

Pesticide Residues in Food

Report of the 1975 Joint FAO/WHO Meeting

Technical Report Series

592



World Health Organization, Geneva 1976

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations.

WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 592

FAO PLANT PRODUCTION AND PROTECTION SERIES

No. 1

PESTICIDE RESIDUES IN FOOD

**Report of the 1975 Joint Meeting of the FAO
Working Party of Experts on Pesticide Residues
and the WHO Expert Committee on
Pesticide Residues**



Published by
FAO and WHO



WORLD HEALTH ORGANIZATION

GENEVA

1976

Monographs containing evaluations, acceptable daily intakes, and tolerances for pesticide residues in food, together with information on identity of the pesticides considered, are issued by FAO and WHO under the title:

1975 Evaluations of Some Pesticide Residues in Food. (FAO AGP/1975/M/12; WHO Pesticide Residues Series, No. 5)

ISBN 92 4 120592 X

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PRINTED IN SWITZERLAND

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* * *

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**1975 JOINT MEETING OF THE FAO WORKING PARTY OF EXPERTS
ON PESTICIDE RESIDUES AND THE
WHO EXPERT COMMITTEE ON PESTICIDE RESIDUES**

Geneva, 24 November–3 December 1975

Members of the FAO Working Party of Experts on Pesticide Residues:

- Dr A. F. H. Besemer, Head, Pesticides Division, Plant Protection Service, Ministry of Agriculture, Wageningen, Netherlands
- Dr G. Bressau, Head, Pesticides Unit, Division of Food Chemistry, Max von Pettenkofer Institute, Federal Health Office, Berlin
- Mr F. Bro-Rasmussen, Head, Department of Pesticides and Contaminants, National Food Institute, Søborg, Denmark (*Rapporteur*)
- Dr K. A. McCully, Chief, Field Sciences Division, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada
- Mr J. T. Snelson, Pesticides Coordinator, Department of Agriculture, Canberra, ACT, Australia (*Vice-Chairman*)
- Dr C. Tomizawa, National Institute of Agricultural Sciences, Nishigahara, Kita-Ku, Tokyo, Japan

Observer invited by FAO:

- Dr A. J. Pieters, Chairman, Codex Committee on Pesticide Residues

Members of the WHO Expert Committee on Pesticide Residues:

- Dr W. F. Almeida, Director, Division of Animal Biology, Biological Institute, São Paulo, Brazil
- Dr V. Benes, Chief, Department of Toxicology and Reference Laboratory, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia (*Rapporteur*)
- Dr G. V. Gracheva, All-Union Scientific Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics, Kiev, USSR.
- Professor F. Coulston, Director, Institute of Comparative and Human Toxicology, Albany Medical College, Union University, Albany, NY, USA (*Chairman*)
- Professor D. V. Parke, Chairman, Department of Biochemistry, University of Surrey, Guildford, England
- Dr E. Poulsen, Director, Institute of Toxicology, National Food Institute, Søborg, Denmark
- Mr Huai-chou Wang, Institute of Hygiene, Chinese Academy of Medical Sciences, Peking, China

Secretariat:

- Dr R. L. Baron, National Environmental Research Center, Environmental Protection Agency, Research Triangle Park, NC, USA (*Temporary Adviser*)
- Dr R. Leski, Chemical Residues and Pollution Section, Joint FAO/IAEA Division of Atomic Energy in Agriculture, International Atomic Energy Agency, Vienna, Austria

Dr F. C. Lu, Chief, Food Additives, WHO, Geneva, Switzerland (*Joint Secretary*)
Mr A. F. Machin, Senior Research Officer, Central Veterinary Laboratory,
Ministry of Agriculture, Weybridge, England (*Consultant*)
Dr E. Middleton, Food Directorate, Health Protection Branch, Department of
National Health and Welfare, Ottawa, Canada (*Temporary Adviser*)
Dr E. E. Turtle, Pesticides Specialist, Plant Protection Service, FAO, Rome,
Italy (*Joint Secretary*)
Dr G. Vettorazzi, Scientist, Food Additives, WHO, Geneva, Switzerland

PESTICIDE RESIDUES IN FOOD

Report of the 1975 Joint FAO/WHO Meeting

A Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues was held in Geneva from 24 November to 3 December 1975. The Meeting was opened by Dr B. H. Dieterich, Director of the Environmental Health Division of the World Health Organization, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. The FAO Working Party had already met in Geneva from 19 to 22 November 1975 in preparation for the Joint Meeting.

Dr Dieterich stated that to meet the increasing need for food there has been a worldwide increase of the use of pesticides in agriculture. However, pesticides, even when applied in accordance with good agricultural practice, sometimes leave residues in food. Man is therefore exposed to them. The tasks of the Meeting were to provide toxicological evaluations aimed at establishing acceptable daily intakes for man, and to recommend limits of certain pesticide residues in specific foods. Dr Dieterich pointed out that the recommendations of the Joint Meeting would provide guidance to countries attempting to control the agricultural use of pesticides and to the Codex Alimentarius Commission and its subsidiary body, the Codex Committee on Pesticide Residues, when recommending international tolerances. Moreover, evaluation of the hazards of pesticides would contribute to the health protection of man from the pollution of the general environment by chemicals.

1. INTRODUCTION

The Joint Meeting was held in pursuance of the recommendations made in 1961, at a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture, that studies be undertaken to evaluate possible hazards to man arising from the occurrence of residues of pesticides in foods.

The reports of previous Joint Meetings (FAO/WHO, 1965a, 1967a, 1968a, 1969a, 1970a, 1971a, 1972a, 1973a, 1974a, 1975a) contain infor-

mation on acceptable daily intakes (ADIs), residue limits, and methods of analysis for the various pesticides considered. The supporting documents (FAO/WHO, 1965b, 1965c, 1967b, 1968b, 1969b, 1970b, 1971b, 1972b, 1973b, 1974b, 1975b) 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 requests of both a general and specific nature contained in the report of the Eighth Session of the Codex Committee on Pesticide Residues held from 3 to 8 May 1975.

During the present Joint Meeting the FAO Working Party was primarily responsible for :

- (a) reviewing data on certain pesticides and their residues ;
- (b) proposing pesticide residue limits and recommending methods of analysis.

The WHO Expert Committee was primarily responsible for :

- (a) reviewing toxicological and other data on certain pesticides and their residues ;
- (b) establishing, where possible, ADIs for man for those pesticides.

Furthermore, each of these groups of experts made recommendations designed to indicate, stimulate, and coordinate research.

2. GENERAL CONSIDERATIONS

2.1 Principles and scope

The Meeting took account of the principles enumerated in previous reports.^a In relation to the substances considered at the present Meeting, members felt that some of those principles should be clarified, rephrased, extended, or reaffirmed.

2.2 Toxicological evaluation and margin of safety

The Meeting adhered to the principles laid down previously in allocating ADIs or temporary ADIs for pesticides.

^a FAO/WHO 1958, 1961, 1967a, 1969a, 1970a, 1971a, 1972, 1972a, 1973a, 1974a, 1975a ; WHO 1967.

Each pesticide is toxicologically evaluated on the basis of all the available data on that compound and taking into account relevant data on related compounds and on compounds that give identical or similar metabolites.

It is an essential part of the evaluation to determine the dose levels where no significant toxicological effect is found. These "no-effect" levels in the relevant animal species and when possible in man are specified in the comments on each pesticide in the published monographs.

A margin of safety is necessary to allow for differences in sensitivity between the animal species and man, the wide variations in sensitivity among human beings, and the fewness of the experimental animals in comparison with the human population that might be exposed.

A thorough discussion of the question of the margin of safety was made by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (WHO 1967, pp. 19-22). The Meeting reaffirmed the conclusions of that Scientific Group especially with respect to increasing or decreasing the margin of safety. For the pesticides evaluated or re-evaluated at this Meeting, the comments stated in the monographs give an indication of the rationale behind each action taken.

It should be emphasized that the magnitude of the margin of safety applied in each individual case is based on the evaluation of all available data. In consideration of any information that gives rise to particular concern, the magnitude of the margin of safety will be increased.

Where the data provide an assurance of safety, the magnitude may be decreased. Therefore it is impossible to recommend fixed rules for the margin of safety to be applied in all instances.

2.3 Availability of data for consideration

The Meeting reaffirmed that it could not allocate ADIs or residue limits on the basis of abstracts or brief summaries of experimental data. To allocate ADIs or residue limits a full review of all data is necessary.

The Meeting appreciated the large volume of information furnished for its consideration by government agencies, industry, the International Union of Pure and Applied Chemistry, etc. In past years the Meeting had agreed to accept and to consider relevant information from all sources whether published or proprietary. The Meeting reaffirmed the previously

stated policy (FAO/WHO, 1970a) to review unpublished but not confidential information, which is available to scientists requesting information or challenging statements made by the Meeting.

The Meeting also reaffirmed the previous policy that on the request of the Secretariat all data should be made available to it in time for the preparation of working papers. The data must be sent to the Secretariat and/or their designated expert and must also be available to the Meeting. The Meeting further reaffirmed its inability to review pesticide chemicals unless these procedures were adhered to.

2.4 Definitions

A glossary of definitions accepted by successive Joint Meetings was added as Appendix IV to the report of the 1969 Joint Meeting (FAO/WHO, 1970a). Additions and amendments to the glossary were given in Annex 3 of the report of the Joint Meeting in 1971 (FAO/WHO, 1972a). The 1971 Joint Meeting noted (para. 2.10) that inconsistencies remained and that attention should be given to the subject at a future meeting. In the light of further developments within the Joint Meeting as well as in the Codex Committee on Pesticide Residues it was considered desirable to publish a revised list of definitions as Annex 3 to the present report. In the revision, attention was given to remarks made during the eighth session of the Codex Committee on Pesticide Residues that the definitions in use by the Joint Meeting and the Codex Committee on Pesticide Residues should agree as far as possible.

The Meeting agreed to the following changes.

(1) A separate definition for "pesticide" in line with the definition given by the Codex Committee on Pesticide Residues is introduced.

(2) The definition of "pesticide residue" is extended to include residues in animal feed and to limit the conversion products included in the definition to those considered to be of toxicological significance.

(3) The expression "negligible residue" has not been used by the Joint Meeting and is deleted.

(4) The use of the expression "unintentional residue" is no longer necessary in view of the new definitions of "maximum residue limit" and "extraneous residue level".

(5) In order to facilitate the work of the Codex Committee on Pesticide Residues and to ensure that recommendations are made on a similar

basis, the definition of "good agricultural practice in the use of pesticides" of the Codex Committee on Pesticide Residues is adopted.

(6) The definition of "temporary acceptable daily intake" now includes the fact that a period of validity must be specified.

(7) The definition of "tentative negligible daily intake" was withdrawn by the 1973 Joint Meeting and is deleted.

(8) The expression "tolerance" has been replaced by "maximum residue limit" in accordance with recent practice. "Temporary tolerance" has been replaced by "temporary maximum residue limit". The limits are expressed as milligrams per kilogram instead of parts per million—a practice that was initiated by the 1972 Joint Meeting.

(9) The term "extraneous residue limit" replaces "practical residue limit" defined in the report of the 1969 Joint Meeting. The latter has caused confusion owing to its similarity to "maximum residue limit" and to inconsistencies in its application to recommendations for residue limits in foods of animal origin.

(10) A definition of "guideline level", introduced by the 1972 Joint Meeting, is included in the glossary.

(11) The definition of "referee methods" is deleted, as proposed by the 1972 Joint Meeting.

(12) Minor changes have been made in some other definitions.

In addition it is proposed to include the definition of a "conditional acceptable daily intake" as a subject for discussion in the agenda of a future Meeting.

3. SPECIFIC PROBLEMS

3.1 Delayed neurotoxicity

A major toxicological problem long recognized to be associated with such organophosphate esters as tri-*o*-cresylphosphate (TOCP) and more recently brought to the attention of the Meeting in the evaluation of leptophos (see section 4) is that known commonly as "delayed neurotoxicity". This term refers to the observations made on patients suffering from acute poisoning with TOCP (and certain other organophosphorus compounds) of an apparent recovery from the acute parasympathomimetic signs of poisoning followed by the onset after 8–14 days of clinical signs of ataxia

muscle weakness and loss of appetite. Extensive reviews on the chemical structure/activity relationship, biochemistry, and histological factors relating to this syndrome have been published.

The delayed neurotoxicity syndrome affects only certain animal species, including man. The most susceptible animal for laboratory bioassay procedures, the adult hen, is not susceptible before 3–4 months of age. While the adult hen is the animal of choice for laboratory testing, cats, dogs, calves and sheep have been shown to be susceptible. Some sub-human primates and rodents are resistant to both the clinical and the histological lesions. In contrast, man has been shown to be highly susceptible to the syndrome, as suggested by studies where occurrences of paralysis have been reported. Although no definite data are available, man may well be the most sensitive species exhibiting delayed neurotoxicity.

There are no known antidotes to delayed neurotoxicity, and recovery from ataxia is predominantly through development of collateral nerve pathways and physical therapy to develop muscles not served by affected nerves. Reference has been made in the literature^a to the induction of neurotoxicity by certain organophosphorus compounds used as pesticides and drugs. The dose in most experimental cases is high, and atropine has been used to protect the animal from acute signs of poisoning to allow time for the neurotoxicity syndrome to develop. While atropine protects against the short-term acute parasympathomimetic signs of poisoning, it is ineffective against delayed neurotoxicity occurring 8–14 days after treatment.

The potential hazards associated with delayed neurotoxicity are two-fold :

- (1) exposure of occupationally or accidentally exposed individuals who would be affected by high doses for short periods ; and
- (2) long-term low-level exposure and possible build-up of the toxicant to threshold levels leading to ataxia.

Although the first aspect does not fall into the direct terms of reference of the Meeting, the toxicological hazard associated with such exposure

^a CAVANAGH, J. B. Peripheral neuropathy caused by toxic agents, *CRC critical reviews in toxicology*, 2 : 365 (1973) ; JOHNSON, M. K. The delayed neuropathy caused by some organophosphorus esters : mechanism and challenge, *CRC critical reviews in toxicology*, 3 : 289–316 (1975) ; DAVIES, D. R. Neurotoxicity of organophosphorus compounds, in : Koelle, G. B., ed. *Handbuch der Experimentellen Pharmakologie* [Handbook of experimental pharmacology], Supplement 15, Berlin, Springer Verlag, 1963, pp.860–882.