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<sup>1</sup>See Section 2.2

<sup>2</sup>T = Toxicology

\* New compound

R = Residue and analytical aspects\*\* Evaluation in CCPR periodic review programme

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**1996 JOINT MEETING OF THE FAO PANEL OF EXPERTS ON  
PESTICIDE RESIDUES IN FOOD AND THE ENVIRONMENT  
AND THE WHO CORE ASSESSMENT GROUP**

Rome, 16-25 September 1996

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### ABBREVIATIONS WHICH MAY BE USED

Ache	acetylcholinesterase
ADI	acceptable daily intake
AFI(D)	alkali flame-ionization (detector)
ai	active ingredient
ALAT	alanine aminotransferase
	approx. approximate
ASAT	aspartate aminotransferase
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
bw	body weight
(not b.w.)	
c	centi- (x 10 <sup>-2</sup> )
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
ChE	cholinesterase
CNS	central nervous system
cv	coefficient of variation
CXL	Codex Maximum Residue Limit (Codex MRL). See MRL.
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-)
DP	dustable powder
DS	powder for dry seed treatment
EBDC	ethylenebis(dithiocarbamate)
EC	(1) emulsifiable concentrate
(2)	electron-capture [chromatographic detector]
ECD	electron-capture detector
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
ERL	extraneous residue limit
ETU	ethylenethiourea
F <sub>1</sub>	filial generation, first
F <sub>2</sub>	filial generation, second
f.p.	freezing point
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration

## Abbreviations

FID	flame-ionization detector
FPD	flame-photometric detector
g (not gm)	gram
̂g	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography - mass spectrometry
G.I.	gastrointestinal
GL	guideline level
GLC	gas-liquid chromatography
GLP	Good Laboratory Practice
GPC	gel-permeation chromatography
GSH	glutathione
h (not hr)	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography - mass spectrometry
IBT	Industrial Bio-Test Laboratories
i.d.	internal diameter
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IR	infrared
IRDC	International Research and Development Corporation (Mattawan, Michigan, USA)
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 <sub>50</sub>	lethal concentration, 50%
LC-MS	liquid chromatography - mass spectrometry
LD <sub>50</sub>	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
MFO	mixed function oxidase
̂m	micrometre (micron)
min	minute(s)

MLD	minimum lethal dose
M	molar
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
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NCI	National Cancer Institute (United States)
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NP(D)	nitrogen-phosphorus (detector)
NTE	neuropathy target esterase
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
s.c.	subcutaneous
SC	suspension concentrate (= flowable concentrate)
SD	standard deviation
SE	standard error
SG	water-soluble granule
SL	soluble concentrate
SP	water-soluble powder
sp./spp.	species (only after a generic name)
sp gr (not sp. gr.)	specific gravity
STMR	supervised trials median residue
t	tonne (metric ton)

## Abbreviations

T <sub>3</sub>	tri-iodothyronine
T <sub>4</sub>	thyroxine
TADI	Temporary Acceptable Daily Intake
<i>tert</i>	tertiary (in a chemical name)
TLC	thin-layer chromatography
TMDI	theoretical maximum daily intake
TMRL	Temporary Maximum Residue Limit
TPTA	triphenyltin acetate
TPTH	triphenyltin hydroxide
TSH	thyroid-stimulating hormone (thyrotropin)
UDMH	1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine)
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet
v/v	volume ratio (volume per volume)
WG	water-dispersible granule
WHO	World Health Organization
WP	wettable powder
wt/vol	weight per volume
w/w	weight ratio (weight per weight)
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to
*	(following residue levels, e.g. 0.01* mg/kg): level at or about the limit of determination



## **PESTICIDE RESIDUES IN FOOD**

### **REPORT OF THE 1996 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 (JMPR) was held in Rome, Italy, from 16 to 25 September 1996. The FAO Panel of Experts had met in preparatory sessions on 11-14 September.

The Meeting was opened by Dr. A. Sawadogo, Assistant Director-General of FAO, and Dr. F. Riveros, Chief of the Crop and Grassland Service of FAO, on behalf of the Directors-General of FAO and WHO.

The opening address recalled that maximum residue limits for pesticide residues in food were recommended for the first time by the Joint FAO/WHO Meeting on Pesticide Residues thirty years ago, and noted a number of salient features of the development of the work of the Joint Meeting since that time.

In the context of current work, the importance of the recent development of methods for estimating more accurately the dietary intake of pesticide residues was stressed. These methods were being applied by the Joint Meeting to facilitate and improve the annual calculations of dietary intakes undertaken by WHO.

A further important aspect of the application of pesticides was the possible risk to the environment from their use. This had been recognised by the inclusion in the Joint Meeting held in Geneva last year of the Environmental Core Assessment Group. Further elaboration of the principle of joint assessment by this Group and the FAO Panel should be encouraged and it was to be hoped that every effort would be made to hold Joint Meetings of all three groups, the Toxicological and Environmental Core Assessment Groups and the FAO Panel, in the future.

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

During the Meeting the FAO Panel of Experts was responsible for reviewing residue and analytical aspects of the pesticides considered, 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 Toxicological Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides. The recommendations of the Joint Meeting, including those for further research and the provision of additional information, are proposed for use by national governments, international organizations and other interested parties.

The Joint Meeting was saddened to hear of the recent deaths of two former Members of the WHO Expert Group, Professor W. Almeida, University of Campinas, Campinas, S<sub>o</sub> Paulo, and Professor U.G. Ahlborg, Karolinska Institute, Stockholm. Both made significant contributions to the science of toxicology and to the work of the JMPR, which are gratefully acknowledged. They will be missed.

## **2. GENERAL CONSIDERATIONS**

### **2.1 MODIFICATIONS TO THE AGENDA**

The re-evaluation of residue and analytical aspects of phosmet within the CCPR periodic review programme was postponed until 1997 at the request of the manufacturer.

### **2.2 PREDICTION OF DIETARY INTAKE**

#### **2.2.1 Revised guidelines for predicting the dietary intake of pesticide residues**

The WHO Secretariat reviewed the development of methods for predicting the dietary intake of pesticide residues. The revision of existing guidelines (WHO, 1989) was the subject of an FAO/WHO Consultation held 2-6 May 1995 in York, United Kingdom. The report of that Consultation (WHO/FNU/FOS/95.11) contained recommendations for improving estimates of dietary intake, most notably the use of supervised trials median residue (STMR) levels in lieu of MRLs in the calculation of International Estimated Daily Intakes (IEDIs). The Consultation also recommended a method for assessing acute hazards posed by the consumption of large portions of food containing pesticide residues. The report was considered at the twenty-eighth Session of the CCPR, which agreed (ALINORM 97/24, para 23) that the draft revised guidelines be included on the agenda for their Session in 1997. The draft revised guidelines will be available in English, French and Spanish to governments before that time.

The WHO Secretariat provided a draft of the revised guidelines to the JMPR and requested comment on the inclusion of the National Theoretical Maximum Daily Intakes (TMDIs), which parallel the international intake assessments. The Meeting agreed that, conceptually, this would be useful, particularly for developing countries; however, it also emphasized that when information was available a best estimate of intake should be derived, using the IEDI method. The Meeting endorsed the report of the York Consultation and noted that many of the recommendations had already been implemented by the JMPR.

The Meeting was also informed of the report of an FAO Panel Workshop held in The Hague in April 1996, where integration of the recommendations of the York Consultation into the work of the JMPR was discussed. Further details of the recommendations of the Workshop are given in Section 2.2.3.

The WHO Secretariat also reported on planning for a Joint FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals, which will be held 10-14 February 1997 at WHO Headquarters in Geneva. The Consultation will follow up certain recommendations of the York Consultation, particularly in the development of regional diets and in addressing issues related to implementation of the recommendation on intake assessment for acute hazards. In addition, the Consultation will consider approaches for extending the methods used for assessing the intake of pesticides to other chemicals considered

by Codex, including food additives, contaminants, veterinary drug residues, and nutrients.

### **2.2.2 Calculation of dietary intake of pesticide residues**

TMDIs were calculated for the JMPR by WHO (GEMS/Food) using the methods described in *Guidelines for predicting dietary intake of pesticide residues* (WHO, 1989), as revised by the recommendations of the York Consultation. When information was available IEDIs were also calculated. The results are summarized in Annex III and will be made available to the 29th Session of the CCPR in April 1997.

The JMPR has established acute reference doses for eight pesticides. While the York Consultation recommended a simple method for assessing short-term intake to compare with acute reference doses, the data and policy decisions that would allow such calculations require further clarification. The Meeting noted that the topic would be discussed at the Joint FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals to be held in February 1997 in Geneva and looked forward to receiving the recommendations of that Consultation.

The Meeting noted that the risk assessment of acutely toxic pesticides required further refinement and invited governments to make available relevant information on national approaches. The Meeting agreed that, when appropriate, the risk assessment of acute hazards should take into account any variability in the individual units in composite samples on which the MRL is based.

### **2.2.3 Estimation of supervised trials median residue levels**

1. The main objectives of the Joint FAO/WHO Consultation on Guidelines for predicting the Dietary Intake of Pesticide Residues, held in York, United Kingdom, 2-6 May 1995, were to review the existing guidelines and to recommend feasible approaches for improving the reliability and accuracy of methods for predicting the dietary intake of pesticide residues. The final published report of this Consultation became available in February 1996.

2. An informal Workshop was convened in The Hague, Netherlands, 11-12 April 1996, at the request of FAO Panel members, to consider the consequences of the recommendations of the York Consultation for individual reviewers and for the JMPR, and to convert the recommendations into practical methods for evaluating data.

3. The Workshop focused on the reviews of data undertaken by FAO Panel members and the estimation of supervised trials median residue (STMR) levels. Several general recommendations and 27 specific recommendations for the evaluation of data were made.

4. The present Meeting recognized that as pesticides are used in a wide variety of situations methods for evaluating data must be developed to take into account cases that are not already covered by the suggested procedures. The Meeting considered the report of the Workshop and agreed to support its recommendations, while recognizing that data evaluation is evolving. Most of the recommendations have already been implemented in the work of the FAO Panel.

5. On the basis of practical examples, the Meeting concluded that the recommendations on acute dietary intake and ectoparasite treatments of farm animals might require further development. In addition, the Meeting agreed that the recommendation on the estimation of STMRs and MRLs in animal commodities arising from residues in feed required further consideration. The Meeting agreed that examples and more specific guidance in this area should be developed at the 1997 JMPR.

6. The Meeting agreed that STMR levels that had already been estimated should be used by the JMPR in estimating consumer intakes resulting from long-term dietary exposure. The need for more realistic estimates of the dietary intake of pesticide residues was pointed out in the opening address to the Meeting.

7. Methods for presenting estimated STMR levels are still being developed. The aim is to communicate the results as clearly and unambiguously as possible; experience may indicate that further changes are necessary.

8. A copy of the report of the Workshop (*Report of an informal workshop on data evaluation in the estimation of dietary intake of pesticide residues for the JMPR*) is included as Annex IV to this report. The Meeting agreed that wide availability of the report of the Workshop would improve the transparency of the JMPR evaluation process and would also provide guidance to national governments.

9. The Meeting recommended that both the general and the specific recommendations of the Workshop be included in future FAO and WHO guidelines.

#### **2.2.4 Example of STMR estimation: parathion-methyl**

The 28th Session of the CCPR (ALINORM 97/24, para 46) welcomed the proposal that a fully worked example of intake assessment, prepared by the Codex Secretariat, be presented to the next Session. At the request of the CCPR, the Meeting considered the worked example of parathion-methyl (*Parathion-methyl, Estimation of Dietary Intake*), which demonstrates the methods used for estimating STMR levels. The STMR levels were combined with information on cultural diets in order to estimate chronic dietary intakes. The example was based on the methods recommended at the Workshop in The Hague, April 1996 (see Section 2.2.3 and Annex IV) and the Meeting confirmed that it reflected the methods used by the FAO Panel at the current Meeting. The Meeting recommended that the example be forwarded to the 1997 Session of the CCPR.

### **2.3 RELATIONSHIP BETWEEN CODEX MAXIMUM RESIDUE LIMITS (MRLS) FOR PESTICIDE RESIDUES, GOOD AGRICULTURAL PRACTICE (GAP), AND FOOD SAFETY**

The World Trade Organization (WTO) agreement on the Application of Sanitary and Phytosanitary Measures brought the Codex MRLs for pesticides to the attention of a wide range of government officials and representatives of non-governmental organizations. The questions and comments raised during various discussions indicated that the relationship between Codex MRLs for pesticide residues and the safety of food was not always clear. In order to assist the uniform, correct interpretation of the role and the use of MRLs for pesticide residues in food, the Meeting was requested to clarify the matter.

The 'Codex maximum residue limit for pesticide residues' is the maximum concentration of a pesticide residue (expressed as mg/kg) recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feeds. MRLs are based on data from trials conducted according to GAP and foods derived from commodities that comply with the respective MRLs are considered to be toxicologically acceptable (*Codex Alimentarius Commission procedural manual*, 9th ed. p.61.)

Codex standards, one of which is the MRL for pesticide residues, aim to protect the health of consumers and ensure fair practices in food trade.

The Codex MRLs for pesticide residues are elaborated by the Codex Committee on Pesticide Residues on the basis of the advice of the JMPR, which scientifically evaluates all relevant information on pesticides: their toxicology, metabolism in laboratory and farm animals and plants, environmental fate, and residues in food resulting from their use according to national GAP. The JMPR recommends, when possible, ADIs and Acute Reference Doses (acute RfDs) of pesticides for humans and MRLs for pesticide residues in food and feed commodities.

The residue levels that the JMPR recommends for use as MRLs are estimated by identifying the highest population (range and magnitude) of pesticide residues resulting from treatments according to GAP for which sufficient data are available. MRLs generally apply to primary food commodities when they enter the market.

Good Agricultural Practice (GAP) in the use of pesticides includes the nationally authorised safe uses of pesticides under actual conditions necessary for effective pest control. It encompasses a range of levels of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable. (*Codex*

*Alimentarius Commission procedural manual*, 9th ed., p. 60). Owing to differences in pest infestation, the resistance of pests, and growing conditions, the level of residues remaining in or on food and feed commodities may differ significantly according to geographical location.

Codex MRLs are intended primarily to enforce and control compliance with nationally authorized uses of pesticides on commodities moving in international trade. The definition of a residue for enforcement purposes may rely on only one component of the total residue if it sufficiently reflects the use of the given pesticide, while the inclusion of additional residue components may be necessary for estimating dietary intake or assessing risk.

The procedure used for estimating maximum residue levels means that MRLs are based on the registered uses of a pesticide and are not directly related to the ADI or acute RfD of the pesticide. The acceptability of the recommended limits for a pesticide from the point of view of food safety is assessed by the JMPR by estimating the dietary intake of that pesticide. In estimating the dietary intake all relevant information, such as the residues in each individual commodity for which MRLs are recommended, regional diets, and the effects of processing and cooking, is taken into account. The estimated daily intake is compared with the permissible intake of the residue, calculated from the ADI or acute RfD.

The Meeting noted that the WTO had decided to use Codex MRLs as criteria for the acceptability of food in international trade, and emphasized that it would continue to base its recommendations on the critical assessment of all available scientific knowledge and information based on experimental data. One of its basic scientific principles is to protect human health and the quality of the environment by recommending MRLs that are no higher than necessary to reflect national GAP and to keep residue levels as low as practicable in order to reduce the exposure of consumers and the environment resulting from the use of pesticides.

## **2.4 ESTIMATION OF EXTRANEEOUS RESIDUE LIMITS (ERLS)**

An Extraneous Residue Limit (ERL) for JMPR purposes refers to a pesticide residue arising from environmental sources (including former agricultural uses) other than the use of the pesticide directly or indirectly on the commodity containing the residue. It is the maximum concentration of a pesticide residue that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed (1990 JMPR report, Section 2.7).

The 1995 report of the JMPR (Section 2.8.2) includes a summary of the general JMPR principles for estimating ERLs. Two views were expressed by governments at the 1996 CCPR on the estimation of ERLs (CX/PR 96/5 Add. 1); a conflicting view was subsequently expressed by a third government. The views emphasized the inclusion or exclusion of 'outliers'.

The Meeting concluded that the meaning of the term 'outlier' should be clear in the context of its use. In the context of ERLs, the JMPR does not consider extreme values to be outliers in a statistical sense, because high residue levels are usually not true statistical outliers but values on the tail of a large distribution. The challenge is to decide when it is reasonable to discard those values in order to reflect the expected gradual decline in the levels of chemicals that are typically subject to ERL estimates, while not creating unnecessary barriers to trade.

Generally, the JMPR considers that the databases needed for estimating ERLs should be significantly larger than those required for the estimation of MRLs, because ERL data do not fit a normal distribution. For example, samples from 598 animals are needed to ensure that the estimated ERLs cover 99.5% of a population, allowing a 0.5% violation rate with 95% confidence (Codex Alimentarius, Vol. II, 2nd Ed., p. 372). As ERL data are derived from the random monitoring of different populations, the JMPR does not normally consider a 'world' population of data, but gives independent consideration to different populations, e.g. of different geographical regions or of different animals, before deciding which data populations might be combined. As noted above, the intention is to avoid unnecessary restrictions to trade.

The JMPR compares data distributions in terms of the likely percentages of violations that might occur if a given ERL is proposed. The JMPR is unaware of any internationally agreed level of violations that is recognised as unacceptable. Generally, the JMPR assumes that violation rates of 0.2-0.5% or greater are unacceptable. The JMPR would welcome views from governments on the levels of violation that are considered unacceptable.

For the reasons given above and on the basis of the approaches to estimating ERLs described in the report of the 1995 JMPR, the JMPR chooses not to endorse the country proposals to include or exclude high values. It is unlikely that governments will give consistent guidance on the use of outliers, and the JMPR cannot be a referee. Another reason is that compounds for which ERLs are estimated are no longer approved for use on agricultural commodities because of existing or previous health or environmental concerns.

It is to be expected that there will be a gradual reduction and/or elimination of residues of the chemicals for which ERLs have been proposed. The JMPR considers that the case-by-case approach described in its 1995 report already accommodates issues that might lead to concern. The 1995 report notes that the reasons for estimating ERLs below the maximum residues reported include discouraging unauthorized uses and encouraging the submission of adequate data. This approach is more likely to be used when the higher residues occur infrequently, and the JMPR attempts to balance its use against unnecessary restrictions to trade if health concerns permit.

Although the JMPR does not use targeted monitoring data for estimating ERLs, it agrees that follow-up studies are important when high residues are found in random monitoring to give a clearer view of the significance of the high levels. If properly conducted, such studies may indicate whether or not the higher residues resulted from intentional unauthorized uses and may allow the identification of areas in which production should be limited or where residue reduction strategies should be implemented.

The above discussion gives some of the reasons for the emphasis placed by the JMPR on the importance of providing complete information for ERL estimates, including possible impacts on trade. For example a better ERL estimate, taking into account trade concerns, was possible in the case of DDT when more extensive data were available. This example also illustrates some of the reasoning and approaches used by the JMPR in estimating ERLs (see DDT, Section 4.8).



## 2.5 ESTIMATION OF GROUP MAXIMUM RESIDUE LEVELS

The 28th (1996) Session of the CCPR retained a proposal of 2 mg/kg for residues of bromopropylate in citrus fruits at Step 7B, to await an opinion from the JMPR on its general policy on recommending group MRLs as opposed to MRLs for individual commodities (ALINORM 97/24, para 50). Similar issues arose in relation to the proposed MRL for fenbutatin oxide in citrus fruits.

In addition to the purely technical questions on general policy and the adequacy of data for group rather than individual MRLs, the 1996 CCPR also invited the JMPR to comment on the possibility of extrapolating residue data to cover minor crops, especially those of interest to developing countries (ALINORM 97/24, para 101). Although this issue was considered by the 1989 JMPR (report, Section 2.11), it can probably best be further addressed by other means, e.g. the development of minimum data requirements under consideration by governments, industry and the Organisation for Economic Co-operation and Development (OECD) (1994 JMPR report, Section 2.4; ALINORM 97/24, para 101) or the FAO guidelines on data evaluation (1992 JMPR report, Section 2.7), which are being developed. It will therefore not be considered further in this discussion.

The establishment of group MRLs as opposed to MRLs for individual commodities has long been recognized as an acceptable procedure at both the national and international levels. The use of the approach is a recognition that economics may not justify residue trials on all of the many cultivars and varieties of crops, and health protection will not usually require it. In principle the approach recognizes that adequate data for the major crops of a group may be sufficient.

Historically the JMPR has always approached the issue of group or individual MRLs on a case-by-case basis and that approach is unchanged. The main reasons for this are the many factors which can affect a decision on whether or not to propose a group MRL and the lack of international consensus on criteria. These considerations have prevented the JMPR from developing specific guidance for estimating group MRLs which might be applied at the international level in all situations.

Although such specific guidance is not yet available, some general guidance has been developed and recorded by the JMPR over the years. The JMPR proposed group MRLs at least as early as 1966, but principles for estimating group maximum residue levels were first addressed in some detail by the 1970 Meeting and amplified somewhat in 1973. This was before the existence of any internationally recognized classification of food and feed commodities by groups. The 1974, 1976, 1977 and 1979 Joint Meetings were encouraged by the on-going development of the Codex classification of foods and feeds and recognized the importance of this to the issue of group MRLs. The 1979 JMPR for the first time recorded the use of the Codex Definition and Classification of Food and Feed Groups to define individual commodities and those to which group MRLs should apply.

The 1981 JMPR (report, Section 2.3) expounded in some detail the concepts involved in the extrapolation of data from one crop to another, for both group and individual MRLs. The 1985, 1986 and 1988 Joint Meetings acknowledged the availability of, and reported the continued use of, a new edition of the Codex Classification (CAC/PR 4-1985). The continued

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use of the system by the JMPR since that time is widely recognized.

In order to respond to the request of the CCPR for an explanation of the general policy for estimating group MRLs, the Meeting took into account previous consideration of the issue by the JMPR (particularly the reports of the 1970, 1973 and 1981 Meetings) as well as the collective experience of its members. From these it was possible to summarize a number of general principles and observations which reflect the current views of the JMPR on estimating group MRLs. The following list is intended to supersede previous general guidance by the JMPR for estimating such MRLs.

(a) The JMPR continues to rely on the Codex Classification of Foods and Feeds as the primary definitional basis for recommending MRLs for individual or grouped commodities.

(b) The JMPR now generally refrains from estimating maximum residue levels for large Codex 'classes' of foods or feeds such as fruits, vegetables, grasses, nuts and seeds, herbs and spices, or mammalian products, which it has done in the past. Residue data and approved uses are usually more likely to refer to smaller Codex 'groups' such as pome fruits, citrus fruits, root and tuber vegetables, pulses, cereal grains, cucurbit fruiting vegetables, milks, meat of cattle, pigs and sheep, etc. As well as being more likely to be justified by the available data on residues and information on GAP, this is judged to be more in line with national approaches and to afford more accurate estimates of dietary intake.

(c) When adequate residue data are available for only a few primary commodities in a food group, separate MRLs should generally be recommended for each commodity on which the data are considered to be adequate.

(d) In some cases the JMPR may, in the absence of sufficient data for one commodity, use data from a similar crop for which GAP is similar to support estimates of maximum residue levels (e.g. pears and apples or broccoli and cauliflower).

(e) If other considerations permit, data on residues in all or most of the major commodities with the potential for high residues within a group may allow estimates of maximum residue levels to be extrapolated to minor crops in the group. An example of a situation in which other considerations do not permit is that in which the variability of the residue levels is too great, even though data on the major crops within the group are available. A group limit cannot then be established.

(f) When residue levels in a number of commodities in a group vary widely, separate recommendations should be made for each commodity. A limit for a group 'except one or more commodities' which are known to deviate from the norm may be justified (e.g. citrus fruits, except mandarins); in such cases separate MRLs should be estimated for the exceptional commodities.

(g) In order for a group limit to be proposed, not only must residue levels in the major commodities in the group not be too different, but the physical nature and other characteristics of the crops that might influence residue levels, as well as cultural practices and GAP for the individual commodities, must also be taken into account.

(h) Residue data for a crop growing quickly in summer cannot be extrapolated to the same or

related crops growing slowly under less favourable conditions (e.g. from summer to winter squash).

(i) In establishing group MRLs, detailed knowledge of the metabolism or mechanism of disappearance of a pesticide in one or more crops must be taken into account.

(j) Group MRLs recommended by the JMPR that generally appear to be acceptable include those for cereal grains (based on data for maize, wheat barley, oats and rice), stone fruits, poultry meat, milks, meat from mammals other than marine mammals, and oilseed.

(k) A group MRL is generally preferred in the case of citrus fruits, but care must be used in estimating a maximum level for the group because of the large variations in fruit size and in the ratio of peel to pulp in view of the propensity for residues of many pesticides to concentrate in the peel. Data on major members of the group are especially important.

Historically, many more Codex limits have been established for citrus fruits as a group (45 pesticides) than for individual citrus fruits (19 pesticides): lemons (2 pesticides); lemons and limes (1); mandarins (4), sweet and sour oranges (8), sweet oranges (1); shaddocks or pomelos (1); and grapefruit (2).

(l) All else being equal, data on a crop picked when immature may sometimes be extrapolated to a closely related species with a lower surface area:weight ratio at the time of the pesticide application which grows quickly to maturity, resulting in a rapid decrease in the ratio of residue to crop weight (dilution by crop growth). Thus estimates of maximum residue levels can be extrapolated from gherkins to cucumbers, but not *vice versa*.

(m) Individual MRLs can be extrapolated more readily to groups when there is no expectation that terminal residues will occur and when this is supported by studies of metabolism. Examples are early treatments, seed treatments, and treatments of orchard crops with herbicides.

While the JMPR generally adheres to these principles on a case-by-case basis, it recognizes certain difficulties or limitations in the acceptance of group limits at the international level. A primary weakness is the lack of formal criteria or an agreed mechanism to determine the members of a group for which data are needed before a group MRL can be established. One approach that is sometimes used effectively at the national level is to identify commodities of a group (often botanical) that represent both major crops within the group and those most likely to contain the highest residues. The factors used to determine whether a crop is a major or representative member of the group include whether some part or growth stage of it is used for animal feed and its dietary significance as a food or feedstuff.

The premise of this approach is that if data are available for representative crops, and if GAP and cultural practices among the individual members are similar, the residue levels will not vary widely and a maximum residue level can be estimated that will suffice for other members of the group for which no data are available. As noted earlier, this approach constitutes the use of common sense and is more or less dictated by the economics of data generation and evaluation.

While the JMPR recognizes real advantages in this approach, there is unfortunately no

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consensus at the international level on the selection of representative commodities for estimating maximum residue levels for groups. Similarly, while the JMPR bases its recommendations on the Codex Classification of Foods and Feeds, this classification has not been fully adopted at the national level in most countries.

There is also no international agreement about which are major and minor commodities. The proposed development by the OECD of minimum database requirements may resolve some of these difficulties, and the JMPR would welcome such a development within the framework of Codex or the OECD.

Until there is more international agreement in this area, the JMPR will continue to make judgements on a case-by-case basis, using the general policy summarized above or as it may be subsequently amended.

### **2.6 USE BY THE WHO CORE ASSESSMENT GROUP OF NATIONAL EVALUATIONS OF STUDIES**

To make use of work that has been performed by other agencies and organizations and to minimize duplication of effort, the Joint Meeting has been encouraged in recent years to make better use of evaluations of studies that have been prepared by national authorities and other organizations. The Meeting agreed that such evaluations should be used to the extent possible.

Detailed evaluations of toxicological studies have been prepared on four substances addressed by the present Meeting: on tebufenozide by the Canadian Pest Management Regulatory Agency, on 2,4-D by the United States Environmental Protection Agency, and on dimethoate and omethoate by the United Kingdom Pesticides Safety Directorate. Preparation of the monographs on these substances for the Meeting was based on the original reports of the studies and other pertinent information and was aided by reference to the national evaluations. However, the Joint Meeting came to independent conclusions about the substances.

The Meeting encouraged the availability of comprehensive evaluations prepared by national authorities and organizations and recommended that they be used to the extent possible by the WHO Core Assessment Group in the future.

### **2.7 INTERACTIONS OF PESTICIDES**

The Meeting was requested at the Twenty-eighth Session of the Codex Committee on Pesticide Residues (ALINORM 97/24, paragraph 97) to consider the possible combined effects of pesticides.

The significance of interactions of pesticides was reviewed by the 1967 JMPR. The 1981 Joint Meeting (report, Section 3.6) gave further consideration to interactions between pesticide residues and concluded that:

- (1) Not only could pesticides interact, but so could all compounds (including those in food) to which man could be exposed. This leads to unlimited possibilities, and there is no special reason why the interactions of pesticide residues (which

are at very low levels) should be highlighted as being of particular concern; (2) very few data on these interactions are available; and (3) the data obtained from acute potentiation studies are of little value in assessing ADIs for man.

The present Meeting noted that effects are not only potentiated, but sometimes mitigated, when two or more pesticides are administered simultaneously to experimental animals. Although a number of studies addressing this issue has been performed since 1981, those that show non-additive effects have been performed at 'effect doses', which are not relevant to mixtures of residues that may be present on food commodities at levels several-fold lower than effect levels.

A report<sup>1</sup> was published recently in which a number of compounds with weak oestrogenic activity were screened in a yeast oestrogen system containing human oestrogen receptor. In this assay, combinations of weak environmental oestrogens were up to 1000 times more potent in human oestrogen receptor-mediated transactivation than any chemical alone. While these results are preliminary, possible potentiation should be investigated further to see if the results can be confirmed and, if so, to ascertain their significance in intact biological systems. It should be kept in mind that the food supply contains many pharmacologically active substances, including phyto-oestrogens. The structures and activities of pesticides give no reason to conclude that they have more oestrogenic activity than many naturally occurring phyto-oestrogens. In addition, any interactions that may occur could result in either antagonistic or synergistic effects.

The Meeting concluded that interactions between pesticide residues, other dietary constituents, and environmental contaminants could occur. The results of such interactions depend on many factors, including the chemical and physical nature of the substances, the dose, and conditions of exposure. The outcome, which cannot be predicted reliably, may be enhanced, mitigated, or additive toxicity. The safety factors that are used for establishing ADIs should provide a sufficient margin of safety to account for potential synergism.

## **2.8 ENVIRONMENTAL CORE ASSESSMENT GROUP**

The Environmental Core Assessment Group could not convene with the Toxicological Core Assessment Group and the FAO Panel of Experts on Pesticide Residues in Food and the Environment at the present Meeting because of budgetary restrictions within the International Programme on Chemical Safety (IPCS). Consequently, the assessments of the environmental fate and ecotoxicity of the pesticides that were scheduled have been delayed until 1997.

The Meeting expressed its regret that the Environmental Core Assessment Group was unable to meet in 1996. Because of the importance of the environmental assessments as an integral component of the comprehensive assessment of pesticides, the Meeting recommended to IPCS that it make every effort to obtain the funds necessary for convening the Environmental Core Assessment Group with the JMPR in the future.

### 3. SPECIFIC PROBLEMS

#### 3.1 DEFINITION OF RESIDUES OF FAT-SOLUBLE COMPOUNDS

The Meeting has for many years included the qualification 'fat-soluble' in the definition of the residues of fat-soluble pesticides, using the expression

'Definition of the residue: [pesticide] (fat-soluble)'

Although previous Meetings recognized that fat-solubility is a property of the residue and not a part of its definition in chemical terms, the practice of treating it as part of the definition had been continued because expression in this way was succinct and because fat-solubility has implications for sampling and analysis, especially of meat and dairy products. As different definitions of residues may be needed for estimating dietary intake and for assessing compliance with MRLs however, the Meeting agreed that 'fat-soluble' should no longer be included in the definition of the residue. In order to avoid confusion while conveying the information that a residue is fat-soluble, the Meeting agreed that the definition of a residue should include only the chemical species of concern and a separate sentence should indicate that the residue is fat-soluble.

Example:

Definition of the residue for compliance with MRLs and for estimation of dietary intake:  
diazinon.

The residue is fat-soluble.

If the definition of a residue for compliance with MRLs differs from its definition for the estimation of dietary intake, both definitions will be given.

#### **4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE FOR HUMANS, SUPERVISED TRIALS MEDIAN RESIDUE LEVELS<sup>1</sup> AND MAXIMUM RESIDUE LIMITS**

##### **Note**

*The residue and analytical aspects of the compounds evaluated are reported more briefly than in recent years. The reasons for the change were given in the report of the 1995 JMPR (Section 2.9.3). Full details of the considerations which led to the estimates and recommendations of the Meeting will be given, as before, in the appraisals accompanying the monographs on the individual compounds in the 1996 Evaluations.*

##### **4.1 ACEPHATE (095)**

###### **RESIDUE AND ANALYTICAL ASPECTS**

Acephate was first evaluated in 1976. The 1994 JMPR withdrew the previous recommendations for the MRLs for broccoli, Brussels sprouts, head cabbages, cauliflowers, citrus fruits and tomato which had been held at Step 7B by the 1989 CCPR (ALINORM 89/24A, para 126). The manufacturer indicated that information on GAP and data on residues found in supervised trials would be available to support new MRLs for these commodities.

The Meeting received data on residues from supervised trials on the commodities mentioned above and information on GAP, the stability of residues in stored analytical samples, methods of residue analysis, and the fate of residues during food processing.

The residues of the metabolite methamidophos were also evaluated and separate MRLs recommended to accommodate methamidophos residues arising both from the use of acephate and the use of methamidophos.

The revised recommendations are listed in Annex I.

## 4.2 ALDICARB (117)

### RESIDUE AND ANALYTICAL ASPECTS

Residue aspects of aldicarb were last evaluated in 1994 within the CCPR periodic review programme. In response to the request of the 1994 Meeting extensive new information was provided on residues resulting from the currently recommended uses on bananas and potatoes, the stability of residues in potatoes during commercial storage, the effect of processing on residues in potatoes, and on the revised GAP for potatoes in the USA. The Meeting was informed about ongoing trial programmes on bananas and potatoes.

The trials were with granular formulations of aldicarb. The samples were mainly analyzed by HPLC methods which determined aldicarb, its sulfoxide and its sulfone individually. In some cases the residues were oxidized to, and determined as, the sulfone. The typical limit of determination was about 0.01-0.02 mg/kg for each residue component. The main residue in bananas and potatoes was aldicarb sulfoxide.

In US trials residues were measured in over 6000 individual potato tubers to determine the effects of the mode of application, irrigation method and climatic conditions on the magnitude and distribution of residues in the middle and end sections of the rows. The data showed that the residues in individual tubers could be much higher than in composite samples on which the MRL is based. Since the between-fields variance of residue levels was much larger than the within-field variance, the Meeting could estimate the maximum residue levels on the basis of the averages of residues found in the sites.

The Meeting could not evaluate the results of South African trials as they were provided only in a summarized form.

The available information enabled the Meeting to estimate a maximum residue level and STMR level for potatoes, and to estimate the maximum residues likely to occur in individual potato tubers. STMRs were also estimated for several potato products. The data were insufficient to estimate a maximum residue level for bananas.

### FURTHER WORK OR INFORMATION

#### Desirable

1. Results of supervised trials according to maximum Spanish and South African GAP on potatoes.
2. Residue data on whole bananas and banana pulp reflecting current GAP.
3. Data on the effect of boiling (cooking) on aldicarb residues in potatoes.



### 4.3 BIFENTHRIN (178)

#### RESIDUE AND ANALYTICAL ASPECTS

Bifenthrin was first evaluated at the 1992 JMPR and MRLs of 0.05\* mg/kg were recommended for barley, maize and wheat to cover field applications. The 1995 JMPR reviewed information about the use of bifenthrin as a grain protectant but made no recommendations and sought further clarification on a number of points.

Information on milling and baking studies on wheat treated with bifenthrin was made available to the Meeting.

No specific information was available on the efficiency of extraction of aged bifenthrin residues from grain by hexane/acetone, but the fact that the bifenthrin residue levels on wheat in storage trials at day 1 were unchanged by week 12 suggests that the solvent adequately extracts aged residues from grain.

Bifenthrin residues were stable on grain stored at 20°C and 25°C and their levels on the grain at the beginning of storage were essentially the same as at the end.

Approximately 16% of the bifenthrin residues were lost in producing wholemeal flour from uncleaned wheat. The bifenthrin level in white flour was about 30% (26-36%), and the level in bran about 3.5 times (3.1-3.8) the level in the uncleaned wheat.

Wholemeal bread and white bread were baked from the wholemeal and white flour produced in the milling studies. The results from these baking trials suggest that about 70% of the bifenthrin disappears on baking wholemeal or white bread. This is not consistent with the behaviour of other pyrethroids, which are mostly retained through the baking process.

The Meeting was reluctant to draw a firm conclusion on the fate of bifenthrin during baking until some aspects of the analytical method had been clarified. Validation of analytical recoveries from bread at the bifenthrin residue levels which occur in practice and at the LOD is needed, as is investigation into the possibility that bifenthrin residues are bound in the bread and not extractable by the current method.

Recommendations for MRLs and estimated STMR levels are listed in Annex I.

#### FURTHER WORK OR INFORMATION

##### Desirable

1. Validation of the analytical method for recoveries of bifenthrin residues from bread at the levels occurring in practice and at the LOD.

2. Information on the degree of extraction of bifenthrin residues from bread by the current procedure.
3. Information on national registrations and MRLs for bifenthrin covering its use on stored grain.
4. Information on the fate of bifenthrin during the commercial malting of barley treated with it post-harvest. The studies should simulate the commercial process (from 1995 JMPR).

#### **4.4 CARBARYL (008)**

### **TOXICOLOGY**

Carbaryl was evaluated for toxicological effects by the Joint Meeting in 1963, 1965, 1966, 1967, 1969, and 1973. An ADI of 0-0.02 mg/kg bw was established in 1963 on the basis of a one-year study in dogs, and this ADI was confirmed in 1965, 1966, and 1967. In 1969, a temporary ADI of 0-0.01 mg/kg bw was established, using an extra safety factor because of concern about effects on the male reproductive system seen in a one-year study by gavage in rats with an NOAEL of 2 mg/kg bw per day, and because a dose of 0.12 mg/kg bw per day may have affected renal function in a six-week study in volunteers. In 1973, the Meeting established an ADI of 0-0.01 mg/kg bw.

The toxicology of the compound was reviewed by the present Meeting within the CCPR periodic review programme. The evaluation is based on a recent Environmental Health Criteria monograph on carbaryl (EHC 153)<sup>ii</sup>

### **MAXIMUM RESIDUE LIMITS**

#### **Note**

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The Meeting received data on residues from supervised trials on the commodities mentioned above and information on GAP, the stability of residues in stored analytical samples, methods of residue analysis, and the fate of residues during food processing.

The residues of the metabolite methamidophos were also evaluated and separate MRLs recommended to accommodate methamidophos residues arising both from the use of acephate and the use of methamidophos.

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Residue aspects of aldicarb were last evaluated in 1994 within the CCPR periodic review programme. In response to the request of the 1994 Meeting extensive new information was provided on residues resulting from the currently recommended uses on bananas and potatoes, the stability of residues in potatoes during commercial storage, the effect of processing on residues in potatoes, and on the revised GAP for potatoes in the USA. The Meeting was informed about ongoing trial programmes on bananas and potatoes.

The trials were with granular formulations of aldicarb. The samples were mainly analyzed by HPLC methods which determined aldicarb, its sulfoxide and its sulfone individually. In some cases the residues were oxidized to, and determined as, the sulfone. The typical limit of determination was about 0.01-0.02 mg/kg for each residue component. The main residue in bananas and potatoes was aldicarb sulfoxide.

In US trials residues were measured in over 6000 individual potato tubers to determine the effects of the mode of application, irrigation method and climatic conditions on the magnitude and distribution of residues in the middle and end sections of the rows. The data showed that the residues in individual tubers could be much higher than in composite samples on which the MRL is based. Since the between-fields variance of residue levels was much larger than the within-field variance, the Meeting could estimate the maximum residue levels on the basis of the averages of residues found in the sites.

The Meeting could not evaluate the results of South African trials as they were provided only in a summarized form.

The available information enabled the Meeting to estimate a maximum residue level and STMR level for potatoes, and to estimate the maximum residues likely to occur in individual potato tubers. STMRs were also estimated for several potato products. The data were insufficient to estimate a maximum residue level for bananas.

## **FURTHER WORK OR INFORMATION**

### Desirable

1. Results of supervised trials according to maximum Spanish and South African GAP on potatoes.
2. Residue data on whole bananas and banana pulp reflecting current GAP.
3. Data on the effect of boiling (cooking) on aldicarb residues in potatoes.

## **4.3 BIFENTHRIN (178)**

### **RESIDUE AND ANALYTICAL ASPECTS**

Bifenthrin was first evaluated at the 1992 JMPR and MRLs of 0.05\* mg/kg were recommended for barley, maize and wheat to cover field applications. The 1995 JMPR reviewed information about the use of bifenthrin as a grain protectant but made no recommendations and sought further clarification on a number of points.

Information on milling and baking studies on wheat treated with bifenthrin was made available to the Meeting.

No specific information was available on the efficiency of extraction of aged bifenthrin residues from grain by hexane/acetone, but the fact that the bifenthrin residue levels on wheat in storage trials at day 1 were unchanged by week 12 suggests that the solvent adequately extracts aged residues from grain.

Bifenthrin residues were stable on grain stored at 20°C and 25°C and their levels on the grain at the beginning of storage were essentially the same as at the end.

Approximately 16% of the bifenthrin residues were lost in producing wholemeal flour from uncleaned wheat. The bifenthrin level in white flour was about 30% (26-36%), and the level in bran about 3.5 times (3.1-3.8) the level in the uncleaned wheat.

Wholemeal bread and white bread were baked from the wholemeal and white flour produced in the milling studies. The results from these baking trials suggest that about 70% of the bifenthrin disappears on baking wholemeal or white bread. This is not consistent with the behaviour of other pyrethroids, which are mostly retained through the baking process.

The Meeting was reluctant to draw a firm conclusion on the fate of bifenthrin during baking until some aspects of the analytical method had been clarified. Validation of analytical recoveries from bread at the bifenthrin residue levels which occur in practice and at the LOD is needed, as is investigation into the possibility that bifenthrin residues are bound in the bread and not extractable by the current method.

Recommendations for MRLs and estimated STMR levels are listed in Annex I.

## **FURTHER WORK OR INFORMATION**

### Desirable

1. Validation of the analytical method for recoveries of bifenthrin residues from bread at the levels occurring in practice and at the LOD.
2. Information on the degree of extraction of bifenthrin residues from bread by the current procedure.
3. Information on national registrations and MRLs for bifenthrin covering its use on stored grain.
4. Information on the fate of bifenthrin during the commercial malting of barley treated with it post-harvest. The studies should simulate the commercial process (from 1995 JMPR).

## **4.4 CARBARYL (008)**

### **TOXICOLOGY**

Carbaryl was evaluated for toxicological effects by the Joint Meeting in 1963, 1965, 1966, 1967, 1969, and 1973. An ADI of 0-0.02 mg/kg bw was established in 1963 on the basis of a one-year study in dogs, and this ADI was confirmed in 1965, 1966, and 1967. In 1969, a temporary ADI of 0-0.01 mg/kg bw was established, using an extra safety factor because of concern about effects on the male reproductive system seen in a one-year study by gavage in rats with an NOAEL of 2 mg/kg bw per day, and because a dose of 0.12 mg/kg bw per day may have affected renal function in a six-week study in volunteers. In 1973, the Meeting established an ADI of 0-0.01 mg/kg bw.

The toxicology of the compound was reviewed by the present Meeting within the CCPR periodic review programme. The evaluation is based on a recent Environmental Health Criteria monograph on carbaryl (EHC 153)<sup>iii</sup> and is supplemented by newly received studies on metabolism, dermal absorption, chronic toxicity and/or oncogenicity in rats and mice, mechanistic studies, and a report of an epidemiological study on exposed workers.

Carbaryl is rapidly and almost completely absorbed after oral administration. Excretion is rapid and occurs predominantly via the urine; enterohepatic cycling of carbaryl metabolites is also considerable. There were no significant dose-related or sex-specific differences in elimination patterns, and there was no evidence of bioaccumulation. Dermal absorption in rats was slow; after 24 h, 16-34% of the administered radioactivity had been absorbed. Higher doses were less readily absorbed. In volunteers, 45% of a dose applied to the skin in acetone was absorbed within 8 h. Carbaryl was rapidly absorbed in the lungs.

The metabolism of carbaryl has been studied in various mammals, including humans. The principal metabolic pathways are ring hydroxylation, hydrolysis, and conjugation. There were no species differences. The principal metabolite in humans is 1-naphthol. The hydrolysis product, *N*-methylcarbamic acid, spontaneously decomposes to methylamine and carbon dioxide. The methylamine is later converted to carbon dioxide and formate, the latter being excreted mainly in the urine. Carbaryl metabolites are also found at small percentages of the absorbed doses in saliva and milk.

Carbaryl is moderately toxic after acute oral administration, the LD<sub>50</sub> in rats being 225-721 mg/kg bw. Interspecies differences in toxicity were found, cats (LD<sub>50</sub>, 150 mg/kg bw) being the most sensitive. The LD<sub>50</sub> was increased threefold when animals were pretreated with small doses of carbaryl. The compound is slightly toxic after acute dermal administration, with an LD<sub>50</sub> > 2000 mg/kg bw. No LC<sub>50</sub> for acute exposure by inhalation was available, but the effects observed in dogs, cats, and rats exposed to dusts or formulations of carbaryl were typical of those resulting from inhibition of cholinesterase activity. In cats exposed to carbaryl dust for 6 h, a concentration of 20 mg/m<sup>3</sup> inhibited cholinesterase activity in plasma and erythrocytes. Carbaryl was weakly irritating to the eye but not the skin and was not considered to be a sensitizer. WHO has classified carbaryl as 'moderately hazardous'.

After the oral administration of carbaryl in capsules to dogs at doses of 0.45, 1.8, or 7.2 mg/kg bw per day for one year, slight effects were observed on the kidney at 7.2 mg/kg bw per day; the NOAEL was 1.8 mg/kg bw per day. In two studies in which dogs were fed diets containing carbaryl at 20-125 ppm for five weeks and 125-1250 ppm for one year, the NOAEL was 125 ppm, equivalent to 3.1 mg/kg bw per day, on the basis of effects on liver weight and inhibition of acetylcholinesterase activity in erythrocytes and brain at 400 ppm.

In cats exposed to carbaryl by inhalation, cholinergic signs were observed at 30 mg/m<sup>3</sup> after exposure for 30 days; the NOAEL was 16 mg/m<sup>3</sup> after exposure for 120 days. In a study in rats, no effects were observed after exposure to 10 mg/m<sup>3</sup> for 90 days.

Several studies of long-term toxicity or carcinogenicity in mice cited in EHC 153 were not considered to be suitable for evaluation of carcinogenicity by either the Environmental

Health Criteria Task Force or the present Meeting, although they were suitable for assessing long-term toxicity. In a recent study of carcinogenicity, mice were given diets providing 0, 100, 1000, or 8000 ppm carbaryl for 104 weeks. Tumours were observed in the liver in females and the kidney in males, and vascular tumours were found in animals of both sexes at the highest dose, which exceeded the maximum tolerated dose (MTD). In male mice, increases in the incidences of vascular tumours were also seen at the two lower doses; after considering all of the available data, the Meeting could not identify an NOAEL for this neoplastic lesion. The NOAEL for non-neoplastic lesions was 100 ppm (equal to 15 mg/kg bw per day), on the basis of inhibition of erythrocyte and brain acetylcholinesterase activity and histopathological changes in the urinary bladder at 1000 ppm. This NOAEL is consistent with the results of the earlier studies. The Meeting concluded that the compound is carcinogenic in mice.

In several studies cited in EHC 153, carbaryl was administered in the diet of rats for 96 days to two years. The most obvious effects were in the kidney at doses of 400 ppm and above. In two one-year studies in rats treated by gavage, effects on the thyroid and on male and female reproductive organs and/or function were observed at doses of 5 mg/kg bw per day and above; the NOAEL was 2 mg/kg bw per day. None of these studies was considered suitable for evaluating carcinogenicity.

In a recent study of long-term toxicity and carcinogenicity, rats were fed diets containing 0, 250, 1500, or 7500 ppm carbaryl for 104 weeks. In animals at the highest dose, which exceeded the MTD, tumours were found in the thyroid in males, in the liver in females, and in the urinary bladder in animals of both sexes. The NOAEL for non-neoplastic findings was 250 ppm, equal to 10 mg/kg bw per day, on the basis of inhibition of erythrocyte and brain acetylcholinesterase and a decrease in mean body weight at 1500 ppm. This NOAEL is consistent with the results of earlier dietary studies. The Meeting concluded that carbaryl is carcinogenic in rats only at levels that exceed the MTD.

The available studies on reproductive toxicity were conducted some time ago and had some deficiencies in relation to currently acceptable scientific standards. In three-generation studies, dietary administration of carbaryl to rats induced reproductive effects (impaired fertility and reduced postnatal survival and growth) at doses above 2000 ppm (equal to 125 mg/kg bw per day); a dose of 100 mg/kg bw per day did not induce maternal toxicity. When carbaryl was administered by gavage, maternal toxicity was not observed at 25 mg/kg bw per day, but both maternal and reproductive toxicity (reduced litter size and viability) were observed at 100 mg/kg bw per day. The Meeting recommended that a new two-generation study of reproductive toxicity be carried out in rats, with special attention to the male reproductive system since effects on this system were observed in some studies of long-term toxicity at gavage doses significantly lower than those evaluated in the dietary studies of reproductive toxicity.

The available studies on developmental toxicity suffered from small group size and had some deficiencies in relation to currently acceptable scientific standards. In two studies in mice, the NOAEL for maternal toxicity was 100 mg/kg bw per day; at 150 mg/kg bw per day, increased litter resorption was found. In rats, administration of carbaryl in the diet for part or all of the gestation period resulted in maternal toxicity at 100 mg/kg bw per day. No overt signs of

fetotoxicity were seen at this dose. In a study in which rats were exposed to carbaryl by gavage and then mated, maternal and embryotoxicity were observed at 100 mg/kg bw per day; no effects were observed at 10 mg/kg bw per day. In guinea-pigs, administration of carbaryl during gestation in the diet or by gavage resulted in an NOAEL for maternal toxicity of 100 mg/kg bw per day. No embryo- or fetotoxicity was observed at 300 mg/kg bw per day, the highest dose tested. In rabbits, teratogenic effects were reported after administration of 200 mg/kg bw per day orally; maternal toxicity was also seen at this dose. In two studies in dogs, maternal toxicity (dystocia, at parturition only) was observed at doses of 3.1 mg/kg bw per day. A variety of birth defects was found after exposure to 5 mg/kg bw per day and above. Thus, the LOAEL for maternal toxicity was 3.1 mg/kg bw per day, and this was the NOAEL for birth defects in the offspring.

The Meeting concluded that carbaryl induces developmental toxicity, manifested as deaths *in utero*, reduced fetal weight, and malformations, but only at doses that cause overt maternal toxicity. The shortcomings of these studies made them inadequate for identifying NOAELs for developmental toxicity that could be used for assessing risk under conditions of exposure other than in the diet.

Carbaryl has been adequately tested in a series of assays *in vitro* and *in vivo*. While chromosomal aberrations have been induced *in vitro* and carbaryl has been shown to disturb spindle fibre mechanisms *in vitro*, there was no evidence from well-conducted experiments that carbaryl is clastogenic *in vivo*. The Meeting concluded that carbaryl is not genotoxic.

The effects of carbaryl on the nervous system are primarily related to cholinesterase inhibition and are usually transitory.

Dietary exposure to doses of 10-20 mg/kg bw per day for 50 days was reported to disrupt learning and performance in rats. In chickens given high doses of carbaryl there was no histological evidence of neurotoxicity.

In controlled studies in volunteers, single oral doses of < 2 mg/kg bw were well tolerated. A single oral dose of 250 mg (about 2.8 mg/kg bw) produced moderate cholinergic symptoms.

In volunteers given repeated daily oral doses over six weeks, the NOAEL was 0.06 mg/kg bw per day, on the basis of an increased ratio of amino acid nitrogen to creatinine in the urine at a dose of 0.13 mg/kg bw per day. This effect may represent a decrease in the ability of the proximal convoluted tubule to reabsorb amino acids. The change was reversible. No inhibition of plasma or erythrocyte cholinesterase activity was observed.

An epidemiological study on carbaryl production workers employed between 1960 and 1978 showed no increase in cancer mortality.

An ADI of 0-0.003 mg/kg bw was established on the basis of the LOAEL of 15 mg/kg bw per day in the study of carcinogenicity in mice, using a safety factor of 5000, which includes an extra safety factor of 50 to account for the presence of vascular tumours at all doses



in male mice. The resulting ADI provides an adequate margin of safety, taking into account the LOAEL in the study of developmental toxicity in dogs and the uncertainties about the effects on the male reproductive system.

A toxicological monograph was prepared, summarizing the data received since the previous Meeting and information from EHC 153.

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: NOAEL not identified. Lowest effective dose: 100 ppm, equal to 15 mg/kg bw per day (two-year study of toxicity and carcinogenicity).

Rat: 250 ppm, equal to 10 mg/kg bw per day (two-year study of toxicity and carcinogenicity).

2 mg/kg bw per day (one-year study of toxicity).

Dog: NOAEL not identified. Lowest effective dose: 3.1 mg/kg bw per day (study of developmental toxicity).

1.8 mg/kg bw per day (one-year study of toxicity).

Human: 0.06 mg/kg bw per day (six-week study of toxicity).

#### Estimate of acceptable daily intake for humans

0-0.003 mg/kg bw

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

1. Study of reproductive toxicity, with special attention to the male reproductive system.
2. Studies of teratogenicity in rats and rabbits.
3. Completion of on-going studies to elucidate the mechanism of tumour formation.
4. Study of developmental neurotoxicity and/or screening for acute or subchronic neurotoxicity.
5. Follow-up of the epidemiological study in workers, taking into consideration the latent period before development of cancer.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULTS/REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> = 225-721 mg/kg bw
	Dermal toxicity, rat	LD <sub>50</sub> > 2000 mg/kg bw
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Slightly irritating
	Dermal sensitization, guinea-pig	Not sensitizing
Medium-term (1-26 weeks)	Repeated oral, five weeks, dog	NOAEL = 3.1 mg/kg bw per day (highest dose tested); no effects on acetylcholinesterase activity
	Repeated oral, six weeks, human	NOAEL = 0.06 mg/kg bw per day; increased ratio of amino acid nitrogen to creatinine in urine
	Inhalation, 90 days, rat	NOAEL = 10 mg/m <sup>3</sup> per day (highest dose tested)
	Inhalation, 120 days, cat	NOAEL = 16 mg/m <sup>3</sup> per day; cholinergic reactions at 30 mg/m <sup>3</sup> after a 30-day exposure
Long-term (≥ one year)	Repeated oral, two years, carcinogenicity, mouse	Vascular tumours in males at 15 mg/kg bw per day, the lowest dose tested
	Repeated oral (gavage), one year, toxicity and carcinogenicity, rat	NOAEL = 2 mg/kg bw per day, effects on thyroid and male and female reproductive organs and/or function
	Repeated oral, two years, toxicity and carcinogenicity, rat	NOAEL = 10 mg/kg bw per day, reduced brain acetylcholinesterase and reduced body weight. Tumours (thyroid, liver, bladder) at 350 mg/kg bw per day, which exceeded the MTD
	Repeated oral (gavage), one year, toxicity, dog	NOAEL = 1.8 mg/kg bw per day, effects on kidney

**4.5 CARBOFURAN (096)**

**TOXICOLOGY**

Carbofuran was evaluated for toxicological effects by the Joint Meeting in 1976, 1979, 1980, and 1982. The 1980 Meeting established an ADI of 0-0.01 mg/kg bw, which was confirmed in 1982. The compound was re-evaluated at the present Meeting within the CCPR periodic review programme.

Carbofuran is rapidly absorbed, metabolized, and eliminated, mainly in the urine, after oral administration to mice and rats. After oral administration of [*phenyl*-<sup>14</sup>C]carbofuran to rats, 92% of the radiolabel was eliminated in the urine and 3% in the faeces. Most of the radiolabel was eliminated within 24 h after treatment. With the [<sup>14</sup>C]carbonyl-labelled compound, 45% was eliminated as [<sup>14</sup>C]carbon dioxide. The metabolic pathway involves hydroxylation, hydrolysis, oxidation and conjugation.

Carbofuran is highly toxic after acute oral administration. The oral LD<sub>50</sub> values in various species ranged from 3 to 19 mg/kg bw. Carbofuran had no sensitizing potential in guinea-pigs, and no local irritation was found in rabbits after repeated dermal applications over 7 or 21 days. WHO has classified carbofuran as 'highly hazardous'.

In a 13-week study in dogs fed diets providing 0, 10, 70, or 500/250 ppm carbofuran (dose reduced because of marked toxicity), an NOAEL was not identified because inhibition of erythrocyte acetylcholinesterase activity and some clinical signs were observed at the lowest dose. In a subsequent four-week study in dogs, the only dose administered was 5 ppm, equal to 0.22 mg/kg bw per day, which was the NOAEL for clinical signs, mortality, body weight, food consumption, and cholinesterase activity in plasma and erythrocytes. In a one-year study in dogs at dietary concentrations of 0, 10, 20, or 500 ppm, the NOAEL was 10 ppm, equal to 0.3 mg/kg bw per day, on the basis of histopathological testicular changes in a single male at 20 ppm; similar changes were observed in animals at 500 ppm. There was no inhibition of erythrocyte or brain acetylcholinesterase at concentrations of 10 or 20 ppm. The overall NOAEL in these short-term studies in dogs was 5 ppm, equal to 0.22 mg/kg bw per day.

In two-year studies of toxicity and carcinogenicity at dietary concentrations of 0, 20, 125, or 500 ppm in mice and 0, 10, 20, or 100 ppm in rats the NOAELs were 20 ppm, equal to 2.8 mg/kg bw per day, in mice and 20 ppm, equivalent to 1 mg/kg bw per day, in rats, on the basis of inhibition of erythrocyte and brain acetylcholinesterase activity. There was no evidence of tumorigenicity.

In a three-generation study of reproductive toxicity in rats at dietary concentrations of 0, 20, or 100 ppm, the NOAEL was 20 ppm, equal to 1.6 mg/kg bw per day, on the basis of reduced body-weight gain in parental animals and reduced pup growth and pup survival at 100 ppm.

In an early study of developmental toxicity, rats were given carbofuran at doses of 0, 0.1, 0.3, or 1 mg/kg bw per day by gavage. An NOAEL could not be identified in this study. Dose-dependent transient clinical signs (chewing motions) were observed in the dams. In a later study in rats at oral doses of 0, 0.25, 0.5, or 1.2 mg/kg bw per day the NOAEL for maternal and fetal toxicity was 1.2 mg/kg bw per day, the highest dose tested. In a further study of teratogenicity in rats, with dietary administration of 0, 20, 60, or 160 ppm carbofuran, the NOAEL for maternal toxicity was 20 ppm, equal to 1.5 mg/kg bw per day, on the basis of a reduction in body-weight gain at 60 ppm. The NOAEL for pup toxicity, based on reduced pup weight, was 60 ppm, equal to 4.4 mg/kg bw per day. None of the studies showed teratogenic potential.

The results of an early study of developmental toxicity in rabbits at oral doses of 0, 0.2, 0.6, or 2 mg/kg bw per day showed an NOAEL of 0.6 mg/kg bw per day for maternal toxicity on the basis of clinical signs, and an NOAEL of 2 mg/kg bw per day for fetotoxicity and teratogenicity. In a subsequent study in rabbits at doses of 0, 0.12, 0.5, or 2 mg/kg bw per day, the NOAEL was 0.5 mg/kg bw per day on the basis of slightly reduced body-weight gain in dams and a slightly increased incidence of skeletal variations in pups at 2 mg/kg bw per day. These studies provided no evidence of teratogenicity.

In a 90-day study of neurotoxicity in rats at dietary concentrations of 0, 50, 500, or 1000 ppm, systemic toxicity (reduction in body-weight gain) was observed at all doses. Clinical signs of neurotoxicity were observed at 500 and 1000 ppm. No histopathological lesions in the nervous system were observed.

In a study of developmental neurotoxicity, carbofuran was administered in the diet to provide concentrations of 0, 20, 75, or 300 ppm from gestation day 6 through lactation day 10. Reductions in body-weight gain in dams and pups and in pup survival and some evidence of delayed pup development were found at 75 ppm and higher. The NOAEL was 20 ppm, equal to 1.7 mg/kg bw per day, on the basis of reduced body-weight gain in dams and signs of fetotoxicity at higher doses.

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

An ADI of 0-0.002 mg/kg bw was allocated on the basis of the NOAEL for erythrocyte acetylcholinesterase inhibition of 0.22 mg/kg bw per day in a four-week study in the most sensitive species, the dog, using a 100-fold safety factor. The use of a short-term study to determine the ADI was justified because the effect observed was reversible and acute.

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

## TOXICOLOGICAL EVALUATION

### Levels that cause no toxic effect

Mouse: 20 ppm, equal to 2.8 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 20 ppm, equivalent to 1 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

20 ppm, equal to 1.2 mg/kg bw per day (three-generation study of reproductive toxicity)

1.2 mg/kg bw per day (highest dose tested in a study of developmental toxicity)

20 ppm, equal to 1.5 mg/kg bw per day (study of developmental toxicity)

20 ppm, equal to 1.7 mg/kg bw per day (study of developmental neurotoxicity)

Rabbit: 0.6 mg/kg bw per day (study of developmental toxicity)

Dog: 5 ppm, equal to 0.22 mg/kg bw per day (four-week study of toxicity)

Estimate of acceptable daily intake for humans

0-0.002 mg/kg bw

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

Further observations in humans.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> = 6-14 mg/kg bw
	Dermal toxicity, rat	LD <sub>50</sub> >500 mg/kg bw
	Inhalation toxicity, rat	LC <sub>50</sub> = 0.088-0.1 mg/litre
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Not available
	Dermal sensitization, guinea-pig	Not sensitizing
Medium-term (1-26 weeks)	Repeated oral, 4 weeks, toxicity, dog	NOAEL = 0.22 mg/kg bw per day

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
	Repeated oral, reproductive toxicity, rat	NOAEL = 1.6 mg/kg bw per day, parental and pup toxicity
	Repeated oral (gavage), developmental toxicity, rat	NOAEL = 1.2 mg/kg bw per day (highest dose tested). No evidence of teratogenicity
	Repeated oral (feeding), developmental toxicity, rat	NOAEL = 1.5 mg/kg bw per day, maternal toxicity
	Repeated oral, developmental toxicity, rabbit	NOAEL = 0.6 mg/kg bw per day, maternal toxicity. No evidence of teratogenicity
	Repeated oral, developmental neurotoxicity, rat	NOAEL = 1.7 mg/kg bw per day
Long-term (≥ one year)	Repeated oral, two years, carcinogenicity, mouse	NOAEL = 2.8 mg/kg bw per day, cholinesterase inhibition. No evidence of carcinogenicity
	Repeated oral, two years, carcinogenicity, rat	NOAEL = 1 mg/kg bw per day, reduced body-weight gain and cholinesterase inhibition. No evidence of carcinogenicity.

**4.6 CHLORFENVINPHOS (014)**

**RESIDUE AND ANALYTICAL ASPECTS**

Chlorfenvinphos was evaluated for residues by the JMPR in 1971 and 1984 and is now being reviewed in the CCPR periodic review programme. It is a contact and soil-applied organophosphorus insecticide used for the control of various pests on a range of vegetable, cereal and oilseed crops. A use for cattle dipping was also reported.

The Meeting received information on physico-chemical properties of the technical material, metabolism, environmental fate in soil, methods of residue analysis, approved use patterns, supervised residue trials, animal transfer studies, the fate of residues during food processing, monitoring data and national MRLs.

Data on metabolism in humans, rats, dogs, lactating cattle, potatoes, cabbage, maize, carrots and onions were reviewed; in all cases the main residue was chlorfenvinphos. These studies, as well as those on the environmental fate, were old and briefly reported with limited

experimental detail. No data on the mobility of chlorfenvinphos in soil were submitted.

Analyses of crop and soil samples for chlorfenvinphos and its metabolites were based on GLC with FP, EC or NP detection. Only limited data on validation of the methods were presented. No information was provided on the stability of residues in stored analytical samples.

Data on residue trials on a number of crops were submitted. Several of the reports of the trials lacked important experimental details or were poorly presented. The Meeting estimated maximum residue levels for onion, head cabbage, cauliflower, carrot, parsnip and rape seed, but these estimates were based mainly on trials in which the duration of sample storage before analysis was not reported.

Summary data on residues in lettuce and lamb's lettuce grown as rotational crops indicated that significant residues may occur in rotational crops after soil applications of chlorfenvinphos.

In studies of ruminant grazing and external treatment, measurable residues were found only in samples of 'fat'.

Data on domestic preparation and processing indicated that most of the residue in carrots is associated with the top of the carrot including the crown.

The Meeting agreed that in view of the lack of studies according to modern standards on metabolism, the stability of residues in stored analytical samples, the mobility of chlorfenvinphos in soil and the residues found in following crops, the estimated maximum residue levels could not be recommended as MRLs. For any future consideration of MRLs, the submission of data on such studies would be needed. The Meeting recommended the withdrawal of the existing CXLs.

## **FURTHER WORK OR INFORMATION**

### Desirable

1. The following physico-chemical properties of the pure active ingredient:  
vapour pressure, melting point, octanol/water partition coefficient, solubility in organic solvents, solubility in water, specific gravity.
2. If significant residues occur in relevant feed items, a study of metabolism and distribution in a lactating ruminant and/or in laying poultry carried out according to modern standards in which treatment is made through oral ingestion.
3. Data on metabolism in a ruminant after the external application of chlorfenvinphos to support the reported approved dipping use in Australia.
4. Plant metabolism and translocation studies carried out according to modern standards.



5. Studies on the stability of pesticide residues in representative analytical samples stored for at least two years. These would help to support data evaluated by the Meeting on residue trials for which the duration of sample storage was not reported.
6. Studies to assess the nature and levels of residues in representative rotational crops other than lettuce and lamb's lettuce.
7. If significant residues are found in animal feed, a transfer study on ruminants according to modern standards (see 1993 JMPR report, Section 2.7).
8. A study of the mobility of chlorfenvinphos in soil, including leaching, adsorption and desorption, according to modern standards.
9. Copies of the product labels supporting the information submitted on GAP.
10. The full reports of the rotational crop studies on lamb's lettuce and lettuce.

#### **4.7 2,4-D (020)**

### **TOXICOLOGY**

2,4-D, 2,4-dichlorophenoxyacetic acid, was evaluated for toxicological effects by the JMPR in 1970, 1971, 1974, and 1975. The 1970 Joint Meeting did not establish an ADI because of the absence of long-term studies. The 1971 Meeting established an ADI of 0-0.3 mg/kg bw on the basis of an NOAEL of 31 mg/kg bw per day in a two-year dietary study in rats. The ADI was not changed by the 1974 Joint Meeting and was reaffirmed by the 1975 Meeting. The compound was reviewed at the present Meeting within the CCPR periodic review programme.

2,4-D was rapidly absorbed, distributed, and excreted after oral administration to mice, rats, and goats. At least 86-94% of an oral dose was absorbed from the gastrointestinal tract in rats. Once absorbed, 2,4-D was widely distributed throughout the body, but did not accumulate because of its rapid clearance from the plasma and rapid urinary excretion. 2,4-D was excreted rapidly and almost exclusively (85-94%) in urine by 48 h after treatment, primarily as unchanged 2,4-D. No metabolites have been reported apart from conjugates. Pharmacokinetic studies with salts and esters of 2,4-D have shown that the salts dissociate and the esters are rapidly hydrolysed to 2,4-D. The similarity in the fate of 2,4-D and its salts and esters explains their similar toxicities.

In humans who have ingested 2,4-D, it was quickly absorbed and excreted rapidly in the urine; about 73% of the administered dose was found in the urine after 48 h. No metabolites were detected.

After dermal applications of 2,4-D to volunteers, 5.8% of the dose was absorbed within 120 h. When the acid and its dimethylamine (DMA) salt were applied, 4.5% of the acid and 1.8% of the salt were absorbed, and of this 85% of the acid and 77% of the salt were recovered in the urine 96 h after application.

2,4-D, its amine salts and its esters are slightly toxic when administered orally or dermally, the oral LD<sub>50</sub> values being 400-2000 mg/kg bw and the dermal LD<sub>50</sub> value generally exceeding 2000 mg/kg bw. In rats exposed to 2,4-D at the maximum attainable concentration (up to 5.4 mg/litre) by inhalation for 4 h, no deaths were seen. While 2,4-D and its amine salts and esters do not induce dermal irritation in rabbits or dermal sensitization in guinea-pigs, they cause severe eye irritation in rabbits. WHO has classified 2,4-D as 'moderately hazardous'.

In mice fed diets that provided 2,4-D at doses of 0, 5, 15, 45, or 90 mg/kg bw per day for three months, renal lesions were observed in animals of both sexes at all doses. An NOAEL was not identified.

In mice fed diets that provided doses of 2,4-D of 0, 1, 15, 100, or 300 mg/kg bw per day for 90 days, treatment-related changes were observed in animals of both sexes at 100 mg/kg bw per day and above. These effects included decreases in glucose level in females, decreases in thyroxine activity in males, and increases in absolute and relative kidney weights in males. The NOAEL was 15 mg/kg bw per day.

In rats fed diets providing doses of 2,4-D of 0, 1, 5, 15 or 45 mg/kg bw per day for 90 days, renal lesions were observed at 5 mg/kg bw per day and above. The NOAEL was 1 mg/kg bw per day.

In rats fed diets providing doses of 2,4-D of 0, 1, 15, 100, or 300 mg/kg bw per day for 90 days, treatment-related changes were observed in animals of both sexes at 100 mg/kg bw per day and above. These effects included decreases in body-weight gain, haematological and clinical chemical alterations, changes in organ weights, and histopathological lesions in the adrenals, liver, and kidneys. The NOAEL was 15 mg/kg bw per day.

In six studies of toxicity rats fed diets containing the diethanolamine (DEA), DMA, isopropylamine (IPA), or tri-isopropanolamine (TIPA) salt or the butoxyethylhexyl (BEH) or 2-ethylhexyl (EH) ester at acid-equivalent doses of 0, 1, 15, 100, or 300 mg/kg bw per day for 13 weeks, the results demonstrated the comparable toxicity of the acid, salts and esters. The NOAEL was 15 mg acid equivalent per kg bw per day for all six compounds.

Dogs were given gelatin capsules containing 2,4-D at 0, 0.3, 1, 3, or 10 mg/kg bw per day or diets containing 2,4-D, the DMA salt, or the EH ester at acid-equivalent doses of 0, 0.5, 1, 3.8, or 7.5 mg/kg bw per day for 13 weeks. Treatment-related findings were observed in the three studies at 3 mg/kg bw per day and above. The NOAEL was 1 mg acid equivalent per kg bw per day in all three studies.

In a two-year study of toxicity and carcinogenicity, mice were fed diets providing doses of 2,4-D of 1, 15, or 45 mg/kg bw per day. Increases in absolute and/or relative kidney weights

and renal lesions were observed at 15 and 45 mg/kg bw per day. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg bw per day.

In another two-year study of toxicity and carcinogenicity, mice were fed diets providing doses of 2,4-D of 0, 5, 62, or 120 mg/kg bw per day (males) or 0, 5, 150, or 300 mg/kg bw per day (females). Dose-related increases in absolute and/or relative kidney weights and renal lesions were observed in animals of both sexes at 62 mg/kg bw per day and above. There was no evidence of carcinogenicity. The NOAEL was 5 mg/kg bw per day.

In another two-year study, rats received diets providing doses of 2,4-D of 0, 1, 5, 15, or 45 mg/kg bw per day. Renal lesions were observed in animals of both sexes at 5 mg/kg bw per day and above. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg bw per day.

In a further two-year study, rats were fed diets providing doses of 2,4-D of 0, 5, 75, or 150 mg/kg bw per day. Treatment-related effects were observed in animals of both sexes at 75 mg/kg bw per day and above. The effects included decreases in body-weight gain and food consumption, increases in serum alanine and aspartate aminotransferase activities, decreased thyroxine concentrations, increases in absolute and relative thyroid weights and histopathological lesions in the eyes, kidneys, liver, lungs, and mesenteric fat. There was no evidence of carcinogenicity. The NOAEL was 75 mg/kg bw per day in males and 5 mg/kg bw per day in females.

Dogs were fed diets providing doses of 2,4-D of 0, 1, 5, or 7.5 mg/kg bw per day for 52 weeks. At 5 and 7.5 mg/kg bw per day body-weight gain was decreased, increases were observed in blood urea nitrogen, creatinine, alanine aminotransferase activity, and cholesterol, and histopathological lesions were observed in the kidneys and liver. The NOAEL was 1 mg/kg bw per day.

In a two-generation study of reproductive toxicity, rats received dietary doses of 2,4-D of 0, 5, 20, or 80 mg/kg bw per day. Reduced body weight in F<sub>1</sub> dams and renal lesions in F<sub>0</sub> and F<sub>1</sub> adults were observed at 20 and 80 mg/kg bw per day. The NOAEL for parental and reproductive toxicity was 5 mg/kg bw per day.

In order to evaluate the dermal toxicity of 2,4-D and its salts and esters, rabbits received 15 dermal applications of the acid, the DEA, DMA, IPA, or TIPA salt or the BEH or EH ester at acid-equivalent doses of 0, 10, 100, or 1000 mg/kg bw per day for 6 h per day on five days per week for 21 days. No systemic toxicity was observed at any dose, and no dermal toxicity was observed with the acid, the TIPA salt, or the BEH ester. Dermal lesions were observed in rabbits treated with the DEA, DMA, or IPA salt, or the EH ester at 100 mg/kg bw per day and above. The lesions were characterized as acanthosis, hyperkeratosis, oedema, inflammation, and epidermal hyperplasia. The NOAEL was 10 mg acid equivalent per kg bw per day for dermal toxicity and 1000 mg acid equivalent per kg bw per day (the highest dose tested) for systemic toxicity.

In a study of developmental toxicity, pregnant Sprague-Dawley rats were given 2,4-D

in corn oil by gavage at doses of 12, 25, 50, 75, or 88 mg/kg bw per day during days 6-15 of gestation. There was no maternal toxicity. Fetotoxicity was manifested as decreased fetal body weights at 50 mg/kg bw per day and above. The NOAELs were 88 mg/kg bw per day for maternal toxicity and 25 mg/kg bw per day for developmental toxicity.

In a further study, pregnant Fischer 344 rats received 2,4-D in corn oil by gavage at doses of 8, 25, or 75 mg/kg bw per day during days 6-15 of gestation. Decreased body-weight gain of the dams during the dosing period and increased incidences of skeletal variations (7th cervical and 14th rudimentary ribs and missing sternbrae) were observed at 75 mg/kg bw per day. The NOAEL was 25 mg/kg bw per day for both maternal and developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters was evaluated in pregnant rats after oral administration during days 6-15 of gestation. The acid-equivalent doses were 11, 55, or 110 mg/kg bw per day for the DEA salt; 12, 50, or 100 mg/kg bw per day for the DMA salt; 9, 25, or 74 mg/kg bw per day for the IPA salt; 12, 37, or 120 mg/kg bw per day for the TIPA salt; 17, 50, or 120 mg/kg bw per day for the BEH ester; and 10, 30, or 90 mg/kg bw per day for the EH ester. The maternal and developmental toxicities of the salts and esters of 2,4-D were comparable to those of the acid. Maternal toxicity, as evidenced by reduced body-weight gain during treatment, was observed in all dams at the high dose of each compound; in addition, mortality, clinical signs, and reduced food consumption were observed in dams given 120 mg/kg bw TIPA salt per day. Although embryo- and fetotoxicity and teratogenicity were observed with the high dose of the TIPA salt, this may be attributed to maternal toxicity; none of the other compounds had such effects. No external gross or visceral anomalies (malformations or variations) were observed in any of the fetuses, but skeletal variations were observed at the high dose of each compound except the IPA salt which were similar to those seen in the fetuses of dams given the acid. The overall NOAELs were approximately 10 mg acid equivalent per kg bw per day for maternal toxicity and 50 mg acid equivalent per kg bw per day for developmental toxicity.

In a study of developmental toxicity, pregnant rabbits were given 2,4-D orally at 0, 10, 30, or 90 mg/kg bw per day during days 6-18 of gestation. Maternal toxicity, which included clinical signs, abortions, and reduced body-weight gain during and after the treatment period, was observed only at the high dose. No gross, visceral, or skeletal malformations or variations were observed in the fetuses at any dose. The NOAELs were 30 mg/kg bw per day for maternal toxicity and 90 mg/kg bw per day (the highest dose tested) for developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters was evaluated in rabbits after oral administration during days 6-18 of gestation. The acid-equivalent doses were 10, 30, or 60 mg/kg bw per day for the DEA salt; 10, 30, or 90 mg/kg bw per day for the DMA salt; 13, 38, or 95 mg/kg bw per day for the IPA salt; and 10, 30, or 75 mg/kg bw per day for the TIPA salt and the BEH and EH esters. Unlike 2,4-D, which produced maternal toxicity only at the high dose, most of the amine salts and the esters were maternally toxic at the middle and high doses, as evidenced by mortality, clinical signs of neurotoxicity, abortions, and decreases in body-weight gain. No gross, visceral, or skeletal malformations or variations were observed in the fetuses at any dose. The overall NOAELs

were approximately 10 mg acid equivalent per kg bw per day for maternal toxicity and 90 mg acid equivalent per kg bw per day (the highest dose tested) for developmental toxicity.

In summary, of the four salts tested for developmental toxicity only the TIPA salt exhibited developmental toxicity in rats and only at a maternally toxic dose; no developmental toxicity was observed in rabbits with this or the other salts. Consequently, the Meeting concluded that the developmental toxicity of the TIPA salt is of little concern.

The genotoxic potential of 2,4-D has been adequately evaluated in a range of assays *in vivo* and *in vitro*. Overall, the responses observed indicate that 2,4-D is not genotoxic, although conflicting results were obtained for mutation in *Drosophila*. In a more limited range of assays, the DEA, DMA, IPA, and TIPA salts and the BEH and the EH esters were not genotoxic *in vivo* or *in vitro*. The Meeting concluded that 2,4-D and its salts and esters are not genotoxic.

In rats given single doses of 2,4-D of 0, 15, 75, or 250 mg/kg bw by gavage, there were no treatment-related gross or neuropathological changes at any dose. Animals of both sexes at the highest dose exhibited inco-ordination and gait abnormalities on day 1, but the signs disappeared by day 5. The NOAEL was 75 mg/kg bw. When rats were fed diets containing 2,4-D at doses of 0, 5, 75, or 150 mg/kg bw per day for 12 months neurotoxicity, manifested as increased relative forelimb grip strength, was observed in animals of both sexes at 150 mg/kg bw per day. The NOAEL was 75 mg/kg bw per day.

Epidemiological studies have suggested an association between the development of soft-tissue sarcoma and non-Hodgkin's lymphoma and exposure to chlorophenoxy herbicides, including 2,4-D. The results of these studies are not, however, consistent; the associations found are weak, and conflicting conclusions have been reached by the investigators. Most of the studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of phenoxy herbicides, a group that includes 2,4,5-T which can be contaminated with dioxins. Case-control studies provide little evidence of an association between the use of 2,4-D and soft-tissue sarcomas. Although some case-control studies have shown a relationship with non-Hodgkin's lymphoma others (even the positive studies) have produced inconsistent results, raising doubt about the causality of the relationship. Cohort studies of exposed workers have not confirmed the hypothesis that 2,4-D causes either neoplasm.

The Meeting was informed of the on-going "Agricultural Health Study" initiated in North Carolina and Iowa, and of a study of pesticide applicators in Finland. The Agricultural Health Study addresses both cancer and non-cancer risks, including neurotoxicity, reproductive effects, immunological effects, kidney disease, non-malignant respiratory disease, and growth and development of children, in men and women directly exposed to pesticides and other agricultural agents.

The Meeting concluded that the toxicities of the salts and esters of 2,4-D were comparable to that of the acid. An ADI was therefore established for the sum of 2,4-D and its salts and esters, expressed as 2,4-D. An ADI of 0-0.01 mg/kg bw was established on the basis of the NOAEL of 1 mg/kg bw per day in the one-year study of toxicity in dogs and the two-

year study in rats, using a safety factor of 100.

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

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 15 mg/kg bw per day (13-week study of toxicity)

5 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 1 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

5 mg/kg bw per day (two-generation study of reproductive toxicity)

10 mg acid-equivalent/kg bw per day (maternal toxicity in a series of studies of developmental toxicity with salts and esters)

15 mg acid-equivalent/kg bw per day (series of 13-week studies of toxicity with salts and esters)

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

Rabbit: 10 mg acid-equivalent/kg bw per day (maternal toxicity in a series of studies of developmental toxicity with salts and esters)

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

90 mg acid-equivalent/kg bw per day (highest dose tested in studies of developmental toxicity with the acid and its salts and esters)

Dog: 1 mg/kg bw per day (13-week and one-year studies of toxicity)

#### Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw (sum of 2,4-D and its salts and esters expressed as 2,4-D)

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

1. Follow-up of the Agricultural Health Study in North Carolina and Iowa in the USA.
2. Follow-up of the study of pesticide applicators in Finland.

**Toxicological criteria for setting guidance values for dietary and non-dietary exposure to 2,4-dichlorophenoxyacetic acid and its amine salts and esters.**

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULTS, REMARKS
Short-term (1-7 days)	Oral toxicity, rat (acid, salts and esters)	LD <sub>50</sub> = 400-2000 mg/kg bw
	Dermal toxicity, rabbit (acid, salts and esters)	LD <sub>50</sub> >2000 mg/kg bw
	Inhalation toxicity, rat (acid, salts and esters)	LC <sub>50</sub> >0.84-5.4 mg/litre
	Dermal irritation, rabbit (acid, salts and esters)	Not irritating
	Ocular irritation, rabbit (acid, salts and esters)	Severely irritating
	Dermal sensitization, guinea-pig (acid, salts and esters)	Not sensitizing
	Oral, single dose, neurotoxicity, rat (acid)	NOAEL = 75 mg/kg bw
Medium-term (1-26 weeks)	Dietary, three months, toxicity, mouse	NOAEL = 15 mg/kg bw per day, renal toxicity
	Dietary, three months, toxicity, rat	NOAEL = 1 mg/kg bw per day, renal lesions
	Dietary, three months, toxicity, rat (salts and esters)	NOAEL = 15 mg/kg acid-equivalent/kg bw per day, renal toxicity
	Dietary or capsule, three months, toxicity, dog	NOAEL = 1 mg acid-equivalent/kg bw per day, reduced body-weight gain and other systemic toxicity
	Dermal, 21 days, repeated dose, rabbit (acid, salts and esters)	NOAEL = 1000 mg acid-equivalent/kg bw per day, highest dose tested
	Dietary, two generations, reproductive toxicity, rat	NOAEL = 5 mg/kg bw per day, reduced body weights in F <sub>1</sub> dams and renal lesions in F <sub>0</sub> and F <sub>1</sub> adults
	Oral, gavage, developmental toxicity, rat	NOAEL = 25 mg/kg bw per day, maternal and developmental toxicity
	Oral, gavage, developmental toxicity, rat (salts and esters)	NOAEL = 10 mg acid-equivalent/kg bw per day for maternal toxicity and 50 mg acid-equivalent/kg bw per day for developmental toxicity
	Oral, gavage, developmental toxicity, rabbit	NOAEL = 30 mg/kg bw per day, maternal toxicity; >90 mg/kg bw per day, developmental toxicity
	Oral, gavage, developmental toxicity, rabbit (salts and esters)	NOAEL = 10 mg acid-equivalent/kg bw per day for maternal toxicity; 90 mg acid-equivalent/kg bw per day (highest dose

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULTS, REMARKS
		tested) for developmental toxicity
Long-term (≥ one year)	Dietary, two years, toxicity and carcinogenicity, mouse	NOAEL = 5 mg/kg bw per day, renal effects; no evidence of carcinogenicity
	Dietary, two years, toxicity and carcinogenicity, rat	NOAEL = 1 mg/kg bw per day, renal lesions; no evidence of carcinogenicity
	Dietary, one year, toxicity, dog	NOAEL = 1 mg/kg bw per day, changes in serum chemistry and lesions in kidneys and liver

**4.8 DDT (021)**

**RESIDUE AND ANALYTICAL ASPECTS**

DDT was first evaluated in 1966 and has been reviewed several times since. The 1993 and 1994 Meetings proposed ERLs for carrots, eggs, meat and milks and confirmed the existing ERL for cereal grains. The 1995 CCPR was informed that additional data on residues in meat were available from Australia, New Zealand and the USA and decided to keep the proposal for meat (1 mg/kg in the fat) at Step 3 pending the evaluation of these data by the 1996 JMPR. The 28th Session of the CCPR (1996) advanced all ERLs except that for meat to Step 8. The existing temporary CXL for meat (from mammals other than marine mammals) is 5 mg/kg (fat).

The Meeting received data on residues in meat from national residue surveys in Australia, Germany, New Zealand, Norway, Thailand, the UK and the USA.

In all, 162,102 samples of meat fat were analyzed in Australia, Germany, Norway, Thailand, the UK and the USA, and residues above 1 mg/kg were found in 85 samples (0.05%). Residues found in New Zealand were of another data population: 1.6% of the 4682 samples analyzed (lambs, adult sheep, adult bovines, suckling calves, pigs, deer and goats) were higher than the proposed ERL of 1 mg/kg, 0.53% were higher than 2 mg/kg and 0.04% higher than 5 mg/kg.

On the basis of the data on residues received from the government of New Zealand, the Meeting concluded that the temporary CXL of 5 mg/kg for meat (fat) should be confirmed.

**4.9 DIAZINON (022)**



## RESIDUE AND ANALYTICAL ASPECTS

Diazinon was first evaluated by the 1965 JMPR and has been reviewed several times since. In 1993 a periodic review was conducted and in 1994 a new MRL was recommended for hops. The 1993 JMPR recommended, among other items, an increase in the CXL for pome fruits from 0.5 to 2 mg/kg and the withdrawal of the CXLs for animal commodities in the absence of animal transfer studies and data from uses to control ectoparasites.

The CCPR in 1995 and 1996 endorsed most of the recommendations of the 1993 JMPR with the exception of the proposed MRL for pome fruits and the recommended withdrawal of the CXLs for milks and the meat of cattle, pigs and sheep. The main focus of the present evaluation was the review of new submissions in support of MRLs for animal products: the Meeting also estimated STMR levels for pome fruits, tomatoes and cabbages (0.12, 0.12 and 0.16 mg/kg respectively) for dietary intake predictions, on the basis of data published in the 1993 Evaluations, in response to concerns raised at the CCPR. The Meeting understood that new trials according to current (revised) US GAP might support a lower MRL for pome fruits than the 1993 JMPR recommendation. The manufacturer expects to be able to submit data from these trials together with the relevant GAP when reports of new supervised trials with diazinon used for the control of ectoparasites are submitted in 1998.

The Meeting reviewed information on current GAP, new and previously submitted metabolism studies and analytical methods, new residue transfer studies with poultry and cattle, and new and previously submitted data from supervised trials of ectoparasite control in cattle and sheep using a variety of application methods. Many of the older supervised trials were not acceptable by current standards and in most cases acceptable data were available only for single treatments whereas GAP allows multiple applications. The Meeting was able to estimate a number of maximum residue levels, but considered additional information on GAP to be highly desirable.

Maximum residue levels recommended for use as MRLs, together with estimated STMR levels, are recorded in Annex I.

## FURTHER WORK OR INFORMATION

### Desirable

1. Studies of the stability of diazinon, diazoxon and hydroxydiazinon in stored analytical samples of meat, fat, edible offal, milk and eggs.
2. Modern dipping and spray trials on sheep and cattle at maximum GAP rates and including multiple dips and sprays. Analyses for diazinon residues in milk, muscle, edible offal and fat (kidney, omental and especially subcutaneous fat) would be desirable, as well as analyses for diazoxon and hydroxydiazinon in addition to diazinon.
3. Data from monitoring analyses of subcutaneous fat of sheep for diazinon, ideally sheep known to have received multiple dip or spray applications at maximum GAP rates.

4. Submission, when the new supervised trials of ectoparasite control are submitted in 1998, of information on current US GAP for pome fruits and cabbages and data from recently completed US supervised trials reflecting that GAP.

#### **4.10 DIMETHOATE, OMETHOATE, AND FORMOTHION (027, 055, 042)**

### **TOXICOLOGY**

Dimethoate was previously evaluated for toxicological effects by the Joint Meeting in 1963, 1965, 1967, 1984, and 1987. In 1987, an ADI of 0-0.01 mg/kg bw was established, on the basis of a no-effect level of 0.2 mg/kg bw per day for the inhibition of erythrocyte acetylcholinesterase in volunteers. The compound was reviewed at the present Meeting within the CCPR periodic review programme.

Omethoate (the oxygen analogue of dimethoate, which has been used as a pesticide in its own right) was evaluated for toxicological effects by the Joint Meeting in 1971, 1975, 1978, 1979, 1981, and 1985. An ADI of 0-0.0003 mg/kg bw was allocated in 1985. The Meeting was informed that the primary manufacturer is no longer producing omethoate; however, since the use of dimethoate on agricultural crops can lead to residues of omethoate in treated produce, the toxicity of omethoate is important in the context of the potential use of dimethoate. Information on the absorption, distribution, excretion, metabolism, and toxicity of omethoate was therefore also considered by the Meeting. These data were taken from published sources such as previous JMPR evaluations of omethoate and national reviews; the original reports were not available for detailed evaluation.

Formothion (an aldehyde derivative of dimethoate, which has also been used as a pesticide in its own right, but is no longer supported by the manufacturer) was evaluated for toxicological effects in 1969 and 1973. An ADI of 0-0.02 mg/kg bw was allocated in 1973. Since the use of dimethoate does not lead to residues of formothion in treated produce, the toxicity of formothion was not considered at the present Meeting.

Preparation of this review was aided by reference to the results of previous reviews conducted by the Pesticides Safety Directorate, United Kingdom.

#### *Dimethoate*

Dimethoate was rapidly and extensively absorbed from the gut and rapidly excreted. There was no accumulation in fat tissue. In rats and humans up to 90% of radiolabel was found in the urine within 24 h. The report of a study with methylcarbamoil-labelled dimethoate indicated that up to 18% of the administered label was excreted in expired air. Four metabolites with anticholinesterase activity have been identified in rats and humans. One seems to result from thiono oxidation, leading to the formation of the oxygen analogue of dimethoate, omethoate; this step was followed by hydrolysis to a thiocarboxyl product, said to be the main metabolite in rats and humans.

Data on the acute oral toxicity of dimethoate gave LD<sub>50</sub> values of about 310 mg/kg bw in rats, 150 mg/kg bw in mice, and 55 mg/kg bw in hens. The signs of toxicity were those

typical of cholinesterase inhibition. WHO has classified dimethoate as "moderately hazardous".

In short-term and long-term studies at dietary concentrations of 75 ppm or above, there were minor reductions in body-weight gain and food consumption. Apart from the inhibition of cholinesterase activity, dimethoate had no effect on the composition of the blood or urine. The liver weights of animals treated at the higher doses tended to be lower than those of the control groups; there were however no microscopic changes, and the effect is unlikely to be of toxicological significance. Investigations of toxicity at higher doses were limited by effects due to cholinesterase inhibition. The NOAELs were thus generally based on reductions in acetylcholinesterase activity in the brain or erythrocytes. On the basis of minimal reductions in acetylcholinesterase activity of 10-20%, the NOAEL in a 12-month study in dogs at doses of 0, 5, 20, or 125 ppm was 5 ppm, equal to 0.2 mg/kg bw per day; in rats the NOAEL in a life-span study at doses of 0, 1, 5, 25, or 100 ppm was 1 ppm, equal to 0.04 mg/kg bw per day. In mice, an NOAEL was not identified, as cholinesterase activity was depressed at all doses after 52 weeks of treatment in a life-span study at doses of 0, 25, 100, or 200 ppm.

The results of long-term studies of toxicity and carcinogenicity in mice (at 0, 25, 100, or 200 ppm) and rats (at 0, 5, 25, or 100 ppm) reported in 1986 and studies reported in 1977 indicate that dimethoate is not carcinogenic to rodents.

In a multigeneration study of reproductive toxicity conducted in 1989-1990 with doses of 0, 1, 15, or 65 ppm, the reproductive performance of rats was impaired at the high dose. The NOAEL for reproductive toxicity appeared to be 15 ppm (equal to 1.2 mg/kg bw per day) and that for parental toxicity was 1 ppm (equal to 0.08 mg/kg bw per day) on the basis of cholinesterase inhibition, but the Meeting noted that there was some indication that reproductive performance may have been affected at lower doses. In a multigeneration study of reproductive toxicity in mice in 1965 at doses of 0, 5, 15 or 50 ppm, there was no overt effect on reproductive capacity, even in the presence of cholinergic toxicity. In a poorly reported study in rabbits, sperm numbers and quality were adversely affected at doses equivalent to one-tenth and one-hundredth of the LD<sub>50</sub>.

Studies of developmental toxicity in rats (at 0, 3, 6, or 18 mg/kg bw per day on days 6-15 of gestation) and rabbits (at 0, 10, 20, or 40 mg/kg bw per day on days 7-19 of gestation) provided no evidence of a teratogenic effect, although maternal toxicity was observed at the high dose in rats and at the high and middle doses in rabbits.

After reviewing the available data on genotoxicity the Meeting concluded that although *in-vitro* studies indicate that dimethoate has mutagenic potential, this potential does not appear to be expressed *in vivo*.

Undiluted dimethoate formulations were irritating to the eye in rabbits. Skin irritation was minimal and confined to slight, transient erythema. Dimethoate was not a skin sensitizer in guinea-pigs, but a 32.7% emulsifiable concentrate formulation induced sensitization in one of 10 guinea-pigs. In a published paper, dimethoate was cited in four human cases of contact dermatitis, and sensitization was confirmed in these individuals by patch testing.

In hens given a single dose of 55 mg/kg bw by subcutaneous injection or orally, dimethoate did not induce delayed neurotoxicity.

In a 39-day study in nine male and female volunteers, the NOAEL for cholinesterase

inhibition was 0.2 mg/kg bw per day. This NOAEL was supported in seven other studies, each involving 6-20 volunteers who received doses ranging from 0.04 to 1.0 mg/kg bw per day for periods up to 57 days.

### *Omethoate*

The oral LD<sub>50</sub> of omethoate in rats was approximately 25 mg/kg bw. The signs of reaction to treatment with omethoate were those consistent with cholinesterase inhibition.

In short-term and long-term studies, the potential toxicity of omethoate was limited by the onset of cholinesterase inhibition. In a 12-month study of toxicity in dogs at doses of 0, 0.025, 0.12, or 0.62 mg/kg bw per day by gavage, the NOAEL was 0.025 mg/kg bw per day on the basis of the inhibition of acetylcholinesterase activity. In life-span studies in rats (at 0, 0.3, 1, 3, or 10 ppm) and mice (0, 1, 3, or 10 ppm), there was no evidence of oncogenic potential. The study in mice was unsuitable for deriving an NOAEL because acetylcholinesterase activity was not investigated; the NOAEL in rats was 0.3 ppm (equivalent to 0.015 mg/kg bw per day) on the basis of the inhibition of acetylcholinesterase activity.

In multigeneration studies of reproductive toxicity in rats at 0, 1, 3, or 10 ppm, a dietary concentration of 10 ppm was associated with reduced viability of the pups; there was evidence that this effect extended to animals treated at 3 ppm. The NOAEL was 1 ppm (equivalent to 0.05 mg/kg bw per day). In a further multigeneration study of reproductive toxicity in rats at doses of 0, 0.5, 3, or 18 ppm in the drinking-water, there was evidence of epididymal vacuolation and fewer pups per dam at the high dose; these pups had lower weight gains and were less viable. The precoital time was increased and the number of non-pregnant females was greater than among controls. The NOAEL for reproductive performance was 3 ppm (equivalent to 0.2 mg/kg bw per day), but cholinesterase inhibition was detected at the lowest dose of 0.5 ppm. In studies of developmental toxicity, there was no evidence of teratogenicity in rats given 0, 0.3, 1, or 3 mg/kg bw omethoate per day on days 6-15 of gestation or in rabbits given 0, 0.1, 0.3, or 1 mg/kg bw omethoate per day on days 6-18 of gestation.

Omethoate has been extensively investigated for genotoxicity *in vitro* and *in vivo*. The Meeting concluded that it has clear mutagenic potential but that the weight of the evidence observed *in vivo* was negative; however, the positive result obtained in a mouse spot test could not be completely disregarded.

In studies in hens given single oral doses of 20-300 mg/kg bw, omethoate did not induce delayed neurotoxicity.

### *Conclusions*

An ADI of 0-0.002 mg/kg bw was established for dimethoate on the basis of the apparent NOAEL of 1.2 mg/kg bw per day for reproductive performance in the study of reproductive toxicity in rats, applying a safety factor of 500. Although a safety factor of 100 would normally be used in deriving an ADI from a study of this type, the Meeting was concerned about the possibility that reproductive performance may have been affected at 1.2 mg/kg bw per day in this study and therefore used a higher-than-normal safety factor. No data were available to assess whether the effects on reproductive performance were secondary to the inhibition of cholinesterase. The Meeting concluded that it was not appropriate to base the ADI on the results of the studies of volunteers since the crucial end-point (reproductive performance) has not been assessed in humans.

This ADI would usually be used only when assessing the intake of dimethoate itself. As the use of dimethoate on crops can give rise to residues of omethoate, and omethoate has been used as a pesticide in its own right, previous Joint Meetings have allocated an ADI to omethoate; however, the primary manufacturer is no longer producing omethoate. The Meeting noted that omethoate is considerably more toxic than dimethoate; however, the levels of residues of omethoate resulting from the use of dimethoate on crops are likely to be low. The Meeting therefore recommended that residues of dimethoate and omethoate resulting from the use of dimethoate be expressed as dimethoate and be assessed in comparison with the ADI for dimethoate.

As the primary manufacturer is no longer producing either omethoate or formothion, toxicological data on these compounds were not made available to the Meeting. The previous ADIs of 0-0.0003 mg/kg bw for omethoate and 0-0.02 mg/kg bw for formothion were therefore withdrawn.

There may be a need to re-evaluate the toxicity of dimethoate after the periodic review of the residue and analytical aspects of dimethoate has been completed if it is determined that omethoate is a major residue.

A toxicological monograph on dimethoate was prepared, summarizing the data received since the previous evaluation and including summaries of the data presented in previous monographs and monograph addenda.

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect (dimethoate)

Rat: 1 ppm, equal to 0.04 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

15 ppm, equal to 1.2 mg/kg bw per day (reproductive performance in a study of reproductive toxicity)

1 ppm, equal to 0.08 mg/kg bw per day (parental toxicity in a study of reproductive toxicity)

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

## dimethoate, omethoate, and formothion

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

Dog: 5 ppm, equal to 0.2 mg/kg bw per day (52-week study of toxicity)

Human: 0.2 mg/kg bw per day (39-day study of cholinesterase inhibition)

Estimate of acceptable daily intake for humans

0-0.002 mg/kg bw (sum of dimethoate and omethoate expressed as dimethoate)

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

1. Further multigeneration study of reproductive toxicity in rats using dimethoate.
2. Mouse spot test using dimethoate.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT/REMARKS
Short term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> = 310 mg/kg bw
	Dermal toxicity, rat	LD <sub>50</sub> >7000 mg/kg bw
	Dermal irritation, rabbit	Slightly irritating
	Ocular irritation, rabbit	Slightly irritating
	Dermal sensitization, human	Positive
Medium term (1-26 weeks)	Repeated dermal, 21 days, toxicity, rabbit	NOAEL = 1000 mg/kg bw per day (highest dose tested)
	Repeated oral, reproductive toxicity, rat	NOAEL = 1.2 mg/kg bw per day, reproductive toxicity NOAEL = 0.08 mg/kg bw per day, parental toxicity
	Repeated oral, developmental toxicity, rat	NOAEL = 6 mg/kg bw per day, maternal toxicity. No evidence of embryotoxicity or teratogenicity at 18 mg/kg bw per day (highest dose tested)
	Repeated oral, developmental toxicity, rabbit	NOAEL = 10 mg/kg bw per day, maternal toxicity. No evidence of embryotoxicity or teratogenicity at 40 mg/kg bw per day (highest dose tested)
Long term (≥one year)	Repeated oral, toxicity and carcinogenicity, rat	NOAEL = 0.04 mg/kg bw per day, cholinesterase inhibition

**4.11 DISULFOTON (074)**

## TOXICOLOGY - ACUTE DIETARY RISK

The twenty-eighth Session of the CCPR raised the issue of the acute toxicity of disulfoton residues and requested the JMPR to derive an acute reference dose.

An ADI of 0-0.0003 mg/kg bw was established for disulfoton by the 1991 Meeting on the basis of an NOAEL of 1 ppm, equal to 0.03 mg/kg bw per day, for the inhibition of brain acetylcholinesterase activity in a two-year study in dogs. This ADI was supported by an NOAEL of 1 ppm, equal to 0.06 mg/kg bw per day, for the inhibition of brain acetylcholinesterase activity in a two-year study in rats.

Disulfoton was not carcinogenic or teratogenic and caused no toxicity other than that associated with acetylcholinesterase inhibition.

Groups of 10 male and 10 female Sprague-Dawley rats, 8-9 weeks old, were given single doses of disulfoton dissolved in polyethylene glycol 400 at 5 ml/kg bw by gavage. The doses were 0, 0.25, 0.75, or 1.5 mg/kg bw for females and 0, 0.25, 1.5, or 5.0 mg/kg bw for males. A functional observational battery and testing of motor activity were carried out 1.5-4 h after treatment. Plasma cholinesterase and erythrocyte acetylcholinesterase activities were determined 24 h after treatment.

Erythrocyte acetylcholinesterase activity was inhibited by 10% in males at the middle dose and 21% in those at the high dose and by 12, 53, and 75% in females at the low, middle and high doses respectively. Plasma cholinesterase activity was inhibited to a similar extent in males but to a lesser extent than that of erythrocyte acetylcholinesterase in females. Clear cholinergic signs were observed in males at 5 mg/kg bw and in females at 1.5 and 0.75 mg/kg bw. The signs appeared on day 0 of dosing but had disappeared by day 3. Functional and motor activity testing showed treatment-related effects at the same doses (Sheets, 1993a). Since cholinesterase activity was not determined when the maximal clinical score was reached, another study was conducted.

Groups of six male and six female fasted Sprague-Dawley rats were given technical-grade disulfoton (purity 99.0%) at doses of 0, 0.25, 0.75 (females only), 1.5, or 5.0 (males only) mg/kg bw by gavage. Cholinesterase activity was determined in the plasma, erythrocytes and brain 3 h after treatment, i.e. approximately at the time of peak clinical signs. Brain acetylcholinesterase activity was inhibited less than that in erythrocytes and plasma. The results are shown in Table 1. The NOAEL for the inhibition of brain acetylcholinesterase activity was 0.25 mg/kg bw in both males and females (Sheets, 1996).

Table 1. Cholinesterase activity 3 h after a single dose of disulfoton<sup>1</sup>

DOSE (mg/kg bw)	SEX	% OF CONTROL CHOLINESTERASE ACTIVITY		
		PLASMA	ERYTHROCYTES	BRAIN
0.25	Female	96	96	97
	Male	94	93	108
0.75	Female	28	55	51
1.50	Male	54	40	73

## disulfoton

5.00	Female	13	21	38
	Male	28	18	42

<sup>1</sup> Percentages of activity of the concurrent controls. For plasma and erythrocyte cholinesterase activities similar percentages were obtained when calculated on the basis of pre-exposure activity

An acute reference dose of 0.003 mg/kg bw was established on the basis of the absence of inhibition of brain acetylcholinesterase activity and clinical signs at 0.25 mg/kg bw in rats treated with a single dose by gavage, applying a 100-fold safety factor.

### References

Sheets, L.P. (1993) An acute oral neurotoxicity screening study with technical grade disulfoton (DI-SYSTON) in rats. Unpublished report No. 92-412-OB from Miles Inc., Stilwell, KS, USA. Submitted to WHO by Bayer AG, Wuppertal, Germany.

Sheets, L.P. (1996) Cholinesterase results from an acute oral study with technical grade disulfoton (DI-SYSTON). Summary report No. 96-412-JH from Miles Inc., Stilwell, KS, USA. Submitted to WHO by Bayer AG, Wuppertal, Germany.

## **4.12 DITHIOCARBAMATES (105)**

### **RESIDUE AND ANALYTICAL ASPECTS**

Ferbam, thiram and ziram were evaluated at the present Meeting within the CCPR periodic review programme. The information on these compounds is discussed under their respective headings.

Recommended MRLs for dithiocarbamates arising from the uses of thiram and ziram are consolidated under the dithiocarbamate heading. The dithiocarbamate MRLs which rely primarily on ziram data will be temporary until data on environmental fate are evaluated. No MRLs for dithiocarbamates arising from uses of ferbam were recommended.

## **4.13 FENARIMOL (192)**

### **RESIDUE AND ANALYTICAL ASPECTS**

Fenarimol was reviewed as a new compound by the 1995 JMPR and a number of maximum residue levels were estimated. However, since no data were submitted to the FAO Panel on the environmental fate of fenarimol in soil, the 1995 Meeting decided that the estimated levels should be recommended only as temporary MRLs.

The current Meeting received a study demonstrating the storage stability of fenarimol residues in dried hops and agreed to recommend the maximum residue level of 5mg/kg



estimated by the 1995 Meeting as an MRL.

The Meeting also received information on the environmental fate of fenarimol in soil. The data indicated that fenarimol was degraded slowly in field conditions with a half-life typically exceeding 100 days. Photodegradation of the compound occurs, especially in water. Fenarimol has a low mobility in soil with almost all the residue associated with the top layer.

The Meeting was informed that no data on the uptake from soil by crops, the bioavailability of fenarimol residues in soil, or the residues in rotational crops were currently available.

The Meeting considered the data on environmental fate to be satisfactory and hence that the maximum residue levels estimated by the 1995 Meeting should now be recommended as MRLs.

## **FURTHER WORK OR INFORMATION**

### Desirable

1. Full details of the methods of analysis used in all the residue studies where this information was not given. Validation of the methods of analysis for which validation data were not submitted (repeated from 1995 JMPR).
2. Information on the melting point, octanol/water partition coefficient, solubility and specific gravity of pure fenarimol (repeated from 1995 JMPR).
3. Submission of the study reports supporting the trials on apples, gooseberries, currants, gherkins and strawberries conducted in The Netherlands (repeated from 1995 JMPR).
4. Submission of the study on residues in rotational crops which the Meeting was informed would be completed in 1997.
5. An investigation into the uptake of fenarimol residues into crops from soil and their translocation. If the data indicate that measurable residues could occur in rotational crops, then a study to assess the nature of the residues in representative rotational crops.

## **4.14 FERBAM (DITHIOCARBAMATES, 105)**

### **TOXICOLOGY**

Ferbam was evaluated for toxicological effects by the Joint Meeting in 1965, 1967, 1970, 1974, 1977, and 1980. A temporary ADI of 0-0.025 mg/kg bw for ferbam or ferbam in combination with other dimethyldithiocarbamates was allocated in 1967, on the basis of a one-year study in dogs. This temporary ADI was lowered to 0.005 mg/kg bw in 1974. A group ADI of 0-0.02 mg/kg bw for ferbam and ziram was allocated in 1977 and confirmed in 1980. The compound was reviewed by the present Meeting within the CCPR periodic review programme.

Ferbam is well absorbed after oral administration to rats and is extensively metabolized. Most of the administered radiolabel was found in the urine, expired air, and bile. In pregnant rats, a small but significant amount crossed the placenta into the fetus. In lactating rats the radiolabel was secreted into the milk, absorbed by the pups, and excreted in the pups' urine. In expired air the main product was carbon disulfide; in the urine the main products were inorganic sulfate, a salt of dimethylamine, and the glucuronide conjugate of dimethyldithiocarbamic acid.

Ferbam has low acute toxicity and has been classified by WHO as unlikely to present an acute hazard in normal use.

In two four-week studies, rats were fed diets providing ferbam at concentrations of 0, 100, 500, 2500, or 5000 ppm or 0 or 2500 ppm. The NOAEL was 100 ppm, equivalent to 10 mg/kg bw per day, on the basis of growth depression at 500 ppm and above. Post-mortem examination revealed no thyroid abnormalities. In another four-week study in which one dog was given ferbam and ziram together, each at a dose of 5 mg/kg bw per day, the only adverse effect was slight anaemia. In another study a dog remained healthy, except for slight anaemia, when given ferbam alone at a dose of 25 mg/kg bw per day for one month or 50 mg/kg bw per day for one week. An attempt to raise the dose to 100 mg/kg bw per day immediately provoked severe vomiting and malaise.

In a study in which dogs were treated with ferbam at doses of 0.5, 5, or 25 mg/kg bw per day for one year, the NOAEL was 5 mg/kg bw per day, on the basis of convulsions at 25 mg/kg bw per day.

In a two-year study of toxicity and carcinogenicity in rats treated at dietary concentrations of 0, 25, 250, or 2500 ppm the NOAEL was 250 ppm, equivalent to 12 mg/kg bw per day, on the basis of depressed growth rate, shortened life span, neurological changes, cystic brain lesions, and testicular atrophy at 2500 ppm. Carcinogenicity was not demonstrated.

Sperm quality was investigated in mice given oral doses of 0, 250, 500, or 1000 mg/kg bw per day for five consecutive days. The NOAEL was 500 mg/kg bw per day, on the basis of an increased frequency of sperm abnormalities at 1000 mg/kg bw per day.

In a three-generation study of reproductive toxicity in rats fed dietary concentrations of 0 or 250 ppm, the NOAEL was 250 ppm, equivalent to 12 mg/kg bw per day.

Few data were available on genotoxicity. Ferbam did not induce reverse mutation in bacteria.

Ferbam was slightly irritating to the skin and eyes of rabbits. It has weak skin-sensitizing properties in guinea-pigs.

The Meeting concluded that the toxicological data specifically generated for ferbam were inadequate to estimate an ADI. However, because of the similarity of the chemical structure of ferbam to that of ziram and the comparable toxicological profile of the two compounds, ferbam was included in the group ADI of 0-0.003 mg/kg bw for ferbam and ziram, which was derived from the information available on ziram.

A toxicological monograph was prepared, summarizing the data received since the

previous evaluation and relevant data from the previous monograph and monograph addendum.

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 500 mg/kg bw per day (study of sperm quality)

Rat: 100 ppm, equivalent to 10 mg/kg bw per day (one-month study of toxicity)

250 ppm, equivalent to 12 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

250 ppm, equivalent to 12 mg/kg bw per day (study of reproductive toxicity)

Dog: 5 mg/kg bw per day (one-year study of toxicity)

#### Estimate of acceptable daily intake for humans

0-0.003 mg/kg bw (group ADI for ferbam and ziram)

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

1. Studies on dissociation in aqueous solutions.
2. Observations in humans.

**Toxicological criteria for setting guidance values for dietary and non-dietary exposure to ferbam.**

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
Short-term (1-7 days)	Oral toxicity, mouse	LD <sub>50</sub> = 1000 mg/kg bw
	Oral toxicity, rat	LD <sub>50</sub> = 11 000 mg/kg bw
	Inhalation toxicity, rat	LC <sub>50</sub> = 0.3 mg/litre
	Dermal irritation, rabbit	Slightly irritating
	Ocular irritation, rabbit	Slightly irritating
	Dermal sensitization, guinea-pig	Weakly sensitizing
	Repeated oral, 5 days, testicular toxicity, mouse	NOAEL = 500 mg/kg bw per day, increased sperm abnormalities
Medium-term (1-26 weeks)	Repeated oral, 4 weeks, toxicity, rat	NOAEL = 10 mg/kg bw per day, reduced body weight
	Repeated oral, reproductive toxicity, rat	NOAEL = 12 mg/kg bw per day, reproductive toxicity
Long-term (≥ one year)	Repeated oral, two years, toxicity and carcinogenicity, rat	NOAEL = 12 mg/kg bw per day, reduced body weight, shortened life span, neurological changes, cystic brain lesions, and atrophied testes. No carcinogenicity
	Repeated oral, one year, toxicity, dog	NOAEL = 5 mg/kg bw per day, convulsions

## RESIDUE AND ANALYTICAL ASPECTS

Ferbam was originally evaluated in 1965 (toxicology) and 1967 (toxicology and residues) and is included in the dithiocarbamate group of compounds. The compound was evaluated at the present Meeting within the CCPR periodic review programme.

Ferbam is a broad-spectrum fungicide used for the control of certain diseases in fruit trees, small fruits and berries, ornamentals, conifers and tobacco.

The Meeting received information on the metabolism of ferbam in goats and sheep, methods of residue analysis, the stability of residues in stored analytical samples, approved use patterns, notably on fruits and potatoes, and supervised residue trials on mangoes.

When lactating goats were dosed with radiolabelled ferbam the total residues in milk increased for 2 or 3 days and then reached a plateau. Levels of the radiolabel were higher in the liver than in other tissues.

The analytical methods for ferbam residues are the same as those for other dithiocarbamates. They rely on acid hydrolysis to release CS<sub>2</sub>, which may then be measured by head-space gas chromatography or by spectrophotometry. These methods were used to analyse samples from the supervised trials. The Meeting agreed that the definition of the residue of the dithiocarbamates should apply also to ferbam.

Ferbam residues in macerated apples fortified at 1 mg/kg and stored at -20°C were stable for 22 weeks.

The Meeting received data from two supervised residue trials with ferbam on mangoes in the USA, but the data could not be evaluated because information on the relevant GAP was not available.

Generally, the information on ferbam was quite limited. Because of the lack of critical supporting studies the Meeting would not have been able to recommend MRLs for dithiocarbamates based on applications of ferbam even if adequate information on GAP and data from supervised trials were available for some commodities. Recommendations for MRLs for dithiocarbamates are derived from supervised trials with specific dithiocarbamate compounds applied according to the relevant GAP. The compounds for which data have been evaluated and found to be adequate to support the recommended MRLs are indicated in the Table in Annex I. Because of the lack of critical supporting studies ferbam is not included in the list of dithiocarbamates with adequate data to support recommended MRLs for dithiocarbamates.

## FURTHER WORK OR INFORMATION

Desirable

1. An adequate set of critical supporting studies for ferbam is needed before it can be included in the list of compounds supporting recommended MRLs for dithiocarbamates (See report of 1995 JMPR, Section 2.5.2).
2. Information on attempts to develop specific methods of analysis for ferbam, whether successful or not.

#### 4.15 FLUMETHRIN (195)

$\alpha$ -cyano-4-fluoro-3-phenoxybenzyl 3-( $\alpha$ ,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate

Flumethrin is a fat-soluble pyrethroid insecticide used in the control of ectoparasites on cattle, sheep, goats, horses, and dogs. It is also marketed for the diagnosis and control of varroaosis in bee hives. Flumethrin as currently produced and used is the result of optimization of the manufacturing process and consists of >90% *trans-Z-1* and *trans-Z-2* isomers (with <2% *cis-Z* and <1% *trans-E* isomers as by-products). Flumethrin was evaluated for the first time by the present Meeting.

#### TOXICOLOGY

The development of flumethrin first led to a substance which was a mixture of 30-45% *trans-Z-1* and *trans-Z-2* isomers and 45-63% *trans-E-1* and *trans-E-2* isomers, the corresponding *cis*-isomers occurring as by-products at <6%. This material was used in a long-term study of toxicity and carcinogenicity in rats and is referred to as flumethrin (low *trans-Z* content).

Flumethrin was absorbed rapidly, but not completely, after oral administration in all species investigated. The concentrations in the tissues of rats two days after dosing were three- to 50-fold lower than those in the blood; the lung contained higher concentrations than other tissues, and the central nervous system had the lowest concentrations. Elimination was mainly in the faeces. The main metabolite was flumethrin acid, which was distinctly less toxic than the parent substance in acute and four-week dietary studies in rats and did not induce reverse mutations in bacteria.

The acute oral toxicity of flumethrin in laboratory animals is moderate to low. The reported manifestations of its toxicity are largely consistent with those known collectively as the choreoathetosis with salivation (CS) syndrome, which is produced by other insecticidal pyrethroids containing an  $\alpha$ -cyano-3-phenoxybenzyl group. After dermal application, the acute toxicity of flumethrin was low; the clinical signs were the same as those seen after oral administration. There was no evidence of acute toxicity after dermal application of 5 ml/kg bw of a 1% pour-on formulation. In tests for dermal and ocular irritancy, the active substance proved not to be irritating. In tests for local irritancy with the 1% pour-on formulation, slight, transient skin changes (mainly barely perceptible erythema and/or swelling), but no changes in the mucous membrane of the eye, were observed. WHO has not classified flumethrin for acute toxicity.

After the oral administration of flumethrin for three months to rats at dietary concentrations of 0, 10, 40, or 160 ppm and to dogs at dietary concentrations of 0, 25, 50, 100, or 200 ppm, the NOAELs were 10 ppm (equal to 0.7 mg/kg bw per day) in rats and 25 ppm (equal to 0.88 mg/kg bw per day) in dogs. In both species the most obvious findings were skin alterations, but these were not due to primary dermatitis caused by flumethrin but to frequent scratching with attendant bleeding and, in some instances, inflammation.  $\alpha$ -Cyano pyrethroids are known to produce paraesthesia, which is considered to be the most likely cause of the observed skin lesions. The toxicological studies provided no evidence of immunotoxicity, e.g. effects on leucocyte counts or on other relevant organs (thymus and spleen).

The results of studies of developmental toxicity in rats at doses of 0, 0.5, 1, or 2 mg/kg bw per day on days 6-15 of gestation and in rabbits at doses of 0, 0.5, 1.7, or 6 mg/kg bw per day on days 7-19 of gestation provided no evidence that flumethrin is teratogenic at doses extending into the range that is toxic to the dams. Some fetotoxicity was observed at doses that also induced maternal toxicity in both species. The NOAELs were 0.5 mg/kg bw per day in rats and 1.7 mg/kg bw per day in rabbits.

A two-generation study of reproductive toxicity in rats exposed to flumethrin at dietary concentrations of 0, 1, 5, or 50 ppm did not indicate primary reproductive toxicity; the reduced pup survival and body-weight gain, and certain postural and behavioural changes in the pups at the highest dose may have been secondary to maternal toxicity. The NOAEL was 5 ppm, equal to 0.36 mg/kg bw per day.

No studies of long-term toxicity or carcinogenicity have been conducted with the currently used isomeric mixture of flumethrin. A 24-month study was available, however, in which rats were fed diets containing flumethrin with a low *trans-Z* content at concentrations of 0, 2, 10, 50, or 250 ppm. Skin lesions developed in rats at 50 and 250 ppm, and there was slight proliferation of the bile ducts in male rats at 250 ppm. Neither the number of tumour-bearing rats nor the incidence of any specific neoplasm was increased. The Meeting considered the following toxicological findings. (i) Flumethrin with a low *trans-Z* content has no carcinogenic potential. (ii) Other pyrethroids, such as cyhalothrin, cypermethrin, fenvalerate and the resmethrins also have no carcinogenic potential. (iii) Treatment with permethrin resulted in small increases in the incidence of lung tumours in female mice in three studies, but no increases were found in either rats or male mice. (iv) Treatment with deltamethrin was associated with unspecified thyroid adenomas in rats in one study, but no tumours were induced in mice or in either species in other studies. (v) Flumethrin had no genotoxic potential in a number of well-conducted tests covering a variety of end-points. (vi) Flumethrin showed no sensitizing potential. (vii) No preneoplastic responses were observed in studies up to 13 weeks in duration. The Meeting considered that the carcinogenic potential of the *trans-Z* isomers that are present in the currently used isomeric mixture of flumethrin had been assessed in the study in rats in which the low *trans-Z* product was tested.

Oral administration of highly toxic doses of flumethrin to rats can cause dysfunction of the nervous system, but the effect is rapidly reversible and is not accompanied by morphological damage to the central or peripheral nervous system.

Pharmacological tests in experimental animals gave no evidence of impairment of vital functions. Studies to establish the tolerance of calves and cattle to flumethrin showed no significant effects, even when animals licked the application site.

flumethrin

An ADI of 0-0.004 mg/kg bw was allocated, on the basis of the NOAEL of 0.36 mg/kg bw per day in the two-generation study of reproductive toxicity in rats, using a 100-fold safety factor.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Rat: 10 ppm, equal to 0.7 mg/kg bw per day (13-week and 15-week studies of toxicity)

5 ppm, equal to 0.36 mg/kg bw per day (two-generation study of reproductive toxicity)

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

Rabbit: 1.7 mg/kg bw per day (maternal and fetal toxicity in a study of developmental toxicity)

Dog: 25 ppm, equal to 0.88 mg/kg bw per day (13-week study of toxicity)

Estimate of acceptable daily intake for humans

0-0.004 mg/kg bw

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

Results of any studies that are planned or in progress in rodents, dogs, or exposed human subjects.

**Toxicological criteria for setting guidance values for dietary and non-dietary exposure to flumethrin.**

EXPOSURE	RELEVANT ROUTE, STUDY, TYPE, SPECIES	RESULT, REMARKS
Short-term (1-7 days)	Oral, toxicity, rat	LD <sub>50</sub> = 41-3800 mg/kg bw, depending on the vehicle
	Dermal toxicity, rat	LD <sub>50</sub> >2000 mg/kg bw
	Inhalation toxicity, rat	LC <sub>50</sub> = 225 mg/m <sup>3</sup>
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Not irritating
	Dermal sensitization, guinea pig	Not sensitizing
Medium-term (1-26 weeks)	Repeated oral, 15-week, toxicity, rat	NOAEL = 0.7 mg/kg bw per day
	Repeated oral, 13-week, toxicity,	NOAEL = 0.88 mg/kg bw per day



EXPOSURE	RELEVANT ROUTE, STUDY, TYPE, SPECIES	RESULT, REMARKS
	dog	
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.36 mg/kg bw per day, reduced body-weight gain of adults
	Repeated oral, developmental toxicity, rat	NOAEL = 1 mg/kg bw per day, developmental toxicity
	Repeated oral, developmental toxicity, rabbit	NOAEL = 1.7 mg/kg bw per day, maternal and developmental toxicity
Long-term ( $\geq$ one year)	Repeated oral, two-year, toxicity and carcinogenicity, rat	NOAEL = 0.5 mg/kg bw per day, skin lesions; no carcinogenicity

### RESIDUE AND ANALYTICAL ASPECTS

The Meeting reviewed extensive studies of metabolism in rats and cattle, information on GAP, methods of analysis, and the results of national monitoring. Data from supervised trials of ectoparasite control on cattle, sheep and goats and of the use of flumethrin in honey-bee colonies were evaluated.

Analysis for residues is usually by HPLC which can determine flumethrin *per se* and in some cases also the predominant metabolite flumethrin acid (BFN 5533A). The residue is defined as the parent compound for regulatory purposes and recommended MRLs for meat apply to the carcass fat.

Although no residues ( $<0.002$  mg/kg) were detected in honey, low residues were found in beeswax. Recommended MRLs for the meat and milk of cattle and, at the limit of determination, for honey are recorded in Annex I, where STMR levels are also recorded for the estimation of dietary intake.

#### FURTHER WORK OR INFORMATION

##### Desirable

1. Information on the stability of flumethrin residues in stored analytical samples of liver and kidney in relation to the periods and conditions of storage of the samples from supervised trials.
2. Submission of data from new supervised trials on animals expected to be available in June 1996 (Webster *et al.*, 1996).
3. Results of analyses of tissues and milk from additional supervised trials on cattle in which multiple, especially pour-on, applications have been made in accordance with approved uses.
4. Studies on the fate of flumethrin in the environment, especially its persistence and mobility in soil.

**4.16 HALOXYFOP (194)**

**RESIDUE AND ANALYTICAL ASPECTS**

Haloxyfop has been developed as a selective herbicide for the control of grass weeds in broad-leaf crops. It was evaluated for the first time by the 1995 JMPR.

The 1995 Meeting could not complete the evaluation of the studies of ruminant and poultry metabolism which were provided in the time available and the evaluation was postponed until the present Meeting. The estimation of a maximum residue level for peas (legume vegetables and their fodders) was also postponed to await clarification of the exact Codex commodities to which the data applied. The 1995 Meeting estimated a number of maximum residue levels but could not recommend them for use as MRLs because of the lack of critical supporting data on the uptake by plants of haloxyfop and its degradation products from soil.

The present Meeting received information on the commodity described as ‘peas’ and data on the uptake of residue from soil. Metabolism studies on lactating goats and laying hens were evaluated.

The Meeting estimated supervised trials median residue levels for bananas, citrus fruits, cotton seed, crude cotton seed oil, fodder beet, grapes, peanuts, peas (pods and succulent seeds), pome fruit, dry pulses, potatoes, rape seed, rape seed meal, crude and edible rape seed oil, unprocessed rice bran, husked and polished rice, soya bean meal, crude and refined soya bean oil, sugar beet, refined sugar, pressed sugar beet pulp, sunflower seed, chicken meat, edible chicken offal and eggs.

The Meeting withdrew the provisionally estimated maximum residue levels for fodder crops and cattle products because information on the moisture content of the fodder crops was lacking and the calculated intake from cattle feed was higher than the highest dosing level in the submitted feeding studies.

**FURTHER WORK ON INFORMATION**

Desirable

- 1. Information on the moisture content of fodder crops.
- 2. Ruminant feeding studies at a feeding level comparable to the maximum residue level found in fodder crops.

**4.17 MALEIC HYDRAZIDE (102)**

**TOXICOLOGY**

Maleic hydrazide was previously evaluated for toxicological effects by the Joint Meeting in 1976, 1980, and 1984. In 1984, an ADI of 0-5 mg/kg bw was established for maleic hydrazide (sodium or potassium salt, 99.9% pure containing <1 mg hydrazine/kg).

The toxicology of the compound was reviewed at the present Meeting within the CCPR periodic review programme.

Maleic hydrazide was rapidly and extensively absorbed after oral administration of single doses of 2 or 100 mg/kg bw or 2 mg/kg bw per day for 15 days. Excretion is rapid (>80% in 24 h) after either oral or intravenous administration, with urinary excretion predominating (>80%). The metabolism of maleic hydrazide is minimal, the parent compound accounting for over 60% in males and 80% in females of the urinary radiolabel; conjugation to sulfate is the only significant reaction. There was no evidence that absorption or metabolism was affected by dose or by repeated administration in rats. The total tissue residues in rats represented < 1% of the administered dose after seven days.

The acute toxicity of maleic hydrazide after administration by the oral, dermal, or inhalation route is low, with LD<sub>50</sub> and LC<sub>50</sub> values greater than the limit doses (5 g/kg bw orally, 20 g/kg bw dermally, and 20 mg/litre by inhalation). No target organs were identified. Maleic hydrazide was only slightly irritating to the skin and eyes and is not a skin sensitizer. The compound has been classified by WHO as unlikely to present an acute hazard in normal use.

After administration of repeated oral doses of maleic hydrazide to rats (0, 30, 100, 300, or 1000 mg/kg bw per day or 0, 0.5, 1, 2 or 5% in the diet) and dogs (0, 750, 2500, or 25,000 ppm) for 12-13 weeks, no marked adverse effects were seen at doses up to 1000 mg/kg bw per day; however, the extent of the examinations performed in these studies was inadequate to permit a reliable NOAEL to be determined.

In rats treated dermally for three weeks, no significant effects were seen on gross or histopathological examination at doses up to 1000 mg/kg bw per day. An increased lymphocyte count in males at 500 or 1000 mg/kg bw per day was considered to be of questionable biological significance in the absence of similar findings in other studies. The NOAEL was 1000 mg/kg bw per day.

In a one-year study of toxicity in dogs treated in the diet at levels of 0, 750, 2500, or 25,000 ppm, reduced body-weight gain, thyroid hypertrophy, and inflammatory lesions of the liver were seen at 25,000 ppm (equal to 500 mg/kg bw per day), with changes in urinary pH, serum enzyme activities, and albumin level. As significant reductions in body-weight gain were seen at 25,000 ppm (35%) and 2500 ppm (20%), the NOAEL was 750 ppm, equal to 25 mg/kg bw per day. Earlier studies with limited protocols were inadequate for deriving reliable NOAELs for dogs but showed no marked effects at doses up to 500 mg/kg bw per day over two years.

In a 23-month study in mice fed diets containing 0, 1000, 3200 or 10,000 ppm, there was a dose-related increase in the prevalence of amyloidosis in males, which also occurred in females at the highest dose. The frequencies of adrenal hyperplasia and carditis or myocarditis were increased in females at the two higher doses. Increases in the frequencies of alveolar adenomas and uterine haemangiomas in females at the highest dose were not statistically significant and do not represent clear evidence of carcinogenic potential. The NOAEL was

1000 ppm (equal to 160 mg/kg bw per day) on the basis of cardiac and adrenal changes in females at 3200 ppm and above. A small increase in the frequency of amyloidosis at 1000 ppm was observed in males, which was not considered to be significant. An earlier long-term study in mice treated by oral or subcutaneous administration provided no evidence of carcinogenicity.

In a two-year study of toxicity and carcinogenicity in rats in which the levels incorporated in the diet were varied to give 0, 25, 500 or 1000 mg/kg bw per day, there was no evidence of an increase in tumour incidence. Reductions in body-weight gain, despite increased food consumption, were noted at 500 and 1000 mg/kg bw per day. An altered pattern of renal lesions, myocarditis, adrenal hyperplasia, and thyroid hyperplasia was seen at 1000 mg/kg bw per day. The NOAEL was 25 mg/kg bw per day on the basis of clear effects on weight gain at doses of 500 mg/kg bw per day and above. Earlier long-term studies in rats provided no evidence of carcinogenicity at doses up to 2% in the diet (equivalent to 1000 mg/kg bw per day).

In a two-generation study of reproductive toxicity in rats given 0, 1000, 10,000, 30,000 or 50,000 ppm in the diet, significant effects on the body-weight gain of parents and pups were evident at the two highest doses, to such an extent that the dose of 50,000 ppm was discontinued after the first generation. There were no adverse effects on reproductive parameters. Increases in organ weight and histological findings indicated a slight effect on the kidneys at 30,000 ppm. The NOAEL was 10,000 ppm (equivalent to 750 mg/kg bw per day).

In a study of developmental toxicity, rats were given 0, 30, 300, or 1000 mg maleic hydrazide/kg bw per day by gavage on days 6-16 of gestation. There was no clear evidence of effects on the fetus or of maternal toxicity, even at the highest dose tested. In a similar study in rabbits treated with 0, 100, 300, or 1000 mg/kg bw per day by gavage on days 7-27 of gestation, there was no clear evidence of fetotoxicity or teratogenicity. Reduced maternal body-weight gain and an increased frequency of late resorptions were seen at 1000 mg/kg bw per day. The NOAEL was 300 mg/kg bw per day.

A wide range of tests for genotoxicity *in vitro* with high concentrations of maleic hydrazide resulted in several positive findings. No positive findings were recorded in four studies *in vivo*. The Meeting concluded that maleic hydrazide is not genotoxic.

An ADI of 0-0.3 mg/kg bw was established on the basis of the NOAEL of 25 mg/kg bw per day in the two-year study of toxicity and carcinogenicity in rats and the one-year study of toxicity in dogs, using a 100-fold safety factor.

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

## TOXICOLOGICAL EVALUATION

### Levels that cause no toxic effect

Mouse: 1000 ppm, equal to 160 mg/kg bw per day (toxicity in a 23-month study of toxicity and carcinogenicity)

Rat: 25 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)

1000 mg/kg bw per day (highest dose tested in a study of developmental toxicity)

10,000 ppm, equivalent to 750 mg/kg bw per day (toxicity in a two-generation study of reproductive toxicity)

Rabbit: 300 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 750 ppm, equal to 25 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.3 mg/kg bw

**Toxicological criteria for setting guidance values for dietary and non-dietary exposure to maleic hydrazide**

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT/REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> >5000 mg/kg bw
	Dermal toxicity, rabbit	LD <sub>50</sub> >20000 mg/kg bw
	Inhalation, 1 h, toxicity, rat	LC <sub>50</sub> >20 mg/litre
	Dermal irritation, rabbit	Slightly irritating
	Ocular irritation, rabbit	Slightly irritating
Medium-term (1-26 weeks)	Dermal sensitization, guinea-pig	Not sensitizing
	Repeated dermal, 21 days, toxicity, rat	NOAEL = 1000 mg/kg bw per day (highest dose tested)
	Repeated oral, reproductive toxicity, rat	NOAEL = 750 mg/kg bw per day, reduced weight gain; no effects on reproduction
	Repeated oral, developmental toxicity, rat	NOAEL = 1000 mg/kg bw per day (highest dose tested),
Long-term (≥one year)	Repeated oral, developmental toxicity, rabbit	NOAEL = 1000 mg/kg bw per day (highest dose tested), embryotoxicity and teratogenicity NOAEL = 300 mg/kg bw per day, maternal toxicity (increased resorptions and decreased weight gain)
	Repeated oral, two years, toxicity and carcinogenicity, rat	NOAEL = 25 mg/kg bw per day, decreased weight gain, increased food intake, and clinical chemical changes
	Repeated oral, one year toxicity, dog	NOAEL = 25 mg/kg bw per day, reduced body-weight gain

#### **4.18 METHAMIDOPHOS (100)**

##### **RESIDUE AND ANALYTICAL ASPECTS**

Methamidophos is a systemic organophosphorus insecticide and also a metabolite of acephate. It was first evaluated in 1976. The 1994 JMPR recommended withdrawal of the CXL for melons except watermelon and the draft MRLs for broccoli, head cabbages, cauliflower, citrus fruits, egg plant, peach and tomato which had been held at Step 7B by the 1992 CCPR (ALINORM 93/24, paras 119-123). The manufacturer indicated that information on GAP and data on residues would be available to support new MRLs for these commodities.

The Meeting received data on supervised trials, and information on GAP, the stability of residues in stored analytical samples, methods of residue analysis, and the fate of residues during food processing. The supervised trials included applications of methamidophos to broccoli, head cabbages, cauliflowers, egg plants, melons, peaches and tomatoes; and of acephate to broccoli, Brussels sprouts, head cabbages, cauliflowers, citrus fruits and tomatoes. The Meeting estimated the residues of methamidophos arising from the use of each compound.

Since methamidophos has been listed by the CCPR as a candidate for periodic review but not yet scheduled, and in view of the difficulties encountered by the present Meeting in evaluating the available data without the original studies, the Meeting recommended that the CCPR should schedule methamidophos for periodic review.

#### **4.19 MEVINPHOS (053)**

##### **TOXICOLOGY**

Mevinphos was evaluated for toxicological effects by the JMPR in 1963 and 1965; in neither case was an ADI assigned. An ADI of 0-0.0015 mg/kg bw was established in 1972. The toxicology of the compound was reviewed at the present Meeting within the CCPR periodic review programme.

Mevinphos is almost completely absorbed when administered orally to rats; a large proportion of the absorbed compound is biotransformed to carbon dioxide. Both metabolites and unchanged mevinphos are observed in the urine but very little in the faeces. Mevinphos depresses cholinesterase activity in the plasma more than in erythrocytes in experimental animals.

The oral LD<sub>50</sub> values of mevinphos in laboratory rodents are 2-12 mg/kg bw. WHO has classified mevinphos as 'extremely hazardous'.

In a three-month range-finding study, mice were fed diets containing mevinphos at concentrations of 0, 0.5, 1, 2, or 10 ppm. The NOAEL was 2 ppm, equal to 0.4 mg/kg bw per day, on the basis of inhibition of brain acetylcholinesterase activity at 10 ppm.

In a 90-day study of toxicity, rats were administered mevinphos by gavage at doses of 0, 0.056, 0.56, 1.1 or 1.7 mg/kg bw per day in males (the highest dose was decreased to 1.1 mg/kg bw per day at day 36 because of high mortality) and at 0, 0.011, 0.056, 0.56, or 0.84 mg/kg bw per day in females. The NOAEL was 0.056 mg/kg bw per day, on the basis of clinical signs and depressed brain acetylcholinesterase activity at higher doses. Dose-related increases in mean cholesterol levels and increased relative liver weights were also observed.

In a one-year study of toxicity in dogs, mevinphos was administered in corn oil in gelatin capsules at doses of 0, 0.025, 0.25 or 0.5 mg/kg bw per day. The NOAEL was 0.25 mg/kg bw per day on the basis of clinical signs and a reduction in brain acetylcholinesterase activity at the highest dose.

In an 18-month study of toxicity and carcinogenicity, mice were fed dietary concentrations of 0, 1, 10, or 25 ppm. Acetylcholinesterase activities were not measured. There was no evidence of carcinogenicity.

In a two-year study of toxicity and carcinogenicity, rats were given mevinphos by gavage in water for five days per week at doses of 0, 0.025, 0.35, or 0.70 mg/kg bw per day. On day 83 of the study, the high dose of the females was reduced to 0.60 mg/kg bw per day because of signs of toxicity. The NOAEL was 0.025 mg/kg bw per day on the basis of inhibition of brain acetylcholinesterase activity and clinical signs at higher doses. There was no evidence of carcinogenicity.

A two-generation study of reproductive toxicity was carried out in which rats were treated by gavage at doses of 0, 0.05, 0.1, or 0.5 mg/kg bw mevinphos per day in water. The NOAEL was 0.1 mg/kg bw per day on the basis of clinical signs and reduced brain acetylcholinesterase activity at the highest dose. This dose also impaired growth and fertility indices and lowered testicular weights in males and ovarian weights in females.

In a study of developmental toxicity in rats, groups were given mevinphos at doses of 0, 0.2, 0.75, or 1.25 mg/kg bw per day on days 6-15 of gestation. High mortality (29%) was observed in the high-dose group, which was therefore terminated. Accordingly, a new high-dose group of 1.0 mg/kg bw per day was added. There were no adverse effects on uterine implantation or fetal weight, sex distribution or external appearance, nor visceral or skeletal malformations, in any group. It was concluded that mevinphos is not embryotoxic, fetotoxic, or teratogenic at doses up to 1 mg/kg bw per day. The NOAEL for maternal toxicity was 0.75 mg/kg bw per day on the basis of clinical signs at higher doses.

In a study of developmental toxicity, mevinphos was administered by gavage to pregnant rabbits at doses of 0, 0.05, 0.5, or 1.5 mg/kg bw per day on days 7-19 of gestation; surviving animals were killed. The NOAEL was 0.5 mg/kg bw per day, on the basis of maternal toxicity. Mevinphos was neither teratogenic nor fetotoxic.

There was some evidence of genotoxic potential *in vitro*, but the limited studies available indicate that such potential is not exhibited *in vivo*.

In a study in hens, the oral dose of 12 mg/kg bw that was administered was slightly greater than the oral LD<sub>50</sub> value, and antidotal treatment was required. There was no evidence of delayed polyneuropathy, either clinically or histopathologically, whereas characteristic

changes were seen in positive controls. Neurotoxic target esterase was not measured during this study.

Two studies of humans were available. In one study, in which male volunteers were given a dose of 0.025 mg/kg bw per day, plasma and erythrocyte cholinesterase activities decreased throughout the 28 days of the study to 13% and 19% less than the respective pre-dose levels. In the second study, daily doses of 1, 1.5, 2.0, or 2.5 mg were given to male volunteers for 30 days, and an NOAEL of 1 mg/day, equivalent to 0.016 mg/kg bw per day, was derived; however, only five people, per dose were studied.

An ADI of 0-0.0008 mg/kg bw was established on the basis of the NOAEL of 0.016 mg/kg bw per day in the 30-day study in volunteers using a 20-fold safety factor because of the small numbers in each group. This ADI is supported by the LOAEL in rats of 0.35 mg/kg bw per day and the NOAELs of 0.5 mg/kg bw per day in rabbits and 0.25 mg/kg bw per day in dogs.

An acute reference dose for humans was derived from the 28-day study in volunteers, on the basis of a dose of 0.025 mg/kg bw per day over four days, using a 10-fold safety factor.

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

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 2 ppm, equal to 0.4 mg/kg bw per day (inhibition of brain acetylcholinesterase in three-month study of toxicity)

Rat: 0.025 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

0.1 mg/kg bw per day (study of reproductive toxicity)

Rabbit: 0.5 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

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

Human: 0.016 mg/kg bw per day (inhibition of cholinesterase activity in a 30-day study of toxicity)

#### Estimate of acceptable daily intake for humans

0-0.0008 mg/kg bw

#### Acute reference dose

0.003 mg/kg bw

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



Study of micronucleus formation in mice *in vivo*.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULTS/REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> = 2.2-6.1 mg/kg bw
	Dermal toxicity, rat	LD <sub>50</sub> >20 mg/kg bw
	Inhalation, 4 h, toxicity, rat	LC <sub>50</sub> = 7.3-12 mg/m <sup>3</sup>
	Dermal irritation, rabbit	Slightly irritating
	Ocular irritation, rabbit	Slightly irritating
	Dermal sensitization, guinea-pig	Not sensitizing
Medium-term (1-26 weeks)	Repeated oral, three months, mouse	NOAEL = 0.4 mg/kg bw per day, inhibition of brain acetylcholinesterase
	Repeated oral, 90 days, rat	NOAEL = 0.056 mg/kg bw per day
	Repeated dermal, 21 days, rabbit	NOAEL = 1 mg/kg bw per day
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.1 mg/kg bw per day, maternal and reproductive toxicity
	Repeated oral, developmental toxicity, rat	NOAEL = 0.75 mg/kg bw per day, maternal toxicity; no developmental toxicity
	Repeated oral, developmental toxicity, rabbit	NOAEL = 0.5 mg/kg bw per day, maternal toxicity; no developmental toxicity
Long-term (≥ one year)	Repeated oral, two years, rat	NOAEL = 0.025 mg/kg bw per day; inhibition of brain acetylcholinesterase activity
	Repeated oral, one year, dog	NOAEL = 0.25 mg/kg bw per day; inhibition of brain acetylcholinesterase activity

**4.20 PHORATE (112)**

**TOXICOLOGY**

Phorate, an organophosphorus insecticide that inhibits cholinesterase, was first reviewed for toxicological effects by the Joint Meeting in 1977. A temporary ADI of 0-0.0002 mg/kg bw was established in 1982. In 1994, the Meeting re-evaluated phorate and allocated an ADI of 0-0.0005 mg/kg bw per day. Because in a limited study in rats it was reported that less than 40% of the administered  $^{32}\text{P}$  label was excreted within 144 h, adequate studies on absorption, distribution, excretion, and metabolism in rats were requested for review in 1996.

Studies on the absorption, distribution, metabolism, and excretion of phorate in rats were reviewed by the present Meeting.  $^{14}\text{C}$ -labelled phorate was rapidly absorbed and excreted by rats after a single dose in corn oil by gavage. The urine was the primary route of elimination, with approximately 80% of the administered radiolabel excreted within 24 h; faecal elimination accounted for about 10% of the label.

The current studies showed essentially total excretion of  $^{14}\text{C}$  after 192 h. The Meeting concluded that phorate and its metabolites are rapidly excreted and that accumulation of a toxic metabolite is not a concern. Thus, the new data did not indicate that the ADI allocated in 1994 should be reassessed. The ADI of 0-0.0005 mg/kg bw allocated on the basis of a NOAEL of 0.05 mg/kg bw per day in a one-year study of toxicity in dogs and a two-year study of toxicity and carcinogenicity in rats, with a 100-fold safety factor, was confirmed.

An addendum to the toxicological monograph was prepared.

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 1 ppm, equal to 0.18 mg/kg bw per day (13-week study of toxicity)

Rat: 1 ppm, equal to 0.05 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rabbit: 0.15 mg/kg bw per day (study of developmental toxicity)

Dog: 0.05 mg/kg bw per day (one-year study of toxicity)

#### Estimate of acceptable daily intake for humans

0-0.0005 mg/kg bw

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

Further observations in humans.

### **4.21 PROPOXUR (075)**

### **RESIDUE AND ANALYTICAL ASPECTS**

The carbamate insecticide propoxur was first evaluated by the 1973 JMPR. Its residue and analytical aspects were reviewed in 1977, 1981, 1983 and 1991.

At the 1994 CCPR several delegations expressed the opinion that the MRLs recommended by the 1991 Meeting for head lettuce and potatoes were based on very old data.

The Meeting received data from supervised trials on lettuce and potatoes, information on analytical methods, and monitoring data.

The data from supervised trials were reviewed and MRLs were recommended for lettuce and potatoes, but the Meeting decided not to estimate STMR levels until the compound is evaluated in the CCPR periodic review programme since CXLs have already been established for many other commodities and metabolic studies were not available.

#### 4.22 TEBUFENOZIDE (196)

##### *N-tert-butyl-N'-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide*

Tebufenozide is a fat-soluble insecticide used to control Lepidoptera pests in fruits, vegetables and other crops. It has a novel mode of action in that it mimics the action of the insect moulting hormone, ecdysone. Lepidoptera larvae cease to feed within hours of exposure and then undergo a lethal, unsuccessful moult.

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

#### TOXICOLOGY

Oral administration to rats of single doses of 3 or 250 mg/kg bw of <sup>14</sup>C-labelled tebufenozide resulted in rapid absorption and excretion in urine and faeces, only trace amounts of <sup>14</sup>C being recovered in expired air. The excretion profiles were similar, regardless of the position of the <sup>14</sup>C label, the dose, the sex, or whether the rats had been pretreated with 30 ppm of unlabelled tebufenozide in the diet for two weeks. A mean total of 87-104% of the administered radioactivity was eliminated within 48 h, primarily via the faeces which accounted for 90% of the <sup>14</sup>C that was excreted; only minor amounts (1-8%) were excreted in urine and trace amounts (0.1-0.4%) in expired air. In animals at 3 mg/kg bw, absorption accounted for 35-39% of the administered radioactivity; 30-34% was excreted in the bile and about 5% in the urine. At 250 mg/kg bw, only about 4% of the administered dose was absorbed and metabolized. The highest levels of <sup>14</sup>C in the blood were measured 0.5-12 h after dosing, and clearance of the radiolabel from the circulation was rapid. Tissue retention of <sup>14</sup>C was low, suggesting that there is little or no bioaccumulation of tebufenozide in the body.

Most of the <sup>14</sup>C excreted in the faeces was in the form of unabsorbed (parent) tebufenozide, which accounted for about 60 and 90% of administered doses of 3 and 250 mg/kg bw per day respectively; no unchanged tebufenozide was detected in the urine. The absorbed [<sup>14</sup>C]tebufenozide was extensively metabolized in rats. There were no significant qualitative differences in the metabolic profiles associated with the position of the <sup>14</sup>C label, the dose, the sex, or whether rats were pretreated with unlabelled tebufenozide. In general, the 13-

15 metabolites identified in the urine, faeces, and bile were identical. The main route of metabolism of tebufenozide appeared to be oxidation of the benzylic carbons (A- or B-ring), resulting in a number of metabolites with various combinations of oxidation state at the three oxidized carbon centres and one metabolite produced by oxidation of the non-benzylic, terminal carbon on the A-ring ethyl group.

Tebufenozide was of low acute toxicity after administration to mice orally or to rats by the oral, dermal or inhalation route. The oral LD<sub>50</sub> in mice and rats was >5000 mg/kg bw; the dermal LD<sub>50</sub> in rats was >5000 mg/kg bw, and the inhalation LC<sub>50</sub> in rats was > 4.3 mg/litre. The metabolites were also of low acute toxicity to mice after oral administration. Tebufenozide was not irritating to the skin and was minimally irritating to the eyes of male rabbits; it was not a skin sensitizer in guinea-pigs. WHO has not classified tebufenozide for acute toxicity.

Repeated short-term oral administration of tebufenozide to mice (2 and 13 weeks), rats (2, 4, and 13 weeks), and dogs (2, 6, 13, and 52 weeks) resulted primarily in haematotoxic effects (regenerative haemolytic anaemia and compensatory responses from the haematopoietic tissues). The NOAEL for these effects was 200 ppm, equal to 35 mg/kg bw per day, in mice in a 13-week study (0, 20, 200, 2000 and 20,000 ppm tested); 200 ppm, equal to 13 mg/kg bw per day, in rats in a 13-week study (0, 20, 200, 2000, and 20,000 ppm tested); 50 ppm, equal to 2.0 mg/kg bw per day, in dogs in a 13-week study (0, 50, 500, and 5000 ppm tested), and 50 ppm, equal to 1.8 mg/kg bw per day, in a one-year study of toxicity in dogs (0, 15, 50, 250, and 1500 ppm tested). Repeated dermal applications of tebufenozide to rats for four weeks caused no systemic toxicity at doses up to 1000 mg/kg bw per day. The dog appeared to be the most sensitive species for both short-term and long-term toxicity.

In an 18-month study of toxicity and carcinogenicity in mice administered tebufenozide in the diet at concentrations of 0, 5, 50, 500, or 1000 ppm, the NOAEL for systemic toxicity was 50 ppm, equal to 7.8 mg/kg bw per day, on the basis of a slightly reduced survival rate and mild regenerative haemolytic anaemia at higher doses. In a two-year study of toxicity and carcinogenicity in rats administered tebufenozide in the diet at 0, 10, 100, 1000, or 2000 ppm, the NOAEL was 100 ppm, equal to 4.8 mg/kg bw per day, on the basis of decreased body weight and food consumption and mild regenerative haemolytic anaemia at higher doses. Tebufenozide was not carcinogenic in mice or rats under the conditions of the studies.

Tebufenozide and its metabolites have been adequately tested for genotoxicity in a range of assays both *in vitro* and *in vivo*. The Meeting concluded that neither tebufenozide nor its metabolites were genotoxic.

In two two-generation studies of reproductive toxicity in rats, with one litter per generation, concentrations of 0, 10, 150, or 2000 ppm and 0, 25, 200, or 2000 ppm were administered. The NOAEL for systemic (parental) toxicity was 25 ppm, equal to 1.6 mg/kg bw per day, on the basis of a consistent increase in the incidence of gross and histopathological lesions in the spleens (congestion, pigment, and extramedullary haematopoiesis) of F<sub>0</sub> and F<sub>1</sub> parental animals at higher doses (200 and 2000 ppm). The NOAEL for reproductive toxicity was 13 mg/kg bw per day on the basis of potential or minor reproductive effects (decreased mean number of implantation sites, prolonged gestation, a slightly greater frequency of total resorptions, and a small increase in the number of dams that died during delivery) at the high dose of 2000 ppm in dams in the first study and in lactating pups (decreased mean weight gain on lactation days 14 and 21) in the second study.

In studies of developmental toxicity in rats and rabbits, doses of 0, 50, 250, or 1000 mg/kg bw per day were administered. There was no evidence of teratogenic potential. The NOAEL for maternal, embryo- and fetotoxicity and teratogenicity was 1000 mg/kg bw per day, the highest dose tested, in both species.

In a study of acute neurotoxicity in rats, no treatment-related effects were seen when single doses of 0, 500, 1000, or 2000 mg/kg bw were administered. The NOAEL for acute neurotoxicity and neuropathological effects was 2000 mg/kg bw, the highest dose tested.

In summary, exposure to tebufenozide by the oral route results primarily in haematotoxicity. The main target of its action is the peripheral haematopoietic system; the pivotal toxicological end-point of concern, which is seen consistently across all species tested, is mild regenerative haemolytic anaemia with compensatory responses from the haematopoietic tissues.

An ADI of 0-0.02 mg/kg bw was established for tebufenozide on the basis of the NOAELs for haematotoxicity of 1.8 mg/kg bw per day in the one-year study in dogs and 1.6 mg/kg bw per day in a two-generation study of reproductive toxicity in rats, using a safety factor of 100.

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

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 200 ppm, equal to 35 mg/kg bw per day (13-week study of toxicity)

50 ppm, equal to 7.8 mg/kg bw per day (haematotoxicity in an 18-month study of toxicity and carcinogenicity)

Rat: 200 ppm, equal to 13 mg/kg bw per day (13-week study of toxicity)

100 ppm, equal to 4.8 mg/kg bw per day (haematotoxicity in a two-year study of toxicity and carcinogenicity)

25 ppm, equal to 1.6 mg/kg bw per day (maternal haematotoxicity in a two-generation study of reproductive toxicity)

200 ppm, equal to 13 mg/kg bw per day (reproductive toxicity in a two-generation study)

1000 mg/kg bw per day, the highest dose tested (maternal, embryo-, and fetotoxicity and teratogenicity in a study of developmental toxicity)

Rabbit: 1000 mg/kg bw per day, the highest dose tested (maternal, embryo-, and fetotoxicity and teratogenicity in a study of developmental toxicity)

Dog: 50 ppm, equal to 1.8 mg/kg bw per day (haematotoxicity in a one-year study of

toxicity)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

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

- 1. Observations in humans.
- 2. Studies on the mechanism of haematotoxicity.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> >5000 mg/kg bw
	Dermal toxicity, rat	LD <sub>50</sub> >5000 mg/kg bw
	Inhalation, 4 h, toxicity, rat	LC <sub>50</sub> >4.3 mg/litre
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Minimally irritating
	Dermal sensitization, guinea-pig	Not sensitizing
Medium-term (1-26 weeks)	Repeated dietary, 90 days, toxicity, dog	NOAEL = 2.0 mg/kg bw per day, primarily haematotoxicity
	Repeated dermal, 28 days, toxicity, rat	NOAEL = 1000 mg/kg bw per day, highest dose tested
	Repeated dietary, reproductive toxicity, rat	NOAEL = 13 mg/kg bw per day, minor reproductive effects
	Repeated gavage, developmental toxicity, rat and rabbit	NOAEL = 1000 mg/kg bw per day (highest dose tested), maternal, embryo- and fetal toxicity and teratogenicity
Long-term (≥ one year)	Repeated dietary, one year, toxicity, dog	NOAEL = 1.8 mg/kg bw per day, primarily haematotoxicity

## RESIDUE AND ANALYTICAL ASPECTS

The Meeting was provided with information on registered uses of tebuconazole on fruits, vegetables and other crops, and received extensive information on metabolism, environmental fate in soil, methods of residue analysis, the stability of residues in stored analytical samples, supervised residue trials, animal transfer studies and the fate of residues during processing. The metabolism studies were on rats, lactating goats, laying hens, fish, apples, grapes, rice and sugar beet. The information on environmental fate included studies of field dissipation and biodegradation in water/sediment systems.

Residues of tebufenozide can be determined by HPLC with UV detection or by GLC with NP detection after methylating the residues. Limits of determination are usually 0.01-0.05 mg/kg in a range of commodities, 0.02 mg/kg in soil and 0.1 µg/l in water.

The Meeting agreed that the residue should be defined as tebufenozide.

The Meeting evaluated residue data from supervised trials and estimated maximum residue levels for apples, grapes, walnuts, rice and pecans.

Information on the fate of tebufenozide during the processing of apples, grapes and tea was provided. In one study the total residue of tebufenozide in apple juice was about 15% of that in the apples. In a number of studies of vinification the mean residue in wine was 36% of that in the grapes. Infusions of tea contained 5-31% of the tebufenozide in the dry tea, with a mean of 17%.

Maximum residue levels estimated by the Meeting which are recommended for establishing MRLs are recorded in Annex I, together with STMR levels.

## FURTHER WORK OR INFORMATION

### Desirable

1. Information on tebufenozide residues in raisins, raisin culls and rice hulls.
2. Information on residues of tebufenozide in foods in commerce or at consumption.
3. A transfer study on poultry.
4. The results of a cow-feeding study which the Meeting was informed was in progress.
5. Data on residues in paddy rice and on the stability of residues in analytical samples of rice stored for longer periods than the 20-21 days already reported.
6. A detailed report of the completed study of uptake by rotational crops that the Meeting was informed was available.
7. Representative data on the storage stability of residues on leafy vegetables for the full duration of the studies that the Meeting was informed are in progress.

## 4.23 TEFLUBENZURON (190)

### RESIDUE AND ANALYTICAL ASPECTS

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

Teflubenzuron, 1-(3,5-dichloro-2,4-difluorophenyl)-3-(2,6-difluorobenzoyl)urea, is a fat-soluble insecticide whose major use is for the control of a wide range of insect pests and some mites in fruits, vegetables, cereals and seeds. The Meeting received extensive information on metabolism in plants and animals, environmental fate in soil, including information on residues in rotational crops and biodegradation in water/sediment systems, methods of residue analysis, stability of residues in stored analytical samples, approved use patterns, supervised residue trials, animal transfer studies and the fate of residues during processing.

Metabolism studies on rats, lactating goats, laying hens, apples, potatoes, cotton and spinach were reviewed. Analytical methods (HPLC and GLC) are available for the determination of teflubenzuron in plant and animal materials, soil, water and air.

The Meeting evaluated residue data from supervised trials and estimated maximum residue levels for pome fruits, plums (including prunes), head cabbages, Brussels sprouts and potatoes. Insufficient data were available to estimate maximum residue levels for citrus fruits, cherries, nectarines, peaches, grapes, broccoli, cucumbers, egg plants, peppers, tomatoes, mushrooms, chinese cabbage, soya bean seeds, forage and hay, maize, cotton seed or coffee beans. Residue data were received from supervised trials on wild blackberries, blueberries and raspberries, kiwifruit, persimmons, peas (immature seeds), alfalfa forage and green grass, but no GAP was available to evaluate the data.

Animal transfer studies in which lactating dairy cows and laying hens were fed with teflubenzuron were reviewed, but as no maximum residue levels had been estimated for feed items the studies could not be evaluated.

Processing studies were available for apples, plums, cherries, grapes, potatoes, tomatoes, soya beans and cotton, but were insufficient to estimate transfer factors.

The residue should be defined as teflubenzuron. It is fat-soluble. Estimates of STMRS and of maximum residue levels which are recommended for use as MRLs are recorded in Annex I.

### FURTHER WORK OR INFORMATION

#### Desirable

1. Physical and chemical properties of the pure active ingredient.
2. Further processing studies on apples and plums to allow the calculation of transfer factors.



#### 4.24 THIRAM (DITHIOCARBAMATES, 105)

##### RESIDUE AND ANALYTICAL ASPECTS

Thiram was originally evaluated in 1965 (toxicology) and 1967 (toxicology and residues) and is included in the dithiocarbamate group of compounds. It was evaluated at the present Meeting within the CCPR periodic review programme.

Thiram is a protective dithiocarbamate fungicide used as a foliar treatment on fruits, vegetables and ornamentals and as a seed treatment to control a number of fungal diseases. The Meeting was provided with information on registered uses on fruits, vegetables and other crops.

The Meeting received extensive information on the metabolism of thiram in rats, farm animals, apples, grapes, soya beans, cotton, wheat and sugar beet; environmental fate in soil and water/sediment systems, methods of residue analysis, the stability of residues in stored analytical samples, approved use patterns, supervised residue trials and the fate of residues during processing.

When animals are dosed with radiolabelled thiram much of the dose is eliminated as volatile CS<sub>2</sub> and CO<sub>2</sub>. Dimethyldithiocarbamic acid, the initial product in animals, plants and soil, forms conjugates with natural products. The intermediate dimethyldithiocarbamoylalanine is converted to different metabolites in plants and animals.

The analytical methods for dithiocarbamates which rely on CS<sub>2</sub> evolution may be used to determine thiram residues. Limits of determination for various commodities are usually 0.05-0.1 mg/kg (as CS<sub>2</sub>). An HPLC method specific for thiram is available for the determination of residues on crops.

Data were available on the stability of thiram residues on plums, and of thiram added to apple juice and pomace, during frozen storage.

The Meeting agreed that the definition of the residue of the dithiocarbamates should apply to thiram. For estimates of dietary intake the supervised trials median residue (STMR) will be expressed as thiram for comparison with the thiram ADI. For estimates of acute intake a residue such as an MRL, which is expressed in terms of CS<sub>2</sub>, must be multiplied by a factor of 1.58 for comparison with an acute reference dose expressed in terms of thiram.

The Meeting received data on thiram residues from supervised trials on apples, pears, peaches, plums, cherries, grapes, strawberries, dwarf French beans, French beans, Savoy cabbage, green peas, head lettuce, spinach and tomatoes. Thiram was determined by CS<sub>2</sub> evolution methods or by HPLC, and in some trials by both methods.

Information on the fate of thiram during the processing of apples and grapes was made available to the Meeting. The thiram level in apple juice was about 30% of its level in the apples. In processing studies with grapes containing thiram residues of 1.2-4.3 mg/kg, thiram was below the LOD of 0.1 mg/kg in the wine as determined by the HPLC analytical method.

Monitoring data for dithiocarbamate residues in commodities in trade were provided from The Netherlands, Belgium and Denmark. Dithiocarbamates were detected in fewer than 15-20% of the samples of most commodities.

## **FURTHER WORK OR INFORMATION**

### Desirable

The rates of hydrolysis of thiram at various pH values should be clarified. Full copies of the reports of the studies should be made available for review.

## **4.25 ZIRAM (DITHIOCARBAMATES, 105)**

### **TOXICOLOGY**

Ziram was evaluated for toxicological effects by the Joint Meeting in 1965, 1967, 1970, 1974, 1977, and 1980. A temporary ADI (0-0.025 mg/kg bw) for ziram or ziram in combination with other dimethyldithiocarbamates was allocated in 1967, on the basis of the NOAEL in a one-year study in dogs. This temporary ADI was lowered to 0.005 mg/kg bw in 1974. A group ADI of 0-0.02 mg/kg bw for ferbam and ziram was allocated in 1977 and confirmed in 1980. The compound was reviewed by the present Meeting within the CCPR periodic review programme.

In experiments with <sup>14</sup>C-labelled ziram in rats, elimination was essentially complete within 48 h. Elimination occurred mainly in expired air, urine, and faeces. Less than 2% of the administered dose remained in the tissues. The biotransformation of ziram has not been studied in rodents. In goats, it is metabolized at least in part via a single-carbon pathway, which results in extensive radiolabelling of natural products.

The primary effect of short- and long-term treatment with ziram in mice, rats, and dogs was on the liver, thyroid gland, and testes. The hepatic effects were increased liver weight, degeneration, and focal-cell necrosis. Effects in the thyroid were C-cell hyperplasia and carcinomas, and that on the testes was sterility.

Ziram had moderate acute oral toxicity in rats and rabbits (LD<sub>50</sub> = 200-400 mg/kg bw). WHO has classified ziram as 'slightly hazardous'.

In a four-week study of toxicity in mice given dietary concentrations of 0, 3000, 4000, or 5000 ppm, an NOAEL was not identified. Reductions in body weight, food intake, efficiency of food use, and brain and heart weight occurred at all doses.

In a 13-week study of toxicity in mice given dietary concentrations of 0, 100, 300, 900, or 2700 ppm, the NOAEL was 100 ppm, equal to 15 mg/kg bw per day, on the basis of lowered spleen weight at higher doses. At 900 and 2700 ppm, the number of corpora lutea was reduced, which was consistent with cellular changes in the uterus.

In two four-week studies of toxicity in rats either given diets containing 0, 100, 500,

2500, or 5000 ppm or treated by gavage with 0, 3, 15 or 100 mg/kg bw per day, the NOAEL was 3 mg/kg bw per day, on the basis of degenerative liver changes. At 100 mg/kg bw per day, degenerative changes in the kidneys and reductions in body weight, food intake, efficiency of food use, and absolute weights of the liver, pituitary, testes, brain, and uterus were seen.

In a 13-week study of toxicity in which rats received dietary levels of 0, 100, 300, or 1000 ppm, the NOAEL was 100 ppm, equal to 7.4 mg/kg bw per day, on the basis of reduced body-weight gain, food intake, and food use and increased brain and spleen weights at higher doses.

In a four-week study of toxicity in dogs given diets providing doses of 0, 1000, 2000, or 5000 ppm, an NOEL was not identified. Increased liver weight occurred at all doses. At 2000 ppm, convulsive episodes were observed.

In a 13-week study of toxicity in dogs given diets providing 0, 100, 300, or 1000 ppm, the NOAEL was 100 ppm, equal to 4.1 mg/kg bw per day, on the basis of increased liver weight, focal liver necrosis, pigment in Kupffer cells, activated partial thromboplastin time, and elevated cholesterol level at higher doses.

In a one-year study of toxicity in which dogs were fed diets providing doses of 0, 50, 180, or 500 ppm, the NOAEL was 50 ppm, equal to 1.6 mg/kg bw per day, on the basis of reductions in body-weight gain, degeneration of hepatocytes, and increased activity of alanine and aspartate aminotransferases and alkaline phosphatase at 180 ppm and above. At 500 ppm, single liver-cell necrosis was observed, and the liver weight and cholesterol values were increased; albumin values were reduced. Inflammatory cell infiltration around the hepatic veins and its branches and aggregates of pigmented Kupffer cells were observed in the liver.

Two long-term studies of toxicity and carcinogenicity in mice have been reported. One was considered inadequate for evaluating the carcinogenicity of ziram. In the other, mice were given diets containing 0, 25, 75, 220, or 680 ppm for 80 weeks. The NOAEL was 25 ppm, equal to 3 mg/kg bw per day, on the basis of reduced brain weight at 75 ppm and above. There was no evidence of carcinogenicity.

In a two-year study of toxicity and carcinogenicity in rats at dietary concentrations of 0, 25, 250, or 2500 ppm, the NOAEL was 250 ppm, equivalent to 12 mg/kg bw per day, on the basis of testicular atrophy and thyroid hyperplasia at 2500 ppm. There was no evidence of carcinogenicity.

In a two-year study of toxicity and carcinogenicity in Fischer 344 rats with dietary concentrations of 0, 300, or 600 ppm, an NOAEL was not identified since the combined incidence of C-cell adenoma and carcinoma of the thyroid in males showed a positive trend. This finding was considered to represent an extension of the known toxicity of the compound to the thyroid, to which the rat is particularly sensitive, and not to indicate carcinogenic potential for humans.

In a study of toxicity and carcinogenicity in CD rats treated with 0, 60, 180, or 540 ppm in the diet for 12-24 months, an NOEL was not identified because dose-related changes in organ weights and histopathological and haematological changes were observed at 60 ppm, equal to 2.5 mg/kg per day. Other effects included reduced body weight, erythrocyte counts, and tri-iodothyronine and thyroxine activity. Cysts in the thyroids, epithelial hyperplasia,

hypertrophy with vacuolation, cortical cystic degeneration of the adrenals, and C-cell hyperplasia of the thyroid were also observed. The tumour incidence was not increased.

In a study of sperm quality in mice treated intraperitoneally with ziram at single doses of 0, 50, or 100 mg/kg bw or repeated doses of 25 mg/kg bw per day for five days, severe morphological abnormalities were observed. The frequency of abnormal sperm was 1.6% in the controls, 5.6% at 50 mg/kg bw, 8.2% at 100 mg/kg bw, and 8.4% after repeated doses of 25 mg/kg bw per day.

In a two-generation study of reproductive toxicity and developmental neurotoxicity, rats were fed ziram at concentrations of 0, 72, 210 or 540 ppm. The NOAEL for maternal toxicity was 210 ppm, equal to 10 mg/kg bw per day, based on reduced food consumption and body-weight gain at 540 ppm. The NOAEL for neonatal toxicity was 210 ppm, equal to 10 mg/kg bw per day, based on reduced body-weight gain at 540 ppm. The NOAEL for reproductive toxicity and developmental neurotoxicity was 540 ppm, equal to 25 mg/kg bw per day.

In a study of developmental toxicity, rats were administered ziram at 0, 1, 4, 16, or 64 mg/kg bw per day on days 6-15 of gestation. The NOAEL for maternal toxicity was 4 mg/kg bw per day, on the basis of decreased body-weight gain and food intake, and increased water intake and salivation at 16 mg/kg bw per day and above. The NOEL for developmental toxicity was 16 mg/kg bw per day, on the basis of decreased litter weight and fetal weight at 64 mg/kg bw per day. No teratogenicity was seen.

In a study of teratogenicity in hamsters treated with single oral doses of 0, 31, 63, 120, or 500 mg/kg bw per day on day 7 or 8 of gestation, the NOAEL was 63 mg/kg bw per day, on the basis of fused ribs and deformed tails and heads, including all degrees of exencephaly, at 120 mg/kg bw per day.

In a study of developmental toxicity in rabbits given ziram at doses of 0, 3, 7.5, or 15 mg/kg bw per day on days 7-19 of gestation, the NOAEL for maternal toxicity and developmental toxicity was 7.5 mg/kg bw per day, on the basis of decreased body-weight gain and food intake in the dams and post-implantation loss, reduced litter size, litter weight, fetal weight, and crown-rump length at 15 mg/kg bw per day. There was no evidence of developmental toxicity.

Ziram is mutagenic in bacteria. It induced chromosomal aberrations in some, but not all, studies with cultured mammalian cells but did not induce unscheduled DNA synthesis in hepatocytes. *In vivo*, ziram induced single-strand breaks of DNA in the livers of rats but not mice. Chromosomal aberrations were not induced in mice *in vivo* in bone-marrow cells or spermatogonia, and micronuclei were not induced in bone-marrow cells or peripheral erythrocytes. Studies for clastogenicity have not been conducted in rats *in vivo*. In an old study of nine workers exposed for three to five years to ziram at a concentration of 2-4 mg/m<sup>3</sup> air, the percentage of peripheral leucocytes with chromosomal aberrations was 5.9%; in a control group the percentage was 0.75%. The Meeting was unable to reach a conclusion about the genotoxicity of ziram.

Ziram caused severe eye irritation but no dermal irritation in rabbits and moderate skin sensitization in guinea-pigs.

In two studies of neurotoxicity in rats treated with single doses of 0, 15, 300, or 600 mg/kg bw or 0, 72, 210, or 540 ppm for 91 days, behavioural effects indicative of neurotoxicity were apparent after single high doses but not after repeated dosing at a lower level. The NOAEL was 210 ppm, equal to 14 mg/kg bw per day, on the basis of reduced body weight and food consumption and inhibition of brain neuropathy target esterase activity at 540 ppm.

An ADI of 0-0.003 mg/kg bw was established on the basis of long-term toxicity in the rat. In this study, effects were seen at all doses, the LOAEL being 60 ppm, equal to 2.5 mg/kg bw per day. In view of the absence of an NOAEL, a safety factor of 1000 was used. The NOAEL of 1.6 mg/kg bw per day observed in a long-term study of toxicity in dogs supported this ADI, which served as the basis for the group ADI that was established for ziram alone or in combination with ferbam.

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

### TOXICOLOGICAL EVALUATION

#### Levels that cause no toxic effect

Mouse: 25 ppm, equal to 3 mg/kg bw per day (80-week study of toxicity and carcinogenicity)

210 ppm, equal to 10 mg/kg bw per day (maternal toxicity in a study of reproductive toxicity)

10 mg/kg bw per day (study of reproductive toxicity)

Rat: NOAEL could not be determined: lowest effective dose 60 ppm, equal to 2.5 mg/kg bw per day (12-24-month study of toxicity, various effects)

100 ppm, equal to 7.4 mg/kg bw per day (13-week study of toxicity)

250 ppm, equivalent to 12 mg/kg bw per day per day (two-year study of toxicity and carcinogenicity)

Hamster: 63 mg/kg bw per day (study of teratogenicity)

Rabbit: 7.5 mg/kg bw per day (maternal toxicity and embryotoxicity in a study of developmental toxicity)

Dog: 50 ppm, equal to 1.6 mg/kg bw per day (one-year study of toxicity)

100 ppm, equal to 4.1 mg/kg bw per day (13-week study of toxicity)

#### Estimate of acceptable daily intake for humans

0-0.003 mg/kg bw (group ADI for ferbam and ziram)

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

1. Further studies on long-term toxicity in rats.
2. Further studies on genotoxicity in rats.
3. Further studies on male reproductive toxicity.
4. Further observations in humans.

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

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
Short-term (1-7 days)	Oral toxicity, rat	LD <sub>50</sub> = 270 mg/kg bw
	Inhalation toxicity, rat	LC <sub>50</sub> = 0.06 mg/litre
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Severely irritating
	Dermal sensitization, guinea-pig	Moderately sensitizing
Medium-term (1-26 weeks)	Repeated oral, 13 weeks, toxicity, mouse	NOAEL = 15 mg/kg bw per day, decreased spleen weight
	Repeated oral, 4 weeks, toxicity, rat	NOAEL = 3 mg/kg bw per day, reduced body weight, food consumption, and degenerative hepatic changes
	Repeated oral, 13 weeks, toxicity, dog	NOAEL = 4.1 mg/kg bw per day, hepatic toxicity
	Repeated oral, reproductive toxicity and developmental neurotoxicity, rat	NOAEL = 25 mg/kg bw per day, reproductive toxicity and development neurotoxicity NOAEL = 10 mg/kg bw per day, maternal and neonatal toxicity (reduced body weight)
	Repeated oral, developmental toxicity, rat	NOAEL = 16 mg/kg bw per day, developmental toxicity (reduced fetal weight) NOAEL = 4 mg/kg bw per day, maternal toxicity (reduced body weight)
	Repeated oral, developmental toxicity, hamster	NOAEL = 63 mg/kg bw per day, developmental toxicity (deformed fetuses)
	Repeated oral, developmental toxicity, rabbit	NOAEL = 7.5 mg/kg bw per day, developmental and maternal toxicity (reduced fetal and maternal weight)
	Repeated oral, neurotoxicity, rat	NOAEL = 14 mg/kg bw per day, inhibition of neuropathy target esterase activity
Long-term (≥)	Repeated oral, 18 months,	NOAEL = 3 mg/kg bw per day, reduced brain

EXPOSURE	RELEVANT ROUTE, STUDY TYPE, SPECIES	RESULT, REMARKS
one year)	toxicity, mouse	weight and hepatic toxicity
	Repeated oral, two years, toxicity and carcinogenicity, rat	No NOAEL identified, LOAEL = 2.5 mg/kg bw per day, haematological toxicity and toxic effects on the thyroid
	Repeated oral, one year, toxicity, dog	NOAEL = 1.6 mg/kg bw per day, reduced body weight and hepatic toxicity

### RESIDUE AND ANALYTICAL ASPECTS

Ziram was originally evaluated in 1965 (toxicology) and 1967 (toxicology and residues) and is included in the dithiocarbamate group of compounds. It was evaluated at the present Meeting within the CCPR periodic review programme.

Ziram is a dithiocarbamate contact fungicide with protective action and is registered for use on fruit, vegetables, tree nuts and ornamentals in many countries. Ziram applied to dormant fruit trees is also used to repel hares and rabbits.

The Meeting received information on the metabolism of ziram in goats and apples, methods of residue analysis, the stability of residues in stored analytical samples, approved use patterns, supervised residue trials and the fate of residues during the processing of apples.

In a study on lactating goats with radiolabelled ziram the total residues in milk reached a plateau within 2-3 days. Levels of the radiolabel were higher in the liver than in other tissues.

The metabolism study on apples demonstrated that ziram residues are essentially on the surface. Most of the residue which becomes incorporated into the tissues no longer contains the CS<sub>2</sub> structure.

Studies of the environmental fate were not provided for review by the FAO Panel, but the Meeting was informed that such studies were available and had been supplied to the Environmental Core Assessment Group. They would be supplied for future evaluation by the FAO Panel. The Meeting agreed to recommend only temporary MRLs pending a review of the data on environmental fate by the FAO Panel.

The analytical methods for ziram rely on acid digestion and CS<sub>2</sub> evolution, as do those for other dithiocarbamates. The Meeting agreed that the definition of the residue of the dithiocarbamates should apply to ziram.

Ziram in fortified macerated apples and peaches stored at -20°C for 3 months was of marginal stability.

The Meeting received data on ziram residues from supervised trials on apples, pears, apricots, cherries, nectarines, peaches, plums, almonds (kernels and hulls analysed), and pecans.

In an apple-processing study, residue levels of ziram in apple juice were about 10% of those in the apples.

### **FURTHER WORK OR INFORMATION**

#### Required (by 1997)

Information on the environmental fate of ziram in soil and in water/sediment systems.

#### Desirable

1. Information on the effect of washing on ziram residues on fruits.
2. Final reports of freezer storage stability studies now in progress on peaches, apples and almonds.
3. Information on attempts to develop specific methods of analysis for ziram, whether successful or not.



## 5. RECOMMENDATIONS

- 5.1 In the interests of public health and agriculture and in view of the needs of the Codex Committee on Pesticide Residues, the Meeting recommended that Joint Meetings on Pesticide Residues should continue to be held annually.
- 5.2 (Section 2.2.2). The Meeting agreed that risk assessments for acute hazards should take into account variability in individual units of composite samples upon which the MRL is based.
- 5.3 (Section 2.2.3). The Meeting:
- (1) agreed to support the recommendations of the informal workshop convened in The Hague, The Netherlands, 11-12 April 1996, on data evaluation, but recognized the need for further development.
  - (2) agreed that STMR levels that it had estimated should be used by the JMPR in estimating consumer intakes resulting from long-term (chronic) exposure.
  - (3) agreed to the need for wide availability of the report of the informal Workshop held in The Hague in April 1996 (*Report of an informal workshop on data evaluation in the estimation of dietary intake of pesticide residues for the JMPR*) which is included as Annex IV to this report.
  - (4) recommended that both the general and specific recommendations of the Workshop be included in future FAO and WHO guidelines.
- 5.4 (Section 2.2.4). The Meeting recommended that a worked example of calculations of Supervised Trials Median Residue (STMR) levels for parathion-methyl ('Parathion-methyl, Estimation of Dietary Intake') should be forwarded to the 1997 CCPR.
- 5.5 (Section 2.5). The Meeting recommended that national evaluations of pesticides should be used to the extent possible in the work of the WHO Core Assessment Group.
- 5.6 (Section 2.7). The Meeting recommended that IPCS make every effort to obtain the funds necessary for convening the Environmental Core Assessment Group simultaneously with the JMPR in the future.
- 5.7 (Section 4.18). Since methamidophos has been listed by the CCPR as a candidate for periodic review but not yet scheduled, and in view of the difficulties encountered by the present Meeting in evaluating the available data without the original studies, the Meeting recommended that the CCPR should schedule methamidophos for periodic review.
- 5.8 (Annex III). The Meeting agreed that a general method, with the inclusion of worked examples, should be developed for estimating dietary exposure to residues of pesticides that have common mechanisms of toxicity.

## 6. FUTURE WORK

The following items should be considered at the 1997 or 1998 Meeting. The compounds listed include those recommended for priority attention by the 28th or earlier Sessions of the CCPR, as well as compounds scheduled for re-evaluation in the CCPR periodic review programme.

### 6.1 1997 Meeting (tentative)

#### Toxicological evaluation

##### New compounds

Chlorpropham  
Fenbuconazole  
Fipronil

##### Periodic review compounds

Fenamiphos (085)  
Guazatine (114)  
Malathion (049)  
Triforine (116)

##### Other evaluations

Amitrole (079)  
Chlormequat (015)  
Ethephon (106)  
Lindane (048)  
Phosalone (060)

#### Residue evaluation

##### New compounds

Chlorpropham  
Fenbuconazole

##### Periodic review compounds

Carbofuran (096)  
Carbosulfan (145)  
Demeton-S-methyl (073)  
Guazatine (114)

Mevinphos (053)  
Phosmet (103)  
Thiabendazole (065)

##### Other evaluations

Abamectin (177)  
Captan (007)  
Chlorothalonil (081)  
Clethodim (187)  
Folpet (041)  
Myclobutanil (181)  
Tebuconazole (189)

**6.2 1998 Meeting (tentative)**Toxicological evaluationNew compounds

-

Periodic review compounds

Amitraz (122)  
 Dicloran (083)  
 Diphenylamine (030)  
 Endosulfan (032)  
 Ethoxyquin (035)  
 Pyrethrins (063)  
 Thiometon (076)

Other Evaluations

Bentazone (172)  
 Dinocap (087)  
 Phosmet (103)

Residue evaluationNew compounds

-

Periodic review compounds

Amitrole (079)  
 Benomyl (069)  
 Carbaryl (008)  
 Carbendazim (072)  
 2,4-D (020)  
 Dicloran (083)  
 Dimethipin (151)  
 Dimethoate (027)  
 Formothion (042)  
 Maleic hydrazide (102)  
 Omethoate (055)  
 Thiophanate-methyl (077)  
 Triforine (116)

Other Evaluations

Aldicarb (117)  
 Captan (007)  
 Dinocap (087)  
 Disulfoton (074)  
 Glufosinate-ammonium (175)  
 Hexythiazox (176)  
 Procymidone (136)  
 Quintozene (064)

## 7. REFERENCES

### PREVIOUS FAO AND WHO DOCUMENTS

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3. FAO/WHO. Evaluations of the toxicity of pesticide residues in food. 1965a Report of the Second Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues. FAO Meeting Report, No. PL/1965/10; WHO/Food Add./26.65.
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## CORRECTIONS TO REPORT OF 1995 JMPR

Additions and changes are shown **bold**. Minor typographical errors are not included.

P. 12 (Section 2.5.2), para 1, line 1

Insert "**fate**" to read "...data on environmental **fate** have been submitted..."

P. 52 (buprofezin), para 1, line 1

Change to read "...residues in food **in** commerce..."

P. 61 (dithianon), last full para, last line

Change to read "...supported the previous estimate of **5** mg/kg."

P. 63 Heading 4.15 FENARIMOL

Change Codex Classification Number to (192)

P. 86 Heading 4.17 FENPYROXIMATE

Change Codex Classification Number to (193)

P. 121 (fenthion), whole of para 6

Change to read

**"Although the use pattern and data suggested a maximum residue level of 1 mg/kg, the Meeting could not support this value on the basis of the risk assessment conducted. The Meeting therefore recommended withdrawal of the existing CXL for milks (0.05 mg/kg, F V)."**

P. 130 Heading 4.21 HALOXYFOP

Change Codex Classification Number to (194)

P. 213 (Annex I), Fenarimol

Change the recommendation for DF 0269 Dried grapes to **0.2 T** mg/kg.

P. 227 (Annex II)

TEBUCONAZOLE

Change Codex Classification Number to (189)

TEFLUBENZURON

Insert Codex Classification Number (**190**)

TOLCLOFOS-METHYL

Change Codex Classification Number to (**191**)



## ANNEX I

### ACCEPTABLE DAILY INTAKES, RESIDUE LIMITS AND SUPERVISED TRIALS MEDIAN RESIDUES PROPOSED AT THE 1996 MEETING

The Table of recommendations includes maximum Acceptable Daily Intakes (ADIs) and Maximum Residue Limits (MRLs). It should be noted that MRLs include draft MRLs and Codex MRLs (CXLs). The MRLs recommended by the JMPR on the basis of its estimates of maximum residue levels enter the Codex procedure as draft MRLs. They become Codex MRLs when they have passed through the procedure and have been adopted by the Codex Alimentarius Commission.

In general, the recommended MRLs listed for compounds which have been reviewed previously are additional to, or amend, those recorded in the reports of earlier Meetings. For compounds re-evaluated in the CCPR periodic review programme however, both new and previous recommendations are listed because such re-evaluations are regarded as replacing the original evaluation rather than supplementing it.

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.)

In response to recommendations of a Joint FAO/WHO Consultation on Guidelines for predicting the Dietary Intake of Pesticide Residues held in York, the UK, in 1995, the 1996 Meeting has extended its estimations of residues to include calculations of the median residues found in supervised trials (STMRs) in order to provide a basis for the estimation of the dietary intake of the pesticides reviewed. The estimated STMRs are included in the Table of ADIs and MRLs. Further details of the response of the Meeting to the York Consultation are given in Section 2.2.1 of this report, and information about an informal workshop held in The Hague, The Netherlands, in April 1996 to consider the implementation of its recommendations by the JMPR in Section 2.2.3. The report of this Workshop is reproduced as Annex IV.

Attention is drawn to Section 3.1 of this report: 'Definition of the residues of fat-soluble compounds'. Residues of such compounds are distinguished in the Table of Recommendations by the parenthetic note '(fat-soluble residue)' on a line below the residue definition.

The following qualifications and abbreviations are used.

\* following At or about the limit of determination  
recommended  
MRL

\* following name New compound  
of pesticide

\*\* following name Compound reviewed in CCPR periodic review programme  
of pesticide

E Extraneous Residue Limit (ERL).

F following The residue is fat-soluble and MRLs for milk and milk  
recommendations products are derived as explained in the introduction  
for milk to Part 2 of the Guide to Codex Maximum Limits for Pesticide Residues  
and to Volume II of the Codex Alimentarius.

(fat) following The recommendation applies to the fat of the meat.  
recommendations  
for meat

Po The recommendation accommodates post-harvest treatment of the  
commodity.

PoP following The recommendation accommodates post-harvest treatment  
recommendations of the primary food commodity.  
for processed foods  
(classes D and E in the  
Codex Classification)

STMR Supervised Trial Median Residue (see explanation on previous page).

STMR-P An STMR for a processed commodity calculated by applying the mean  
concentration or reduction factor for the process to the STMR calculated for the raw  
agricultural commodity.

T following ADIs The ADI is temporary, and due for re-evaluation in the year indicated.

T following MRLs The MRL is temporary, irrespective of the status of the ADI,  
until required information has been provided and evaluated.

V following The recommendation accommodates veterinary uses.  
recommendations  
for commodities  
of animal origin

W in place of an The previous recommendation is withdrawn.

MRL

If a recommended MRL is an amendment, the previous value is also recorded. The absence of a figure in the "Previous" column indicates that the recommendation is the first for the commodity or group concerned.

The Table includes the Codex Classification Numbers (CCNs) of both the compounds and the commodities listed, to facilitate reference to the Guide to Codex Maximum Limits for Pesticide Residues and other Codex documents.

Commodities are listed in alphabetical order. This is a change from earlier practice where commodities were listed in the order of the "Types" in the Codex Classification of Foods and Animal Feeds, and in alphabetical order within each Type. The change was made to facilitate checking and comparison with the CCPR Tables of MRLs, which are in alphabetical order.

**ACCEPTABLE DAILY INTAKES (ADIs), MAXIMUM RESIDUE LIMITS (MRLs) AND SUPERVISED TRIALS MEDIAN RESIDUES (STMRs)<sup>iv</sup>**

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Acephate (095)	0.03	VB 0400	Broccoli	2	- <sup>1</sup>	0.11
		VB 0041	Cabbages, Head	2	- <sup>1</sup>	0.33
		VB 0404	Cauliflower	2	- <sup>1</sup>	0.11
		VO 0448	Tomato	1	- <sup>1</sup>	0.38
			Tomato, canned			0.19 P <sup>2</sup>
			Tomato, canned juice			0.35 P
			Tomato, bulk paste			1.52 P
			Tomato, canned puree			0.68 P
			Tomato, wet pomace			0.23 P
			Tomato, dry pomace			0.38 P

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	



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Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
<sup>2</sup> STMR-P						
Aldicarb	0.003	VR 0589	Potato	0.5	0.5 T	0.077
(117)			Potato chips			0.056 P <sup>1</sup>
			Potato fries			0.045 P
			Potato, microwaved			0.065 P
			Potato, baked			0.050 P

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Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		Notes: <sup>1</sup> STMR-P				
Bifenthrin	0.02	GC 0654	Wheat	0.5 Po	0.05*	0.255
(178)		CM 0654	Wheat bran, unprocessed	2 PoP	-	0.89 P <sup>1</sup>
		CF 1211	Wheat flour	0.2 PoP	-	0.076 P
		CF 1212	Wheat wholemeal	0.5 PoP	-	0.21 P

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		<u>Notes:</u> <sup>1</sup> STMR-P					
Carbaryl** (008)	0.003						

## Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		Periodic review was only for toxicology					
Carbofuran** (096)	0.002						

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		Periodic review was only for toxicology					
Chlorfenvinphos**	0.0005	VB 0400	Broccoli	W	0.05		
(014)		VB 0402	Brussels sprouts	W	0.05		
		VB 0041	Cabbages, head	W	0.05		
		VR 0577	Carrot	W	0.4		
		VB 0404	Cauliflower	W	0.1		
		VS 0624	Celery	W	0.4		
		FC 0001	Citrus fruits	W	1		
		SO 0691	Cotton seed	W	0.05		
		VO 0440	Egg plant	W	0.05		
		VR 0583	Horseradish	W	0.1		
		VA 0384	Leek	W	0.05		
		GC 0645	Maize	W	0.05		
		MM 0095	Meat (from mammals, other than marine mammals)	W	0.2 (fat) V		
		ML 0107	Milk of cattle, goats and sheep	W	0.008 F V		
		VO 0450	Mushrooms	W	0.05		
		VA 0385	Onion, bulb	W	0.05		
		SO 0697	Peanut	W	0.05		
		VR 0589	Potato	W	0.05		
		VR 0494	Radish	W	0.1		
		GC 0649	Rice	W	0.05		
		CM 1205	Rice, polished	W	0.05		
		VR 0497	Swede	W	0.05		
		VR 0508	Sweet potato	W	0.05		
		VO 0448	Tomato	W	0.1		
		VR 0506	Turnip, Garden	W	0.05		

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		Periodic review was only for toxicology					
DDT (021)	0.02 (PTDI <sup>1</sup> )	MM 0095	Meat (from mammals other than marine mammals)	5 (fat) E	1 (fat) E		

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		Notes: <sup>1</sup> provisional tolerable daily intake. See 1994 report, Section 2.3				
Diazinon <sup>1</sup>	0.002	PO 0840	Chicken, Edible offal of	0.02*	-	0
(022)		PE 0840	Chicken eggs	0.02*	-	0
		PM 0840	Chicken meat	0.02*	-	0
		MM 0814	Goat meat	2 (fat) V	-	0.3 (fat) 0.02 (whole muscle)
		MO 0098	Kidney of cattle, goats, pigs and sheep	0.03 V	-	0.01
		MO 0099	Liver of cattle, goats, pigs and sheep	0.03 V	-	0.01
		MM 0097	Meat of cattle, pigs and sheep	2 (fat) V	W <sup>1</sup>	0.3 (fat) 0.02 (whole muscle)
		ML 0106	Milks	0.02 F V	W <sup>1</sup>	0.02
		<u>Residue</u> (for MRLs & STMRs): diazinon				

## Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Notes: <sup>1</sup> Withdrawal of existing CXL proposed by 1993 JMPR.						
Dimethoate** (027)	0.002					



Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		Periodic review was only for toxicology				
Disulfoton (074)	0.0003	Acute RfD 0.003 mg/kg bw.				
Dithiocarbamates		AM 0660	Almond hulls	20 <sup>1</sup> <u>mb</u> <sup>2</sup> , <u>zm</u>	20	
(105)		TN 0660	Almonds	0.1* <u>mb</u> , <u>zm</u>	0.1*	
		TN 0672	Pecan	0.1* T <u>zm</u>	-	
		FP 0009	Pome fruits	5 <u>mz</u> , <u>mt</u> , <u>pb</u> , <u>th</u> , <u>zm</u>	5	
		FS 0012	Stone fruits	7 <sup>3</sup> T <u>th</u> , <u>zm</u>	-	
		FB 0275	Strawberry	5 <u>th</u>	-	

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Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		<sup>3</sup> The estimated maximum residue level for dithiocarbamates arising from the use of thiram to accommodate uses of ziram on stone fruits.					
Fenarimol (192)	0.01	AB 0226	Apple pomace,dry	5	5 T		
		VS 0620	Artichoke, Globe	0.1	0.1 T		
		FI 0327	Banana	0.2	0.2 T		
		MO 1280	Cattle, kidney	0.02*	0.02* T		
		MO 1281	Cattle, liver	0.05	0.05 T		

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		MM 0812	Cattle meat	0.02*	0.02* T	
		FS 0013	Cherries	1	1 T	
		DF 0269	Dried grapes (= Currants, Raisins and Sultanas)	0.2	0.2 T	
		FB 0269	Grapes	0.3	0.3 T	
		DH 1100	Hops, dry	5	-	
		VC 0046	Melons, except Watermelon	0.05	0.05 T	
		FS 0247	Peach	0.5	0.5 T	
		TN 0672	Pecan	0.02*	0.02* T	
		VO 0445	Peppers, Sweet	0.5	0.5 T	
		FP 0009	Pome fruits	0.3	0.3 T	
		FB 0275	Strawberry	1	1 T	
<u>Residue</u> (for MRLs & STMRs): fenarimol						
Ferbam** (Dithiocarbamates, 105)	0.003					

## Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		Previous ADI was 0.02 mg/kg bw, also for ferbam and ziram.					
Flumethrin* (195)	0.004	MM 0812	Cattle meat	0.2 (fat) <sup>1</sup> V	-	0.01 (fat) 0.005 (whole muscle)	
		ML 0812	Cattle milk	0.05 F V	-	0.01	
			Honey	0.005*	-	0.005	
<p><u>Residue</u> (for MRLs &amp; STMRs): flumethrin</p> <p><u>Notes:</u> <sup>1</sup>maximum residue in whole meat (muscle) reflecting approved uses was 0.01 mg/kg. Recommended MRL is on carcase fat basis.</p>							
Haloxyfop (194)	0.0003	AL 1021	Alfalfa forage (green)	W	Prov. <sup>1</sup>		
		FI 0327	Banana	0.05*	Prov. <sup>1</sup>	0	
		MO 0812	Cattle, Edible offal of	W	Prov. <sup>1</sup>		
		MF 0812	Cattle fat	W	Prov. <sup>1</sup>		
		MM 0812	Cattle meat	W	Prov. <sup>1</sup>		
		ML 0812	Cattle milk	W	Prov. <sup>1</sup>		
		FM 0812	Cattle milk fat	W	Prov. <sup>1</sup>		
		PO 0840	Chicken, Edible offal of	0.1	Prov. <sup>1</sup>	0.01	
		PE 0840	Chicken eggs	0.01*	Prov. <sup>1</sup>	0.01	
		PM 0840	Chicken meat	0.01*	Prov. <sup>1</sup>	0.01	

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMTR (mg/kg)	
		CCN	Name	New	Previous		
		FC 0001	Citrus fruits	0.05*	Prov. <sup>1</sup>	0	
		SO 0691	Cotton seed	0.2	Prov. <sup>1</sup>	0.09	
		OC 0691	Cotton seed oil, crude	0.5	Prov. <sup>1</sup>	0.1 P <sup>2</sup>	
		AM 1051	Fodder beet	0.3	Prov. <sup>1</sup>		
		AV 1051	Fodder beet leaves or tops	W	Prov. <sup>1</sup>		
		FB 0269	Grapes	0.05*	Prov. <sup>1</sup>	0	
		SO 0697	Peanut	0.05	Prov. <sup>1</sup>	0.03	
		VP 0063	Peas (pods and succulent = immature seeds)	0.2	-	0.02	
		FP 0009	Pome fruits	0.05*	Prov. <sup>1</sup>	0	
		VD 0070	Pulses (dry)	0.2	Prov. <sup>1</sup>	0.03	
		VR 0589	Potato	0.1	Prov. <sup>1</sup>	0.04	
		SO 0495	Rape seed	2	Prov. <sup>1</sup>	0.17	
			Rape seed meal			0.15 P	
		OC 0495	Rape seed oil, crude	5	Prov. <sup>1</sup>	0.36 P	
		OR 0495	Rape seed oil, edible	5	Prov. <sup>1</sup>	0.28 P	
		CM 1206	Rice bran, unprocessed	0.02*	Prov. <sup>1</sup>	0.02 P	
		CM 0649	Rice, husked	0.02*	Prov. <sup>1</sup>	0	
		CM 1205	Rice, polished	0.02*	Prov. <sup>1</sup>	0	
			Soya bean			0.03 (Pulses (dry))	
			Soya bean meal			0.03 P	
		OC 0541	Soya bean oil, crude	0.2	Prov. <sup>1</sup>	0.02 P	
		OR 0541	Soya bean oil, refined	0.2	Prov. <sup>1</sup>	0.02 P	
		VR 0596	Sugar beet	0.3	Prov. <sup>1</sup>	0.02	
		AV 0596	Sugar beet leaves or tops	W	Prov. <sup>1</sup>		
			Sugar beet pressed pulp			0.008 P	
			Sugar, refined			0.002 P	
		SO 0702	Sunflower seed	0.2	Prov. <sup>1</sup>	0.05	
		<u>Residue</u> (for MRLs & STMTRs): haloxyfop esters, haloxyfop and its conjugates expressed as					

## Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		<p>Notes: <sup>1</sup>Provisional estimates of maximum residue levels were made by the 1995 JMPR, but were not or use as MRLs.</p> <p><sup>2</sup>STMR-P</p>					

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
Maleic hydrazide** (102)	0.3	Periodic review was only for toxicology					
Methamidophos (100)	0.004	VB 0041	Cabbage, Head	0.5	- <sup>1</sup>	0.01	
		VB 0404	Cauliflower	0.5	- <sup>1</sup>	0.01	
		FS 0247	Peach	1	- <sup>1</sup>	0.16	
			Peach, washed fruit			0.10	
			Peach, juice (100% basis)			0.11 P <sup>2</sup>	
			Peach, jam			0.10 P	
			Peach, canned fruit			0.08 P	
		VO 0448	Tomato	1	- <sup>1</sup>	0.12	
		Residue (for MRLs & STMRs): methamidophos					
		Notes: <sup>1</sup> Withdrawn by 1994 JMPR					
		<sup>2</sup> STMR-P					
		Recommended MRLs are based on residues from the use of methamidophos or					

## Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		acephate					
Mevinphos** (053)	0.0008						



Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)	
		CCN	Name	New	Previous		
		Periodic review was only for toxicology					
Phorate (112)	0.0005	<u>Notes:</u> Previous ADI confirmed					
Propoxur (075)	0.02	VL 0482	Lettuce, Head	0.5	3		
		VR 0589	Potato	0.02*	0.1*		
<u>Residue</u> (for MRLs): propoxur							
Tebufenozide* (196)	0.02	FB 0269	Grapes	0.5	-	0.12	
		FP 0009	Pome fruits	1	-	0.16	
		CM 0649	Rice, husked	0.1	-	0.03	
		TN 0678	Walnut	0.05	-	0.003	
			Apple pomace, wet			0.4 P <sup>1</sup>	
			Apple juice			0.02 P	
			Apple puree			0.04 P	
			Grape pomace, wet			0.36 P	
			Wine			0.03 P	
<u>Residue</u> (for MRLs & STMRs): tebufenozide							

Annex I

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
<p>Notes: <sup>1</sup>STMR-P</p>						
Teflubenzuron*	0.01	VB 0402	Brussels sprouts	0.5	-	0.21
(190)		VB 0041	Cabbages, Head	0.2	-	0.05
		FS 0014	Plums (including Prunes)	0.1	-	0.04
		FP 0009	Pome fruits	1	-	0.48
		VR 0589	Potato	0.05*	-	0
<p><u>Residue</u> (for MRLs &amp; STMRs): teflubenzuron</p>						
<p>Notes: First evaluation of residue and analytical aspects. Toxicology was evaluated in 1994.</p>						

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Thiram**	0.01		Apple juice			0.55 P <sup>1</sup>
(Dithiocarbamates, 105)			Apple pomace, wet			1.9 P
			Apple pomace, dry			6.93 P
		FS 0013	Cherries	1	-	0.72
		FS 0014	Plums (including Prunes)	1	-	0.72
		FP 0009	Pome fruits	5	5	1.9
		FB 0275	Strawberry	5	-	2.1
		<p><u>Residue</u> for MRLs: see dithiocarbamates for STMRs: thiram</p> <p><u>Notes:</u> <sup>1</sup>STMR-P Periodic review was only for residues.</p>				
Ziram**	0.003	AM 0660	Almond hulls	10 T	20	10.6
(Dithiocarbamates, 105)		TN 0660	Almonds	0.1* T	0.1*	0.04
			Apple juice			0.204 P
			Apple pomace, wet			2.81 P
			Apple pomace, dry			3.82 P
		TN 0672	Pecan	0.1* T	-	0.04
		FP 0009	Pome fruits	5 T	5	2.1
		FS 0012	Stone fruits	7 T	-	2.2

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STM (mg/kg)	
		CCN	Name	New	Previous		
		<p>Previous ADI was 0.02 mg/kg bw, also for ferbam and ziram.</p>					

## ANNEX II

## INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

ABAMECTIN (177)	1992 (T,R) <sup>v</sup> , 1994 (T,R), 1995 (T)
ACEPHATE (095)	1976 (T,R), 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 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)
AMITRAZ (122)	1980 (T,R), 1983 (R), 1984 (T,R), 1985 (R), 1986 (R), 1989 (R), 1990 (T,R), 1991 (R & corr. to 1990 R evaluation)
AMITROLE (079)	1974 (T,R), 1977 (T), 1993 (T,R)
	ANILAZINE (163) 1989 (T,R), 1992 (R)
	AZINPHOS-ETHYL 1973 (T,R), 1983 (R)
AZINPHOS-METHYL(068)	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 (129)	1979 (R), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1989 (T,R), 1991 (R), 1994 (T)
BENALAXYL (155)	1986 (R), 1987 (T), 1988 (R), 1992 (R), 1993 (R)
BENDIOCARB (137)	1982 (T,R), 1984 (T,R), 1989 (R), 1990 (R)
	BENOMYL (069) 1973 (T,R), 1975 (T,R), 1978 (T,R), 1983 (T,R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)
BENTAZONE (172)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1995 (R)
BHC (technical)	1965 (T), 1968 (T,R), 1973 (T,R) (see also lindane)
BIFENTHRIN (178)	1992 (T,R), 1995 (R), 1996 (R)

BINAPACRYL (003)	1969 (T,R), 1974 (R), 1982 (T), 1984 (R), 1985 (T,R)
BIORESMETHRIN (093)	1975 (R), 1976 (T,R), 1991 (T,R)
BIPHENYL	see diphenyl
	BITERTANOL (144) 1983 (T), 1984 (R), 1986 (R), 1987 (T), 1988 (R), 1989 (R), 1991 (R)
BROMIDE ION (047)	1968 (R), 1969 (T,R), 1971 (R), 1979 (R), 1981 (R), 1983 (R), 1988 (T,R), 1989 (R), 1992 (R)
BROMOMETHANE (052)	1965 (T,R), 1966 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R), 1992 (R)
	BROMOPHOS (004) 1972 (T,R), 1975 (R), 1977 (T,R), 1982 (R), 1984 (R), 1985 (R)
BROMOPHOS-ETHYL (005)	1972 (T,R), 1975 (T,R), 1977 (R)
BROMOPROPYLATE (070)	1973 (T,R), 1993 (T,R)
BUTOCARBOXIM (139)	1983 (R), 1984 (T), 1985 (T), 1986 (R)
BUPROFEZIN (173)	1991 (T,R), 1995 (R), 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)
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 (072)	1973 (T,R), 1976 (R), 1977 (T), 1978 (R), 1983 (T,R), 1985 (T,R), 1987 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)
CARBOFURAN (096)	1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R), 1996 (T)
CARBON DISULPHIDE (009)	1965 (T,R), 1967 (R), 1968 (R), 1971 (R), 1985 (R)
CARBON	1965 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R),

## Annex II

TETRACHLORIDE (010)	1985 (R)
CARBOPHENOTHION	1972 (T,R), 1976 (T,R), 1977 (T,R), 1979 (T,R), 1980 (011) (T,R), 1983 (R)
CARBOSULFAN (145)	1984 (T,R), 1986 (T), 1991 (R), 1992 (corr. to 1991 rpt), 1993 (R)
CARTAP (097)	1976 (T,R), 1978 (T,R), 1995 (T,R)
CHINOMETHIONAT (080)	1968 (T,R) (as oxythioquinox), 1974 (T,R), 1977 (T,R), 1981 (T,R), 1983 (R), 1984 (T,R), 1987 (T)
CHLORBENSIDE	1965 (T)
CHLORDANE (012)	1965 (T), 1967 (T,R), 1969 (R), 1970 (T,R), 1972 (R), 1974 (R), 1977 (T,R), 1982 (T), 1984 (T,R), 1986 (T)
CHLORDIMEFORM (013)	1971 (T,R), 1975 (T,R), 1977 (T), 1978 (T,R), 1979(T), 1980(T), 1985(T), 1986 (R), 1987 (T)
CHLORFENSON	1965 (T)
CHLORFENVINPHOS (014)	1971 (T,R), 1984 (R), 1994 (T), 1996 (R)
CHLORMEQUAT (015)	1970 (T,R), 1972 (T,R), 1976 (R), 1985 (R), 1994 (T,R)
CHLOROBENZILATE (016)	1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R), 1980 (T)
CHLOROPICRIN	1965 (T,R)
CHLOROPROPYLATE	1968 (T,R), 1972 (R)
CHLOROTHALONIL (081)	1974 (T,R), 1977 (T,R), 1978 (R), 1979 (T,R), 1981 (T,R), 1983 (T,R), 1984 (corr. to 1983 rpt and T evaluation), 1985 (T,R), 1987 (T), 1988 (R), 1990 (T,R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R)
CHLORPROPHAM	1965 (T)
CHLORPYRIFOS (017)	1972 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1981 (R), 1982(T,R), 1983 (R), 1989 (R), 1995 (R)
CHLORPYRIFOS-METHYL (090)	1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990 (R), 1991 (T,R), 1992 (T) and corr. to 1991, 1993 (R), 1994 (R)
CHLORTHION	1965 (T)
CLETHODIM (187)	1994 (T,R)
CLOFENTEZINE (156)	1986 (T,R), 1987 (R), 1989 (R), 1990 (R), 1992 (R)
COUMAPHOS (018)	1968 (T,R), 1972 (R), 1975 (R), 1978 (R), 1980 (T,R), 1983(R),1987 (T), 1990 (T,R)

CRUFOMATE (019)	1968 (T,R), 1972 (R)
CYANOFENPHOS (091)	1975 (T,R), 1978 (T: ADI extended, but no evaluation), 1980, (T), 1982 (R), 1983 (T)
CYCLOXYDIM (179)	1992 (T,R), 1993 (R)
CYFLUTHRIN (157)	1986 (R), 1987 (T and corr. to 1986 rpt), 1989 (R), 1990 (R), 1992 (R)
CYHALOTHRIN (146)	1984 (T,R), 1986 (R), 1988 (R)
CYHEXATIN (TRICYCLOHEXYLTIN HYDROXIDE) (067)	1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R), 1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T), 1989 (T), 1991 (T,R), 1992 (R), 1994 (T)
CYPERMETHRIN (118)	1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985(R), 1986 (R), 1987 (corr. to 1986 evaluation), 1988 (R), 1990 (R)
CYROMAZINE (169)	1990 (T,R), 1991 (corr. to 1990 R evaluation), 1992 (R)
2,4-D (020)	1970 (T,R), 1971 (T,R), 1974 (T,R), 1975 (T,R), 1980 (R), 1985, (R), 1986 (R), 1987 (corr. to 1986 rpt, Annex I), 1996 (T)
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)
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-DIBROMOETHANE (023)	1965 (T,R), 1966 (T,R), 1967 (R), 1968 (R), 1971 (R), 1979 (R), 1985 (R)
DICHLORFLUANID (082)	1969 (T,R), 1974 (T,R), 1977 (T,R), 1979 (T,R), 1981 (R), 1982 (R), 1983 (T,R), 1985 (R)
1,2-DICHLOROETHANE (024)	1965 (T,R), 1967 (R), 1971 (R), 1979 (R), 1985 (R)



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DICHLORVOS (025)	1965 (T,R), 1966 (T,R), 1967 (T,R), 1969 (R), 1970 (T,R), 1974 (R), 1977 (T), 1993 (T,R)
DICLORAN (083)	1974 (T,R), 1977 (T,R)
DICOFOL (026)	1968 (T,R), 1970 (R), 1974 (R), 1992 (T,R), 1994 (R)
DIELDRIN (001)	1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (R), 1970, (T,R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)
DIFLUBENZURON (130)	1981 (T,R), 1983 (R), 1984 (T,R), 1985 (T,R), 1988 (R)
DIMETHIPIN (151)	1985 (T,R), 1987 (T,R), 1988 (T,R)
DIMETHOATE (027)	1965 (T), 1966 (T), 1967 (T,R), 1970 (R), 1973 (R in evaluation of formothion), 1977 (R), 1978 (R), 1983 (R) 1984 (T,R) 1986(R), 1987 (T,R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1994 (R), 1996 (T)
DIMETHRIN	1965 (T)
DINOCAP (087)	1969 (T,R), 1974 (T,R), 1989 (T,R), 1992 (R)
DIOXATHION (028)	1968 (T,R), 1972 (R)
DIPHENYL (029)	1966 (T,R), 1967 (T)
DIPHENYLAMINE (030)	1969 (T,R), 1976 (T,R), 1979 (R), 1982 (T), 1984 (T,R)
DIQUAT (031)	1970 (T,R), 1972 (T,R), 1976 (R), 1977 (T,R), 1978 (R), 1994 (R)
DISULFOTON (074)	1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1996 (T)
DITHIANON (180)	1992 (T,R), 1995 (R), 1996 (corr. to 1995 rpt.)
DITHIOCARBAMATES	1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R propineb, thiram), 1984 (R (105) propineb), 1985 (R), 1987 (T thiram), 1988 (R thiram), 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)
ENDRIN (033)	1965 (T), 1970 (T,R), 1974 (R), 1975 (R), 1990 (R), 1992 (R)
ETHEPHON (106)	1977 (T,R), 1978 (T,R), 1983 (R), 1985 (R), 1993 (T), 1994 (R), 1995 (T)

ETHIOFENCARB (107)	1977 (T,R), 1978 (R), 1981 (R), 1982 (T,R), 1983 (R)
ETHION (034)	1968 (T,R), 1969 (R), 1970 (R), 1972 (T,R), 1975 (R), 1982 (T), 1983 (R), 1985 (T), 1986 (T), 1989 (T), 1990 (T), 1994 (R)
ETHOPROPHOS (149)	1983 (T), 1984 (R), 1987 (T)
ETHOXYQUIN (035)	1969 (T,R)
ETHYLENE DIBROMIDE	see 1,2-dibromoethane
ETHYLENE DICHLORIDE	see 1,2-dichloroethane
ETHYLENE OXIDE	1965 (T,R), 1968 (T,R), 1971 (R)
ETHYLENETHIOUREA (ETU) (108)	1974 (R), 1977 (T,R), 1986 (T,R), 1987 (R), 1988 (T,R), 1990 (R), 1993 (T,R)
ETOFENPROX (184)	1993 (T,R)
ETRIMFOS (123)	1980 (T,R), 1982 (T,R <sup>3</sup> ), 1986 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)
FENAMIPHOS (085)	1974 (T,R), 1977 (R), 1978 (R), 1980 (R), 1985 (T), 1987 (T),
FENARIMOL (192)	1995 (T,R,E), 1996 (R & corr. to 1995 rpt.)
FENBUTATIN OXIDE (109)	1977 (T,R), 1979 (R), 1992 (T), 1993 (R)
FENCHLORPHOS (036)	1968 (T,R), 1972 (R), 1983 (R)
FENITROTHION (037)	1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R)
FENPROPATHRIN (185)	1993 (T,R)
FENPROPIMORPH (188)	1994 (T), 1995 (R)
FENPYROXIMATE (193)	1995 (T,R), 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.)
FENTIN COMPOUNDS (040)	1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R), 1993 (R), 1994 (R)

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<sup>3</sup>R evaluation omitted. Published 1986.

## Annex II

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)
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)
FORMOTHION (042)	1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R)
GLUFOSINATE-AMMONIUM (175)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R)
GLYPHOSATE (158)	1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1994 (R)
GUAZATINE (114)	1978 (T,R), 1980 (R)
HALOXYFOP (194)	1995 (T,R), 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)
HEXACHLOROBENZENE (044)	1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)
HEXACONAZOLE (170)	1990 (T,R), 1991 (R and corr. to 1990 R evaluation), 1993 (R)
HEXYTHIAZOX (176)	1991 (T,R), 1994 (R)
HYDROGEN CYANIDE (045)	1965 (T,R)
HYDROGEN PHOSPHIDE (046)	1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1971 (R)
IMAZALIL (110)	1977 (T,R), 1980 (T,R), 1984 (T,R), 1985 (T,R), 1986 (T), 1988 (R), 1989 (R), 1991 (T), 1994 (R)
IPRODIONE (111)	1977 (T,R), 1980 (R), 1992 (T), 1994 (R), 1995 (T)
ISOFENPHOS (131)	1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986 (T,R), 1988 (R), 1992 (R)
LEAD ARSENATE	1965 (T), 1968 (T,R)

	LEPTOPHOS (088)	1974 (T,R), 1975 (T,R), 1978 (T,R)
LINDANE (048)		1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R) (publ. as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R)
MALATHION (049)		1965 (T), 1966 (T,R), 1967 (corr. to 1966 R), 1968 (R), 1969 (R), 1970 (R), 1973 (R), 1975 (R), 1977 (R), 1984 (R)
MALEIC HYDRAZIDE (102)		1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R), 1996 (T)
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 <sup>4</sup> ), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R), 1996 (R)
METHIDATHION (051)		1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,R), 1994 (R)
METHIOCARB (132)		1981 (T,R), 1983 (T,R), 1984 (T), 1985 (T), 1986 (R), 1987 (T,R), 1988 (R)
METHOMYL (094)		1975 (R), 1976 (R), 1977 (R), 1978 (R), 1986 (T,R), 1987 (R), 1988 (R), 1989 (T,R), 1990 (R), 1991 (R)
METHOPRENE (147)		1984 (T,R), 1986 (R), 1987 (T and corr. to 1986 rpt), 1988 (R), 1989 (R)
METHOXYCHLOR		1965 (T), 1977 (T)
METHYL BROMIDE (052)		See bromomethane
METIRAM (186)		1993 (T), 1995 (R)
MEVINPHOS (053)		1965 (T), 1972 (T,R), 1996 (T)
MGK 264		1967 (T,R)
MONOCROTOPHOS (054)		1972 (T,R), 1975 (T,R), 1991 (T,R), 1993 (T), 1994 (R)
MYCLOBUTANIL (181)		1992 (T,R)
NABAM		see dithiocarbamates, 1965 (T), 1976 (T,R)

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<sup>4</sup>R evaluation omitted. Published 1989.

NITROFEN (140)	1983 (T,R)
OMETHOATE (055)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1979 (T), 1981(T,R),1984 (R), 1985 (T), 1986 (R), 1987 (R), 1988 (R), 1990 (R)
ORGANOMERCURY COMPOUNDS	1965 (T), 1966 (T,R), 1967 (T,R)
OXAMYL (126)	1980 (T,R), 1983 (R), 1984 (T), 1985 (T,R), 1986 (R)
OXYDEMETHON- (R)	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)
OXYTHIOQUINOX	see chinomethionat
PACLOBUTRAZOL (161)	1988 (T,R), 1989 (R)
PARAQUAT (057)	1970 (T,R), 1972 (T,R), 1976 (T,R), 1978(R), 1981 (R), 1982 (T), 1985 (T), 1986 (T)
PARATHION (058)	1965 (T), 1967 (T,R), 1969 (R), 1970 (R), 1984 (R), 1991 (R), 1995 (T,R)
PARATHION-METHYL (R), 1995 (T)	1965 (T), 1968 (T,R), 1972 (R), 1975 (T,R), 1978 (T,R), 1979 (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 (056)	1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 1990 (T,R)
PHENOTHRIN (127)	1979 (R), 1980 (T,R), 1982 (T), 1984 (T), 1987 (R), 1988 (T,R)
PHENTHOATE (128)	1980 (T,R), 1981 (R), 1984 (T)
PHORATE (112)	1977 (T,R), 1982 (T), 1983 (T), 1984 (R), 1985 (T), 1990 (R), 1991 (R), 1992 (R), 1993 (T), 1994 (T), 1996 (T)
PHOSALONE (060)	1972 (T,R), 1975 (R), 1976 (R), 1993 (T), 1994 (R)
PHOSMET (103)	1976 (R), 1977 (corr. to 1976 evaluation), 1978 (T,R), 1979 (T,R), 1981 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1994 (T)
PHOSPHINE	see hydrogen phosphide
PHOSPHAMIDON (061)	1965 (T), 1966 (T), 1968 (T,R), 1969 (R), 1972 (R), 1974 (R), 1982 (T), 1985 (T), 1986 (T)

PHOXIM (141)	1982 (T), 1983 (R), 1984 (T,R), 1986 (R), 1987 (R), 1988 (R)
PIPERONYL BUTOXIDE (062)	1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1972 (T,R), 1992 (T,R), 1995 (T)
PIRIMICARB (101)	1976 (T,R), 1978 (T,R), 1979 (R), 1981 (T,R), 1982 (T), 1985 (R)
PIRIMIPHOS-METHYL (086)	1974 (T,R), 1976 (T,R), 1977 (R), 1979 (R), 1983 (R), 1985 (R), 1992 (T), 1994 (R)
PROCHLORAZ (142)	1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (corr. to 1990 rpt, Annex I, and evaluation), 1992 (R)
PROCYMIDONE (136) (R)	1981 (R), 1982 (T), 1989 (T,R), 1990 (R), 1991 (corr. to 1990 Annex I), 1993 (R)
PROFENOFOS (171)	1990 (T,R), 1992 (R), 1994 (R), 1995 (R)
PROPAMOCARB (148)	1984 (T,R), 1986 (T,R), 1987 (R)
PROPARGITE (113)	1977 (T,R), 1978 (R), 1979 (R), 1980 (T,R), 1982 (T,R)
PROPHAM (183)	1965 (T), 1992 (T,R)
PROPICONAZOLE (160)	1987 (T,R), 1991 (R), 1994 (R)
PROPINEB	1977 (T,R), 1980 (T), 1983 (T), 1984 (R), 1985 (T,R), 1993 (T,R)
PROPOXUR (075)	1973 (T,R), 1977 (R), 1981 (R), 1983 (R), 1989 (T), 1991 (R), 1996 (R)
PROPYLENETHIOUREA (PTU) (150)	1993 (T,R), 1994 (R)
PYRAZOPHOS (153)	1985 (T,R), 1987 (R), 1992 (T,R), 1993 (R)
PYRETHRINS (063)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T), 1972 (T,R), 1974 (R)
QUINTOZENE (064)	1969 (T,R) 1973 (T,R), 1974 (R), 1975 (T,R), 1976 (Annex I, corr. to 1975 R), 1977 (T,R), 1995 (T,R)
2,4,5-T (121)	1970 (T,R), 1979 (T,R), 1981 (T)
TEBUCONAZOLE (189)	1994 (T,R), 1996 (corr. to Annex II of 1995 rpt.)
TEBUFENOZIDE (196)	1996 (T,R)
TECNAZENE (115)	1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R), 1994 (T,R)
TEFLUBENZURON (190)	1994 (T), 1996 (R)
TERBUFOS (167)	1989 (T,R), 1990 (T,R)

THIABENDAZOLE (065)	1970 (T,R), 1971 (R), 1972 (R), 1975 (R), 1977 (T,R), 1979 (R), 1981 (R)
THIODICARB (154)	1985 (T,R), 1986 (T), 1987 (R), 1988 (R)
THIOMETON (076)	1969 (T,R), 1973 (T,R), 1976 (R), 1979 (T,R), 1988 (R)
THIOPHANATE-METHYL (077)	1973 (T,R), 1975 (T,R), 1977 (T), 1978 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)
THIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1970 (T,R), 1974 (T), 1977 (T), 1983 (R), 1984 (R), 1985 (T,R), 1987 (T), 1988 (R), 1989 (R), 1992 (T), 1996 (R)
TOLCLOFOS-METHYL (191)	1994 (T,R) 1996 (corr. to Annex II of 1995 rpt.)
TOLYLFLUANID (162)	1988 (T,R), 1990 (R), 1991 (corr. to 1990 rpt)
TOXAPHENE	see camphechlor
TRIADIMEFON (133)	1979 (R), 1981 (T,R), 1983 (T,R), 1984 (R), 1985 (T,R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1989 (R), 1992 (R), 1995 (R)
TRIADIMENOL (168)	1989 (T,R), 1992 (R), 1995 (R)
TRIAZOLYLALANINE	1989 (T,R)
TRIAZOPHOS (143)	1982 (T), 1983 (R), 1984 (corr. to 1983 rpt, Annex I), 1986 (T,R), 1990 (R), 1991 (T and corr. to 1990 evaluation), 1992 (R), 1993 (T,R)
TRICHLORFON (066)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1987 (R)
TRICHLORONAT	1971 (T,R)
TRICHLOROETHYLENE	1968 (R)
TRICYCLOHEXYLTIN HYDROXIDE	see cyhexatin
TRIFORINE (116)	1977 (T), 1978 (T,R)
TRIPHENYLTIN COMPOUNDS	see fentin compounds
VAMIDOTHION (078)	1973 (T,R), 1982 (T), 1985 (T,R), 1987 (R), 1988 (T), 1990 (R), 1992 (R)
VINCLOZOLIN (159)	1986 (T,R), 1987 (R and corr. to 1986 rpt and R evaluation), 1988 (T,R), 1989 (R), 1990 (R), 1992 (R), 1995 (T)
ZINEB (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1993 (T)
ZIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1996 (T,R)

## ANNEX III

### INTAKE PREDICTIONS

At the request of the Meeting, WHO (GEMS/Food) calculated the predicted intakes of residues of the pesticides on the agenda of the Joint Meeting using the methods described in *Guidelines for Predicting Dietary Intake of Pesticide Residues* (WHO, 1989) as revised by *Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues* (WHO/FNU/FOS/95.11).

Theoretical Maximum Daily Intakes (TMDIs) and, when information was available, International Estimated Daily Intakes (IEDIs) were calculated for those pesticides considered by the JMPR on the basis of the ADIs and MRLs proposed by the Meeting and existing and draft MRLs in the Codex system. For calculating IEDIs, Supervised Trials Median Residue (STMR) levels were available for newly evaluated pesticides and for some pesticide/commodity combinations of previously considered pesticides. In a few cases, processing data were also available for refining the assessments of dietary exposure.

The TMDI and/or the IEDI did not exceed the ADI for the following compounds:

acephate, aldicarb, bifenthrin, 2,4-D, diazinon, DDT, fenarimol, flumethrin, haloxyfop, maleic hydrazide, methamidophos, propoxur, tebufenozide, and teflubenzuron.

The TMDI exceeded the ADI for the following compounds, but information on STMR levels and processing factors must be reviewed before IEDIs can be calculated:

carbaryl, carbofuran, dimethoate, mevinphos, and phorate.

For thiram and ziram, the assessment covered the total intake of all dithiocarbamates, including mancozeb, maneb, metiram, propineb and zineb, and took into account the relative ADIs, molecular mass adjustments for residues expressed as carbon disulfide, and the relevance of individual dithiocarbamate compounds for each MRL. While the calculated IEDI for dithiocarbamates exceeded the ADI for three of the five regional diets considered, STMR levels were available for only a few pesticide/commodity combinations. Further refinement of the intake assessment will therefore be required. The Meeting agreed that a general method should be developed, with the inclusion of worked examples, for estimating the dietary intake of residues of pesticides that have common mechanisms of toxicity.

The dietary intake was not estimated for chlorfenvinphos because it was recommended that all existing MRLs should be withdrawn, or for ferbam because no MRLs were recommended.

It should be noted that the calculated TMDIs grossly over-estimate the true intake of



pesticide residues. It should, therefore, not be concluded that the MRLs recommended by the Meeting are unacceptable when the TMDI exceeds the ADI. Calculations of TMDIs can be used as a screening tool, and the IEDI should be calculated when data are available.

## ANNEX IV

### **Report of an informal workshop on data evaluation in the estimation of dietary intake of pesticide residues for the JMPR**

#### **INTRODUCTION**

A Joint FAO/WHO Consultation on Guidelines for predicting the Dietary Intake of Pesticide Residues was held in York, United Kingdom from 2-6 May 1995. The main objectives of the Consultation were to review the existing guidelines and to recommend feasible approaches for improving the reliability and accuracy of methods for predicting dietary intake of pesticide residues. The final published report of this Consultation<sup>vi</sup> became available in February 1996.

An informal Workshop was convened in the Hague, Netherlands from 11th-12th April 1996. Dr W. H. van Eck, of the Netherlands Ministry of Health, Welfare and Sport served as chairman. The Workshop had been arranged at the request of the FAO Panel members in order to consider the consequences of the recommendations of the York Consultation for individual reviewers as well as for the JMPR.

The focus of the Workshop was on the issues relating to the reviews of residue data undertaken by the FAO Panel members.

A list of participants is given. The participants considered a number of working examples on quintozene, dithiocarbamates, parathion-methyl and fenpropimorph, which illustrated issues of interest to the FAO Panel.

#### **OBJECTIVES**

The chairman explained that the implementation of the York consultation recommendations would have practical consequences for the way the FAO Panel members carried out their evaluations, how those data would be presented and how consumer risk assessments would be carried out by the JMPR. Guidance was needed for the FAO Panel members as to how recommendations are to be implemented. In addition, criteria need to be established in order to ensure consistency and transparency in the work of the FAO Panel.

The Workshop focused mainly on practical considerations of the application of the York consultation recommendations to the work of the FAO Panel. Discussion centred on the following issues:

- the criteria for the selection of residues trials data used to calculate the Supervised Trials Median Residue (STMR) level.
- the presentation in the JMPR monographs of intake related information (eg. median residue levels).
- the approach for dealing with residues at the limit of determination (LOD), also referred to as the limit of quantitation (LOQ).
- practical considerations of the cases where the residue definition for consumer risk assessment is different from that recommended for enforcement

- evaluation of data on edible portion and processing (combined supervised trials data with processing information)
- identification of appropriate residue values for acute intake assessments

Guidelines were developed in order to give guidance to the FAO Panel reviewers. In addition, a few general recommendations were made. The Workshop recognised that additional guidelines will need to be developed by the JMPR in the future, as experience is gained by the reviewers.

## **GUIDANCE TO THE FAO PANEL REVIEWERS ON THE IMPLEMENTATION OF THE YORK CONSULTATION RECOMMENDATIONS**

### **The Workshop recommended that:**

#### Comparability

Residues data from countries are evaluated against the GAP in the country of the trials or a neighbouring country with similar climate and cultural practices.

In identifying the STMR, the trials values selected should be comparable with the maximum registered use (ie. maximum application rate, maximum number of treatments, minimum PHI) on which the MRL is based.

In establishing comparability of uses in the residue trials to the maximum registered use, the application rates in the trials should generally be no more than  $\pm 25$  to 30% of the maximum application rate. Deviations from this should be explained in the appraisal. Similarly,  $\pm 25$  to 30% should also be used as a guide for establishing comparability of PHI; however, in this case the latitude of acceptable PHIs will also depend on the rate of decline of residues of the compound under evaluation. Consideration as to whether the number of treatments reported in trials are comparable to the registered maximum number of treatments will depend on the persistence of the compound and the interval between applications. Nevertheless, when a large number of treatments are made in the trials (more than 5 or 6) the residue level should be considered very little influenced by further treatments unless the compound is persistent or the treatments are made with unusually short intervals.

In establishing comparability of residue trials data in which more than one parameter (i.e application rate, number of treatments or PHI) deviate from the maximum registered use, consideration should be given to the combination effect on the residue value which may lead to an underestimation or overestimation of the STMR. For example, a trial result should not normally be selected for the estimation of the STMR if both the application rate is lower (perhaps 0.75 kg/ha in the trial; 1kg ai/ha GAP) than the maximum rate registered and the PHI is longer (perhaps 18 days in the trial, 14 days GAP) than the minimum registered PHI, since these parameters would combine to underestimate the residue. When results are selected for the estimation of STMRs, despite combination effects, the reasons should be explained in the appraisal.

If the residue value arising from a use considered comparable with the maximum registered use is lower than another residue value from the same trial which is within GAP, then the higher residue value should be selected in identifying the STMR. For example, if the GAP specified a

minimum PHI of 21 days and the residue levels in a trial reflecting GAP were 0.7, 0.6 and 0.9 mg/kg at 21, 28 and 35 days respectively, then the residue value of 0.9 mg/kg would be selected.

#### Trials with more than one residue value

In identifying the STMR only one data point should be taken from each trial (ie. site location)

Where several residue values have been reported from replicate plots from a single trial (ie. site location) the highest residue should be selected for the purpose of identifying the STMR.

Where several residue values have been reported from replicate analyses of the same field sample taken from a single trial (ie. site location) the mean residue should be selected for the purpose of identifying the STMR.

#### Rounding of results

In identifying the STMR from a residue trial the actual residue value should be used in the estimation of dietary intake without rounding up or down. This would even be the case where the actual results were below the practical limit of determination considered appropriate for enforcement purposes. Rounding of residue values is inappropriate since the STMRs are used at an intermediate stage in the dietary intake calculation.

#### Residue definition

The WHO Panel consider routinely indicating in their evaluations which metabolites should be included in the dietary risk assessment.

If it is recommended that the residue definition for the risk assessment is different from that for enforcement, then this is clearly stated in the appraisal.

Close communication should be established between the FAO Panel reviewers and the respective reviewers on the Toxicological and Environmental Groups, on questions such as which metabolites are of toxicological significance, prior to the JMPR meeting.

In tabulating the residue trials data the FAO Panel reviewer should indicate the levels of relevant metabolites separately from those of the parent compound, but in a way which would allow subsequent combination, in order to ensure that changes in the residue definition can be accommodated at the JMPR meeting.

In those cases where it is not possible to finalise the risk assessment at the JMPR (September, year 1) usually because of a change in residue definition, then the MRLs would still be recommended to the CCPR (by way of Codex circular letter for comment at step 3) and the compound would be rediscussed at the following years JMPR meeting (September, year 2). The recommended MRLs together with the conclusion of the risk assessment would be available for the next CCPR (April, year 3).

If two compounds, for which STMRs can be calculated, produce the same analyte in compliance monitoring (eg. CS<sub>2</sub> for dithiocarbamates) it is possible to separate the intake assessments, if required, because the intake assessment is no longer based on the MRL but is based on residue data specific to the individual compounds.

#### Combining of populations of data for the calculation of STMRs

In identifying the STMR, residue data reflecting different countries GAPs would normally be combined. However, if the trials data reflecting different countries GAPs appear to give rise to different populations of data then these data sets should not be combined. In these cases the STMR should be calculated from the population(s) of data which is (are) driving the MRL. In deciding whether the results of trials reflecting different countries GAPs give rise to different populations of residues data, the size of the database reflecting the different countries GAPs should be taken into account.

#### Residues below the limit of determination

That as a general rule, where all residue trials data are <LOD, the STMR would be assumed to be at the LOD, unless there is scientific evidence that residues are "essentially zero". Such supporting evidence would include residues from related trials at shorter PHIs, exaggerated, but related, application rates or a greater number of applications, expectations from metabolism studies or data from related commodities.

Where there are two or more sets of trials with different LODs, and no determinable residues have been reported in the trials, then the lowest LOD should normally be used for the purpose of STMR selection (unless the residues can be assumed to be essentially zero as given above). The size of the trials database supporting the lowest LOD value should be taken into account in the decision.

#### Processing, cooking factors and edible portion residue data

In using data on the effects on residue levels of processing or cooking practices, the mean reduction or concentration factor should be applied to the STMR estimated for the raw agricultural commodity as already described. The STMR value estimated in this way for the processed commodity should be referred to as the STMR-P.

If data are available for the residues in the edible portion of the commodity (eg. banana pulp) then a STMR should be estimated directly using the edible portion residue values from maximum registered use trials (as opposed to using pesticide values for the whole commodity).

#### Acute dietary intake

The attention of the FAO Panel members is drawn to the recommendation that for the purpose of acute risk assessment the MRL, or the highest residue in the edible portion, should be used in estimating dietary intake.

#### Estimation of MRLs for products of animal origin

In estimating MRLs for products of animal origin, theoretical feed intakes for domestic animals should be calculated using the STMR for each feed item (derived from supervised trials comparable with the maximum registered use), rather than the MRL, together with the maximum feed incorporation rates. This is in conformity with past JMPR decisions.

#### Estimation of STMRs for commodity groups

Where there are adequate trials data the STMRs should, in principle, be identified for the individual commodities and these values used for the intake assessment. However, where the MRL has been established for a group of commodities (eg. pome fruit) a single STMR should be calculated for the group of commodities.

### Presentation of STMRs in the JMPR monographs and report

The GAP(s) on which trials data have been selected for the purpose of identifying the STMR should be clearly identified in the monographs.

In tabulating trials data in the monographs the reviewer should ensure that in addition to the normal underlining of trials data that are within GAP (and therefore have been used for the MRL evaluation), the single residue values selected for the estimation of the STMR should be double underlined.

Information on the residue values on which the STMR is based should not only be identified in the tabulated trials data (see above) but a list of the residue values selected should be included in the appraisal, in numerical order, with the median residue underlined. Where the residue situation is complex (eg. a number of metabolites to be considered) these data may best be tabulated in the appraisal. In addition, the STMR values should be included in the recommendation table in the appraisal and in Annex 1 of the report.

The range for the rates and PHIs used in the selection of residue values for STMR should be clearly identified in the appraisal (eg. trials data with application rates from 1.8 - 3.0 kg ai/ha have been selected).

### **RECOMMENDATIONS**

#### **The Workshop recommended that:**

- a) The recommendations of the York Joint FAO/WHO Consultation are implemented in full into the work of the JMPR.
- b) The acronym "STMR" be used in the JMPR monographs and report for the Supervised Trials Median Residue level.
- c) The FAO Panel identify STMRs routinely for each commodity as part of all future evaluation of compounds in order to facilitate more realistic estimates of long-term dietary intake.
- d) The guidance given in section 3 above is used by the FAO Panel reviewers in their evaluations for the 1996 JMPR.
- e) The report of the York Consultation be considered by 1996 JMPR together with worked examples that demonstrate the FAO Panel guidance given in section 3.
- f) GAP information when submitted by either the manufacturer or member governments, clearly identify which of the rates and PHIs are statutory conditions of use or taken directly from the product label and which are estimates made by the manufacturer or member governments (eg. whether the application rates in kg ai/ha have been calculated from the kg ai/hl application concentrations).
- g) The concepts contained in the FAO Panel guidance, as given in section 3, be incorporated into the draft document currently entitled "FAO Guidelines in the evaluation of pesticide residues data and the estimation of the Maximum Residue Limits in Food and Feed".

### **OTHER CONSIDERATIONS**

As a result of the examination of a worked example for STMR estimation, the Workshop noted that significant residues of HCB may result in commodities following applications of quintozone. When quintozone is re-evaluated by the JMPR, consideration should be given to the risk associated with the residues of the impurity HCB.

The WHO informed the Workshop that in revising the Guidelines for the prediction of dietary intake of pesticide residues, they would include hypothetical worked examples of intake calculations in order to give further guidance to member governments.

#### **LIST OF PARTICIPANTS** (*in alphabetical order*)

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<sup>i.</sup>Arnold, S.F., Klotz, D.M., Collins, B.M., Vonier, P.M., Guillette, L.J. Jr., & McLachlan, J.A. (1996). *Synergistic activation of estrogen receptor with combinations of environmental chemicals*. *Science* **272**, 1489-1492.

<sup>ii.</sup>See Section 2.2.3

<sup>iii.</sup>WHO (1994) *Carbaryl* (Environmental Health Criteria 153), Geneva

<sup>iv.</sup>See explanation on p. 93

<sup>v.</sup>T = Toxicology

R = Residue and analytical aspects

E = Environmental Fate evaluation by the Environmental Core Assessment Group

<sup>vi.</sup>Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues', Report of a FAO/WHO Consultation; World Health Organisation 1995.