 1982 (T), 1984 (T,R), 1991 (R), 1992 (R), 1994 (R),
1995 (T)

PENCONAZOLE (182) 1992 (T,R), 1995 (R)

PERMETHRIN (120) 1979 (T,R), 1980 (R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R),
1985 (R), 1986 (T,R), 1987 (T), 1988 (R), 1989 (R), 1991 (R),
1992 (corr. to 1991 rpt)

2-PHENYLPHENOL   1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 1990 (T,R)
(056)

PHENOTHRIN (127) 1979 (R), 1980 (T,R), 1982 (T), 1984 (T), 1987 (R), 1988 (T,R)

PHENTHOATE (128) 1980 (T,R), 1981 (R), 1984 (T)

PHORATE (112)   1977 (T,R), 1982 (T), 1983 (T), 1984 (R), 1985 (T), 1990 (R),
                         1991 (R), 1992 (R), 1993 (T), 1994 (T), 1996 (T)

PHOSALONE (060)   1972 (T,R), 1975 (R), 1976 (R), 1993 (T), 1994 (R), 1997 (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), 1994 (T), 1997 (R); 1998 (T)

PHOSPHINE   see hydrogen phosphide

PHOSPHAMIDON   1965 (T), 1966 (T), 1968 (T,R), 1969 (R), 1972 (R), 1974 (R),
       (061)   1982 (T), 1985 (T), 1986 (T)

PHOXIM (141)   1982 (T), 1983 (R), 1984 (T,R), 1986 (R), 1987 (R), 1988 (R)

PIPERONYL   1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1972 (T,R),
BUTOXIDE (062)   1992 (T,R), 1995 (T)

PIRIMICARB (101)   1976 (T,R), 1978 (T,R), 1979 (R), 1981 (T,R), 1982 (T), 1985 (R)

PIRIMIPHOS-   1974 (T,R), 1976 (T,R), 1977 (R), 1979 (R), 1983 (R), 1985 (R),
METHYL (086)   1992 (T), 1994 (R)

PROCHLORAZ (142)   1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R),
                         1991 (corr. to 1990 rpt, Annex I, and evaluation), 1992 (R)

PROCYMIDONE (136) 1981 (R), 1982 (T), 1989 (T,R), 1990 (R), 1991 (corr. to 1990
                         Annex I), 1993 (R); 1998 (R)

PROFENOFOS (171)   1990 (T,R), 1992 (R), 1994 (R), 1995 (R)

PROPAMOCARB (148) 1984 (T,R), 1986 (T,R), 1987 (R)

PROPARGITE (113)   1977 (T,R), 1978 (R), 1979 (R), 1980 (T,R), 1982 (T,R)

PROPHAM (183)   1965 (T), 1992 (T,R)

PROPICONAZOLE   1987 (T,R), 1991 (R), 1994 (R)
       (160)

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),
                         1996 (R)

PROPYLENETHIO   1993 (T,R), 1994 (R)
UREA (PTU, 150)

PYRAZOPHOS (153)   1985 (T,R), 1987 (R), 1992 (T,R), 1993 (R)

PYRETHRINS (063)   1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T), 1972 (T,R), 1974 (R)

QUINTOZENE (064)   1969 (T,R) 1973 (T,R), 1974 (R), 1975 (T,R), 1976 (Annex I, corr. to 1975 R), 1977 (T,R), 1995 (T,R); 1998 (R)

2,4,5-T (121)   1970 (T,R), 1979 (T,R), 1981 (T)

TEBUCONAZOLE   1994 (T,R), 1996 (corr. to Annex II of 1995 rpt.), 1997 (R)
     (189)

TEBUFENOZIDE   1996 (T,R), 1997 (R)
     (196)

TECNAZENE (115)   1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R), 1994 (T,R)

TEFLUBENZURON   1994 (T), 1996 (R)
     (190)

TERBUFOS (167)   1989 (T,R), 1990 (T,R)

THIABENDAZOLE   1970 (T,R), 1971 (R), 1972 (R), 1975 (R), 1977 (T,R), 1979 (R),
     (065)   1981 (R), 1997 (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-   1973 (T,R), 1975 (T,R), 1977 (T), 1978 (R), 1988 (R),
METHYL (077)   1990 (R), 1994 (R), 1995 (T,E); 1998 (T,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), 1996 (R)

TOLCLOFOS-   1994 (T,R) 1996 (corr. to Annex II of 1995 rpt.)
METHYL (191)

TOLYLFLUANID   1988 (T,R), 1990 (R), 1991 (corr. to 1990 rpt)
     (162)

TOXAPHENE   see camphechlor

TRIADIMEFON   1979 (R), 1981 (T,R), 1983 (T,R), 1984 (R), 1985 (T,R), 1986 (R),
     (133)   1987 (R and corr. to 1986 evaluation), 1988 (R), 1989 (R), 1992 (R), 1995 (R)

TRIADIMENOL (168)   1989 (T,R), 1992 (R), 1995 (R)

TRIAZOLYL   1989 (T,R)
ALANINE

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   see cyhexatin
HYDROXIDE

TRIFORINE (116)   1977 (T), 1978 (T,R), 1997 (T)

TRIPHENYLTIN   see fentin compounds
COMPOUNDS

VAMIDOTHION   1973 (T,R), 1982 (T), 1985 (T,R), 1987 (R), 1988 (T), 1990 (R),
    (078)   1992 (R)

VINCLOZOLIN (159)   1986 (T,R), 1987 (R and corr. to 1986 rpt and R evaluation), 1988
                     (T,R), 1989 (R), 1990 (R), 1992 (R), 1995 (T)

ZINEB (105)   see dithiocarbamates, 1965 (T), 1967 (T,R), 1993 (T)

ZIRAM (105)   see dithiocarbamates, 1965 (T), 1967 (T,R), 1996 (T,R)

ANNEX III

DIETARY INTAKES OF PESTICIDES IN RELATION TO ADIs

The following Tables give details of the estimated daily intakes of the pesticides evaluated by the Meeting for the five GEMS/Food regional diets, and show the ratios of the estimated intakes to the corresponding ADIs.

(*) at or about the LOD.

The ranges of the intake/ADI ratios for all the compounds evaluated are tabulated in Section 3, page 22.

AMITRAZ (122)   **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
MM 0812	Cattle meat	0.05		18.5	0.0009	3.5	0.0002	10.4	0.0005	30.0	0.0015	63.3	0.0032
FS 0013	Cherries	0.5		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0015
SO 0691	Cotton seed	0.5		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
OC 0691	Cotton seed oil, crude	0.05		3.8	0.0002	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
VC 0424	Cucumber	0.5		4.8	0.0024	4.5	0.0023	0.0	0.0000	8.3	0.0041	9.0	0.0045
MO 0097	Edible offal of cattle, pigs and sheep	0.2		3.8	0.0008	1.3	0.0003	2.3	0.0005	6.0	0.0012	12.3	0.0025
ML 0106	Milks	0.01	(*)	116.8	0.0012	32.0	0.0003	41.8	0.0004	160.0	0.0016	294.0	0.0029
FC 0004	Oranges, Sweet, Sour	0.5		31.5	0.0158	4.0	0.0020	4.8	0.0024	31.0	0.0155	29.8	0.0149
FS 0247	Peach	0.5		2.5	0.0013	0.5	0.0003	0.0	0.0000	0.8	0.0004	12.5	0.0063
MM 0818	Pig meat	0.05		0.0	0.0000	27.2	0.0014	2.6	0.0001	10.5	0.0005	75.8	0.0038
FP 0009	Pome fruits	0.5		10.8	0.0054	7.5	0.0038	0.3	0.0001	6.5	0.0033	51.3	0.0257
MM 0822	Sheep meat	0.1		13.5	0.0014	0.7	0.0001	2.0	0.0002	3.0	0.0003	10.3	0.0010
VO 0448	Tomato	0.5		81.5	0.0408	7.0	0.0035	16.5	0.0083	25.5	0.0128	66.0	0.0330
			TOTAL =		0.0699		0.0140		0.0126		0.0412		0.0991
			% ADI =		12%		3%		2%		7%		17%
			ROUNDED % ADI =		10%		3%		2%		7%		20%

AMITROLE (079)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.002 mg/kg body weight or 0.120 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0009	Pome fruits	0.05	0	1	(*)	0	10.8	0.0000	7.5	0.0000	0.3	0.0000	6.5	0.0000	51.3	0.0000
FS 0012	Stone fruits	0.05	0	1	(*)	0	7.3	0.0000	1.0	0.0000	0.0	0.0000	0.8	0.0000	22.8	0.0000
FB 0269	Grapes	0.05	0.02	1		0.02	15.8	0.0003	1.0	0.0000	0.0	0.0000	1.3	0.0000	13.8	0.0003
						TOTAL =		0.0003		0.0000		0.0000		0.0000		0.0003
						% ADI =		0%		0%		0%		0%		0%

BENTAZONE (172)   THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.1 mg/kg body weight or 6.000 mg/person

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
GC 0640	Barley	0.05	(*)	1.0	0.0001	3.5	0.0002	1.8	0.0001	6.5	0.0003	19.8	0.0010
VD 0071	Beans (dry)	0.05	(*)	2.3	0.0001	4.8	0.0002	0.0	0.0000	13.0	0.0007	3.6	0.0002
VD 0523	Broad bean (dry)	0.05	(*)	4.5	0.0002	2.0	0.0001	0.0	0.0000	0.5	0.0000	0.8	0.0000
VP 0526	Common bean (pods and/or immature seeds)	0.2		3.5	0.0007	0.8	0.0002	0.0	0.0000	4.0	0.0008	12.0	0.0024
PE 0112	Eggs	0.05	(*)	14.6	0.0007	13.1	0.0007	3.7	0.0002	11.9	0.0006	37.6	0.0019
VD 0561	Field pea (dry)	0.05	(*)	0.5	0.0000	1.7	0.0001	0.0	0.0000	1.3	0.0001	1.8	0.0001
VP 0528	Garden pea (young pods)	0.2		5.5	0.0011	0.7	0.0001	0.0	0.0000	0.3	0.0001	14.0	0.0028
VP 0534	Lima bean (young pods/immature beans)	0.05		0.4	0.0000	0.1	0.0000	0.0	0.0000	0.4	0.0000	1.2	0.0001
GC 0645	Maize	0.05	(*)	48.3	0.0024	31.2	0.0016	106.2	0.0053	41.8	0.0021	8.8	0.0004
MM 0095	Meat	0.05	(*)	37.0	0.0019	32.8	0.0016	23.8	0.0012	47.0	0.0024	155.5	0.0078
ML 0106	Milks	0.05	(*)	116.8	0.0058	32.0	0.0016	41.8	0.0021	160.0	0.0080	294.0	0.0147
GC 0647	Oats	0.05	(*)	0.0	0.0000	0.0	0.0000	0.2	0.0000	0.8	0.0000	2.0	0.0001
VA 0385	Onion, bulb	0.1		23.0	0.0023	11.5	0.0012	7.3	0.0007	13.8	0.0014	27.8	0.0028
SO 0697	Peanut	0.05		0.3	0.0000	0.2	0.0000	2.3	0.0001	0.3	0.0000	3.0	0.0002
VR 0589	Potato	0.1		59.0	0.0059	19.2	0.0019	20.6	0.0021	40.8	0.0041	240.8	0.0241
GC 0649	Rice	0.1		48.8	0.0049	279.3	0.0279	103.4	0.0103	86.5	0.0087	11.8	0.0012
GC 0650	Rye	0.05	(*)	0.0	0.0000	1.0	0.0001	0.0	0.0000	0.0	0.0000	1.5	0.0001

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
GC 0651	Sorghum	0.05	(*)	2.0	0.0001	9.7	0.0005	26.6	0.0013	0.0	0.0000	0.0	0.0000
VD 0541	Soya bean (dry)	0.05	(*)	4.5	0.0002	2.0	0.0001	0.5	0.0000	0.0	0.0000	0.0	0.0000
GC 0654	Wheat	0.05	(*)	327.3	0.0164	114.8	0.0057	28.3	0.0014	116.8	0.0058	178.0	0.0089
			TOTAL =		0.0428		0.0437		0.0249		0.0350		0.0686
			% ADI =		1%		1%		0%		1%		1%

BITERTANOL (144)   THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
FS 0240	Apricot	1		3.0	0.0030	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.5	0.0035
FI 0327	Banana	0.5		8.3	0.0041	26.2	0.0131	21.0	0.0105	102.3	0.0511	22.8	0.0114
FS 0013	Cherries	2		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0060
VP 0526	Common bean (pods and/or immature seeds)	0.5		3.5	0.0018	0.8	0.0004	0.0	0.0000	4.0	0.0020	12.0	0.0060
VC 0424	Cucumber	0.5		4.8	0.0024	4.5	0.0023	0.0	0.0000	8.3	0.0041	9.0	0.0045
FS 0245	Nectarine	1		1.3	0.0013	0.3	0.0003	0.0	0.0000	0.4	0.0004	6.3	0.0063
GC 0647	Oats	0.1	(*)	0.0	0.0000	0.0	0.0000	0.2	0.0000	0.8	0.0001	2.0	0.0002
FS 0247	Peach	1		1.3	0.0013	0.3	0.0003	0.0	0.0000	0.4	0.0004	6.2	0.0062
SO 0697	Peanut	0.1	(*)	0.3	0.0000	0.2	0.0000	2.3	0.0002	0.3	0.0000	3.0	0.0003
FS 0014	Plums (including Prunes)	2		1.8	0.0035	0.5	0.0010	0.0	0.0000	0.0	0.0000	4.3	0.0086
FP 0009	Pome fruits	2		10.8	0.0215	7.5	0.0150	0.3	0.0005	6.5	0.0130	51.3	0.1026
GC 0650	Rye	0.1	(*)	0.0	0.0000	1.0	0.0001	0.0	0.0000	0.0	0.0000	1.5	0.0002
GC 0654	Wheat	0.1	(*)	327.3	0.0327	114.8	0.0115	28.3	0.0028	116	0.0117	178.0	0.0178
			TOTAL =		0.0715		0.0439		0.0141		0.0828		0.1735
			% ADI =		12%		8%		2%		14%		29%
			ROUNDED % ADI =		10%		8%		2%		10%		30%

CARBENDAZIM (072)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.03 mg/kg body weight or 1.800 mg/person

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FI 0327	Banana	0.2	0.03	1	B	0.03	8.3	0.0002	26.2	0.0008	21.0	0.0006	102.3	0.0031	22.8	0.0007
GC 0640	Barley	0.5	0.05	1	C	0.05	1.0	0.0001	3.5	0.0002	1.8	0.0001	6.5	0.0003	19.8	0.0010
VD 0071	Beans (dry)	0.5	0.165	1	T	0.165	6.8	0.0011	6.8	0.0011	0.0	0.0000	13.5	0.0022	4.3	0.0007
VB 0402	Brussels sprouts	0.5	0.065	1	B	0.065	0.5	0.0000	1.0	0.0001	0.0	0.0000	1.1	0.0001	2.7	0.0002
VR 0577	Carrot	0.2	0.04	1	B	0.04	2.8	0.0001	2.5	0.0001	0.0	0.0000	6.3	0.0003	22.0	0.0009
MM 0812	Cattle meat	0.05	0	1	(*) B	0	18.5	0.0000	3.5	0.0000	10.4	0.0000	30.0	0.0000	63.3	0.0000
VC 0424	Cucumber	0.05	0.03	1	(*) B	0.03										
VC 0424	Cucumber	0.05	0.05	1	(*) C	0.05	2.4	0.0001	2.3	0.0001	0.0	0.0000	4.1	0.0002	4.5	0.0002
MO 0105	Edible offal (mammalian)	0.05	0	1	(*) B	0	4.2	0.0000	1.4	0.0000	2.4	0.0000	6.1	0.0000	12.4	0.0000
PE 0112	Eggs	0.05	0	1	B	0	14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
VP 0529	Garden pea, shelled	0.02	0.01	1	T	0.01	4.0	0.0000	0.5	0.0000	0.0	0.0000	0.2	0.0000	10.1	0.0001
VC 0425	Gherkin	0.05	0.03	1	B	0.03										
VC 0425	Gherkin	0.05	0.05	1	C	0.05	2.4	0.0001	2.3	0.0001	0.0	0.0000	4.1	0.0002	4.5	0.0002
FB 0269	Grapes	3	0.87	1	T	0.870	15.8	0.0137	1.0	0.0009	0.0	0.0000	1.3	0.0011	13.8	0.0120
FB 0269	Grapes	3	0.84	1	B	0.84										
ML 0106	Milks	0.05	0	1	(*) B	0	116.8	0.0000	32.0	0.0000	41.8	0.0000	160.0	0.0000	294.0	0.0000
FC 0004	Oranges, Sweet, Sour	1	0.325	1	B	0.325	31.5	0.0102	4.0	0.0013	4.8	0.0016	31.0	0.0101	29.8	0.0097
FJ 0004	Orange juice		0.13	1	B	0.3	29.2	0.0088	4.0	0.0012	4.8	0.0015	1.2	0.0004	18.0	0.0054
FS 0247	Peach	2	0.255	1	B	0.255	2.5	0.0006	0.5	0.0001	0.0	0.0000	0.8	0.0002	12.5	0.0032
FI 0393	Pineapple	5	0.03	1	B	0.03	0.0	0.0000	9.3	0.0003	2.6	0.0001	15.5	0.0005	1.3	0.0390
FS 0014	Plums (including prunes)	0.5	0.06	1	B	0.06	1.8	0.0001	0.5	0.0000	0.0	0.0000	0.0	0.0000	3.8	0.0002
FP 0009	Pome fruits	3	0.6	1	B	0.60	10.8	0.0065	7.5	0.0045	0.3	0.0002	6.5	0.0039	51.3	0.0308
FP 0009	Pome fruits	3	0.555	1	T	0.555										
FP 0009	Pome Fruits	3	0.455	1	C	0.455										
PM 0110	Poultry meat	0.05	0	1	(*) B	0	31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
SO 0697	Rape seed	0.05	0	1	(*) C	0	0.3	0.0000	0.2	0.0000	2.3	0.0000	0.3	0.0000	3.0	0.0000
CM 0649	Rice, husked	2	0.05	1	B	0.05	48.8	0.0024	279.3	0.0140	103.4	0.0052	86.5	0.0043	11.8	0.0006
VO 0448	Tomato	0.5	0.045	1	B	0.045										
VO 0448	Tomato	0.5	0.16	1	C	0.16	81.5	0.0130	7.0	0.0011	16.5	0.0026	25.5	0.0041	66.0	0.0106
GC 0654	Wheat	0.05	0.01	1	T	0.01										
GC 0654	Wheat	0.05	0.03	1	B	0.03	327.3	0.0098	114.8	0.0034	28.3	0.0009	116.8	0.0035	178.0	0.0053
						TOTAL =		0.0668		0.0285		0.012		0.0313		0.0811
						% ADI =		4%		2%		1%		2%		5%

1/ Residues resulting from the use of benomyl, carbendazim and thiophanate-methyl are considered together as carbendazim and compared to its ADI.

2/ For commodities with STMRs for more than one compound, the highest STMR (underlined) was used for the dietary intake calculation.

C = Residues of carbendazim arising from the use of carbendazim

B = Residues of carbendazim and benomyl expressed as carbendazim arising from the use of benomyl

T = Residues of carbendazim and thiophanate-methyl expressed as carbendazim arising from the use of thiophanate-methyl

2,4-D (020)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FB 0018	Berries and other small fruits	0.1	0.05	1	(*)	0.05	0.0	0.0000	16.0	0.0008	1.0	0.0001	0.0	0.0000	1.5	0.0001
MO 0105	Edible offal (mammalian)	10	2.75	1		2.75	4.2	0.0116	1.4	0.0039	2.4	0.0066	6.1	0.0168	12.4	0.0341
PE 0112	Eggs	0.01	0	1	(*)	0	14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
FB 0269	Grapes		0	1		0	15.8	0.0000	1.0	0.0000	0.0	0.0000	1.3	0.0000	13.8	0.0000
FC 0203	Grapefruit	0.1	0.05	1		0.05	1.5	0.0001	0.9	0.0000	0.1	0.0000	3.3	0.0002	2.0	0.0001
GC 0645	Maize	0.05	0.01	1	(*)	0.01	16.5	0.0002	0.0	0.0000	0.0	0.0000	1.5	0.0000	0.0	0.0000
CF 01255	Maize flour		0.01	1		0.01	31.8	0.0003	31.2	0.0003	106.2	0.0011	40.3	0.0004	8.8	0.0001
MM 0095	Meat	0.2	0.125	1	1/	0.125	37.0	0.0046	32.8	0.0041	23.8	0.0030	47.0	0.0059	155.5	0.0194
ML 0106	Milks	0.1	0.043	1		0.043	116.8	0.0050	32.0	0.0014	41.8	0.0018	160.0	0.0069	294.0	0.0126
FC 0004	Oranges, Sweet, Sour	0.1	0.05	1		0.05	31.5	0.0016	4.0	0.0002	4.8	0.0002	31.0	0.0016	29.8	0.0015
JF 0004	Orange juice concentrated		0.02	1	2/	0.02	7.3	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	4.5	0.0001
FP 0009	Pome fruits	0.01	0	1	(*)	0	10.8	0.0000	7.5	0.0000	0.3	0.0000	6.5	0.0000	51.3	0.0000
VR 0589	Potato	0.2	0.05	1		0.05	59.0	0.0030	19.2	0.0010	20.6	0.0010	40.8	0.0020	240.8	0.0120
PM 0110	Poultry meat	0.05	0	1	(*)	0	31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
PO 0111	Poultry, edible offal of	0.05	0	1	(*)	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
CM 0649	Rice, husked	0.1	0.01	1		0.01	48.8	0.0005	279.3	0.0028	103.4	0.0010	86.5	0.0009	11.8	0.0001
GC 0650	Rye	2	0.22	1		0.22	0.0	0.0000	1.0	0.0002	0.0	0.0000	0.0	0.0000	1.5	0.0003
GC 0651	Sorghum	0.01	0.01	1		0.01	2.0	0.0000	9.7	0.0001	26.6	0.0003	0.0	0.0000	0.0	0.0000
VD 0541	Soya bean (dry)	0.01	0	1	(*)	0	4.5	0.0000	2.0	0.0000	0.5	0.0000	0.0	0.0000	0.0	0.0000
FS 0012	Stone fruits	0.05	0	1	(*)	0	0.0	0.0000	7.5	0.0000	1.0	0.0000	0.0	0.0000	0.8	0.0000
GS 0659	Sugar cane	0.02	0.01	1		0.01	18.5	0.0002	7.3	0.0001	15.9	0.0002	3.5	0.0000	0.0	0.0000
VO 0447	Sweet corn (corn-on-the- cob)	0.05	0.05	1	(*)	0.05	0.0	0.0000	0.0	0.0000	4.4	0.0002	0.0	0.0000	8.3	0.0004
TN 0085	Tree nuts	0.2	0.05	1		0.05	1.0	0.0001	13.5	0.0007	3.4	0.0002	17.5	0.0009	3.8	0.0002
GC 0654	Wheat	2	0.22	1		0.22	4.3	0.0009	0.8	0.0002	0.0	0.0000	4.8	0.0010	2.3	0.0005
CF 0654	Wheat bran		0.803	1		0.803	0.1	0.0001	0.1	0.0001	0.1	0.0001	0.1	0.0001	0.1	0.0001
CF 1211	Wheat flour		0.024	1		0.024	323.0	0.0078	114.0	0.0027	28.3	0.0007	112.0	0.0027	175.8	0.0042
						TOTAL =		0.0359		0.0185		0.0164		0.0393		0.0859
						% ADI =		6%		3%		3%		7%		14%

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
						ROUNDED % ADI =		6%		3%		3%		7%		10%

1/ Except marine mammals   2/ Based on STMR for orange juice of 0.005 mg/kg and a concentration factor of 4: 1

DICLORAN (083)

INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VR 0577	Carrot	15	6.11	1		6.11	2.8	0.0168	2.5	0.0153	0.0	0.0000	6.3	0.0382	22.0	0.1344
VA 0385	Onion, Bulb	0.2	0.1	1		0.1	23.0	0.0023	11.5	0.0012	7.3	0.0007	13.8	0.0014	27.8	0.0028
						TOTAL =		0.0191		0.0164		0.0007		0.0396		0.1372
						% ADI =		3%		3%		0%		7%		23%
						ROUNDED % ADI =		3%		3%		0%		7%		20%

DIMETHOATE (027)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.002 mg/kg body weight or 0.120 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VS 0621	Asparagus	0.05	0.02				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0000
VS 0621	Asparagus		0.02	10	1/	0.2	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0003
GC 0640	Barley	2	0.26				1.0	0.0003	3.5	0.0009	1.8	0.0005	6.5	0.0017	19.8	0.0051
GC 0640	Barley		0.015	10	1/	0.15	1.0	0.0002	3.5	0.0005	1.8	0.0003	6.5	0.0010	19.8	0.0030
VB 0402	Brussels sprouts	1	0.065				0.5	0.0000	1.0	0.0001	0.0	0.0000	1.1	0.0001	2.7	0.0002
VB 0402	Brussels sprouts		0.03	10	1/	0.3	0.5	0.0002	1.0	0.0003	0.0	0.0000	1.1	0.0003	2.7	0.0008
VB 0041	Cabbages, head	2	0.46				4.5	0.0021	8.7	0.0040	0.0	0.0000	9.5	0.0043	24.1	0.0111
VB 0041	Cabbages, head		0.165	10	1/	1.65	4.5	0.0074	8.7	0.0144	0.0	0.0000	9.5	0.0156	24.1	0.0397
VB 0403	Cabbages, Savoy	0.05	0.02		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VB 0403	Cabbages, Savoy		0.175	10	1/	1.75	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002
MO 0812	Cattle, edible offal of	0.05	0		(*)		2.5	0.0000	0.3	0.0000	1.8	0.0000	5.0	0.0000	6.0	0.0000
VB 0404	Cauliflower	0.5	0.065				1.3	0.0001	1.5	0.0001	0.0	0.0000	0.3	0.0000	13.0	0.0008
VB 0404	Cauliflower		0.01	10	1/	0.1	1.3	0.0001	1.5	0.0002	0.0	0.0000	0.3	0.0000	13.0	0.0013
FS 0013	Cherries	2	0.06				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0002
FS 0013	Cherries		0.27	10	1/	2.7	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0081
PE 0112	Eggs	0.05	0		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
FB 0269	Grapes	2	0.48				15.8	0.0076	1.0	0.0005	0.0	0.0000	1.3	0.0006	13.8	0.0066
FB 0269	Grapes		0.11	10	1/	1.1	15.8	0.0173	1.0	0.0011	0.0	0.0000	1.3	0.0014	13.8	0.0151
VL 0482	Lettuce, head	0.5	0.02				2.3	0.0000	0.0	0.0000	0.0	0.0000	5.8	0.0001	22.5	0.0005
VL 0482	Lettuce, head		0.03	10	1/	0.3	2.3	0.0007	0.0	0.0000	0.0	0.0000	5.8	0.0017	22.5	0.0068
MF 0100	Mammalian fats	0.05	0		(*)		0.7	0.0000	1.7	0.0000	0.7	0.0000	4.4	0.0000	7.6	0.0000
MF 0100	Mammalian fats		0	10	1/	0	0.7	0.0000	1.7	0.0000	0.7	0.0000	4.4	0.0000	7.6	0.0000
MM 0096	Meat of cattle, goats, horses, pigs & sheep	0.05	0		(*)		34.0	0.0000	32.0	0.0000	17.5	0.0000	44.3	0.0000	150.3	0.0000
MM 0096	Meat of cattle, goats, horses, pigs & sheep		0	10	1/	0	34.0	0.0000	32.0	0.0000	17.5	0.0000	44.3	0.0000	150.3	0.0000
ML 0107	Milk of cattle, goats & sheep	0.05	0		(*)		114.5	0.0000	32.0	0.0000	41.3	0.0000	160.0	0.0000	294.0	0.0000
ML 0107	Milk of cattle, goats & sheep		0	10	1/	0	114.5	0.0000	32.0	0.0000	41.3	0.0000	160.0	0.0000	294.0	0.0000
VA 0385	Onion, bulb	0.05	0.02		(*)		23.0	0.0005	11.5	0.0002	7.3	0.0001	13.8	0.0003	27.8	0.0006
VA 0385	Onion, bulb		0.02	10	1/	0.2	23.0	0.0046	11.5	0.0023	7.3	0.0015	13.8	0.0028	27.8	0.0056
FP 0009	Pome fruits	0.5	0.07				10.8	0.0008	7.5	0.0005	0.3	0.0000	6.5	0.0005	51.3	0.0036
FP 0009	Pome fruits		0.05	10	1/	0.5	10.8	0.0054	7.5	0.0038	0.3	0.0001	6.5	0.0033	51.3	0.0257
VP 0063	Peas	1	0.065				5.5	0.0004	0.7	0.0000	0.0	0.0000	0.2	0.0000	10.1	0.0007
VP 0063	Peas		0.02	10	1/	0.2	5.5	0.0011	0.7	0.0001	0.0	0.0000	0.2	0.0000	10.1	0.0020
FS 0014	Plums (including prunes)	1	0.1				1.8	0.0002	0.5	0.0001	0.0	0.0000	0.0	0.0000	4.3	0.0004
FS 0014	Plums (including Prunes)		0.05	10	1/	0.5	1.8	0.0009	0.5	0.0003	0.0	0.0000	0.0	0.0000	4.3	0.0022
VR 0589	Potato	0.05	0.01				59.0	0.0006	19.2	0.0002	20.6	0.0002	40.8	0.0004	240.8	0.0024
VR 0589	Potato		0.01	10	1/	0.1	59.0	0.0059	19.2	0.0019	20.6	0.0021	40.8	0.0041	240.8	0.0241
PO 0111	Poultry, edible offal of	0.05	0		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
PO 0111	Poultry, edible offal of		0	10	1/	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
PF 0111	Poultry fats	0.05	0		(*)		3.1	0.0000	1.3	0.0000	0.6	0.0000	2.5	0.0000	5.3	0.0000
PF 0111	Poultry fats		0	10	1/	0	3.1	0.0000	1.3	0.0000	0.6	0.0000	2.5	0.0000	5.3	0.0000
PM 0110	Poultry meat	0.05	0		(*)		31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
PM 0110	Poultry meat		0	10	1/	0	31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
MO 0822	Sheep, edible offal of	0.05	0		(*)		1.3	0.0000	0.0	0.0000	0.5	0.0000	0.0	0.0000	1.3	0.0000
MO 0822	Sheep, edible offal of		0	10	1/	0	1.3	0.0000	0.0	0.0000	0.5	0.0000	0.0	0.0000	1.3	0.0000
GC 0651	Sorghum	0.01	0.01		(*)		2.0	0.0000	9.7	0.0001	26.6	0.0003	0.0	0.0000	0.0	0.0000
GC 0651	Sorghum		0.01	10	1/	0.1	2.0	0.0002	9.7	0.0010	26.6	0.0027	0.0	0.0000	0.0	0.0000

	Commodity	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VR 0596	Sugar beet	0.05	0.01				0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
VR 0596	Sugar beet		0.01	10	1/	0.1	0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
VO 0448	Tomato	2	0.21				44.1	0.0093	5.7	0.0012	14.6	0.0031	25.5	0.0054	42.2	0.0089
VO 0448	Tomato		0.05	10	1/	0.5	44.1	0.0221	5.7	0.0029	14.6	0.0073	25.5	0.0128	42.2	0.0211
VJ 0448	Tomato juice		0.03			0.03	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0001
VJ 0448	Tomato juice		0.009	10	1/	0.09	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0002
	Tomato paste		0.6			0.6	5.8	0.0035	0.2	0.0001	0.3	0.0002	0.0	0.0000	4.0	0.0024
	Tomato paste		0.07	10	1/	0.7	5.8	0.0040	0.2	0.0001	0.3	0.0002	0.0	0.0000	4.0	0.0028
VR 0506	Turnip, garden	0.1	0.1				0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
VR 0506	Turnip, garden		0.1	10	1/	1	0.5	0.0005	0.0	0.0000	0.0	0.0000	0.3	0.0003	2.0	0.0020
GC 0654	Wheat	0.2	0.09				327.3	0.0295	114.8	0.0103	28.3	0.0026	116.8	0.0105	178.0	0.0160
GC 0654	Wheat		0.01	10	1/	0.1	327.3	0.0327	114.8	0.0115	28.3	0.0028	116.8	0.0117	178.0	0.0178
						TOTAL =		0.1581		0.0587		0.0239		0.0789		0.2384
						% ADI =		132%		49%		20%		66%		199%
						ROUNDED % ADI =		130%		50%		20%		70%		200%

1/ Includes residues of omethoate arising from the use of dimethoate
2/ Residues of omethoate adjusted for their greater toxicity (factor of 10) than those of dimethoate

DINOCAP (087)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.008 mg/kg body weight or 0.480 mg/person

	Commodity	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	0.2	0.05	1		0.05	7.5	0.0004	4.7	0.0002	0.3	0.0000	5.5	0.0003	40.0	0.0020
FB 0269	Grapes	1	0.105	1		0.105	15.8	0.0017	1.0	0.0001	0.0	0.0000	1.3	0.0001	13.8	0.0014
FB 0275	Strawberry	0.5	0.06	1		0.06	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0003
FS 0247	Peach	0.1	0.05	1		0.05	2.5	0.0001	0.5	0.0000	0.0	0.0000	0.8	0.0000	12.5	0.0006
VO 0051	Peppers	0.2	0.06	1		0.06	3.4	0.0002	2.1	0.0001	5.4	0.0003	2.4	0.0001	10.4	0.0006
VC 0045	Fruiting vegetables, cucurbits	0.05	0.05	1	(*)	0.05	80.5	0.0040	18.2	0.0009	0.0	0.0000	30.5	0.0015	38.5	0.0019
						TOTAL =		0.0064		0.0014		0.0003		0.0021		0.0069
						% ADI =		1%		0%		0%		0%		1%

DIPHENYLAMINE (030)   THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.08 mg/kg body weight or 4.800 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name			Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
FP 0226	Apple	5		7.5	0.0375	4.7	0.0233	0.3	0.0013	5.5	0.0275	40.0	0.2000
			TOTAL =		0.0375	4.7	0.0233	0.3	0.0013	5.5	0.0275	40.0	0.2000
			% ADI =		1%		1%		0%		1%		4%

DISULFOTON (074)   DIETARY INTAKE ESTIMATE (DIE)

ADI = 0.0003 mg/kg body weight or 0.018 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VS 0621	Asparagus	0.02		1	1/	0.02	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0000
GC 0640	Barley	0.2	0.02	1		0.02	1.0	0.0000	3.5	0.0001	1.8	0.0000	6.5	0.0001	19.8	0.0004
VD 0071	Beans (dry)	0.2	0.01	1		0.01	6.8	0.0001	6.8	0.0001	0.0	0.0000	13.5	0.0001	4.3	0.0000
VB 0400	Broccoli	0.1	0.025	1		0.025	0.5	0.0000	1.0	0.0000	0.0	0.0000	1.1	0.0000	2.7	0.0001
VB 0041	Cabbages, Head	0.2	0.02	1		0.02	4.5	0.0001	8.7	0.0002	0.0	0.0000	9.5	0.0002	24.1	0.0005
VB 0404	Cauliflower	0.05	0.01	1		0.01	1.3	0.0000	1.5	0.0000	0.0	0.0000	0.3	0.0000	13.0	0.0001
SB 0716	Coffee beans	0.2		0.3	1/ 2/	0.06	5.3	0.0003	0.4	0.0000	0.0	0.0000	3.6	0.0002	7.9	0.0005
VP 0526	Common bean (pods and/or immature seeds)	0.2		1	1/	0.2	3.5	0.0007	0.8	0.0002	0.0	0.0000	4.0	0.0008	12.0	0.0024
SO 0691	Cotton seed	0.1	0.03	1		0.03	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
PE 0840	Eggs, chicken	0.02		1	1/	0.02	14.5	0.0003	13.0	0.0003	3.6	0.0001	11.8	0.0002	37.5	0.0008
VP 0529	Garden pea, shelled	0.02	0.01	1		0.01	5.5	0.0001	0.7	0.0000	0.0	0.0000	0.3	0.0000	14.0	0.0001
VL 0482	Lettuce, Head	1	0.05	1		0.05	2.3	0.0001	0.0	0.0000	0.0	0.0000	5.8	0.0003	22.5	0.0011
VL 0483	Lettuce, Leaf	1	0.11	1		0.11	2.3	0.0002	0.0	0.0000	0.0	0.0000	5.8	0.0006	22.5	0.0025
GC 0645	Maize	0.02	0.01	1	(*)	0.01	16.5	0.0002	0.0	0.0000	0.0	0.0000	1.5	0.0000	0.0	0.0000
CF 1255	Maize flour		0.0025	0.25	3/	0.000625	31.8	0.0000	31.2	0.0000	106.2	0.0001	40.3	0.0000	8.8	0.0000
ML 0107	Milks	0.01		1	1/	0.01	114.5	0.0011	32.0	0.0003	41.3	0.0004	160.0	0.0016	294.0	0.0029
GC 0647	Oats	0.02	0	1		0	0.0	0.0000	0.0	0.0000	0.2	0.0000	0.8	0.0000	2.0	0.0000
SO 0697	Peanut	0.1	0.01	1		0.01	0.3	0.0000	0.2	0.0000	2.3	0.0000	0.3	0.0000	3.0	0.0000
TN 0672	Pecan	0.1	0.01	1		0.01	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000
FI 0353	Pineapple	0.1	0	1		0	0.0	0.0000	0.8	0.0000	10.2	0.0000	3.1	0.0000	15.8	0.0000

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VR 0589	Potato	0.5	0.08	0.44	4/	0.0352	59.0	0.0021	19.2	0.0007	20.6	0.0007	40.8	0.0014	240.8	0.0085
PM 0110	Poultry meat	0.02		1	1/	0.02	31.0	0.0006	13.2	0.0003	5.5	0.0001	25.3	0.0005	53.0	0.0011
VR 0591	Radish, Japanese	0.2	0.025	1		0.025	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
GC 0649	Rice	0.5		1	1/	0.5	48.8	0.0244	279.3	0.1397	103.4	0.0517	86.5	0.0433	11.8	0.0059
GC 0651	Sorghum	1		1	1/	1	2.0	0.0020	9.7	0.0097	26.6	0.0266	0.0	0.0000	0.0	0.0000
GC 0654	Wheat	0.2	0.02	1		0.02	4.3	0.0001	0.8	0.0000	0.0	0.0000	4.8	0.0001	2.3	0.0000
CF 1211	Wheat flour		0.004	0.21		0.00084	323.0	0.0003	114.0	0.0001	28.3	0.0000	112.0	0.0001	175.8	0.0001
						TOTAL =		0.0327		0.1515		0.0798		0.0497		0.0271
						% ADI =		182%		842%		443%		276%		151%
						ROUNDED % ADI =		180%		840%		440%		280%		150%

1/ STMR not determined

2/ Processing factor based on roasting

3/ Processing factor based on milling

4/ Processing factor based on peeling and boiling

ENDOSULFAN (032)   THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.006 mg/kg body weight or 0.360 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name			Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VP 0522	Broad bean (green pods/immature seeds)	0.5		0.4	0.0002	0.1	0.0000	0.0	0.0000	0.4	0.0002	1.2	0.0006
VB 0400	Broccoli	0.5		0.5	0.0003	1.0	0.0005	0.0	0.0000	1.1	0.0005	2.7	0.0013
VB 0041	Cabbages, Head	1		4.5	0.0045	8.7	0.0087	0.0	0.0000	9.5	0.0095	24.1	0.0241
VB 0403	Cabbage, Savoy	2		0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002
SB 0715	Cacao beans	0.1		0.5	0.0001	0.0	0.0000	0.0	0.0000	1.3	0.0001	3.1	0.0003
VR 0577	Carrot	0.2		2.8	0.0006	2.5	0.0005	0.0	0.0000	6.3	0.0013	22.0	0.0044
VB 0404	Cauliflower	0.5		1.3	0.0006	1.5	0.0008	0.0	0.0000	0.3	0.0001	13.0	0.0065
VS 0624	Celery	2		0.5	0.0010	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.0	0.0040
FS 0013	Cherries	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0030
SB 0716	Coffee beans	0.1		5.3	0.0005	0.4	0.0000	0.0	0.0000	3.6	0.0004	7.9	0.0008
VP 0526	Common bean (pods and/or immature seeds)	0.5		3.5	0.0018	0.8	0.0004	0.0	0.0000	4.0	0.0020	12.0	0.0060
OC 0691	Cotton seed oil, crude	0.5		3.8	0.0019	0.5	0.0003	0.5	0.0003	0.5	0.0003	0.0	0.0000

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VC 0424	Cucumber	0.5		4.8	0.0024	4.5	0.0023	0.0	0.0000	8.3	0.0041	9.0	0.0045
VP 0528	Garden pea (young pods)	0.5		5.5	0.0028	0.7	0.0003	0.0	0.0000	0.3	0.0001	14.0	0.0070
FB 0269	Grapes	1		15.8	0.0158	1.0	0.0010	0.0	0.0000	1.3	0.0013	13.8	0.0138
VL 0480	Kale	1		0.5	0.0005	0.0	0.0000	0.0	0.0000	0.3	0.0003	2.0	0.0020
VL 0482	Lettuce, Head	1		1.2	0.0012	0.0	0.0000	0.0	0.0000	2.9	0.0029	22.5	0.0225
VL 0483	Lettuce, Leaf	1		1.1	0.0011	0.0	0.0000	0.0	0.0000	2.9	0.0029	11.3	0.0113
GC 0645	Maize	0.1		48.3	0.0048	31.2	0.0031	106.2	0.0106	41.8	0.0042	11.3	0.0011
MM 0095	Meat	0.1	(fat)	7.4	0.0007	6.6	0.0007	4.8	0.0005	9.4	0.0009	31.1	0.0031
VC 0046	Melons, except Watermelon	0.5		16.0	0.0080	2.0	0.0010	0.0	0.0000	2.8	0.0014	18.3	0.0092
ML 0106	Milks	0.004		116.8	0.0005	32.0	0.0001	41.8	0.0002	160.0	0.0006	294.0	0.0012
VA 0385	Onion, bulb	0.2		23.0	0.0046	11.5	0.0023	7.3	0.0015	13.8	0.0028	27.8	0.0056
FC 0004	Oranges, Sweet, Sour	0.5		31.5	0.0158	4.0	0.0020	4.8	0.0024	31.0	0.0155	29.8	0.0149
FI 0353	Pineapple	2		0.0	0.0000	0.8	0.0015	10.2	0.0203	3.1	0.0062	15.8	0.0315
FS 0014	Plums (including Prunes)	1		1.8	0.0018	0.5	0.0005	0.0	0.0000	0.0	0.0000	4.3	0.0043
FP 0009	Pome fruits	1		10.8	0.0108	7.5	0.0075	0.3	0.0003	6.5	0.0065	51.3	0.0513
VR 0589	Potato	0.2		59.0	0.0118	19.2	0.0038	20.6	0.0041	40.8	0.0082	240.8	0.0482
SO 0495	Rape seed	0.5		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
GC 0649	Rice	0.1		48.8	0.0049	279.3	0.0279	103.4	0.0103	86.5	0.0087	11.8	0.0012
VD 0541	Soya bean (dry)	1		4.5	0.0045	2.0	0.0020	0.5	0.0005	0.0	0.0000	0.0	0.0000
VL 0502	Spinach	2		0.5	0.0010	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.0	0.0040
VC 0431	Squash, Summer	0.5		10.5	0.0053	2.2	0.0011	0.0	0.0000	14.0	0.0070	3.5	0.0018
VR 0596	Sugar beet	0.1		0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
SO 0702	Sunflower seed	1		1.0	0.0010	0.0	0.0000	0.6	0.0006	0.0	0.0000	0.0	0.0000
VR 0508	Sweet potato	0.2		1.5	0.0003	81.3	0.0163	14.3	0.0029	13.8	0.0028	1.3	0.0003
DT 1114	Tea, Green, Black	30		2.3	0.0690	1.2	0.0360	0.5	0.0150	0.5	0.0150	2.3	0.0690
VO 0448	Tomato	0.5		81.5	0.0408	7.0	0.0035	16.5	0.0083	25.5	0.0128	66.0	0.0330
GC 0654	Wheat	0.2		327.3	0.0655	114.8	0.0230	28.3	0.0057	116.8	0.0234	178.0	0.0356
			TOTAL =		0.2860		0.1473		0.0835		0.1428		0.4274
			% ADI =		79%		44%		23%		40%		119%
			ROUNDED % ADI =		80%		40%		20%		40%		120%

ETHOXYQUIN (035)   **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.005 mg/kg body weight or 0.300 mg/person

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	3		7.5	0.0225	4.7	0.0140	0.3	0.0008	5.5	0.0165	40.0	0.1200
FP 0230	Pear	3		3.3	0.0098	2.8	0.0085	0.0	0.0000	1.0	0.0030	11.3	0.0338
			TOTAL =		0.0323		0.0225		0.0008		0.0195		0.1538
			% ADI =		11%		8%		0%		7%		51%
			ROUNDED % ADI =		10%		8%		0%		7%		50%

GLUFOSINATE-AMMONIUM (175)   **DAILY INTAKE ESTIMATE (DIE)**

ADI = 0.02 mg/kg body weight or 1.200 mg/person

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VS 0621	Asparagus	0.05		1	(*)	0.05	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0001
FI 0030	Assorted tropical & subtropical fruits – inedible peel (except Banana)	0.05	0.05	1	(*)	0.05	2.3	0.0001	34.1	0.0017	11.0	0.0006	45.6	0.0023	10.3	0.0005
FI 0327	Banana	0.2		1		0.2	8.3	0.0017	26.2	0.0052	21.0	0.0042	102.3	0.0205	22.8	0.0046
FB 0018	Berries and other small fruits	0.1		1		0.1	0.0	0.0000	16.0	0.0016	1.0	0.0001	0.0	0.0000	1.5	0.0002
VD 0523	Broad bean (dry)	2		1		2	4.5	0.0090	2.0	0.0040	0.0	0.0000	0.5	0.0010	0.8	0.0015
VR 0577	Carrot	0.05		1	(*)	0.05	2.8	0.0001	2.5	0.0001	0.0	0.0000	6.3	0.0003	22.0	0.0011
FC 0001	Citrus fruits	0.1		1		0.1	54.3	0.0054	6.3	0.0006	5.1	0.0005	54.8	0.0055	49.0	0.0049
VD 0526	Common bean (dry)	2		1		2	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002
VP 0526	Common bean (pods and/or immature seeds)	0.05		1	(*)	0.05	3.5	0.0002	0.8	0.0000	0.0	0.0000	4.0	0.0002	12.0	0.0006
VL 0470	Corn salad	0.05		1	(*)	0.05	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FB 0021	Currants, Black, Red, White	0.5		1		0.5	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0002
GC 0645	Maize	0.1		1	(*)	0.1	48.3	0.0048	31.2	0.0031	106.2	0.0106	41.8	0.0042	8.8	0.0009
VA 0385	Onion, bulb	0.05		1		0.05	23.0	0.0012	11.5	0.0006	7.3	0.0004	13.8	0.0007	27.8	0.0014
VD 0072	Peas (dry)	3		1		3	0.5	0.0015	1.7	0.0050	0.0	0.0000	1.3	0.0038	1.8	0.0053
FP 0009	Pome fruits	0.05		1	(*)	0.05	10.8	0.0005	7.5	0.0004	0.3	0.0000	6.5	0.0003	51.3	0.0026
VR 0589	Potato	0.5		1		0.5	59.0	0.0295	19.2	0.0096	20.6	0.0103	40.8	0.0204	240.8	0.1204
SO 0495	Rape seed	5		1		5	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VR 0596	Sugar beet	0.05		1	(*)	0.05	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
VD 0541	Soya bean (dry)	0.1		1		0.1	4.5	0.0005	2.0	0.0002	0.5	0.0001	0.0	0.0000	0.0	0.0000
FS 0012	Stone fruits	0.05		1	(*)	0.05	7.3	0.0004	1.0	0.0001	0.0	0.0000	0.8	0.0000	22.8	0.0011
SO 0702	Sunflower seed	5		1		5	1.0	0.0050	0.0	0.0000	0.6	0.0029	0.0	0.0000	0.0	0.0000
OC 0702	Sunflower seed oil, crude	0.05		1	(*)	0.05	9.3	0.0005	0.5	0.0000	0.3	0.0000	0.8	0.0000	8.5	0.0004
TN 0085	Tree nuts	0.1	0.05	1		0.05	1.0	0.0001	13.5	0.0007	3.4	0.0002	17.5	0.0009	3.8	0.0002
						TOTAL =		0.0606		0.0331		0.0300		0.0602		0.1461
						% ADI =		5%		3%		3%		5%		12%
						ROUNDED % ADI =		5%		3%		3%		5%		10%

HEXYTHIAZOX (176) **DAILY INTAKE ESTIMATE (DIE)**

ADI = 0.03 mg/kg body weight or 1.800 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	0.5		1		0.5	7.5	0.0038	4.7	0.0023	0.3	0.0001	5.5	0.0028	40.0	0.0200
FS 0013	Cherries	1		1		1	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0030
FC 0001	Citrus fruits	0.5		1		0.5	54.3	0.0271	6.3	0.0032	5.1	0.0025	54.8	0.0274	49.0	0.0245
VP 0526	Common bean (pods and/or immature seeds)	0.5		1		0.5	3.5	0.0018	0.8	0.0004	0.0	0.0000	4.0	0.0020	12.0	0.0060
VC 0424	Cucumber	0.1		1		0.1	4.8	0.0005	4.5	0.0005	0.0	0.0000	8.3	0.0008	9.0	0.0009
FB 0279	Currant, Red, White	0.2		1		0.2	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0001
FB 0269	Grapes	1		1		1	15.8	0.0158	1.0	0.0010	0.0	0.0000	1.3	0.0013	13.8	0.0138
DH 1100	Hops, dry	2	0.79	0	1/	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FS 0247	Peach	1		1		1	2.5	0.0025	0.5	0.0005	0.0	0.0000	0.8	0.0008	12.5	0.0125
FP 0230	Pear	0.5		1		0.5	3.3	0.0016	2.8	0.0014	0.0	0.0000	1.0	0.0005	11.3	0.0056
FS 0014	Plums (including Prunes)	0.2		1		0.2	1.8	0.0004	0.5	0.0001	0.0	0.0000	0.0	0.0000	4.3	0.0009
FB 0275	Strawberry	0.5		1		0.5	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0026
VO 0448	Tomato	0.1		1		0.1	81.5	0.0082	7.0	0.0007	16.5	0.0017	25.5	0.0026	66.0	0.0066
						TOTAL =		0.0615		0.0101		0.0043		0.0380		0.0964
						% ADI =		3%		1%		0%		2%		5%

1/ Processing factor based on beer production

HEXACHLOROBENZENE (044) 1/   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.00016 mg/kg body weight or 0.010 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
SO 0697	Peanut	-	0.0072	1		0.0072	0.3	0.0000	0.2	0.0000	2.3	0.0000	0.3	0.0000	3.0	0.0000
OR 0697	Peanut oil, edible	-	0.0281	1		0.0281	0.0	0.0000	1.8	0.0001	3.5	0.0001	0.5	0.0000	1.8	0.0000
						TOTAL =		0.0000		0.0001		0.0001		0.0000		0.0001
						% ADI =		0%		1%		1%		0%		1%

1/ Hexachlorobenzene arising from the use of quintozene (64)
2/ Dietary intake compared to Provisional Tolerable Daily Intake (PTDI) as recommended in "Hexachlorobenzene - Environmental Health Criteria 195", WHO, Geneva (1997)

KRESOXIM-METHYL (199)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.4 mg/kg body weight or 24.000 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
GC 0640	Barley	0.1	0.05	1		0.05	1.0	0.0001	3.5	0.0002	1.8	0.0001	6.5	0.0003	19.8	0.0010
VC 0424	Cucumber	0.05	0.05	1	(*)	0.05	4.8	0.0002	4.5	0.0002	0.0	0.0000	8.3	0.0004	9.0	0.0005
DF 0269	Dried grapes	2	0.32	1		0.32	0.3	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0001	2.3	0.0007
MO 0105	Edible offal (mammalian)	0.05	0.01	1	(*)	0.01	4.2	0.0000	1.4	0.0000	2.4	0.0000	6.1	0.0001	12.4	0.0001
FB 0269	Grapes	1	0.2	1		0.2	15.8	0.0032	1.0	0.0002	0.0	0.0000	1.3	0.0003	13.8	0.0028
MF 0095	Mammalian fats	0.05	0.01	1	(*)	0.01	0.7	0.0000	1.7	0.0000	0.7	0.0000	4.4	0.0000	7.7	0.0001
MM 0095	Meat, mammalian	0.05	0.01	1	(*) 1/	0.01	37.0	0.0004	32.8	0.0003	23.8	0.0002	47.0	0.0005	155.5	0.0016
ML 0106	Milks	0.01	0.002	1	(*)	0.002	116.8	0.0002	32.0	0.0001	41.8	0.0001	160.0	0.0003	294.0	0.0006
FP 0009	Pome fruits	0.2	0.05	1		0.05	10.8	0.0005	7.5	0.0004	0.3	0.0000	6.5	0.0003	51.3	0.0026
PM 0110	Poultry meat	0.05	0.01	1	(*)	0.01	31.0	0.0003	13.2	0.0001	5.5	0.0001	25.3	0.0003	53.0	0.0005
GC 0650	Rye	0.05	0.05	1	(*)	0.05	0.0	0.0000	1.0	0.0001	0.0	0.0000	0.0	0.0000	1.5	0.0001
GC 0654	Wheat	0.05	0.05	1	(*)	0.05	327.3	0.0164	114.8	0.0057	28.3	0.0014	116.8	0.0058	178.0	0.0089
						TOTAL =		0.0214		0.0073		0.0019		0.0084		0.0193
						% ADI =		0%		0%		0%		0%		0%

1/ Except marine mammals

MALEIC HYDRAZIDE (102)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.3 mg/kg body weight or 18.000 mg/person

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VA 0381	Garlic	15	4.3	1		4.3	2.0	0.0086	2.2	0.0093	0.0	0.0000	0.5	0.0022	3.0	0.0129
VA 0385	Onion, bulb	15	4.3	1		4.3	23.0	0.0989	11.5	0.0495	7.3	0.0315	13.8	0.0591	27.8	0.1193
VA 0388	Shallot	15	4.3	1		4.3	0.0	0.0000	2.0	0.0086	1.5	0.0065	4.0	0.0172	1.0	0.0043
VR 0589	Potato	50	11	0.52	1/	5.7	59.0	0.3363	19.2	0.1093	20.6	0.1173	40.8	0.2323	240.8	1.3723
						TOTAL =		0.4438		0.1766		0.1553		0.3108		1.5088
						% ADI =		2%		1%		1%		2%		8%

1/ Processing factor based on boiling

METHIOCARB (132)   THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.02 mg/kg body weight or 1.200 mg/person

Commodity				Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	Notes	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VS 0620	Artichoke globe	0.05	(*)	2.3	0.0001	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.5	0.0003
VB 0400	Broccoli	0.2		0.5	0.0001	1.0	0.0002	0.0	0.0000	1.1	0.0002	2.7	0.0005
VB 0402	Brussels sprouts	0.2		0.5	0.0001	1.0	0.0002	0.0	0.0000	1.1	0.0002	2.7	0.0005
VB 0041	Cabbages, Head	0.2		4.0	0.0008	7.7	0.0015	0.0	0.0000	8.4	0.0017	21.4	0.0043
VB 0404	Cauliflower	0.2		1.3	0.0003	1.5	0.0003	0.0	0.0000	0.3	0.0001	13.0	0.0026
GC 0080	Cereal grains	0.05	(*)	430.8	0.0215	452.3	0.0226	318.4	0.0159	252.5	0.0126	226.3	0.0113
FC 0001	Citrus fruits	0.05	(*)	54.3	0.0027	6.3	0.0003	5.1	0.0003	54.8	0.0027	49.0	0.0025
PE 0112	Eggs	0.05	(*)	14.6	0.0007	13.1	0.0007	3.7	0.0002	11.9	0.0006	37.6	0.0019
TN 0666	Hazelnuts	0.05	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	0.3	0.0000
VL 0482	Lettuce, Head	0.2		2.3	0.0005	0.0	0.0000	0.0	0.0000	5.8	0.0012	22.5	0.0045
VL 0483	Lettuce, Leaf	0.2		2.3	0.0005	0.0	0.0000	0.0	0.0000	5.8	0.0012	22.5	0.0045
MM 0095	Meat	0.05	(*)	37.0	0.0019	32.8	0.0016	23.8	0.0012	47.0	0.0024	155.5	0.0078
ML 0106	Milks	0.05	(*)	116.8	0.0058	32.0	0.0016	41.8	0.0021	160.0	0.0080	294.0	0.0147
PM 0110	Poultry meat	0.05	(*)	31.0	0.0016	13.2	0.0007	5.5	0.0003	25.3	0.0013	53.0	0.0027
SO 0495	Rape seed	0.05	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
VR 0596	Sugar beet	0.05	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
VO 0447	Sweet corn (corn-on-the-cob)	0.05	(*)	0.0	0.0000	0.0	0.0000	4.4	0.0002	0.0	0.0000	8.3	0.0004
			TOTAL =		0.0365		0.0297		0.0201		0.0320		0.0585
			% ADI =		3%		3%		2%		3%		5%

MYCLOBUTANIL (181)   **DAILY INTAKE ESTIMATE (DIE)**

ADI = 0.03 mg/kg body weight or 1.800 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FI 0327	Banana	2	0.15	1		0.15	8.3	0.0012	26.2	0.0039	21.0	0.0032	102.3	0.0153	22.8	0.0034
MM 0812	Cattle meat	0.01		1	(*)	0.01	18.5	0.0002	3.5	0.0000	10.4	0.0001	30.0	0.0003	63.3	0.0006
ML 0812	Cattle milk	0.01		1	(*)	0.01	79.5	0.0008	23.2	0.0002	35.8	0.0004	159.3	0.0016	287.0	0.0029
MO 0812	Cattle, Edible offal of	0.01		1	(*)	0.01	2.5	0.0000	0.3	0.0000	1.8	0.0000	5.0	0.0001	6.0	0.0001
FB 0278	Currant, black	0.5	0.26	1		0.26	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
PE 0112	Eggs	0.01		1	(*)	0.01	14.6	0.0001	13.1	0.0001	3.7	0.0000	11.9	0.0001	37.6	0.0004
FB 0269	Grapes	1		1		1	15.8	0.0158	1.0	0.0010	0.0	0.0000	1.3	0.0013	13.8	0.0138
DH 1100	Hops, dry	2	0.0515	0	1/	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FS 0014	Plums (including prunes)	0.2		1		0.2	1.8	0.0004	0.5	0.0001	0.0	0.0000	0.0	0.0000	4.3	0.0009
FP 0009	Pome fruits	0.5		1		0.5	10.8	0.0054	7.5	0.0038	0.3	0.0001	6.5	0.0033	51.3	0.0257
PM 0110	Poultry meat	0.01		1	(*)	0.01	31.0	0.0003	13.2	0.0001	5.5	0.0001	25.3	0.0003	53.0	0.0005
PO 0111	Poultry, edible offal of	0.01		1	(*)	0.01	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
DF 0014	Prunes	0.5		1		0.5	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0003
FS 0012	Stone fruits	2	0.62	1	2/	0.62	5.5	0.0034	0.5	0.0003	0.0	0.0000	0.8	0.0005	19.0	0.0118
FB 0275	Strawberry	1	0.19	1		0.19	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0010
VO 0448	Tomato	0.3	0.06	1		0.06	44.4	0.0027	5.7	0.0003	14.6	0.0009	25.5	0.0015	48.2	0.0029
	Tomato juice		0.06	0.85		0.05	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0001
	Tomato paste		0.06	0.3		0.02	5.8	0.0001	0.2	0.0000	0.3	0.0000	0.0	0.0000	4.0	0.0001
						TOTAL =		0.0304		0.0100		0.0047		0.0242		0.0642
						% ADI =		2%		1%		0%		1%		4%

1/ Processing factor based on beer production
2/ Except plums

OXYDEMETON-METHYL (166)   **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.0003 mg/kg body weight or 0.018 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	0.05	0.01	1		0.01	10.8	0.0001	7.5	0.0001	0.3	0.0000	6.5	0.0001	51.3	0.0005
GC 0640	Barley	0.05	0.04	1	(*)	0.04	1.0	0.0000	3.5	0.0001	1.8	0.0001	6.5	0.0003	19.8	0.0008
VB 0041	Cabbages, head	0.05	0.03	1	(*)	0.03	5.0	0.0002	9.7	0.0003	0.0	0.0000	10.5	0.0003	26.8	0.0008
MF 0812	Cattle fat	0.05	0	1	(*)	0	0.3	0.0000	0.3	0.0000	0.3	0.0000	1.5	0.0000	0.0	0.0000
VD 0526	Common bean (dry)	0.1	0.01	1		0.01	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
OR 0691	Cotton seed oil, edible		0.002	1		0.002	3.8	0.0000	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
PE 0112	Eggs	0.05	0	1	(*)	0	14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
FB 0269	Grapes	0.1	0.04	1		0.04	15.8	0.0006	1.0	0.0000	0.0	0.0000	1.3	0.0001	13.8	0.0006
VL 0480	Kale	0.01	0.01	1	(*)	0.01	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
VB 0405	Kohlrabi	0.05	0.02	1		0.02	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
FC 0204	Lemon	0.2	0.01	1		0.01	1.9	0.0000	0.2	0.0000	0.0	0.0000	5.4	0.0001	2.4	0.0000
MM 0097	Meat of cattle, pigs and sheep	0.05	0	1	(*)	0	32.0	0.0000	31.3	0.0000	15.0	0.0000	43.5	0.0000	149.3	0.0000
ML 0106	Milks	0.01	0	1	(*)	0	116.8	0.0000	32.0	0.0000	41.8	0.0000	160.0	0.0000	294.0	0.0000
FC 0004	Oranges, sweet, sour	0.2	0.01	1		0.01	31.5	0.0003	4.0	0.0000	4.8	0.0000	31.0	0.0003	29.8	0.0003
FP 0230	Pear	0.05	0.01	1		0.01	3.3	0.0000	2.8	0.0000	0.0	0.0000	1.0	0.0000	11.3	0.0001
MF 0818	Pig fat	0.05	0	1	(*)	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VR 0589	Potato	0.05	0.02	1	(*)	0.02	59.0	0.0012	19.2	0.0004	20.6	0.0004	40.8	0.0008	240.8	0.0048
PF 0111	Poultry fats	0.05	0	1	(*)	0	3.1	0.0000	1.3	0.0000	0.6	0.0000	2.5	0.0000	5.3	0.0000
PM 0110	Poultry meat	0.05	0	1	(*)	0	31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
GC 0650	Rye	0.05	0.04	1	(*)	0.04	0.0	0.0000	1.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0001
MF 0822	Sheep fat	0.05	0	1	(*)	0	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VR 0596	Sugar beet	0.05	0.04	1	(*)	0.04	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
GC 0654	Wheat	0.05	0.04	1	(*)	0.04	327.3	0.0131	114.8	0.0046	28.3	0.0011	116.8	0.0047	178.0	0.0071
						TOTAL =		0.0156		0.0056		0.0017		0.0066		0.0152
						% ADI =		87%		31%		9%		37%		85%
						ROUNDED % ADI =		90%		30%		9%		40%		80%

PHOSMET (103)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	10	3.4	1		3.4	7.5	0.0255	4.7	0.0159	0.3	0.0009	5.5	0.0187	40.0	0.1360
FS 0240	Apricot	10	2.9	1		2.9	3.0	0.0087	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.5	0.0102
SO 0691	Cotton seed	0.05	0	1		0	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
FB 0269	Grapes	10	3.1	1		3.1	15.8	0.0488	1.0	0.0031	0.0	0.0000	1.3	0.0039	13.8	0.0426
FS 0247	Peach	10	2.9	1		2.9	2.5	0.0073	0.5	0.0015	0.0	0.0000	0.8	0.0022	12.5	0.0363
VR 0589	Potato	0.05	0.05	1	(*)	0.05	59.0	0.0030	19.2	0.0010	20.6	0.0010	40.8	0.0020	240.8	0.0120
						TOTAL =		0.0932		0.0214		0.0019		0.0268		0.2371
						% ADI =		16%		4%		0%		4%		40%
						ROUNDED % ADI =		20%		4%		0%		4%		40%

PROCYMIDONE (136)   DAILY INTAKE ESTIMATE (DIE)

ADI = 0.1 mg/kg body weight or 6.000 mg/person

Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VB 0041	Cabbages, Head	2	0.26	1		0.26	5.0	0.0013	9.7	0.0025	0.0	0.0000	10.5	0.0027	26.8	0.0070
VB 0404	Cauliflower	2	0.05	1		0.05	1.3	0.0001	1.5	0.0001	0.0	0.0000	0.3	0.0000	13.0	0.0007
VP 0526	Common bean	1		1	1/	1	3.5	0.0035	0.8	0.0008	0.0	0.0000	4.0	0.0040	12.0	0.0120
FS 0013	Cherries	10		1	1/	10	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0300
VC 0424	Cucumber	2		1	1/	2	2.4	0.0048	2.3	0.0045	0.0	0.0000	4.1	0.0083	4.5	0.0090
VP 0528	Garden pea (young pods)	3	0.6	1		0.6	5.5	0.0033	0.7	0.0004	0.0	0.0000	0.3	0.0002	14.0	0.0084
VP 0528	Garden pea, shelled	1	0.08	1		0.08	5.5	0.0004	0.7	0.0001	0.0	0.0000	0.3	0.0000	14.0	0.0011
VC 0425	Gherkin	2		1	1/	2	2.4	0.0048	2.3	0.0045	0.0	0.0000	4.1	0.0083	4.5	0.0090
FB 0269	Grapes	5		1	1/	5	15.8	0.0788	1.0	0.0050	0.0	0.0000	1.3	0.0063	13.8	0.0688
VL 0482	Lettuce, Head	5		1	1/	5	2.3	0.0113	0.0	0.0000	0.0	0.0000	5.8	0.0288	22.5	0.1125
VA 0385	Onion, bulb	0.2		1	1/	0.2	23.0	0.0046	11.5	0.0023	7.3	0.0015	13.8	0.0028	27.8	0.0056
FS 0247	Peach	2	0.7	1		0.7	2.5	0.0018	0.5	0.0004	0.0	0.0000	0.8	0.0005	12.5	0.0088
FP 0230	Pear	1	0.43	1		0.43	3.3	0.0014	2.8	0.0012	0.0	0.0000	1.0	0.0004	11.3	0.0048
VO 0051	Peppers	5		1	1/	5	3.4	0.0170	2.1	0.0105	5.4	0.0270	2.4	0.0120	10.4	0.0520
FS 0014	Plums (including prunes)	2	0.74	1		0.74	1.8	0.0013	0.5	0.0004	0.0	0.0000	0.0	0.0000	4.3	0.0032
FB 0272	Raspberries, red, black	10		1	1/	10	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0050
FB 0275	Strawberry	10		1	1/	10	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0525

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
SO 0702	Sunflower seed	0.2		1	1/	0.2	1.0	0.0002	0.0	0.0000	0.6	0.0001	0.0	0.0000	0.0	0.0000
OR 0702	Sunflower seed oil, edible	0.5		1	1/	0.5	9.3	0.0046	0.5	0.0003	0.3	0.0001	0.8	0.0004	8.5	0.0043
VO 0448	Tomato	5		1	1/	5	81.5	0.4075	7.0	0.0350	16.5	0.0825	25.5	0.1275	66.0	0.3300
						TOTAL =		0.5465		0.0679		0.1112		0.2020		0.7244
						% ADI =		9%		1%		2%		3%		12%
	1/ STMR not determined					ROUNDED % ADI =		9%		1%		2%		3%		10%

QUINTOZENE (064)   INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.01 mg/kg body weight or 0.600 mg/person

Commodity						Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
GC 0640	Barley	0.01	0.005	1	(*)	0.005	1.0	0.0000	3.5	0.0000	1.8	0.0000	6.5	0.0000	19.8	0.0001
VB 0400	Broccoli	0.05	0.0585	1		0.0585	0.5	0.0000	1.0	0.0001	0.0	0.0000	1.1	0.0001	2.7	0.0002
VB 0041	Cabbages, Head	0.1	0.0052	1		0.0052	4.5	0.0000	8.7	0.0000	0.0	0.0000	9.5	0.0000	24.1	0.0001
PO 0840	Chicken, edible offal of	0.1	0.03	1	(*)	0.03	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	0.3	0.0000
PM 0840	Chicken meat	0.1	0.04	1	(*) fat	0.04	3.1	0.0001	1.2	0.0000	0.6	0.0000	2.5	0.0001	4.4	0.0002
VP 0526	Common bean	0.1	0.0342	1		0.0342	3.5	0.0001	0.8	0.0000	0.0	0.0000	4.0	0.0001	12.0	0.0004
VD 0526	Common bean (dry)	0.02	0.002	1		0.002	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
SO 0691	Cotton seed	0.01	0.016	1		0.016	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
PE 0112	Eggs	0.03	0.01	1	(*)	0.01	14.6	0.0001	13.1	0.0001	3.7	0.0000	11.9	0.0001	37.6	0.0004
GC 0645	Maize	0.01	0.005	1	(*)	0.005	48.3	0.0002	31.2	0.0002	106.2	0.0005	41.8	0.0002	8.8	0.0000
SO 0697	Peanut	0.5	0.353	1		0.353	0.3	0.0001	0.2	0.0001	2.3	0.0008	0.3	0.0001	3.0	0.0011
VD 0072	Peas (dry)	0.01	0.005	1		0.005	0.5	0.0000	1.7	0.0000	0.0	0.0000	1.3	0.0000	1.8	0.0000
VO 0445	Peppers, Sweet	0.05	0.05	1	(*)	0.05	3.3	0.0002	2.0	0.0001	5.3	0.0003	2.3	0.0001	10.3	0.0005
VR 0596	Sugar beet	0.01	0.005	1	(*)	0.005	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
VD 0541	Soya beans (dry)	0.05	0.005	1		0.005	4.5	0.0000	2.0	0.0000	0.5	0.0000	0.0	0.0000	0.0	0.0000
VO 0448	Tomato	0.02	0.002	1		0.002	81.5	0.0002	7.0	0.0000	16.5	0.0000	25.5	0.0001	66.0	0.0001
GC 0654	Wheat	0.01	0.005	1		0.005	327.3	0.0016	114.8	0.0006	28.3	0.0001	116.8	0.0006	178.0	0.0009
						TOTAL =		0.0028		0.0012		0.0019		0.0016		0.0040
						% ADI =		0%		0%		0%		0%		1%