WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Miscellaneous Pesticides

VOLUME 30

IARC, LYON, FRANCE

January 1983

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Miscellaneous Pesticides

VOLUME 30

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
which met in Lyon,

15-22 June 1982

March 1983

IARC MONOGRAPHS

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. In 1980, the programme was expanded to include the evaluation of the carcinogenic risk associated with employment in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals and complex mixtures to which humans are known to be exposed, and on specific occupational exposures, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

This project was supported by PHS Grant No. 1UO1 CA33193-01 awarded by the National Cancer Institute, DHHS.

International Agency for Research on Cancer 1983

ISBN 92 832 1230 4 (soft-cover edition)

ISBN 92 832 1530 3 (hard-cover edition)

PRINTED IN FRANCE

CONTENTS

LIST OF PARTICIPANTS 5

NOTE TO THE READER 9

PREAMBLE
- Background 11
- Objective and Scope 11
- Selection of Chemicals for Monographs 12
- Working Procedures 13
- Data for Evaluations 13
- The Working Group 14
- General Principles for Evaluating Carcinogenic Risk of Chemicals 14
- Explanatory Notes on the Monograph Contents 20

GENERAL REMARKS ON THE SUBSTANCES CONSIDERED 33

CANCER EPIDEMIOLOGY OF PESTICIDE MANUFACTURERS, FORMULATORS AND USERS 37

THE MONOGRAPHS

Insecticides (including acaricides)
- Chlordimeform 61
- Chlorobenzilate 73
- Dicofol 87
- Malathion 103
- Methyl parathion 131
- Parathion 153
- Piperonyl butoxide 183
- Tetrachlorvinphos 197
- Trichlorfon 207

Herbicides
- Diallate 235
- Fluometuron 245
- MCPA 255
- Nitrofen 271
- Sulfallate 283

Fungicides
- Captan 295
- Chlorothalonil 319
- *ortho*-Phenylphenol and its sodium salt 329

Rodenticide
- 1-Naphthylthiourea (ANTU) 347

APPENDIX. GENERAL CONSIDERATIONS ON *N*-NITROSATABLE PESTICIDES 359

SUPPLEMENTARY CORRIGENDA TO VOLUMES 1-29 407

CUMULATIVE INDEX TO THE MONOGRAPHS SERIES 409

IARC WORKING GROUP ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: MISCELLANEOUS PESTICIDES

Lyon, 15-22 June 1982

Members

E.A. Bababunmi, Department of Biochemistry, University of Ibadan, Ibadan, Nigeria

S.V. Bhide, Head, Carcinogenesis Division, Tata Memorial Centre, Cancer Research Institute, Parel, Bombay 400012, India

B.A. Bridges, Director, Medical Research Council Cell Mutation Unit, University of Sussex, Falmer, Brighton BN1 9QG, UK (*Co-rapporteur section 3.2*)

J.E. Davies, University of Miami, Department of Epidemiology and Public Health, School of Medicine (R-699), PO Box 016069, Miami, FL 33101, USA (*Vice-Chairman*; *co-rapporteur section 3.3*)

J. Fajen, National Institute for Occupational Safety and Health, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, OH 45226, USA

W.J. Hayes, Jr, Vanderbilt University, Center in Toxicity, Department of Biochemistry, School of Medicine, Station 17, Nashville, TN 37232, USA

C.A. van der Heijden, National Institute of Public Health, Head, Laboratory for Carcinogenesis and Mutagenesis, Antonie van Leeuwenhoeklaan 9, PO Box 1, 3720 BA Bilthoven, The Netherlands

K.S. Khera, Toxicology Research Division, Health and Welfare Canada, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario K1A OL2, Canada (*Co-rapporteur section 3.2*)

R.D. Kimbrough, Center for Environmental Health, Centers for Disease Control, 1600 Clifton Road, Atlanta, GA 30333, USA

R.A. Lemen, National Institute for Occupational Safety and Health, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, OH 45226, USA

W. Lijinsky, Director, Chemical Carcinogenesis Program, National Cancer Institute, Frederick Cancer Research Facility, PO Box B, Frederick, MD 21701, USA

M. Lotti, University of California, Northern California Occupational Health Center, San Francisco General Hospital, Building 30, 5th floor, Potrero Avenue, San Francisco, CA 94110, USA

G. Martire, Faculty of Medicine and Surgery, University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy

D.P. Morgan, Department of Preventive Medicine and Environmental Health, College of Medicine, University of Iowa, Iowa City, IA 52242, USA (*Co-rapporteur section 3.2*)

R. Preussmann, German Cancer Research Center, Institute for Toxicology and Chemotherapy, Postfach 101949, 6900 Heidelberg 1, Federal Republic of Germany (*Chairman; co-rapporteur section 3.1*)

J.K. Reddy, Northwestern University, Department of Pathology, The Medical School, Ward Memorial Building, 303 East Chicago Avenue, Chicago, IL 60611, USA

A. Somogyi, Federal Institute of Health, Thielalle 88/92, Postfach 33 0013, 1000 Berlin 33, Federal Republic of Germany

N. Staiano, Faculty of Medicine and Surgery, University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy

D. Wassermann, Department of Occupational Health, The Hebrew University, Hadassah Medical School, PO Box 1172, Jerusalem, Israel

J.S. Wassom, Director, Environmental Mutagen Information Center, Environmental Teratology Information Center, Oak Ridge National Laboratory, Union Carbide Corporation, PO Box Y, Oak Ridge, TN 37830, USA

Representative from the National Cancer Institute

T.P. Cameron, Assistant Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, MD 20205, USA

Representative from SRI International

K.E. McCaleb, Director, Chemical-Environmental Department, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025, USA (*Co-rapporteur sections 1 and 2*)

Representative from the World Health Organization

M. Vandekar, Pesticides Development and Safe Use, Division of Vector Biology and Control, World Health Organization, Via Appia, 1211 Geneva 27, Switzerland

Representative from the Commission of the European Communities

M.-T. van der Venne, Directorate General Employment, Social Affairs and Education, Health and Safety Directorate, Commission of the European Communities, Batiment Jean Monnet, Plateau du Kirchberg, BP 1907, Luxembourg, Grand Duchy of Luxembourg

Representatives from the US Environmental Protection Agency

R. McGaughy, Acting Director, Carcinogen Assessment Group, Environmental Protection Agency, 401 M Street SW, RD 689, Washington DC 20460, USA

M.D. Waters, Director, Genetic Toxicology Division (MD-68), Health Effects Research Laboratory, Environmental Protection Agency, Research Triangle Park, NC 27711, USA

Representative from the International Group of National Associations of Manufacturers of Agrochemical Products

E.A. Pelfrène, Rhone-Poulenc Agrochimie, 14-20 rue Pierre Baizet, BP 9163, 69263 Lyon Cedex 1, France

Representatives from the National Agricultural Chemicals Association

B.L. Hollis, National Agricultural Chemicals Association, Suite 514, The Madison Building, 1155 Fifteenth Street NW, Washington DC 20005, USA

C. Reinhardt, E.I. du Pont de Nemours Co., Haskell Laboratory, Elkton Road, Newark, DE 19711, USA

Secretariat

H. Bartsch, Head, Unit of Environmental Carcinogens and Host Factors (*Co-rapporteur section 3.2*)
J. Cabral, Unit of Mechanisms of Carcinogenesis
L. Fishbein (Temporary adviser)[1]

---

[1]Present address: Director, Office of Scientific Intelligence, National Center for Toxicological Research, Jefferson, AR 72079, USA

M. Friesen, Unit of Environmental Carcinogens and Host Factors
L. Haroun, Unit of Retrieval and Coordination of Carcinogenicity Data (*Co-secretary*)
E. Heseltine, Lyon, France (*Editor*)
P. Honchar, Unit of Analytical Epidemiology
A. Likhachev, Unit of Mechanisms of Carcinogenesis
G. Mahon, Unit of Biostatistics
D. Mietton, Unit of Retrieval and Coordination of Carcinogenicity Data (*Library assistant*)
R. Montesano, Head, Unit of Mechanisms of Carcinogenesis (*Co-rapporteur section 3.1*)
N. Muñoz, Unit of Analytical Epidemiology
I. O'Neill, Unit of Environmental Carcinogens and Host Factors (*Co-rapporteur sections 1 and 2*)
C. Partensky, Unit of Retrieval and Coordination of Carcinogenicity Data (*Technical officer*)
I. Peterschmitt, Unit of Retrieval and Coordination of Carcinogenicity Data, Geneva (*Bibliographical researcher*)
R. Saracci, Acting Head, Unit of Analytical Epidemiology (*Co-rapporteur section 3.3*)
L. Simonato, Unit of Analytical Epidemiology
L. Tomatis, Director
J. Wahrendorf, Unit of Biostatistics
G. Weiss, Unit of Retrieval and Coordination of Carcinogenicity Data, Geneva
J. Wilbourn, Head, Unit of Retrieval and Coordination of Carcinogenicity Data (*Co-secretary*)
H. Yamasaki, Unit of Mechanisms of Carcinogenesis

Secretarial assistance

M.-J. Ghess
K. Masters
J. Mitchell
S. Reynaud

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical for humans is encouraged to make this information available to the Unit of Retrieval and Coordination of Carcinogenicity Data, International Agency for Research on Cancer, Lyon, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Retrieval and Coordination of Carcinogenicity Data, so that corrections can be reported in future volumes.

IARC MONOGRAPH PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS[1]

PREAMBLE

1. BACKGROUND

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans with the object of producing monographs on individual chemicals. The criteria established at that time to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs* series. In October 1977, a joint IARC/WHO *ad hoc* Working Group met to re-evaluate these guiding criteria; this preamble reflects the results of their deliberations(1) and those of subsequent IARC *ad hoc* Working Groups which met in April 1978(2)and February 1982(3).

An *ad hoc* Working Group, which met in Lyon in April 1979 to prepare criteria to select chemicals for *IARC Monographs*(4), recommended that the *Monographs* programme be expanded to include consideration of human exposures to complex mixtures which occur, for example, in selected occupations. The Working Group which met in June 1980 therefore considered occupational exposures in the wood, leather and some associated industries; their deliberations resulted in Volume 25 of the *Monographs* series. A further Working Group which met in June 1981 evaluated the carcinogenic risks associated with occupations in the rubber manufacturing industry, and their conclusions were published as Volume 28 of the *Monographs* series.

2. OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals, groups of chemicals or industrial processes to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

---

[1]This project was supported by PHS Grant No. 1 UO1 CA33193-01 awarded by the US National Cancer Institute, DHSS.

The critical analyses of the data are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendations are given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or other international agencies. In this connection, WHO recommendations on food additives(5), drugs(6), pesticides and contaminants(7) and occupational carcinogens(8) are particularly informative.

In February 1982, a special *ad hoc* Working Group met in Lyon to re-evaluate all chemicals, groups of chemicals, industrial processes or occupational exposures evaluated in volumes 1-29 of the *IARC Monographs*(3) and for which some data on carcinogenicity to humans (case reports or epidemiological studies) had been published in the literature. Re-evaluations of the data on humans, the data on experimental animals and the data on short-term tests were made for each agent and an overall evaluation of the carcinogenicity to humans was then made. The Working Group concluded that seven industrial processes or occupational exposures were causally associated with cancer in humans, as were 23 chemicals or groups of chemicals. Sixty-one chemicals, groups of chemicals or industrial processes were considered to be probably carcinogenic to humans. In addition, for 175 chemicals there is *sufficient evidence* of their carcinogenicity in experimental animals.

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental chemicals. The first users' survey, made in 1976, indicates that the monographs are consulted routinely by various agencies in 24 countries. Up to December 1982, 30 volumes of the *Monographs* had been published or were in press; and a cross index of synonyms and trade names in volumes 1 to 26 was published as Supplement 3 to the *Monographs*(9). Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. The monographs are also available *via* the WHO Distribution and Sales Service.

3. SELECTION OF CHEMICALS FOR MONOGRAPHS

The chemicals (natural and synthetic, including those which occur as mixtures and in manufacturing processes) are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues are also considered. The scientific literature is surveyed for published data relevant to the monograph programme. In addition, the IARC *Survey of Chemicals Being Tested for Carcinogenicity*(10) often indicates those chemicals that may be scheduled for future meetings.

Inclusion of a chemical in a volume does not imply that it is carcinogenic, only that the published data have been examined. The evaluations must be consulted to ascertain the conclusions of the Working Group. Equally, the fact that a chemical has not appeared in a monograph does not mean that it is without carcinogenic hazard.

As new data on chemicals for which monographs have already been prepared and new principles for evaluating carcinogenic risk receive acceptance, re-evaluations will be made at subsequent meetings, and revised monographs will be published as necessary.

4. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; in addition to the published literature, US Public Health Service Publication No. 149(11) has been particularly valuable and has been used in conjunction with other recognized sources of information on chemical carcinogenesis and systems such as CANCERLINE, MEDLINE and TOXLINE. The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production, use, occurrence and on analysis are carried out by SRI International, Stanford, CA, USA under a separate contract with the US National Cancer Institute. Most of the data so obtained on production, use and occurrence refer to the United States and Japan; SRI International and IARC supplement this information with that from other sources in Europe. Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, TN, USA.

Six months before the meeting, reprints of articles containing relevant biological data are sent to an expert(s), or are used by the IARC staff, for the preparation of first draft monographs. These drafts are compiled by IARC staff and are sent prior to the meeting to all participants of the Working Group for their comments. The Working Group then meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, then edited by a professional editor and prepared for reproduction. The monographs are usually published within six months after the Working Group meeting.

5. DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few ad-hoc exceptions have been made; in certain instances, reports from government agencies that have undergone peer review and are widely available are considered. The monographs do not cite all of the literature on a particular chemical: only those data considered by the Working Group to be relevant to the evaluation of the carcinogenic risk of the chemical to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals for which monographs have appeared is urged to make them available to the Unit of Retrieval and Coordination of Carcinogenicity Data, Division of Environmental Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

6. THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for the evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the committee; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to make an evaluation of the carcinogenic risk of the chemical.

Working Group participants who contributed to the consideration and evaluation of chemicals within a particular volume are listed, with their addresses, at the beginning of each publication. Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies, organizations and industrial associations.

7. GENERAL PRINCIPLES FOR EVALUATING THE CARCINOGENIC RISK OF CHEMICALS

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, and/or the induction by chemicals of more neoplasms than are usually found - although fundamentally different mechanisms may be involved in these three situations. Etymologically, the term 'carcinogenesis' means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours. In the monographs, the words 'tumour' and 'neoplasm' are used interchangeably. (In scientific literature the terms 'tumourigen', 'oncogen' and 'blastomogen' have all been used synonymously with 'carcinogen', although occasionally 'tumourigen' has been used specifically to denote a substance that induces benign tumours.)

(*a*) *Experimental Evidence*

(i) *Qualitative aspects*

Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical involve several qualitatively important considerations, including: (a) the experimental parameters under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.; (b) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which target organ(s); (c) the spectrum of neoplastic response, from benign neoplasm to multiple malignant tumours; (d) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others are promoters only; and (e) the possible role of modifying factors.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities are also considered in the interpretation of data.

Many chemicals induce both benign and malignant tumours. Few instances are recorded in which only benign neoplasms are induced by chemicals that have been studied extensively. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end-points' that do not readily undergo transition to malignancy. If a substance is found to induce only benign tumours in experimental animals, it should be suspected of being a carcinogen and requires further investigation.

(ii) *Hormonal carcinogenesis*

Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both endogenously and exogenously; in many instances, long exposure is required; tumours occur in the target tissue in association with a stimulation of non-neoplastic growth, but in some cases hormones promote the proliferation of tumour cells in a target organ. Hormones that occur in excessive amounts, hormone-mimetic agents and agents that cause hyperactivity or imbalance in the endocrine system may require evaluative methods comparable with those used to identify chemical carcinogens; particular emphasis must be laid on quantitative aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

(iii) *Quantitative aspects*

Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age), route(s) of administration and in dose/duration of exposure; often, target organs at which a cancer occurs and its histological type may vary with these parameters. Nevertheless, indices of carcinogenic potency in particular experimental systems [for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless(12)] have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other systems, including humans.

Chemical carcinogens differ widely in the dose required to produce a given level of tumour induction, although many of them share common biological properties, which include metabolism to reactive [electrophilic(13-15)] intermediates capable of interacting with DNA. The reason for this variation in dose-response is not understood, but it may be due either to differences within a common metabolic process or to the operation of qualitatively distinct mechanisms.

(iv) *Statistical analysis of animal studies*

Tumours which would have arisen had an animal lived longer may not be observed because of the death of the animal from unrelated causes, and this possibility must be allowed for. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates(12), with associated significance tests(16,17), have been recommended.

For internal neoplasms which are discovered 'incidentally'(16) at autopsy but which did not cause the death of the host, different estimates(18) and significance tests(16,17) may be necessary for the unbiased study of the numbers of tumour-bearing animals.

All of these methods(12,16-18) can be used to analyse the numbers of animals bearing particular tumour types, but they do not distinguish between animals with one or many such tumours. In experiments which end at a particular fixed time, with the simultaneous sacrifice of many animals, analysis of the total numbers of internal neoplasms per animal found at autopsy at the end of the experiment is straightforward. However, there are no adequate statistical methods for analysing the numbers of particular neoplasms that kill an animal. The design and statistical analysis of long-term carcinogenicity experiments were recently reviewed, in Supplement 2 to the *Monographs* series(19).

(*b*) *Evidence of Carcinogenicity in Humans*

Evidence of carcinogenicity in humans can be derived from three types of study, the first two of which usually provide only suggestive evidence: (i) reports concerning individual cancer patients (case reports), including a history of exposure to the supposed carcinogenic agent; (ii) descriptive epidemiological studies in which the incidence of cancer in human populations is found to vary (spatially or temporally) with exposure to the agent; and (iii) analytical epidemiological studies (e.g., case-control or cohort studies) in which individual exposure to the agent is found to be associated with an increased risk of cancer.

An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, on the basis of the following criteria: (a) There is no identifiable positive bias. (By 'positive bias' is meant the operation of factors in study design or execution which lead erroneously to a more strongly positive association between an agent and disease than in fact exists. Examples of positive bias include, in case-control studies, better documentation of exposure to the agent for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in individuals exposed to the agent than in individuals not exposed.) (b) The possibility of positive confounding has been considered. (By 'positive confounding' is meant a situation in which the relationship between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between that agent and another agent which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking.) (c) The association is unlikely

to be due to chance alone. (d) The association is strong. (e) There is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship; however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias; (b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of exposure or outcome have been weighed. In addition, it must be recognized that in any study there are confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above the upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement. Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

The Working Group whose deliberations resulted in Supplement 4 to the *Monographs*(3) defined the degrees of evidence for carcinogenicity from studies in humans as:

i. *Sufficient evidence* of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

ii. *Limited evidence* of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.

iii. *Inadequate evidence*, which applies to both positive and negative evidence, indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias or confounding; (c) studies were available which do not show evidence of carcinogenicity.

(c) *Relevance of Experimental Data to the Evaluation of Carcinogenic Risk to Humans*

Information compiled from the first 29 volumes of the *IARC Monographs*(3,20,21) shows that of the chemicals or groups of chemicals now generally accepted to cause or probably to cause cancer in humans (Groups 1 and 2A), all (with the possible exception of arsenic) of those which have been tested appropriately produce cancer in at least one animal species. For several of the chemicals (e.g., aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

Assessment of evidence of carcinogenicity from studies in experimental animals

Overall evidence of carcinogenicity in experimental animals was classified into four groups:

i. *Sufficient evidence* of carcinogenicity, which indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

ii. *Limited evidence* of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung adenomas and adenocarcinomas and liver tumours in certain strains of mice).

iii. *Inadequate evidence*, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

iv. *No data* indicates that data were not available to the Working Group.

The categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

For many of the chemicals evaluated in the first 30 volumes of the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. **In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.** The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw/day) of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. Some data, however, suggest that such a relationship may exist(22,23), at least for certain classes of carcinogenic chemicals, but no acceptable methods are currently available for quantifying the possible errors that may be involved in such an extrapolation procedure.

Assessment of data from short-term tests

In recent years, several short-term tests for the detection of potential carcinogens have been developed. When only inadequate experimental animal data are available, positive results in a variety of validated short-term tests (see section 8(*c*)(ii)) can be taken as an indication that the compound is a potential carcinogen and that it should be further tested in animals for an assessment of its carcinogenicity. Negative results from short-term tests cannot be considered as evidence to rule out carcinogenicity(3). Whether short-term tests will eventually be as reliable as long-term tests in predicting carcinogenicity in humans will depend on further demonstrations of consistency with long-term experiments and with data from humans.

In view of the limitations of current knowledge about mechanisms of carcinogenesis, certain cautions should be emphasized: (i) at present, these tests should not be used by themselves to conclude whether or not an agent is carcinogenic; (ii) even when positive results are obtained in one or more of these tests, it is not clear that they can be used reliably to predict the relative potencies of compounds as carcinogens in intact animals; (iii) since the currently available tests do not detect all classes of agents that are active in the carcinogenic process (e.g., hormones, promoters), one must be cautious in utilizing these tests as the sole criterion for setting priorities in carcinogenesis research and in selecting compounds for animal bioassays.

The Working Group which met in February 1982 to re-evaluate chemicals and industrial processes associated with cancer in humans(3) sometimes considered the results from short-term tests in making an overall evaluation of the carcinogenic risk of chemicals to humans. In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests warranted its transfer from Group 3 to 2B or from Group 2B to 2A.

Because of the large number and wide variety of short-term tests that may be relevant for the prediction of potential carcinogens, assessing the overall evidence of activity of a compound in short-term tests is difficult. The data relative to each compound can, however, be classified by grouping results under the type of test used and the biological complexity of the test system. *'DNA damage'* would include evidence for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria, and a positive response in tests of comparative survival in DNA repair-proficient and DNA repair-deficient bacteria. *'Mutagenicity'* refers to induction of mutations in cultured cells or in organisms (e.g., heritable alterations in phenotype, including forward or reverse point mutations, recombination, gene conversion, and specific-locus mutation). *'Chromosomal anomalies'* refers to the induction of chromosomal aberrations, including breaks, gaps, rearrangements and micronuclei, sister chromatid exchange and aneuploidy. (This classification does not imply that some chromosomal anomalies are not mutational events.) *'Other'* refers to various additional endpoints, including cell transformation, i.e., morphological transformation and colony formation in agar; dominant lethal tests; morphological abnormalities in sperm; and mitochondrial mutation. Biological systems include: *'Prokaryotes'*, i.e., bacteria, in the presence or absence of a cellular or subcellular metabolic activation system; *'Fungi and plants'*; *'Insects'*, usually *Drosophila melanogaster*; *'Mammalian cells* (in vitro)', either rodent or human somatic cells or cell lines in culture; *'Mammals* (in vivo)', studies in which the test compound was administered to intact experimental animals; and *'Humans* (in vivo)', studies of cells from groups of individuals drawn from a population exposed to the substance in question.

Overall evidence of activity in short-term tests is adjudged to fall into one of four categories, *sufficient*, *limited*, *insufficient* or *no evidence*. The criteria generally used are:

i. *Sufficient evidence*, when there were at least three positive results in at least two of three test systems measuring DNA damage, mutagenicity or chromosomal anomalies. When two of the positive results were for the same biological endpoint, they had to be derived from systems of different biological complexity.

ii. *Limited evidence*, when there were at least two positive results, either for different endpoints or in systems representing two levels of biological complexity.

iii. *Insufficient evidence*, when there were generally negative or only one positive test results. Up to two positive test results were considered insufficient if they were accompanied by two or more negative test results.

iv. *No evidence*, when the available results from a variety of short-term tests with different biological endpoints and at different levels of biological complexity indicate no activity in the test systems used.

In establishing these categories greater weight may be given to the three primary endpoints - DNA damage, mutagenicity and chromosomal anomalies - and judgements made on the quality as well as on the quantity of the evidence. In a minority of cases, strict interpretation of these criteria may be affected by consideration of a variety of other factors (such as the purity of the test compound, problems of metabolic activation, appropriateness of the test system) such that, in the judgement of the Working Group, a compound may be placed in a lower or higher category.

Assignment of a chemical to one of these categories involves several arbitrary decisions, since many of the test systems are still under validation. Thus, the selection of specific tests remains flexible and should reflect the most advanced state of knowledge in this field.

8. EXPLANATORY NOTES ON THE MONOGRAPH CONTENTS

(a) Chemical and Physical Data (Section 1)

The Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name (9th Collective Index)(24) and the IUPAC Systematic Name(25) are recorded in section 1. Other synonyms and trade names are given, but no comprehensive list is provided. Further, some of the trade names are those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular, data that might be relevant to carcinogenicity (e.g., lipid solubility) and those that concern identification.

A separate description of the composition of technical products includes available information on impurities and formulated products.

(*b*) *Production, Use, Occurrence and Analysis (Section 2)*

The purpose of section 2 is to provide indications of the extent of past and present human exposure to the chemical.

(i) *Synthesis*

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. In addition, methods of synthesis used in past and present commercial production are described. This information allows a reasonable estimate to be made of the date before which no human exposure could have occurred.

(ii) *Production*

Since Europe, Japan and the United States are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those countries. It should not, however, be inferred that those nations are the sole or even the major sources or users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications by chemical economists in the three geographical areas. In some cases, separate production data on organic chemicals manufactured in the United States are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be inferred from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the sales value or the weight of the annual production exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals and plastics; in fact, the minimal annual sales value is between $1 000 and $50 000, and the minimal annual weight of production is between 450 and 22 700 kg. Data on production in some European countries are obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled by country, and the resulting estimates of production are included in the individual monographs.

(iii) *Use*

Information on uses is meant to serve as a guide only and is not complete. It is usually obtained from published data but is often complemented by direct contact with manufacturers of the chemical. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.

Statements concerning regulations and standards (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries are mentioned as examples only. They may not reflect the most recent situation, since such legislation is in a constant state of change; nor should it be taken to imply that other countries do not have similar regulations.

(iv) *Occurrence*

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupational environments, air, water, soil, foods and tissues of animals and humans. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

(v) *Analysis*

The purpose of the section on analysis is to give the reader an indication, rather than a complete review, of methods cited in the literature. No attempt is made to evaluate critically or to recommend any of the methods.

(c) *Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)*

In general, the data recorded in section 3 are summarized as given by the author; however, comments made by the Working Group on certain shortcomings of reporting, of statistical analysis or of experimental design are given in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

(i) *Carcinogenicity studies in animals*

The monographs are not intended to cover all reported studies. Some studies are purposely omitted (a) because they are inadequate, as judged from previously described criteria(19,26-29) (e.g., too short a duration, too few animals, poor survival); (b) because they only confirm findings that have already been fully described; or (c) because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when it is the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the compound has been adequately tested and of all species in which relevant tests have been done(7,28). In most cases, animal strains are given. [General characteristics of mouse strains have been reviewed(30).] Quantitative data are given to indicate the order of magnitude of the effective carcinogenic doses. In general, the doses and schedules are indicated as they appear in the paper; sometimes units have been converted for easier comparison. Experiments in which the compound was administered in conjunction with known carcinogens and experiments on factors that modify the carcinogenic effect are also reported. Experiments on the carcinogenicity of known metabolites and derivatives are also included.

(ii) *Other relevant biological data*

Lethality data are given when available, and other data on toxicity are included when considered relevant. The metabolic data are restricted to studies that show the metabolic fate of the chemical in animals and humans, and comparisons of data from animals and

humans are made when possible. Information is also given on absorption, distribution, excretion and placental transfer.

Effects on reproduction and prenatal toxicity. Data on effects on reproduction, teratogenicity and feto- and embryotoxicity from studies in experimental animals and from observations in humans are also included. There appears to be no causal relationship between teratogenicity(31) and carcinogenicity, but chemicals often have both properties. Evidence of prenatal toxicity suggests transplacental transfer, which is a prerequisite for transplacental carcinogenesis.

Indirect tests (mutagenicity and other short-term tests). Data from indirect tests are also included. Since most of these tests have the advantage of taking less time and being less expensive than mammalian carcinogenicity studies, they are generally known as 'short-term' tests. They comprise assay procedures which rely on the induction of biological and biochemical effects in *in vivo* and/or *in vitro* systems. The end-point of the majority of these tests is the production not of neoplasms in animals but of changes at the molecular, cellular or multicellular level as described in section 7(c).

The induction of cancer is thought to proceed by a series of steps, some of which have been distinguished experimentally(32-36). The first step - 'initiation' - is thought to involve damage to DNA resulting in heritable modifications in, or rearrangements of, genetic information. Proliferation of cells whose properties have been permanently altered during initiation (which may involve somatic mutation) is thought to result in the formation of clones of cells whose further progress to malignancy is dependent on a series of events - 'promotion' and 'progression' - the underlying mechanisms of which are largely unknown. Although this is a useful model, it should be kept in mind that the carcinogenic process may not always proceed by such a multi-step mechanism.

The idea that damage to DNA is a critical event in the initiation of carcinogenesis is based on a large body of data which show that many carcinogens are reactive electrophiles *per se*, or can be readily converted to reactive electrophiles by enzymic pathways characteristic of eukaryotic metabolism(37). A variety of DNA-carcinogen adducts, formed by reaction of electrophilic moieties with nucleophilic centres in DNA, have been identified in DNA recovered from reactions performed with carcinogens *in vitro*, or from cultured cells or intact organisms treated with carcinogens(35,38,39). Moreover, the recognition that many classes of carcinogens (including ionizing and ultra-violet radiation and chemicals of a very wide range of structure and reactivity) are mutagenic(40) supports the idea that DNA is a critical target of carcinogenic agents. Assays for mutagenicity and related effects all exploit this characteristic ability of carcinogens to cause DNA damage or chromosomal anomalies either directly or indirectly. It should be noted, however, that some carcinogens may act by mechanisms that do not involve DNA damage (41) and thus would not cause such genetic effects.

In many of the short-term tests, the indicator organism may not possess or may have lost, following culture, the range of enzyme systems known in intact mammals to metabolize chemically unreactive carcinogens to reactive electrophiles. It is often necessary, therefore, to provide an exogenous source of such activity in the form of a tissue extract or cell feeder-layer or whole-cell systems prepared from mammalian sources(19). In-vitro metabolic systems may not accurately reflect the fate of a chemical subjected to the checks and balances afforded by absorption, distribution, metabolism and excretion in mammals(19), and this must be borne in mind when evaluating the results from short-term tests which employ in-vitro metabolic activation.

Tests have been devised which exploit the useful attributes of microbial or cellular genetic systems without compromising the integrity of mammalian pharmacodynamics and metabolism. Such 'host-mediated' assays involve the inoculation of indicator organisms into mammals (usually rodents) which are then dosed with the test chemical. There are limitations to both the numbers and types of organisms which can be introduced and recovered from dosed animals and to the access of indicator organisms to activated metabolites. Lack of sensitivity may therefore be a problem.

A group of short-term tests use 'transformation' of cultured mammalian cells, rather than manifestation of DNA damage or chromosomal anomalies, as an indicator of carcinogenic potential. Some of the assays also employ an exogenous metabolic activation system. Cell transformation is assessed by scoring characteristic changes in cellular and colonial morphology, or changes in growth characteristics (e.g., growth of colonies in soft agar) following treatment with the test compound. In some protocols, the ability of transformed cells to produce tumours is tested by injecting the cells into appropriate animals.

Studies may also be conducted on cells taken from people exposed to putative chemical carcinogens. The cells are examined for mutation and for chromosomal anomalies either directly or after short-term culture *in vitro* or samples of sperm from such individuals may be analysed for morphological abnormalities. Evidence of absorption of putative carcinogens may be adduced from the assay of body fluids and excreta for DNA-damaging activity, using, for example, bacterial mutation assays.

The present state of knowledge does not permit the selection of a specific test(s) as the most appropriate for identifying all classes of potential carcinogens, although certain systems are more sensitive to some classes. Ideally, a compound should be tested in a battery of short term tests. For optimum usefulness, data on purity must be given. For several recent reviews on the use of short-term tests see IARC(19), Montesano *et al.*(42), de Serres and Ashby(43), Sugimura *et al.*(44), Bartsch *et al.*(45) and Hollstein *et al.*(46).

(iii) *Case reports and epidemiological studies*

Observations in humans are summarized in this section. The criteria for including a study in this section are described above (section 7(*b*)).

(*d*) *Summary of Data Reported and Evaluation (Section 4)*

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

(i) *Experimental data*

Data relevant to the evaluation of the carcinogenicity of the chemical in animals are summarized in this section. The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated. Dose-response data are given when available.

Results from validated mutagenicity and other short-term tests and from tests for prenatal toxicity are reported if the Working Group considered the data to be relevant. The degree of evidence of activity in short-term tests is mentioned in this section.

(ii) *Human data*

Human exposure to the chemical is summarized on the basis of data on production, use and occurrence. Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Other biological data which are considered to be relevant are also mentioned.

(iii) *Evaluation*

This section comprises the overall evaluation by the Working Group of the carcinogenic risk of the chemical, complex mixture or occupational exposure to humans. All of the data in the monograph, and particularly the summarized experimental and human data, are considered in order to make this evaluation. This section should also be read in conjunction with section 7c of this Preamble.

References

1. IARC (1977) IARC Monograph Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Preamble. *IARC intern. tech. Rep. No. 77/002*

2. IARC (1978) Chemicals with *sufficient evidence* of carcinogenicity in experimental animals - *IARC Monographs* volumes 1-17. *IARC intern. tech. Rep. No. 78/003*

3. IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 4, *Chemicals and Industrial Processes Associated with Cancer in Humans*, 292 pages

4. IARC (1979) Criteria to select chemicals for *IARC Monographs. IARC intern. tech. Rep. No. 79/003*

5. WHO (1961) Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of carcinogenic hazard of food additives. *WHO tech. Rep. Ser., No. 220*, pp. 5, 18, 19

6. WHO (1969) Report of a WHO Scientific Group. Principles for the testing and evaluation of drugs for carcinogenicity. *WHO tech. Rep. Ser., No. 426*, pp. 19, 21, 22

7. WHO (1974) Report of a WHO Scientific Group. Assessment of the carcinogenicity and mutagenicity of chemicals. *WHO tech. Rep. Ser., No. 546*

8. WHO (1964) Report of a WHO Expert Committee. Prevention of cancer. *WHO tech. Rep. Ser., No. 276*, pp. 29, 30

9. IARC (1972-1983) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Volumes 1-30, Lyon, France

   Volume 1 (1972) Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds and Natural Products (19 monographs), 184 pages

   Volume 2 (1973) Some Inorganic and Organometallic Compounds (7 monographs), 181 pages

   Volume 3 (1973) Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds (17 monographs), 271 pages

   Volume 4 (1974) Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents (28 monographs), 286 pages

   Volume 5 (1974) Some Organochlorine Pesticides (12 monographs), 241 pages

   Volume 6 (1974) Sex Hormones (15 monographs), 243 pages

   Volume 7 (1974) Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals (23 monographs), 326 pages

   Volume 8 (1975) Some Aromatic Azo Compounds (32 monographs), 357 pages

Volume 9 (1975) Some Aziridines, *N*-, *S*- and *O*-Mustards and Selenium (24 monographs), 268 pages

Volume 10 (1976) Some Naturally Occurring Substances (32 monographs), 353 pages

Volume 11 (1976) Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics (24 monographs), 306 pages

Volume 12 (1976) Some Carbamates, Thiocarbamates and Carbazides (24 monographs), 282 pages

Volume 13 (1977) Some Miscellaneous Pharmaceutical Substances (17 monographs), 255 pages

Volume 14 (1977) Asbestos (1 monograph), 106 pages

Volume 15 (1977) Some Fumigants, the Herbicides, 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals (18 monographs), 354 pages

Volume 16 (1978) Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents, and Miscellaneous Industrial Chemicals (32 monographs), 400 pages

Volume 17 (1978) Some *N*-Nitroso Compounds (17 monographs), 365 pages

Volume 18 (1978) Polychlorinated Biphenyls and Polybrominated Biphenyls (2 monographs), 140 pages

Volume 19 (1979) Some Monomers, Plastics and Synthetic Elastomers, and Acrolein (17 monographs), 513 pages

Volume 20 (1979) Some Halogenated Hydrocarbons (25 monographs), 609 pages

Volume 21 (1979) Sex Hormones (II) (22 monographs), 583 pages

Volume 22 (1980) Some Non-Nutritive Sweetening Agents (2 monographs), 208 pages

Volume 23 (1980) Some Metals and Metallic Compounds (4 monographs), 438 pages

Volume 24 (1980) Some Pharmaceutical Drugs (16 monographs), 337 pages

Volume 25 (1981) Wood, Leather and Some Associated Industries (7 monographs), 412 pages

Volume 26 (1981) Some Antineoplastic and Immunosuppressive Agents (18 monographs), 411 pages

Volume 27 (1981) Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations (18 monographs), 344 pages

Volume 28 (1982) The Rubber Manufacturing Industry (1 monograph), 486 pages

Volume 29 (1982) Some Industrial Chemicals (18 monographs), 416 pages

Volume 30 (1982) Some Miscellaneous Pesticides (18 monographs), 424 pages

Supplement 1 (1979) Chemicals and Industrial Processes Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 20), 71 pages

Supplement 2 (1980) Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal, 426 pages

Supplement 3 (1982) Cross Index of Synonyms and Trade Names in Volumes 1 to 26, 199 pages

Supplement 4 (1982) Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29), 292 pages

10. IARC (1973-1979) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, Numbers 1-8, Lyon, France

Number 1 (1973) 52 pages
Number 2 (1973) 77 pages
Number 3 (1974) 67 pages
Number 4 (1974) 97 pages
Number 5 (1975) 88 pages
Number 6 (1976) 360 pages
Number 7 (1978) 460 pages
Number 8 (1979) 604 pages
Number 9 (1981) 294 pages

11. PHS 149 (1951-1980) Public Health Service Publication No. 149, *Survey of Compounds which have been Tested for Carcinogenic Activity*, Washington DC, US Government Printing Office

1951 Hartwell, J.L., 2nd ed., Literature up to 1947 on 1329 compounds, 583 pages

1957 Shubik, P. & Hartwell, J.L., Supplement 1, Literature for the years 1948-1953 on 981 compounds, 388 pages

1969 Shubik, P. & Hartwell, J.L., edited by Peters, J.A., Supplement 2, Literature for the years 1954-1960 on 1048 compounds, 655 pages

1971 National Cancer Institute, Literature for the years 1968-1969 on 882 compounds, 653 pages

1973 National Cancer Institute, Literature for the years 1961-1967 on 1632 compounds, 2343 pages

1974 National Cancer Institute, Literature for the years 1970-1971 on 750 compounds, 1667 pages

1976 National Cancer Institute, Literature for the years 1972-1973 on 966 compounds, 1638 pages

1980 National Cancer Institute, Literature for the year 1978 on 664 compounds, 1331 pages

12. Pike, M.C. & Roe, F.J.C. (1963) An actuarial method of analysis of an experiment in two-stage carcinogenesis. *Br. J. Cancer, 17*, 605-610

13. Miller, E.C. & Miller, J.A. (1966) Mechanisms of chemical carcinogenesis: nature of proximate carcinogens and interactions with macromolecules. *Pharmacol. Rev., 18*, 805-838

14. Miller, J.A. (1970) Carcinogenesis by chemicals: an overview - G.H.A. Clowes Memorial Lecture. *Cancer Res., 30*, 559-576

15. Miller, J.A. & Miller, E.C. (1976) *The metabolic activation of chemical carcinogens to reactive electrophiles.* In: Yuhas, J.M., Tennant, R.W. & Reagon, J.D., eds, *Biology of Radiation Carcinogenesis*, New York, Raven Press

16. Peto, R. (1974) Guidelines on the analysis of tumour rates and death rates in experimental animals. *Br. J. Cancer, 29*, 101-105

17. Peto, R. (1975) Letter to the editor. *Br. J. Cancer, 31*, 697-699

18. Hoel, D.G. & Walburg, H.E., Jr (1972) Statistical analysis of survival experiments. *J. natl Cancer Inst., 49*, 361-372

19. IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal*, Lyon

20. IARC Working Group (1980) An evaluation of chemicals and industrial processes associated with cancer in humans based on human and animal data: *IARC Monographs* Volumes 1 to 20. *Cancer Res., 40*, 1-12

21. IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 1, *Chemicals and Industrial Processes Associated with Cancer in Humans*, Lyon

22. Rall, D.P. (1977) *Species differences in carcinogenesis testing.* In: Hiatt, H.H., Watson, J.D. & Winsten, J.A., eds, *Origins of Human Cancer*, Book C, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 1383-1390

23. National Academy of Sciences (NAS) (1975) *Contemporary Pest Control Practices and Prospects: the Report of the Executive Committee*, Washington DC

24. Chemical Abstracts Services (1978) *Chemical Abstracts Ninth Collective Index (9CI), 1972-1976*, Vols 76-85, Columbus, OH

25. International Union of Pure & Applied Chemistry (1965) *Nomenclature of Organic Chemistry*, Section C, London, Butterworths

26. WHO (1958) Second Report of the Joint FAO/WHO Expert Committee on Food Additives. Procedures for the testing of intentional food additives to establish their safety and use. *WHO tech. Rep. Ser., No. 144*

27. WHO (1967) Scientific Group. Procedures for investigating intentional and unintentional food additives. *WHO tech. Rep. Ser., No. 348*

28. Berenblum, I., ed. (1969) Carcinogenicity testing. *UICC tech. Rep. Ser., 2*

29. Sontag, J.M., Page, N.P. & Saffiotti, U. (1976) Guidelines for carcinogen bioassay in small rodents. *Natl Cancer Inst. Carcinog. tech. Rep. Ser., No. 1*

30. Committee on Standardized Genetic Nomenclature for Mice (1972) Standardized nomenclature for inbred strains of mice. Fifth listing. *Cancer Res., 32*, 1609-1646

31. Wilson, J.G. & Fraser, F.C. (1977) *Handbook of Teratology*, New York, Plenum Press

32. Berenblum, I. (1975) *Sequential aspects of chemical carcinogenesis: Skin.* In: Becker, F.F., ed., *Cancer. A Comprehensive Treatise*, Vol. 1, New York, Plenum Press, pp. 323-344

33. Foulds, L. (1969) *Neoplastic Development*, Vol. 2, London, Academic Press

34. Farber, E. & Cameron, R. (1980) The sequential analysis of cancer development. *Adv. Cancer Res., 31*, 125-226

35. Weinstein, I.B. (1981) The scientific basis for carcinogen detection and primary cancer prevention. *Cancer, 47*, 1133-1141

36. Slaga, T.J., Sivak, A. & Boutwell, R.K., eds (1978) *Mechanisms of Tumor Promotion and Cocarcinogenesis*, Vol. 2, New York, Raven Press

37. Miller, E.C. & Miller, J.A. (1981) Mechanisms of chemical carcinogenesis. *Cancer, 47*, 1055-1064

38. Brookes, P. & Lawley, P.D. (1964) Evidence for the binding of polynuclear aromatic hydrocarbons to the nucleic acids of mouse skin: relation between carcinogenic power of hydrocarbons and their binding to deoxyribonucleic acid. *Nature, 202*, 781-784

39. Lawley, P.D. (1976) *Carcinogenesis by alkylating agents.* In: Searle, C.E., ed., *Chemical Carcinogens (ACS Monograph 173)*, Washington DC, American Chemical Society, pp. 83-244

40. McCann, J. & Ames, B.N. (1976) Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals: Discussion. *Proc. natl Acad. Sci. USA, 73*, 950-954

41. Weisburger, J.H. & Williams, G.M. (1980) *Chemical carcinogens*. In: Doull, J., Klaassen, C.D. & Amdur, M.O., eds, *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 2nd ed., New York, MacMillan, pp. 84-138

42. Montesano, R., Bartsch, H. & Tomatis, L., eds (1980) *Molecular and Cellular Aspects of Carcinogen Screening Tests (IARC Scientific Publications No. 27)*, Lyon

43. de Serres, F.J. & Ashby, J., eds (1981) *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program*, Amsterdam, Elsevier/North-Holland Biomedical Press

44. Sugimura, T., Sato, S., Nagao, M., Yahagi, T., Matsushima, T., Seino, Y., Takeuchi, M. & Kawachi, T. (1976) *Overlapping of carcinogens and mutagens*. In: Magee, P.N., Takayama, S., Sugimura, T. & Matsushima, T., eds, *Fundamentals in Cancer Prevention*, Tokyo/Baltimore, University of Tokyo/University Park Press, pp. 191-215

45. Bartsch, H., Tomatis, L. & Malaveille, C. (1982) *Qualitative and quantitative comparison between mutagenic and carcinogenic activities of chemicals*. In: Heddle, J.A., ed., *Mutagenicity: New Horizons in Genetic Toxicology*, New York, Academic Press, pp. 35-72

46. Hollstein, M., McCann, J., Angelosanto, F.A. & Nichols, W.W. (1979) Short-term tests for carcinogens and mutagens. *Mutat. Res.*, *65*, 133-226

GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

In this thirtieth volume of the *IARC Monographs* are considered a number of miscellaneous pesticides, including some insecticides, herbicides, fungicides and the rodenticide 1-naphthylthiourea. Data on the pyrethrin synergist, piperonyl butoxide, were also evaluated. Two compounds, chlorobenzilate and diallate, had been evaluated by previous Working Groups (IARC, 1974, 1976); new data that had become available on those compounds were included in the present monographs and taken into consideration in the evaluations.

A monograph on rotenone, an extract of cube root which is used as a selective non-systemic botanical insecticide and fish poison, was considered for inclusion in this volume; however, since available data on its carcinogenicity in mice and rats suffered from serious limitations, and in view of the fact that three bioassays are presently being performed on this compound (IARC, 1981), it was decided to postpone consideration of rotenone until the new data became available.

Several pesticides containing secondary or tertiary amino groups can be nitrosated by a variety of nitrosating agents to form an *N*-nitroso compound; a possibility also exists that *N*-nitroso compounds could be formed *in vivo* from pesticide residues. Under some circumstances, *N*-nitroso derivatives can be formed during the manufacture or storage of the pesticide, such that the commercial product may contain an *N*-nitroso compound. An Appendix to this volume was thus prepared, which includes a consideration of the formation of *N*-nitroso derivatives and a table of published studies on the testing of the pesticide alone, of the pesticide in combination with a nitrite, and of the *N*-nitroso derivative itself, in long-term carcinogenicity tests in experimental animals and in mutagenicity and related short-term tests.

Consideration of three draft monographs, on chloramben, simazine and trifluralin, originally included in a tentative list of substances to be considered, was postponed due to lack of time. However, since two of those compounds, simazine and trifluralin, can be *N*-nitrosated, relevant data from the draft were included in the Appendix.

The Working Group noted that some pesticides considered here contain, or may contain, impurities of known carcinogenicity or mutagenicity. The studies considered often involved testing of particular commercial formulations, and they may not have provided the same results as tests of other commercial formulations, since variations in the pattern of impurities can be expected.

Pesticides are used extensively in many developed and developing countries. Therefore, exposure occurs in a variety of occupations, during their manufacture, formulation and use; the general population is also exposed, through ingestion of residues or through home use of pesticides. The Working Group noted that no comprehensive information exists on the exposure of the world population to pesticides, in the occupational or the general environment. What little data on exposure exist come primarily from the United States and Sweden and are largely limited to nonagricultural industries. Regulations and/or guidelines on occupational exposure limits for several of

the chemicals evaluated in these monographs have been established in a number of industrial countries. The Working Group noted a lack of information on whether equivalent regulations have been enacted in developing countries, where use of many of the pesticides considered may be even more widespread and exposure more intensive than in industrialized countries.

The scientific evaluation of pesticides for carcinogenicity and other relevant biological data for the purposes of the *IARC Monographs* includes only published data, and this rule has been strictly observed in the programme since its inception. Unpublished data are submitted to WHO for use by the WHO/FAO Expert Groups on Pesticide Residues for setting Acceptable Daily Intakes (ADIs) and maximum residue limits and for evaluating health risks with regard to involuntary exposure to residues in food. Summaries of these evaluations are available as WHO/FAO publications.

Many of the carcinogenicity studies reviewed in this volume were performed as part of the bioassay programme of the US Public Health Service, National Cancer Institute. In most of these studies, dosing was not consistent throughout the exposure period: although the intention was to use maximal tolerated doses, the inherent cumulative toxicity of many of the pesticides tested often resulted in chronic toxic effects in the exposed animals, and doses had to be reduced during the course of the experiment. Furthermore, exposure lasted anywhere from 59-80 weeks, followed by an observation period of 10-34 weeks; the bioassays did not, therefore, usually represent two-year feeding studies. Many of these studies were conducted simultaneously; control animals were pooled for several tests, and limited numbers of them were assigned to each experiment.

Apart from possible carcinogenic risks, some compounds, particularly the organophosphates, present severe toxic hazards to pesticide handlers. Signs and symptoms of acute systemic poisoning that are similar in all organophosphate poisonings are related to inhibition of acetylcholinesterase. The consequent accumulation of endogenous acetylcholine causes the characteristic peripheral (nicotinic and muscarinic) and central nervous system symptoms of such poisoning. The onset of the symptoms after exposure to organophosphorus compounds is usually rapid; the duration of intoxication is generally from one to two days when the case is not severe, but may be much longer in cases that require treatment. A few organophosphorus insecticides can, at high doses, also cause another type of toxicity, not related to acetylcholinesterase inhibition, called 'delayed neurotoxicity'. This consists in a degeneration of long axons, mainly in the peripheral nervous system, which is clinically evident only 10-14 days after a single exposure; the time of onset of symptoms after repeated exposures might be unpredictable.

Organophosphates are usually absorbed rapidly by inhalation, ingestion and through the skin but do not accumulate in the body. Some organophosphates require metabolic activation in order to act as esterase inhibitors, while others do not. Detoxifying metabolism is usually very rapid and, for some of these pesticides, highly efficient only in mammals: this represents the pharmacological basis for their selective toxicity to pests. The presence of other organophosphates and/or impurities in the spray mixtures, however, might interfere with these detoxifying mechanisms. The metabolites of some organophosphates excreted by humans have been shown to be the same as those excreted by laboratory animals; measurement of such metabolites can be used to monitor pesticide absorption.

A major problem that arose in evaluating the data on mutagenicity was that much of it exists in a form in which little or no experimental detail or information on the criteria used to determine positivity or negativity were available for examination. At their extreme, such data consist only of plusses and minuses in a summary table; this is exemplified in the extensive Japanese cooperative programme summarized in a previous IARC publication (Kawachi *et al.*, 1980). When such results are consistent with other published data or when full details of conditions, protocols and decisional criteria are given, no great problem arose in making an overall evaluation. When, however, the result was the only one obtained using a particular test system or when it was in disagreement with the result of similar tests, there was no way in which a comparative evaluation could be made. The Working Group was unwilling to use different standards for evaluating mutagenicity data from those used in evaluating carcinogenicity for *IARC Monographs*, even if this should mean disregarding a substantial proportion of the data base. The policy adopted, therefore, was to cite such reports in section 3.2 of the monographs, but to identify them as 'abstract', or 'details not given'. Such results were not considered in summarizing the data on mutagenicity in section 4.2.

Because of the paucity of epidemiological studies on individual compounds considered in this volume, studies on mixed exposures to pesticides were also considered. These are grouped in the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users', which follows. Some of these studies were also covered in volumes 5, 15, 20 and 23 of the *Monographs*. It was noted that for some of the pesticides considered insufficient time has elapsed to enable epidemiological studies to detect excesses of cancer in humans.

References

IARC (1974) *IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, Lyon, pp. 75-81

IARC (1976) *IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, Lyon, pp. 69-75

IARC (1981) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, No. 9, Lyon, pp. 133, 154, 156

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugimura, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan*. In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

CANCER EPIDEMIOLOGY OF PESTICIDE MANUFACTURERS, FORMULATORS AND USERS

Since pesticides are ubiquitous and a number of them have been shown to be oncogenic in animal studies and active in short-term tests, the risk of cancer from exposure to some pesticides is of concern. In most parts of the world almost everyone is exposed to pesticides; however, for the purpose of this review, only the cancer risk factors of those populations who are occupationally exposed to pesticides is discussed, as these offer the best opportunity to detect an increase in cancer risk. Since exposures are virtually always multiple, only the cancer risks of mixed exposures are reviewed here. Epidemiological studies of exposure to arsenical pesticides were described and evaluated in a previous monograph (IARC, 1980) and are therefore not included here. Monographs on other pesticides, such as DDT, phenoxyacetic acid herbicides, chlordane/heptachlor, were included in Volumes 5, 7, 12, 15 and 20 of the *Monographs* series.

Even in the occupational setting, the epidemiological study of pesticides in relation to cancer is complicated by shortcomings in data on human exposure, the multiplicity of pesticide exposures, changes in pesticide use patterns, a rapid turnover of employees and the long latency of cancer. While some of these problems are inherent in all epidemiological studies of occupational exposures, they are particularly relevant with regard to agricultural workers. Epidemiological studies of long-term effects of occupational exposure on cancer risks have been conducted in people occupationally exposed through the manufacture and packaging of insecticides and through their application, as structural pest control operators and termite control operators. These populations present the advantages for research of comprising a sizeable number of exposed individuals who, in comparison with the agricultural workers, are less subject to rapid turnover. In addition, the manufacturing scene may be less likely to involve exposure to mixtures of pesticides, as is the case in agriculture, although the degree of human exposure during the manufacturing o pesticides is less than that which occurs during formulation, mixing and application of pesticides in the fiels.

In spite of these difficulties, however, in the last decade a sizeable body of epidemiological data from case reports, cross-sectional studies, case-control and cohort studies has appeared in the medical literature, which is beginning to contribute to a better recognition of whether these chemicals represent a carcinogenic risk to man. Significant contributions from these types of studies have been made with regard to exposures to herbicides and fungicides, and especially phenoxy acid herbicides.

INSECTICIDES

Case reports

In a review of 13 cases of colorectal carcinoma in adolescents admitted to St Jude Children's Research Hospital in Memphis, Tennessee, USA between October 1974 and December 1976, Pratt *et al.* (1977) described nine cases who lived in a rural area of the

Mississippi delta, an area of high pesticide usage, and four living in an urban community. Exposure to farm sprays and agricultural chemicals was reported for eight of the nine rural patients; and one of the four urban cases had been exposed during spraying of insecticides. Three of the patients had themselves sprayed insecticides, with length of exposure ranging from two to more than five years. [The occurrence of an apparent rural cluster was not examined for other types of malignancy admitted to that hospital.] Caldwell *et al.* (1981) measured pesticide residues in the serum of 10 of these 13 patients, and in controls, who comprised 24 adolescents from the same geographical area roughly matched for race and sex. The arithmetic mean total DDT [see IARC, 1974a] in sera from eight patients from rural areas and one from an urban area was 65.6 ppb [μg/l] (or 22.9, when two outlying values were excluded), compared with 28.3 ppb in the 24 controls. The mean serum levels of dieldrin [see IARC, 1974b] and hexachlorocyclohexane [see IARC, 1979a] were 2.8 and 3.8 ppb, respectively, in cases and 1.0 and 3.0 ppb in controls. [The way in which the controls were selected and used was not clear.]

Although aplastic anaemia is not a malignant disorder, it is frequently associated with leukaemia, particularly of the non-lymphatic type, and most clinicians regard aplastic anaemia as possibly premonitory for leukaemia. Jenkyn *et al.* (1979) described a 14-year-old girl who developed aplastic anaemia and pseudotumour cerebri after working in a tobacco field where mixtures of zineb [see IARC, 1976a], ziram [see IARC, 1976b], malathion [see this volume], carbaryl [see IARC, 1976c], naphthyl and methyl carbamates [see IARC, 1976d] had been applied. [The length of exposure was not given.] Reeves *et al.* (1981) described six children who developed aplastic anaemia and one child with acute lymphoblastic leukaemia shortly after domestic application of pesticides. One of the patients with aplastic anaemia developed an acute lymphoblastic leukaemia which converted to a leukaemia [unspecified] of the central nervous system. Parents of six of the seven patients reported domestic exposure to a combination of dichlorvos [see IARC, 1979b] and propoxur [see this volume, Appendix], and the seventh was reported to have been exposed to malathion [see this volume].

Geographical and time-trend studies

Clark *et al.* (1978), in an abstract, reviewed the geographical associations of age-adjusted, sex- and race-specific mortality rates in people aged 30-69 years who had died from cancers of the lung, colon, liver, haematopoietic system and from all neoplasms in the southeastern US with pesticide use on the basis of county and agricultural area. Correlation with an exposure index based on estimates of environmental pesticide exposure demonstrated a significant association for white men and women of total cancers and of lung cancers and a geographic excess in the coastal plains of the southeastern US. [Smoking was not adjusted for. Since that report, Blot *et al.* (1978), in a case-control study of lung cancer in the coastal regions of Georgia, revealed a significantly increased risk of lung cancer in those employed in shipyards during the Second World War, where exposures to asbestos cannot be ruled out.]

Geographical patterns of leukaemia in the US were reviewed by Blair *et al.* (1980). Age-adjusted mortality rates for leukaemia during 1950-1969 were correlated by race and sex with demographic, industrial and agricultural data from 3056 US counties. Despite relatively uniform mortality across the country, high rates were noted among whites in northern and south central states and among nonwhites in the northeast and midwest. After adjusting for demographic, ethnic, industrial and regional factors, leukaemia

mortality was positively correlated with cotton and wheat production. [The Working Group noted that this did not necessarily indicate an association with pesticide use.]

Saracci and Repetto (1980) reviewed data on primary liver cancer from 30 selected cancer registries covering 37 populations in 18 countries over two periods (two- to five-years long) between 1956 and 1972. Over these intervals, all-ages incidence rates, standardized to world population, showed a statistically significant increase in 17 (45.9%) of the male populations and in 10 (27%) of the female populations. All-ages-standardized rates ranged from 0-64.6 per 100 000 for men and 0.1-34.2 per 100 000 for women. Increases were most clearly recognized in Kracow, Poland; Alberta, Canada; Bombay, India; and in the Jewish population of Israel. [The Working Group noted that liver cancer, the principal type to have been reported in laboratory animals exposed to pesticides under experimental conditions, is not necessarily the type induced in humans. This study, which was not designed specifically to evaluate the risk of pesticide use, did not take into consideration the short latency since introduction of some pesticides.]

Doll and Peto (1981) noted that there has been no general increase in mortality from liver tumours in the US since the long-lasting pesticides were introduced. They report that in the population under age 65, there was a nonsignificant increase in mortality from liver cancer among women and a nonsignificant decrease in men. Since liver cancer remains virtually incurable, such mortality data are a good indication of incidence rates.

Case-control studies

(*a*) *Tissue residue studies*

Residues of organochlorine pesticides stored in adipose depots or tumour tissue from cancer patients have been compared in several studies with mean pesticide concentrations in control subjects. [The Working Group noted that there is not necessarily a causal association between the presence of a chemical in the tissues of a cancer patient and tumour production.] In six cross-sectional studies of organochlorine pesticide residues (Maier-Bode, 1960; Hoffman *et al.*, 1967; Casarett *et al.*, 1968; Radomski *et al.*, 1968; Kasai *et al.*, 1972; Unger & Olson, 1980), no consistent pattern was noted; however, interpretation was difficult because of inadequacies of analysis or reporting. One group (Unger & Olson, 1980) explored the confounding effect of age on the analysis, but only Hoffman *et al.* (1967) explored the data by race; monitoring surveys emphasize that DDT residue levels are higher in blacks than in whites (Davies *et al.*, 1968; Kutz *et al.*, 1977).

Dacre and Jennings (1970) found that lung tissues from lung cancer deaths in New Zealand contained substantially higher concentrations of DDT and dieldrin than those from deceased persons without lung cancers. [Demographic confounding variables and confounding due to cachexia were not considered.] Wassermann *et al.* (1978) reported that lipid-extractable concentrations of total DDT were higher in gastric carcinoma than in adjacent normal gastric mucosa. [No data on age or weight loss were reported.]

Davies *et al.* (1975) compared total DDT and dieldrin residues in adipose tissue from 122 cancer cases coming to surgery or autopsy and in 122 controls matched for age, race, sex and social class. The cases comprised 24 primary lung cancers, 14 gastrointestinal cancers, 29 breast cancers and 15 generalized metastatic carcinomatosis. The mean total DDT was 8.0 mg/kg in cases and 7.8 mg/kg in controls, a difference which was not

significant at the p = 0.05 level. The mean dieldrin residue in both cancer cases and controls was 0.3 mg/kg.

Pimentel and Menezes (1979) described in an abstract a granulomatous disorder involving the lung and lymph nodes in 26 Portugese rural and industrial workers. The patients were 28-67 years old and had been exposed by inhalation to DDT powder for periods ranging from four to 18 years. DDT and its metabolites were identified in the lesions. Alveolar-cell carcinomas were found in five cases. [This condition was compared by the authors with previous observations on 'vineyard sprayer's lung' and other diseases of inhalatory origin.]

(*b*) *Interview studies*

Case-control studies have been made of insecticide exposure, both occupational and incidental, in relation to the occurrence of bladder cancers, brain tumours in children, leukaemia, aplastic anaemia and angiosarcoma of the liver.

Gold *et al.* (1979) conducted a case-control study of 127 children under 20 years of age diagnosed between 1965 and 1975 with primary malignant tumours of the brain in the Baltimore, Maryland, USA area in 15 participating hospitals. Data were obtained from hospital records and interviews with the parents of patients. Controls consisted of (1) normal controls, who were children with no known malignancy, matched for sex, date of birth ($\pm$ one year) and race; and (2) cancer controls, consisting of children with malignancies other than brain tumours, matched for sex, race, age and date of diagnosis. Information was sought on the chemical exposure of the mother during pregnancy and of the father at work, and both parents were asked whether the child had sustained any exposure to insecticides through extermination in the home prior to the onset of illness. Interviews yielded 73 matched pairs with normal controls and 78 matched pairs with cancer controls. No significant difference was noted for mother's prenatal or father's occupational exposure to chemicals, but the parents of more children with brain tumours reported exposure through extermination, with an odds ratio of 2.3 (p = 0.10) when compared with normal controls, and of 1.2 when compared with cancer controls.

Musicco *et al.* (1982) conducted a case-control study in 47 adult glioma cases matched by age, sex and area of residence to meningioma cases and to neurological subjects without tumours. A relative risk of 6 was found for agricultural workers active only after 1960, a relative risk of 3 for those active before and after 1960, and a relative risk of 1 for those active only before 1960. (1960 had been selected as the best discriminating year between usage of arsenical pesticides [see IARC, 1980], prior to that year, and usage of organophosphorus-organochlorine pesticides, after that year.)

Blair and Thomas (1979) investigated the occupational exposure of cases of leukaemia among farmers in Nebraska, USA through a study of death certificates for the period 1957-1974. Occupation as shown on death certificates was compared for 1084 leukaemia deaths and 2168 deaths from other causes, matched for age at death, year of death, county of residence, race and sex. An elevated risk of leukaemia was found among farmers (odds ratio = 1.25). The risk was greatest among farmers born after 1900 and dying before age 66 (odds ratio = 1.83). Stratification by county of residence showed a significantly elevated risk for farmers in counties where corn was produced in large quantities; but risks of leukaemia were similar for farmers from counties with differing levels of insecticide use.

Cantor (1982) analysed mortality from non-Hodgkin's lymphoma over the period 1968-1976 in the state of Wisconsin in a case-control study, to test the hypothesis that farming carries a higher risk. The study group comprised 774 male cases and 1651 male controls matched by year of death, five-year age group and county of residence. The occupation of farmer was more frequent in cases than in controls (odds ratio, 1.22; 95% confidence interval, 0.98-1.51). The risk for reticulum-cell sarcoma was higher in younger decedents (2.7; 1.54-4.5). Factorial analysis showed an elevated risk for reticulum-cell sarcoma in younger decedents in counties with a high number of acres planted with small grains and a high number of acres treated with insecticides (6.6; 2.8-15.6) and in counties with a high wheat acreage (4.4; 1.83-10.6).

A study was carried out on the basis of the death certificates of 1675 white men in Iowa, USA, aged 30 or more, who had died of leukaemia in 1964-1978. Each case was matched to two controls by age at death, county of residence and year of death. Analysis of the data for usual occupation as recorded on the death certificate gave an odds ratio for farmers of dying from chronic or unspecified lymphatic leukaemia of 1.24 ($p < 0.05$). The highest rates were for those born after 1890, those who died after 1970 and those who died at 65 or younger; high risks were also observed for farmers born between 1890 and 1900 living in counties with extensive production of soya beans and corn. For farmers born after 1900, risks were increased for those in counties with the greatest numbers of egg-laying chickens and the largest number of acres treated with herbicides. Mortality from unspecified lymphatic leukaemia was associated with amount of corn produced by acre, number of milk cows and number of egg-laying chickens (Burmeister *et al.*, 1982).

Milham (1982) analysed the occupations of about 400 000 male deaths occurring during 1950-1979 in Washington state, USA, using a proportional mortality approach. Excesses were found for the following subgroups who possibly had exposure to pesticides: orchardists (lung cancer PMR = 130); nurserymen (pancreatic cancer PMR = 222); cattle ranchers (renal cancer PMR = 187); dairy farmers (stomach cancer PMR = 137); wheat farmers (leukaemia PMR = 144); and poultry farmers (leukaemia PMR = 241).

[While the latter three studies do not specifically associate increased leukaemia incidence with exposure to pesticides, they do not rule out such an association.]

Blair and Watts (1980) reported in a letter to the editor that they had conducted a death certificate search between 1968 and 1976 of 1386 deaths from bladder cancer among white males in Wisconsin, USA. Controls were matched by age, sex, race, year of death and county of residence, and had died from causes other than bladder cancer. A positive history of farming was observed in 271 cases and in 277 controls, giving an odds ratio of 0.97.

Wang and Grufferman (1981) conducted a case-control study of 60 males aged 15 to 65 from North Carolina, who died from aplastic anaemia between 1968 and 1977. Two male controls, matched for year of death, age at death and race, were selected by taking the subsequent names on the list of deaths who had died from causes other than aplastic anaemia. Occupational exposure to pesticides was primarily to organochlorines; the relevant occupations included farming, landscaping, gardening and pest exterminating. The relative risk for employment in an occupation involving the use of organochlorine insecticides was 0.67, with 95% confidence limits of 0.26-1.7. The authors concluded that the study does not suggest a dose-dependent causal relationship between occupational exposure to pesticides and aplastic anaemia but cannot exclude the possibility that pesticides may induce idiosyncratic bone-marrow reactions in rare cases.

[The Working Group noted that the occupation of farmer does not necessarily imply exposure to pesticides.]

Cohort studies

Barthel (1976) found 30 cases of cancer on follow-up of 316 men exposed to a variety of herbicides (2,4-D [see IARC, 1977a] and MCPA [see this volume]), insecticides (DDT [see IARC, 1974a], hexachlorocyclohexane [see IARC, 1979a], toxaphene [see IARC, 1979c], parathion [see this volume], DNOC [4,6-dinitro-*ortho*-cresol]), fungicides (copper-containing and other) and, to some extent, arsenic [see IARC, 1980], in the German Democratic Republic. There were 11 lung cancers, four prostatic cancers, three stomach cancers, three skin cancers, two bladder cancers, two rectal cancers, one each in the kidney, oesophagus, gall bladder and epiglottis and one lymphoma. The expected number of lung cancers was estimated to be 0.55. [The expected number would be higher if it were calculated correctly, by multiplication of the population annual incidence rate by the man-years at risk in each age group rather than by the number of men in each age group. It was not possible to distinguish in this study between the possible effects of the many chemicals to which the men were exposed.]

Wang and MacMahon (1979a) conducted a retrospective mortality cohort study of 16 126 men employed for three months or longer between 1967-1976 in three nationwide pest control companies in the US in job categories involving potential exposure to insecticides commonly used by pest control operators. The insecticide exposure of the entire cohort was to fumigants, organophosphates, carbamates, organochlorine insecticides and botanical insecticides. The data on termite control operators were analysed separately, since this group was exposed primarily to heptachlor and chlordane [see IARC, 1979d]. Mortality data, obtained from the Social Security Administration, showed 311 deaths, for which 269 death certificates were available. In order to estimate the causes of death for those for whom no death certificate was available, they were distributed in the same way as those of the 269 deaths that had been verified by death certification. The expected number of deaths was 370.9, giving an overall Standard Mortality Ratio (SMR) of 84 (95% confidence interval, 75-94); and 54.3 cancers were observed and 65.2 expected (64-109). SMRs exceeded 100 for three types of cancer: lung cancer (115; 77-170); skin cancers (173; 63-473); and bladder cancer (277; 101-761). The excess was not significant for lung or skin cancer and was of borderline significance for bladder cancer. None of the differences in SMRs between termite control operators and others was significant, and the slight excess of lung cancer was restricted to non-termite control operators. [Relatively few of the study subjects were followed for 10 years or more, and none of those with lung cancer fell into this category. Only 15% of the person-years were attributed to workers who had more than five years of employment and who were observed for more than 10 years after first employment. Because of the short observation period, little significance can be attached to the negative findings.]

Wang and MacMahon (1979b) also conducted a retrospective cohort mortality study of 1403 white male workers employed for three months or more in the manufacture of chlordane and heptachlor [see IARC, 1979d]. The study design was very similar to that of the preceding study. There were 113 deaths observed in this group, compared with 157 expected, giving an SMR of 72; 24 were due to cancer, where 29.3 were expected, for an SMR of 82. Here, too, there was a nonsignificant excess of deaths from lung cancer (12 observed *versus* 9.0 expected), giving an SMR of 134 (95% confidence interval, 73-228); one death was attributed to cancer of the liver, whereas 0.59 was expected. No pattern

suggesting a relationship of occupational exposure with lung cancer was noted; however, the study population was small and the duration of follow-up short. [No data on cigarette smoking were available.]

Ditraglia *et al.* (1981) conducted similar mortality cohort studies in four organochlorine pesticide manufacturing plants in different areas of the US. Approximately 2100 individuals who had been employed for at least six months prior to January 1964 were followed up to 31 December 1976. The first of the plants was involved in the manufacture of chlordane [see IARC, 1979d] and the second in that of heptachlor [see IARC, 1979d]; these were the same plants studied by Wang and MacMahon, although the time and minimal duration of employment differed. Endrin [see IARC, 1974c] had also been produced for a time in the second plant. The third plant produced a variety of different pesticides, but had also produced endrin, aldrin [see IARC, 1974d] and dieldrin [see IARC, 1974b] for 20 years or more. The fourth plant produced DDT [see IARC, 1974a]. The method of analysis for mortality was similar to that used by Wang and MacMahon. The SMRs and 95% confidence intervals for all causes of death were 68 (52-87), 66 (42-98), 84 (72-98) and 86 (62-116), for the four plants, respectively. The SMRs and 95% confidence intervals for all malignant neoplasms were 69 (35-125), 91 (33-198), 82 (58-116) and 68 (25-147), respectively, for the four plants. In the first plant, three deaths were due to stomach cancer, with only 0.99 expected. In the third plant there were slight excesses of cancer of the oesophagus (2 observed, 0.85 expected) and of cancer of the lymphatic and haematopoietic system (6 observed, 4.09 expected). In the first two plants, which were the same ones in which Wang and MacMahon noted a small increase in respiratory cancer, the combined observed deaths for respiratory cancer were 9, whereas 7.87 were expected. [The statistical power of this study to detect an excess in cancer risk was limited because of the small size of the cohorts.]

HERBICIDES AND FUNGICIDES

Because global use of herbicides continues to increase and because especially the phenoxy acid herbicides [see IARC, 1977] and chlorophenols [see IARC, 1979e,f] are contaminated with traces of polychlorodibenzodioxins and polychlorodibenzofurans, the cancer potential of this group of pesticides is of special concern. Cases of soft-tissue sarcoma and malignant lymphoma in relation to such exposures have been reported; and case-control and cohort studies have suggested that these rare forms of sarcoma may be related to occupational and accidental exposures to the phenoxy herbicides, to chlorophenol compounds, to contamination with 2,3,7,8-tetrachlorodibenzodioxin (TCDD) [see IARC, 1977b] and to the original compounds (such as trichlorophenol [see IARC, 1979f]) which are used to manufacture these groups of pesticides.

Case reports

The first indication that occupational exposure to phenoxy acid herbicides might be associated with an increased risk of soft-tissue sarcoma arose following Hardell's (1977) report that five of seven patients with soft-tissue sarcomas were forestry workers with reported occupational exposure to phenoxy acids; the remaining two had been exposed

indirectly to these compounds because their work involved clearing phenoxy acid-treated areas. In 1979, Hardell described a histologically confirmed malignant lymphoma in a patient who had reported a 'massive' exposure to phenoxyacetic acids. In a subsequent pilot study, Hardell interviewed a case series of 17 malignant lymphoma patients. Of these, 11 reported past occupational exposure to phenoxyacetic acids or chlorophenols.

Moses and Selikoff (1981) reported a death from a soft-tissue sarcoma (a malignant schwannoma) in a maintenance worker from a plant that produced trichlorophenol [see IARC, 1979f] and 2,4,5-T [see IARC, 1977c].

Two additional cases from another plant, in a father and son, have been reported by Johnson *et al.* (1981) and identified by them as soft-tissue sarcomas. The father, who had a liposarcoma of the thigh, had sustained prolonged occupational exposure in the plant which manufactured large amounts of chlorophenols. In the case of the son, who died with a metastasizing fibrosarcomatous mesothelioma, the latent period between his first exposure and the onset of disease was short. [No information on possible exposure to asbestos was given.]

Olsson and Brandt (1981) described a series of 123 cases of non-Hodgkin's lymphoma; four of five presenting solely with cutaneous manifestations reported occupational exposure to phenoxy acid herbicides. Bishop and Jones (1981) also described two cases of non-Hodgkin's lymphoma in the skin among 158 employees in a plant which manufactured pentachlorophenol [see IARC, 1979e] and its sodium salt, which were contaminated particularly by hexachloro- and octachlorodibenzodioxins [see IARC, 1977b]. One patient who developed a tumour in the scalp had worked in the plant from 1959-1972; he also had mild chloracne on the face and trunk. The second patient, also employed in the plant from 1957 to 1978, had severe chloracne on the face, neck, trunk and genital area and developed a tumour in the right occipital region of the scalp. [The authors gave no detail concerning the work force of 158 and did not describe how they calculated an expected number of 0.28.]

Greene *et al.* (1978) described a familial cluster of Hodgkin's disease including two brothers who had been employed by a small fencing installation company for 15 and 20 years, respectively, principally in applying pentachlorophenol to cedar wood. The other two cases in this family had no history of exposure to pentachlorophenol. A third, unrelated 31-year-old man working for the same company also developed Hodgkin's disease.

Case-control studies[1]

In the same paper, Greene *et al.* (1978) reported a case-control study on Hodgkin's disease and occupational exposure to pentachlorophenol. Between 1956 and 1974, 167 deaths from Hodgkin's disease that occurred in North Carolina, USA, among white men

---

[1] The Working Group noted that studies were in progress on malignant soft-tissue neoplasms in relation to phenoxyacetic acids; cancer risk in relation to pentachlorophenol; malignant lymphomas in relation to phenoxyacetic acids and chlorophenols; the role of exposure to chlorophenols and phenoxyacetic acids in the origin of soft-tissue sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma; and soft-tissue sarcoma in relation to chlorophenols and phenoxyacetic acids (Muir & Wagner, 1981).

were matched individually with the death certificates of two controls who had died of other causes and were of the same sex, race, county of death, age and year of death. The only excess risk was found for wood and paper workers (relative risk, 1.4; 95% confidence interval, 0.8-2.3). Within that category, the highest risk (4.2; 1.4-12.5) was found for carpenters and lumbermen.

Hardell's (1977, 1981) case reports suggesting an unexpectedly high frequency of soft-tissue sarcomas among people occupationally exposed to phenoxyacetic acid herbicides prompted a case-control study of soft-tissue sarcoma in forestry workers exposed to phenoxyacetic acids and chlorophenols. Results of this study of 52 cases (21 living and 31 dead) in a northern area of Sweden, who were diagnosed during the period 1970-1977 as having malignant mesenchymal soft-tissue sarcomas, appeared in two publications (Hardell & Sandström, 1978, 1979). For each live and dead case, four controls, matched for age, sex, place of residence and vital status, were chosen. The study was limited to men between the ages of 26 and 80. Information on occupational exposure to chemicals was obtained by a questionnaire, filled in by live cases and by the next-of-kin of dead cases, which included a variety of questions about previous and present occupation, exposure to chemicals in the work environment and smoking habits. It was meant in this way to avoid special emphasis on phenoxyacetic acid and chlorophenol exposures. The questionnaire was followed up by telephone contact when necessary. It was found that 36.5% of cases and 9.2% of controls had been exposed to phenoxyacetic acids (2,4-D, 2,4,5-T and MCPA) or chlorophenols. Exposure was considered to have occurred only if for longer than one day, beginning more than five years before diagnosis of the tumour. The relative risk in unmatched analyses of exposure to both phenoxyacetic acids and chlorophenols was 5.7 (95% confidence interval, 2.9-11.3); the relative risk for exposure to phenoxyacetic acids alone was 5.3 (2.4-11.5); and that to chlorophenols alone was 6.6 (95% confidence interval, not stated). Only two patients and two controls had been exposed to herbicides not likely to contain TCDDs, so that relative risks obtained for phenoxyacetic acids and chlorophenols could clearly have been caused by dioxins, since all chlorophenols and 2,4,5-T contain chlorinated dibenzodioxins as an impurity. Four cases and 14 controls reported exposure to DDT, giving a relative risk of 1.2 (95% confidence interval, not stated). No difference between cases and controls was found for exposure to cigarette smoking or exhaust fumes from motorized saws.

Eriksson *et al.* (1981) conducted a similar case-control study in southern Sweden, in order to investigate potential exposure to MCPA and 2,4-D. A group of 110 men, aged 25-75, diagnosed as having soft-tissue sarcomas and reported to a cancer registry between 1974-1978, were each matched for age, year of death, place of residence and vital status with two controls. The soft-tissue sarcomas included 33 leiomyosarcomas, 19 malignant fibrous histiocytomas, 15 liposarcomas and 11 neurogenic sarcomas. Questions about present and previous smoking history and other factors were posed by questionnaire or by interviewers; employers, agricultural commissions and neighbours were also interviewed. Exposure to phenoxyacetic acids or chlorophenols was reported by 22.7% of cases and 5.9% of controls, giving a relative risk of 5.1 (95% confidence interval, 2.5-10.4). Exposure to phenoxyacetic acids alone gave a relative risk of 6.8 (2.6-17.3) and exposure to chlorophenols alone, a relative risk of 3.3 (1.3-8.1). Exposure was again considered to have occurred only if it had been for more than one day beginning more than five years before diagnosis of cancer. Seven cases and four controls had been exposed only to phenoxyacetic acids that are comparatively free from contamination by dioxins and dibenzofurans. These exposures gave a relative risk of 4.2 [95% confidence limits calculated by Coggon and Acheson (1982), 1.2-14.9]. The relative risk of exposure to phenoxyacetic acids containing dioxins was 17 (95% confidence limits, not given). The

authors concluded that exposure to phenoxy acids may be a contributory factor in the development of soft-tissue sarcoma and that the risk is not limited to phenoxy acids that may contain chlorinated dibenzodioxins and dibenzofurans. The data were also analysed for exposure to other chemicals, such as organic solvents, DDT and mercury, to check for confounding factors. In the patients and controls, the respective frequencies of exposure were 21.8% and 11% for pesticides in general, 0.9% and 0.5% for amitrole [see IARC, 1974e], 1.8% and 0.9% for bromophos [*O*-(4-bromo-2,5-dichlorophenyl)-*O*,*O*-dimethyl phosphorothioate], 6.4% and 5% for DDT [see IARC, 1974a], 2.7% and 0.9% for dinoseb [2-*sec*-butyl-4,6-dinitrophenol], 0.9% and 0.5% for fenitrothion [*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate], 8.2% and 4.6% for mercurial seed-dressing agents, 0.9% and 0.5% for lindane [see IARC, 1979a], 0.9% and 0.9% for sodium chlorate, 2.7% and 0.5% for nicotine and 13.6% and 6.8% for other pesticides. More patients also reported exposure to tobacco smoke, asbestos [see IARC, 1977d], glass fibre, power-saw exhaust or organic solvents. Although most of these exposures were higher in cases than controls, none was of a degree that suggested they were confounding.

Hardell *et al.* (1981) conducted a case-control study of malignant lymphoma in male patients attending a department of clinical oncology in northern Sweden. The study design was the same as that used previously by Hardell and his colleagues for a case-control evaluation of soft-tissue sarcoma. The population comprised 169 cases and 338 controls; 60 patients had Hodgkin's disease and 109 had non-Hodgkin's lymphoma; all had been diagnosed between 1974-1978. It was found that 36.1% of cases and 9.6% of controls had been exposed to phenoxy acids or chlorophenols. The relative risk of malignant lymphoma from exposure to both types of pesticide was 6.0 (95% confidence interval, 3.7-9.7); the relative risk for exposure to phenoxy acids alone was 4.8 (2.9-8.1). Exposure to chlorophenols was divided into high and low grade, with exposures of not more than one week or repeated brief exposures totalling at most one month being classified as low-grade exposures. The relative risk for high-grade exposure to chlorophenols was 8.4 (4.2-16.9) and that for low-grade exposure was 2.9 (1.6-5.2), suggesting an effect of dose on increasing risk. The relative risk for all exposures to chlorophenols was 4.3 (2.7-6.9). Exposure to organic solvents - trichloroethylene [see IARC, 1979g], tetrachloroethylene [see IARC, 1979h], genzene [see IARC, 1982] and styrene [see IARC, 1979i] - gave a relative risk of 4.6 (1.9-11.4); a risk of 2.8 (1.6-4.8) was found for high-grade exposure and 1.2 (0.5-2.6) for low-grade exposure (all solvents).

Primarily in order to rule out a possible recall bias for cases with occupational exposure to phenoxy acids and chlorophenols, Hardell (1981) evaluated the occupational exposure of patients with colonic cancer, using the same controls as those of the study by Hardell *et al.* (1981). The relative risk for the 154 men who answered the questionnaire, when adjusted for age and place of residence, was 1.3 (0.6-2.8) for phenoxy acids and 1.8 (0.6-5.3) for chlorophenols.

[Potential limitations of the three studies carried out in Sweden include the heterogeneous nature of soft-tissue sarcomas and the possibility of differential recall of exposure between cases and controls, particularly during telephone interviews probing the exposures most relevant to the studies' hypothesis. However, the data published in the various papers reporting these investigations do not provide evidence that the potential limitations materially affect their validity.]

A summary of the results of these studies is given in Table 1.

Table 1. Results of case-control studies carried out in Sweden

Chemical exposure	Type of cancer and place	Relative risk (95% confidence interval)	Reference
Phenoxyacetic acids (2,4,5-T, 2,4-D, MCPA and TCDD) and/or chlorophenols	Soft-tissue sarcoma, northern Sweden	5.7 (2.9-11.3)	Hardell & Sandström (1978, 1979)
Phenoxyacids alone (2,4,5-T, 2,4-D, MCPA and TCDD)		5.3 (2.4-11.5)	
Chlorophenols alone		6.6	
DDT		1.2	
Phenoxyacetic acids and/or chlorophenols	Soft-tissue sarcoma, southern Sweden	5.1 (2.5-10.4)	Eriksson *et al.* (1981)
Phenoxyacids without TCDD (2,4-D, MCPA, mecoprop[b], dichloroprop[c]) alone		4.2 (1.3-14.5)[a]	
Phenoxy acids with TCDD alone		17	
All phenoxy acids alone		6.8 (2.6-17.3)	
Chlorophenols alone		3.3 (1.3-8.1)	
Phenoxyacetic acids (2,4,5-T, 2,4-D), chlorophenols, amitrole and picloram[d]	Malignant lymphoma, northern Sweden	6.0 (3.7-9.7)	Hardell *et al.* (1981)
Phenoxyacids alone		4.8 (2.9-8.1)	
Chlorophenols alone (all exposures)		4.3 (2.7-6.9)	
Chlorophenols alone (high exposure)		8.4 (4.2-16.9)	
Chlorophenols alone (low exposure)		2.9 (1.6-5.2)	
Solvents (tetrachloroethylene, trichloroethylene, benzene, styrene) (high exposure)		4.6 (1.9-11.4)	
Other solvents (high exposure)		2.8 (1.6-4.8)	
Solvents (low exposure)		1.2 (0.5-2.6)	
Phenoxy acids	Colonic cancer	1.3 (0.6-2.8)	Hardell (1981)
Chlorophenols		1.8 (0.6-5.3)	

[a]Calculated by Coggon and Acheson (1982)
[b]2-(4-Chloro-2-methylphenoxy)propanoic acid
[c](±)-2-(2,4-Dichlorophenoxy)propanoic acid
[d]4-Amino-3,5-6-trichloropicolinic acid

Cohort studies

(*a*) *Occupational users of phenoxy acids/chlorophenols*

Swedish investigators have also looked at the carcinogenic risk of occupational exposures to herbicides and fungicides through retrospective cohort studies.

Follow-up of 348 railroad workers exposed for more than 45 days during the period 1957-1972 to the herbicides 2,4-D, 2,4,5-T [see IARC, 1977a,c], atrazine [2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine], mecoprop [2-(4-chloro-2-methylphenoxy)propanoic acid],

dichloropropionic acid and amitrole [see IARC, 1974e] resulted in 2978 person-years of observation (Axelson & Sundell, 1974). The authors found a significant increase in cancer mortality and morbidity among workers exposed to amitrole.

Axelson *et al.* (1980) reported a further follow-up of these workers, through October 1978, accumulating 5541 person-years. The herbicide exposure of the workers was analysed in terms of exposure to (a) amitrole, (b) phenoxy acids and (c) both amitrole and phenoxy acids. A 10-year lapse period from the first day of exposure was used as the induction latency. They found 15 cases of cancer *versus* 6.87 expected (relative risk, 2.2). In the cohort with combined exposure to amitrole and phenoxy acids, 6 cases were observed *versus* 1.78 expected (relative risk, 3.4); in the group exposed to amitrole alone, 3 tumours were observed *versus* 1.95 expected (relative risk, 1.5); and 6 cancers were observed *versus* 3.14 expected (relative risk, 1.9) in the phenoxy acid-exposed group. All cancers and cancers of the stomach occurred in statistically significant excesses in the cohort as a whole. In the groups exposed to amitrole plus phenoxy acids, there was a significant excess of all cancers. In the group exposed only to phenoxy acids, stomach cancer occurred in a significant excess (2 observed, 0.33 expected; relative risk, 6.1). [No soft-tissue sarcoma was identified, but the statistical power of this study to detect an excess of a rare cancer was limited.]

Hogstedt and Westerlund (1980) conducted a restrospective mortality study of 142 forestry workers exposed to phenoxy pesticides and 244 unexposed forestry workers, comparing their mortality experience with national statistics. Work supervisors, who have a more intense exposure to phenoxy herbicides than others, had a significantly elevated tumour mortality (5 observed, 1.4 expected). No particular tumour type predominated, and no soft-tissue sarcoma was observed, although the authors noted that the study had limited statistical power and was inconclusive, due to the relatively short follow-up period.

(*b*) *Industrial exposures*

Reports of cancer following explosions or chloracne outbreaks at 2,4,5-T [see IARC, 1974c] and trichlorophenol [see IARC, 1979f] manufacturing plants occurred in The Netherlands in 1963 (IARC, 1978); Czechoslovakia in 1965 (Jirásek *et al.*, 1973); Bolsover, UK in 1968 (May, 1973); and Seveso and neighbouring towns in northern Italy in 1976 (Bert *et al.*, 1976). These studies are still not completed, although in several locations long-term health effects are being followed.

Theiss *et al.* (1982) followed the mortality experience of a cohort of 74 workers employed at a trichlorophenol manufacturing plant, 70 of whom sustained TCDD exposure during an accident in 1953 and four of whom were involved in the subsequent operations of cleaning and testing. Comparisons were made with the external regional and national rates available for the period 1970-1975 and with an internal control cohort from the same factory who were not exposed to trichlorophenol, matched by age and date of entry. Of 21 deaths, 7 were due to cancer, compared with 5 in the internal control group and 4.1 expected on the basis of the regional rates. Among those with 20 years of observation, 5 cancer deaths were observed (0.77 expected from regional rates): 2 stomach cancers (0.23 expected); 1 colonic cancer (0.10 expected) and 2 lung cancers (0.44 expected).

Zack and Suskind (1980) investigated cancer deaths in a selected subcohort of 121 male workers who had developed chloracne after the accidental release in 1949 of large amounts of TCDD during an accident in a plant manufacturing trichlorophenol in Nitro,

West Virginia, USA. They found that nine cancer deaths had occurred during the 29-year observation period; five of the deaths were from lung cancer, three from neoplasms of the lymphatic or haematopoeitic tissue and one from a malignant fibrous histiocytoma of soft-tissue origin. The SMR for all malignant neoplasms was 1.00. Because of the small size of the cohort and the small number of deaths, the authors noted that the study could not be considered conclusive.

Ott *et al.* (1980) described the mortality experience of 204 employees at a US plant where 2,4,5-T was manufactured. Each member of the cohort had worked for at least one month between 1951-1971 at one of four jobs in which there was potential exposure to 2,4,5-T; 75% had worked for less than 12 months in one of these jobs. A total of 11 deaths were observed, of which only one was a malignant neoplasm (3.6 expected). [The cohort followed was small.]

Cook *et al.* (1980) reviewed the mortality experience of 61 trichlorophenol production workers among whom an outbreak of chloracne had occurred in 1964 and who were followed up to December 1978. A total of four deaths were observed, three of which were from cancer (1.6 expected); one was an adenocarcinoma at an unspecified site, one a glioma and one a fibrosarcoma. The authors stated that the cohort was small and that the study therefore had limited statistical power to detect any cancer excess.

Honchar and Halperin (1981) reviewed the studies by Ott *et al.* (1980), Cook *et al.* (1980), Zack and Suskind (1980) and an unpublished study by Zack of 2,4,5-T synthesis workers. After combining the numbers of deaths from the four cohorts, they found that of the 105 deaths, three (2.9%) were due to soft-tissue sarcoma, whereas only about 0.07% would have been expected in 1975 among American males between the ages of 20 and 84 years.

Cook (1981) reported a fourth incident case of soft-tissue sarcoma (a malignant fibrous histiocytoma) in the cohort described by Cook *et al.* (1980).

SUMMARY AND EVALUATION

Insecticides

Few epidemiological data are available on the specific compounds considered in this volume of monographs; therefore, insecticides were considered collectively. Reference should also be made to *IARC Monographs* volumes 5, 15, 20 and 23.

Six cases of aplastic anaemia, one of which subsequently developed into leukaemia, and one leukaemia have been reported in children after domestic application of organophosphorus pesticides; and one case of aplastic anaemia developed after occupational exposure to a mixture of pesticides. In a correlation study in the US, leukaemia mortality was positively correlated with cotton and wheat production. A number of reports have been published on the levels of pesticide residues, particularly DDT and dieldrin, in tissues of subjects with cancer (including lung cancer, gastrointestinal cancer, breast cancer and generalized metastatic carcinomas) and in tissues of control subjects. No consistent pattern has emerged, but in those studies in which confounding variables such as age, sex and race were controlled, no statistically significant difference between cases and controls was demonstrated. A case-control study using death certificates has shown no association of bladder cancer with farming, and another case-control study did not detect an association between aplastic anaemia and occupations involving the use of

chlorinated hydrocarbon insecticides. Two case-control studies have shown an association between leukaemia and the occupation of farmer. A further such study, using death certificates, showed a correlation between non-Hodgkin's lymphoma, in particular reticulum-cell sarcoma, and farming. A case-control study of brain tumours in children has found an increased risk in children exposed to insecticides through extermination in the home; and a second study on gliomas in adults has shown an association with occupation as an agricultural worker. Retrospective mortality studies of pest control applicators and of four organochlorine manufacturing plants showed no overall excess rates of cancer, although small excesses of cancers of the lung, skin, bladder, stomach, oesophagus and lymphatic system were noted in individual studies. In every study, insecticide exposures were multiple and no information was available on cigarette smoking.

Evaluation[1]

The available data from case reports and from epidemiological studies provide inadequate evidence to evaluate the carcinogenicity of organic pesticides, as a broad class or as individual compounds.

Herbicides

Increased carcinogenic risks of malignant lymphoma of the histiocytic type and of soft-tissue sarcomas have been demonstrated in case-control studies of people in Sweden occupationally exposed to phenoxyacetic acid and chlorophenol herbicides, presumably contaminated with tetrachlorodibenzo-*para*-dioxin (TCDD). Occupational exposures to herbicides that are less likely to be contaminated with TCDD also resulted in an increased risk of developing soft-tissue sarcoma. Development of soft-tissue sarcoma has also been described in case reports and in case-control and cohort studies in the US in workers exposed occupationally and accidentally in factories where trichlorophenol and 2,4,5-T were produced.

Of a series of 123 cases of non-Hodgkin's lymphoma, five presented solely with cutaneous manifestations. Four of these reported occupational exposure to phenoxy acid herbicides.

Evaluation

Case reports of cutaneous non-Hodgkin's lymphoma and epidemiological results from three case-control studies from one country and from some relatively small cohorts in another country provide *limited evidence* for the carcinogenicity of phenoxy acids and chlorophenols, but do not allow unequivocal identification of the compounds involved (including those present as impurities in technical-grade compounds).

Exposure to MCPA alone was reported for some cases in one of three case-control studies, but this provides inadequate evidence to evaluate the carcinogenicity of MCPA alone (see monograph on MCPA, p. 255).

---

[1] The evaluation of arsenic and arsenic compounds (including inorganic arsenic pesticides, here omitted from consideration) led to the conclusion (IARC, 1980) that inorganic arsenic compounds are skin and lung carcinogens in humans, and that the data suggesting an increased risk of cancer at other sites are inadequate for evaluation.

References

Axelson, O. & Sundell, L. (1974) Herbicide exposure, mortality and tumor incidence. An epidemiological investigation on Swedish railroad workers. *Work environ. Health*, *11*, 21-28

Axelson, O., Sundell, L., Andersson, K., Edling, C., Hogstedt, C. & Kling, H. (1980) Herbicide exposure and tumor mortality. An updated epidemiological investigation on Swedish railroad workers. *Scand. J. Work environ. Health*, *6*, 73-79

Barthel, E. (1976) High incidence of lung cancer in persons with chronic occupational exposure to pesticides in agriculture (Ger.). *Z. Erkrank Atm.-Org.*, *146*, 266-274

Bert, G., Manacorda, P.M. & Terracini, B. (1976) Health control: Health uncontrolled (Ital.). *Sapere*, *796*, 50-60

Bishop, C.M. & Jones, A.H. (1981) Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. *Lancet*, *ii*, 369

Blair, A., Fraumeni, J.F., Jr & Mason, T.J. (1980) Geographic patterns of leukemia in the United States. *J. chronic Dis.*, *33*, 251-260

Blair, A. & Thomas, T.L. (1979) Leukemia among Nebraska farmers: A death certificate study. *Am. J. Epidemiol.*, *110*, 264-273

Blair, A. & Watts, D. (1980) Bladder cancer and dairy farming (Letter). *J. occup. Med.*, *22*, 576-577

Blot, W.J., Harrington, J.M., Toledo, A., Hoover, R., Heath, C.W., Jr & Fraumeni, J.F., Jr (1978) Lung cancer after employment in shipyards during World War II. *New Engl. J. Med.*, *229*, 620-624

Burmeister, L.F., Van Lier, S.F. & Isacson, P. (1982) Leukemia and farm practices in Iowa. *Am. J. Epidemiol.*, *115*, 720-728

Caldwell, G.G., Cannon, S.B., Pratt, C.B. & Arthur, R.D. (1981) Serum pesticide levels in patients with childhood colorectal carcinoma. *Cancer*, *48*, 774-778

Cantor, K.P. (1982) Farming and mortality from non-Hodgkin's lymphoma: A case-control study. *Int. J. Cancer*, *29*, 239-247

Casarett, L.J., Fryer, G.C., Yauger, W.L. & Klemmer, H.W. (1968) Organochlorine pesticide residues in human tissue - Hawaii. *Arch. environ. Health*, *17*, 306-311

Clark, L., Shy, C.M., Portier, K.M., Most, B.M. & Florin, J.W. (1978) Cancer mortality and agricultural activity: An association with cotton production and large farms in the southeastern United States (Abstract). *Am. J. Epidemiol.*, *108*, 242

Coggon, D. & Acheson, E.D. (1982) Do phenoxy herbicides cause cancer in man? *Lancet*, *i*, 1057-1059

Cook, R.R. (1981) Dioxin, chloracne and soft tissue sarcoma. *Lancet, i*, 618-619

Cook, R.R., Townsend, J.C., Ott, M.G. & Silverstein, L.G. (1980) Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J. occup. Med., 22*, 530-532

Dacre, J.C. & Jennings, R.W. (1970) Organochlorine insecticides in normal and carcinogenic human lung tissues (Abstract no. 15). *Toxicol. appl. Pharmacol., 17*, 277

Davies, J.E., Edmundson, W.F., Schneider, N.J. & Cassady, J.C. (1968) Problems of prevalence of pesticide residues in humans. *Pestic. Monit. J., 2*, 80-85

Davies, J.E., Barquet, A., Morgade, C. & Raffonelli, A. (1975) *Epidemiologic studies of DDT and dieldrin residues and their relationship to human carcinogenesis.* In: *Proceedings of International Symposium, Recent Advances in the Assessment of the Health Effects of Environmental Pollution (EUR 5360)*, Vol. 2, Luxembourg, Commission of the European Communities, pp. 695-702

Ditraglia, D., Brown, D.P., Namekata, T. & Iverson, N. (1981) Mortality study of workers employed at organochlorine pesticide manufacturing plant. *Scand. J. Work environ. Health, 7*, Suppl. 4, 140-146

Doll, R. & Peto, R. (1981) The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J. natl Cancer Inst., 66*, 1193-1308

Eriksson, M., Hardell, L., Berg, N.O., Möller, T. & Axelson, O. (1981) Soft-tissue sarcomas and exposure to chemical substances: A case referent study. *Br. J. ind. Med., 38*, 27-33

Gold, E., Gordis, L., Tonascia, J. & Szklo, M. (1979) Risk factors for brain tumors in children. *Am. J. Epidemiol., 109*, 309-319

Greene, M.H., Brinton, L.A., Fraumeni, J.F. & D'Amico, R. (1978) Familial and sporadic Hodgkin's disease associated with occupational wood exposure. *Lancet, ii*, 626-627

Hardell, L. (1977) Malignant mesenchymal tumours and exposure to phenoxy acids. A clinical observation (Swed.). *Läkartidningen, 74*, 2753-2754

Hardell, L. (1979) Malignant lymphomas of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet, i*, 55-56

Hardell, L. (1981) Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. *Scand. J. Work environ. Health, 7*, 119-130

Hardell, L. & Sandström, A. (1978) Malignant mesenchymal soft tissue tumours and exposure to phenoxy acids or chlorophenols (Swed.). *Läkartidningen, 75*, 3535-3536

Hardell, L. & Sandström, A. (1979) Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br. J. Cancer, 39*, 711-717

Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. *Br. J. Cancer*, *43*, 169-176

Hoffman, W.S., Adler, H., Fishbein, W.I. & Bauer, F.C. (1967) Relation of pesticide concentrations in fat to pathological changes in tissues. *Arch. environ. Health.*, *15*, 758-765

Hogstedt, C. & Westerlund, B. (1980) Cohort study of the causes of death among forestry workers with and without exposure to phenoxy acid preparations (Swed.). *Läkartidningen*, *77*, 1828-1831

Honchar, P.A. & Halperin, W.E. (1981) 2,4,5-T, trichlorophenol, and soft tissue sarcoma. *Lancet*, *i*, 268-269

IARC (1974a) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, pp. 83-124

IARC (1974b) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, pp. 125-156

IARC (1974c) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, pp. 157-171

IARC (1974d) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, pp. 25-38

IARC (1974e) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 7, *Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals*, pp. 31-43

IARC (1976a) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, pp. 245-257

IARC (1976b) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, pp. 259-270

IARC (1976c) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, pp. 37-53

IARC (1976d) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, pp. 151-159

IARC (1977) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*

IARC (1977a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, pp. 111-138

IARC (1977b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, pp. 41-102

IARC (1977c) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, pp. 273-299

IARC (1977d) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 14, *Asbestos*

IARC (1978) Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. *IARC tech. Rep. Ser. No. 78/001*

IARC (1979a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 195-239

IARC (1979b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 97-127

IARC (1979c) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 327-348

IARC (1979d) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 45-65, 129-154

IARC (1979e)*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 303-325

IARC (1979f) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 349-367

IARC (1979g) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 545-572

IARC (1979h) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, pp. 491-514

IARC (1979i) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, pp. 231-274

IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 23, *Some Metals and Metallic Compounds*, pp. 39-141

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 29, *Some Industrial Chemicals and Dyestuffs*, pp. 93-148

Jenkyn, L.R., Budd, R.C., Fein, S.H. & Cornell, C.J. (1979) Insecticide/herbicide exposure, aplastic anaemia and pseudotumor cerebri. *Lancet, ii*, 368

Jirásek, L., Kalenskyé, J. & Kubeck, K. (1973) Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides (Czech.). *Czech. Dermatol., 48*, 306-317

Johnson, F.E., Kugler, M.A. & Brown, S.M. (1981) Soft tissue sarcomas and chlorinated phenols. *Lancet, ii*, 40

Kasai, A., Asanuma, S. & Nakamura, S. (1972) Studies on organochlorine pesticide residues in human organs. III. *J. Jpn. Assoc. rural Med., 21*, 296-297

Kutz, F.W., Yobs, A.R. & Strassman, S.C. (1977) Racial stratification of organochlorine insecticide residues in human adipose tissue. *J. occup. Med., 19*, 619-622

Maier-Bode, H. (1960) DDT in body fat of people (Ger.). *Med. exp., 1*, 146-152

May, G. (1973) Chloracne from the accidental production of tetrachlorodibenzodioxin. *Br. J. ind. Med., 30*, 276-283

Milham, S., Jr (1982) *Occupational Mortality in Washington State, 1950-1979* (Contract No. 210-80-0088), Cincinnati, OH, National Institute for Occupational Safety & Health (in press)

Moses, M. & Selikoff, I.J. (1981) Soft tissue sarcomas, phenoxy herbicides and chlorinated phenols. *Lancet, i*, 1370

Muir, C.S. & Wagner, G. (1981) *Directory of On-Going Research in Cancer Epidemiology, 1981 (IARC Scientific Publications No. 38)*, Lyon, pp. 190 (Abstract no. 519), 232 (624), 328 (906), 331-332 (917), 368 (1018)

Musicco, M., Filippini, G., Melotto, A., Morello, G. & Berrino, F. (1982) Gliomas and professional exposure to carcinogens: Case-control study. *Am. J. Epidemiol.* (in press)

Olsson, H. & Brandt, L. (1981) Non-Hodgkin's lymphoma of the skin and occupational exposure to herbicides. *Lancet, ii*, 579

Ott, M.G., Holder, B.B. & Olson, R.D. (1980) A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. *J. occup. Med., 22*, 47-50

Pimentel, J.C. & Menezes, A.P. (1979) Granulomatous disease with alveolar cell carcinoma due to the inhalation of powdered DDT (Abstract). *Pathology, 165*, 140

Pratt, C.B., Rivera, G., Shanks, E., Johnson, W.W., Howarth, C., Terrell, W. & Kumar, A.P.M. (1977) Colorectal carcinoma in adolescents. Implications regarding etiology. *Cancer, 40*, 2464-2472

Radomski, J.L., Deichmann, W.B., Clizer, E.E. & Rey, A. (1968) Pesticide concentrations in the liver, brain and adipose tissue of terminal hospital patients. *Food Cosmet. Toxicol., 6*, 209-220

Reeves, J.D., Driggers, D.A. & Kiley, V.A. (1981) Household insecticide associated aplastic anaemia and acute leukaemia in children. *Lancet, ii*, 300-301

Saracci, R. & Repetto, F. (1980) Time trends of primary liver cancer: Indication of increased incidence in selected cancer registry populations. *J. natl Cancer Inst., 65*, 241-247

Theiss, A.M., Frentzel-Beyme, R., & Link, R. (1982) Mortality study of persons exposed to dioxin in a trichlorophenol process accident which occurred in the BASF AG on November 17, 1953. *Am. J. ind. Med.* (in press)

Unger, M. & Olsen, J. (1980) Organochlorine compounds in the adipose tissue of deceased people with and without cancer. *Environ. Res.*, *23*, 257-263

Wang, H.H. & Grufferman, S. (1981) Aplastic anemia and occupational pesticide exposure: A case-control study. *J. occup. Med.*, *23*, 364-366

Wang, H.H. & MacMahon, B. (1979a) Mortality of pesticide applicators. *J. occup. Med.*, *21*, 741-744

Wang, H.H. & MacMahon, B. (1979b) Mortality of workers employed in the manufacture of chlordane and heptachlor. *J. occup. Med.*, *21*, 745-748

Wassermann, M., Nogueira, D.P., Cucos, S., Mirra, A.P., Shibata, H., Arie, G., Miller, H. & Wassermann, D. (1978) Organochlorine compounds in neoplastic and adjacent apparently normal gastric mucosa. *Bull. environ. Contam. Toxicol.*, *20*, 544-553

Zack, J. & Suskind, R.R. (1980) The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *J. occup. Med.*, *22*, 11-14

THE MONOGRAPHS

INSECTICIDES

CHLORDIMEFORM

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 6164-98-3

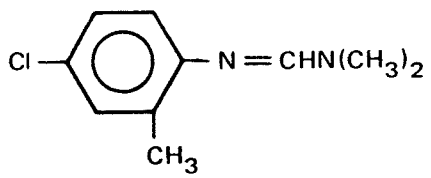
Chem. Abstr. Name: Methanimidamide, *N'*-(4-chloro-2-methylphenyl)-*N,N*-dimethyl-

IUPAC Systematic Name: N^2-(4-Chloro-*ortho*-tolyl)-N^1,N^1-dimethylformamidine

Synonyms: Chlorodimeform; chlorophenamidin; chlorophenamidine; *N'*-(4-chloro-*ortho*-tolyl)-*N,N*-dimethylformamidine; chlorphenamidine; *N,N*-dimethyl-*N'*-(2-methyl-4-chlorophenyl)formamidine; ENT 27335; ENT 27567; EP-333; *N'*-(2-methyl-4-chlorophenyl)-*N,N*-dimethylformamidine

Trade Names: Acaron; Bermat; C 8514; Carzol; Chlorfenamidine; Ciba 8514; Ciba - C8514; Fundal; Fundal 500; Fundex; Galecron; RS 141; Schering 36268; SN 36268; Spanon; Spanone

1.2 Structural and molecular formulae and molecular weight



$C_{10}H_{13}ClN_2$ Mol. wt: 196.7

1.3 Chemical and physical properties of the pure substance

From Worthing (l979), unless otherwise specified

(*a*) *Description:* Colourless crystals

(*b*) *Boiling-point*: 163-165°C at 14 mm Hg

(*c*) *Melting-point*: 32°C

(*d*) *Density*: d^{30} 1.10

(*e*) *Spectroscopy data*: Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981)

(*f*) *Solubility*: Slightly soluble in water (250 mg/l at 20°C); soluble in acetone (>200 g/l at 20°C), benzene, chloroform, ethyl acetate, hexane and methanol

(*g*) *Volatility*: Vapour pressure, 3.6 x 10^{-4} mm Hg at 20°C

(*h*) *Stability*: Hydrolyses in neutral and acidic aqueous media, initially to 4-chloro-*ortho*-tolylformamide and then to *para*-chloro-*ortho*-toluidine [see IARC, 1978]

(*i*) *Reactivity:* Forms salts with acids

1.4 Technical products and impurities

The technical grade has been reported to be more than 96% pure (Worthing, 1979). Major impurities have been reported to be 2-methyl-4-chlorformamidine, *para*-chloro-*ortho*-toluidine hydrochloride and sodium chloride (WHO, 1972). Chlordimeform has been available as a water-soluble powder (as its hydrochloride) and as an emulsifiable concentrate (Worthing, 1979); the powder contained 95% of the hydrochloride and 5% inert ingredients (Ciba-Geigy Corp., 1973a), and the emulsifiable concentrate contained 48.5% chlordimeform, 43.4% aromatic petroleum distillates and 8.1% inert ingredients (Ciba-Geigy Corp., 1973b).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Chlordimeform was introduced as a commercial chemical in 1966. It can be made by either: (1) the reaction of *para*-chloro-*ortho*-toluidine with dimethylformamide, using

either phosphorus oxychloride, sulphuryl chloride or phosgene to effect the condensation, or (2) chlorination of N^1,N^1-dimethyl-N^2-*ortho*-tolylformamidine. In both cases, the free base is liberated with sodium hydroxide (Worthing, 1979). The former method is probably used for commercial production.

Commercial production of chlordimeform in the US was begun by two companies in 1969 or earlier, although the first year for which the US International Trade Commission (1979) reported production was 1978, when one of the two companies was listed as a producer. That company was still listed as a producer in 1980 (US International Trade Commission, 1981a), but it is not believed to be producing chlordimeform presently. Imports of chlordimeform through the principal US customs districts amounted to 198 thousand kg in 1980 (US International Trade Commission, 1981b), down from the 745 thousand kg imported in 1979 (US International Trade Commission, 1980). These imports are believed to have come from the Federal Republic of Germany. Separate data on US exports of chlordimeform are not available.

This compound is believed to be produced by one company in the Federal Republic of Germany and to have been produced in Argentina. It is not produced commercially in Japan.

(*b*) *Use*

Chlordimeform is used as an insecticide/acaricide/ovicide for the control of insects in agricultural applications.

In 1974, total US usage of chlordimeform is estimated to have been 590 thousand kg, 77% of which was used on cotton, 15% on deciduous fruits/nuts and 8% on vegetables. In 1976, 2.0 million kg of chlordimeform were used by US farmers on major crops, representing 3.4% of the total quantity of active insecticide ingredients used on those crops in that year (US Department of Agriculture, 1978); however, in the same year, the US manufacturer voluntarily removed the product from the market until questions about its toxicological properties could be cleared up; usage was dropped at that time. In 1979, it was again made available, but for use on cotton only, with special safeguards to minimize exposure. In 1980, total US usage of chlordimeform is estimated to have been 227 thousand kg, all of which was used on cotton to control budworm/bollworm.

The Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues established in December 1979 a temporary acceptable daily intake of 0-0.0001 mg/kg bw chlordimeform for humans (FAO, 1980). In 1978, that group recommended the following tolerances for residues of chlordimeform on commodities (mg/kg): cottonseed and cottonseed (crude), 2; cottonseed oil (edible), meat (of cattle, pigs, poultry and sheep) and milk and milk products, no residues at the current limit of detection (0.05) (FAO, 1979).

Tolerances have been established in the US for residues of chlordimeform and those of its metabolites that contain the *para*-chloro-*ortho*-toluidine moiety in or on: (a) a variety of 22 raw agricultural commodities, including fruits, vegetables, cottonseed, animal and poultry meat and fat, eggs, milk and walnuts (0.1-12 mg/kg) (US Environmental Protection Agency, 1980); (b) dried prunes, from application of chlordimeform to the growing plums (15 mg/kg); and (c) dried apples (25 mg/kg) and cottonseed hulls (10 mg/kg) from application to the growing crops (US Food & Drug Administration, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Chlordimeform is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Gorup on the number of workers exposed to chlordimeform during its production, formulation or use.

(*c*) *Soil and plants*

Chlordimeform residues of 0.18-9.16 mg/kg were found in air-dried rice straw from rice fields treated one to five times 13-115 days before harvest. It was detected at lower levels in rice bran, and no residue was detected in polished rice (Kanazawa *et al.*, 1976).

2.3 Analysis

Standard methods used for the analysis of chlorodimeform in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of chlordimeform

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations				
Free base	Dissolve (methanol/water)	Potentiometric titration	not given	Voss et *al.* (1974)
Free base	Melt	GC/TCD	not given	Voss *et al.* (1974)
Hydrochloride salt	Convert to free base; extract (chloroform); evaporate; dissolve (methanol/water)	Potentiometric titration	not given	Voss *et al.* (1974)
Fruits, crops, animal products and soils	Hydrolyse (acetic acid/sodium hydroxide); steam distill; extract (isooctane); derivatize to form iodide	GC/ECD	0.05 mg/kg	Voss *et al.* (1974); Markus & Puma (1973)
Fruits vegetables and soils	Hydrolyse and extract as above; diazotize and couple to *N*-ethyl-1-naphthylamine; chromatograph (cellulose column)	Colorimetry	0.05 mg/kg	Voss *et al.* (1974)

[a]Abbreviations: GC/TCD, gas chromatography/thermal conductivity detection; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

No published study on the carcinogenicity of chlordimeform was available to the Working Group[1].

Carcinogenicity of metabolites

Mouse: Groups of 25 male and 25 female weanling random bred CD-1 mice derived from HaM/ICR mice were fed dietary levels of 0, 750 or 1500 mg/kg (males) and 0, 2000 or 4000 mg/kg (females) *para*-chloro-*ortho*-toluidine hydrochloride (97-99% purity) for 18 months and observed for an additional three months. Haemangiosarcomas or haemangiomas were seen in 13/20 high-dose males, 12/20 low-dose males, 12/16 high-dose females and 18/19 low-dose females, mainly in the spleen and the subcutaneuous and retroperitoneal adipose tissue. These tumours were not observed in simultaneous controls but occurred in 5/99 pooled male controls and 9/102 pooled female controls (Weisburger *et al.*, 1978).

Groups of 50 male and 50 female $B6C3F_1$ mice, six weeks old, were fed *ad libitum* a diet containing 3750 or 15 000 mg/kg (males) or 1250 or 5000 mg/kg (females) *para*-chloro-*ortho*-toluidine hydrochloride (purity, 99%) for 99 weeks. Matched controls consisted of 20 untreated mice of each sex. All males lived beyond 52 weeks of the study; of the females, 49/50 of the high-dose group, 48/50 of the low-dose group and 19/20 in the control group were still alive at that time, but all high-dose females had died by 92 weeks. Haemangiosarcomas occurred in 3/50 low-dose males, 37/50 high-dose males, 40/49 low-dose females and 39/50 high-dose females, mainly in the fatty tissue adjacent to the genital organs. No such tumour occurred in matched controls. There was no significant difference in the incidence of other types of malignant tumours among treated and control mice (National Cancer Institute, 1979).

Rat: Groups of 25 male weanling Sprague-Dawley rats received 2000 or 4000 mg/kg *para*-chloro-*ortho*-toluidine hydrochloride (97-99% pure) in the diet for three months; the doses were then reduced to 500 and 1000 mg/kg for 15 months. Twenty-five male rats served as controls. All animals were killed after 24 months. No statistically significant increase in the incidence of tumours was found among the different groups using the Fisher exact test (Weisberger *et al.*, 1978). [The Working Group noted the short duration of treatment.]

Groups of 50 male and 50 female Fischer 344 rats, six weeks old, were fed diets containing 1250 mg/kg or 5000 mg/kg *para*-chloro-*ortho*-toluidine hydrochloride (purity, 99%) for 107 weeks, when all surviving rats were killed. A matched control group consisted of 20 rats of each sex. Chromophobe adenomas of the pituitary were observed in 1/19 control females, 13/47 low-dose females and 15/48 high-dose females; in males the incidence of these tumours was dose-related ($p = 0.006$): 2/19 controls, 6/48 low-dose

---

[1] Unpublished carcinogenicity data on chlordimeform were reviewed by the FAO/WHO Expert Committees on Pesticide Residues in Food and the Environment (FAO, 1980).

and 15/47 high-dose animals. The incidence of other neoplasms in males and females displayed no statistically significant dose-related trend (National Cancer Institute, 1979). [The Working Group noted the reduced survival among controls and the unusually low incidence of chromophobe adenomas among matched controls compared with that in historical controls (Tarone *et al.*, 1981).]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The acute oral LD_{50} of chlordimeform is 285 mg/kg bw in mice (Hollingworth, 1976), 340 mg/kg bw in rats and 625 mg/kg bw in rabbits (Worthing, 1979).

An i.p. dose of 200 mg/kg bw to rats and mice caused marked hyperexcitation 5-10 min after dosing, followed by a gradual fall into a state of sedation; recovery was complete within 24 hours. Death occurs during the early hyperexcitation period (1-3 hours) (Matsumura & Beeman, 1976). Two of three cats given 50 mg/kg bw chlordimeform subcutaneously daily for up to five days exhibited severe degeneration and sloughing of the bladder epithelium and other manifestations of kidney and liver injury (Folland *et al.*, 1978; Kimbrough, 1980).

Although chlordimeform and its demethylation products have been shown to inhibit monoamine oxidase *in vitro* (Matsumura & Beeman, 1976), their lethality is not due to this mechanism (Robinson *et al.*, 1975; Robinson & Smith, 1977). A precise definition of the mechanisms of their lethality in mammals has not been achieved; however, chlordimeform, like local anaesthetics, exerts a depressive effect on the cardiovascular system and marked central nervous system stimulation with enhanced sympathetic outflow (Hollingworth *et al.*, 1979).

In chronic feeding studies described in section 3.1 of this monograph, the mean body weights of male and female rats fed diets containing 5000 mg/kg [the highest concentration tested] of *para*-chloro-*ortho*-toluidine for two years were lower than those of the corresponding controls. The mean body weights of male and female mice fed 3750 and 15 000 mg/kg of diet *para*-chloro-*ortho*-toluidine for two years were lower than those of the corresponding controls, especially in females, and were dose-related throughout the bioassay. In mice of both sexes there was dose-related mortality (National Cancer Institute, 1979).

Effects on reproduction and prenatal toxicity

Rats were fed chlordimeform [purity not stated] mixed into the diet (approximate daily intake, 100 μg/kg bw) starting from the fifth day of pregnancy and were allowed to litter [data on termination of dietary feeding and survival of progeny not given]. Except for an impaired ability in swimming between 7-17 days of age, the progeny exhibited no other behavioural effect (Olson *et al.*, 1978).

Absorption, distribution, excretion and metabolism

The metabolism of chlordimeform was reviewed by Knowles (1970). Rats, dogs and goats treated orally with chlordimeform(tolyl methyl-^{14}C) rapidly metabolized the compound and eliminated the radioactivity primarily *via* the urine. In rats, 85% of the dose was excreted in the urine within 24 hours and 7.5% in the faeces by 72 hours; the equivalent values for dogs and goats were 65 and 80% and 0.6 and 1.8%, respectively. Less than 10% (dogs, goats) and 25% (rats) of the urinary radioactivity was organosoluble; most of the water-soluble metabolites were glucuronides and/or ethereal sulphates. The following metabolites of chlordimeform are indicated: desmethyl chlordimeform; *N*-formyl-*para*-chloro-*ortho*-toluidine; *para*-chloro-*ortho*-toluidine; *N*-formyl-5-chloroanthranilic acid; and 5-chloroanthranilic acid; in addition to a number of other, unidentified metabolites. Storage of ^{14}C-chlordimeform or its metabolites in rat and dog tissue and its elimination in goat milk were negligible. *Para*-Chloro-*ortho*-toluidine comprised only 0.9% of the total radioactivity in selected tissues of rats sacrificed 72 hours after its administration (Knowles Gupta, 1970).

Rat liver microsomal enzymes catalyse the *N*-demethylation and hydrolysis of chlordimeform *in vitro*. The major product, 4'-chloro-*ortho*-formotoluidine (*N*-formyl-*para*-chloro-*ortho*-toluidine), is further converted by a liver enzyme to *para*-chloro-*ortho*-toluidine (Knowles, 1970). ^{14}C-Chlordimeform is also metabolized by human embryonic lung cells in culture to 4'-chloro-*ortho*-formotoluidine (82%) and *para*-chloro-*ortho*-toluidine (2.3%) (Lin *et al.*, 1975).

When ^{14}C-*para*-chloro-*ortho*-toluidine was given orally to rats, 71% of the dose was eliminated in urine and 24.5% in the faeces within 72 hours (Knowles & Gupta, 1970).

After i.p. administration to rats of 14 mg/kg bw [^{14}C-methyl]-*para*-chloro-*ortho*-toluidine, it was incorporated metabolically into DNA, RNA and protein of rat liver. These macromolecules in other tissues contained little radioactivity. In in-vitro studies, a phenobarbital-inducible liver microsomal enzyme converts *para*-chloro-*ortho*-toluidine to the more reactive metabolite, 5-chloro-2-hydroxyaminotoluene (Hill *et al.*, 1979).

Chlordimeform (50 mg/kg bw i.p.) and some of its metabolites inhibit ethanol metabolism in mice (Knowles & Benezet, 1979).

Mutagenicity and other short-term tests

Chlordimeform [purity not stated] was negative in the *rec*-assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*) and in a simple spot test using auxotrophic strains of *Escherichia coli* and *Salmonella typhimurium* (Shirasu *et al.*, 1976). The negative result in the rec-assay was confirmed by Simmon *et al.* (1979) and Waters *et al.* (1982) using technical-grade chlordimeform. All these experiments were carried out in the absence of exogenous metabolic activation.

No mutagenic effect was detected with technical-grade chlordimeform in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 or in *E. coli* WP2 *uvr*A, and no induction of mitotic recombination was observed in the *Saccharomyces cerevisiae* D3 system, in the presence or absence of an Aroclor-induced rat liver microsomal preparation. No induction of unscheduled DNA synthesis was found in WI38 human lung fibroblasts, with or without an uninduced mouse liver microsomal preparation (Simmon *et al.*, 1979; Waters *et al.*, 1982).

(*b*) *Humans*

Toxic effects

An episode of acute poisoning following intensive occupational exposure specifically to chlordimeform occurred in Tennessee, USA in 1975 (Folland *et al.*, 1978). Nine of 22 workers packaging the chemical in powdered form complained of dysuria, nocturia, gross haematuria, penile discharge, abdominal pain, back pain and 'feeling hot'. Other common symptoms were drowsiness, skin rash, anorexia and a sweet taste in the mouth. All of the manifestations of illness, including cystitis, resolved slowly over about three to eight weeks. Studies of three hospitalized workers revealed haematuria and pyuria, proteinuria, low creatinine clearance, decreased serum complement level, elevated serum glutamic oxaloacetic transaminase, small urinary bladder capacity and ureteral reflux. Bladder biopsy specimens from these patients showed severe haemorrhagic cystitis.

Microscopic haematuria was also found in one of six farmers who had used chlordimeform; it resolved three weeks after he stopped spraying with this compound (Folland *et al.*, 1978).

It is not known whether chlordimeform itself is a bladder irritant. The capacity of *para*-chloro-*ortho*-toluidine to cause urinary-tract injury in man is, however, well established: Currie (1933) noted gross haematuria and stranguria among workers in a chemical plant in England exposed to *para*-chloro-*ortho*-toluidine. He reported a total of 11 cases, most of whom had suprapubic pain and all of whom developed symptoms within days after the first exposure. Follow-up examination of three patients within three years of their illness showed that one had had no bladder trouble, one had had slight cystitis and urethritis and one had a carcinoma of the bladder.

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Urine specimens from three patients hospitalized for acute chlordimeform poisoning contained 3-11 μg/ml total amines, 1.2-4.2 μg/ml unconjugated and 1.2-8.7 μg/ml conjugated *para*-chloro-*ortho*-toluidine and 0.04-2.2 μg/ml unmetabolized chlordimeform (Folland *et al.*, 1978).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

One case of bladder carcinoma was reported by Currie (1933) in a worker who, three years earlier, had been exposed to *para*-chloro-*ortho*-toluidine, a metabolite of chlordimeform, resulting in gross haematuria and stranguria.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

No published study on the carcinogenicity of chlordimeform was available.

para-Chloro-*ortho*-toluidine, a metabolite of chlordimeform, was tested for carcinogenicity in two strains of mice and two strains of rats by oral administration in the diet. It was carcinogenic in both strains of mice, producing haemangiosarcomas. The studies in rats were not indicative of a carcinogenic effect, but certain limitations in their design were noted.

Chlordimeform is metabolized to a number of compounds, including *para*-chloro-*ortho*-toluidine, which has been identified in the urine of several animal species and of humans.

The available data were inadequate to evaluate the teratogenicity of chlordimeform to experimental animals.

Chlordimeform was negative in tests for DNA damage or mutagenicity in several cellular systems. No data were available, however, with regard to its mutagenicity in mammals, and no overall evaluation of the mutagenicity of chlordimeform could be made.

4.2 Human data

Chlordimeform was introduced in 1966. Its production, formulation and use as an insecticide on cotton are potential sources of occupational exposure.

No data were available to evaluate the teratogenic or chromosomal effects of chlordimeform in humans.

No case report or epidemiological study of the carcinogenicity of chlordimeform alone was available to the Working Group; however, it should be noted that the latent period since introduction of this compound may be too short for a carcinogenic effect to be detected in humans. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

No data were available on the carcinogenicity of chlordimeform to experimental animals. However, results of experiments in mice provide *sufficient evidence* that *para*-chloro-*ortho*-toluidine, a metabolite of chlordimeform, is carcinogenic to experimental animals. No relevant data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of chlordimeform to humans.

---

[1]This evaluation should be read in conjunction with section 7(*b*)(*c*) of the preamble.

5. References

Ciba-Geigy Corp. (1973a) *Galecron SP. Insecticide-Miticide Sample Label*, Greensboro, NC

Ciba-Geigy Corp. (1973b) *Galecron 4EC. Insecticide-Miticide Sample Label*, Greensboro, NC

Currie, A.N. (1933) Chemical haematuria from handling 5-chloro-*ortho*-toluidine. *J. ind. Hyg.*, *15*, 205-213

FAO (1979) *Pesticide Residues in Food: 1978 Evaluations*, Rome, pp. 51-78

FAO (1980) *Pesticide Residues in Food: 1979 Evaluations*, Rome, pp. 129-135

Folland, D.S., Kimbrough, R.D., Cline, R.E., Swiggart, R.C. & Schaffner, W. (1978) Acute hemorrhagic cystitis. Industrial exposure to the pesticide chlordimeform. *J. Am. med. Assoc.*, *239*, 1052-1055

Hill, D.L., Shih, T.-W. & Struck, R.F. (1979) Macromolecular binding and metabolism of the carcinogen 4-chloro-2-methylaniline. *Cancer Res.*, *39*, 2528-2531

Hollingworth, R.M. (1976) Chemistry, biological activity and uses of formamidine pesticides. *Environ. Health Perspect.*, *14*, 57-69

Hollingworth, R.M., Leister, J. & Ghali, G. (1979) Mode of action of formamidine pesticides: An evaluation of monoamine oxidase as the target. *Chem.-biol. Interactions*, *24*, 35-49

IARC (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 16, *Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals*, pp. 277-285

Kanazawa, J., Ueji, M., Masuda, T., Iizuka, H., Takigawa, N., Otake, A. & Kamano, S. (1976) Residue analysis of eight main pesticides in rice plants. *Nogyo Gijutsu Kenkyusho Hokoku C*, *30*, 65-82 [*Chem. Abstr.*, *85*, 29523p]

Kimbrough, R.D. (1980) Human health effects of selected pesticides, chloroaniline derivatives. *J. environ. Sci. Health*, *B15*, 977-992

Knowles, C.O. (1970) Metabolism of two acaricidal chemical, *N'*-(4-chloro-*o*-tolyl)-*N,N*-dimethylformamidine (chlorphenamidine) and *m*-{[(dimethylamino)methylene]-amino}phenyl methylcarbamate hydrochloride (formetanate). *J. agric. Food Chem.*, *19*, 1038-1047.

Knowles, C.O. & Benezet, H.J. (1979) Inhibition of ethanol and acetate metabolism in mice by chlordimeform and related compounds. *Gen. Pharmacol.*, *10*, 499-503

Knowles, C.O. & Gupta, A.K.S. (1970) *N'*-(4-Chloro-*o*-tolyl)-*N,N*-dimethylformamide-^{14}C (Galecron) and 4-chloro-*o*-toluidine-^{14}C metabolism in the white rat. *J. econ. Entomol.*, *63*, 856-859

Lin, T.H., North, H.H. & Menzer, R.E. (1975) The metabolic fate of chlordimeform (*N*-(4-chloro-*o*-tolyl)-*N'*,*N'*-dimethylformamidine) in human embryonic lung cell cultures. *J. agric. Food Chem.*, *23*, 257-258

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual*, Vol. II, *Methods for Individual Pesticide Residues*, *Pesticide Reg. Sec. 180.285*, Washington DC, US Food & Drug Administration

Matsumura, F. & Beeman, R.W. (1976) Biochemical and physiological effects of chlordimeform. *Environ. Health Perspect.*, *14*, 71-82

National Cancer Institute (1979) *Bioassay of 4-Chloro-o-toluidine Hydrochloride for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 165; DHEW Publ. No. (NIH) 79-1721*), Washington DC, US Government Printing Office

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Olson, K.L., Boush, G.M. & Matsumura, F. (1978) Behavioral effects of perinatal exposure of chlordimeform in rats. *Bull. environ. Contam. Toxicol.*, *20*, 760-768

Robinson, C.P. & Smith, P.W. (1977) Lack of involvement of monoamine oxidase inhibition in the lethality of acute poisoning by chlordimeform. *J. Toxicol. environ. Health*, *3*, 565-568

Robinson, C.P., Smith, P.W., Zelenski, J.D. & Endecott, B.R. (1975) Lack of an effect of interference with amine mechanisms on the lethality of chlordimeform in rat. *Toxicol. appl. Pharmacol.*, *33*, 380-383

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.*, *40*, 19-30

Simmon, V.F., Riccio, E.S., Robinson, D.E. & Mitchell, A.D. (1979) In vitro *Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Fifteen Pesticides* (SRI Project LSU-3493, Contract No. 68-01-2458, prepared for Environmental Protection Agency), Menlo Park, SRI International

Tarone, R.E., Chu, K.C. & Ward, J.M. (1981) Variability in the rates of some common naturally occurring tumors in Fischer 344 rats and (C57BL/6N x 63H/HeN)F_1 (B6C3F_1) mice. *J. natl Cancer Inst.*, *66*, 1175-1181

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976* (*Agricultural Economic Report No. 418*), Washington DC, Economics, Statistics and Cooperatives Service, p. 16

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 180.285, p. 585

US Food & Drug Administration (1980) Food and drugs. *Us Code Fed. Regul.*, *Title 21*, part 193.60, pp. 367, 368; part 561.80, p. 511

US International Trade Commission (1979) *Synthetic Organic Chemicals, US Production and Sales, 1978* (*USITC Publ. 1001*), Washington DC, US Government Printing Office, p. 287

US International Trade Commission (1980) *Imports of Benzenoid Chemicals and Products, 1979* (*USITC Publ. 1083*), Washington DC, US Government Printing Office, p. 110

US International Trade Commission (1981a) *Synthetic Organic Chemicals, US Production and Sales, 1980* (*USITC Publ. 1183*), Washington DC, US Government Printing Office, p. 239

US International Trade Commission (1981b) *Imports of Benzenoid Chemicals and Products, 1980* (*USITC Publ. 1163*), Washington DC, US Government Printing Office, p. 105

Voss, G., Kossmann, K. & Geissbühler, H. (1974) *Chlorodimeform.* In: Zweig, G. & Sherma, J., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VII, New York, Academic Press, pp. 211-230

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity.* In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology. An Agricultural Perspective*, New York, Plenum Press (in press)

Weisburger, E.K., Russfield, A.B., Homburger, F., Weisburger, J.H., Boger, E., Van Dongen, C.G. & Chu, K.C. (1978) Testing of twenty-one environmental aromatic amines or derivatives for long-term toxicity or carcinogenicity. *J. environ. Pathol. Toxicol.*, *2*, 325-356

WHO (1972) Evaluations of some pesticide residues in food. *WHO Pestic. Residue Ser.*, *No. 1*, 3-45

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 95

CHLOROBENZILATE

This substance was considered by a previous Working Group, in October 1973 (IARC, 1974a). Since that time, new data have become available and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 510-15-6

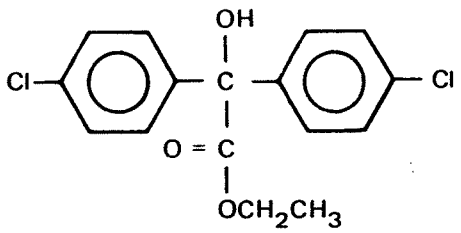
Chem. Abstr. Name: Benzeneacetic acid, 4-chloro-α-(4-chlorophenyl)-α-hydroxy-, ethyl ester

IUPAC Systematic Name: Ethyl 4,4′-dichlorobenzilate

Synonyms: Chlorbenzilat; chlorbenzilate; chlorbenzylate; 4,4′-dichlorobenzilate; 4,4′-dichlorobenzilic acid ethyl ester; ENT 18596; ethyl 4-chloro-α-(4-chlorophenyl)-α-hydroxybenzeneacetate; ethyl *para,para*′-dichlorobenzilate; ethyl 4,4′-dichlorodiphenyl glycollate; ethyl 4,4′-dichlorophenyl glycollate; ethyl di(*para*-chlorophenyl)glycollate; ethyl 2-hydroxy-2,2-bis(3-chlorophenyl)acetate; NCI-C00408

Trade Names: Acar; Acaraben; Acaraben 4E, 250 EC, 500 EC, 25 WP; Akar; Akar 50; Akar 338; Benzilan; Benz-0-Chlor; Compound 338; Folbex; Folbex smokestrips; G338; G23992; Geigy 338; Kop-Mite

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_{14}Cl_2O_3$ Mol. wt: 325.2

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description:* Colourless solid

(*b*) *Boiling-point:* 156-158°C at 0.07 mm Hg

(*c*) *Melting-point:* 35-37°C

(*d*) *Spectroscopy data*: Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1981) have been reported.

(*e*) *Solubility*: Practically insoluble in water; soluble in most organic solvents, including petroleum oils

(*f*) *Volatility*: Vapour pressure, 6.8×10^{-6} mm Hg at 20°C

(*g*) *Stability*: Hydrolysed by alkalies and strong acids to the free carboxylic acid or its salts (Martin, 1971)

1.4 Technical products and impurities

Technical chlorobenzilate is a brown liquid with $d_4^{20} = 1.2816$ (Martin, 1971).

In 1972, the following components were reported in 13 batches of technical chlorobenzilate: chlorobenzilate, 93.8-97.3%; ethyl 4-chlorobenzoate, 0.23-0.47%; 4,4′-dichlorobenzophenone, 0.04-0.23%; chloropropylate, not detected-0.05%; 2,4′-chlorobenzilate, <0.01%; ethyl ether of chlorobenzilate, 0.14-0.59%; 2,2′- and 4,4′-dichlorobenzil, <0.01-0.11% combined; and six unknown components, 0.38% or less for each (WHO, 1973).

Chlorobenzilate has been available as an emulsifiable concentrate and as a 25% water-dispersible powder (Geigy Chemical Corp., undated a). The emulsifiable concentrate contains 45.5% ethyl 4,4′-dichlorobenzilate, 43.5% xylene and 11% inert ingredients (Geigy Chemical Corp., undated b).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Chlorobenzilate was introduced as a commercial chemical in 1952. It is made by the reaction of 4,4′-dichlorobenzilic acid with diethyl sulphate [see IARC, 1974b] (Worthing,

1979) or with ethanol in the presence of a catalyst. Chlorobenzilate was first produced commercially in the US in 1964 (US Tariff Commission, 1965). Only one US company presently produces it and production data are not disclosed [see preamble, section 8(*b*)(ii)]; however, the company is estimated to have an annual production capacity of approximately 900 thousand kg.

Imports of chlorobenzilate through the principal US customs districts were last reported in 1978, when they amounted to 64 thousand kg (US International Trade Commission, 1979), down from the 230 thousand kg imported in 1976 (US International Trade Commission, 1977). Separate data on US exports of chlorobenzilate are not available.

It is not produced commercially in western Europe. Commercial production of chlorobenzilate was begun in Japan in 1977. Production by the sole Japanese producer in 1980 is estimated to have been 44 thousand kg, down from the 102 thousand kg produced in 1978. There have been no imports of chlorobenzilate into Japan in recent years, and exports have been negligible.

(*b*) *Use*

Chlorobenzilate is used as an acaricide in agricultural applications.

In 1976, a total of 318 thousand kg of all miticides except Omite were used by US farmers on major crops, representing 70% of the total quantity of active miticide ingredients used on those crops in that year (US Department of Agriculture, 1978). Separate data on US usage of chlorobenzilate were not available. The results of a survey of citrus growers in 1977 indicated the following approximate usage (thousand kg) of chlorobenzilate: California/Arizona, 23; Florida, 618; and Texas, 121 (Haydu, 1981). In 1978, total US usage of chlorobenzilate is estimated to have been 360 thousand kg, all of which was used on citrus crops.

In countries other than the US, chlorobenzilate is believed to be used on crops other than citrus, and, in the form of smokestrips, as a fumigant to control mites in beehives. In Japan, an estimated 44 thousand kg of chlorobenzilate were used in 1980, 65% of this as an insecticide and 35% as a fumigant.

The Joint Meeting of the FAO Working Party of Experts and the WHO Expert Committee on Pesticide Residues established in December 1968 an acceptable daily intake of chlorobenzilate for humans of 0-0.02 mg/kg bw (WHO, 1969). In 1972, that group recommended the following tolerances for residues of chlorobenzilate on commodities (mg/kg): apples, pears and grapes, 2; citrus fruits, melons and cantaloupes, 1; almonds, walnuts (shelled) and tomatoes, 0.2; milk (from the feeding of treated forage), 0.05 (WHO, 1973). In 1975, an additional tolerance of 5 mg/kg chlorobenzilate on apples was recommended (WHO, 1976).

A Council Directive in 1976 of the European Communities fixed a maximum acceptable level for residues of chlorobenzilate in and on fruit and vegetables at 1.5 mg/kg (Council of the European Communities, 1976). In 1981, there was a proposal to amend the Council Directive and to fix the maximum level for such resiundui at 0.2 mg/kg for nuts and 2 mg/kg for other products (Council of the European Communities, 1982).

In early 1979, the US Environmental Protection Agency (1979) announced that it was initiating action to cancel unconditionally the registrations of the non-citrus uses of

chlorobenzilate and to impose restrictions on the citrus uses (application by certified applicators wearing protective clothing, etc), and limited such use to Florida, Texas, California and Arizona. [No final action appears to have been taken.] Tolerances in the US for residues of chlorobenzilate in or on raw agricultural commodities are presently 0.2-15 ppm (mg/kg) for a variety of 14 commodities, including fruits, nuts, cottonseed and animal meats, fats and meat by-products (US Environmental Protection Agency, 1980a). This compound has been identified as a toxic waste, and persons who generate, transport, treat, store or dispose of it must comply with the regulations of the Federal hazardous waste management programme (US Environmental Protection Agency, 1980b). Shipments of chlorobenzilate in the US are subject to a wide variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1981).

2.2 Occurrence

(*a*) *Natural occurrence*

Chlorobenzilate is not known to occur as a natural product.

(*b*) *Occupational exposure*

Approximately 650-1250 spray applicators and approximately 25 400 citrus fruit pickers in Florida were exposed to chlorobenzilate in 1978. The level of exposure for spray applicators was estimated to be 1 mg/day by inhalation and 12-40 mg/day by dermal exposure in the absence of protective clothing (US Environmental Protection Agency, 1978).

Occupational exposure to chlorobenzilate can be measured by determining the level of *para,para'*-dichlorobenzophenone in the urine (Levy *et al.*, 1981; Brady *et al.*, 1982). Thirty-five urine samples from five workers exposed to chlorobenzilate (and other pesticides) in the Florida citrus industry were found to contain 0.07-6.2 mg/l chlorobenzilate equivalent (analysed as *para,para'*-dichlorobenzophenone), with a mean of 1.3 mg/l (Levy *et al.*, 1981).

No data were available to the Working Group on the number of workers exposed in the two nonagricultural activities most likely to involve exposure to chlorobenzilate, namely, its production and its formulation into the products applied by agricultural workers.

(*c*) *Soil and plants*

In Korea, residues of chlorobenzilate were detected in soil samples taken from citrus orchards which had been under cultivation for 5-30 years, but no values were reported (Lee, 1980).

(*d*) *Food, beverages and animal feeds*

No intake of chlorobenzilate from food was found in the US Total Diet Study (a sampling of US food consumption) (Corneliussen, 1972). Monitoring of specific fruits and vegetables in the US during 1975-1976 showed residues of chlorobenzilate in a few of the samples analysed: 0.04-1.00 mg/kg in large fruits, 0.04-0.10 mg/kg in vine and ear

vegetables, and 0.07-0.08 mg/kg in tomatoes. Typical of the results for whole fresh citrus fruits are those from Florida during 1975-1976: 35% of the samples analysed contained residues of chlorobenzilate, with an average level of 0.36 mg/kg and a range of 0.07-1.06 mg/kg. All of the residue that could be measured occurred in the peel (US Environmental Protection Agency, 1978). Residues of chlorobenzilate have also been measured in orange oil (36-53 mg/kg) and in grapefruit oil (86-91 mg/kg) (US Environmental Protection Agency, 1979).

Chlorobenzilate was measured at a level of 0.2-1.5 mg/kg in pears (Roth, 1958). It was not detected (limit of detection, 0.05 mg/kg) in wine made from white and red grapes containing chlorobenzilate near the accepted maximum residue limit for grapes (FAO, 1978). No residue of chlorobenzilate was detected in milk or orange juice intended for human consumption in the US (US Environmental Protection Agency, 1979).

Residues of this insecticide have been measured in some samples of animal feeds in the US: in silage, 0.51-1.50 mg/kg; in processed animal feed (fruit by-products), 0.11-2.01 mg/kg; and in animal feed made from Florida citrus pulp, 0.39-2.02 mg/kg (US Environmental Protection Agency, 1978).

In Japan, no residue of chlorobenzilate was detected in strawberries (Yamazaki, 1979) or in a variety of fruits and vegetables (Mishima *et al.*, 1979).

2.3 Analysis

Standard methods used for the analysis of chlorobenzilate in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of chlorobenzilate

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract; dechlorinate (metallic sodium)	Potentiometric titration with silver ion	not given	Margot & Stammbach (1964)
Surface of fruits	Extract; saponify; nitrate	Colorimetry	2 μg	Margot & Stammbach (1964)
Human or animal adipose tissue	Macerate; a sequence of extractions; chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Sediment	Dry; chromatograph; extract; chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)

[a]Abbreviations; GC/ECD, gas chromatography/electron capture detection

[b]Confirmation by thin-layer chromatography or extraction *p* values, where the *p* value (determined by distributing a solute between equal volumes of two immiscible phases) is defined as the fraction of the total solute partitioning into the upper phase.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 and the same numbers of (C57BL/6 x AKR)F_1 mice were treated with chlorobenzilate (purity, 99.3%) as follows: At the age of seven days they received by gavage a single dose of 215 mg/kg bw in 0.5% gelatine. Not taking into account subsequent weight gains, this treatment was repeated daily until the animals were weaned, at the age of four weeks. Then chlorobenzilate, mixed into the diet to give a final concentration of 603 mg/kg, was fed until the animals were 83 weeks. [The dose was the maximum tolerated dose for infant and young mice but not necessarily that for adults.] Appropriate negative (vehicle or untreated) and positive (using seven known carcinogens) controls were also included in the study. Hepatomas were found in mice of both strains, but only in males, the incidence being 9/17 in (C57BL/6 x C3H/Anf)F_1 mice compared with 8/79 in male controls and 7/17 in (C57BL/6 x AKR)F_1 mice compared with 5/90 in male controls. The incidences of other neoplasms (i.e., pulmonary tumours and lymphomas) were similar in both treated and control animals (National Technical Information Service, 1968; Innes *et al.*, 1969). [The Working Group noted that the slides of this study were reviewed and reinterpreted (Reuber, 1977, 1980). Apart from differences concerning the terminology of hepatic and pulmonary tumours, gastric lesions were also reported. Of female (C57BL/6 x C3H/Anf)F_1 mice receiving chlorobenzilate, 10/18 animals developed carcinomas of the forestomach, while in controls papillomas of the forestomach (6/17) but no carcinomas were detected.]

Groups of 50 male and 50 female B6C3F_1 mice, approximately six weeks old, were fed chlorobenzilate (technical-grade, purity at least 90%; impurities not specified) dissolved in corn oil and mixed into a powdered diet. Preliminary experiments failed to establish chlorobenzilate levels in feed that were well tolerated during the entire course of the study; hence, in order to ascertain adequate survival rates, treatment had to be interrupted repeatedly. There were several exposure levels: Males were maintained on feed containing chlorobenzilate at concentrations of 6000 mg/kg of diet for nine weeks and 4000 mg/kg of diet for the subsequent 69 weeks (referred to as 'low-dose'), for a time-weighted average concentration of 4231 mg/kg of diet; 'high-dose' males received 12 000 mg/kg for nine weeks and 8000 mg/kg continuously for the subsequent 43 weeks and with interruptions for the following 26 weeks (i.e., one week on control diet alternated with four weeks of chlorobenzilate feeding), to give a time-weighted average concentration of 7846 mg/kg of diet. Low-dose females received feed containing chlorobenzilate at a concentration of 3200 mg/kg continuously for 78 weeks; high-dose females received 6400 mg/kg for the same period and with the same schedule of interruptions as described above for high-dose males, to give a time-weighted average concentration of 5908 mg/kg. For the remaining 12 (males) or 13 (females) weeks of the study, control diet (powdered chow supplemented with 2% corn oil) was fed. Twenty additional mice of each sex, serving as controls, received this feed for the entire duration of the 90-week bioassay. A significantly increased incidence of hepatocellular carcinoma was found in animals of both sexes at all levels of chlorobenzilate exposure: Males, 4/19 controls, 32/48 low-dose ($p = 0.001$), 22/45 high-dose ($p = 0.034$); females, 0/20 controls, 11/49 low-dose ($p =$

0.016), 13/50 high-dose (p = 0.007) (p values calculated by the Fisher exact test) (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, approximately six-weeks old, were fed chlorobenzilate (technical-grade, purity at least 90%; impurities not specified) dissolved in corn oil and mixed into a powdered diet. Preliminary experiments failed to establish exposure levels that were well tolerated during the entire course of the study; hence, in order to ascertain adequate survival rates, treatment had to be interrupted repeatedly. There were several exposure levels: Males and females were maintained for 78 weeks on feed containing chlorobenzilate at concentrations of 1600 and 1175 mg/kg, respectively (referred to as 'low-dose'); and 'high-dose' animals were fed 3200 mg/kg continuously for 57 weeks (males) or 2350 mg/kg for 62 weeks (females). Thereafter, animals were given the control diet for one week, alternated with four weeks of chlorobenzilate feeding, for 21 and 16 weeks for males and females, respectively. For the remaining 32 (males) or 33 (females) weeks, all experimental groups received the control diet (powdered chow supplemented with 2% corn oil), as did 50 male and 50 female rats, referred to as controls, during the entire 111-week bioassay. Adrenocortical adenomas occurred in both males (0/46 controls; 6/49 low-dose, p = 0.016; 3/49 high-dose, nonsignificant) and females (0/50 controls; 2/47 low-dose, nonsignificant; 5/47 high-dose, p = 0.024). The incidence of haemangiosarcomas was lower in both males (12/49 controls; 4/50 low-dose, p = 0.049; 1/50 high-dose, p = 0.001) and females (4/50 controls; 1/49 low-dose; 0/50 high-dose) (National Cancer Institute, 1978). [Attention was drawn to the short duration of treatment, the unusually low incidence of cortical adenomas among the controls, the absence of a dose-response relationship among males and the poorly understood significance of the occurrence of cortical adenomas in aged rats in general. This study was subsequently reviewed and the assertion made (Reuber, 1980) that, in addition, there was a significant increase in the incidence of tumours at all sites in animals of both sexes, in the endocrine organs of males and in the liver of females. However, the extent of information provided to support this assertion and the lack of explanation for the obvious discrepancy between the actual numbers in the original report and in its republication make an evaluation impossible.]

Groups of 20 CF weanling rats of each sex were fed a diet containing either 0, 50 (males only) or 500 mg/kg technical chlorobenzilate for two years. Some 13-14 rats/treatment group and 16 male and 12 female controls were still alive at the end of the experiment. No difference in tumour incidence between treated and control animals was reported (Horn *et al.*, 1955). [The Working Group noted the small number of animals, the low dose given and the inadequate histopathological evaluation of the study.]

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 1000 mg/kg bw chlorobenzilate (99.3% pure) in dimethyl sulphoxide on the 28th day of life and were observed until they were about 78 weeks of age, at which time 16, 16, 16 and 18 mice were still alive in the four groups, respectively. Several control groups comprised untreated animals and animals treated with gelatine, corn oil or dimethyl sulphoxide. No significant increase in the incidence of tumours was observed in treated animals compared with controls (National Technical Information Service, 1968). [The Working Group noted that a negative result following a single s.c. injection of a compound is not an adequate basis for discounting carcinogenicity.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The acute oral LD_{50} of chlorobenzilate in mice, rats (Horn *et al.*, 1955) and hamsters (Cabral *et al.*, 1979) is about 700 mg/kg bw. In rats and mice toxic symptoms included depressed motor activity, lachrymation and a rapid wheezing respiration. Death was preceded by coma (Horn *et al.*, 1955).

Dogs tolerated daily oral doses of 64 mg/kg bw for 35 weeks, and rats, 500 mg/kg in the diet for two years (Horn *et al.*, 1955). In female Wistar rats 100 mg/kg chlorobenzilate in the diet for four weeks produced liver enlargement (McKinley & Grice, 1960). In the chronic feeding studies described in section 3.1 of this monograph, there was a dose-related depression in mean body weight in both species, and testicular atrophy was observed in male Osborne-Mendel rats fed 1600 or 3200 mg/kg in the diet (time-weighted average concentration over 78 weeks for the high dose: 2995 mg/kg) (National Cancer Institute, 1978).

Effects on reproduction and prenatal toxicity

A 25% water-dispersible powder of chlorobenzilate was mixed into a diet to give concentrations of 25 or 50 mg/kg chlorobenzilate, and the diet was fed to male and female rats for three generations (two matings per generation). The numbers of pups at birth and weaning from two litters of each generation, the number of uterine implants and the body weights of the progeny showed no significant deviation from control values. No teratogenic change was observed in the offspring (Bartsch *et al.*, 1971).

Absorption, distribution, excretion and metabolism

When daily doses of 12.8 mg/kg bw chlorobenzilate were given orally to male mongrel dogs on five days a week for 35 weeks, approximately 40% of the total dose was excreted unchanged or as metabolites in the urine. No significant storage of chlorobenzilate was reported in the depot fat of rats or dogs (Horn *et al.*, 1955).

Chlorobenzilate is metabolized by rat liver homogenates to *para,para'*-dichlorobenzilic acid, *para,para'*-dichlorobenzyhydrol, *para*-chlorobenzoic acid and *para,para*-dichlorobenzophenone (Knowles & Ahmad, 1971).

Mutagenicity and other short-term tests

Chlorobenzilate [purity not stated], without exogenous metabolic activation, did not induce reverse mutations in the two auxotrophic strains a21 and a742 of *Serratia marcescens* or induce forward mutations to galactose protrophy [details not given] or to streptomycin resistance (Fahrig, 1974) in *Escherichia coli*. Chlorobenzilate ($\geqslant$97% pure) did not induce reverse mutations in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100, with or without an Aroclor-induced rat liver microsomal preparation (Rinkus & Legator, 1980).

Chlorobenzilate did not induce mitotic gene conversion at the *ade* 2 or *trp* 5 loci of *Saccharomyces cerevisiae* (Fahrig, 1974) [details not given].

(*b*) *Humans*

Toxic effects

One case of systemic poisoning due to exposure to chlorobenzilate was reported in a worker involved in mixing and spraying the compound on trees; he developed muscle pains, ataxia, mild delirium and fever (Ravindran, 1978).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Chlorobenzilate and its metabolites, present in the urine of exposed workers, can be oxidized to *para,para'*-dichlorobenzophenone, and this can be analysed to monitor human exposure. Using this method, 35 urine samples from five workers exposed to chlorobenzilate (and other pesticides) in the Florida citrus industry were found to contain 0.07-6.2 mg/l chlorobenzilate equivalent (analysed as *para,para'*-dichlorobenzophenone), with a mean of 1.3 mg/l (Levy *et al.*, 1981; Brady *et al.*, 1982).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chlorobenzilate was tested for carcinogenicity by administration in the diet in three strains of mice and in two strains of rats. It induced hepatocellular carcinomas in both sexes of mice of one strain and in males of the two other strains. The data on rats were inadequate for evaluation.

Although no adverse effect was observed on reproduction in a three-generation study of rats, the teratogenic potential of chlorobenzilate has not been fully determined.

Chlorobenzilate was not mutagenic to *Salmonella typhimurium* with or without exogenous metabolic activation. Data from studies on other organisms were considered insufficient for evaluation, and no overall evaluation of the mutagenicity of chlorobenzilate could be made.

4.2 Human data

Chlorobenzilate was introduced in 1952. Its production, formulation and use as an acaricide on citrus and other crops are sources of potential exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of chlorobenzilate in humans.

No case report or epidemiological study of the carcinogenicity of chlorobenzilate alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

Results of the experiments in mice provide *limited evidence* that chlorobenzilate is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of chlorobenzilate to humans.

5. References

Bartsch, E., Eberoe, D., Ramsteiner, K., Tomann, A. & Spindler, M. (1971) The carbinole acaricides: Chlorobenzilate and chloropropylate. *Residue Rev.*, *39*, 1-88

Brady, S.S., Levy, K.A., Enos, H.F., Duncan, R.C. & Pfaffenberger, C.D. (1980) *Development of methodology for determining human exposure to chlorobenzilate.* In: Plimmer, J.R., ed., *Pesticide Residues and Exposure* (*American Chemical Society Symposium Series No. 182*), Washington DC, American Chemical Society, pp. 105-118

Cabral, J.R.P., Raitano, F., Mollner, T., Bronczyk, S. & Shubik, P. (1979) Acute toxicity of pesticides in hamsters (Abstract no. 384). *Toxicol. appl. Pharmacol.*, *48*, A192

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *L340*, 26-31

Commission of the European Communities (1982) Proposal for a Council Directive amending Annex II to Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *C95*, 6-10

Corneliussen, P.E. (1972) Pesticide residues in total diet samples (VI). *Pestic. Monit. J.*, *5*, 313-330

[1] This evaluation should be read in conjunction with p. 18 of the preamble.

Fahrig, R. (1974) *Comparative mutagenicity studies with pesticides.* In: Montesano, R. & Tomatis, L., eds, *Chemical Carcinogenesis Essays* (*IARC Scientific Publications No. 10*), Lyon, International Agency for Research on Cancer, pp. 161-181

FAO (1978) *Pesticide Residues in Food: 1977 Evaluations*, Rome, pp. 85-86

Geigy Chemical Corp. (undated a) *Chlorobenzilate* (*Tech. Bull. No. 65-1*), Ardsley, NY, Geigy Agricultural Chemicals Division

Geigy Chemical Corp. (undated b) *Chlorobenzilate Miticide Sample Label*, Ardsley, NY, Geigy Agricultural Chemicals Division

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem.*, *54*, 1040-1082

Haydu, J.J. (1981) *Pesticide Use in United States Citrus Production, 1977* (*ESS Staff Report No. AGESS 810203*), Washington DC, US Department of Agriculture, pp. 10, 17, 24

Horn, H.J., Bruce, R.B. & Paynter, O.E. (1955) Toxicology of chlorobenzilate. *Agric. Food Chem.*, *3*, 752-756

IARC (1974a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, Lyon, pp. 75-81

IARC (1974b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man,* Vol. 4, *Some Aromatic Amines, Hydrazine and Related Substances,* N-*Nitroso Compounds and Miscellaneous Alkylating Agents,* Lyon, pp. 277-281

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst.*, *42*, 1101-1114

Knowles, C.O. & Ahmad, S. (1971) Comparative metabolism of chlorobenzilate, chloropropylate, and bromopropylate acaricides by rat hepatic enzymes. *Can. J. Physiol. Pharmacol., 49,* 590-597

Lee, K.S. (1980) A survey of pesticide residues of citrus fruits and citrus orchard soil in Jeju Island. Part 2. On the pesticide residue of citrus orchard soil. *Hanguk Nonghwa Hakhoe Chi*, *23*, 184-188 [*Chem. Abstr.*, *94*, 115984g]

Levy, K.A., Brady, S.S. & Pfaffenberger, C.D. (1981) Chlorobenzilate residues in citrus worker urine. *Bull. environ. Contam. Toxicol.*, *27*, 235-238

Margot, A. & Stammbach, K. (1964) *Chlorobenzilate.* In: Zweig, G., ed, *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. II, *Insecticides*, New York, Academic Press, pp. 66-73

Martin, H., ed. (1971) *Pesticide Manual*, 2nd ed., Ombersely, British Crop Protection Council, p. 97

McKinley, W.P. & Grice, H.C. (1960) Identification of pesticide residues in extracts of fruit, vegetables and animal fats. III. Metabolites of chlorinated hydrocarbon pesticides in animal depot fat. *J. Assoc. off. agric. Chem.*, *43*, 725-731

Mishima, Y., Sugano, T. & Konishi, Y. (1979) Survey on pesticidal residues. 5. Organochlorine pesticides in soil, fruits and vegetables (Jpn.). *Sendaishi Eisei Shikenshoho*, *7*, 143-146 [*Chem. Abstr.*, *93*, 68827a]

National Cancer Institute (1978) *Bioassay of Chlorobenzilate for Possible Carcinogenicity* (*NCI-CG-TR-75; DHEW Publ. No. (NIH) 78-1325*), Bethesda, MD

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study* (*PB-223159*), Washington DC, US Department of Commerce

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Ravindran, M. (1978) Toxic encephalopathy from chlorobenzilate poisoning: Report of a case. *Clin. Encephalography*, *9*, 170-172

Reuber, M.D. (1977) Carcinomas of the liver and forestomach in mice ingesting chlorobenzilate. *Digestion*, *16*, 308-316

Reuber, M.D. (1980) Carcinogenicity of chlorobenzilate in mice, rats and dogs. *Clin. Toxicol.*, *16*, 67-98

Rinkus, S.J. & Legator, M.S. (1980) *The need for both in vitro and in vivo systems in mutagenicity screening.* In: de Serres, F.J. & Hollaender, A., eds, *Chemical Mutagens: Principles and Methods for Their Detection*, Vol. 6, New York, Plenum Press, pp. 365-473

Roth, F.J. (1958) A one-shot, two-filter application of the Schechter method for mixed DDT and chlorobenzilate spray residues. *J. Assoc. off. anal. Chem.*, *41*, 662-673

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976* (*Agricultural Economic Report No. 418*), Washington DC, Economics, Statistics and Cooperatives Service, p. 24

US Department of Transportation (1981) Listing of hazardous materials. *US Code Fed. Regul.*, *Title 49*, part 172; *Fed. Regist.*, *46*, 17738, 17739

US Environmental Protection Agency (1978) *Exposure Analysis for Chlorobenzilate*, Washington DC, Office of Pesticide Programs, pp. 1-22

US Environmental Protection Agency (1979) Chlorobenzilate. *Fed. Regist.*, *44*, 9548-9567

US Environmental Protection Agency (1979) Chlorobenzilate. Notice of intent to cancel registrations and deny applications for registration of pesticide products containing chlorobenzilate pursuant to section 6(b)(1) and 3(d) of Federal Insecticide, Fungicide, and Rodenticide Act. *Fed. Regist.*, *44*, 9548-9567

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.109, p. 540

US Environmental Protection Agency (1980b) Hazardous waste management system: Identification and listing of hazardous waste. *US Code Fed. Regul., Title 40*, part 261; *Fed. Regist., 45*, 33084, 33122-33126, 33132

US International Trade Commission (1977) *Imports of Benzenoid Chemicals and Products, 1976 (USITC Publ. 828)*, Washington DC, US Government Printing Office, p. 101

US International Trade Commission (1979) *Imports of Benzenoid Chemicals and Products, 1976 (USITC Publ. 990)*, Washington DC, US Government Printing Office, p. 97

US Tariff Commission (1965) *Synthetic Organic Chemicals, US Production and Sales, 1964 (TC Publ. 167)*, Washington DC, US Government Printing Office, p. 174

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, Sect. 5A(1)(a); 11B; 12B; 12C

WHO (1969) *1968 Evaluations of Some Pesticide Residues in Food (WHO/Food Add./69.35)*, Geneva, 42-57

WHO (1973) 1972 Evaluations of some pesticide residues in food. *WHO Pestic. Residue Ser., No. 2*, 131-141

WHO (1976) 1975 Evaluations of some pesticide residues in food. *WHO Pestic. Residue Ser., No. 5*, 105-107

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 106

Yamazaki, T. (1979) Dicofol residue in strawberry and analysis by high-performance liquid chromatography. *Fukuoka-shi Eisei Shikenshoho 1978, 4*, 91, 92 [*Chem. Abstr., 93*, 24624c]

DICOFOL

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 115-32-2

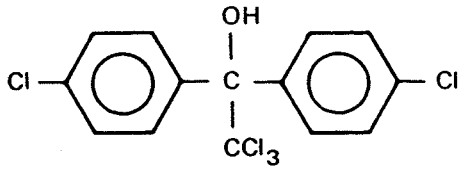
Chem. Abstr. Name: Benzenemethanol, 4-chloro-α-(4-chlorophenyl)-α-(trichloromethyl)-

IUPAC Systematic Name: 2,2,2-Trichloro-1,1-bis(4-chlorophenyl)ethanol

Synonyms: 1,1-Bis(chlorophenyl)-2,2,2-trichloroethanol; 1,1-bis(*para*-chlorophenyl)-2,2,2-trichloroethanol; 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol; CPCA; di-(*para*-chlorophenyl)trichloromethylcarbinol; 4,4′-dichloro-α-(trichloromethyl)benzhydrol; DTMC; ENT 23,648; NCI CO0486; 2,2,2-trichloro-1,1-bis(*para*-chlorophenyl)ethanol; 2,2,2-trichloro-1,1-di(4-chlorophenyl)ethanol

Trade Names: Acarin; Carbax; Cekudifol; Childion; Decofol; Dichlorokelthane; FW 293; Hilfol; Hilfol 18.5 EC; Keltane; Kelthane; *para,para'*-Kelthane; Kelthane A, AP, EC, MF, & 35; Kelthane Dust Base; Kelthanethanol; Milbol; Mitigan

1.2 Structural and molecular formulae and molecular weight



$C_{14}H_9Cl_5O$ Mol. wt: 370.5

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless solid

(*b*) *Melting-point*: 78.5-79.5°C

(*c*) *Spectroscopy data*: Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1981) have been reported.

(*d*) *Solubility*: Practically insoluble in water; soluble in most aliphatic and aromatic solvents

(*e*) *Stability:* Hydrolysed by alkalis to 4,4′-dichlorobenzophenone and chloroform [see IARC, 1979] (Metcalf, 1981). After ultra-violet and sunlight irradiation of apples treated with dicofol, traces of 4,4′-dichlorobenzophenone were found (Archer & Toscano, 1972).

(*f*) *Reactivity*: Inhibits lipase *in vitro* (Christensen & Riedel, 1981)

1.4 Technical products and impurities

Technical dicofol is a brown viscous oil with a d^{25} of 1.45 (Worthing, 1979). Its purity was reported to be 82-88% (WHO, 1969). The content of 1,1-dichloro-2,2-bis(*para*-chlorophenyl)ethylene (DDE) [see IARC, 1974] found in dicofol formulations was calculated to be 1-2% (WHO, 1975). The active component of technical dicofol is reported to be a mixture of approximately 80% 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol, and 20% 1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethanol and the major impurity was 1,1,1,2-tetrachloro-2,2-bis(4-chlorophenyl)ethane (Baum *et al.*, 1976). Up to 18 impurities were reported to be components of various samples of technical dicofol (Rothman, 1980).

Dicofol is available as 18.5 and 35% active water-dispersible powders, as 18.5 and 42% active emulsifiable concentrates, as a 20% active emulsion, as a 30% active dust base, and in a combination with the acaracide tetradifon (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Dicofol was introduced as a commercial chemical in 1955. It can be made by the chlorination of 1,1-bis(4-chlorophenyl) ethanol or from 1,1,1,2-tetrachloro-2,2-bis(4-chlorophenyl)ethane either by the reaction of silver acetate followed by hydrolysis of the resulting acetate ester (Worthing, 1979) or by reaction with aqueous formic acid (Sittig, 1980).

Dicofol was first produced commercially in the US in 1957 (US Tariff Commission, 1958); commercial production has not been reported since 1978, when one company produced it in undisclosed amounts (see preamble, section 8(*b*)(ii)) (US International Trade Commission, 1979), although production in 1971 is estimated to have been 1.8

million kg. Imports of dicofol through the principal US customs districts amounted to 1.18 million kg in 1980 (US International Trade Commission, 1981), continuing an upward trend from the 5 thousand kg imported in 1976 (US International Trade Commission, 1977).

Dicofol is produced by two companies in Italy and by one company in Spain. It is not produced in commercial quantities in Japan. In 1980, Japanese imports of dicofol amounted to 403 thousand kg, while only 102 thousand kg were imported in 1976 and none in 1977. Japanese imports of formulations containing dicofol have also been increasing in recent years.

This compound is also believed to be produced by one company in Israel.

(*b*) *Use*

Dicofol is used as an acaricide (miticide) in agricultural and nonagricultural applications.

In 1976, a total of 318 thousand kg of all miticides except Omite were used by US farmers on major crops, representing 70% of the total quantity of active miticide ingredients used on those crops in that year, and 772 thousand kg miticides were estimated to have been used on other crops (US Department of Agriculture, 1978). Separate data on US usage of dicofol were not available. The results of a survey of citrus growers in 1977 indicated the following approximate usage (thousand kg) of dicofol: California/Arizona, 37; Florida, 167; and Texas, 60 (Haydu, 1981). In 1978, total US usage of dicofol is estimated to have been 1.27 million kg, 50% of which was used on cotton, 29% on citrus, 13% on deciduous fruits/nuts, 4% on ornamentals, and 4% in home and garden applications. In 1979, 264 thousand kg were used in California, with 59% on cotton and 11% on beans (California Department of Food & Agriculture, 1980).

An estimated 459 thousand kg of dicofol were used in Japan in 1980.

The Joint Meeting of the FAO Working Party of Experts and the WHO Expert Committee on Pesticide Residues established in December 1968 an acceptable daily intake of dicofol for humans of 0.0-0.025 mg/kg bw (WHO, 1969). In 1974, that group recommended the following tolerances for residues of dicofol on commodities (mg/kg): strawberries and tomatoes, 1; cucumbers and gherkins, 2; and other fruits and vegetables, 5 (WHO, 1975).

In 1981, a proposal was submitted to the Council of the European Communities for amendment of the Council Directive of 23 November 1976 to fix the following maximum acceptable levels for dicofol residues (mg/kg): cucumber and gherkins, 2; tomatoes and strawberries, 1; other fruit, 3; and other vegetables, 0.5 (Commission of the European Communities, 1982).

Tolerances in the US for residues of dicofol in or on raw agricultural commodities are presently 0.1-30 mg/kg for a variety of 47 commodities, including fruits, nuts, beans, melons, hops, cottonseed, and peppermint and spearmint hays (US Environmental Protection Agency, 1980a). A residue tolerance of 45 mg/kg is established for dried tea for human consumption when present as a result of application of the insecticide to growing tea (US Food & Drug Administration, 1980). The US Environmental Protection Agency (1980b) announced in April 1980 that it had begun to prepare registration standards for dicofol. Notification must be given to the Environmental Protection Agency

of any discharges into waterways of 2270 kg or more of dicofol (US Environmental Protection Agency, 1980c).

Shipments of dicofol in the US are subject to a variety of labelling, packaging, quantity and shipping restrictions, consistent with its designation as a hazardous material (US Department of Transportation, 1980).

2.2 Occurrence

(a) *Natural occurrence*

Dicofol has not been reported to occur as a natural product.

(b) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to dicofol, nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to dicofol, namely its production and its formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that approximately 117 thousand US workers in 65 nonagricultural industries were exposed to dicofol.

(c) *Air*

Air emissions from the manufacture of dicofol in one US plant have been reported to be 0.5 kg/1000 kg produced (Archer *et al.*, 1978).

(d) *Water and sediments*

Dicofol was not detected (limit of detection, 0.01 μg/l) in stream water samples from 11 agricultural watersheds in southern Ontario, Canada, during 1975-1977, even though a small amount had been used in those areas in 1975 (Braun & Frank, 1980). Up to 0.397 mg/l of dicofol has been detected in industrial wastewater in the USSR (National Cancer Institute, 1978).

(e) *Soil and plants*

In the US National Soils Monitoring Program, in which cropland soils from 37 states were analysed in 1972, dicofol residues were found in seven samples from California and Florida (0.5% of all samples) at levels of 0.06-2.15 mg/kg dry weight (Carey *et al.*, 1979). In US soils with a known history of dicofol application, average residues were in the range of 0.00-3.48 mg/kg; samples from only four of the 17 sites contained mean residues greater than or equal to 2.00 mg/kg. Dicofol was not detected in soils with no known application of the pesticide (Lyman & Anderson, 1979).

Harris *et al.* (1977) reported 1.5 mg/kg dicofol residues in soil samples taken from an apple orchard and 3.3 mg/kg in those from an orchard converted to a municipal park in south-western Ontario, Canada, in 1974. Another study in Canada in 1972-1975 reported levels in dried soil of < 0.0004 (not detected)-2.40 mg/kg in 31 apple orchards, < 0.0004

(not detected)-0.32 mg/kg in 12 sour-cherry orchards, < 0.0004 (not detected)-0.32 mg/kg in 16 sweet-cherry orchards and < 0.0004 (not detected)-1.54 mg/kg in 11 peach orchards in southern Ontario and the Niagara Peninsula. No dicofol was detected in soil samples from 16 vineyards on the Niagara Peninsula. Previous studies had reported levels of 4.0 mg/kg in 1964 and 3.3 mg/kg in 1969 in apple-orchard soil samples from south-western Ontario (Frank *et al.*, 1976).

A Japanese study reported dicofol residues in the soils of vegetable patches (Mishima *et al.*, 1979). Dicofol was also detected in citrus orchard soil samples from Jeju Island, South Korea; residue levels decreased with increasing soil depth and increased with longer cultivation periods (Lee, 1980a).

(*f*) *Food, beverages and animals feeds*

In the Total Diet Program of the US Food and Drug Administration (a sampling of US food consumption), dicofol was detected in food composites of fruits and leafy vegetables from 20-32 cities during the years 1971-1976 at levels of traces-0.77 mg/kg (Manske & Johnson, 1975, 1977; Johnson & Manske, 1976, 1977; Johnson *et al.*, 1981). Dicofol was detected in 1972 in the US National Soils Monitoring Program in one sample from a standing crop of an unspecified type of dry bean at a level of 0.15 mg/kg dry weight (Carey *et al.*, 1979).

A total diet study in Canada reported dicofol levels of 0-0.028 mg/kg in composite samples of leafy vegetables, garden fruits, and fruits from Winnipeg, Manitoba in 1972 and levels of 0-0.070 mg/kg in samples of fruits from Toronto, Ontario in 1973 (Smith *et al.*, 1975). A total diet study of foods from five Canadian regions during the years 1976-1978 reported dicofol residues in fruits at levels of 10 µg/kg in Vancouver, British Columbia and 20 µg/kg in Toronto, Ontario. Daily intake of dicofol (µg/person) was reported to be 0.1 in leafy vegetables from Toronto and 2.4 and 0.6 in fruits from Toronto and Vancouver, respectively. Average dietary intakes of dicofol by Canadians (µg/kg bw) have been estimated as follows: 0.054 in Ottawa, Ontario, 1969; 0.016 in Halifax, Nova Scotia, 1971; 0.020 in Winnipeg, Manitoba, 1972; 0.050 in Toronto, Ontario, 1973; and 0.002 in Canada as a whole, 1976-1978 (McLeod *et al.*, 1980). A survey of agricultural commodities on the Canadian market reported mean levels of 5 µg/kg in apples and 52 µg/kg in oranges in 1972-1975 (Coffin & McKinley, 1979).

Dicofol has been detected in strawberries sold in Fukuoka, Japan, at levels of 0-0.91 mg/kg (average, 0.19 mg/kg) (Yamazaki, 1979), and at levels below an unspecified tolerance limit in the peel of apples and oranges harvested in Hokkaido, Japan (Shitara *et al.*, 1978).

All citrus fruits collected on Jeju Island, South Korea, contained dicofol residues at levels of traces-0.007 mg/kg; dicofol residues tended to be higher in fruit from orchards that had been under cultivation for longer (Lee, 1980b). Citrus fruits imported from Argentina, Cyprus, Israel, Italy, Morocco, South Africa, Spain and the US and collected at the wholesale level in France had dicofol residues in the range of 0.005-0.2 mg/kg (Mestres *et al.*, 1977).

Fruits and vegetables acquired over a one-year period from a market in Valencia, Spain, in 1971-1972 for a total diet study contained dicofol residues at levels of 0-0.2 mg/kg. Use of pesticides is higher in Valencia than in the rest of Spain (Carrasco *et al.*, 1976).

2.3 Analysis

Standard methods used for the analysis of dicofol in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of dicofol

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Technical grade and formulations	Hydrolyse (alcoholic potassium hydroxide)	Titration	not given	Gordon Schuckert
	Hydrolyse (alcoholic potassium hydroxide)	Potentiometric titration	not given	Baum *et al.* (1976); Horwitz (1980)
	Melt; dissolve (methanol)	HPLC/UV	not given	Rothman (1980)
Fruits, vegetables, tea, alfalfa, cotton, milk and animal tissue	Extract (hexane); concentrate; hydrolyse (basic solution); react with pyridine/aqueous sodium hydroxide	Colorimetry	0.02-0.1 mg/kg	Gordon & Schuckert (1964); Markus & Puma (1973)
Human or animal adipose tissue	Macerate (sand); extract (petroleum ether); extract (acetonitrile); dilute (water); partition (petroleum ether); concentrate; chromatograph (Florisil); concentrate	GC/ECD; confirmation (TLC)	not given	Watts (1980)
Soil	Dissolve (water); add isopropanol; extract (benzene); chromatograph (Florisil); evaporate and dissolve (hexane); dry (sodium sulphate)	GC/ECD	0.01 mg/kg	Lyman & Anderson (1979)

[a]Abbreviations: HPLC/UV, high-performance liquid chromatography/ultra-violet detection; GC/ECD, gas chromatography/electron capture detection; TLC, thin-layer chromatography

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks old, were fed diets containing dicofol [technical-grade, purity not specified and impurities not determined].

Groups of 20 males and 20 females were kept as controls. Males in the low-dose group received levels that varied between 150 and 300 mg/kg of diet resulting in a time-weighted average dietary level of 264 mg/kg; males in the high-dose group received levels between 300 and 600 mg/kg of diet, resulting in a time-weighted average level of 528 mg/kg. Females in the low-dose group received dietary levels between 55 and 150 mg/kg, resulting in a time-weighted average of 122 mg/kg; females in the high-dose group received between 110 and 300 mg/kg, resulting in a time-weighted average level of 243 mg/kg. All animals were treated for 78 weeks and followed for an additional 14-15 weeks before they were killed, at the same time as their respective controls. Of the male mice, 38/50 at the high dose and the same number at the low dose and only 7/20 controls were still alive at the end of the experiment. Among the females, 48/50 at the high dose, 42/50 at the low dose, and 19/20 of the controls were still alive at that time. The only dose-related effect observed was an increased incidence of tumours of the liver in males: hepatocellular carcinomas occurred in 3/18 controls, 22/50 ($p = 0.035$) of the low-dose males and 35/47 ($p < 0.001$) of the high-dose males (Cochran-Armitage test for positive trend: $p < 0.001$). No excess of hepatocellular carcinomas was observed in exposed female mice (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, six weeks old, were fed dietary levels of 380 or 760 mg/kg technical dicofol [purity not specified and impurities not determined]. Groups of 20 male and 20 female rats were kept as controls. Females were exposed for 78 weeks and then observed for an additional 34 weeks before they were killed. Males received the initial doses of dicofol for 19 weeks, increased to either 500 or 1000 mg/kg of diet for 59 weeks, whereupon the animals were followed for an additional 34 weeks before they were killed. The time-weighted average concentrations of dicofol in the diet of male rats were 471 and 942 mg/kg of diet. Of the males, 36/50 at the high dose, 32/50 at the low dose and 11/20 of the control group survived for at least 100 weeks; of the females, 44/50 at the high dose, 46/50 at the low dose and 16/20 of the controls survived that time. No significant difference was seen between treated and control rats when the data were analysed by the Fisher exact test and the Cochran-Armitage test (National Cancer Institute, 1978). [The Working Group noted the short duration of the treatment period for male and female rats and the short period of observation of male rats.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The acute oral LD_{50} of technical-grade dicofol (20% in corn oil) in adult male and female rats was 809 and 684 mg/kg bw, respectively (Smith *et al.*, 1959); LD_{50} values of dicofol in rats ranged between 575 and 2000 mg/kg bw by the oral route and from 100 to 1230 mg/kg bw by the dermal route (Ben-Dyke *et al.*, 1970). The oral LD_{50} of technical-grade dicofol (20% in corn oil) is >4000 mg/kg bw in dogs and 1810 mg/kg bw in rabbits. The percutaneous LD_{50} in male rabbits is 2100 mg/kg bw for technical-grade dicofol (30% in dimethyl phthalate) and >10 ml/kg bw for the emulsion concentrate (18.5% active ingredient) (Smith *et al.*, 1959).

In male rabbits, the minimal lethal dose after single daily cutaneous application on five days a week for 13 weeks was found to be 1.0 ml/kg bw for technical-grade dicofol (30%

in dimethyl phthalate); 0.1 ml/kg bw for the emulsion concentrate (18.5% active ingredient); and 500 mg/kg bw for the water-dispersible powder (18.5% active ingredient) mixed with two parts of water. Technical-grade dicofol in dimethyl phthalate and the emulsion concentrate were both irritating to the skin; the water-dispersible powder was only mildly irritating (Smith *et al.*, 1959). [It is possible that the toxic properties of the dimethyl phthalate vehicle influenced the results of these tests.]

In rats fed diets containing up to 2500 mg/kg dicofol (technical-grade, 80% pure) for three months, survival was affected in animals of both sexes fed levels of 1250 or 2500 mg/kg, and growth was inhibited in females given 100 mg/kg and more and in males given 1250 or 2500 mg/kg (Smith *et al.*, 1959). In a two-year feeding study in rats, survival was unaffected in animals given dietary levels of less than 1000 mg/kg dicofol (technical-grade, 80% pure) (the highest level tested), but growth was depressed in females fed 250 mg/kg and more and in males fed 500 mg/kg and more (Smith *et al.*, 1959).

In the chronic feeding studies described in section 3.1 of this monograph, there was a dose-related depression in mean body weight in female mice from about week 40 and in both male and female rats (National Cancer Institute, 1978).

No effect was seen in dogs fed diets containing 300 mg/kg or less dicofol (technical-grade, 80% pure) for one year. Death occurred in some animals fed levels of 900 mg/kg but the survivors showed no toxic effect (Smith *et al.*, 1959).

Effects on reproduction and prenatal toxicity

A dietary concentration of 7 mg/kg technical dicofol [impurities unspecified] fed to mice for three generations produced alopecia and cephalic defects in 12-day-old offspring of the third generation (An der Lan, 1964). These results were not confirmed in a subsequent study (Brown, 1972) in mice fed diets containing 7-500 mg/kg of technical dicofol [impurities unspecified] containing 84.8% active ingredient. The mice were bred to produce five generations with two litters at each generation, and, in addition, a third litter at the fifth generation, which was killed at term for teratologic assessment. The 500 mg/kg level caused reductions in body weight of offspring and in litter size and high postnatal mortality, but concentrations of 225 mg/kg and lower produced no effect.

Dietary concentrations of 100 mg/kg of the active ingredient had no effect on reproduction in rats but adversely affected preimplantation stages of embryonal development (Brown, 1972). A dicofol formulation containing 20% active ingredient as an emulsion in water was administered orally at a concentration of 5 or 10 mg/kg bw per day for two months to rats which were then inseminated three times per week during the third month, resulting in a higher ratio of nonpregnant to total inseminated rats than in controls (Trifonova & Gladenko, 1980).

Absorption, distribution, excretion and metabolism

After a single i.p. dose of 230 mg/kg bw dicofol or repeated oral administration (74.8 mg/kg bw per day for 40 days) to rats, dicofol and 4,4′-dichlorobenzophenone (DCB) were found to be stored in fat and skeletal muscle; the parent compound and DCB were excreted predominantly *via* the faeces. In the acute experiment, dicofol and DCB accumulated initially in the liver; the concentration then declined after day 15. In the same study in rats, 1,1-dichloro-2,2-bis(*para*-chlorophenyl)ethylene (DDE) [see IARC, 1974] and DCB were identified in a variety of tissues and in the faeces (Brown *et al.*, 1969). [The

possibility that DDE was a contaminant of dicofol and not a metabolite cannot be established unequivocally because the impurities in the dicofol preparation used in this study were not specified.] In rats fed 10 mg/kg dicofol in the diet for 10 weeks, the concentration in the adipose tissue of females was 31.2 mg/kg and that in males 13.9 mg/kg (Smith *et al.*, 1959).

After oral administration of radiolabelled dicofol to mice, radioactivity associated with water-soluble metabolites was detected in the urine (Tabata *et al.* 1979). Dicofol fed at levels of 100-200 mg/kg in the diet to male rats for two weeks was shown to be an inducer of mixed-function oxidase enzymes in the liver (Den Tonkelaar & Van Esch, 1974).

Mutagenicity and other short-term tests

Dicofol [purity not stated] was negative in the *rec* assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*) in the presence or absence of an induced rat liver microsomal preparation (Kawachi *et al.*, 1980) [details not given]. It was not mutagenic to *Escherichia coli* WP2 *trp*$^-$ in a simple spot test in the absence of exogenous metabolic activation (Ashwood-Smith *et al.*, 1972; Shirasu *et al.*, 1976). No mutagenic effect was detected when dicofol (homogeneous by thin-layer chromatography) was tested in the reversion mutation assay, using *Salmonella typhimurium* strains TA98 and TA100, either in the presence or absence of an Aroclor-induced mouse liver microsomal preparation (Planche *et al.*, 1979). A similar negative result, using dicofol of unspecified purity, with and without metabolic activation [unspecified], was obtained by Kawachi *et al.* (1980) [details not given].

Exposure of *Vicia faba* root meristem cells to dicofol was reported to produce the formation of anaphase bridges and relatively scarce micronuclei (Gopalan & Njagi, 1979) [abstract, details not given].

In a table summarizing work carried out in the Japanese cooperative programme [details not given], dicofol was reported to be ineffective in inducing chromosomal aberrations in Chinese hamster lung fibroblast cells, but positive in the micronucleus test in rat bone-marrow cells (Kawachi *et al.*, 1980).

(*b*) *Humans*

Toxic effects

Green-house workers exposed to dicofol and trichlorfon [see monograph, this volume] were reported to suffer frequently from allergic dermatitis (Zolotnikova & Somov, 1978).

Effects on reproduction and prenatal exposure

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Dicofol (technical-grade) was tested for carcinogenicity in mice and rats by administration in the diet. It induced hepatocellular carcinomas in male mice. The study in rats was considered to be inadequate for evaluation.

Dicofol (technical-grade), even when given at high doses, had no effect on reproduction or foetal development in mice; however, high doses in rats appeared to have an adverse effect on preimplantation stages of embryonal development.

Dicofol was negative in bacterial tests for mutagenicity and for DNA damage, with or without exogenous metabolic activation. The experimental protocols and results of studies with eukaryotes were not presented in adequate detail for an evaluation to be made. No overall evaluation of the mutagenicity of dicofol could be made.

4.2 Human data

Dicofol was introduced in 1955. Its production, formulation and widespread use as an acaricide on cotton and edible crops are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of dicofol in humans.

No case report or epidemiological study of the carcinogenicity of dicofol alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

Results of the experiment in mice provide *limited evidence* that dicofol is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of dicofol to humans.

---

[1]This evaluation should be read in conjunction with p. 18 of the preamble.

5. References

An der Lan, H. (1964) Toxicological problems of modern plant prophylactics (Ger.). *Umschau, 21*, 649-652

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization (EPA-600/2-78-004d)*, Washington DC, US Environmental Protection Agency, p. 134

Archer, T.E. & Toscano, R.A. (1972) Fate of kelthane residues on apple pomace exposed to drying in the dark, sunlight and ultraviolet light irradiation. *Bull. environ. Contam. Toxicol., 7*, 353-357

Ashwood-Smith, M.J., Trevino, J. & Ring, R. (1972) Mutagenicity of dichlorvos. *Nature, 240*, 418-420

Baum, H., Black, R.F. & Kurtz, C.P. (1976) Dicofol: Collaborative study of the hydrolyzable chlorine method. *J. Assoc. off. anal. Chem., 59*, 1109-1112

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970). *World Rev. Pestic. Control, 9*, 119-127

Braun, H.E. & Frank, R. (1980) Organochlorine and organophosphorus insecticides: Their use in eleven agricultural watersheds and their loss to stream waters in southern Ontario, Canada, 1975-1977. *Sci. total Environ., 15*, 169-192

Brown, J.R. (1972) *The effect of dietary Kelthane on mouse and rat reproduction.* In: *Proceedings of the 2nd International IUPAC Congress of Pesticide Chemistry*, Vol. 6, New York, Gorden & Breach, pp. 531-548

Brown, J.R., Hughes, H. & Viriyanondha, S. (1969) Storage, distribution, and metabolism of 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol. *Toxicol. appl. Pharmacol., 15,* 30-37

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 93-95

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1979) Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). *Pestic. Monit. J., 12*, 209-229

Carrasco, J.M., Cunat, P., Martinez, M. & Primo, E. (1976) Pesticide residues in total diet samples, Spain - 1971-72. *Pestic. Monit. J., 10*, 18-23

Christensen, G.M. & Riedel, B. (1981) Effect of water pollutants and other chemicals upon the activity of lipase in vitro. *Arch. environ. Contam. Toxicol., 10*, 357-363

Coffin, D.E. & McKinley, W.P. (1979) *Chemical contaminants of foods.* In: Chiba, H., Fujimaki, M., Iwai, K., Mitsuda, H. & Morita, Y., eds, *Proceedings of the Fifth International Congress of Food Science and Technology (Developments in Food Science 2)*, Tokyo, Kodansha Ltd & Amsterdam-Oxford-New York, Elsevier, pp. 163-169

Commission of the European Communities (1982) Proposal for a Council Directive amending Annex II to Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities, C95*, 6-10

Den Tonkelaar, E.M. & Van Esch, G.J. (1974) No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. *Toxicology, 2*, 371-380

Frank, R., Braun, H.E., Ishida, K. & Suda, P. (1976) Persistent organic and inorganic pesticide residues in orchard soils and vineyards of southern Ontario. *Can. J. Soil Sci., 56*, 463-484

Gopalan, H.N.B. & Njagi, G.D.E. (1979) Cytogenetic studies in *Vicia faba* with some insecticides, fungicides and herbicides (Abstract no. Ca-7). *Environ. Mutagenesis, 1*, 141-142

Gordon, C.F. & Schuckert, R.J. (1964) *Kelthane*. In: Zweig, G., ed, *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. II, *Insecticides*, New York, Academic Press, pp. 263-271

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem., 54*, 1040-1082

Harris, C.R., Chapman, R.A. & Miles, J.R.W. (1977) Insecticide residues in soils on fifteen farms in southwestern Ontario, 1964-1974. *J. environ. Sci. Health, B12*, 163-177

Haydu, J.J. (1981) *Pesticide Use in United States Citrus Production, 1977 (ESS Staff Report No. AGESS 810203)*, Washington DC, US Department of Agriculture, pp. 10, 17, 24

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 104-105

IARC (1974) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 5, *Some Organochlorine Pesticides*, Lyon, pp. 83-124

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, Lyon, pp. 401-427

Johnson, R.D. & Manske, D.D. (1976) Pesticide residues in total diet samples (IX). *Pestic. Monit. J., 9*, 157-169

Johnson, R.D. & Manske, D.D. (1977) Pesticide residues in total diet samples (XI). *Pestic. Monit. J., 11*, 116-131

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975 - July 1976. *Pestic. Monit. J., 15*, 54-69

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan*. In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, International Agency for Research on Cancer, pp. 323-330

Lee, K.S. (1980a) A survey of pesticide residues of citrus fruits and citrus orchard soil in Jeju Island. Part 2. On the pesticide residue of citrus orchard soil (Korean). *Hanguk Nonghwa Hakhoe Chi*, *23*, 184-188 [*Chem. Abstr.*, *94*, 115984g]

Lee, K.S. (1980b) A survey of pesticide residues of citrus fruits and citrus orchard soil in Jeju Island. Part 1. Pesticide residue of citrus fruits (Korean). *Hanguk Nonghwa Hakhoe Chi*, *23*, 178-183 [*Chem. Abstr.*, *94*, 137934t]

Lyman, W.R. & Anderson, R.J. (1979) Dicofol residues in United States soils having a known history of its use as a miticide, 1974. *Pestic. Monit. J.*, *13*, 72-74

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII). *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual*, Vol. 2, *Methods for Individual Pesticide Residues*, Pesticide Reg. Sec. 120.163, Washington DC, US Food & Drug Administration

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Mestres, R., Illes, S., Campo, M. & Tourte, J. (1977) A multiple residue method for citrus fruits: Its technique and some data. *Proc. int. Soc. Citriculture*, *2*, 426-429

Metcalf, R.L. (1981) *Insect control technology*. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley & Sons, pp. 413, 461, 485

Mishima, Y., Sugano, T. & Konishi, Y. (1979) Survey on pesticidal residues. 5. Organochlorine pesticides in soil, fruits, and vegetables (Jpn.). *Sendai-shi Eisei Shikenshoho*, *7*, 143-146 [*Chem. Abstr.*, *93*, 68827a]

National Cancer Institute (1978) *Bioassay of Dicofol for Possible Carcinogenicity* (*NCI-CG-TR-90; DHEW Publ. No. (NIH) 78-1340*), Bethesda, MD

National Institute for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards*, Cincinnati, OH, p. 77

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, pp. 1372-1373 (generics included); 903 (generics excluded)

NIH/EPA Chemical Information System (19810 *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Planche, G., Croisy, A., Malaveille, C., Tomatis, L. & Bartsch, H. (1979) Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethyl acetate (Kelthane acetate) as mutagens in *Salmonella typhimurium* and of 1,1-bis(*p*-chlorophenyl)ethylene oxide, a likely metabolite, as an alkylating agent. *Chem.-biol Interactions*, *25*, 157-175

Rothman, A.M. (1980) High performance liquid chromatographic analysis of dicofol acaricide. *J. Assoc. off. anal. Chem.*, *63*, 1296-1299

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.*, *40*, 19-30

Shitara, Y., Saito, T. & Hori, Y. (1978) Agricultural chemical residues in foods. XI. Pesticide residues in agricultural products produced in Hokkaido (Japan) 1977 (Jpn.). *Hokkaidoritsu Eisei Kenkyusho Ho*, *28*, 57-62 [*Chem. Abstr.*, *91*, 54713g]

Sittig, M., ed. (1980) *Pesticide Manufacturing and Toxic Material Control Encyclopedia*, Park Ridge, NJ, Noyes Data Corporation, pp. 296-299

Smith, D.C., Leduc, R. & Tremblay, L. (1975) Pesticide residues in the total diet in Canada. IV. 1972 and 1973. *Pestic. Sci.*, *6*, 75-82

Smith, R.B., Jr, Larson, P.S., Finnegan, J.K., Haag, H.B., Hennigar, R.G. & Cobey, F. (1959) Toxicological studies on 2,2-bis-(chlorophenyl)-2,2,2-trichloroethanol (Kelthane). *Toxicol. appl. Pharmacol.*, *1*, 119-134

Tabata, K., Miyata, T. & Saito, T. (1979) Water soluble metabolites of dicofol in mouse urine. *Appl. Entomol. Zool.*, *14*, 490-493

Trifonova, T.K. & Gladenko, I.N. (1980) Determination of gonado- and embryotoxicity of pesticides (Russ.). *Veterinariya (Moscow)*, *6*, 58-59

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976 (Agricultural Economic Report No. 418)*, Washington DC, Economics, Statistics, and Cooperative Service, p. 24

US Department of Transportation (1980) Identification numbers, hazardous wastes, hazardous substances, international descriptions, improved descriptions, forbidden materials, and organic peroxides. *US Code Fed. Regul., Title 49*, parts 171-174, 176, 177; *Fed. Regist.*, *45*, 34560, 34622

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.163, p. 558

US Environmental Protection Agency (1980b) Reregistration of pesticides. *US Code Fed. Regul., Title 40*, part 162; *Fed. Regist.*, *45*, 26370-26373

US Environmental Protection Agency (1980c) Protection of environment. *US Code Fed. Regul., Title 40*, parts 116, 117, pp. 35-50

US Food & Drug Administration (1980) Food and drugs. *US Code Fed. Regul., Title 21*, part 193.80, p. 368

US International Trade Commission (1977) *Imports of Benzenoid Chemicals and Products, 1976* (*USITC Publ. 828*), Washington DC, US Government Printing Office, p. 102

US International Trade Commission (1979) *Synthetic Organic Chemicals, US Production and Sales, 1978* (*USITC Publ. 1001*), Washington DC, US Government Printing Office, p. 286

US International Trade Commission (1981) *Imports of Benzenoid Chemicals and Products, 1980* (*USITC Publ. 1163*), Washington DC, US Government Printing Office, p. 106

US Tariff Commission (1958) *Synthetic Organic Chemicals, US Production and Sales, 1957*, Washington DC, US Government Printing Office, p. 139

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, sect. 5A(1)(a); 12B

WHO (1969) *1968 Evaluation of Some Pesticide Residues in Food* (*WHO/Food Add./69.35*), Geneva, pp. 115-127

WHO (1975) 1974 Evaluation of some pesticide residues in food. *WHO Pestic. Residue Ser., No. 4*, 247-251

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 183

Yamazaki, T. (1979) Dicofol residue in strawberry and analysis by high-performance liquid chromatography (Jpn.). *Fukuoka-shi Eisei Shikenshoho, 4*, 91-92 [*Chem. Abstr., 93*, 24624c]

Zolotnikova, G.P. & Somov, B.A. (1978) On the role of pesticides in the occurrence of occupational dermatitis in workers of hothouses. *Vestn. Dermatol. Venerol., 4*, 76-79

MALATHION

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 121-75-5

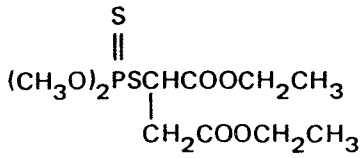
Chem. Abstr. Name: Butanedioic acid,[(dimethoxyphosphinothioyl) thio]-, diethyl ester

IUPAC Systematic Name: *S*-l,2-Bis(ethoxycarbonyl)ethyl *O,O*-dimethyl phosphorodithioate

Synonyms: *S*-[1,2-Bis(carbethoxy)ethyl] *O,O*-dimethyl dithiophosphate; *S*-1,2-bis(ethoxycarbonyl)ethyl-*O,O*-dimethyl thiophosphate; carbofos; NCI COO215; *S*-(1,2-dicarbethoxyethyl)- *O,O*-dimethyldithiophosphate; dicarbethoxyethyl *O,O*-dimethyl phosphorodithioate; *S*-[1,2-di(ethoxycarbonyl)ethyl] dimethyl phosphorothiolothionate; diethyl (dimethoxyphosphinothioylthio) butanedioate; diethyl(dimethoxyphosphinothioylthio)succinate; diethyl mercaptosuccinate, *O,O*-dimethyl dithiophosphate, *S*-ester; diethyl mercaptosuccinate, *O,O*-dimethyl phosphorodithioate, diethyl mercaptosuccinate, *O,O*-dimethyl thiophosphate; diethyl mercaptosuccinic acid *O,O*-dimethyl phosphorodithioate; *O,O*-dimethyl *S*-[1,2-bis-(ethoxycarbonyl)ethyl] dithiophosphate; *O,O*-dimethyl *S*-(1,2-dicarbethoxyethyl) dithiophosphate; *O,O*-dimethyl *S*-(1,2-dicarbethoxyethyl) phosphorodithioate; *O,O*-dimethyl *S*-(1,2-dicarbethoxyethyl) thiothionophosphate; *O,O*-dimethyl *S*-1,2-di(ethoxycarbamyl)ethyl phosphorodithioate; *O,O*-dimethyldithiophosphate diethylmercaptosuccinate; diethyl mercaptosuccinate *S*-ester with *O,O*-dimethyl phosphorodithioate; *O,O*-dimethyl phosphorodithioate of diethyl mercaptosuccinate; ENT 17,034; mercaptosuccinic acid diethyl ester, *S*-ester with *O,O*-dimethyl phosphorodithioate; mercaptothion; mercaptotion; phosphorodithioic acid *O,O*-dimethyl ester, *S*-ester with diethyl mercaptosuccinate

Trade Names: 8059 HC; American Cyanamid 4,049; Calmathion; Carbetovur; Carbetox; Carbophos; Celthion; Chemathion; Cimexan; Compound 4049; Cythion; Detmol MA; El 4049; Emmatos; Emmatos Extra; Ethiolacar; Etiol; Extermathion; Fog 3; Formal; For-Mal; Forthion; Fosfothion; Fosfotion; Four Thousand Forty Nine; Fyfanon; Hilthion; Hilthion 25WDP; Insecticide No. 4049; Karbofos; Kopthion; Kypfos; Malacide; Malafor; Malagran; Malakill; Malamar; Malamar 50; Malaphele; Malasol; Malaspray; Malathion E50; Malathiozol; Malathiozoo; Malathon; Malathyl LV Concentrate & ULV Concentrate; Malatol; Malatox; Maldison; Malmed; Malphos; Maltox MLT; Moscarda; Oleophosphothion; Ortho Malathion; Phosphothion; Prioderm; Sadofos; Sadophos; SF60; Siptox 1; Siptox I; Sumitox; TAK; TM-4049; Vegfru Malatox; Vetiol; Zithiol

1.2 Structural and molecular formulae and molecular weight



$C_{10}H_{19}O_6PS_2$ Mol. wt: 330.3

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Clear, amber liquid

(*b*) *Boiling-point*: 156-157°C at 0.7 mm Hg

(*c*) *Melting-point*: 2.85°C

(*d*) *Density*: d_4^{25} 1.23

(*e*) *Refractive index:* n_D^{25} 1.4985

(*f*) *Spectroscopy data:* Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1982) have been reported.

(*g*) *Solubility*: Slightly soluble in water (145 mg/l at room temperature); miscible with most organic solvents but has limited solubility in petroleum oils

(*h*) *Volatility*: Vapour pressure, 4 x 10^{-5} mm Hg at 30°C

(*i*) *Stability*: Easily hydrolysed above pH 7.0 and below pH 5.0 (Metcalf, 1981). Hydrolysis produces thiomalic acid and dimethyl thiophosphate (Mulla *et al.*, 1981). Reacts with heavy metals; incompatible with alkaline materials (Thomson, 1979)

1.4 Technical products and impurities

Technical-grade malathion is about 95% pure (Worthing, 1979). The following impurities were identified in one sample: *O,O,O*-trimethyl phosphorothioate; diethyl maleate; *O,O,S*-trimethyl phosphorodithioate; diethyl thiomalate; diethyl 2-methylthiosuccinate; *O,O,O,O*-tetramethyl trithiopyrophosphate; and an unidentified isomer of malathion (Warner, 1975).

Malathion is available as emulsifiable concentrates with various levels of active ingredient; as 25 and 50% active water-dispersible powders; dusts (usually 4% active); and 92% active ultra-low volume (ULV) concentrates (Worthing, 1979). In Japan, technical malathion contains a minimum of 93% active ingredient.

The WHO (1978) has specified that the content of isomalathion (the *S*-methyl isomer of malathion, i.e., dicarbethoxyethyl *O*-methyl *S*-methyl phosphorodithioate) in water-dispersible powders of malathion shall not exceed 1.8% of the nominal malathion content after storage of the powder for six days at 55°C.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

A review on malathion includes extensive information on production processes and uses in the early 1970s (Midwest Research Institute, 1975).

(a) *Production*

Malathion was introduced as a commercial chemical in 1950. It is made by the reaction of *O,O*-dimethyl hydrogen phosphorodithioate with diethyl maleate in the presence of hydroquinone to prevent polymerization of the maleate (Worthing, 1979). Malathion was first produced commercially in the US in 1952 (US Tariff Commission, 1953). Only one US company presently produces it and its production in 1978 is estimated to have been 14 million kg; the company's production capacity is approximately 16 million kg. Imports of malathion through the principal US customs districts were last reported in 1977, when they amounted to 2.9 thousand kg (US International Trade Commission, 1978). Separate data on US exports are not published, but exports in 1978 are estimated to have been 5 million kg.

Malathion is believed to be produced by one company each in Denmark, France, Italy and Spain.

The only company that produced malathion in Japan ceased production in 1980. Production in 1979 amounted to 505 thousand kg; none was produced in 1976 and 163 thousand kg in 1977. Japanese imports of malathion since 1976 have ranged from 63 thousand kg in 1977 to 600 thousand kg in 1980; exports were negligible.

Several companies market malathion in India but the number that manufacture it is not known; 1264 thousand kg were produced in 1980-1981 (GIFAP, 1982). Malathion is also believed to be produced by one company each in Brazil, Mexico and Taiwan.

(*b*) *Use*

Malathion is used as a broad spectrum insecticide and acaricide in a wide variety of agricultural and nonagricultural applications, including the control of lice, flies and mosquitoes.

In 1976, 772 thousand kg of malathion were used by US farmers on major crops, representing 1.3% of the total quantity of active insecticide ingredients used on those crops in that year. Another 501 thousand kg were used as a livestock insecticide, making

malathion the third largest volume livestock insecticide, after toxaphene and methoxychlor. Separate data on use of malathion as a miticide in 1976 are not available, but a total of 318 thousand kg of all miticides except Omite were used by US farmers on major crops, representing 70% of the total quantity of miticides used on those crops in that year, and 772 thousand kg of miticides were estimated to have been used on other crops (US Department of Agriculture, 1978).

In 1978, total US usage of malathion is estimated to have been 6.9 million kg, 18% of which was applied to cotton, 13% for aquatic use, 11% for home and garden use, 9% on vegetables, 9% on lawns and turf, 9% for miscellaneous field crops, 7% for livestock and poultry use, 5% on ornamental plants, 5% on alfalfa, and a total of 14% for commercial/household and industrial establishments, tobacco, soya beans, sorghum, citrus, corn, deciduous fruits/nuts and wheat. The usage is believed to be distributed approximately equally among governmental use (vector control), household use, and agricultural use. It is estimated that malathion is used in 3.12 million households in the US (Savage *et al.*, 1981).

In 1979, 254 thousand kg were used in California, 51% of which was for structural pest control (California Department of Food & Agriculture, 1980).

The estimated 600 thousand kg of malathion used in Japan in 1980 was principally as an insecticide on rice, vegetables and fruits.

The Joint Meeting of the FAO Working Committe on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues in March 1965 established an acceptable daily intake of malathion for humans of 0-0.02 mg/kg bw (WHO, 1965). In 1966, that group recommended the following tolerances for residues of malathion on commodities (mg/kg): fruit, dried fruit, nuts, cereals and cereal products, 8; vegetables (leafy), 6; vegetables other than leafy, 3; and citrus, 4 (WHO, 1967). In 1973, a tolerance of 8 mg/kg was recommended on pulses (dried beans, lentils) (WHO, 1974), and in 1977, a tolerance of 20 mg/kg was recommended on bran of rye and wheat (FAO, 1978).

The Council of the European Communities has fixed a maximum acceptable level for residues of malathion in and on fruit and vegetables at 3.0 mg/kg for vegetables, except root vegetables, and at 0.5 mg/kg for other products (Commission of the European Communities, 1976).

Tolerances in the US for residues of malathion in or on raw agricultural commodities are presently at 0.1-135 ppm (mg/kg) for a variety of 222 commodities, including milk, eggs, grasses, hays, straws, seeds, grains, forages, fruits, vegetables, beans, nuts and animal meats, fats and by-products. In addition, tolerances are in effect of 12 mg/kg on processed ready-to-eat raisins (resulting from drying of grapes on treated trays and from application to grapes before harvest); of 0.6 mg/kg in refined safflower oil (resulting from application to the growing safflower plant); of 50 mg/kg in dehydrated citrus pulp for cattle feed (as the result of the application of the pesticide to bagged citrus pulp during storage); and of 10 mg/kg in nonmedicated cattle feed concentrate blocks (resulting from its application as a pesticide to paper used in packaging the blocks) (US Environmental Protection Agency, 1980a,b; US Food & Drug Administration, 1980a,b).

Notification must be given to the US Environmental Protection Agency (1980c) of any discharge into waterways of 4.54 kg or more of malathion. The effluent guidelines and standards of that Agency require that the average daily effluent value of all regulated

organic active ingredients manufactured at a malathion production plant over 30 consecutive days not exceed 0.0018 kg/1000 kg of organic pesticide chemical (US Environmental Protection Agency, 1980d). Shipments of malathion in the US are subject to a variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1980).

Permissible levels of malathion in the working environment have been established in at least 12 countries by regulation or recommended guidelines. These standards are listed in Table 1.

Table 1. National occupational exposure limits for malathion[a]

Country	Year	Air concentration (mg/m^3)	Interpretation[b]	Status
Belgium	1978	10	Ceiling[c]	Regulation
Bulgaria	1971	0.6	Maximum[c]	Regulation
Finland	1975	10	Ceiling	Regulation
Federal Republic of Germany	1979	15	TWA	Guideline
Italy	1978	10	TWA[c]	Guideline
The Netherlands	1978	10	Ceiling	Regulation
Poland	1976	15	Ceiling	Regulation
Romania	1975	10	TWA[c]	Regulation
		15	Maximum	Regulation
Switzerland	1978	10	TWA[c]	Regulation
US (OSHA)	1978	15	TWA	Regulation
		5000	Ceiling (30 min)[c]	Regulation
USSR	1977	0.5	Maximum[c]	Regulation
Yugoslavia	1971	0.5	Ceiling[c]	Regulation
ACGIH[d,e]	1981	10	TWA[c]	Guideline

[a]From International Labour Office (1980)

[b]TWA - time-weighted average

[c]A notation points out that percutaneous absorption may contribute to overall exposure.

[d]The OSHA regulation and the ACGIH guideline are used in the US for both agricultural and nonagricultural workers.

[e]From American Conference of Governmental Industrial Hygienists (1981)

2.2 Occurrence

(a) *Natural occurrence*

Malathion is not known to occur as a natural product.

(b) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to malathion, nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to malathion,

namely, its production and its formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that approximately 126 thousand US workers in 73 nonagricultural industries were exposed to malathion.

The potential dermal and respiratory exposures to malathion have been reported for workers who were applying malathion spray (0.03-0.08% active ingredient), malathion dust (4%) and malathion aerosol (2.5-5%), and for field workers during and after such applications. Mean dermal exposures ranged from 2.1 mg/h for field workers to 67 mg/h for employees using high-pressure power hand-guns; mean respiratory exposures ranged from <0.02 mg/h for field workers to 0.73 mg/h for employees using a power duster (Wolfe *et al.*, 1967). Those authors also summarized published studies of potential dermal and respiratory exposures to malathion (Table 2).

Table 2. Potential dermal and respiratory exposures to malathion[a]

Activity	Exposure	
	Dermal (mg/h)	Respiratory (mg/h)
Operating aerosol machine	(6.6)[b]	(0.3)
Air-blast spraying fruit orchards	2.5	0.08
Air-blast spraying fruit orchards	30	0.11
Persons outdoors during air application to populated area	(0.89)	(0.055)
Persons indoors during air application to populated area	(0.25)	(0.012)

[a]From Wolfe *et al.* (1967)

[b]Values shown in parentheses were not included in the original papers but were calculated.

Potential dermal and respiratory exposures of individuals were also measured during and for one hour after aerial spraying with malathion (0.46 lbs per acre [0.5 kg/ha]) for mosquito control. Atmospheric concentrations of malathion averaged 0.067 mg/m^3 in unprotected areas, 0.056 mg/m^3 in semisheltered areas, and 0.014 mg/m^3 indoors. Dermal exposure was 0.45-2.82 μg/cm^2 for a man working outdoors and 0.25-0.56 μg/cm^2 for a man working indoors (Caplan *et al.*, 1956).

Five workers applying 2.5% or 5% malathion for two weeks as an aerosol cloud for mosquito control were exposed to mean atmospheric concentrations ranging from 0.55 mg/m^3 at 69 m distance from the aerosol generator to 7.70 mg/m^3 at 9 m. The highest total exposures measured were 0.50-1.33 mg/kg bw for dermal exposure and 0.16-0.32 mg/kg bw for respiratory exposure. The man who received the highest exposures was working in an atmosphere with an average air concentration of 3.3 mg/m^3 (Culver *et al.*, 1956). The exposure of four operators was estimated during spraying of malathion (2 g/l of 25% water-dispersible powder) on fields of grain and vegetables. Breathing-zone samples had a mean concentration of 0.59 mg/m^3; the mean respiratory exposure was found to be 0.08 mg/h and the mean dermal dose, 2.5 mg/h (National Institute for Occupational Safety & Health, 1976).

Concentrations of malathion observed in work areas and in the air of an agricultural community as a result of crop treatment have been reported as 0.01-0.60 mg/m^3 and 0.1

ng/m^3, respectively. The highest value recorded in a community as a result of the application of malathion was 0.00014 mg/m^3 (Hayes, 1971).

Malathion has been detected at a level of 126-130 ng/m^3 in ambient air samples from insecticide storage rooms, and at levels of 48-106 ng/m^3 from the ambient air of vehicles used in commercial pest control (Wright & Leidy, 1980).

(*c*) *Air*

Concentrations of malathion in air determined in studies on occupational exposure are given in section (*b*).

This insecticide has been detected in the air of Orlando, Florida, at a maximum level of 2.0 ng/m^3 (Midwest Research Institute, 1975). Emissions from malathion manufacture in one US plant were reported to contain 0.5 kg/1000 kg produced (Archer *et al.*, 1978).

(*d*) *Water and sediments*

Malathion was detected at concentrations of 0.24-1.8 µg/l on five occasions in 1976-1977 in stream water in southern Ontario as a result of indoor use of malathion in mushroom houses with drainage access to the stream (Braun & Frank, 1980). Residues of malathion have reportedly been identified in the Rhine River in the Federal Republic of Germany at levels of 0.01-0.1 µg/kg (Midwest Research Institute, 1975). In studies in the Virgin Islands, where malathion is used extensively for insect control, only two of 49 water samples taken from cisterns contained malathion, at levels of 0.14 and 0.01 µg/kg (Midwest Research Institute, 1975; National Research Council, 1977).

(*e*) *Soil and plants*

In the US National Soils Monitoring Program (1970 and 1972), the following levels of malathion were detected in crops that were mature and/or ready for harvest (mg/kg): alfalfa/bur clover, 0.03-0.26; corn stalks, 0.04-0.25; cotton (stalks, green bolls), 0.01-2.17; grass hay, 0.02-0.22; mixed hay, 0.02-0.09; silage, 2.64; and sorghum (grain, stalks), 0.04-0.29 (Crockett *et al.*, 1974; Carey *et al.*, 1979).

Malathion was detected at levels of 0.08-0.19 mg/kg in cropland soil in several US states (Carey *et al.*, 1978, 1979) and at levels of <0.01-0.02 mg/kg in soil from farms in south-western Ontario (Harris *et al.*, 1977).

In a US study, three samples from 105 lots of imported flowers were found to contain a mean concentration of 0.19 mg/kg malathion (Morse *et al.*, 1979).

(*f*) *Food, beverages and animal feeds*

The US Department of Agriculture (1981) reported that no malathion was found in 1980 in 23 samples of liver from food-producing animals.

'Market basket' surveys conducted by the US Food and Drug Administration revealed that most of the organophosphorus insecticide residues in food are malathion: the four-year average concentration of malathion for 1965-1969 was 0.00013 mg/kg, whereas the total concentration of all organophosphate residues was 0.00017 mg/kg. The highest levels were present in grain and cereal products (National Research Council, 1977).

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration for the period June 1971 to July 1976, the following levels of malathion were detected in food composites from US cities (mg/kg; 'trace' implies that

residues were detected and qualitatively confirmed at too low a level to be quantified, the limit of quantitation varying with food class): grain and cereal products, trace-0.099; fruits, trace-0.073; leafy vegetables, 0.005-0.020; oils, fats and shortening, trace-0.492; and sugar and adjuncts, trace-0.04 (Johnson & Manske, 1976, 1977; Johnson *et al.*, 198l; Manske & Johnson, 1975, 1977).

In a study of pesticide residues in the total diet in Canada, the estimated daily intake (μg/person) of malathion in food composites from five Canadian regions was in the range of 0.4-3.9 from cereals, 0-0.2 from fruits and 0-0.6 from oils and fats. The minimum detectable level of malathion was 3 μg/kg. Average dietary intake of malathion by Canadians for the period 1970 to 1978 ranged from <0.001-0.042 μg/kg bw (McLeod *et al.*, 1980). Malathion was detected at average levels of 0.007 mg/kg in cereals, 0.004 mg/kg in legumes, and 0.016-0.031 mg/kg in oils and fats from Winnipeg, Manitoba in 1972; and at a level of 0.013 mg/kg in cereals from Toronto, Ontario in 1973 (Smith *et al.*, 1975).

In the period August 1974-July 1975, malathion was detected in infant food composites obtained in 10 US cities at levels of 0.006-0.173 mg/kg; it was found at levels of 0.004-0.125 mg/kg in 'toddler' food composites (Johnson *et al.*, 1979).

In a study of food in Calcutta, India, the average concentration of malathion in all samples was 2.3 mg/kg. It was detected at a mean concentration of 2.6 mg/kg in vegetables, 2.5 mg/kg in animal products, 1.6 mg/kg in fruits, grains and water, and 1.3 mg/kg in condiments. In other surveys carried out in Calcutta and other parts of India, this pesticide was detected in food at mean concentrations of 0.4-19 mg/kg (Mukherjee *et al.*, 1980).

Malathion was detected at levels of less than 0.10 mg/kg in several samples of vegetable oils, pears and apples obtained from a Spanish market. The highest level detected in vegetable oils was 0.04 mg/kg (Carrasco *et al.*, 1976). Levels of 0.004-0.25 mg/kg were detected in citrus fruits in France (Mestres *et al.*, 1977). Residues of malathion in samples of rye and wheat from the Federal Republic of Germany were below 0.001 mg/kg. Two samples of wheat of unknown origin contained 0.006 and 0.011 mg/kg (FAO, 1978).

Malathion was found in vegetables and fruit collected in the Carpathian region of the USSR in 1970-1972 (Popov *et al.*, 1977). In a Japanese study, malathion residues were found in the skin but not in the flesh of grapes (Hiramatsu & Furutani, 1978).

A US study of pesticides in commercial feeds for laboratory animals reported the following levels of malathion (mg/kg): rat diet, 0.04-0.13; guinea-pig diet, 0.05-0.40; hamster diet, 0.04-0.06; rabbit diet, 0.04-0.09; cat diet, 0.02-0.08; and monkey diet, 0.04 (Coleman & Tardiff, 1979).

(*g*) *Tobacco and tobacco smoke*

A mean content of 4 ng/g malathion was measured in cured tobacco leaves from farms in southern Ontario in 1978 (Frank *et al.*, 1980).

(*h*) *Animals*

Malathion was detected in tissue samples from fish from 144 estuaries throughout the US (Butler & Schutzmann, 1978).

2.3 Analysis

Standard methods used for the analysis of malathion in a variety of matrices are listed in Table 3.

Table 3. Methods for the analysis of malathion

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Liquids, technical material and solids	Dilute (acetonitrile or chloroform)	GC/FID	not given	Horwitz (1980); Zweig & Sherma (1972)
Liquids, granules and dusts	Extract (methanol)	HPLC/UV	not given	US Environmental Protection Agency (1976)
Emulsifiable concentrate, technical liquid and powders	Extract (hexane); chromatograph (cellulose); evaporate; dissolve (ethanol or isopropanol); add potassium hydroxide, water and nitric acid	Potentiometric titration (argentimetric)	not given	Horwitz (1980)
Emulsifiable concentrates, dusts, granules and water-dispersible powders	Extract (carbon disulphide)	IR spectroscopy	not given	US Environmental Protection Agency (1976)
Emulsifiable concentrates, technical materials, water-dispersible powders and dusts	Extract (solvent specific to matrix); hydrolyse (sodium hydroxide/organic solvent); complex (cupric naphthenate)	Colorimetry	not given	Horwitz (1980)
Plant material	Prepare as above (cupric salt method)	Colorimetry	0.2 mg/kg (fruit) 0.5 mg/kg (vegetables)	Sutherland (1964); Markus & Puma (1973)
Fruits, vegetables and fresh foliage	Extract (chloroform); dry (sodium sulphate); evaporate; dissolve (acetone)	GC/FID	0.05 mg/kg	Zweig & Sherma (1972)
Oily seeds, nuts, grains and dry hays	Extract (chloroform); dry (sodium sulphate); partition to remove oils (acetonitrile/hexane); evaporate acetonitrile layer; dissolve (acetone); precipitate; filter; then proceed as above for fruits, etc.	GC/FID	0.05 mg/kg	Zweig & Sherma (1972)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Non-fatty food products: fruits and vegetables	Extract (acetonitrile); dilute water extract (petroleum ether); chromatograph (Florisil)	GC/TD or GC/FPD[b]	0.01 mg/kg	Horwitz (1980)
	Extract (ethyl acetate/sodium sulphate); decant; concentrate; sweep co-distill clean-up	GC/TD	0.01 mg/kg	Horwitz (1980)
Milk	Sweep co-distill	GC/FID	0.01 mg/kg	Markus & Puma (1973)
Human milk, human and animal tissue	Macerate (acetonitrile); partition (aqueous sodium sulphate/hexane); concentrate; chromatograph (Florisil); concentrate	GC/ECD[b]	not given	Watts (1980)
Human tissue and excreta	Extract (ageuous acetone); concentrate; saturate with sodium chloride; extract (hexane); chromatograph (deactivated silica gel); concentrate	GC/FPD[b]	< 0.1 mg/kg	Watts (1980)
Human and animal adipose tissue	Macerate (sand); extract (petroleum ether); extract (acetonitrile); partition (petroleum ether); concentrate; chromatograph (Florisil); concentrate	GC/ECD[b]	not given	Watts (1980)
Air	Collect on filter; extract (isooctane)	GC/FPD	8-35 mg/m^3	Taylor (1977)
Ambient air	Soxhlet extract (hexane/diethyl ether/acetone); concentrate	GC/FPD[b]	0.9 ng/m^3	Watts (1980)
Water	Extract (dichloromethane); chromatograph (deactivated silica gel)	GC/FPD[b]	4 µg/kg	Watts (1980)
Sediment	Air dry; elute on chromatographic column (acetone/hexane); extract (aqueous sodium sulphate); extract water layer (hexane/dichloromethane); combine solvent extracts; wash (water); dry (sodium sulphate); concentrate; chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; HPLC/UV, high-performance liquid chromatography/ultra-violet, absorbance detection; IR spectroscopy, infra-red spectroscopy; GC/TD, gas chromatography/potassium chloride thermionic detection; GC/FPD, gas chromatography/flame photometric detection; GC/ECD, gas chromatography/electron capture detection

[b]Confirmation by thin-layer chromatography, extraction *p* values or polarography

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female weanling Charles River B6C3F$_1$ mice were fed diets containing 8000 or 16 000 mg/kg malathion (purity, 95%; impurities unspecified) for 80 weeks and observed 14-15 weeks. A matched control group comprising 10 animals of each sex was observed for 95 weeks; as the number of animals in the matched control group was small, an additional pooled control group of 50 animals of each sex was used for statistical analysis. In the high-dose group, which received a maximum tolerated dose, 94% of the males and 88% of the females were still alive at the end of the experiment; survival was somewhat lower in the low-dose and control groups. In female mice, no statistically significant increase in tumour incidence was found. In male mice the incidences of hepatocellular carcinomas plus neoplastic nodules were: 2/10 in matched controls, 8/49 in pooled controls, 7/48 in the low-dose group and 7/49 in the high-dose group [Cochran-Armitage test for positive trend, $p = 0.041$ (using matched controls) or $p = 0.019$ (using pooled controls); Fisher exact test, high-dose *versus* pooled controls, $p = 0.031$]. When a time-adjusted analysis was performed, eliminating those male mice that died before week 52 of the study, the following incidences resulted: matched controls, 2/9; pooled controls, 8/48; low-dose, 7/47; and high-dose, 17/49. Neither the Fisher exact test nor the Cochran-Armitage test showed these incidences to be significant when the matched controls were used; when the incidences of hepatocellular carcinoma and neoplastic nodules were analysed separately, none of the results were significant (National Cancer Institute, 1978). [The Working Group noted the short duration of treatment].

Rat: Groups of 20 male rats [age and strain not given] were administered malathion (purity, 65%; impurities unspecified) in the diet at concentrations of 0, 100, 1000 or 5000 mg/kg for two years. Survival was 60, 75, 90 and 65%, respectively. No compound-related lesion was reported by the authors (Hazleton & Holland, 1953). [The Working Group noted the small number of animals and the incompleteness of the reporting.]

Groups of 50 male and 50 female weanling Osborne-Mendel rats were fed diets containing various levels of malathion (purity, 95%; impurities unspecified): initially, animals were given 8000 and 12 000 mg/kg of diet; then, because the high dose appeared to be too toxic, the level given to the high-dose group was reduced after three weeks to 8000 mg/kg, and that to the low-dose group to 4000 mg/kg after 14 weeks. The total dosing period was 80 weeks. Time-weighted average doses over this period were 4700 and 8150 mg/kg of diet. The low-dose group was observed for 33 weeks and the high-dose group for 29 weeks. Two groups of matched controls comprising five or 10 animals of each sex were observed for 108-113 weeks; as the number of animals in the matched control groups was small, an additional pooled control group of 55 animals of each sex was used for statistical analyses. In the high-dose group, which received a maximum tolerated dose, 58% of the males and 67% of the females were still alive at the end of

the experiment; survival was higher in the low-dose and control groups. In male rats, no statistically significant increase in tumour incidence was found. In female rats a statistically significant increase was observed only for the combination of thyroid follicular-cell adenomas and follicular-cell carcinomas: 0/15 matched controls, 0/46 pooled controls, 0/48 low-dose animals and 4/49 high-dose animals [Cochran-Armitage test for positive trend using pooled controls, $p = 0.026$]. Historical female control rats were reported to have a spontaneous incidence of 2.2% for both types of tumour (National Cancer Institute, 1978). [The Working Group noted the short duration of treatment and small matched control groups).

Three groups of 50 male and 50 female Fischer 344 rats, six weeks old, were fed diets containing malathion (purity, 95%; impurities unspecified) at concentrations of 0, 2000 or 4000 mg/kg for 103 weeks. They were observed for a further two to three weeks and then killed; surviving rats in the matched control group were killed after 105-106 weeks on study. Of the male rats, 88% of the control group, 86% of the low-dose group and 80% of the high-dose group survived the experimental period; while of the females, 94% of the control group, 98% of the low-dose group and 90% of the high-dose group were still alive at termination of the experiment. Females may not have received a maximum tolerated dose, as indicated by gain in body weight. No statistically significant increase in tumour incidence was found in female rats. In male rats, the incidence of adrenal pheochromocytomas appeared to be increased in the low-dose group (11/48) compared with the control group (2/49, $p = 0.006$), whereas in the high-dose group only 6/49 pheochromocytomas were seen (National Cancer Institute, 1979a).

(*b*) *Carcinogenicity of metabolites*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, seven weeks old, were fed diets containing malaoxon [*O,O*-dimethyl *S*-1,2-bis(ethoxycarbonyl) ethyl phosphorothioate] (purity, >95%; impurities unspecified) at concentrations of 0, 500 or 1000 mg/kg for 103 weeks. They were observed for a further one to two weeks and then killed; surviving mice in the matched control group were killed after 103-105 weeks of study. The high-dose group received a maximum tolerated dose. Of the male mice, 90% of the control group, 84% of the low-dose group and 74% of the high-dose group were still alive at week 103; while of the female rats, 78% of the control group, 76% of the low-dose group and 90% of the high-dose group were alive at that time. No statistically significant increase in tumour incidence was observed in animals of either sex (National Cancer Institute, 1979b).

Rat: Groups of 50 male and 50 female Fischer 344 rats, six weeks old, were fed diets containing malaoxon (purity, >95%; impurities unspecified) at concentrations of 0, 500 or 1000 for 103 weeks. They were observed for a further one to two weeks and then killed; surviving rats in the matched control group were killed after 103-105 weeks of study. The high-dose group received a maximum tolerated dose. Of the male rats, 80% of the control group, 82% of the low-dose group and 64% of the high-dose group were alive at week 90 of study; while of the female rats, 82% of the control group, 90% of the low-dose group and 80% of the high-dose group were alive at that time. No statistically significant increase in tumour incidence was observed in male rats. In female rats, there was a statistically significant increase in the incidence of thyroid C-cell adenomas and carcinomas combined (National Cancer Institute, 1979b). [The abnormally low incidence of these tumours in the matched controls, in comparison with that in historical controls (see Tarone *et al.*, 1981) was noted.]

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Reviews on the toxicology of organophosphates (Taylor, 1980), and specifically that of malathion, are available (National Institute of Occupational Safety & Health, 1976). [See also the section 'General Remarks on the Substances Considered'.]

The acute toxicity and LD_{50}s of malathion depend on the purity of the compound tested. The oral LD_{50}s of 65% technical malathion to male mice and male rats were 1260 and 369 mg/kg bw and those of >99% pure malathion were 4059 and 5843 mg/kg bw, respectively (Hazleton & Holland, 1953). The oral LD_{50} in rats of malathion of high purity was 10 000 mg/kg bw (Aldridge *et al.*, 1979). LD_{50}s of malathion of unspecified purity were summarized by the National Institute for Occupational Safety and Health (1976): in rats, the oral LD_{50} ranged from 200 to 1500 mg/kg bw and the i.p. LD_{50} from 136 to 750 mg/kg bw. The i.p. LD_{50} was 193 mg/kg bw in male mice, 500 mg/kg bw in female guinea-pigs and 1600 mg/kg bw in male dogs. The dermal LD_{50} exceeded 4400 mg/kg bw in both male and female rats.

The acute toxicity of malathion is due to inhibition of acetylcholinesterase at nerve endings, leading to an accumulation of endogenous acetylcholine. The effects are manifested by muscarinic, nicotinic and central nervous system signs and symptoms: sweating, salivation, diarrhoea, bronchorrhoea, bradycardia, bronchoconstriction, muscle fasciculations and coma. The cause of death is primarily respiratory failure (Taylor, 1980).

In rats given 90% technical malathion in the diet for four to six weeks, to give average daily intakes of 62 and 68 mg/kg bw to males and females, respectively, cholinesterase activity in brain, plasma and erythrocytes was inhibited by about 50%; no adverse effect was noted in the animals. In a two-year feeding study in male rats, a level of 100 mg/kg 90% technical-grade malathion (6 mg/kg bw), the lowest dose tested, resulted in a 10-30% depression of brain, plasma and erythrocyte cholinesterase activity, with no effect on food intake or growth (National Institute for Occupational Safety & Health, 1976).

In chronic feeding studies, in which Osborne-Mendel rats received time-weighted average dietary levels of 4700 or 8150 mg/kg malathion and $B6C3F_1$ mice 8000 or 16 000 mg/kg, no dose-related trend in mortality was observed, although animals of both species showed signs of acute organophosphate toxicity (National Cancer Institute, 1978). In a similar study, no cholinergic effect was observed in male or female Fischer 344 rats given 2000 or 4000 mg/kg in the diet; but decreased mean body weights, increased mortality, gastritis and gastric ulcers occurred in a dose-related manner in male rats (National Cancer Institute, 1979a).

Malathion did not cause delayed neurotoxicity in chicken (Witter & Gaines, 1963).

Effects on reproduction and prenatal toxicity

Malathion (technical grade, 95% pure) was fed to rats at a dietary concentration of 4000 mg/kg (approximate daily intake, 240 mg/kg bw) for two generations. Males and females 70-100 days of age were bred after 10 weeks on test; survival of the progeny on days 7 and 21 after birth was found to be reduced, and the surviving offspring showed growth retardation and an increased incidence of ring-tail disease (Kalow & Marton, 1961). A single i.p. injection of 600 or 900 mg/kg bw malathion on day 11 of pregnancy to

Sherman rats produced maternal toxicity; foetal weight reduction but no malformation was induced with the high dose only (Kimbrough & Gaines, 1968). Technical-grade malathion [purity not specified] administered daily at maternally tolerated doses of 50-300 mg/kg bw by gastric intubation to Wistar rats on days 6-15 of pregnancy induced no embryotoxicity (Khera *et al.*, 1978).

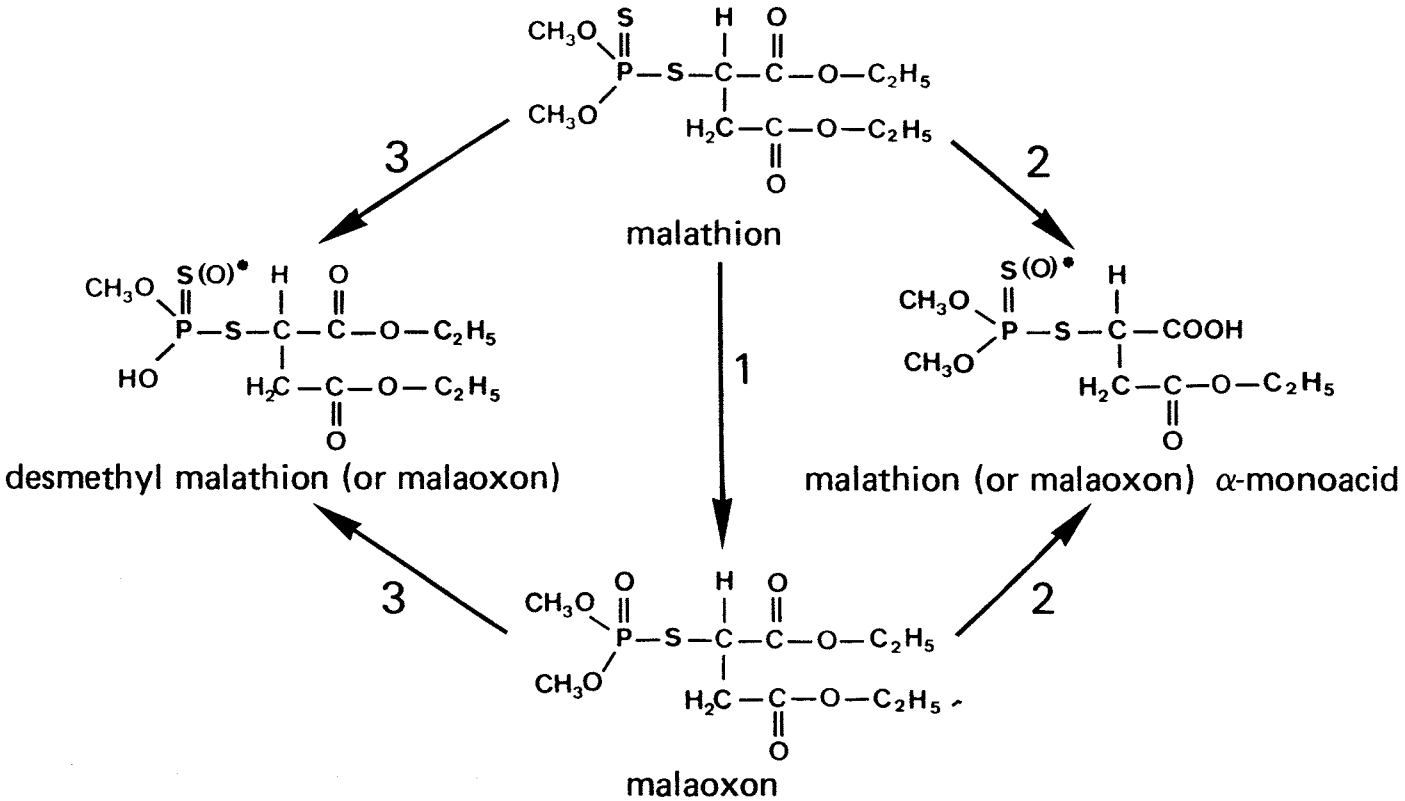
Absorption, distribution, excretion and metabolism

Malathion is absorbed from the gut, respiratory tract and skin (Hazleton & Holland, 1953; O'Brien & Dannelly, 1965).

The metabolism, distribution and excretion of ^{32}P-malathion have been studied in several species, including mice and hens (March *et al.*, 1956a), hens (Gupta & Paul, 1977), a lactating cow (O'Brien *et al.*, 1961) and calves (March *et al.*, 1956b). Malathion is metabolized rapidly and eliminated from the body within 24 hours. In the cow, 90% of the dose was excreted in the urine.

Some of the important metabolic pathways of malathion in biological systems are shown in Figure 1. The toxic effects of malathion are attri buted to its oxidative desulphuration by liver microsomal enzymes, leading to the formation of malaoxon (reaction 1) (Dauterman & Main, 1966). Malathion and malaoxon are hydrolysed and thus detoxified by carboxylesterases in the liver and other organs (reaction 2) (March *et al.*, 1956a; Cook & Yip, 1958; Cook *et al.*, 1958; Talcott, 1979). Detoxification, mainly by the liver soluble fraction, also occurs through dealkylation (reaction 3), probably by glutathione-*S*-transferases (Nomeir & Dauterman, 1978).

Figure 1. Metabolism of malathion[a]



[a]Malaoxon may be metabolized *via* the same pathways as malathion, resulting in the oxygen analogue, indicated by the presence of (O)* in the figure.

The rapid enzymatic hydrolysis by carboxylesterases (reaction 2) accounts for the lower toxicity of malathion in mammals than in insects, which have relatively little capacity to hydrolyse this compound (Krueger & O'Brien, 1959; Murphy, 1967). Potentiation of malathion toxicity by some impurities in technical formulations is related to inactivation of carboxylesterases (Aldridge *et al.*, 1979; Talcott *et al.*, 1979a). The same mechanism is involved in the potentiation of its toxicity by other organophosphorus esters (Frawley *et al.*, 1957; Murphy *et al.*, 1959).

Malaoxon is both an inhibitor of carboxylesterases as well as a substrate (Dauterman & Main, 1966), but its detoxification by hydrolysis is probably the dominant reaction (Main & Dauterman, 1967).

Mutagenicity and other short-term tests

The mutagenicity of malathion has been reviewed (Wild, 1975)

Malathion [purity unspecified] produced low but significant breakage in Col E1 plasmid DNA in *Escherichia coli* K12 *in vitro* (Griffin & Hill, 1978). Relative toxicity assays, performed in *E. coli* and *Bacillus subtilis*, gave negative (Shirasu *et al.*, 1976; Simmon *et al.*, 1977) or questionable (Shiau *et al.*, 1980) results. Negative results were obtained with pure and commercial formulations in the reverse mutation assay using several strains of *Salmonella typhimurum*, either in the presence or absence of rat liver microsomal preparations (McCann *et al.*, 1975; Byeon *et al.*, 1976; Shirasu *et al.*, 1976; Simmon *et al.*, 1977; Shiau *et al.*, 1980); however, a positive result with metabolic activation was reported in *S. typhimurium* strain TA100 (Kawachi *et al.*, 1980) [details not given]. Malathion was not mutagenic to *E. coli* in either the reverse mutation assay in strains WP2 (without metabolic activation) and WP2 *uvrA* (with or without metabolic activation) (Ashwood-Smith *et al.*, 1972; Dean, 1972; Nagy *et al.*, 1975; Shirasu *et al.*, 1976; Simmon *et al.*, 1977) or in the forward mutation assay for 5-methyltryptophan resistance in strain K12 (Mohn, 1973). However, weak mutagenic activity was detected in a reverse mutation assay using *B. subtilis* strain TKJ 6321 (Shiau *et al.*, 1980).

No mutagenic activity was detected when malathion was tested for the induction of forward mutations at the ade-6 locus in *Schizosaccharomyces pombe*, with or without an Aroclor-induced rat liver microsomal preparation (Barale *et al.*, 1979; Degraeve *et al.*, 1980) or for mitotic gene recombination in *Saccharomyces cerevisiae* (D3 system) (Simmon *et al.*, 1977).

An increased incidence of chromosomal aberrations was reported in barley (*Hordeum vulgare* L.) after seeds were exposed to solutions of 0.02-0.5% commercial Cythion [malathion content not specified] (Singh *et al.*, 1977).

Malathion was ineffective in inducing sex-linked recessive lethal mutations in *Drosophila melanogaster* fed solutions containing 0.25 or 0.5 mg/l of the compound (Valencia, 1977; Waters *et al.*, 1980).

Concentrations of up to 400 µg/ml of 95% malathion failed to increase chromosomal aberrations in human haematopoietic B411-4, RPMI-1788 and RPMI-7191 cell cultures (Huang, 1973); however, Walter *et al.* (1980) reported a positive, although not dose-related, result in human lymphocytes with 99% pure malathion. Positive results were also reported from the Japanese cooperative programme in Chinese hamster fibroblasts (Kawachi *et al.*, 1980) [details not given].

Malathion (99% pure) caused a significant increase in sister chromatid exchanges in human foetal lung fibroblasts after a single exposure to 40 μg/ml or double exposure to 20 μg/ml (Nicholas *et al.*, 1979); similar results were obtained in Chinese hamster V79 cells exposed to doses of up to 40 μg/ml of 94% malathion (Chen *et al.*, 1981) and in Chinese hamster ovary cells exposed to 0.03-1 mM malathion (99% pure) (Nishio & Uyeki, 1981). No sister chromatid exchange was reported in human foetal fibroblasts in another study [details not given] (Kawachi *et al.*, 1980). None of these tests employed exogenous metabolic activation. No increase in unscheduled DNA synthesis was observed in malathion-treated WI-38 human fibroblasts, with or without an uninduced mouse liver microsomal preparation (Simmon *et al.*, 1977).

In-vivo studies have shown an increased incidence of chromosomal aberrations in primary spermatocytes of CFW male mice after oral administration of daily doses of 0.5 ml of a 0.3% solution of Sadofos 30 (30% malathion) for 50 or 100 days (Bulsiewicz *et al.*, 1976). In a table summarizing work carried out in the Japanese cooperative programme [details not given], malathion was reported to induce a slight increase in the incidence of chromosomal aberrations in the bone-marrow cells of rats exposed *in vivo* (Kawachi *et al.*, 1980).

No dominant lethality was observed in a study in which three groups of 20 mice were fed malathion for seven weeks at concentrations of 1250, 2500 and 5000 mg/kg in the diet (Simmon *et al.*, 1977). A similar result was reported by Degraeve *et al.* (1980) [abstract].

(*b*) *Humans*

Toxic effects

A relatively low acute toxicity of malathion to humans is indicated by the fact that a daily oral dosage of 24 mg given for more than 14 days was necessary to lower blood cholinesterase activities in adult volunteers (Moeller & Rider, 1962). Despite its low inherent toxicity, however, malathion has been the cause of numerous fatalities, due to its wide availability and frequent abuse as a suicidal agent (Frost & Poulsen, 1964; Mootoo & Singh, 1966; Nalin, 1973; Baker *et al.*, 1978).

Manifestations of acute poisoning in humans by malathion are similar to those in experimental animals (Baker *et al.*, 1978). There may be some significant cardiological abnormalities in severe acute poisonings (mainly arrhythmia and atrioventricular block), but the principal factor in causing death is respiratory failure (Namba *et al.*, 1970). There is no documented case of peripheral neuropathy due to malathion exposure, although other organophosphate pesticides have been shown to have this effect. (See also 'General Remarks on the Substances Considered'.)

There is a single report of an association between brief anecdotal exposure to malathion and subsequent fatal aplastic anaemia (Reeves *et al.*, 1981).

The basis for a poisoning epidemic in Pakistan, in which 2800 applicators became ill with symptoms typical of organophosphate poisoning and five died, has been investigated. The probable cause was high concentrations in the formulated pesticide of contaminants which strongly inhibit carboxylesterase enzymes of the liver. The principal

contaminants were isomalathion and trimethyl phosphorothioates (Baker *et al.*, 1978; Aldridge *et al.*, 1979). Isomalathion occurs only in low concentrations in technical malathion but is formed in larger amounts in some powder formulations (WHO, 1978).

Isomalathion has been shown to inhibit the malathion carboxylesterase enzyme in human liver (Talcott *et al.*, 1979b).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

The equivalent of 23% of an ingested oral dose of 58 mg was recovered in 16.3 hours from the urine of a human volunteer (Mattson & Sedlak, 1960).

In a study of the absorption and excretion of malathion in men exposed to dusting powders containing 1-10% malathion, malathion metabolites in the urine represented 4-10% of the dermally applied dose (Hayes *et al.*, 1960). About 8% of an applied dose of malathion was absorbed through the skin in another study (Maibach *et al.*, 1971). Ten workers exposed to malathion excreted 0.45 to 1.07 μg/ml potassium dimethyldithiophosphate in the urine (Drevenkar *et al.*, 1979).

The urine from a poisoning case was collected 24 to 28 hours after malathion ingestion and the following metabolites detected: monocarboxylic acid of malathion (223 mg/l), dimethylthiophosphate (96 mg/l), dimethyl phosphate (50 mg/l), dimethyldithiophosphate (20 mg/l), the dicarboxylic acid of malathion (12 mg/l) and monomethyl phosphate (8 mg/l) (Bradway & Shafik, 1977).

In man, malathion is metabolized by (1) hydrolytic cleavage of ethyl groups from the succinic acid moiety of the molecule by carboxylesterase enzymes; and (2) hydrolysis of the succinate moiety from the dialkyl thiophosphate. As in rats, the principal urinary metabolite of malathion is the monoacid (Main & Braid, 1962).

Mutagenicity and chromosomal effects

A significant increase in chromosomal aberrations was found in the lymphocytes of a group of 14 people intoxicated with a commercial formulation of malathion (Fosfotion), as compared with that in healthy controls. Aberrations observed included chromatid breaks, chromatid isobreaks, chromatid exchanges and unstable chromosomal and structural aberrations. No dose-effect relationship was evident, since high frequencies of aberrations were also detected in cases of mild intoxication (van Bao *et al.*, 1974). [The small number of subjects involved and the inappropriateness of the control group used does not permit the association to be established as causal.]

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Malathion and its metabolite malaoxon were tested for carcinogenicity in mice and rats by administration in the diet. No evidence of carcinogenicity was found.

There was no evidence of teratogenicity or embryotoxicity in rats given maternally tolerated doses of malathion during pregnancy. In animals fed very high doses for two generations, malathion had no effect on reproduction other than to decrease survival in the first generation and to reduce growth in the second generation of rats.

Malathion was not mutagenic in most studies of bacteria or in two studies of yeast. No mutagenic action was observed in *Drosophila melanogaster*. Malathion increased sister chromatid exchange frequency in cultured mammalian cells but did not induce unscheduled DNA synthesis. Chromosomal aberrations were increased in certain types of cultured mammalian cells and in mice treated *in vivo* with malathion. Dominant lethal tests in mice were reported to be negative. There is thus limited evidence for the mutagenicity of malathion.

4.2 Human data

Malathion was introduced in 1950. Its production, formulation and widespread use as an insecticide in a variety of agricultural, vector control and household applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic effects of malathion in humans. The available data were insufficient to evaluate the chromosomal effects of malathion in humans.

No case report or epidemiological study of the carcinogenicity of malathion alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation

The available data do not provide evidence that malathion or its metabolite malaoxon is carcinogenic to experimental animals. No data on humans were available.

The available data provide no evidence that malathion is likely to present a carcinogenic risk to humans.

5. References

Aldridge, W.N., Miles, J.W., Mount, D.L. & Verschoyle, R.D. (1979) The toxicological properties of impurities in malathion. *Arch. Toxicol.*, *43*, 95-106

American Conference of Governmental Industrial Hygienists (1981) *TLVs*^{R} *Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981*, Cincinnati, OH, p. 21

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization* (*EPA - 600/2/78-004d*), Washington DC, US Environmental Protection Agency, p. 135

Ashwood-Smith, M.J., Trevino, J. & Ring, R. (1972) Mutagenicity of dichlorvos. *Nature*, *240*, 418-420

Baker, E.L., Jr, Zack, M., Miles, J.W., Alderman, L., Warren, McW., Dobbin, R.D., Miller, S. & Teeters, W.R. (1978) Epidemic malathion poisoning in Pakistan malaria workers. *Lancet*, *i*, 31-34

van Bao, I., Szabó, I., Ruzicska, P. & Czeizel, A. (1974) Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. *Humangenetik*, *24*, 33-57

Barale, R., Presciuttini, S. & Rossi, A.M. (1979) *Schizosaccharomyces pombe*-forward mutation (Ital.). In: Magni, G.E., ed., *Mutagenesi Ambiantale; Metodiche di Analisi*, Vol. 1, *Test in vitro*, pp. 105-121

Bradway, D.E. & Shafik, T.M. (1977) Malathion exposure studies: Determination of mono- and dicarboxylic acids and alkyl phosphates in urine. *J. agric. Food Chem.*, *25*, 1342-1344

Braun, H.E. & Frank, R. (1980) Organochlorine and organophosphorus insecticides: Their use in eleven agricultural watersheds and their loss to stream waters in southern Ontario, Canada, 1975-1977. *Sci. total Environ.*, *15*, 169-192

Bulsiewicz, H., Rózewicka, L., Januszewska, H. & Bajko, J. (1976) Aberrations of meiotic chromosomes induced in mice with insecticides. *Folia Morphol.* (*Warsaw*), *35*, 361-368

Butler, P.A. & Schutzmann, R.L. (1978) Residues of pesticides and PCBs in estuarine fish, 1972-1976 - National Pesticide Monitoring Program. *Pestic. Monit. J.*, *12*, 51-59

Byeon, W., Hyun, H.H. Lee, S.Y. (1976) Mutagenicity of pesticides in the *Salmonella*/ microsomal enzyme activation system. *Korean J. Microbiol.*, *14*, 128-134

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 151-153

Caplan, P.E., Culver, D. & Thielen, W.C. (1956) Human exposures in populated areas during airplane application of malathion. *Arch. ind. Health*, *14*, 326-332

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1978) Pesticide residue levels in soils and crops, 1971 - National Soils Monitoring Program (III). *Pestic. Monit. J.*, *12*, 117-136

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1979) Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). *Pestic. Monit. J.*, *12*, 209-229

Carrasco, J.M., Cunat, P., Martinez, M. & Primo, E. (1976) Pesticide residues in total diet samples, Spain - 1971-72. *Pestic. Monit. J.*, *10*, 18-23

Chen, H.H., Hsueh, J.L., Sirianni, S.R. & Huang, C.C. (1981) Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. *Mutat. Res.*, *88*, 307-316

Coleman, W.E. & Tardiff, R.G. (1979) Contaminant levels in animal feeds used for toxicity studies. *Arch. environ. Contam. Toxicol.*, *8*, 693-701

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *L340*, 26-31

Cook, J.W. & Yip, G. (1958) Malathionase. II. Identity of a malathion metabolite. *J. Assoc. off. agric. Chem.*, *41*, 407-411

Cook, J.W., Blake, J.R., Yip, G. & Williams, M. (1958) Malathionase. I. Activity and inhibition. *J. Assoc. off. agric. Chem.*, *41*, 399-407

Crockett, A.B., Wiersma, G.B., Tai, H., Mitchell, W.G., Sand, P.F. & Carey, A.E. (1974) Pesticide residue levels in soils and crops, FY-70-National Soils Monitoring Program (II). *Pestic. Monit. J.*, *8*, 69-97

Culver, D., Caplan, P. & Batchelor, G.S. (1956) Studies of human exposure during aerosol application of malathion and chlorthion. *Arch. ind. Health*, *13*, 37-50

Dauterman, W.C. & Main, A.R. (1966) Relationship between acute toxicity and *in vitro* inhibition and hydrolysis of a series of carbalkoxy homologues of malathion. *Toxicol. appl. Pharmacol.*, *9*, 408-418

Dean, B.J. (1972) The mutagenic effects of organophosphorus pesticides on micro-organisms. *Arch. Toxicol.*, *30*, 67-74

Degraeve, N., Gilot-Delhalle, J., Moutschen, J., Moutschen-Dahmen, M., Colizzi, A., Chollet, M. & Houbrechts, N. (1980) Comparison of the mutagenic activity of organophosphorus insecticides in mouse and the yeast *Schizosaccharomyces pombe* (Abstract no. 65). *Mutat. Res.*, *74*, 201-202

Drevenkar, V., Fröbe, Z., Vasilicé, Z., Tkalcevicé, B. & Stefanac, Z. (1979) The rate of urinary excretion of phosalone residues in occupationally exposed persons. *Sci. total Environ.*, *13*, 235-243

FAO (1978) *Pesticide Residues in Food: 1977 Evaluations*, Rome, pp. 349-352

Frank, R., Braun, H.E., Stonefield, K.I., Elliott, J.M. & Zilkey, B.F. (1980) Insecticide residues and metal contents in flue-cured tobacco and tobacco soil of southern Ontario, 1976-1978. *Tobacco Int.*, *182*, 59-63

Frawley, J.P., Fuyat, H.N., Hagan, E.C., Blake, J.R. & Fitzhugh, O.G. (1957) Marked potentiation in mammalian toxicity from simultaneous administration of two anti-cholinesterase compounds. *J. Pharmacol. exp. Ther.*, *121*, 96-106

Frost, J. & Poulsen, E. (1964) Poisoning due to parathion and other organophosphorus insecticides in Denmark. *Dan. med. Bull.*, *11*, 169-177

GIFAP (1982) *GIFAP Bulletin*, Vol. 8, No. 7, Brussels, International Group of National Associations of Agrochemical Manufacturers, p. 9

Gore, R.F., Hannah, R.W., Pattacini, S.C., & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem.*, *54*, 1040-1082

Griffin, D.E., III & Hill, W.E. (1978) *In vitro* breakage of plasmic DNA by mutagens and pesticides. *Mutat. Res.*, *52*, 161-169

Gupta, P.K. & Paul, B.S. (1977) Biological fate of 32P malathion in *Gallus domesticus* (Desi poultry birds). *Toxicology*, *7*, 169-177

Harris, C.R., Chapman, R.A. & Miles, J.R.W. (1977) Insecticide residues in soils on fifteen farms in southwestern Ontario, 1964-1974. *J. environ. Sci. Health*, *B12*, 163-177

Hayes, W.J., Jr (1971) Studies on exposure during the use of anticholinesterase pesticides. *Bull. World Health Organ.*, *44*, 277-288

Hayes, W.J., Jr, Mattson, A.M., Short, J.G. & Witter, R.F. (1960) Safety of malathion dusting powder for louse control. *Bull. World Health Organ.*, *22*, 503-514

Hazleton, L.W. & Holland, E.G. (1953) Toxicity of malathion. Summary of mammalian investigations. *Arch. ind. Hyg. occup. Med.*, *8*, 399-405

Hiramatsu, R. & Furutani, F. (1978) Persistences of sprayed malathion and trichlorfon in grape berries and grape products (Jpn.). *Yamaguchi-ken Nogyo Shikenjo Kenkyu Hokoku*, *30*, 37-44 [*Chem. Abstr.*, *89*, 192446g]

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 113-116, 466-479, 490-491

Huang, C.C. (1973) Effect on growth but not on chromosomes of the mammalian cells after treatment with three organophosphorus insecticides. *Proc. Soc. exp. Biol. Med.*, *142*, 36-40

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 138, 139

Johnson, R.D. & Manske, D.D. (1976) Pesticide residues in total diet samples (IX). *Pestic. Monit. J.*, *9*, 157-169

Johnson, R.D. & Manske, D.D. (1977) Pesticide and other chemical residues in total diet samples (XI). *Pestic. Monit. J.*, *11*, 116-131

Johnson, R.D., Manske, D.D., New, D.H. & Podrebarac, D.S. (1979) Pesticides and other chemical residues in infant and toddler total diet samples - (I) - August 1974-July 1975. *Pestic. Monit. J.*, *13*, 87-98

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975-July 1976. *Pestic. Monit. J.*, *15*, 54-69

Kalow, W. & Marton, A. (1961) Second-generation toxicity of malathion in rats. *Nature*, *192*, 464-465

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No.27*), Lyon, pp. 323-330

Khera, K.S., Whalen, C. & Trivett, G. (1978) Teratogenicity studies on linuron, malathion, and methoxychlor in rats. *Toxicol. appl. Pharmacol.*, *45*, 435-444

Kimbrough, R.D. & Gaines, T.B. (1968) Effect of organic phosphorus compounds and alkylating agents on the rat fetus. *Arch. environ. Health*, *16*, 805-808

Krueger, H.R. & O'Brien, R.D. (1959) Relationship between metabolism and differential toxicity of malathion in insects and mice. *J. econ. Entomol.*, *52*, 1063-1067

Maibach, H.I., Feldmann, R.J., Milby, T.H. & Serat, W.F. (1971) Regional variation in percutaneous penetration in man. *Arch. environ. Health*, *23*, 208-211

Main, A.R. & Braid, P.E. (1962) Hydrolysis of malathion by ali-esterases *in vitro* and *in vivo*. *Biochem. J.*, *84*, 255-263

Main, A.R. & Dauterman, W.C. (1967) Kinetics for the inhibition of carboxylesterase by malaoxon. *Can. J. Biochem.*, *45*, 757-771

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII). *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

March, R.B., Fukuto, T.R., Metcalf, R.L. & Maxon, M.G. (1956a) Fate of P^{32} labeled malathion in the laying hen, white mouse, and American cockroach. *J. econ. Entomol.*, *49*, 185-195

March, R.B., Metcalf, R.L., Fukuto, T.R. & Gunther, F.A. (1956b) Fate of P^{32}-labeled malathion sprayed on Jersey heifer calves. *J. econ. Entomol.*, *49*, 679-682

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.111

Mattson, A.M. & Sedlak, V.A. (1960) Ether-extractable urinary phosphates in man and rats derived from malathion and similar compounds. *J. agric. Food Chem.*, *8*, 107-110

McCann, J., Choi, E., Yamasaki, E. & Ames, B.N. (1975) Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc. natl Acad. Sci. USA*, *72*, 5135-5139

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Mestres, R., Illes, S., Campo, M. & Tourte, J. (1977) A multiple residue method for citrus fruits: Its technique and some data. *Proc. int. Soc. Citriculture*, *2*, 426-429

Metcalf, R.L. (1981) *Insect control technology*. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley & Sons, p. 441

Midwest Research Institute (1975) *Substitute Chemical Program. Initial Scientific and Minieconomic Review of Malathion* (*PB-241 818*), Washington DC, US Department of Commerce, National Technical Information Service

Moeller, H.C. & Rider, J.A. (1962) Plasma and red blood cell cholinesterase activity as indications of the threshold of incipient toxicity of ethyl-p-nitrophenyl thionobenzene-phosphonate (EPN) and malathion in human beings. *Toxicol. appl. Pharmacol.*, *4*, 123-130

Mohn, G. (1973) 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12. Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. *Mutat. Res.*, *20*, 7-15

Mootoo, C.L. & Singh, B. (1966) Review of 210 deaths by poisoning in British Guiana (1959-1964). *West Indian med. J.*, *15*, 11-17

Morse, D.L., Baker, E.L. & Landrigan, P.J. (1979) Cut flowers: A potential pesticide hazard. *Am. J. public Health*, *69*, 53-56

Mukherjee, D., Roy, B.R., Chakraborty, J. & Ghosh, B.N. (1980) Pesticide residues in human foods in Calcutta. *Indian J. med. Res.*, *72*, 577-582

Mulla, M.S., Mian, L.S. & Kawecki, J.A. (1981) Distribution, transport, and fate of the insecticides malathion and parathion in the environment. *Residue Rev.*, *81*, 116-125

Murphy, S.D. (1967) Malathion inhibition of esterases as a determinant of malathion toxicity. *J. Pharmacol. exp. Ther.*, *156*, 352-365

Murphy, S.D., Anderson, R.L. & DuBois, K.P. (1959) Potentiation of toxicity of malathion by triorthotolyl phosphate. *Proc. Soc. exp. Biol. Med.*, *100*, 483-487

Nagy, Z., Mile, I. & Antoni, F. (1975) The mutagenic effect of pesticides on *Escherichia coli* WP2 try$^-$. *Acta microbiol. acad. sci. hung.*, *22*, 309-314

Nalin, D.R. (1973) Epidemic of suicide by malathion poisoning in Guyana: Report of 264 cases. *Trop. geogr. Med.*, *25*, 8-14

Namba, T., Greenfield, M. & Grob, D. (1970) Malathion poisoning: A fatal case with cardiac manifestations. *Arch. environ. Health, 21*, 533-541

National Cancer Institute (1978) *Bioassay of Malathion for Possible Carcinogenicity (Tech. Rep. Ser. No. 24; DHEW Publ. No. (NIH) 78-824)*, Washington DC, US Department of Health, Education & Welfare

National Cancer Institute (1979a) *Bioassay of Malathion for Possible Carcinogenicity (Tech. Rep. Ser. No. 192; DHEW Publ. No. (NIH) 79-1748)*, Washington DC, US Department of Health, Education, & Welfare

National Cancer Institute (1979b) *Bioassay of Malathion for Possible Carcinogenicity (Tech. Rep. Ser. No. 135; DHEW Publ. No. (NIH) 79-1390)*, Washington DC, US Department of Health, Education, & Welfare

National Institute for Occupational Safety & Health (1976) *Criteria for a Recommended Standard - Occupational Exposure to Malathion*, Washington DC, US Department of Health, Education, & Welfare

National Institute for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards,* Cincinnati, OH, p. 79

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche) Cincinnati, OH, pp. 3,36l; 4,561-2

National Research Council (1977) *Drinking Water and Health*, Washington DC, National Academy of Sciences, p. 621

Nicholas, A.H., Vienne, M. & Van Den Berghe, H. (1979) Induction of sister-chromatid exchanges in cultured human cells by an organophosphorous insecticide: Malathion. *Mutat. Res., 67*, 167-172

NIH/EPA Chemical Information System (1982) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Nishio, A. & Uyeki, E.M. (1981) Induction of sister chromatid exchanges in Chinese hamster ovary cells by organophosphate insecticides and their oxygen analogs. *J. Toxicol. environ. Health, 8*, 939-946

Nomeir, A.A. & Dauterman, W.C. (1978) *In vitro* degradation of malathion by mouse liver. *Biochem. Pharmacol., 27*, 2975-2976

O'Brien, R.D. & Cannelly, C.E. (1965) Penetration of insecticides through rat skin. *J. agric. Food Chem., 13*, 245-247

O'Brien, R.D., Dauterman, W.C. & Niedermeier, R.P. (1961) The metabolism of orally administered malathion by a lactating cow. *J. agric. Food Chem., 9*, 39-42

Popov, V.V., Dmitrochenko, A.S., Vetchinin, V.V. & Romanov, O.I. (1977) Pesticide residues in the food eaten by people of the Carpathian Mountain region (Russ.). *Ratsion. Pitan., 12*, 81-83, 98-102 [*Chem. Abstr., 93*, 112441w]

Reeves, J.D., Driggers, D.A. & Kiley, V.A. (1981) Household insecticide associated aplastic anaemia and acute leukaemia in children. *Lancet, ii*, 300-301

Savage, E.P., Keefe, T.J., Wheeler, H.W., Mounce, L., Helwic, L., Appelhans, F., Goes, E., Goes, T., Mihlan, G., Rench, J. & Taylor, D.K. (1981) Household pesticide usage in the United States. *Arch. environ. Health, 36*, 304-309

Shiau, S.Y., Huff, R.A., Wells, B.C. & Felkner, I.C. (1980) Mutagenicity and DNA-damaging activity for several pesticides tested with *Bacillus subtilis* mutants. *Mutat. Res., 71*, 169-179

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res., 40*, 19-30

Simmon, V.F., Mitchell, A.D. & Jorgenson, T.A. (1977) *Evaluation of Selected Pesticides as Chemical Mutagens.* In vitro *and* in vivo *Studies (EPA - 600/1-77-028)*, Research Triangle Park, NC, US Environmental Protection Agency, p. 143

Singh, B.D., Singh, Y., Singh, R.B., Singh, R.M., Sarma, N.D.R.K. & Singh, J. (1977) Cytogenetic aberrations and morphological changes induced by insecticide treatments of barley seeds. *Indian J. exp. Biol., 15*, 688-691

Smith, D.C., Leduc, R. & Tremblay, L. (1975), Pesticide residues in the total diet in Canada. IV. 1972 and 1973. *Pestic. Sci., 6*, 75-82

Sutherland, G.L. (1964) *Malathion.* In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. II, *Insecticides*, New York, Academic Press, pp. 284-293

Talcott, R.E. (1979) Hepatic and extrahepatic malathion carboxylesterases. Assay and localization in the rat. *Toxicol. appl. Pharmacol., 47*, 145-150

Talcott, R.E., Mallipudi, N.M., Umetsu, N. & Fukuto, T.R. (1979a) Inactivation of esterases by impurities isolated from technical malathion. *Toxicol. appl. Pharmacol., 49*, 107-112

Talcott, R.E., Denk, H. & Mallipudi, N.M. (1979b) Malathion carboxylesterase activity in human liver and its inactivation by isomalathion. *Toxicol. appl. Pharmacol., 49*, 373-376

Tarone, R.E., Chu, K.C. & Ward, J.M. (1981) Variability in the rates of some common naturally occurring tumors in Fischer 344 rats and (C57BL/6N x C3H/HeN)F_1 (B6C3F_1) mice. *J. natl Cancer Inst., 66*, 1175-1181

Taylor, D.G. (1977) *NIOSH Manual of Analytical Methods*, 2nd ed., Part II, *Standards Completion Program Validated Methods*, Vol. 3, *Method 8370 DHEW (NIOSH)*, Washington DC, US Government Printing Office, pp. S370-1 - S370-7

Taylor, P. (1980) *Anticholinesterase agents.* In: Gilman, A.G., Goodman, L.S. & Gilman, A., eds, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed., New York, MacMillan, pp. 100-119

Thomson, W.T. (1979) *Agricultural Chemicals*, Book 1, *Insecticides, Acaricides and Ovicides, 1979-80 Rev.*, Fresno, CA, Thomson Publications, p. 170

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976, Agricultural Economic Report No. 418*, Washington DC, Economics, Statistics, and Cooperatives Service, pp. 16, 24, 26

US Department of Agriculture (1981) *Monitoring Phase Biological Residue Report, January 1980 through December 1980*, Washington DC, Residue Evaluation and Surveillance Division

US Department of Transportation (1980) Transport of hazardous wastes and hazardous substances. *US Code Fed. Regul., Title 49*, parts 171-174, 176, 177; *Fed. Regist., 45*, 34560, 34624

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Washington DC, Office of Pesticide Programs, Association of Official Analytical Chemists, Malathion EPA-1, EPA-2

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.111, pp. 540, 541

US Environmental Protection Agency (1980b) Malathion: Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. *Fed. Regist., 45*, 76145, 76146

US Environmental Protection Agency (1980c) Protection of environment. *US Code Fed. Regul., Title 40,* parts 116, 117, pp. 35-50

US Environmental Protection Agency (1980d) Protection of the environment. *US Code Fed. Regul., Title 40*, parts 455.20, 455.22, pp. 285, 286

US Food & Drug Administration (1980a) Food and drugs. *US Code Fed. Regul., Title 21*, part 193.260, pp. 374, 375; part 193.520, p. 381

US Food & Drug Administration (1980b) Food and drugs. *US Code Fed. Regul., Title 21*, part 561.270, p. 518

US International Trade Commission (1978) *Imports of Benzenoid Chemicals and Products, 1977 (USITC Publ. 900)*, Washington DC, US Government Printing Office, p. 96

US Tariff Commission (1953) *Synthetic Organic Chemicals, US Production and Sales, 1952 (Report No. 190, Second Series)*, Washington DC, US Government Printing Office

Valencia, R. (1977) *Mutagenesis Screening of Pesticides Using* Drosophila *(Contract No. 68-01-2474)*, Madison, WI, WARF Institute, Inc.

Walter, Z., Czajkowska, A. & Lipecka, K. (1980) Effect of malathion on the genetic material of human lymphocytes stimulated by phytohemagglutinin (PHA). *Human Genet., 53*, 375-381

Warner, J.S. (1975) *Identification of impurities in technical-grade pesticides.* In: *Substitute Chemical Program - the First Year of Progress. Proceedings of a Symposium*, Vol. IV, *Chemical Method Workshop* (*PB - 261 007*), Washington DC, Environmental Protection Agency, pp. 31-65

Waters, M.D., Simmon, V.F., Mitchell, A.D., Jorgenson, T.A. & Valencia, R. (1980) An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. *J. environ. Sci. Health, B15*, 867-906

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, Sect. 5A(1)(a); 5A(2)(a),(b); 6A(1); 8B; 10A; 11B; 12B; 12C; 12F

WHO (1965) *Evaluation of the Toxicity of Pesticide Residues in Food* (*WHO/Food Add./27.65*), Geneva, pp. 136-141

WHO (1967) *Evaluation of Some Pesticide Residues in Food* (*WHO/Food Add./67.32*), Geneva, pp. 172-187

WHO (1974) *1973 Evaluations of Some Pesticide Residues in Food* (*WHO Pest. Residue Ser. No. 3*), Geneva, pp. 328-329

WHO (1978) *Chemistry and Specifications of Pesticides. Second Report of the WHO Expert Committee on Vector Biology and Control* (*Tech. Rep. Ser. 620*), Geneva, pp. 23-24

Witter, R.F. & Gaines, T.B. (1963) Relationship between depression of brain or plasma cholinesterase and paralysis in chickens caused by certain organic phosphorus compounds. *Biochem. Pharmacol., 12*, 1377-1386

Wolfe, H.R., Durham, W.F. & Armstrong, J.F. (1967) Exposure of workers to pesticides. *Arch. environ. Health, 14*, 622-633

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 321

Wright, C.G. & Leidy, .R.B. (1980) Insecticide residues in the air of buildings and pest control vehicles. *Bull. environ. Contam. Toxicol., 24*, 582-589

Zweig, G. & Sherma, J. (1972) *Malathion.* In: Zweig, G., ed., *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, New York, Academic Press, pp. 418-431

METHYL PARATHION[1]

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 298-00-0

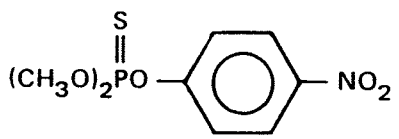
Chem. Abstr. Name: Phosphorothioic acid, *O,O*-dimethyl *O*-(4-nitrophenyl) ester

IUPAC Systematic Name: *O,O*-Dimethyl *O*-4-nitrophenyl phosphorothioate

Synonyms: Demethylfenitrothion; dimethyl *para*-nitrophenyl monothiophosphate; *O,O*-dimethyl *O*-(*para*-nitrophenyl) phosphorothioate; dimethyl *para*-nitrophenyl phosphorothionate; dimethyl 4-nitrophenyl phosphorothionate; *O,O*-dimethyl *O*-(*para*-nitrophenyl) thionophosphate; dimethyl *para*-nitrophenyl thiophosphate; *O,O*-dimethyl *O*-(*para*-nitrophenyl) thiophosphate; dimethyl parathion; ENT 17292; metaphos; methyl-parathion; methylthiophos; MPT; NCI CO2971; parathion-methyl; parathion methyl homolog; phosphorothioic acid *O,O*-dimethyl *O*-(4-nitrophenyl) ester; phosphorothioic acid *O,O*-dimethyl *O*-(*para*-nitrophenyl) ester

Trade Names: 8056 HC; A-Gro; Azofos; Azophos; Bay 11405; Bladan M; Cekumethion; Dalf; Drexel Methyl Parathion 4E & 601; Dygun; Dypar; E601; Ekatox; Folidol M, M40 & 80; Fosferno M50; Gearphos; Mepaton; Meptox; Metacid 50; Metacide; Metafos; Metaphor; Methyl-E 605; Methyl Fosferno; Metron; M-Parathion; Niletar; Niran M-4; Nitran; Nitrox; Nitrox 80; Oleovofotox; Parapest M-50; Parataf; Paratox; Paridol; Partron M; Penncap M & MLS; Sinafid M-48; Sixty-Three Special E.C. Insecticide; Tekwaisa; Thiophenit; Thylpar M-50; Toll; Unidol; Vertac Methyl Parathion Technisch 80%; Vofatox; Wofatox; Wofotox

1.2 Structural and molecular formulae and molecular weight



$C_8H_{10}NO_5PS$ Mol. wt: 263.2

[1]The common name 'parathion-methyl' is approved by the British Standards Institution and the International Organization for Standardization (Worthing, 1979)

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 35-36°C

(*c*) *Density*: d_4^{20} 1.358

(*d*) *Refractive index*: n_D^{35} 1.5515

(*e*) *Spectroscopy data*: Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*f*) *Solubility:* Slightly soluble in water (55-60 mg/l), light petroleum and mineral oils; soluble in most other organic solvents

(*g*) *Volatility*: Vapour pressure, 9.7×10^{-6} mm Hg at 20°C

(*h*) *Stability*: Hydrolysed by alkalis. Isomerizes to the *O,S*-dimethyl isomer on heating.

1.4 Environmental chemistry

Methyl parathion is degraded in the environment to dimethyl thiophosphoric acid, *para*-nitrophenol and methyl paraoxon (WHO, 1976); the formation of methyl paraoxon is enhanced by ultra-violet light after 8 hours (Kronenberg *et al.*, undated).

1.5 Technical products and impurities

Technical methyl parathion is available as a solution containing 80.0% active ingredient, 16.7% xylene and 3.3% inert ingredients. It is a beige to brown semi-solid with a garlic-like odour, a specific gravity of 1.225-1.235 at 25°/15.6°C, and a flash-point of 46°C. Stabilized methyl parathion is available as a solution containing 80.00% active ingredient, 14.75% xylene and 5.25% inert ingredients. It is a light-brown mobile liquid with a specific gravity of 1.2280 at 25°/15.6°C (Monsanto, undated). The following impurities were identified in one sample of technical-grade methyl parathion: *O,O*-dimethyl *S*-methyl dithiophosphate; nitroanisole; nitrophenol; isomers of methyl parathion; and the dithio analogue of methyl parathion (Warner, 1975). Methyl parathion is available as emulsifiable concentrates, as water-dispersible powders and as dusts, with various of levels of active ingredient (Worthing, 1979). Several combinations with other pesticides are also available (Berg, 1981). One emulsifiable concentrate contains 43.3% methyl parathion, 2.3% related compounds, 47.9% aromatic petroleum derivative solvent and 6.5% inert ingredients (Monsanto, 1980).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

A review on methyl parathion, which includes extensive information on production processes and uses, is available (Midwest Research Institute, 1975).

(*a*) *Production*

Methyl parathion was introduced as a commercial chemical in 1949. It is made by the reaction of *O,O*-dimethyl phosphorochloridothioate with the sodium salt of 4-nitrophenol (Worthing, 1979). It was first produced commercially in the US in 1952 (US Tariff Commission, 1953). US production of this chemical was about 23.2 million kg in 1973 (National Research Council, 1977); 24.4 million kg were reported by four companies in 1975 (US International Trade Commission, 1977), and 18 million kg by three companies in 1977, the last year for which separate production data were reported (US International Trade Commission, 1978). Two US companies reported commercial production in 1980 (US International Trade Commission, 1981a), but only one is believed to be producing methyl parathion presently and is believed to have a combined annual production capacity for methyl parathion and parathion of 29 million kg.

Imports of methyl parathion through the principal US customs districts amounted to 413 thousand kg in 1980 (US International Trade Commission, 1981b); in 1971 only 3 million kg were imported (US Tariff Commission, 1972). US exports during the first nine months of 1981 amounted to 1.39 million kg (US Department of Commerce, 1981a); 5.19 million kg were exported in 1980 (US Department of Commerce, 1981b).

Methyl parathion is believed to be produced by one company in Denmark and one in the Federal Republic of Germany. Annual production of this pesticide in western Europe is estimated to be in the range of 5-10 million kg. It is not produced commercially in Japan, but it is believed that one company each in Brazil, India and Mexico produces it.

(*b*) *Use*

Methyl parathion is used as a broad-spectrum insecticide in a wide variety of agricultural applications.

In 1976, 10.4 million kg of methyl parathion were used by US farmers on major crops, representing 17.5% of the total quantity of all active insecticide ingredients used on those crops in that year (US Department of Agriculture, 1978). In 1978, total US usage of methyl parathion is estimated to have been 11.3 million kg (less than the estimated 24 million kg used in 1974), 85% of which was used on cotton, 5% on soya beans, 4% on wheat and a total of 6% on vegetables, alfalfa, sorghum, deciduous fruits/nuts and tobacco. The estimated 9.7 million kg of methyl parathion used on cotton made it the insecticide used in by far the largest volume on cotton in 1978. The reduction in use (from the estimated 21.8 million kg used in 1974) is generally attributed to both the development of resistant insect strains and the use of integrated pest management practices.

In 1979, 143 thousand kg were used in California, 51% of which was on rice, artichokes and alfalfa (California Department of Food & Agriculture, 1980).

The Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues established in December 1979 a temporary acceptable daily intake of methyl parathion for humans of 0-0.001 mg/kg (FAO, 1980). In 1975, the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee in Pesticide Residues recommended the following tolerances for residues of methyl parathion on commodities (mg/kg): vegetables, 1; cole crops, *Cucurbitaceae* and fruit, 0.2; and processed cottonseed oil, 0.05 (WHO, 1976).

The Council of the European Communities has fixed a maximum acceptable level for residues of methyl parathion (including methyl paraoxon) in and on fruit and vegetables at 0.15 mg/kg (Commission of the European Communities, 1976). In 1981, a proposal was submitted to amend the Council Directive and fix the maximum acceptable level for residues of these compounds at 0.2 mg/kg (Commission of the European Communities, 1982).

Tolerances in the US for residues of methyl parathion in or on raw agricultural commodities are presently 0.1-5 ppm (mg/kg) for a variety of 102 commodities, including grains, hays, fodders, forages, grasses, seeds, fruits, vegetables, beans and nuts. In addition, an interim tolerance for residues of methyl parathion in or on rye of 0.5 mg/kg is established (US Environmental Protection Agency, 1980a). This compound has been identified as a toxic waste, and persons who generate, transport, treat, store or dispose of it must comply with the regulations of the Federal hazardous waste management programme (US Environmental Protection Agency, 1980b).

Notification must be given to the US Environmental Protection Agency (1980c) of any discharge into waterways of 45.4 kg or more of methyl parathion. The effluent guidelines and standards of that Agency require that the average daily effluent value of all regulated organic active ingredients manufactured at a methyl parathion production plant over 30 consecutive days not exceed 0.0018 kg/1000 kg of organic pesticide chemical (US Environmental Protection Agency, 1980d).

Shipments of methyl parathion in the US are subject to a variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1980).

Use in the US of formulations containing methyl parathion as pesticides must be carried out by or under the direct supervision of a certified applicator (US Environmental Protection Agency, 1980e), and no worker is allowed to enter a field treated with methyl parathion less than 48 hours after the treatment (US Environmental Protection Agency, 1980f).

Permissible levels of methyl parathion in the working environment have been established in at least 13 countries by regulation or recommended guidelines. These standards are listed in Table 1.

Table 1. National occupational exposure limits for methyl parathion[a]

Country	Year	Air concentration (mg/m³)	Interpretation[b]	Status
Australia	1978	0.2	Ceiling[c]	Guideline
Belgium	1978	0.2	Ceiling[c]	Regulation
Bulgaria	1971	0.1	Maximum	Regulation
Finland	1975	0.2	Ceiling[c]	Regulation
German Democratic Republic	1979	0.1	Maximum average[c] (30 min)	Regulation
Hungary	1974	0.1	TWA[c,d]	
The Netherlands	1978	0.2	Ceiling[c]	Guideline
Poland	1976	0.1	Ceiling	Regulation
Romania	1975	0.1	TWA[c]	Regulation
		0.3	Maximum	Regulation
Switzerland	1978	0.2	TWA[c]	Regulation
US (NIOSH)[e,f]	1976	0.2	TWA[c]	Guideline
USSR	1977	0.1	Maximum[c]	Regulation
Yugoslavia	1971	0.1	Ceiling	Regulation
ACGIH[g]	1981	0.2	TWA[c]	Guideline
		0.6	STEL[c]	Guideline

[a]From International Labour Office (1980)
[b]TWA - time-weighted average; STEL - short-term exposure limit
[c]A notation points out that percutaneous absorption may contribute to overall exposure.
[d]May be exceeded twice per shift as long as average does not exceed value
[e]From National Institute for Occupational Safety & Health (1980)
[f]The NIOSH and ACGIH guidelines are used in the US for both agricultural and nonagricultural workers.
[g]From American Conference of Governmental Industrial Hygienists (1981)

2.2 Occurrence

(*a*) *Natural occurrence*

Methyl parathion is not known to occur as a natural product.

(*b*) *Occupational exposure*

Approximately 150 000 US workers are potentially exposed to methyl parathion in the following occupational settings (National Institute for Occupational Safety & Health, 1976):

Aerial application personnel	Flag persons (who direct aerial application)
Area clean-up crews	Ground applicator vehicle drivers
Bagging machine operators	Janitorial personnel
Basic manufacturing employees	Laundry workers
Haulers of laundry	Maintenance personnel
Drum fillers	Mixer and blender operators
Drum reconditioning personnel	Refuse haulers
Dump personnel	Tractor tank loaders
Field checkers	Truck loaders
Fieldworkers (e.g., exposed to residues on crops and foliage)	Warehouse personnel

Potential dermal and respiratory exposures to methyl parathion in the US have been estimated as 0.7 mg/h and <0.01 mg/h, respectively, for workers checking cotton for insect damage (Hayes, 1971). In a study of exposures among these workers in 1958, methyl parathion was deposited on their gloves after application of the pesticide (0.5 lb/acre [0.6 kg/ha]) at levels of 2.69 mg/h five minutes after application, 2.22 mg/h 1.5 to 3.5 hours after application, and 0.56 mg/h 4 to 5 hours after application. Methyl parathion has been detected at a level of 1.7 mg on the trousers of cotton checkers after application of pesticides containing it to cotton fields. The workers' inhalation was estimated to be 1.2 μg over a five-hour exposure. In a similar study, an average of 15.9 mg were detected on the trousers of the workers, and the maximal airborne concentration was estimated to be 1.77 μg/m^3 (National Institute for Occupational Safety & Health, 1976).

Levels of methyl parathion in wrist washings from workers in a plant manufacturing this pesticide in the USSR ranged from 0.8 to 310 mg/m^2. Concentrations of methyl parathion in air samples from the plants were reported to be mostly <0.1 mg/m^3, with very few samples reaching 0.2 mg/m^3 (National Institute for Occupational Safety & Health, 1976).

Methyl parathion was detected in 13 of 52 indoor air samples from the households of pesticide formulators in the US at levels of 0.04 to 9.40 μg/m^2, and in three of 53 samples of outdoor air near formulators' households at levels of 0.15 to 0.71 μg/m^2 (Midwest Research Institute, 1975).

(*c*) *Air*

Concentrations of methyl parathion in air determined in studies on occupational exposure are given in section (*b*).

Maximum atmospheric levels of 29.6 ng/m^3 were detected in Alabama, USA, 5.4 ng/m^3 in Florida, and 129 ng/m^3 in Mississippi (Midwest Research Institute, 1975).

In Tennessee, USA, average hourly concentrations of methyl parathion in air were <0.57 ng/m^3 (maximum, 2.9 ng/m^3) at one site located one mile south-east of a parathion plant and one mile west of a plant producing the nematocide ethoprophos (*O*-ethyl *S*,*S*-dipropyl phosphorodithioate), and <0.64 ng/m^3 (maximum, 5.1 ng/m^3) at another site located one mile north of a methyl parathion plant. Particulate samples collected from the two sites contained <0.086 ng/m^3 methyl parathion (Foster, 1974). Air emissions from another US methyl parathion factory were reported to contain 1.0 kg/1000 kg of pesticide produced; 7.4 mg/1000 kg of pesticide produced are potentially emitted from holding ponds or lagoons by evaporation (Archer *et al.*, 1978).

(*d*) *Water and sediments*

Methyl parathion was detected in three out of 18 surface drain effluent water samples in California, USA, at concentrations of 10-190 ng/kg and in eight out of 60 subsurface drain effluent water samples at concentrations of 10-170 ng/kg (US Environmental Protection Agency, 1975).

In water samples from ten sites in the Cape Fear River Basin in North Carolina, USA, taken monthly from July 1974 through June 1975 (except October), maximum concentrations of methyl parathion in dissolved fractions and in particulate-associated fractions were 468 ng/l and 123 ng/l, respectively (Pfaender *et al.*, 1977).

Methyl parathion was detected in wastewater from a parathion production plant in the US at levels of 2.0 mg/l in pre-treatment water, 3.2 mg/l in mid-treatment water, and <0.004 mg/l in post-treatment water (Marcus *et al.*, 1978).

(*e*) *Soil and plants*

In the US National Soils Monitoring Program (1970, 1971 and 1972), the following levels of methyl parathion were detected in crops that were mature and/or ready for harvest (mg/kg): alfalfa/bur clover, 4.57; cotton (stalks, green bolls, seeds), 0.01-6.20; field corn (kernels), 0.09; mixed hay, 0.01-0.02; and sorghum (grain), 0.01 (Crockett *et al.*, 1974; Carey *et al.*, 1978, 1979).

Methyl parathion was detected at a level of 0.01 mg/kg in cropland soil in South Dakota, USA (Carey *et al.*, 1979), and at levels of 0.09 to 1.90 mg/kg in soil samples from onion-producing US states (Midwest Research Institute, 1975).

Residues were also identified in leatherstem (*Jatropha dioica*) leaves in Texas, USA, at levels of 0.01-0.09 mg/kg (Midwest Research Institute, 1975).

In a US study, 11 samples from 105 lots of imported flowers were found to contain a mean concentration of 0.30 mg/kg methyl parathion (Morse *et al.*, 1979).

(*f*) *Food, beverages and animal feeds*

The US Department of Agriculture (1981) has reported that no methyl parathion was found in 1980 in 23 samples of liver from food-producing animals.

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration for the period June 1971 to July 1975, the following levels of methyl parathion were detected in food composites from US cities (mg/kg; 'trace' implies that residues were detected and qualitatively confirmed at too low a level to be quantified, the limit of quantitation varying with food class): fruits, 0.007; and leafy vegetables, trace-0.010 (Johnson & Manske, 1976, 1977; Manske & Johnson, 1975, 1977). In 'market basket' surveys conducted by the US Food and Drug Administration in 1966-1969, methyl parathion was detected in leafy and stem vegetables at levels of 0->2.00 mg/kg and in root vegetables at levels of 0-1.00 mg/kg (Midwest Research Institute, 1975). 'Dislodgable' methyl parathion residues were found on sweet corn in the US at levels of 0-0.14 μg/cm^2 one and two days after application of the pesticide (Wicker *et al.*, 1979).

Methyl parathion was detected at levels of 0.018-0.029 mg/kg in leafy vegetables from Winnipeg, Canada in 1972 (Smith *et al.*, 1975), and at levels of 0.003-0.007 mg/kg in fruit and 0.002-0.008 mg/kg in tinned food from Auckland and Wellington, New Zealand in 1974 (Dick *et al.*, 1978). It was detected in citrus fruits in France at levels of 0.003-1.25 mg/kg (Mestres *et al.*, 1977).

(*g*) *Animals*

Methyl parathion was detected in tissue samples from estuarine fish at a mean level of 47 μg/kg (Butler & Schutzmann, 1978). It has been detected at a concentration of 59 μg/kg in the ovaries of spotted sea trout (*Cynoscion nebulosus*) collected in Texas, USA (Midwest Research Institute, 1975).

2.3 Analysis

Standard methods used for the analysis of methyl parathion in a variety of matrices are listed in Table 2.

Table 2. Methods for the analysis of methyl parathion

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Liquid formulations	Add carbon disulphide containing internal standard	GC/FID	not given	Horwitz (1980)
Emulsifiable concentrates	Dilute (carbon disulphide); dry (sodium sulphate)	IR spectroscopy	not given	US Environmental Protection Agency (1976)
Technical material and emulsifiable concentrates	Dilute (chloroform)	HPLC	not given	Horwitz (1980)
Water-dispersible powders	Extract (chloroform/acetone); concentrate; add carbon disulphide containing internal standard	GC/FID	not given	Horwitz (1980)
Duts and water-dispersible powders	Extract (ethanol); hydrolyse (potassium hydroxide) in presence of hydrogen peroxide	Colorimetry	not given	US Environmental Protection Agency (1976)
Granular formulations	Extract (acetone); dry (sodium sulphate); centrifuge; evaporate; dissolve (carbon disulphide); dry (sodium sulphate)	IR spectroscopy	not given	US Environmental Protection Agency (1976)
Micro-encapsulated formulations	Grind; extract (acetonitrile)	GC/FID	not given	Karr (1977); Horwitz (1980); Association of Official Analytical Chemists (1980)
Food products, excluding fats and oils	Reduce to amine (zinc); diazotize; derivatize [N-(1-naphthyl)ethylenediamine] (also determines parathion)	Colorimetry	0.2 mg/kg	Markus & Puma (1973)
Nonfatty foods	Extract (acetonitrile); dilute (water); extract (petroleum ether); chromatograph (Florisil)	GC/TD[b]	0.1 mg/kg	Horwitz (1980)
Kale, endive, carrots, lettuce, apples, potatoes and strawberries	Extract (ethyl acetate/sodium sulphate); decant; concentrate; sweep co-distill clean-up	GC/TD	0.01 mg/kg	Horwitz (1980)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Human or animal adipose tissue	Macerate (sand); extract (petroleum ether, acetonitrile); partition (petroleum ether); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Human milk, human and animal tissue	Macerate (acetonitrile); partition (aqueous sodium sulphate/ hexane); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Human tissue and excreta	Extract (aqueous acetone); saturate (sodium chloride); extract (hexane); chromatograph (deactivated silica gel)	GC/FPD[b]	not given	Watts (1980)
Water	Extract (dichloromethane); chromatograph (deactivated silica gel)	GC/FPD[b]	36 µg/kg	Watts (1980)
Ambient air	Soxhlet extract sampling medium (hexane/diethyl ether/acetone)	GC/FPD[b]	2 ng/m^3	Watts (1980)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; IR spectroscopy, infra-red spectroscopy; HPLC, high-performance liquid chromatography; GC/TD, gas chromatography/potassium chloride thermionic detection; GC/ECD, gas chromatography/electron capture detection; GC/FPD, gas chromatography/flame photometric detection

[b]Confirmation by thin-layer chromatography, extraction *p* values or polarography

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 female B6C3F$_1$ mice, six weeks of age, received a diet containing 62.5 or 125 mg/kg methyl parathion (purity, 94.6%; impurities not specified) for 102 weeks. Groups of 50 males received a diet containing 62.5 or 125 mg/kg methyl parathion for 37 weeks, reduced thereafter to 20 or 50 mg/kg diet up to week 102. A group of 20 male and 20 female matched controls were untreated. By the end of the study, 86% of the high- and low-dose males, 80% of the high- and low-dose females and 80% and 85% of the control males and females were still alive. No statistically significant increase in tumour incidence was found (National Cancer Institute, 1979).

Rat: Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were fed diets containing 20 or 40 mg/kg methyl parathion (purity, 94.6%; impurities not specified)

for 105 weeks. A group of 20 male and 20 female matched controls were not treated. By the end of the study, 78% of the high-dose males, 74% of the low-dose males and 85% of the control males were still alive; at that time, only 46% of the high-dose females were alive, but 82% of the low-dose females and 95% of the control females survived to the end of the study. No statistically significant difference in tumour incidence was observed (National Cancer Institute, 1979).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

A review on the toxicology of organophosphates, including methyl parathion, is available (Taylor, 1980). (See also the section, 'General Remarks on the Substances Considered'.)

LD_{50}s of methyl parathion of unspecified purity were summarized by the National Institute for Occupational Safety and Health (1976): the oral LD_{50} for male and female mice ranged from 17-200 mg/kg bw, but was greater than 200 mg/kg bw for the *S*-methyl isomer. The i.v. LD_{50} ranged from 2.3-13 mg/kg bw, the s.c. LD_{50} was 18 mg/kg bw, and the i.p. LD_{50} was 8.6-32 mg/kg bw. The oral LD_{50} for male and female rats ranged from 12-24.5 mg/kg bw. The i.p., i.v. and dermal LD_{50}s were 3.5-5.8 mg/kg bw, 4.1-14.5 mg/kg bw and 67-120 mg/kg bw, respectively. In male guinea-pigs the oral LD_{50} was 417 mg/kg bw and the i.v. LD_{50}, 50 mg/kg bw.

The acute toxicity of methyl parathion is due to inhibition of acetylcholinesterase at nerve endings, leading to an accumulation of endogenous acetylcholine. The effects are manifested by muscarinic, nicotinic and central nervous system signs and symptoms: sweating, salivation, diarrhoea, bronchorrhoea, bradycardia, bronchoconstriction, muscle fasciculations and coma. The cause of death is primarily respiratory failure (Taylor, 1980). Methyl parathion does not cause delayed polyneuropathy (Barnes & Denz, 1953).

Dogs fed diets containing up to 50 mg/kg technical methyl parathion for 90 days showed no sign of toxicity or depression of plasma or erythrocyte acetylcholinesterase (Williams *et al.*, 1959). No sign of cholinergic toxicity was reported in a two-year study in rats that were fed diets containing up to 40 mg/kg or in female mice fed up to 125 mg/kg and male mice up to 77 mg/kg (the latter as a time-weighted average concentration). Cholinesterase inhibition was not measured (National Cancer Institute, 1979).

Effects on reproduction and prenatal toxicity

Doses of methyl parathion injected as a single i.p. administration of 20 or 60 mg/kg bw to ICR-JCL mice on day 10 of pregnancy caused convulsions, hypersalivation, ataxia and tremors. The higher dose killed five of the 14 litters and induced mortality, body weight reduction, cleft palate and increased incidence of cervical ribs in foetuses. The lower dose was associated with the occurrence of cleft palate, increased number of cervical ribs and underdeveloped sternebrae, in statistically non-significant incidences when compared with controls (Tanimura *et al.*, 1967). [The Working Group noted the high doses used.]

Methyl parathion crossed the placenta in rats and was present in foetal tissues (Ackermann & Engst, 1970). No foetal effect was observed following i.p. treatment of

Holzmann (Sprague-Dawley derived) rats with 4 or 6 mg/kg bw methyl parathion on the 9th or the 15th day of pregnancy (Fish, 1966). A single i.p. injection of 5, 10 or 15 mg/kg bw to Wister rats on day 12 of pregnancy produced signs of toxicity and body weight reduction in dams in all dose groups. Mean foetal weight was reduced with 15 mg/kg bw, but there was no evidence of teratogenicity at any dose (Tanimura *et al.*, 1967). One group of rats were given 0.1, 1 or 3 mg/kg bw orally on six alternate days between days 5-15 of pregnancy, and another received 3 mg/kg bw on eight alternate days between days 5-19 of pregnancy. The high dose, irrespective of duration of treatment, caused increased resorptions, decreased foetal body weight but no malformations; lower doses had no significant effect (Fuchs *et al.*, 1976).

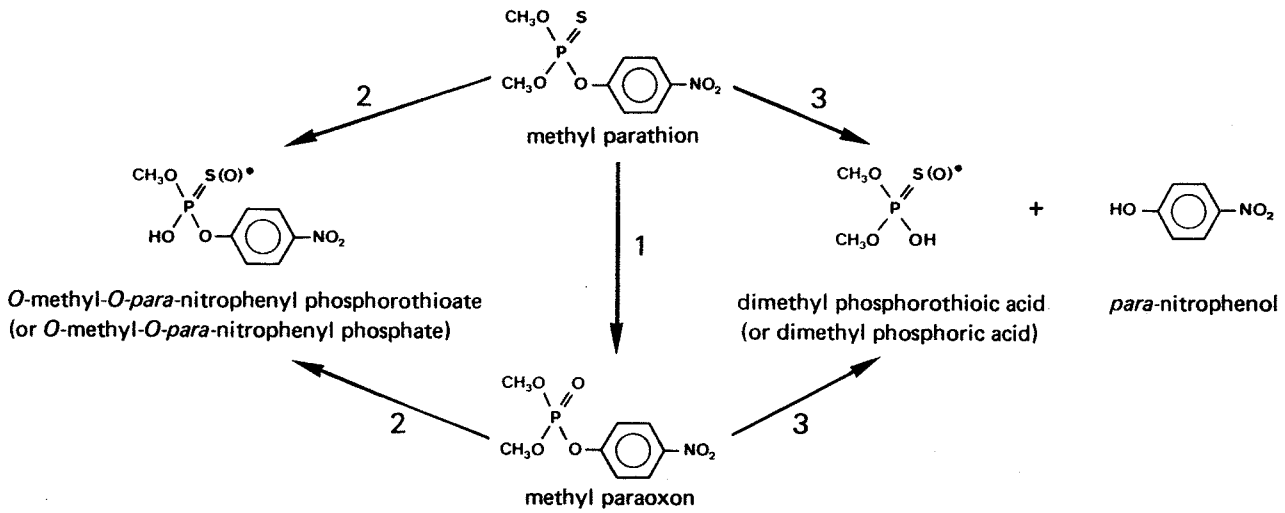
In a three-generation reproduction study, rats were fed dietary concentrations of 0, 10 or 30 mg/kg methyl parathion, and two litters of each generation were evaluated. With 30 mg/kg (about 1.5 mg/kg bw), reproductive performance of parents and survival and body weight of weanling rats were reduced, but no consistent pattern was apparent among generations or litters. With 10 mg/kg (about 0.5 mg/kg/day), postnatal survival at weaning was reduced in F_{1b} and F_{3a} (Midwest Research Institute, 1975).

Absorption, distribution, excretion and metabolism

Methyl parathion is absorbed through the gut, the skin and the respiratory tract (National Institute for Occupational Safety & Health, 1976). After an oral dose of ^{32}P-methyl parathion to mice, 75% of the radioactivity appeared rapidly as metabolites in the urine and up to 10% was excreted in the faeces (Hollingworth *et al.*, 1967).

Some hepatic metabolic pathways occurring in rodents are shown in Figure 1. The principal metabolites in mammals of methyl parathion are *para*-nitrophenol and dimethyl phosphate (Benke & Murphy, 1975). The toxic action of methyl parathion requires the metabolic formation of its oxygen analogue, methyl paraoxon (reaction 1) by liver microsomal oxidases. Detoxification reactions 2 and 3 require glutathione-dependent alkyl and aryl transferases, respectively. Formation of *para*-nitrophenol may also be catalysed by microsomal and nonmicrosomal hydrolases. Excretion of *para*-nitrophenol can be used to monitor exposure; absorption can be monitored by measuring phosphate derivatives of this compound in the urine (Benke & Murphy, 1975).

Figure 1. Metabolism of methyl parathion[a]



[a]Methyl paraoxon may be metabolized *via* the same pathways as methyl parathion, resulting in the oxygen analogue, indicated by the presence of (O)* in the figure.

Maturing rats become much less sensitive to the acute effects of methyl parathion, due to increased rates of detoxification (Benke & Murphy, 1975).

Mutagenicity and other related short-term tests

The mutagenicity of methyl parathion has been reviewed (Wild, 1975).

Methyl parathion [purity unspecified] induced DNA breaks *in vitro* in the plasmid Col E1 of *Escherichia coli* K12 (Griffin & Hill, 1978), and it gave negative results when assayed for relative toxicity without metabolic activation in the *rec⁻ hcr⁻* strain of *Proteus mirabilis* (Adler *et al.*, 1976).

Methyl parathion [purity unspecified and 80% pure, respectively] was not mutagenic to *Salmonella typhimurium* strains TA1535, TA1538, TA1536, TA1537 or TA100 with or without metabolic activation by an Aroclor-induced rat liver microsomal preparation (Carere *et al.*, 1978; Simmon *et al.*, 1977). A preparation [purity unspecified] tested for the induction of forward mutations in *E. coli* to streptomycin- or 5-methyltryptophan-resistance and to galactose prototrophy showed a weak positive effect (Mohn, 1973; Fahrig, 1974; Wild, 1975). It was also reported to be weakly mutagenic to *Serratia marcescens* strains *a21* and *a742* [details not given] (Fahrig, 1974). These studies did not employ exogenous metabolic activation. No reversion of *E. coli* WP2 and WP2*uvrA* to prototrophy was observed, with or without an Aroclor-induced rat liver microsomal preparation (Dean, 1972; Simmon *et al.*, 1977).

Methyl parathion [purity unspecified] failed to induce mutations to streptomycin resistance in a spot test with *Streptomyces coelicolor* without exogenous metabolic activation (Carere *et al.*, 1978).

Mutagenic activity was observed in the absence of exogenous metabolic activation in the ade-6 forward mutation assay in *Schizosaccharomyces pombe* (Barale *et al.*, 1979; Degraeve *et al.*, 1980). Mitotic gene conversion or gene recombination was induced in *Saccharomyces cerevisiae* with or without Aroclor-induced rat liver microsomal preparations (Fahrig, 1974; Simmon *et al.*, 1977), but neither recombinogenic activity nor point mutations were induced in *Aspergillus nidulans* in the absence of exogenous metabolic activation (Morpurgo *et al.*, 1977).

Methyl parathion [80% pure] was negative in the sex-linked recessive lethal test in male *Drosophila melanogaster* treated with 0.25 or 0.5 mg/l in feeding solutions (Waters *et al.*, 1980).

A V79 Chinese hamster cell line and human lymphoid B35M and Jeff cell lines, grown in the presence of up to 40 μg/ml methyl parathion (96.8% pure) for 28-72 hours, showed a significant dose-related increase in sister chromatid exchanges (Chen *et al.*, 1981). No increase in chromosomal aberrations was observed in human lymphoid B411-4, RMPI-1788 or RMPI-7191 cell lines treated with up to 50 μg/ml methyl parathion (98% pure) for 6-50 hours (Huang, 1973). No exogenous metabolic activation was employed in either study. Sister chromatid exchanges were induced in Chinese hamster ovary cells treated with methyl parathion (80% pure) in the presence but not in the absence of Aroclor-induced rat liver microsomal preparations (Jones *et al.*, 1982; Waters *et al.*, 1982). Methyl parathion (80% pure) did not induce unscheduled DNA synthesis in human foetal lung WI-38 fibroblasts, either in the presence or absence of an uninduced mouse liver microsomal preparation (Simmon *et al.*, 1977).

Methyl parathion (80% pure) induced presumed gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells. The effect was greater in the presence of an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

Chromosomal aberrations were not increased in bone-marrow cells of ICR male mice treated intraperitoneally with up to 100 mg/kg bw of 98% pure methyl parathion (Huang, 1973).

No increase in the number of dead implants was reported in a dominant lethal test using male mice fed methyl parathion (80% pure) at dose levels of 20, 40 and 80 mg/kg of diet for seven weeks (Simmon *et al.*, 1977) or treated with a single i.p. dose [not specified] (Degraeve *et al.*, 1980).

para-Nitrophenol, a metabolite of methyl parathion, induced mitotic gene conversion at the *ade*2 and *trp*5 loci of *S. cerevisiae* in the absence of exogenous metabolic activation (Fahrig, 1974), but did not induce reversion of *S. typhimurium* strain *his* G46 or *Serratia marcescens* strain a21 *leu* in a host-mediated assay in NMRI mice treated intraperitoneally with 75 mg/kg bw (Buselmaier *et al.*, 1972).

(*b*) *Humans*

Toxic effects

Repeated daily doses [length of treatment unspecified] of 24 mg methyl parathion caused inhibition of red blood cell and plasma cholinesterase activities in two of five human volunteers (Rider *et al.*, 1970).

Manifestations of acute poisoning by methyl parathion are similar to those described in experimental animals (Durham & Hayes, 1962; Fazekas & Rengei, 1967).

There is no documented case of peripheral neuropathy due to exposure to methyl parathion, although other organophosphate pesticides have been shown to have this effect. (See also, 'General Remarks on the Substances Considered'.) There is one report of protracted neuropsychiatric illness in two aerial applicator pilots circumstantially associated with exposure to organophosphate pesticides; methyl parathion was specified as one of the chemicals to which one of the patients had been exposed (Dille & Smith, 1964).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Methyl parathion, like parathion, is absorbed by ingestion, by inhalation and through dermal penetration.

The metabolites recovered from urine following administration of methyl parathion to human subjects were *para*-nitrophenol and dimethyl phosphate, the major metabolites of methyl parathion in experimental mammals and in man. *para*-Nitrophenol excretion was almost complete eight hours after dosing; after 24 hours, excretion of *para*-nitrophenol represented about 27% of the administered dose of methyl parathion. Excretion of

dimethyl phosphate (from hydrolysis of methyl paraoxon) represented 12% of the administered dose and was more protracted than excretion of *para*-nitrophenol (Morgan *et al.*, 1977).

Measurement of these urinary metabolites was used to monitor exposure of workers to methyl parathion or parathion and to follow its elimination in cases of poisoning (Elliott *et al.*, 1960; Arterberry *et al.*, 1961; Shafik & Enos, 1969; Wolfe *et al.*, 1970; Ware *et al.*, 1974; National Institute for Occupational Safety & Health, 1976).

The metabolism of methyl parathion in humans is similar to that reported in experimental animals, as shown in Figure 1 (Benke & Murphy, 1975; Morgan *et al*, 1977).

Mutagenicity and chromosomal effects

No increase in the frequency of chromosomal aberrations was observed in lymphocyte cultures from factory workers chronically exposed mostly to methyl parathion in combination with other pesticides (de Cassia Stocco *et al.*, 1982). Stable chromosomal aberrations were increased in lymphocytes cultured one month after acute intoxication of a group of five people with a commercial formulation of methyl parathion (Wofatox) in comparison with those of healthy controls (van Bao *et al.*, 1974). [The small number of subjects involved and the inappropriateness of the control group used do not permit the association to be established as causal.]

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Methyl parathion was tested for carcinogenicity in mice and rats by administration in the diet. No evidence of carcinogenicity was found.

Methyl parathion, administered intraperitoneally at maternally lethal doses, was teratogenic to mice. In rats, decreased viability and body weight were seen in the progeny of treated animals, but no teratogenicity was observed.

Methyl parathion was weakly or not mutagenic in bacterial systems and in *Drosophila melanogaster*, but it was mutagenic in yeasts. In mammalian cells, sister chromatid exchange and presumed gene mutations were induced, but neither chromosomal aberration nor unscheduled DNA synthesis was elicited. Chromosomal aberrations and dominant lethal mutations were not increased in mice treated with methyl parathion. There is sufficient evidence that methyl parathion is mutagenic in a variety of cellular systems, but insufficient evidence that it is mutagenic in mammals.

4.2 Human data

Methyl parathion was introduced in 1949. Its production, formulation and use as an insecticide on cotton and other crops are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic effects of methyl parathion in humans. The available data were insufficient to evaluate the chromosomal effects of methyl parathion in humans.

No case report or epidemiological study of the carcinogenicity of methyl parathion alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation

The available data do not provide evidence that methyl parathion is carcinogenic to experimental animals. No data on humans were available.

The available data provide no evidence that methyl parathion is likely to present a carcinogenic risk to humans.

5. References

Ackermann, H. & Engst, R. (1970) Presence of organophosphate insecticides in the foetus (Ger.). *Arch. Toxicol.*, *26*, 17-22

Adler, B., Braun, R., Schöneich, J. & Böhme, H. (1976) Repair-defective mutants of *Proteus mirabilis* as a prescreening system for the detection of potential carcinogens. *Biol. Zentralbl.*, *95*, 463-469

American Conference of Governmental Industrial Hygienists (1981) *TLVs*^{R} *Threshold Limit Values for Chemical Substances and Physical Agents in Workroom Environment with Intended Changes for 1981*, Cincinnati, OH, p. 23

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization* (*EPA-600/2-78-004d*), Washington DC, US Environmental Protection Agency, p. 135

Arterberry, J.D., Durham, W.F., Elliot, J.W. & Wolfe, H.R. (1961) Exposure to parathion. *Arch. environ. Health*, *3*, 112-121

Association of Official Analytical Chemists (1980) Changes in official methods of analysis made at the ninety-third annual meeting, October 15-18, 1979. 1st supplement to 13th edition Official Methods of Analysis. *J. Assoc. off. anal. Chem.*, *63*, 380-381

van Bao, T., Szabó, I., Ruzicska, P. & Czeizel, A. (1974) Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. *Humangenetik*, *24*, 33-57

Barale, R., Presciuttini, S. & Rossi, A.M. (1979) *Schizosaccharomyces pombe*-forward mutation (Ital.). In: Magni, G.E., ed., *Mutagenesi Ambiantale; Metodiche di Analisi*, Vol. 1, *Test* in vitro, pp. 105-121

Barnes, J.M. & Denz, F.A. (1953) Experimental demyelination with organo-phosphorous compounds. *J. Pathol. Bacteriol.*, *65*, 597-605

Benke, G.M. & Murphy, S.D. (1975) The influence of age on the toxicity and metabolism of methyl-parathion and parathion in male and female rats. *Toxicol. appl. Pharmacol.*, *31*, 254-269

Berg, G.L. (1981) *Farm Chemicals Handbook, 1981*, Willoughby, OH, Meister Publishing Co., pp. C218, C219

Buselmaier, W., Röhrborn, G. & Propping, P. (1972) Mutagenicity study with pesticides in the host-mediated assay and the dominant lethal test in the mouse. *Biol. Zentralbl.*, *91*, 311-325

Butler, P.A. & Schutzmann, R.L. (1978) Residues of pesticides and PCBs in estuarine fish, 1972-1976 - National Pesticide Monitoring Program. *Pestic. Monit. J.*, *12*, 5l-59

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 171, 172

Carere, A., Ortali, V.A., Cardamone, G. & Morpurgo, G. (1978) Mutagenicity of dichlorvos and other structurally related pesticides in *Salmonella* and *Streptomyces*. *Chem.-biol. Interactions*, *22*, 297-308

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1978) Pesticide residue levels in soils and crops, 1971 - National Soils Monitoring Program (III). *Pestic. Monit. J.*, *12*, 117-136

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1979) Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). *Pestic. Monit. J.*, *12*, 209-229

de Cassia Stocco, R., Becak, W., Gaeta, R. & Rabello-Gay, M.N. (1982) Cytogenetic study of workers exposed to methyl-parathion. *Mutat. Res.*, *103*, 71-76

Chen, H.H., Hsueh, J.L., Sirianni, S.R. & Huang, C.C. (1981) Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. *Mutat. Res.*, *88*, 307-316

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residue in and on fruit and vegetables. *Off. J. eur. Communities*, *L340*, 26-31

Commission of the European Communities (1982) Proposal for a Council Directive amending Annex II to Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. eur. Communities, C95*, 6-10

Crockett, A.B., Wiersma, G.B., Tai, H., Mitchell, W.G., Sand, P.F. & Carey, A.E. (1974) Pesticide residue levels in soils and crops, FY-70-National Soils Monitoring Program (II). *Pestic. Monit. J., 8*, 69-97

Dean, B.J. (1972) The mutagenic effects of organophosphorus pesticides on micro-organisms. *Arch. Toxicol., 30*, 67-74

Degraeve, N., Gilot-Delhalle, J., Moutschen, J., Moutschen-Dahmen, M., Colizzi, A., Chollet, M. & Houbrechts, N. (1980) Comparison of the mutagenic activity of organophosphorus insecticides in mouse and in the yeast *Schizosaccharomyces pombe* (Abstract no. 65). *Mutat. Res., 74*, 201-202

Dick, G.L., Heenan, M.P., Love, J.L., Udy, P.B. & Davidson, F. (1978) Survey of trace elements and pesticide residues in the New Zealand diet. 2. Organochlorine and organophosphorus pesticide residue content. *N. Z. J. Sci., 21*, 71-78

Dille, J.R. & Smith, P.W. (1964) Central nervous system effects of chronic exposure to organophosphate insecticides. *Aerosp. Med., 35*, 475-478

Durham, W.F. & Hayes, W.J., Jr (1962) Organic phosphorus poisoning and its therapy. *Arch. environ. Health, 6*, 21-47

Elliott, J.W., Walker, K.C., Penick, A.E. & Durham, W.F. (1960) A sensitive procedure for urinary *p*-nitrophenol determination as a measure of exposure to parathion. *J. agric. Food Chem., 8*, 111-113

Fahrig, R. (1974) *Comparative mutagenicity studies with pesticides.* In: Montesano, R. & Tomatis, L., eds, *Chemical Carcinogenesis Essays (IARC Scientific Publications No. 10)*, Lyon, pp. 161-181

FAO (1980) *Pesticide Residues in Food: 1979 Evaluations*, Rome, pp. 367-368

Fazekas, I.G. & Rengei, B. (1967) Methyl parathion content of human organs after lethal Wofatex poisoning (Ger.). *Arch. Toxikol., 22*, 381-386

Fish, S.A. (1966) Organophosphorus cholinesterase inhibitors and fetal development. *Am. J. Obstet. Gynecol., 96*, 1148-1154

Foster, R.L. (1974) Detection and measurement of ambient organophosphate pesticides. *Proc. Annu. Ind. Air Pollut. Control Conf., 4*, 66-98

Fuchs, V., Golbs, S., Kühnert, M. & Osswald, F. (1976) Studies on prenatal toxic action of methyl parathion on Wistar rats and comparison with cyclophosphamide and trypan blue (Ger.). *Arch. exp. Vet. Med. (Leipzig), 30*, 343-350

Griffin, D.E., III & Hill, W.E. (1978) In vitro breakage of plasmid DNA by mutagens and pesticides. *Mutat. Res., 52*, 161-169

Hayes, W.J., Jr (1971) Studies on exposure during the use of anticholinesterase pesticides. *Bull. World. Health Organ.*, *44*, 272-288

Hollingworth, R.M., Metcalf, R.L. & Fukuto, T.R. (1967) The selectivity of sumithion compared with methyl parathion. Metabolism in the white mouse. *J. agric. Food Chem.*, *15*, 242-249

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 118-119, 466-479

Huang, C.C. (1973) Effect on growth but not on chromosomes of the mammalian cells after treatment with three organophosphorus insecticides. *Proc. Soc. exp. Biol. Med.*, *142*, 36-40

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 150, 151

Johnson, R.D. & Manske, D.D. (1976) Pesticide residues in total diet samples (IX). *Pestic. Monit. J.*, *9*, 157-169

Johnson, R.D. & Manske, D.D. (1977) Pesticide and other chemical residues in total diet samples (XI). *Pestic. Monit. J.*, *11*, 116-131

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

Karr, J.J. (1977) Collaborative study of gas-liquid chromatographic method for analysis of microencapsulated methyl parathion insecticide. *J. Assoc. off. anal. Chem.*, *60*, 862-864

Kronenberg, G., Macklin, W.B. & Dolinger, P.M. (undated) *Methyl Parathion* (*Monograph no. 7 Environmental Health Evaluations of California Restricted Insecticides*), Menlo Park, CA, Peter M. Bolinger Associates

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII). *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

Marcus, M., Spigarelli, J. & Miller, H. (1978) *Organic Compounds in Organophosphorus Pesticide Manufacturing Wastewaters* (*PB-289821*), Springfield, VA, National Technical Information Service, p. 22

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. II, Washington DC, Food & Drug Administration, Pesticide Reg. Sec. 120.121

Mestres, R., Illes, S., Campo, M. & Tourte, J. (1977) A multiple residue method for citrus fruits: Its technique and some data. *Proc. Int. Soc. Citriculture, 2*, 426-429

Midwest Research Institute (1975) *Substitute Chemical Program. Initial Scientific and Minieconomic Review of Methyl Parathion (PB-241 840)*, Springfield, VA, National Technical Information Service, pp. 37, 108, 109, 112, 113, 114, 122-124, 129, 130, 143-155

Mohn, G. (1973) 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12. Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. *Mutat. Res., 20*, 7-15

Monsanto (undated) *Parathion, Methyl Parathion, Stabilized Methyl Parathion (Tech. Bull. No. AG-1b (EX))*, St Louis, MO, Agricultural Division, pp. 12-21

Monsanto (1980) *Niran M-4 Insecticide by Monsanto*, St Louis, MO, Agricultural Division

Morgan, D.P., Hetzler, H.L., Slach, E.F. & Lin, L.I. (1977) Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. *Arch. environ. Contam. Toxicol., 6,* 159-173

Morpurgo, G., Aulicino, F., Bignami, M., Conti, L. & Velcich, A. (1977) Relationship between structure and mutagenicity of dichlorvos and other pesticides. *Rend. Cl. Sci. fis. mat. nat., Ser. 8, 62*, 692-701

Morse, D.L., Baker, E.L. & Landrigan, P.J. (1979) Cut flowers: A potential pesticide hazard. *Am. J. public Health, 69*, 53-56

National Cancer Institute (1979) *Bioassay of Methyl Parathion for Possible Carcinogenicity (Tech. Rep. Ser. No. 157; DHEW Publ. No. (NIH) 79-1713)*, Washington DC, US Department of Health, Education, & Welfare

National Institute for Occupational Safety & Health (1976) *Criteria for a Recommended Standard - Occupational Exposure to Methyl Parathion (DHEW (NIOSH) Publ. No. 77-106)*, Washington DC, US Department of Health, Education, & Welfare

National Institute for Occupational Safety & Health (1980) *Summary of NIOSH Recommendations for Occupational Health Standards*, Cincinnati, OH

National Research Council (1977) *Drinking Water and Health*, Part II, Ch. 6 & 7, *A Report of the Safe Drinking Water Committee*, Washington, DC, National Academy of Sciences, pp. VI-156, VI-157

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Pfaender, F.K., Shuman, M.S., Dempsey, H. & Harden, C.W. (1977) *Monitoring Heavy Metals and Pesticides in the Cape Fear River Basin of North Carolina*, Chapel Hill, NC, Water Resources Research Institute, University of North Carolina, pp. 29, 119

Rider, J.A., Swader, J.I. & Puletti, E.J. (1970) Methyl parathion and guthion anticholinesterase effects in human subjects (Abstract no. 588). *Fed. Proc., 29*, 349

Shafik, M.T. & Enos, H.F. (1969) Determination of metabolic and hydrolytic products of organophosphorus pesticide chemicals in human blood and urine. *J. agric. Food Chem.*, *17*, 1186-1189

Simmon, V.F., Mitchell, A.D. & Jorgenson, T.A. (1977) *Evaluation of Selected Pesticides as Chemical Mutagens. In vitro and in vivo Studies* (*EPA-600/1-77-028*), Research Triangle Park, NC, US Environmental Protection Agency

Smith, D.C., Leduc, R. & Tremblay, L. (1975) Pesticide residues in the total diet in Canada. IV. 1972 and 1973. *Pestic. Sci.*, *6*, 75-82

Tanimura, T., Katsuya, T. & Nishimura, H. (1967) Embryotoxicity of acute exposure to methyl parathion in rats and mice. *Arch. environ. Health*, *15*, 609-613

Taylor, P. (1980) *Anticholinesterase agents.* In: Gilman, A.G., Goodman, L.S. & Gilman, A., eds, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed., New York, MacMillan, pp. 100-119

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976*, *Agricultural Economic Report No. 418*, Washington DC, Economics, Statistics, and Cooperatives Service, p. 16

US Department of Agriculture (1981) *Monitoring Phase Biological Residue Report, January 1980 through December 1980*, Washington DC, Residue Evaluation and Surveillance Division

US Department of Commerce (1981a) *US Exports, Schedule E Commodity by Country* (*FT410/September 1981*), Washington DC, Bureau of the Census, US Government Printing Office, p. 2-88

US Department of Commerce (1981b) *US Exports, Schedule E Commodity by Country* (*FT410/September 1980*), Washington DC, Bureau of the Census, US Government Printing Office, p. 2-88

US Department of Transportation (1980) Transport of hazardous wastes and hazardous substances. *US Code Fed. Regul.*, *Title 49*, parts 171-174, 176, 177; *Fed. Regist.*, *45*, 34560, 34626

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices, Methyl Parathion*, Washington DC, Office of Pesticide Programs, Association of Official Analytical Chemists, EPA-2; EPA-3; EPA-4; EPA-5

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 180.121, p. 544; part 180.319, pp. 591, 592

US Environmental Protection Agency (1980b) Hazardous waste management system; identification and listing of hazardous waste. *US Code Fed. Regul.*, *Title 40*, part 261; *Fed. Regist.*, *45*, 33085, 33122-33127, 33132

US Environmental Protection Agency (1980c) Protection of environment. *US Code Fed. Regul.*, *Title 40*, parts 116, 117, pp. 35-50

US Environmental Protection Agency (1980d) Protection of environment. *US Code Fed. Regul., Title 40*, parts 455.20, 455.22, pp. 285, 286

US Environmental Protection Agency (1980e) Protection of environment. *US Code Fed. Regul., Title 40*, part 162.31, pp. 427-431

US Environmental Protection Agency (1980f) Protection of environment. *US Code Fed. Regul., Title 40*, part 170.3, p. 480

US International Trade Commission (1977) *Synthetic Organic Chemicals, US Production and Sales, 1975* (*USITC Publ. 804*), Washington DC, US Government Printing Office, pp. 181, 187

US International Trade Commission (1978) *Synthetic Organic Chemicals, US Production and Sales, 1977* (*USITC Publ. 920*), Washington DC, US Government Printing Office, pp. 321, 330

US International Trade Commission (1981a) *Synthetic Organic Chemicals, US Production and Sales, 1980* (*USITC Publ. 1183*), Washington DC, US Government Printing Office, p. 239

US International Trade Commission (1981b) *Imports of Benzenoid Chemicals and Products, 1980* (*USITC Publ. 1163*), Washington DC, US Government Printing Office, p. 106

US Tariff Commission (1953) *Synthetic Organic Chemicals, US Production and Sales, 1952* (*Report No. 190, Second Series*), Washington DC, US Government Printing Office, p. 133

US Tariff Commission (1972) *Imports of Benzenoid Chemicals and Products, 1971* (*TC Publ. 496*), Washington DC, US Government Printing Office, p. 96

Ware, G.W., Morgan, D.P., Estesen, B.J. & Cahill, W.P. (1974) Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Azodrin, ethyl and methyl parathion. *Arch. environ. Contam. Toxicol., 2*, 117-129

Warner, J.S. (1975) *Identification of impurities in technical-grade pesticides*. In: *Substitute Chemical Program - the First Year of Progress. Proceedings of a Symposium*, Vol. IV, *Chemical Methods Workshop* (*PB-261 007*), Washington DC, US Department of Commerce, National Technical Information Service, pp. 31-65

Waters, M.D., Simmon, V.F., Mitchell, A.D., Jorgenson, T.A. & Valencia, R. (1980) An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. *J. environ. Sci. Health, B15*, 867-906

Waters, M.D., Sandhu, S.S., Simmon, V.V., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity*. In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health

Effects Research Laboratory, Environmental Toxicology Division, sect. 5A(1)(a); 5A(2)(a)(b); 6A(1); 8B; 10A; 12B; 12C; 12F

WHO (1976) *1975 Evaluations of Some Pesticide Residues in Food* (*WHO Pestic. Residue Ser., No. 5*), Geneva, pp. 242-255

Wicker, G.W., Williams, W.A. & Guthrie, F.E. (1979) Exposure of field workers to organophosphorus insecticides: Sweet corn and peaches. *Arch. environ. Contam. Toxicol.*, *8*, 175-182

Wild, D. (1975) Mutagenicity studies on organophosphorus insecticides. *Mutat. Res.*, *32*, 133-150

Williams, M.W., Fuyat, H.N. & Fitzhugh, O.G. (1959) The subacute toxicity of four organic phosphates to dogs. *Toxicology*, *1*, 1-7

Wolfe, H.R., Wash, W., Durham, W.F. & Armstrong, J.F. (1970) Urinary excretion of insecticide metabolites. Excretion of *para*-nitrophenol and DDA as indicators of exposure to parathion. *Arch. environ. Health*, *21*, 711-716

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 402

PARATHION

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 56-38-2

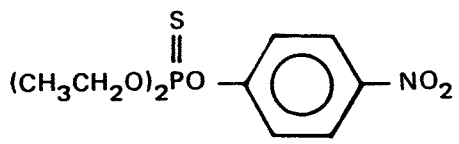
Chem. Abstr. Name: Phosphorothioic acid, *O,O*-diethyl *O*-(4-nitrophenyl) ester

IUPAC Systematic Name: *O,O*-Diethyl *O*-4-nitrophenyl phosphorothioate

Synonyms: Diethyl *para*-nitrophenol thiophosphate; diethyl *para*-nitrophenyl phosphorothionate; diethyl 4-nitrophenyl phosphorothionate; *O,O*-diethyl *O*-(*para*-nitrophenyl) phosphorothioate; diethyl-*para*-nitrophenyl monothiophosphate; diethyl *para*-nitrophenyl thionophosphate; *O,O*-diethyl *O*-(*para*-nitrophenyl) thionophosphate; *O,O*-diethyl *O*-*para*-nitrophenyl thiophosphate; *O,O*-diethyl *O*-4-nitrophenyl thiophosphate; diethyl parathion; DNTP; ENT 15,108; ethyl parathion; NCI CO0226; parathion-ethyl; phosphorothioic acid *O,O*-diethyl *O*-(4-nitrophenyl) ester; phosphorothioic acid *O,O*-diethyl *O*-(*para*-nitrophenyl) ester; SNP; thiophos

Trade Names: AAT; AATP; AC 3422; ACC 3422; Alkron; Alleron; American Cyanamid 3422; Aphamite; Aralo; Bayer E-605; Bladan; Bladan F; Corothion; Danthion; Drexel Parathion 8E; E 605; E 605f; Ethlon; Ekatin WF & WF ULV; Ekatox; Etilon; Folidol; Folidol E & E 605; Folidol oil; Fosfermo; Fosferno; Fosferno 50; Fostox; Gearphos; Genithion; Lirothion; Niran; Niran E-4; Nitrostygmine; NIU1F 100; Nourithion; Oleofos 20; Oleoparaphene; Oleoparathion; Orthophos; Pacol; Panthion; Paradust; Paraflow; Paramar; Paramar 50; Paraphos; Parathene; Parawet; Pencap E; Penncap E; Penphos; Phoskil; Phos-Kil; Phosphenol; RB; Rhodiasol; Rhodiatox; Rhodiatrox; Selephos; Sixty-Three Special E.C. Insecticide; Soprathion; Stathion; Sulphos; Super Rodiatox; Thiophos; Thiophos 3422; Vapophos; Vitrex

1.2 Structural and molecular formulae and molecular weight



$C_{10}H_{14}NO_5PS$ Mol. wt: 291.3

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Pale-yellow liquid

(*b*) *Boiling-point*: 157-162°C at 0.6 mm Hg

(*c*) *Melting point*: 6.1°C (Weast, 1982)

(*d*) *Density*: d_4^{25} 1.265

(*e*) *Refractive index:* n_D^{25} 1.5370

(*f*) *Spectroscopy data:* Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1981) have been reported.

(*g*) *Solubility:* Very slightly soluble in water (24 mg/l at 25°C); slightly soluble in petroleum oils; miscible with most organic solvents

(*h*) *Volatility:* Vapour pressure, 3.78×10^{-5} mm Hg at 20°C

(*i*) *Stability:* Rapidly hydrolysed in alkaline media to diethylphosphorothioic acid and *para*-nitrophenol; slowly isomerizes to the *O,S*-diethyl isomer on heating above 130°C (Metcalf, 1981)

(*j*) *Reactivity:* Readily reduced to *O,O*-diethyl *O-para*-aminophenyl phosphorothioate; oxidized with difficulty to diethyl *para*-nitrophenyl phosphate (Metcalf, 1981)

1.4 Environmental chemistry

Parathion undergoes three important chemical conversions in the environment. The first is substitution of oxygen for the sulphur bound to phosphorus, yielding paraoxon. The formation of paraoxon is enhanced in the presence of ultra-violet light, and the decomposition also results in the following products: *O,S*-diethyl *O*-4-nitrophenyl phosphorothioate; *O,O*-diethyl *S*-4-nitrophenyl phosphorothioate; *O,O*-bis(4-nitrophenyl) *O*-ethyl phosphorothioate; *O,O*-bis(4-nitrophenyl) *O*-ethyl phosphate; *O,O*-diethyl *O*-phenyl phosphorothioate and *O,O*-diethyl *O*-phenyl phosphate (Mulla *et al.*, 1981).

The second chemical reaction to which parathion is subject is hydrolysis at the ester linkage, yielding diethylphosphorothioic acid and *para*-nitrophenol. This is the principal mechanism by which parathion degrades in the environment. Paraoxon is similarly hydrolysed, yielding diethylphosphoric acid. Esterase enzymes in animal tissues accelerate hydrolysis (Heath, 1961).

The third chemical reaction involves reduction of the aromatic nitro group to form aminoparathion, with a resultant loss of biological activity (Menzie, 1969).

1.5 Technical products and impurities

Technical parathion is available as a dark-brown liquid containing 98.5% active ingredient and 1.5% inert ingredients. It has a specific gravity of 1.260-1.280 at 25°/25°C

and a minimal crystallizing-point of 0°C (Monsanto, undated). The following impurities were identified in one sample of technical-grade parathion: *O,O*-diethyl thiophosphoryl chloride; *O,O,O*-triethyl thiophosphate; *O,O*-diethyl *S*-ethyl thiophosphate; *O,O*-diethyl *S*-ethyl dithiophosphate; nitrophenetole; nitrophenol; parathion isomers; and the dithio analogue of parathion (Warner, 1975). Parathion is available as water-dispersible powders and emulsifiable concentrates, with various levels of active ingredient, and as dusts, smokes and aerosol concentrates. It is also available in a combination with the insecticide thiometon (*S*-2-ethylthioethyl *O,O*-dimethyl phosphorodiethioate) (Worthing, 1979). One emulsifiable concentrate contains 44.3% parathion, 2.3% related compounds, 47.9% xylene-range aromatic solvents, and 5.5% inert ingredients (Monsanto, 1980).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Parathion was introduced as a commercial chemical in 1947. It is made by the reaction of *0,0*-diethyl phosphorochloridothioate with the sodium salt of 4-nitrophenol (Worthing, 1979). It was first produced commercially in the US in 1948 (US Tariff Commission, 1949). Separate production data were last reported in 1970, when four companies reported total production of 6.9 million kg (US Tariff Commission, 1972). Total US production by three companies in 1972 has been estimated to have been 6.4 million kg (US Environmental Protection Agency, 1975). Only one US company presently produces it and is believed to have a combined annual production capacity for parathion and methyl parathion of 29 million kg.

Imports of parathion through the principal US customs districts amounted to 17 thousand kg in 1980 (US International Trade Commission, 1981). Separate data on US exports of parathion are not available; however, in 1977 combined US exports of parathion and methyl parathion were 6.1 million kg (US Department of Commerce, 1978), and exports of parathion (technical-grade and as formulations) in 1972 have been estimated to have been 1.8 million kg active ingredient (US Environmental Protection Agency, 1975).

Parathion is believed to be produced by one company in Denmark and one in the Federal Republic of Germany. Annual production of this pesticide in western Europe is estimated to be in the range of 2-5 million kg. It is not produced commercially in Japan.

Parathion is produced in India; in 1980-1981, 1213 thousand kg were made (GIFAP, 1982). It is also believed to be produced by one company in Brazil and possibly in Mexico.

(*b*) *Use*

A review of the uses of parathion in the early 1970s has been published (Midwest Research Institute, 1975). It is used as a broad-spectrum insecticide in agricultural applications.

In 1976, 3 million kg of parathion were used by US farmers on major crops, representing 5.1% of the total quantity of all active insecticide ingredients used on those crops in that year (US Department of Agriculture, 1978). The results of a survey of citrus growers in 1977 indicated that approximately 79.5 thousand kg were used in California/Arizona and 0.5 thousand kg in Florida (Haydu, 1981). In 1978, total US usage of parathion is estimated to have been 3.9 million kg (down from an estimated 4.7 million kg in 1974), 35% of which was used on wheat, 14% on deciduous fruits/nuts, 12% on vegetables, 12% on miscellaneous field crops, 9% on sorghum, 7% on cotton, 5% on citrus, and a total of 7% on alfalfa, corn and soya beans. In 1979, 350 thousand kg were used in California, 53% of which was on almonds, prunes, peaches and oranges (California Department of Food & Agriculture, 1980).

Use of parathion in Japan has been suspended. In 1977, it was reported that possession of parathion in Jamaica had been banned (Diggory *et al.*, 1977).

The Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues in March 1965 established an acceptable daily intake of parathion for humans of 0-0.005 mg/kg bw (WHO, 1965).

The Council of the European Communities has fixed a maximum acceptable level for residues of parathion (including paraoxon) in and on fruit and vegetables at 0.5 mg/kg (Commission of the European Communities, 1976). In 1981, a proposal was submitted to amend the Council Directive and fix the maximum acceptable levels for residues of these compounds at 1 mg/kg in or on citrus fruit, apricots and peaches, and 0.5 mg/kg for other products (Commission of the European Communities, 1982).

Tolerances in the US for residues of parathion in or on raw agricultural commodities are presently 0.1-5 mg/kg for a variety of 102 commodities, including grains, hays, fodders, forages, grasses, seeds, fruits, vegetables, beans and nuts. In addition, an interim tolerance for residues of parathion in or on rye of 0.5 mg/kg is established (US Environmental Protection Agency, 1980a). This compound has been identified as a toxic waste, and persons who generate, transport, treat, store or dispose of it must comply with the regulations of the Federal hazardous waste management programme (US Environmental Protection Agency, 1980b).

Notification must be given to the US Environmental Protection Agency (1980c) of any discharge into waterways of 0.454 kg or more of parathion. The effluent guidelines and standards of this Agency require that the average daily effluent value of all regulated organic active ingredients manufactured at a parathion production plant over 30 consecutive days not exceed 0.0018 kg/1000 kg of organic pesticide chemical (US Environmental Protection Agency, 1980d).

Shipments of parathion in the US are subject to a variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1980).

Use in the US of formulations containing parathion as pesticides must be carried out by or under the direct supervision of a certified applicator (US Environmental Protection Agency, 1980e), and no worker is allowed to enter a field treated with parathion less than 48 hours after the treatment (US Environmental Protection Agency, 1980f).

Permissible levels of parathion in the working environment have been established in at least 14 countries by regulation or recommended guidelines. These standards are listed in Table 1.

Table 1. National occupational exposure limits for parathion[a]

Country	Year	Air concentration (mg/m^3)	Interpretation[b]	Status
Australia	1978	0.1	Ceiling[c]	Guideline
Belgium	1978	0.1	Ceiling[c]	Regulation
Bulgaria	1971	0.05	Maximum[c]	Regulation
Finland	1975	0.1	Ceiling[c]	Regulation
Federal Republic of Germany	1979	0.1	TWA[c]	Guideline
Hungary	1974	0.05	TWA[c,d]	Regulation
Italy	1978	0.1	TWA[c]	Guideline
Japan	1978	0.1	Ceiling[c]	Guideline
The Netherlands	1978	0.1	Ceiling[c]	Guideline
Romania	1975	0.05	TWA[c]	Regulation
		0.15	Maximum	Regulation
Switzerland	1978	0.1	TWA[c]	Regulation
US OSHA[e,f]	1978	0.1	TWA[c]	Regulation
		20	Ceiling (30 min)[c]	Regulation
NIOSH[e,f]	1976	0.05	TWA[c]	Guideline
USSR	1977	0.05	Maximum[c]	Regulation
Yugoslavia	1971	0.1	Ceiling[c]	Regulation
ACGIH[e,f,g]	1981	0.1	TWA[c]	Guideline
		0.3	STEL[c]	Guideline

[a]From International Labour Office (1980)
[b]TWA - time-weighted average; STEL - short-term exposure limit
[c]A notation points out that percutaneous absorption may contribute to overall exposure.
[d]May be exceeded twice per shift as long as average does not exceed value
[e]The OSHA regulation and the NIOSH and ACGIH guidelines are used in the US for both agricultural and nonagricultural workers.
[f]From National Institute for Occupational Safety & Health (1980a)
[g]From American Conference of Governmental Industrial Hygienists (1981)

2.2 Occurrence

(*a*) *Natural occurrence*

Parathion is not known to occur as a natural product.

(*b*) *Occupational exposure*

(i) *Populations exposed*: No data were available to the Working Group on the number of agricultural workers exposed to parathion, nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to parathion, namely, its production and formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980b, 1981) estimated that 10 thousand US workers in six nonagricultural industries were exposed to parathion.

The following occupations are reported to be potential sources of exposure to parathion (National Institute for Occupational Safety & Health, 1976):

Aerial application personnel	Flaggers (who direct aerial application)
Area clean-up crews	Ground applicator vehicle drivers
Bagging machine operators	Janitorial personnel
Basic manufacturing employees	Laundry workers
Haulers of laundry	Maintenance personnel
Drum fillers	Mixer and blender operators (formulators, "swampers")
Drum reconditioning personnel	Refuse haulers
Dump personnel	Tractor tank loaders
Field checkers	Truck loaders
Field workers (exposed to "residues" on fruits, vegetables, foliage, etc)	Warehouse personnel

(ii) *Potential dermal, respiratory and oral exposure*: The mean potential dermal and respiratory exposures of workers in two US plants formulating 25% parathion as a water-dispersible powder were reported to be 67.3 and 0.62 mg/h of work activity, respectively. The highest levels of dermal and respiratory exposure observed were 335.3 and 3.38 mg/h, respectively, for a pesticide bagger (Wolfe *et al.*, 1978). These exposures were also measured for workers who were applying parathion spray (0.05%-0.09%) and parathion dust (l%-2%) and for field workers during application of an aerial parathion spray (9%). Mean dermal exposures ranged from 4.7 mg/h for workers operating tractor-mounted boom ground sprayers in row crops to 84 mg/h for workers flagging for aeroplane application of a 9% parathion spray to fruit orchards; mean respiratory exposures ranged from <0.0l mg/h for workers operating tractor-mounted boom ground sprayers in row crops to 0.16 mg/h for workers operating dusters under the same conditions (Wolfe *et al.*, 1967). Those authors also summarized published studies of potential dermal and respiratory exposures to parathion (Table 2).

Table 2. Potential dermal and respiratory exposures to parathion during spraying[a]

Activity	*Exposure (mg/h)*	
	Dermal	*Respiratory*
Air blast spraying fruit orchards	2.4-77.7	0.02-0.16
Concentrated air blast spraying fruit orchards	28	0.06
High-pressure power hand-gun spraying fruit orchards	55.8	0.19
Hand knapsack mist spraying tomato bushes	9.1	0.29

[a]From Wolfe *et al.* (1967)

The mean respiratory and dermal exposures of US workers spraying orchards with parathion were 0.24 mg and 137.9 mg per work period, respectively (Durham *et al.*, 1972). The estimated whole-body doses for 15 volunteer orange harvesters (respiratory and dermal exposure) ranged from 132-317 μg (Popendorf, 1976). Average amounts of technical parathion deposited on the bodies of operators spraying apple orchards in north-central Washington, USA ranged from 12.8 mg/ft^2 [137.8 mg/m^2] per hour to 21.5 mg/ft^2 [231.4 mg/m^2] per hour. Potential dermal and respiratory exposures were estimated to be 6.4-8.9 mg/kg bw and 0.005-0.022 mg/kg bw, respectively (Batchelor & Walker, 1954).

Dermal exposures of two pilots involved in crop spraying in Israel were in the range of 35-180 μg/h. Skin absorption among aircraft loaders ranged from 10-540 μg/h (Richter *et al.*, 1980). In a similar study, respiratory intake of parathion by pilots was estimated to be 9-620 μg/h and dermal exposures for pilots and ground crews were 5-200 μg/h and 40-5000 μg/h, respectively. Previous studies showed that for pilots respiratory doses averaged 20 μg/h and dermal exposure, 13 000 μg/h (Cohen *et al.*, 1979).

In studies of oral exposure to parathion, it was estimated that US workers thinning apples in an orchard sprayed 24 or 48 hours earlier would potentially ingest up to 0.190 mg parathion on their lunches; food carried on the workers contained <0.001-2.065 mg. Levels of parathion on the workers' hands ranged from 2.5-5.7 mg; levels on the hands of spraymen using a 25% water-dispersible powder ranged from 0.1-19.2 mg/h of work activity (Armstrong *et al.*, 1973). Men applying parathion to apple orchards by means of air-blast machines deposited 0.003-0.235 mg parathion per cigarette when smoking (Hayes, 1971), and up to 2.3 μg/cigarette was disposited on cigarettes carried in shirt pockets during spraying (Wolfe *et al.*, 1975a).

Potential dermal and respiratory exposures to parathion of an apple thinner in an orchard sprayed with a pesticide solution containing 0.03% parathion were reported (Wolfe *et al.*, 1975b) (Table 3).

Table 3. Potential dermal and respiratory exposures to parathion at various times after spraying[a]

Time after spraying (h)	*Exposure (mg/h)*	
	Dermal	*Respiratory*
1	4.1-11.3	0.031-0.150
24	3.7-14.2	0.012-0.146
48	1.7-8.9	0.017-0.078
72	1.6-8.1	0.016-0.05
96	1.0-4.8	0.009-0.03

[a]From Wolfe *et al.* (1975b)

Levels of 38.8 μg and 0.1 μg parathion were detected in hexane hand rinsings from two farmers 31 and 60 days after spraying, respectively. Parathion was also detected on the hands of a farmer two months after he had moved a bottle of the pesticide (Kazen *et al.*, 1974).

(iii) *Workplace air*: Concentrations of 0.03-0.15 mg/m^3 parathion have been reported in work areas after crop treatment (Hayes, 1971). Ambient air concentrations in an orchard where aerial application of parathion was being conducted and in residential areas near the treated orchard ranged from 0-100 μg/m^3 and 0-20 μg/m^3, respectively. The highest concentration observed was in the area of loading and mixing the pesticide and ranged from a trace to 5530 μg/m^3 (Foster, 1974).

Parathion concentrations in air during crop spraying in Israel were 290-360 μg/m^3 in an aircraft washing area, 0-440 μg/m^3 in cockpits of aeroplanes, 13-97 μg/m^3 in a hangar, 43 μg/m^3 in an outside office, 20 μg/m^3 in a mechanics' workshop, 4-63 μg/m^3 in a loading area and 11-68 μg/m^3 on ground crew (personal samples) (Richter *et al.*, 1980).

Air residues of parathion within a plum orchard after treatment with 2.2 kg/ha of a 25 wt% water-dispersible powder were 4100 ng/m^3 and 16.1 ng/m^3, 1 and 21 days,

respectively, after treatment of the orchard; 100 m downwind from the orchard, the air residues were 35.0 ng/m^3 and 0.86 ng/m^3 2 and 21 days, respectively, after treatment (Woodrow *et al.*, 1977).

Levels of parathion in air after spray application in an orchard ranged from 0-5.53 mg/m^3. The highest levels were found during loading and mixing of the pesticide. Other reported values for air concentrations of parathion range from 0.04-15 mg/m^3 during spray operations, 16-26 mg/m^3 during mixing and 0.1-0.8 mg/m^3 in a parathion manufacturing plant (Batchelor & Walker, 1954).

Parathion was detected in indoor air samples from pesticide formulators' households at a mean concentration of 2.24 μg/m^2, and in samples from farmers' households at a mean concentration of 0.26 μg/m^2. Levels of parathion in outdoor air samples near formulators' and farmers' homes ranged from 0.0-12.92 μg/m^2 (Midwest Research Institute, 1975).

(*c*) *Air*

Concentrations of parathion in air determined in studies on occupational exposure are given in section (*b*).

Parathion was detected in the air in Orlando, Florida, USA at a maximum level of 465 ng/m^3 of air (Midwest Research Institute, 1975). The maximum level of parathion in air samples taken within the city limits of Fresno, California, USA, 25 miles from an orchard, was 0.3 ng/m^3 (Woodrow *et al.*, 1977).

Air emissions from parathion manufacture in the US have been reported to contain 1.0 kg/1000 kg of pesticide produced; 0.014 kg/1000 kg of pesticide produced are potentially emitted from holding ponds or lagoons by evaporation (Archer *et al.*, 1978).

(*d*) *Water and sediments*

Parathion was detected in three out of 14 surface drain effluent water samples in California at concentrations of 6-500 ng/kg (Midwest Research Institute, 1975). It was detected in wastewater from a parathion production plant in the US at levels of 0.24, <0.006 and <0.006 mg/l in pre-treatment, mid-treatment and post-treatment water samples, respectively (US Environmental Protection Agency, 1978). Residues of 0.3-70 μg/l parathion have been detected in water from a variety of sources (Sethunathan *et al.*, 1977).

In 1975-1977, no parathion was detected in rain water, stream water or in stream bed sediments in 11 agricultural watersheds in southern Ontario where parathion was being used (limit of detection for water, 0.l μg/l, and approximately 200 times higher for sediments) (Braun & Frank, 1980).

Residues of parathion have reportedly been identified in water of the Rhine River in the Federal Republic of Germany at levels of 0.01-0.1 μg/l (Midwest Research Institute, 1975).

(*e*) *Soil and plants*

In the US National Soils Monitoring Program (1970 to 1972), the following levels of parathion were detected in crops that were mature and/or ready for harvest (mg/kg):

alfalfa/bur clover, 3.2-36.2; corn stalks, 0.36; cotton (stalks, green bolls, seeds), 0.01-7.32; grass hay, 0.01; and sorghum (grain, stalks), 0.02-0.03 (Crockett *et al.*, 1974; Carey *et al.* 1978, 1979). In 1969, 1971 and 1972, parathion was detected at levels of 0.01-3.01 mg/kg in cropland soil in several US states (Midwest Research Institute, 1975; Carey *et al.*, 1978, 1979). It was detected in 10 soil samples from Massachusetts at levels of 1.0-1.3 μg/kg (Deubert & Gray, 1976). In selected California citrus groves in 1975, parathion residue levels ranged from 35-70 ng/cm^2 in soil-dust and from 1710-2050 ng/cm^2 in soil to 1-cm depth (Spear *et al.*, 1977). This pesticide was detected in soil in the US on which onions were grown, at levels of 0.02-2.55 mg/kg (Midwest Research Institute, 1975).

Parathion was detected in surface soils (0-15 cm) of 31 apple orchards and 16 sweet-cherry orchards in Ontario, Canada, at maximum levels of 0.021 and 0.006 mg/kg, respectively. Less than 0.004 mg/kg were detected in subsurface soil (15-30 cm) in the cherry orchards (Frank *et al.*, 1976). This pesticide was found in soil from farms in south-western Ontario at levels of 0.01-0.03 mg/kg (Harris *et al.*, 1977). Residues of parathion were also detected in soils in south-western Ontario, particularly after its repeated application for onion maggot control. Levels of 0.01-0.06 mg/kg have been recovered from the 0- to 10-cm layer of a light sandy soil; little or no residue was found in the deeper layers, even after regular and repeated applications over a 15-year period (Sethunathan *et al.*, 1977).

Top-soil samples from 37 pesticide spray tank fill sites throughout the Wenatchee Valley in Washington, USA contained from 0.3-330 mg/kg parathion (Midwest Research Institute, 1975).

Parathion residues were found in one of nine samples of leatherstem (*Jatropha dioica*) leaves (0.01 mg/kg)) and in one of nine samples of surface soil (0.01 mg/kg) in Texas, USA (Midwest Research Institute, 1975). Residues in soil after treatment of a California, USA plum orchard with 2.2 kg/ha of a 25 wt% water-dispersible powder ranged from 1.32-0.52 mg/kg 0 to 14 days after application. Residues of parathion in the leaves after treatment ranged from 147 to 0.43 mg/kg 0 to 21 days after application (Woodrow *et al.*, 1977).

Parathion residues on leaves in an apple orchard in the US after spraying with a pesticide solution containing 0.03% parathion ranged from 2.8-4.7 μg/cm^2 one hour after spraying to 0.3-0.9 μg/cm^2 after 96 hours. In another study, after application of parathion to apples during a one-week period, 1320 ng/cm^2 were detected in foliage after one day and 106 ng/cm^2 after seven days (Wolfe *et al.*, 1975b). Residues on leaves in selected Californian (USA) citrus groves in 1975 ranged from 1.4-10.8 ng/cm^2 (Spear *et al.*, 1977).

In a US study, six samples from 105 lots of imported flowers contained a mean concentration of 0.41 mg/kg parathion (Morse *et al.*, 1979).

(*f*) *Food, beverages and animal feeds*

The US Department of Agriculture (1981) reported that no parathion was found in 1980 in 23 samples of liver from food-producing animals.

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration for the period June 1971 to July 1976, the following levels of parathion were detected in food composites from US cities (mg/kg; 'trace' implies that residues were detected and qualitatively confirmed at too low a level to be quantified,

the limit of quantitation varying with food class): leafy vegetables, trace-0.022; garden fruits, trace-0.009; grain and cereal, 0.006; legume and root vegetables, trace-0.005; fruits, trace-0.003; and potatoes, oils, fats and shortening, trace (Manske & Johnson, 1975, 1977; Johnson & Manske, 1976, 1977; Johnson *et al.*, 198l).

In 'market basket' surveys conducted by the US Food and Drug Administration in 1964-1969, parathion was detected in large fruits and small fruits at levels of 0-1.50 mg/kg; in grains and cereal for human use and in beans at levels of 0-0.50 mg/kg; in leafy, stem and root vegetables at 0->2.00 mg/kg and in vine and ear vegetables at 0-2.00 mg/kg (Midwest Research Institute, 1975).

'Dislodgable' parathion residues found on sweet corn and peaches ranged from 0-0.26 μg/cm^2 one to two days after pesticide application and from 0-2.36 μg/cm^2 two to seven days after application (Wicker *et al.*, 1979).

In a study of pesticide residues in the total diet in Canada, the estimated daily intake (μg/person) of parathion in food composites from five Canadian regions was in the range of 0-0.04 from leafy vegetables and 0-3.3 from fruits (limit of detection, 8 μg/kg). Average dietary intake of parathion by Canadians for the period 1970 to 1978 ranged from <0.001-0.006 μg/kg bw (McLeod *et al.*, 1980). An average of 0.001 mg/kg was detected in leafy vegetables obtained in Toronto, Ontario in 1973 (Smith *et al.*, 1975).

During the period August 1974-July 1975, a trace level of parathion was detected in only one of 10 composite samples of infant vegetable preparations from US cities (Johnson *et al.*, 1979).

In a study of pesticide residues in the New Zealand diet, the estimated daily intake of parathion was reported to be 0.5-4 μg. It was detected in fruit samples at levels of 0.001-0.003 mg/kg and in canned food samples at levels of 0.001-0.002 mg/kg (Dick *et al.*, 1978).

Parathion residues were detected in 3/52 fruit samples obtained in Rome, but no values were reported (Botre *et al.*, 1974). Levels of 0.004-0.08 mg/kg were detected in citrus fruits in France (Mestres *et al.*, 1977).

Parathion was not detected in commercial animal feeds for laboratory animals (limit of detection, 5 μg/kg) (Coleman & Tardiff, 1979).

(*g*) *Animals*

Fish and shellfish specimens collected in the US in May 1973 contained 0.01-0.04 mg/kg parathion. Homogenates of clams (*Mya arenaria*) from Massachusetts, USA contained 0.02-0.03 mg/kg, extracts of two rainbow trout contained 0.015 and 0.017 mg/kg, and a shellfish homogenate (oyster) contained 38-41 μg/kg parathion (Deubert & Gray, 1976). This insecticide was detected in tissue samples from fish from 144 estuaries throughout the US at mean levels of 10-75 μg/kg (Butler & Schutzmann, 1978).

Parathion residues were detected in two of 20 samples of muscle tissue of rodents (0.04, 0.11 mg/kg); in three of 19 samples of whole lizards (0.01-0.10 mg/kg); and in six of 19 samples of bird muscle (0.01-0.21 mg/kg) collected in Texas, USA (Midwest Research Institute, 1975).

(*h*) *Human tissues and secretions*

The blood of a victim of accidental parathion poisoning (caused by dermal contact during harvesting of tobacco plants less than 24 hours after application of parathion) was found to contain 0.034 mg/l parathion (Lores *et al.*, 1978).

2.3 Analysis

Standard methods used for the analysis of parathion in a variety of matrices are listed in Table 4.

Table 4. Methods for the analysis of parathion

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Liquid formulations	Dilute (chloroform) or extract (methanol)	HPLC/UV	not given	Horwitz (1980); US Environmental Protection Agency (1976)
	Dilute (carbon disulphide) or extract (acetone)	GC/FID	not given	Horwitz (1980); US Environmental Protection Agency (1976)
Dusts and powders	Soxhlet extract (diethyl ether); extract (chilled aqueous sodium carbonate); acidify (acetic/hydrochloric acids); heat; reduce (zinc); filter; add sodium bromide	Titration with sodium nitrite	not given	Horwitz (1980); Sutherland & Miskus (1964)
	Extract (ethanol); filter; reflux (potassium hydroxide/aqueous ethanol)	Colorimetry	not given	Horwitz (1980)
Micro-encapsulated formulations	Grind; extract (acetonitrile)	GC/FID	not given	Association of Official Analytical Chemists (1980); Horwitz (1980); Karr (1980)
Fruit	Strip (benzene); dissolve (aqueous ethanol); acidify (hydrochloric acid); reduce (zinc); add sodium nitrite and sodium sulphamate; derivatize [*N*-(1-naphthyl)ethylene-diamine]	Colorimetry	5 µg	Sutherland & Miskus (1964)
Nonfatty foods	Extract (acetonitrile); dilute (water); extract (petroleum ether); chromatograph (Florisil)	GC/TD[b]	0.01 mg/kg	Horwitz (1980)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Vegetables	Extract (ethyl acetate/sodium sulphate); decant; sweep co-distill	GC/TD	0.01 mg/kg	Horwitz (1980)
Human or animal adipose tissue	Macerate (sand); extract (petroleum ether, acetonitrile); partition (petroleum ether); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Human milk, human and animal tissue	Macerate (acetonitrile); partition (aqueous sodium sulphate/hexane); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Human tissue and excreta	Extract (aqueous acetone); saturate (sodium chloride); extract (hexane); chromatograph (silica gel)	GC/FPD[b]	not given	Watts (1980)
Plasma	Extract (acidified hexane); centrifuge	GC/ECD	not given	Zweig & Sherma (1972)
Air	Collect (impinger with ethylene glycol); extract (hexane)	GC/FPD	5 μg/m^3	Taylor (1977a)
Air	Collect (glass-fibre filter); extract (iso-octane)	GC/FPD	0.07 mg/m^3	Taylor (1977b)
Ambient air	Soxhlet extract sampling medium (hexane/diethyl ether/acetone)	GC/FPD[b]	4 ng/m^3	Watts (1980)
Water	Extract (dichloromethane); chromatograph (deactivated silica gel)	GC/FPD[b]	16 μg/kg	Watts (1980)
Sediment	Dry; blend; transfer to a chromatograph; elute (acetone, hexane); extract (aqueous sodium sulphate); extract water layer (hexane/dichloromethane); combine extracts; wash (water); dry (sodium sulphate); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)

[a]Abbreviations: HPLC/UV, high-performance liquid chromatography/ultra-violet absorbance detection; GC/FID, gas chromatography/flame ionization detection; GC/TD, gas chromatography/potassium chloride thermionic detection; GC/ECD, gas chromatography/electron capture detection; CG/FPD, gas chromatography/flame photometric detection

[b]Confirmation by thin-layer chromatography, extraction *p* values or polarography

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, five weeks of age, were fed diets containing 80 or 160 mg/kg parathion (purity, 99.5%; impurities unspecified) for 71 and 62 weeks, respectively (males), and for 80 weeks (females) and were observed for 18 and 28 weeks, respectively (males), and 9 and 10 weeks, respectively (females). A matched control group of 10 animals of each sex was observed for 90 weeks; a pooled control group of 140 males and 130 females was used for statistical analysis. The high-dose group received a maximum tolerated dose. By the end of the experiment, 80% of high-dose males, 92% of high-dose females, 92% of low-dose males and females, 100% of the matched control males and 80% of control females were still alive. No statistically significant increase in tumour incidence was found (National Cancer Institute, 1979). [The Working Group noted the short duration of treatment.]

Rat: Groups of albino rats [strain unspecified], about four weeks of age, were fed diets containing parathion (purity, 95-97%; impurities unspecified). High-dose groups of male animals received 50 (10 rats) or 100 mg/kg (8 rats) of diet for 104 weeks; low-dose groups of 20 male rats received 10 or 25 mg/kg of diet for 88 weeks; control groups of 10 and 20 male rats, respectively, were available. Groups of 8-9 female rats received levels of 10 or 50 mg/kg for 64 weeks; 6 females served as controls. Another group of female rats [number not given] received 100 mg/kg of diet for an unstated period. Survival was 68% in the males receiving 10 mg/kg, 87% in those receiving 25 mg/kg and 70% in the control group; 80% in the males receiving 50 mg/kg, 63% in the 100 mg/kg group and 60% in controls. Survival of females was 100% in the 10 mg/kg group, 63% in the 50 mg/kg group and 66% in the control group. The rats in the highest dose group received a maximum tolerated dose. Histological examination of a limited number of tissues from survivors of the high-dose groups revealed no tumours (Hazleton & Holland, 1950). [Because of limitations in experimental design, such as the small number of animals used and the limited histopathology, the absence of a carcinogenic effect could not be considered to be conclusive.]

Groups of 36 male and 36 female albino rats [strain unspecified], six weeks of age, were administered parathion (76.8% pure) in the diet on six days per week at concentrations of 10, 20 or 50 mg/kg of diet for up to one year and at concentrations of 75 and 100 mg/kg of diet for 27 and 19 days, respectively. The last two groups were observed for a further nine months. A control group of 30 rats per sex was observed for one year. After one year, survival was 98%, 97%, 97% and 61% in the groups receiving 0, 10, 20 and 50 mg/kg, respectively; mortality during the dosing period was 82% in the 75 mg/kg group and 90% in the 100 mg/kg group. Histological examination of about 20% of rats which died and 9-14 rats/group receiving 0, 10, 20 and 50 mg/kg still alive after one year showed no tumour incidence, except one spindle-cell sarcoma of the mediastinum in one rat receiving 20 mg/kg. No tumour was seen on histological examination of five rats that died during the dosing period, of the 13 survivors after nine months in the group receiving 75 mg/kg group and of the seven survivors after nine months of those receiving 100 mg/kg (Barnes & Denz, 1951). [Because of limitations in experimental design, such as the short

duration of the exposure and observation periods and the fact that tissues from only a few rats were examined, the absence of a carcinogenic effect could not be considered to be conclusive.]

Groups of 50 male and 50 female Osborne-Mendel rats, five weeks of age, were fed diets containing parathion (purity, 99.5%; impurities unspecified) at various levels. Male rats received 40 or 30 mg/kg of diet (low-dose) and 80 or 60 mg/kg of diet (high-dose) for 13 and 67 weeks, respectively, giving time-weighted average doses of 32 and 63 mg/kg of diet. Female rats received 20, 30 or 20 mg/kg of diet (low-dose) and 40, 60 or 40 mg/kg of diet (high-dose) for 13, 21 and 46 weeks, respectively, giving time-weighted average doses of 23 and 45 mg/kg of diet. All rats were subsequently observed for 32-33 weeks. The high-dose groups received a maximum tolerated dose. A matched control group of 10 males and 10 females was observed for 112 weeks; a pooled control group of 90 males and 90 females was used for statistical analysis. Survival was 72% of the males and 68% of the females in the high-dose groups, 62% of the males and 72% of the females in the low-dose groups, and 70% for males and females in the matched control group. In males, the combined incidence of adrenal cortical adenomas and carcinomas was 3/80 in pooled controls, 0/9 in matched controls, 7/49 in the low-dose group and 11/46 in the high-dose group (Cochran-Armitage test for positive trend: $p < 0.001$ using pooled controls, $p = 0.048$ using matched controls; Fisher exact test: high-dose *versus* pooled controls, $p < 0.001$, low-dose *versus* pooled controls, $p = 0.035$). The incidence of cortical adenomas alone was 2/80 in pooled controls, 0/9 in matched controls, 5/49 in the low-dose group and 9/46 in the high-dose group (Cochran-Armitage test for positive trend: $p = 0.001$ using pooled controls; Fisher exact test: high-dose *versus* pooled controls, $p = 0.002$). The incidence of islet-cell carcinomas of the pancreas in males was: 0/79 in pooled controls, 0/9 in matched controls, 1/49 in the low-dose group and 3/46 in the high-dose group (Cochran-Armitage test for positive trend: $p = 0.024$ using pooled controls; Fisher exact test: high-dose *versus* pooled controls, $p = 0.048$). The incidence of follicular-cell adenomas of the thyroid in males was: 5/76 in pooled controls, 3/10 in matched controls, 2/46 in the low-dose group and 8/43 in the high-dose group (Cochran-Armitage test for positive trend: $p = 0.037$ using pooled controls; Fisher exact test: low-dose *versus* pooled controls, $p = 0.035$, high-dose *versus* pooled controls, $p = 0.046$). In females, the combined incidence of adrenal cortical adenomas and carcinomas was: 4/78 in the pooled controls, 1/10 in the matched controls, 6/47 in the low-dose group and 13/42 in the high-dose group (Cochran-Armitage test for positive trend: $p < 0.001$ using pooled controls, $p = 0.028$ using matched controls; Fisher exact test: high-dose *versus* pooled controls, $p < 0.001$) (National Cancer Institute, 1979). [The Working Group noted the short duration of treatment, the fact that at present the significance of the occurrence of adrenal cortical adenomas in aged rats is not well understood, and that adrenal cortical carcinomas occurred in only two rats of each sex and treatment group.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The toxicity of organophosphates, including parathion, has been reviewed (Taylor, 1980). (See also the section 'General Remarks on the Substances Considered'.)

LD_{50}s of parathion of unspecified purity were summarized by the National Institute for Occupational Safety and Health (1976): the oral LD_{50} was 13 mg/kg bw in male rats and 3.6 mg/kg bw in female rats; the respective dermal LD_{50}s were 21 and 6.8 mg/kg bw. The i.p. LD_{50} was 7 mg/kg bw in male rats, 4 mg/kg bw in female rats, and 9-10 mg/kg bw in mice. The single dermal LD_{50} in rabbits was 40-50 mg/kg bw. The i.v. LD_{50} was 3-5 mg/kg bw in cats and 12-20 mg/kg bw in dogs. The LC_{50} (4-h exposure) was 84.0 mg/m^3 in male rats and >37.1 mg/m^3 in male dogs.

The acute toxicity of parathion is due to inhibition of acetylcholinesterase at nerve endings, leading to an accumulation of endogenous acetylcholine. The effects are manifested by muscarinic, nicotinic and central nervous system signs and symptoms: sweating, salivation, diarrhoea, bronchorrhoea, bradycardia, bronchoconstriction, muscle fasciculations and coma. The cause of death is primarily respiratory failure (Taylor, 1980). Parathion does not cause delayed polyneuropathy (Barnes & Denz, 1953).

Red-blood cell acetylcholinesterases were inhibited in rats after exposure to parathion by inhalation (National Institute for Occupational Safety & Health, 1976). The maximum dietary concentrations of parathion that had no effect on red-cell cholinesterase activity in rats and pigs were 20 and 1000 μg/kg bw per day, respectively, over a period of 25-122 days (Edson *et al.*, 1964). No potentiation with other anticholinesterase compounds has been observed (DuBois, 1963). Single or repeated administration of the phenothiazine derivatives chlorpromazine and promazine increased the toxicity of a single dose of parathion in male rats (Gaines, 1962).

Toxic doses of parathion produced a dose-dependent necrosis of rat skeletal muscle within 24 hours after treatment (Kibler, 1973; Wecker & Dettbarn, 1976; Wecker *et al.*, 1978a,b).

Effects on reproduction and prenatal toxicity

I.p. injection of 4-12 mg/kg bw parathion (analytical grade) on days 12, 13 and 14 of pregnancy to Swiss-Webster mice caused resorptions and a significant reduction in foetal weight. With the lowest dose, foetal body weight was reduced, but the incidence of resorptions was within the control range (Harbison, 1975).

In rats, i.p. injection of maternally toxic doses of 3 and 3.5 mg/kg bw on day 11 of pregnancy resulted in an increased number of resorptions, a reduced number of foetuses/litter, reductions in foetal and placental weight but no malformation (Kimbrough & Gaines, 1968). In another study, rats were injected subcutaneously with 1.5 or 2.0 mg/kg bw per day for 4 days beginning on day 1, 7 or 13 of pregnancy. Four of 52 dams recieving 2 mg/kg died, and all remaining treated dams showed loss of body weight and signs of poisoning. The offspring of groups beginning treatment on day 7 or 13 of pregnancy showed a transient reduction in growth from birth but no other effect (Talens & Woolley, 1973). In a two-generation reproduction study in rats, a reduction in litter size at birth and high postnatal mortality during the first generation were observed with dietary concentrations of 20 and 50 mg/kg, and increased pup mortality was seen in the second generation with 10 mg/kg (Barnes & Denz, 1951).

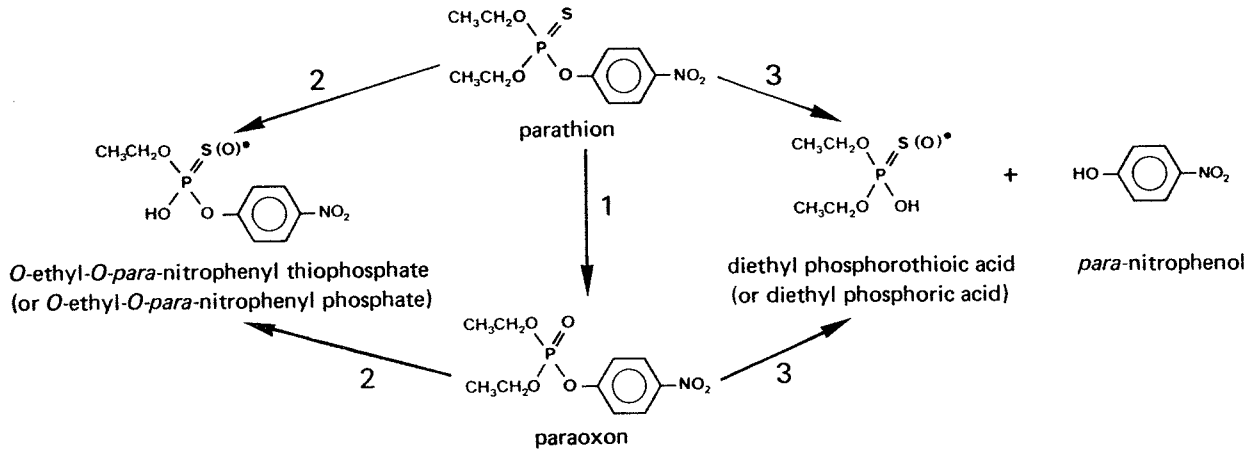
A reduction in pseudocholinesterase and plasma renin activities and altered electrocardiographic patterns were observed in the 24-day-old progeny of rats given oral doses of 0.01, 0.1 or 1.0 mg/kg bw per day on days 2-15 of pregnancy (Deskin *et al.*, 1979).

Absorption, distribution, excretion and metabolism

Parathion is absorbed through the skin (Fredriksson, 1961), the gut and by inhalation (National Institute for Occupational Safety & Health, 1976). In mice, parathion is absorbed twice as rapidly through the gut as through the skin (Ahdaya *et al.*, 1978). After s.c. injections of ^{32}P-parathion to mice, autoradiography showed it to be very slowly absorbed, with a low level of radioactivity in the blood. The highest activity appeared in the salivary glands and cervical fat, followed by the liver, kidney, gastric wall, thyroid, spleen and lungs. Less activity was noted in the central nervous system, musculature and bone marrow (Fredriksson & Bigelow, 1961). Percutaneous absorption rates of parathion and its metabolite paraoxon were used to compare i.v. infusion and dermal absorption in rabbits: paraoxon was absorbed about five times more rapidly than parathion (Nabb *et al.*, 1966).

Parathion is metabolized primarily in the liver but also in the brain and lungs (Norman & Neal, 1976). Some of the important hepatic metabolic pathways of parathion in biological systems are shown in Figure 1.

Figure 1. Metabolism of parathion[a]



[a]Paraoxon may be metabolized *via* the same pathways as parathion, resulting in the oxygen analogue, indicated by the presence of (O)* in the figure.

The toxic effects of parathion are attributed to its oxidative desulphuration to paraoxon by liver microsomal oxidase (reaction 1). Detoxification reactions 2 and 3 might require glutathione-dependent alkyl and aryl transferases, respectively. Reaction 3 may also be catalysed by microsomal and nonmicrosomal hydrolases. The occurrence of the urinary metabolites of parathion, *para*-nitrophenol and alkyl phosphates is used to monitor worker exposure to parathion (Arterberry *et al.*, 1961).

Mutagenicity and other short-term tests

Parathion was negative in the *rec*-assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*) and the *Escherichia coli Pol*-assay without exogenous metabolic activation (Simmon *et al.*, 1977). In a large number of tests, it did not induce gene mutations in *E.coli*, *Salmonella typhimurium*, *Serratia marcescens*, *Saccharomyces cerevisiae*, or *Schizosaccharomyces pombe*, with or without exogenous

metabolic activation (Mohn, 1973; Fahrig, 1974; Simmon *et al.*, 1977; Bartsch *et al.*, 1980; Degraeve *et al.*, 1980).

para-Nitrophenol, a metabolite of parathion, was not mutagenic to *S. marcescens* or *S. typhimurium* G46 in a mouse host-mediated assay following i.p. administration of 75 mg/kg bw (Buselmaier *et al.*, 1972). *para*-Nitrophenol (Wild, 1975), but not parathion (Fahrig, 1974; Simmon *et al.*, 1977), has been reported to induce mitotic gene conversion in the yeast *Saccharomyces cerevisiae*. Samples of unspecified purity of another metabolite, paraoxon, were reported in two abstracts to be weakly mutagenic to *S. typhimurium* TA98 and TA1538, without metabolic activation (Quinto *et al.*, 1981) and to induce a few lethal mutations in mice treated with 0.3 mg/kg bw (Degraeve *et al.*, 1979).

No excess of sex-linked recessive lethal mutations was induced in *Drosophila melanogaster* by parathion (99% pure) (Valencia, 1977; Waters *et al.*, 1982). Negative results have also been reported for the induction of unscheduled DNA synthesis by parathion (99% pure) in WI38 human fibroblasts, with or without uninduced mouse liver microsomal fractions (Jones *et al.*, 1982; Waters *et al.*, 1982). No dominant lethal mutation was induced in mice fed parathion (99% pure) for seven weeks at dose levels of 62.5, 125 or 250 mg/kg of diet (Simmon *et al.*, 1977) or following a single i.p. injection (Degraeve *et al.*, 1980).

Decloitre (1978) has reported in an abstract that radiolabelled metabolites from ^{14}C-parathion bound to DNA *in vitro* in the presence of a rat liver microsomal metabolizing system. When ^{14}C-parathion was fed at 6 mg/kg in the diet to rats and mice for four weeks or administered by a single i.p. injection of 3 mg/kg bw, activity was found in liver.

(*b*) *Humans*

Toxic effects

Parathion has been the cause of hundreds of human poisonings, many of which were fatal. These have occurred as a result of occupational contact (Grob *et al.*, 1949; Quinby & Lemmon, 1958; Milby *et al.*, 1964), suicidal use (Toivonen *et al.*, 1959) and accidental ingestion (Toivonen *ef al.*, 1959; Kanagaratnam *et al.*, 1960; Mootoo & Singh, 1966; Eitzman & Wolfson, 1967; Davies *et al.*, 1970). The major sources of accidental poisoning by parathion have been the contamination of food during transport and storage. According to Hayes (1960, 1965), most of such accidents take place in developing countries.

Manifestations of acute poisoning in humans by parathion are similar to those described in experimental animals (Aldridge, 1950; Namba, 1971; National Institute for Occupational Safety & Health, 1976). There is no documented case of peripheral neuropathy due to parathion exposure, although other organophosphate pesticides have been shown to have this effect. (See also 'General Remarks on the Substances Considered'.)

In eight adult volunteers who consumed 0.05 mg/kg bw parathion, no depression of red-blood cell or plasma cholinesterase activities and no symptom of illness was observed; lower doses induced an increase in the plasma cholinesterase level (Rider *et al.*, 1958; Williams *et al.*, 1958). Repeated daily doses of 6 mg/day administered to adult volunteers slightly inhibited plasma cholinesterase (Rider *et al.*, 1969). The maximum dietary concentration of parathion that had no effect on red-blood cell cholinesterase activity in man was 50 μg/kg bw per day over a period of 25-122 days (Edson *et al.*, 1964).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Parathion is absorbed from the skin of human volunteers (Maibach *et al.*, 1971), and of workers; it is also absorbed from the cornea, the conjunctiva and the respiratory mucosa (Durham *et al.*, 1972). Inhalation of parathion vapour and/or aerosol leads to rapid absorption with imminent risk of poisoning (Hartwell *et al.*, 1964; Hartwell & Hayes, 1965). The frequency and severity of poisonings that follow parathion ingestion (Kanagaratnam *et al.*, 1960; Mootoo & Singh, 1966; Leuzinger *et al.*, 1971) attest to the efficiency its absorption through the gut.

Within 48 hours following oral administration of 2-mg doses of parathion to adult volunteers, 30-40% of parathion metabolites were eliminated in the urine (Morgan *et al.*, 1977). *para*-Nitrophenol and diethyl thiophosphate are excreted the most rapidly, and very little of these metabolites appears in the urine eight hours after dosing. Diethyl phosphate (from hydrolysis of paraoxon) persisted in the urine up to 24 hours after dosing. Measurement of these urinary metabolites can be used to monitor absorption of parathion by exposed workers (Shafik & Enos, 1969; Wolfe *et al.*, 1970) and to follow excretion of the compound in cases of parathion poisoning (Davies *et al.*, 1966; Haley *et al.*, 1978). Metabolites of parathion are readily detectable in urine after exposures that are too low to depress blood cholinesterase activity (Morgan *et al.*, 1977).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

Barthel *et al.* (1976) found 30 cases of cancer on follow up of 316 men exposed to a variety of herbicides (2,4-D and MCPA), insecticides (DDT, hexachlorocyclohexane, toxaphene, parathion, DNOC [4,6-dinitro-*ortho*-cresol]), fungicides (copper-containing and other) and, to some extent, arsenic, in the German Democratic Republic. There were 11 cases of lung cancer, 4 of prostatic cancer, 3 of stomach cancer, 3 of skin cancer, 2 of bladder cancer, 2 of rectal cancer, one each of kidney, oesophagus, gall-bladder and epiglottis cancer and one lymphoma. The expected number of lung cancers was estimated to be 0.54. [The expected number would be higher if it were calculated correctly, by multiplication of the population annual incidence rate by the man-years at risk in each age group rather than by the number of men in each age group. Due to the fact that the exposure was to many chemicals, including arsenic, it was not possible to determine the specific carcinogenic effect of any one pesticide.]

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Parathion was tested for carcinogenicity in one strain of mice and in three strains of rats by administration in the diet. Although a dose-related increase in the incidence of adrenal cortical adenomas was observed in male and female rats of one strain, the significance of the occurrence of those lesions in aged rats is not well understood. A low incidence of carcinomas at this site was observed in each of the treated groups in animals of both sexes. The other experiments in rats and the experiment in mice were considered to be inadequate for evaluation.

Parathion produced embryocidal effects and foetal growth reduction but no malformation in mice and rats at doses that were generally below the level that is toxic for the maternal organism.

Parathion was not mutagenic to a wide range of microorganisms in the presence or absence of rat liver microsomal preparations. It did not induce unscheduled DNA synthesis in cultured mammalian cells, recessive lethal mutations in *Drosophila melanogaster* or dominant lethal mutations in mice. Thus, no evidence has been found that parathion is mutagenic.

4.2 Human data

Parathion was introduced in 1947. Its production, formulation and use as an insecticide in a variety of agricultural applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of parathion in humans.

No case report or epidemiological study of the carcinogenicity of parathion alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation

There is inadequate evidence to evaluate the carcinogenicity of parathion to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of parathion to humans.

5. References

Ahdaya, S.M., Shah, P.V. & Guthrie, F.E. (1978) Comparative penetration (*in vivo*) of insecticides through the skin and gastrointestinal tract of mice (Abstract no. 235). *Toxicol. appl. Pharmacol.*, *45*, 320

Aldridge, W.N. (1950) Some properties of specific cholinesterase with particular reference to the mechanism of inhibition of diethyl p-nitrophenyl thiophosphate (E 605) and analogues. *Biochem. J.*, *46*, 451-460

American Conference of Governmental Industrial Hygienists (1981) *TLVs*^{R} *Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981*, Cincinnati, OH, p. 24

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization* (*EPA-600/2-78-004d*), Washington DC, US Environmental Protection Agency, pp. 80, 135

Armstrong, J.F., Wolfe, H.R., Comer, S.W & Staiff, D.C. (1973) Oral exposure of workers to parathion through contamination of food items. *Bull. environ. Contam. Toxicol.*, *10*, 321-327

Arterberry, J.D., Durham, W.F., Elliottt, J.W. & Wolfe, H.R. (1961) Exposure to parathion. Measurement by blood cholinesterase level and urinary *p*-nitrophenol excretion. *Arch. environ. Health*, *3*, 476-485

Association of Official Analytical Chemists (1980) Changes in official methods of analysis made at the ninety-third annual meeting, October 15-18, 1979. 1st supplement to 13th edition Official Methods of Analysis - AOAC. *J. Assoc. off. anal. Chem.*, *63*, 380-381

Barnes, J.M. & Denz, F.A. (1951) The chronic toxicity of *p*-nitrophenyl diethyl thiophosphate (E. 605). A long-term feeding experiment with rats. *J. Hyg.*, *49*, 430-441

Barnes, J.M. & Denz, F.A. (1953) Experimental demyelination with organo-phosphorus compounds. *J. Pathol. Bacteriol.*, *65*, 597-605

Barthel, E. (1976) High incidence of lung cancer in persons with chronic professional exposure to pesticides in agriculture (Ger.). *Z. Erkr. Atmos. Org.*, *146*, 266-274

Bartsch, H., Malaveille, C., Camus, A.-M., Martel-Planche, G., Brun, G., Hautefeuille, A., Sabadie, N., Barbin, A., Kuroki, T., Drevon, C., Piccoli, C. & Montesano, R. (1980) Validation and comparative studies on 180 chemicals with *S. typhimurium* strains and V79 Chinese hamster cells in the presence of various metabolizing systems. *Mutat. Res.*, *76*, 1-50

Batchelor, G.S. & Walker, K.C. (1954) Health hazards involved in use of parathion in fruit orchards of north central Washington. *Arch. ind. Hyg. occup. Med.*, *10*, 522-529

Botre, C., Ielmini, M., Mancini, G. & Porcelli, G. (1974) Pollution by pesticides. Control of fruit delivered to consumption through the markets of Rome (Ital.). *Rass. Chim.*, *26*(4), 173-180 [*Chem. Abstr.*, *82*, 71688j]

Braun, H.E. & Frank, R. (1980) Organochlorine and organophosphorus insecticides: Their use in eleven agricultural watersheds and their loss to stream waters in southern Ontario, Canada, 1975-1977. *Sci. total Environ.*, *15*, 169-192

Buselmaier, W., Röhrborn, G. & Propping, P. (1972) Mutagenicity studies with pesticides in the host-mediated assay and in the dominant lethal test in the moust (Ger.). *Biol. Zentralbl.*, *91*, 311-325

Butler, P.A. & Schutzmann, R.L. (1978) Residues of pesticides and PCBs in estuarine fish, 1972-76 - National Pesticide Monitoring Program. *Pestic. Monit. J.*, *12*, 51-59

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 196, 197

Carey, A.E., Gowen,J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1978) Pesticide residue levels in soils and crops, 1971 - National Soils Monitoring Program (III). *Pestic. Monit. J.*, *12*, 117-136

Carey, A.E., Gowen, J.A., Tai, H., Mitchell, W.G. & Wiersma, G.B. (1979) Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). *Pestic. Monit. J.*, *12*, 209-229

Cohen, B., Richter, E., Weisenberg, E., Schoenberg, J. & Luria, M. (1979) Sources of parathion exposures for Israeli aerial spray workers, 1977. *Pestic. Monit. J.*, *13*, 8l-86

Coleman, W.E. & Tardiff, R.G. (1979) Contaminant levels in animal feeds used for toxicity studies. *Arch. environ. Contam. Toxicol.*, *8*, 693-702

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *L340*, 26-31

Commission of the European Communities (1982) Proposal for a Council Directive amending Annex II to Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *C95*, 6-10

Crockett, A.B., Wiersma, G.B., Tai, H., Mitchell, W.G., Sand, P.F. & Carey, A.E. (1974) Pesticide residue levels in soils and crops, FY-70 - National Soils Monitoring Program (II). *Pestic. Monit. J.*, *8*, 69-97

Davies, J.E., Davis, J.H., Frazier, D.E., Mann, J.B. & Welke, J.O. (1966) *Urinary p-nitrophenol concentrations in acute and chronic exposures.* In: Rosen, S.A. & Kraybill, H.F., eds, *Organic Pesticides in the Environment* (*American Chemical Society Series No. 60*), p. 67

Davies, J.E., Jewett, J.S., Welke, J.O., Barquet, A. & Freall, M.S., III (1970) *Epidemiology and chemical diagnosis of organophosphate poisoning.* In: Deichman, W.B., ed., *Pesticides Symposia*, Miami, FL, Halos & Associates, p. 183

Decloitre, F. (1978) Evaluation of the rat-liver DNA damage by parathion in relation with its non-mutagenicity (Abstract no. 53) *Mutat. Res.*, *53*, 175

Degraeve, N., Moutschen, J., Moutschen-Dahmen, M., Gilot-Delhalle, J., Colizzi, A., Honbrechts, N. & Cholett, M.C. (1979) Genetic effects of organophosphate insecticides in mouse (Abstract no. 49). *Mutat. Res.*, *64*, 131

Degraeve, N., Gilot-Delhalle, J., Moutschen, J., Moutschen-Dahmen, M., Colizzi, A., Chollet, M. & Houbrechts, N. (1980) Comparison of the mutagenic activity of organophosphorus insecticides in mouse and in the yeast *Schizosaccharomyces pombe* (Abstract no. 65). *Mutat. Res.*, *74*, 201-202

Deskin, R., Rosenstein, L., Rogers, N. & Westbrook, B. (1979) Parathion toxicity in perinatal rats exposed in utero. *Toxicol. Lett.*, *3*, 11-14

Deubert, K.H. & Gray, R.S. (1976) Parathion residues in environmental samples from untreated areas. *Bull. environ. Contam. Toxicol.*, *15*, 613-616

Dick, G.L., Heenan, M.P., Love, J.L., Udy, P.B. & Davidson, F. (1978) Survey of trace elements and pesticide residues in the New Zealand diet. 2. Organochlorine and organophosphorus pesticide residue content. *N. Z. J. Sci.*, *21*, 71-78

Diggory, H.J.P., Landrigan, P.J., Latimer, K.P., Ellington, A.C., Kimbrough, R.D., Liddle, J.A., Cline, R.E. & Smrek, A.L. (1977) Fatal parathion poisoning caused by contamination on flour in international commerce. *Am. J. Epidemiol.*, *106*, 145-153

DuBois, K.P. (1963) *Toxicological evaluation of the anticholinesterase agents.* In: Eichler, O. & Farah, A., eds, *Handbuch der Experimentellen Pharmakologie*, Vol. 15, Berlin, Springer, pp. 833-859

Durham, W.F., Wolfe, H.R. & Elliott, J.W. (1972) Absorption and excretion of parathion by spraymen. *Arch. environ. Health*, *24*, 381-387

Edson, E.G. *et al.* (1964) Summaries of toxicological data. No-effect levels of three organophosphates in the rat, pig and man. *Food Cosmet. Toxicol.*, *2*, 311-316

Eitzman, D.V. & Wolfson, S.L. (1967) Acute parathion poisoning in children. *Am. J. Dis. Child.*, *114*, 397-400

Fahrig, R. (1974) *Comparative mutagenicity studies with pesticides.* In: Montesano, R. & Tomatis, L., eds, *Chemical Carcinogenesis Essays* (*IARC Scientific Publications No. 10*), Lyon, pp. 161-181

Foster, R.L. (1974) *Detection and measurement of ambient organophosphate pesticides.* In: *Proc. Ann. Ind. Air Pollut. Control Conf.*, *4*, 66-98

Frank, R., Braun, H.E., Ishida, K. & Suda, P. (1976) Persistent organic and inorganic pesticide residues in orchard soils and vineyards of southern Ontario. *Can. J. Soil Sci.*, *56*, 463-484

Fredriksson, T. (1961) Studies on the percutaneous absorption of parathion and paraoxon. *Acta derm. venereol.*, *41*, 353-362

Fredriksson, T. & Bigelow, J.K. (1961) Tissue distribution of P^{32} labeled parathion. *Arch. environ. Health*, *2*, 663-667

Gaines, T.B. (1961) Poisoning by organic phosphorus pesticides potentiated by phenothiazine derivatives. *Science, 138,* 1260-1261

GIFAP (1982) *GIFAP Bulletin*, Vol. 8, No. 7, Brussels, International Group of National Associations of Agrochemical Manufacturers, p. 9

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem., 54*, 1040-1082

Grob, D., Garlick, W.L., Merrill, G.G. & Freimuth, H.C. (1949) Death due to parathion, an anticholinesterase insecticide. *Ann. intern. Med., 35*, 899-904

Haley, T.J., Reichert, E.R. & Klemmer, H.W. (1978) Acute human poisoning with parathion and mevinphos (Abstract no. 183). *Toxicology, 37*, 247

Harbison, R.D. (1975) Parathion-induced toxicity and phenobarbital-induced protection against parathion during prenatal development. *Toxicol. appl. Pharmacol., 32*, 482-493

Harris, C.R., Chapman, R.A. & Miles, J.R.W. (1977) Insecticide residues in soils on fifteen farms in Southwestern Ontario, 1964-1974. *J. environ. Sci. Health, B12*, 163-177

Hartwell, W.V. & Hayes, G.R., Jr (1965) Respiratory exposure to organic phosphorus insecticides. *Arch. environ. Health, 11*, 564-568

Hartwell, W.V., Hayes, G.R., Jr & Funckes, A.J. (1964) Respiratory exposure of volunteers to parathion. *Arch. environ. Health, 8*, 820-825

Haydu, J.J. (1981) *Pesticide Use in United States Citrus Production, 1977* (*ESS Staff Report No. AGESS 8102030*), Washington DC, US Department of Agriculture, pp. 10, 24

Hayes, W.J., Jr (1960) Pesticides in relation to public health. *Ann. Rev. Entomol., 5*, 379-404

Hayes, W.J., Jr (1971) Studies on exposure during the use of anticholinesterase pesticides. *Bull. World Health Organ., 44*, 277-288

Hayes, W.J., Jr (1975) *Toxicology of Pesticides*, Baltimore, Williams & Wilkins Co., pp. 323-324

Hazleton, L.W. & Holland, E.G. (1950) Pharmacology and toxicology of parathion. *Adv. Chem. Ser., 1*, 31-38

Heath, D.F. (1961) *Organophosphorus Poisons. Anticholinesterases and Related Compounds*, New York, Pergamon Press, pp. 164-170

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 116-118, 466-478

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 166, 167

Johnson, R.D. & Manske, D.D. (1976) Pesticide residues in total diet samples (IX). *Pestic. Monit. J.*, *9*, 157-169

Johnson, R.D. & Manske, D.D. (1977) Pesticide and other chemical residues in total diet samples (XI). *Pestic. Monit. J.*, *11*, 116-131

Johnson, R.D., Manske, D.D., New, D.H. & Podrebarac, D.S. (1979) Pesticides and other chemical residues in infant and toddler total diet samples - (I) - August 1974-July 1975. *Pestic. Monit. J.*, *13*, 87-98

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975-July 1976. *Pestic. Monit. J.*, *15*, 54-69

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

Kanagaratnam, K., Boon, W.H. & Hoh, T.K. (1960) Parathion poisoning from contaminated barley. *Lancet*, *i*, 538-542

Karr, J.J. (1980) Gas-liquid chromatographic method for the analysis of microencapsulated ethyl parathion and methyl parathion insecticides: Collaborative study. *J. Assoc. off. anal. Chem.*, *63*, 999-1002

Kazen, C., Bloomer, A., Welch, R., Oudbier, A. & Price, H. (1974) Persistence of pesticides on the hands of some occupationally exposed people. *Arch. environ. Health*, *29*, 315-318

Kibler, W.B. (1973) Skeletal muscle necrosis secondary to parathion. *Toxicol. appl. Pharmacol.*, *25*, 117-112

Kimbrough, R.D. & Gaines, T.B. (1968) Effect of organic phosphorus compounds and alkylating agents on the rat fetus. *Arch. environ. Health*, *16*, 805-808

Leuzinger, S., Pasi, A. & Dolder, R. (1971) Synoptic interpretation of 536 alkylphosphate poisonings (Ger.). *Schweiz. med. Wochenschr.*, *101*, 563-570

Lores, E.M., Bradway, D.E. & Moseman, R.F. (1978) Organophosphorus pesticide poisonings in humans: Determination of residues and metabolites in tissues and urine. *Arch. environ. Health*, *33*, 270-276

Maibach, H.I., Feldmenn, R.J., Milby, T.H. & Serat, W.F. (1971) Regional variation in percutaneous penetration in man. *Arch. environ. Health*, *23*, 208-211

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII). *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Menzie, C.M. (1969) *Metabolism of Pesticides* (*Special Scientific Report - Wildlife No. 127*), Washington DC, Bureau of Sport Fisheries and Wildlife, pp. 264-271

Mestres, R., Illes, S., Campo, M. & Tourte, J. (1977) A multiple residue method for citrus fruits: Its technique and some data. *Proc. Int. Soc. Citriculture*, *2*, 426-429

Metcalf, R.L. (1981) *Insect control technology*. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley & Sons, pp. 438-439, 485

Midwest Research Institute (1975) *Substitute Chemical Program. Initial Scientific and Microeconomic Review of Parathion* (*PB-241 819*), Washington DC, National Technical Information Service

Milby, T.H., Ottoboni, F. & Mitchell, H.W. (1964) Parathion residue poisoning among orchard workers. *J. Am. med. Assoc.*, *189*, 351-356

Mohn, G. (1973) 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12. Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. *Mutat. Res.*, *20*, 7-15

Monsanto (undated) *Parathion, Methyl Parathion, Stabilized Methyl Parathion* (*Tech. Bull. No. Ag-1b(EX)*), St Louis, MO, Agricultural Division, p. 5

Monsanto (1980) *Niran E-4 Insecticide by Monsanto*, St Louis, MO, Agricultural Division

Mootoo, C.L. & Singh, B. (1966) Review of 210 deaths by poisoning in British Guiana (1959-1964). *West Indian med. J.*, *15*, 11-17

Morgan, D.P., Hetzler, H.L., Slach, E.F. & Liu, L.I. (1977) Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. *Arch. environ. Health*, *6*, 159-173

Morse, D.L., Baker, E.L. & Landrigan, P.J. (1979) Cut flowers: A potential pesticide hazard. *Am. J. public Health*, *69*, 53-56

Mulla, M.S., Mian, L.S. & Kawecki, J.A. (1981) Distribution, transport, and fate of the insecticides malathion and parathion in the environment. *Residue Rev.*, *81*, 118

Nabb, D.P., Stein, W.J. & Hayes, W.J., Jr (1966) Rate of skin absorption of parathion and paraoxon. *Arch. environ. Health*, *12*, 501-505

Namba, T. (1971) Cholinesterase inhibition by organophosphorus compounds and its clinical effects. *Bull. World Health Organ.*, *44*, 289-307

National Cancer Institute (1979) *Bioassay of Parathion for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 70; DHEW Publ. No. (NIH) 79-1320*), Washington DC, US Department of Health, Education & Welfare

National Institute for Occupational Safety & Health (1976) *Criteria for a Recommended Standard - Occupational Exposure to Parathion* (*HEW Publ. No. (NIOSH) 76-190*), Washington DC, US Department of Health, Education, & Welfare

National Institute for Occupational Safety & Health (1980a) *Summary of NIOSH Recommendations for Occupational Health Standards*, Cincinnati, OH

National Institute for Occupational Safety & Health (1980b) *Projected Number of Occupational Exposures to Chemical and Physical Hazards*, Cincinnati, OH, p. 58

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, pp. 6649, 9117

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Norman, B.J. & Neal, R.A. (1976) Examination of the metabolism *in vitro* of parathion (diethyl *p*-nitrophenyl phosphorothionate) by rat lung and brain. *Biochem. Pharmacol.*, *25*, 37-45

Popendorf, W.J. (1976) *An Industrial Hygiene Investigation into the Occupational Hazards of Parathion Residues to Citrus Harvesters* (Thesis), Berkeley, CA, University of California, p. 180

Quinby, G.E. & Lemmon, A.B. (1958) Parathion residues as a cause of poisoning in crop workers. *J. Am. med. Assoc.*, *166*, 740-746

Quinto, I., Martire, G., Vricella, G., Riccardi, F., Perfumo, A., Giulivo, R. & De Lorenzo, F. (1981) Screening of 24 pesticides by *Salmonella*/microsome assay: Mutagenicity of benazolin, metoxuron and paraoxon (Abstract). *Mutat. Res.*, *85*, 265

Richter, E.D., Cohen, B., Luria, M., Schoenberg, J., Weisenberg, E. & Gordon, M. (1980) Exposures of aerial spray workers to parathion. *Isr. J. med. Sci.*, *16*, 96-100

Rider, J.A., Moeller, H.C., Swader, J. & Weilerstein, R.W. (1958) The effect of parathion on human red blood cell and plasma cholinesterase. Section II. *Arch. ind. Health*, *18*, 442-445

Rider, J.A., Moeller, H.C., Puletti, E.J. & Swader, J.I. (1969) Toxicity of parathion, systox, octamethyl pyrophosphoramide and methyl parathion in man. *Toxicol. appl. Pharmacol.*, *14*, 603-611

Sethunathan, N., Siddaramappa, R., Rajaram, K.P., Barik, S. & Wahid, P.A. (1977) Parathion: Residues in soil and water. *Residue Rev.*, *68*, 9l-122

Shafik, M.T. & Enos, H.F. (1969) Determination of metabolic and hydrolytic products of organophosphorus pesticide chemicals in human blood and urine. *J. agric. Food Chem.*, *17*, 1186-1189

Simmon, V.F., Mitchell, A.D. & Jorgenson, T.A. (1977) *Evaluation of Selected Pesticides and Chemical Mutagens. 'In vitro' and 'In vivo' Studies* (*EPA-60 0/1-77-028*), Research Triangle Park, NC, US Environmental Protection Agency

Smith, D.C., Leduc, R. & Tremblay, L. (1975) Pesticide residues in the total diet in Canada. IV. I972-1973. *Pestic. Sci.*, *6*, 75-82

Spear, R.C., Popendorf, W.J., Spencer, W.F. & Milby, T.H. (1977) Worker poisonings due to paraoxon residues. *J. occup. Med.*, *19*, 411-414

Sutherland, G.L. & Miskus, R. (1964) *Parathion*. In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. II, *Insecticides*, New York, Academic Press, pp. 321-330

Talens, G. & Woolley, D. (1973) Effects of parathion administration during gestation in the rat on development of the young. *Proc. West. Pharmacol. Soc.*, *16*, 141-145

Taylor, D.G. (1977a) *NIOSH Manual of Analytical Methods*, 2nd ed., Part I, *NIOSH Monitoring Methods*, Vol. 1, *Method 158-1 DHEW (NIOSH)*, Washington DC, US Government Printing Office, pp. 158-1 - 158-9

Taylor, D.G. (1977b) *NIOSH Manual of Analytical Methods*, 2nd ed., Part II, *Standards Completion Program Validated Methods*, Vol. 3, *Method S295 DHEW (NIOSH)*, Washington DC, US Government Printing Office, pp. S295-1 - S295-6

Taylor, P. (1980) *Anticholinesterase agents*. In: Gilman, A.G., Goodman, L.S. & Gilman, A., eds, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed., New York, MacMillan, pp. 100-119

Toivonen, T., Ohela, K. & Kaipainen, W.J. (1959) Parathion poisoning: Increasing frequency in Finland. *Lancet*, *ii*, 175-176

US Department of Agriculture (1978) *Farmers' Use of Pesticide in 1976, Agricultural Economic Report No. 418*, Washington DC, Economics, Statistics, and Cooperatives Service, p. 16

US Department of Agriculture (1981) *Monitoring Phase Biological Residue Report, January 1980 through December 1980*, Washington DC, Residue Evaluation and Surveillance Division

US Department of Commerce (1978) *US Exports, Schedule B Commodity by Country (FT410/December 1977)*, Bureau of the Census, Washington DC, US Government Printing Office, pp. 2-85, 2-86

US Department of Transportation (1980) Transport of hazardous wastes and hazardous substances. *US Code Fed. Regul., Title 49*, parts 171-174, 176, 177; *Fed. Regist.*, *45*, 34560, 34631

US Environmental Protection Agency (1975) *Substitute Chemical Program. Initial Scientific and Minieconomic Review of Parathion (EPA 540/1-75-001)*, Springfield, VA, National Technical Information Service, pp. 45, 46, 184-187, 192-194, 212, 213, 219-221, 237-246, 251

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Office of Pesticide Programs, Washington DC, Association of Official Analytical Chemists, Parathion EPA-1, EPA-2

US Environmental Protection Agency (1978) *Organic Compounds in Organophosphorus Pesticide Manufacturing Wastewaters (PB 28982l)*, Springfield, VA, National Technical Information Service, p. 40

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.121 p. 544, part 180.319, pp. 591, 592

US Environmental Protection Agency (1980b) Hazardous waste management system; identification and listing of hazardous waste. *US Code Fed. Regul., Title 40*, part 261; *Fed. Regist., 45*, 33085, 33122-33127, 33132

US Environmental Protection Agency (1980c) Protection of environment. *US Code Fed. Regul., Title 40*, parts 116, 117, pp. 35-50

US Environmental Protection Agency (1980d) Protection of environment. *US Code Fed. Regul., Title 40*, parts 455.20, 455.22, pp. 285, 286

US Environmental Protection Agency, (1980e) Protection of environment. *US Code Fed. Regul., Title 40*, part 162.31, pp. 427-431

US Environmental Protection Agency (1980f) Protection of environment. *US Code Fed. Regul., Title 40*, part 170.3, p. 480

US International Trade Commission (1981) *Imports of Benzenoid Chemicals and Products, 1980 (USITC Publ. 1163)*, Washington DC, US Government Printing Office, p. 106

US Tariff Commission (1949) *Synthetic Organic Chemicals, US Production and Sales, 1948 (Report No. 164, Second Series)*, Washington DC, US Government Printing Office, p. 129

US Tariff Commission (1972) *Synthetic Organic Chemicals, US Production and Sales, 1970 (TC Publ. 479)*, Washington DC, US Government Printing Office, pp. 198, 203

Valencia, R. (1977) *Mutagenesis Screening of Pesticides Using Drosophila* (Contract no. 68-01-2474), Madison, WI, WARF Institutes, Inc.

Warner, J.S. (1975) *Identification of impurities in technical-grade pesticides.* In: *Substitute Chemical Program - the First Year of Progress. Proceedings of a Symposium.*, Vol. IV, *Chemical Methods Workshop (PB-261 007)*, Washington DC, US Department of Commerce, National Technical Information Service, pp. 31-65

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study on pesticide genotoxicity.* In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, sect. 5A(1)(a); 5A(2)(a)(b); 6A(1); 8B; 10A; 11B; 12B; 12C; 12F

Weast, R.C., ed. (1982) *CRC Handbook of Chemistry and Physics*, 62nd ed., Boca Raton, FL, Chemical Rubber Co., p. C-413

Wecker, L. & Dettbarn, W.-D. (1976) Paraoxon-induced myopathy: Muscle specificity and acetylcholine involvement. *Exp. Neurol.*, *51*, 281-291

Wecker, L., Laskowski, M.B. & Dettbarn, W.-D. (1978a) Neuromuscular dysfunction induced by acetylcholinesterase inhibition. *Fed. Proc.*, *37*, 2818-2822

Wecker, L., Kiauta, T. & Dettbarn, W.-D. (1978b) Relationship between acetylcholinesterase inhibition and the development of a myopathy. *J%. Pharmacol. exp. Ther.*, *206*, 97-104

WHO (1965) *Evaluation of the Toxicity of Pesticide Residues in Food* (*WHO/Food Add./27.65*), Geneva, pp. 153-157

Wicker, G.W., Williams, W.A. & Guthrie, F.E. (1979) Exposure of field workers to organophosphorus insecticides: Sweet corn and peaches. *Arch. environ. Contam. Toxicol.*, *8*, 175-182

Wild, D. (1975) Mutagenicity studies on organophosphorus insecticides. *Mutat. Res.*, *32*, 133-150

Williams, M.W., Cook, J.W., Blake, J.R., Jorgensen, P.S. & Frawley, J.P. (1958) The effect of parathion on human red blood cell and plasma cholinesterase. Section I. *Arch. ind. Health*, *18*, 441-442

Wolfe, H.R., Durham, W.F. & Armstrong, J.F. (1967) Exposure of workers to pesticides. *Arch. environ. Health*, *14*, 622-633

Wolfe, H.R., Durham, W.G. & Armstrong, J.F. (1970) Urinary excretion of insecticide metabolites. Excretion of *para*-nitrophenol and DDA as indicators of exposure to parathion. *Arch. environ. Health*, *21*, 711-716

Wolfe, H.R., Armstrong, J.F., Staiff, D.C. & Comer, S.W. (1975a) Potential exposure of workers to parathion through contamination of cigarettes. *Bull. environ. Contam. Toxicol.*, *13*, 369-376

Wolfe, H.R., Armstrong, J.F., Staiff, D.C., Comer, S.W. & Durham, W.F. (1975b) Exposure of apple thinners to parathion residues. *Arch. environ. Contam. Toxicol.*, *3*, 257-267

Wolfe, H.R., Staiff, D.C. & Armstrong, J.F. (1978) Exposure of pesticide formulating plant workers to parathion. *Bull. environ. Contam. Toxicol.*, *20*, 340-343

Woodrow, J.E., Seiber, J.N., Crosby, D.G., Moilanen, K.W., Soderquist, C.J. & Mourer, C. (1977) Airborne and surface residues of parathion and its conversion products in a treated plum orchard environment. *Arch. environ. Contam. Toxicol.*, *6*, 175-191

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Pest Control Council, pp. 401, 515

Zweig, G. & Sherma, J. (1972) *Parathion*. In: Zweig, G., ed., *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, *Gas Chromatographic Analysis*, New York, Academic Press, pp. 445-446

PIPERONYL BUTOXIDE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 51-03-6

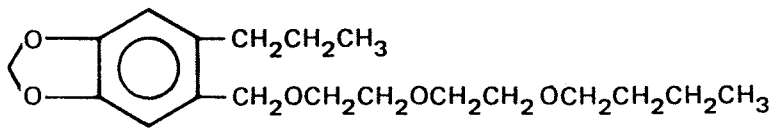
Chem. Abstr. Name: 1,3-Benzodioxole, 5[(2-[2-butoxyethoxy]ethoxy)methyl]-6-propyl

IUPAC Systematic Name: 5-[2-(2-Butoxyethoxy)ethoxymethyl]- 6-propyl-1,3-benzodioxole

Synonyms: α-[2-(2-Butoxyethoxy)ethoxy]4,5-(methylenedioxy)- 2-propyltoluene; α-[2-(2-*n*-butoxyethoxy)ethoxy]-4,5-methylene dioxy-2-propyltoluene; butyl carbitol 6-propylpiperonyl ether; butyl carbityl (3-propylpiperonyl)ether; ENT 14,250; (3,4-methylenedioxy- 6-propylbenzyl)(butyl)diethylene glycol ether; 3,4-methylenedioxy 6-propylbenzyl *n*-butyl diethyleneglycol ether; NCI CO28l3; 6-propylpiperonyl butyl diethylene glycol ether

Trade Names: Butacide; Butocide; Butoxide; FAC 5273; NIA 5273; Nusyn-Noxfish; Prentox; Pybuthrin; Pyrenone 606; Synpren-Fish

1.2 Structural and molecular formulae and molecular weight



$C_{19}H_{30}O_5$ Mol. wt: 338.4

1.3 Chemical and physical properties of the substance

Information on the pure substance was not available to the Working Group. The following properties are for a technical product containing a minimum of 85 mol% piperonyl butoxide and a maximum of 15 mol% related compounds (from Worthing, 1979, unless otherwise specified).

1.4 Technical products and impurities

Technical piperonyl butoxide is described above. In 1972, the following components were identified in three samples of technical piperonyl butoxide: piperonyl butoxide, 71.6-90.1%; butyl carbitol, 0.6-3.5%; bis(2-propyl-4,5-methylenedioxyphenyl) methane, 2.7-6.4%; 2-propyl-4,5-dimethoxybenzyl *n*-butyl diethyleneglycol ether, 0.4-2.3%; and di(2-propyl-4,5-methylenedioxybenzyl) ether, 0.3-1.0%. Several other identified and unidentified components were present at lower levels (Albro *et al.*, 1972). Piperonyl butoxide is available in combinations with pyrethrins (containing 5-20 parts of pyrethrin per part of piperonyl butoxide) as solutions, aerosol concentrates, emulsions and dusts. It is also available in combinations with the insecticides bioresmethrin, tetramethrin (Worthing, 1979), pyrethrum and rotenone (Berg, 1981).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Piperonyl butoxide was developed as a pyrethrum synergist in 1947. It is made by the reaction of 5-chloromethyl-6-propyl-1,3-benzodioxole with the sodium salt of diethylene glycol monobutyl ether (Worthing, 1979). This pesticide was first produced commercially in the US in 1966 (US Tariff Commission, 1968a). Separate production data were last reported in 1978, when three companies reported total production of 334 thousand kg (US International Trade Commission, 1979).

Imports of piperonyl butoxide through the principal US customs districts were last reported in 1967, when 5 thousand kg were imported (US Tariff Commission, 1968b). In 1977, one US company reported imports of 4.54-45.4 thousand kg (NIH/EPA Chemical Information System, 1982). Separate data on US exports of piperonyl butoxide are not available.

This compound is believed to be produced by one company each in the Federal Republic of Germany and the UK. It is not produced commercially in Japan.

(*b*) *Use*

Piperonyl butoxide is used as a synergist for pyrethrins and related insecticides. In 1978, a total of 450 thousand kg were used in the US, 80% in nonagricultural applications and 20% on livestock and poultry.

The Joint Meeting of the FAO Working Party of Experts and the WHO Expert Committee on Pesticide Residues in November 1966 established a temporary acceptable daily intake

of piperonyl butoxide for humans of 0-0.03 mg/kg bw. Tolerances for residues of piperonyl butoxide on commodities were recommended to be 20 mg/kg on cereals and cereal products and 8 mg/kg on fresh fruit (for canning only), dried fruits, tree nuts, dried vegetables, peanuts and oil seeds (WHO, 1967).

Tolerances in the US for residues of piperonyl butoxide in or on raw agricultural commodities are presently 0.1-20 mg/kg for a variety of 50 fruits, vegetables, eggs and meat products. Piperonyl butoxide is exempt from the requirement of a tolerance when applied to growing crops in accordance with 'good agricultural practice' (US Environmental Protection Agency, 1980). A tolerance of 10 mg/kg has been established for residues of piperonyl butoxide when present in certain dried feeds as a result of migration from multiwall paper or cotton bags. Use of this pesticide is permitted by the US Environmental Protection Agency in combination with pyrethrins for insect control on bags intended for dried feed and dried food, in cereal grain mills and storage areas for milled cereal grain products, and in food processing and food storage areas, provided the food is removed or covered prior to such use; a tolerance of 10 mg/kg has been established in milled fractions derived from cereal grains, dried foods and treated foods (US Food & Drug Administration, 1980).

A drug containing 25% squalene, 0.05% pyrethrins and 0.50% technical piperonyl butoxide is approved for use in the US for treatment of ear mites in cats and dogs (US Food & Drug Administration, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Piperonyl butoxide is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to piperonyl butoxide nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to piperonyl butoxide, namely its production and formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute of Occupational Safety and Health (1980, 1981) estimated that 234 thousand US workers in 102 nonagricultural industries were exposed to this compound.

2.3 Analysis

Standard methods used for the analysis of piperonyl butoxide in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of piperonyl butoxide

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Dilute (deodorized kerosene); heat with tannic acid reagent	Colorimetry	not given	Velenovsky (1964); US Environmental Protection Agency (1976); Horwitz (1980)
	Dilute (heptane or acetone)	GC/FID	not given	Zweig & Sherma (1972); Sherma (1976); US Environmental Protection Agency (1976)
Natural products	Extract (hexane or petroleum ether); chromatograph (activated alumina); concentrate; heat with tannic acid, acetic acid, phosphoric acid	Colorimetry	not given	Velenovsky (1964)
Wheat, pinto beans, Alaska peas, hull rice, oats and barley	Digest (sulphuric acid); react with chromotropic acid	Colorimetry	0.5 mg/kg	Markus & Puma (1973); Horwitz (1980)
Eggs and tissue	Extract (ethanol/diethyl ether/ hexane); saponify (alcoholic potassium hydroxide); chromatograph (column not specified)	GC/ECD	not given	Sherma (1976)
Milk and milk products	Extract (solvent not specified); partition (acetonitrile/petroleum ether); chromatograph (column not specified); chromatograph (microfibre strips)	GC/ECD	not given	Sherma (1976)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice received piperonyl butoxide (80% pure) according to the following schedule: 100 mg/kg bw in 0.5% gelatin at seven days of age by stomach tube and the same amount (not adjusted for increasing body weight) daily up to four weeks of age; subsequently, the mice were fed 300 mg/kg of diet. [The dose was the maximum tolerated dose for infant and young mice but not necessarily that for adults.] The experiment was terminated at 70 weeks of age, when all animals were killed. Tumour incidences were compared with those in 79-90 necropsied mice of each sex and strain, which had either been untreated or had received gelatine only. No significant difference in the incidence of tumours was found between treated and control mice (National Technical Information Service, 1968; Innes *et al.*, 1969). [The Working Group noted the short duration of treatment.]

Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice received piperonyl butoxide as 'Butacide' according to the following schedule: 464 mg/kg bw in 0.5% gelatin at seven days of age by stomach tube and the same amount (not adjusted for increasing body weight) daily up to four weeks of age; subsequently, the mice were fed 1112 mg/kg of diet. [The dose was the maximum tolerated dose for infant and young mice but not necessarily that for adults.] The experiment was terminated at 70 weeks of age, when all animals were killed. Tumour incidences were compared with those in 79-90 necropsied mice of each sex and strain, which had either been untreated or had received gelatine only. No significant difference in the incidence of tumours was found between treated and control mice (National Technical information Service, 1968; Innes *et al.*, 1969). [The Working Group noted the short duration of treatment.]

Groups of 50 male and 50 female B6C3F_1 mice, six weeks of age, were fed diets containing piperonyl butoxide (technical grade; purity 88.4%; containing 2.1% butyl carbinol, 2.4% of an isomer of piperonyl butoxide and several minor contaminants) as follows: the low-dose group received 2500 mg/kg of diet for 30 weeks and 500 mg/kg for an additional 82 weeks (time-weighted average dose, 1036 mg/kg of diet); and the high-dose group, 5000 mg/kg of diet for 30 weeks and 2000 mg/kg for an additional 82 weeks (time-weighted average dose, 2804 mg/kg of diet). All surviving animals were killed at 112 weeks. A matched control group consisted of 20 male and 20 female mice. Although variations in tumour incidence were observed, no significant difference attributable to treatment was found for any tumour type (National Cancer Institute, 1979). [The Working Group noted the short duration of treatment.]

Rat: Groups of 50 male and 50 female Fischer 344 rats, six weeks old, were fed *ad libitum* diets containing either 5000 or 10 000 mg/kg piperonyl butoxide (technical grade;

---

[1]The Working Group was aware of a study in progress in rats by oral administration (IARC, 1981).

purity 88.4%; containing 2.1% butyl carbinol, 2.4% piperonyl butoxide isomer and several minor contaminants) for 107 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at 107 weeks. Of the treated females, 7/50 in the low-dose group and 15/50 in the high-dose group ($p = 0.02$) developed lymphomas, compared with 1/20 matched controls. [Although these tumours occurred at incidences that were dose-related ($p = 0.007$), the validity of the results was considered questionable in view of the high incidences of lymphomas and leukaemias in historical female controls of that strain (0-32%) (Tarone *et al.*, 1981)]. No significant difference attributable to treatment was found for any tumour type in male rats (National Cancer Institute, 1979).

In a reproduction study, groups of 12 male and 12 female Wistar rats, four weeks of age, were fed piperonyl butoxide (technical grade; 80% pure; impurities undefined) at concentrations of 100, 1000, 10 000 or 25 000 mg/kg of diet for up to 104 weeks. A group of 12 male and 12 female rats served as controls. Male and female rats from the corresponding groups were paired to assess reproductive efficacy. By 68 weeks, all of the rats fed the highest dose had died, presumably due to liver damage. A few tumours were found in the liver and lymphoid system in similar incidences in treated and non-treated groups (Sarles & Vandegrift, 1952).

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 1000 mg/kg bw piperonyl butoxide as 'Butacide' in corn oil on the 28th day of life and were observed until they were about 78 weeks of age, at which time almost all mice were still alive. A group of negative controls comprised untreated animals and animals treated with gelatine, corn oil or dimethyl sulphoxide. No significant difference in tumour incidence was observed (National Technical Information Service, 1968). [The Working Group noted the short duration of treatment.]

Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 100 mg/kg bw piperonyl butoxide (80% pure) in corn oil on the 28th day of life and were observed until they were about 78 weeks of age, at which time 17, 16, 17 and 18 mice were still alive in the four groups, respectively. A group of negative controls comprised untreated animals and animals treated with gelatine, corn oil or dimethyl sulphoxide. No increased incidence in tumour incidence was observed between treated and control animals (National Technical Information Service, 1968). [The Working Group noted the short duration of treatment.]

Neonatal Swiss mice (ICR/Ha strain) were given s.c. injections of 5 mg piperonyl butoxide alone at the ages of one and seven days and 10 mg at the ages of 14 and 21 days (total dose, 30 mg); a few mice also received 5 mg on days 3, 5 and 11 and 10 mg on days 15, 17 and 19. Further groups were given the same doses in combination with 'Freon' 112 or 113, at dosages of 10 mg at one and seven days and 20 mg at 14 and 21 days. Control animals were treated with the solvent, tricaprylin. The mice were weaned at the age of one month; all surviving animals were killed at the end of 52 weeks. No tumour was found in animals treated with piperonyl butoxide. The incidence of hepatomas in male mice given piperonyl butoxide plus Freons was significantly increased ($p < 0.001$) when compared with that in groups receiving solvent, piperonyl butoxide or 'Freon' alone (Epstein *et al.*, 1967).

3.2 Other relevant biological data

(a) *Experimental data*

Toxic effects

The oral LD_{50} of piperonyl butoxide was 8.3 g/kg bw in mice and 11.5 g/kg bw in fasted rats (Draize *et al.*, 1948) or 12.8 g/kg bw in non-fasted rats (Lehman, 1948).

Signs of acute piperonyl butoxide toxicity in laboratory animals included anorexia, vomiting, diarrhoea, haemorrhagic enteritis and bloody discharge from the nose and eyes (Sarles *et al.*, 1949). Acute administration of high levels of piperonyl butoxide to mammals inhibited mixed-function oxidase activities. Chronic administration had a stimulatory effect on these enzyme activities (Conney *et al.*, 1971, 1972; Friedman & Eaton, 1978).

Among the enzymes inhibited in mice and hamsters are hepatic *N*-nitrosodimethylamine *N*-demethylase and arylhydrocarbon hydroxylase (Friedman *et al.*, 1975; Friedman Sanders, 1976; Friedman, 1979). Enzymes that were induced in rats by piperonyl butoxide include hepatic microsomal [aminopyrine]demethylase, *para*-nitroanisole demethylase (Bick Fishbein, 1972), hexobarbital oxidase, aniline hydroxylase and glucuronyl transferase (Goldstein *et al.*, 1973).

Effects on reproduction and prenatal toxicity

No adverse effect on foetal development was seen with technical-grade piperonyl butoxide, containing 80% active ingredient, administered at oral doses of 62.5, 125, 250 or 500 mg/kg bw per day to Wistar rats from days 6-15 of pregnancy (Khera *et al.*, 1979). These findings were similar to those from a previous study (Kennedy *et al.*, 1977).

In a reproduction study, rats were fed diets containing 0, 100, 1000, 10 000 or 25 000 mg/kg piperonyl butoxide (technical grade, 80% pure) for three generations. None of the females fed 25 000 mg/kg were fertile; and there were marked reductions in the incidence of pregnancies, in number of litters per dam, in the general condition of offspring and in the average weight of weanlings of dams fed 10 000 mg/kg. No adverse effect on reproduction was observed in three generations of progeny fed diets containing concentrations of up to 1000 mg/kg (Sarles & Vandegrift, 1952).

Absorption, distribution, excretion and metabolism

After i.v. injection of [methylenedioxy-^{14}C]- and [α-methylene-^{14}C]-radiolabelled piperonyl butoxide to rats, the compound was widely distributed in tissues, and prolonged biliary and urinary elimination of metabolites was noted; a large percentage of unchanged piperonyl butoxide was detected in lung and adipose tissue by chromatographic methods. After oral administration, piperonyl butoxide was poorly absorbed from the gut and was rapidly eliminated in urine and faeces. Intratracheal administration resulted in a high initial level of elimination in the bile and urine (Fishbein *et al.*, 1969, 1972).

Metabolism of piperonyl butoxide in mammals involves: cleavage of the methylenedioxy ring and modification of the side groups (Casida *et al.*, 1966). Following a single i.v. administration of [methylenedioxy-^{14}C]- and [α-methylene-^{14}C]-piperonyl butoxide to

rats, 13 and 24 biliary metabolites and 11 and 26 urinary metabolites, respectively, were detected (Fishbein *et al.*, 1969). A metabolite of piperonyl butoxide competes for binding sites on cytochrome P-450 and forms a relatively stable complex (Franklin, 1972a,b,c).

Mutagenicity and other short-term tests

No mutagenic activity was detected in a back mutation system in *Escherichia coli* WP2 *trp* in the absence of exogenous metabolic activation (Ashwood-Smith *et al.*, 1972) or in spot tests with *Salmonella typhimurium* strains TA1537, TA98 and TA100 in the presence or absence of liver homogenate (White *et al.*, 1978) [details not given].

In a summary of a Japanese cooperative programme, piperonyl butoxide was reported to give negative results for *S. typhimurium* back mutation (strains TA98 and TA100, tested in the presence and absence of a rat liver postmitochondrial supernatant), in the *rec*-assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*), in tests for chromosomal aberrations in cultured Chinese hamster cells and rat bone marrow and for mutations in silkworms (Kawachi *et al.*, 1980) [details not given].

No dominant lethal mutation was induced in mice administered 200 or 1000 mg/kg bw by i.p. injection. After five oral administrations of 1000 mg/kg bw, a finding of 0.96 early deaths per pregnancy was of borderline significance at the 5% level (Epstein *et al.*, 1972). [The number of animals used was small compared with currently accepted protocols.]

(*b*) *Humans*

Toxic effects

A single oral dose of 50 mg (about 0.71 mg/kg bw) piperonyl butoxide given to adult volunteers did not influence the metabolism of antipyrine, and no sign of toxicity was recorded (Conney *et al.*, 1972).

Effects on reproduction and prenatal toxicity

Two sisters who were exposed during the first trimester of pregnancy to large amounts of insect repellent and insecticides containing piperonyl butoxide, *N*-octyl bicycloheptene dicarboximide, allethrin, pyrethrins, diethyl toluamide and 2,2-dichlorovinyl dimethyl phosphate each gave birth to a male infant with coarctation of the aorta (Hall *et al.*, 1975).

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Piperonyl butoxide was tested for carcinogenicity in two studies in rats and in three studies in mice by oral administration. It was also tested in mice of three strains by subcutaneous administration (in one, neonatally). No statistically significant incidence of tumours was observed in mice or rats.

Treatment of rats with high doses of piperonyl butoxide during organogenesis did not affect foetal development; however, its continued administration at high dose levels for three generations caused reduction in the number of pregnancies and offspring.

Piperonyl butoxide has been reported to be nonmutagenic to bacteria, silkworms and cultured mammalian cells. A dominant lethal study in mice was inconclusive. Lack of availability to the Group of much of the detailed data prevented overall evaluation of the mutagenicity of piperonyl butoxide, but all cited results have been negative.

4.2 Human data

Piperonyl butoxide was developed in 1947. Its production, formulation and use as an insecticide synergist in a variety of nonagricultural and agricultural applications are potential sources of exposure, both of workers and of the general population.

The available data were insufficient to evaluate the teratogenicity of piperonyl butoxide to humans. No data were available to evaluate its chromosomal effects in humans.

No case report or epidemiological study of the carcinogenicity of piperonyl butoxide alone was available to the Working Group. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation

The available data do not provide evidence that piperonyl butoxide is carcinogenic to experimental animals. No data on humans were available.

The available data provide no evidence that piperonyl butoxide is likely to present a carcinogenic risk to humans.

5. References

Albro, P.W., Fishbein, L. & Fawkes, J. (1972) Purification and characterization of pesticidal synergists. I. Piperonyl butoxide. *J. Chromatogr.*, *65*, 521-532

Ashwood-Smith, M.J., Trevino, J. & Ring, R. (1972) Mutagenicity of dichlorvos. *Nature*, *240*, 418-420

Berg, G.L., ed. (1981) *Farm Chemical Handbook, 1981*, Willoughby, OH, Meister Publishing Co., p. C266

Bick, M. & Fishbein, L. (1972) The inductive effect of piperonyl butoxide on microsomal demethylase activity. *Sci. total Environ.*, *1*, 197-203

Cardy, R.H., Renne, R.A., Warner, J.W. & Cypher, R.L. (1979) Carcinogenesis bioassay of technical-grade piperonyl butoxide in F344 rats. *J. natl Cancer Inst.*, *62*, 569-578

Casida, J.E., Engel, J.L., Essac, E.G., Kamienski, F.X. & Kuwatsuka, S. (1966) Methylene-C^{14}-dioxyphenyl compounds: Metabolism in relation to their synergistic action. *Science*, *153*, 1130-1133

Conney, A.H., Welch, R., Kuntzman, R., Chang, R., Jacobson, M., Munro-Faure, A.D., Peck, A.W., Bye, A., Poland, A., Poppers, P.J., Finster, M. & Wolff, J.A. (1971) Effects of environmental chemicals on the metabolism of drugs, carcinogens and normal body constituents in man. *Ann. N.Y. Acad. Sci.*, *179*, 155-172

Conney, A.H., Chang, P., Levin, W.N., Garbut, A., Munro-Faure, A.D., Peck, A.W. & Bye, A. (1972) Effect of piperonyl butoxide on drug metabolism in rodents and man. *Arch. environ. Health*, *24*, 97-106

Draize, J.H., Alvarez, E., Whitesell, M.F., Woodward, G., Hagan, E.C. & Nelson, A.A. (1948) Toxicological investigations of compounds proposed for use as insect repellents. A. Local and systemic effects following topical skin application. B. Acute oral toxicity. C. Pathological examination. *J. Pharmacol. exp. Ther.*, *93*, 26-39

Epstein, S.S., Joshi, S., Andrea, J., Clapp, P., Falk, H. & Mantel, N. (1967) Synergistic toxicity and carcinogenicity of 'Freons' and piperonyl butoxide. *Nature*, *214*, 526-528

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol.*, *23*, 288-325

Fishbein, L., Falk, H.L., Fawkes, J., Jordan, S. & Corbett, B. (1969) The metabolism of piperonyl butoxide in the rat with ^{14}C in the methylenedioxy or α-methylene group. *J. Chromatogr.*, *41*, 61-79

Fishbein, L., Falk, H.L., Fawkes, J. & Jordan, S. (1972) *The metabolism of ^{14}C-piperonyl butoxide in the rat.* In: Tahori, A.S., ed., *Fate of Pesticides in the Environment*, New York, Gordon & Breach, pp. 503-519

Franklin, M.R. (1972a) Inhibition of hepatic oxidative xenobiotic metabolism by piperonyl butoxide. *Biochem. Pharmacol.*, *21*, 3287-3299

Franklin, M.R. (1972b) Cytochrome P-450 and methylenedioxyphenyl metabolism (Abstract no. 1887). *Fed. Proc.*, *31*, 548

Franklin, M.R. (1972c) Piperonyl butoxide metabolism by cytochrome P-450: Factors affecting the formation and disappearance of the metabolite-cytochrome P-450 complex. *Xenobiotica*, *2*, 517-527

Friedman, M.A. (1979) Subchronic effects of piperonyl butoxide on carcinogen metabolism in hamster liver. *Bull. environ. Contam. Toxicol.*, *21*, 815-821

Friedman, M.A. & Eaton, L.R. (1978) Potentiation of methylmercury toxicity by piperonyl butoxide. *Bull. environ. Contam. Toxicol.*, *20*, 9-16

Friedman, M.A. & Sander, V. (1976) Effects on piperonyl butoxide on dimethylnitrosamine metabolism and toxicity in Swiss mice. *J. Toxicol. environ. Health*, *2*, 67-75

Friedman, M.A., Woods, S., Sanders, V. & Couch, D.B. (1975) Effect of piperonyl butoxide on dimethylnitrosamine metabolism and toxicity in Swiss mice (Abstract no. 638). *Proc. Am. Assoc. Cancer Res.*, *16*, 160

Goldstein, J.A., Hickman, P. & Kimbrough, R.D. (1973) Effect of purified and technical piperonyl butoxide on drug-metabolizing enzymes and ultrastructure of rat liver. *Toxicol. appl. Pharmacol.*, *26*, 444-458

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem.*, *54*, 1040-1082

Hall, J.G., McLaughlin, J.F. & Stamm, S. (1975) Coarctation of the aorta in male cousins with similar maternal environmental exposure to insect repellent and insecticides. *Pediatrics*, *55*, 425-427

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 88-89, 495

IARC (1981) *Information Bulletin on the Survey of Chemical Being Tested for Carcinogenicity*, No. 9, Lyon, p. 88

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassays of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst.*, *42*, 1101-1114

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

Kennedy, G.L., Jr, Smith, S.H., Kinoshita, F.K., Keplinger, M.L. & Calandra, J.C. (1977) Teratogenic evaluation of piperonyl butoxide in the rat. *Food Cosmet. Toxicol.*, *15*, 337-339

Khera, K.S., Whalen, C., Angers, G. & Trivett, G. (1979) Assessment of the teratogenic potential of piperonyl butoxide, biphenyl, and phosalone in the rat. *Toxicol. appl. Pharmacol.*, *47*, 353-358

Lehman, A.J. (1948) The toxicity of the newer agricultural chemicals. *Assoc. Food Drug Off. U.S. Q. Bull.*, *12*, 82-89

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sect. 120.127

National Cancer Institute (1979) *Bioassay of Piperonyl Butoxide for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 120; DHEW Publ. No. (NIH) 79-1375*), Washington DC, US Government Printing Office

National Institute for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards*, Cincinnati, OH, p. 108

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, pp. 7076-7077, 9704-9706

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study* (*PB-223159*), Washington DC, US Department of Commerce

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

NIH/EPA Chemical Information System (1982) *TSCA-Plant and Production*, Washington DC, Information Sciences Corporation

Sarles, M.P. & Vandegrift, W.B. (1952) Chronic oral toxicity and related studies on animals with the insecticide and pyrethrum synergist, piperonyl butoxide. *Am. J. trop. Med. Hyg.*, *1*, 862-883

Sarles, M.P., Dove, W.E. & Moore, D.H. (1949) Acute toxicity and irritation tests on animals with the new insecticide piperonyl butoxide. *Am. J. trop. Med.*, *29*, 151-167

Sherma, J. (1976) *Pyrethrum*. In: Zweig, G. & Sherma, J., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VIII, New York, Academic Press, pp. 231-238

Tarone, R.E., Chu, K.C. & Ward, J.M. (1981) Variability in the rates of some common naturally occurring tumors in Fischer 344 rats and (C57BL/6N x C3H/HeN)F_1 (B6C3F_1) mice. *J. natl Cancer Inst.*, *66*, 1175-1181

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Office of Pesticide Programs, Washington DC, Association of Official Analytical Chemists, Piperonyl Butoxide EPA-1, EPA-2

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 180.127, p. 546; part 180.1001, pp. 605, 606

US Food & Drug Administration (1980) Foods and drugs. *US Code Fed. Regul., Title 21*, part 178.3730, p. 288; part 193.360, pp. 377, 378; part 524.2140, p. 258; part 561.310, pp. 519, 520

US International Trade Commission (1979) *Synthetic Organic Chemicals, US Production and Sales, 1978* (*USITC Publ. 1001*), Washington DC, US Government Printing Office, pp. 279, 288

US Tariff Commission (1968a) *Synthetic Organic Chemicals, US Production and Sales, 1966* (*TC Publ. 248*), Washington DC, US Government Printing Office, p. 165

US Tariff Commission (1968b) *Imports of Benzenoid Chemicals and Products, 1967* (*TC Publ. 264*), Washington DC, US Government Printing Office, p. 86

Velenovsky, J.J. (1964) *Piperonyl butoxide.* In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. II, *Insecticides*, New York, Academic Press, pp. 394-398

White, T.J., Goodman, D., Shulgin, A.T., Castagnoli, N., Jr, Lee, R. & Petrakis, N.L. (1978) Mutagenic activity of some centrally active aromatic amines in *Salmonella typhimurium. Mutat. Res.*, *56*, 199-202

WHO (1967) *Evaluation of Some Pesticide Residues in Food* (*WHO/Food Add./67.32*), Geneva, pp. 204-216

Worthing, C.R., ed. (19769) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, pp. 43, 429, 460, 506

Zweig, G. & Sherma, J. (1972) *Piperonyl butoxide.* In: Zweig, G., ed., *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, New York, Academic Press, pp. 458-460

TETRACHLORVINPHOS

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 22248-79-9

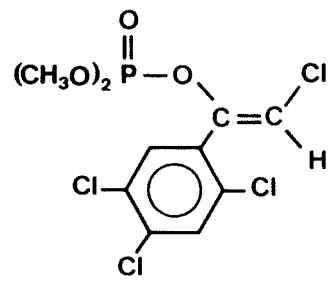
Chem. Abstr. Name: Phosphoric acid, 2-chloro-1-(2,4,5-trichlorophenyl)ethenyl dimethyl ester, (Z)-

IUPAC Systematic Name: (Z)-2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate

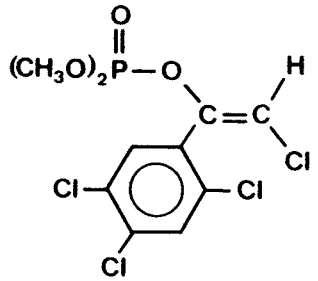
Synonyms: 2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate; 2-chloro-1-(2,4,5-trichlorophenyl)vinyl phosphoric acid dimethyl ester; CVMP; dimethyl 2,4,5-trichloro-α-(chloromethylene)benzyl phosphate; dimethyl-1-(2,4,5-trichlorophenyl)-2-chlorovinyl phosphate; ENT 2541; NCI CO0168; stirofos; stirophos; 2,4,5-trichloro-α-(chloromethylene)benzyl alcohol, dimethyl phosphate; vinfos

Trade Names: Appex; Dust M; Gardicide; Gardona; *cis*-Gardona; Rabon; Rabon Oral Larvicide (ROL); Rabond Ravap; ROL; SD 8447

1.2 Structural and molecular formulae and molecular weight



(E) (α, *trans*)



(Z) (β, *cis*)

$C_{10}H_9Cl_4O_4P$

Mol. wt. 366.0

1.3 Chemical and physical properties of the substance

The following properties (except for the vapour pressure) are given for the technical product, which typically contains 98% Z-stereoisomer and 2% E-stereoisomer (from Worthing, 1979, unless otherwise specified). The vapour pressure given is that of the pure Z-isomer.

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 95-97°C

(*c*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*d*) *Solubility*: Very slightly soluble in water (11 mg/l at 20°C); soluble at 20°C in acetone (< 200 g/kg), chloroform (400 g/kg), dichloromethane (400 g/kg), and xylene (< 150 g/kg)

(*e*) *Volatility*: Vapour pressure, 4.2×10^{-8} mm Hg at 20°C

(*f*) *Stability*: Stable below 100°C; slowly hydrolysed by water

1.4 Technical products and impurities

Technical tetrachlorvinphos is described above. Tetrachlorvinphos is available as a 24% active emulsifiable concentrate, as 50 and 75% active water-dispersible powders, as 5% active granules, and as a 70% active concentrate in suspension (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Tetrachlorvinphos was introduced as a commercial chemical in 1966. It is made by the reaction of trimethyl phosphate with 2,2,2′,4′,5′-pentachloroacetophenone (Worthing, 1979).

It was first produced commercially in the US in 1967 (US Tariff Commission, 1969) by one company, which last reported production in 1978 (US International Trade Commission, 1979). The company is believed to have had an annual production capacity of approximately 450 thousand kg. Separate data on US imports and exports of tetrachlorvinphos are not available.

Tetrachlorvinphos is not produced commercially in western Europe or Japan. In 1980, Japanese imports of tetrachlorvinphos amounted to 18 thousand kg, down slightly from the 19 thousand kg imported in 1979. Tetrachlorvinphos was not imported into Japan prior to 1979.

(*b*) *Use*

Tetrachlorvinphos is used as an insecticide. In 1978, total US usage is estimated to have been 45 thousand kg, essentially all of which was for controlling insects on livestock and poultry. It is believed to be used both to control adult flies and as a larvicide.

Tolerances in the US for residues of tetrachlorvinphos in or on raw agricultural commodities are presently 0.1-110 mg/kg in a variety of 18 fodders (tolerance, 110 mg/kg), fruits, grains, livestock and poutry fats, and eggs (tolerance, 0.1 mg/kg) (US Environmental Protection Agency, 1980).

Tetrachlorvinphos is approved for use in the US: (1) as a feed additive for beef and dairy cattle at a rate of 1.5 mg/kg bw per day, and (2) to control faecal flies in manure from treated cattle (US Food & Drug Administration, 1980).

In 1977, the USSR established a regulation that occupational exposure to tetrachlorvinphos not exceed 1 mg/m^3 in workplace air (International Labour Office, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Tetrachlorvinphos is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of workers exposed to tetrachlorvinphos during its production, formulation or use as an insecticide.

(*c*) *Food, beverages and animal feeds*

The US Department of Agriculture (1981) reported that no tetrachlorvinphos was found in 1980 in nine samples of liver nor in one sample of fat from food-producing animals.

2.3 Analysis

Standard methods for the analysis of tetrachlorvinphos in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of tetrachlorvinphos

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Crops and animal tissue	Grind; extract (oily crops and tissue, solvent partition); chromatograph (Florisil/Celite)	GC/Phosphorus-sensitive thermionic emission detector	0.03 mg/kg	Markus & Puma (1973)
Milk	A sequence of extractions	GC/Phosphorus-sensitive thermionic emission detector	0.03 mg/kg	Markus & Puma (1973)
Human or animal adipose tissue	Macerate; a sequence of extractions; chromatograph (Florisil)	GC/ECD	not given	Watts (1980)

[a]Abbreviations: GC, gas chromatography; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female weanling B6C3F$_1$ mice were fed diets containing 8000 or 16 000 mg/kg tetrachlorvinphos (technical grade; minimum purity, 94%; 98% Z-isomer; impurities neither identified nor quantified) for 80 weeks; all surviving animals were killed at 92 weeks. Matched controls consisted of 10 untreated mice of each sex; statistical comparisons were also based on pooled controls of 50 male and 50 female mice. Of the treated males, 36/50 in the low-dose group and 40/50 in the high-dose group developed hepatocellular carcinomas, compared with 0/9 matched controls and 5/49 pooled controls. The combined incidences of neoplastic nodules and hepatocellular carcinomas in the low-dose and high-dose females were 19/49 ($p < 0.001$) and 11/47 ($p = 0.019$), respectively, compared with 3/48 in pooled controls and 0/9 in matched controls. There was no significant difference in the incidence of other types of tumours among treated and control mice (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female weanling Osborne-Mendel rats were fed tetrachlorvinphos (technical grade; purity as described above) in the diet for 80 weeks: the low-dose groups were fed 8000 mg/kg of diet for five weeks and 4000 mg/kg of diet for 75 weeks (time-weighted average dose, 4250 mg/kg of diet), and the high-dose groups, 16 000 mg/kg of diet for five weeks and 8000 mg/kg of diet for 75 weeks (time-weighted average dose, 8500 mg/kg of diet). All surviving rats were killed at 111 weeks. A matched control group consisted of 10 rats of each sex; statistical comparisons were based on both matched controls and pooled controls of 55 male and 55 female rats. The incidence of C-cell adenoma of the thyroid in female rats showed a significant dose-related trend: pooled control, 1/46; low-dose, 2/50; high-dose, 7/46 ($p = 0.013$). Likewise, the incidences of C-cell hyperplasia of the thyroid in both low-dose (7/50) and high-dose (16/46) females were significantly higher compared with that in pooled controls (0/50). In addition, female rats developed adrenal cortical adenomas: in 0/50 pooled controls, 2/49 low-dose, and 5/50 high-dose animals ($p = 0.017$). The incidences of other neoplasms in male and female animals displayed no statistically significant dose-related trend (National Cancer Institute, 1978). [The Working Group noted the short duration of treatment (80 weeks) and period of observation (31 weeks) prior to termination of the study.]

Groups of 25 male and 25 female weanling Porton strain rats were fed 5, 25, 125 or 2000 ppm (mg/kg) tetrachlorvinphos (E-isomer, 95% pure) in the diet for 24 months. Groups of 45 males and 45 females served as controls. There was no signficiant difference in tumour incidence between treated and control rats (Walker *et al.*, 1972). [The Working Group noted that the doses used were relatively low.]

3.2 Other relevant biological data

(*a*) Experimental systems

Toxic effects

The acute oral LD_{50}s for tetrachlorvinphos were 4200 and 17 000 mg/kg bw in male and female mice, and 4000 and 9100 mg/kg bw in male and female rats, respectively. The

i.p. LD_{50}s were 1170 and 1410 in male and female mice and 1160 and 1450 mg/kg bw in male and female rats. The s.c. LD_{50}s were 16 000 and 15 000 in male and female mice and >15 000 mg/kg bw for both male and female rats. The dermal LD_{50}s were >7500 and >10 000 in mice and >10 000 for rats (Nishimura *et al.*, 1974). [There are significant differences in the oral, but not in the i.p. or s.c. LD_{50} values between male and female rats and mice, suggesting that absorption of tetrachlorvinphos *via* the gut is limited in female animals.]

Reduced uptake of thyroid iodine was noted in rats after a single s.c. or i.p. dose of 500 mg/kg bw. This effect was apparently unrelated to a depression of cholinesterase activity (Bojadziev & Manolov, 1975). Morphological changes were observed in the liver, kidney, lung and brain of chicken acutely intoxicated with tetrachlorvinphos (Kokhtiuk & Sukhomlinova, 1977).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

A single oral dose to rats of ^{14}C-labelled (at both vinyl carbon atoms) tetrachlorvinphos was almost completely eliminated in the urine in four days (44-78% during the first 24 hours and 4-15% during the second 24 hours); 78% of the radioactive material was excreted in urine, 16.5% in the faeces and 0.5% in the expired air, probably as $^{14}CO_2$. In dogs given ^{14}C-tetrachlorvinphos, 92% of the radioactive material was excreted in the urine and faeces within four days. The compound was completely metabolized in both rats and dogs, and the following metabolites were found (percentages found in rat urine and dog urine, respectively): 2,4,5-trichlorophenylethanediol glucuronide (8 and 12%); [1-(2,4,5-trichlorophenyl) ethyl-β-D-glucopyranosid]uronic acid (35 and 0%); 2,4,5-trichloromandelic acid (24 and 12%); 2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl hydrogen phosphate (4 and 46%); 2,4,5-trichlorophenylethanediol (2.5 and 4%) and 1-(2,4,5-trichlorophenyl)ethanol (2 and 0%). There was no significant sex difference in the pattern of elimination (Akintonwa & Hutson, 1967). Certain of these metabolites were also found in the urine of cows following oral administration of tetrachlorvinphos (Akhtar & Foster, 1980).

No residue of tetrachlorvinphos or 2,4,5-trichloroacetophenone (a metabolite) was detected in the milk and tissues of a cow given dietary concentrations of 5 mg/kg of the insecticide (Gutenmann *et al.*, 1971).

Mutagenicity and other short-term tests

Tetrachlorvinphos did not induce reverse mutations in *Escherichia coli* WP2 or WP2 *trp* without exogenous metabolic activation (Dean, 1972; Nagy *et al.*, 1975) nor in *Salmonella typhimurium* strains TA98 or TA100, with or without a microsomal supernatant from Aroclor-induced mouse liver (Bartsch *et al.*, 1980).

It was reported in an abstract that unscheduled DNA synthesis was induced in EUE human embryo fibroblasts (Benigni & Dogliotti, 1980) [details not given]; a weak clastogenic effect was observed in cultured human lymphocytes, as the frequency of cells with aberrations increased from 1.7% in controls to 4% in cells treated with 2.7×10^{-4} M tetrachlorvinphos (Kurinniy & Pilinskaya, 1977).

No increase in the frequency of chromosomal aberrations was reported in the bone-marrow cells of male mice treated i.p. with 100 mg/kg bw tetrachlorvinphos (Kurinniy, 1975).

(*b*) *Humans*

Toxic effects

Repeated daily doses of up to 15 mg tetrachlorvinphos fed to human volunteers were reported in an abstract to have no effect on plasma or red-cell cholinesterase activities (Rider & Puletti, 1969).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No relevant data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Tetrachlorvinphos was tested for carcinogenicity in mice and rats by administration in the diet. It produced hepatocellular carcinomas in male mice and benign and malignant liver-cell tumours in female mice. In rats, it increased the incidences of C-cell adenoma of the thyroid and of cortical adenoma of the adrenal in females.

No data were available to evaluate the teratogenicity of tetrachlorvinphos to experimental animals.

Tetrachlorvinphos was not mutagenic to bacteria in the systems studied. It was a weak inducer of chromosomal aberrations in human lymphocytes *in vitro*. No overall evaluation of the mutagenicity of tetrachlorvinphos could be made.

4.2 Human data

Tetrachlorvinphos was introduced in 1966. Its production, formulation and use as an insecticide on livestock and poultry are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of tetrachlorvinphos in humans.

No case report or epidemiological study of the carcinogenicity of tetrachlorvinphos alone was available to the Working Group; however, it should be noted that the period since introduction of this compound may be too short for a carcinogenic effect to be detected in humans. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

Results of experiments in mice and rats provide *limited evidence* that tetrachlorvinphos is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of tetrachlorvinphos to humans.

5. References

Akhtar, M.H., & Foster, T.S. (1980) Fate of tetrachlorvinphos and its isomer in a soluble fraction (105,000 g) from goose and turkey liver homogenates. *J. agric. Food Chem.*, *28*, 693-697

Akintonwa, D.A.A. & Hutson, D.H. (1967) Metabolism of 2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate in the dog and rat. *J. agric. Food Chem.*, *15*, 632-637

Bartsch, H., Malaveille, C., Camus, A.-M., Martel-Planche, G., Brun, G., Hautefeuille, A., Sabadie, N., Barbin, A., Kuroki, T., Drevon, C., Piccoli, C. & Montesano, R. (1980) Validation and comparative studies on 180 chemicals with *S. typhimurium* strains and V79 Chinese hamster cells in the presence of various metabolizing systems. *Mutat. Res.*, *76*, 1-50

Benigni, R. & Dogliotti, E. (1980) UDS studies on selected environmental chemicals (Abstract no. 97). *Mutat. Res.*, *74*, 217

[1]This evaluation should be read in conjunction with p. 18 of the preamble.

Bojadziev, S.B. & Manolov, K.G. (1975) On the mechanism of some organophosphorus compounds influence on the functional state of the rat thyroid. *Agressologie*, *16*, 67-72

Dean, B.J. (1972) The mutagenic effects of organophosphorus pesticides on micro-organisms. *Arch. Toxikol.*, *30*, 67-74

Gutenmann, W.H., St John, L.E., Jr & Lisk, D.J. (1971) Metabolic studies with Gardona insecticide in the dairy cow. *J. agric. Food Chem.*, *19*, 1259-1260

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 120, 121

Kokhtiuk, F.P. & Sukhomlinova, G.K. (1977) Diagnosis of poisoning by gardona in chickens (Russ.). *Veterinariya*, *10*, 101-102

Kurinniy, A.I. (1975) Comparative investigation of cytogenetic effect of certain organophosphorus pesticides (Russ.). *Genetika*, *11*, 64-69

Kurinniy, A.I. & Pilinskaya, M.A.(1977) Cytogenetic activity of pesticides imidan, dipterex and gardona in cultured human lymphocytes (Russ.). *Genetika*, *13*, 337-339

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual*, Vol. 2, *Methods for Individual Pesticide Residues*, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120-252

Nagy, Zs., Mile, I. & Antoni, F. (1975) The mutagenicity effect of pesticides on *Escherichia coli* WP2 try⁻. *Acta microbiol. acad. sci. hung.*, *22*, 309-314

National Cancer Institute (1978) *Bioassay of Tetrachlorvinphos for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 33; DHEW Publ. No. (NIH) 78-833*), Washington DC, US Government Printing Office

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Nishimura, M., Sakama, H., Aoki, H. & Nishiwaki, K. (1974) Inhalation toxicity of agricultural pesticides. 2. Toxicity of 2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate (CVMP) (Jpn.). *Jpn. J. ind. Health*, *16*, 523-530

Rider, J.A. & Puletti, E.J. (1969) Studies on the anticholinesterase effects of Gardona, methyl parathion and guthion in human subjects (Abstract no. 1245). *Fed. Proc.*, *28*, 479

US Department of Agriculture (1981) *Monitoring Phase Biological Residue Report, January 1980 through December 1980*, Washington DC, Residue Evaluation and Surveillance Division

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul.*, *Title 40*, parts 180.252, 180.253, pp. 577, 578

US Food & Drug Administration (1980) Food and drugs. *US Code Fed. Regul., Title 21*, part 561.91. p. 511

US International Trade Commission (1979) *Synthetic Organic Chemicals, US Production and Sales, 1978* (*USITC Publ. 1001*), Washington DC, US Government Printing Office, p. 287

US Tariff Commission (1969) *Synthetic Organic Chemicals, US Production and Sales, 1967* (*TC Publ. 295*), Washington DC, US Government Printing Office, p. 163

Walker, A.I.T., Brown, V.K.H., Stevenson, D.E. & Thorpe, E. (1972) Toxicological studies with the insecticide tetrachlorvinphos. *Pestic. Sci., 3*, 517-525

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, sect. 5A(1)(a)

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 504

TRICHLORFON

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 52-68-6

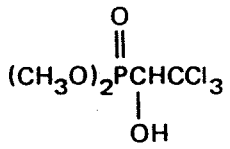
Chem. Abstr. Name: Phosphoric acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester

IUPAC Systematic Name: Dimethyl 2,2,2-trichloro- 1-hydroxyethylphosphonate

Synonyms: Chlorophos; clorofos; DEP; DETF; dimethoxy- 2,2,2-trichloro-1-hydroxyethyl phosphine oxide; dimethyl ester of 2,2,2-trichloro-1-hydroxyethyl phosphonate; dimethyl 1-hydroxy-2,2,2-trichloroethylphosphonate; *O,O*-dimethyl (1-hydroxy-2,2,2-trichloroethyl)phosphonate; dimethyltrichlorohydroxyethyl phosphonate; *O,O*-dimethyl (2,2,2-trichloro-1-hydroxyethyl)phosphonate; dipterex; ENT 19,763; 1-hydroxy-2,2,2-trichloroethylphosphonic acid dimethyl ester; methyl chlorophos; NCI-C54831; trichlorofon; (2,2,2-trichloro- 1-hydroxyethyl) dimethylphosphonate; (2,2,2-trichloro- 1-hydroxyethyl) phosphonic acid dimethyl ester; trichlorophon; trichlorphon; trichlorphone

Trade Names: Aerol 1; Agroforotox; Anthon; Bay 15922; Bayer 15922; Bayer L 13/59; Bilarcil; Bovinox; Briten; Briton; Cekufon; Chlorak; Chlorfos; Chlorofos; Chloroftalm; Chlorophthalm; Chloroxyphos; Ciclosom; Clorfos; Combot; Crimex; Danex; Depthon; Dicontal; Dimetox; Dipterax; Dipterex; Dipterex 50; Diptevur; Ditrifon; Dylox; Dylox-Metasystox-R; Dyrex; Dyvon; Equino-Aid; Flibol E; Fliegenteller; Forotox; Foschlor; Foschlor R & R50; Foschlorem; Hypodermacid; Loisol; Masoten; Mazoten; Metifonate; Metrifonate; Metriphonate; Neguvon; Neguvon A; Phoschlor; Phoschlor R50; Polfoschlor; Proxol; Ricifon; Ritsifon; Satox 20WSC; Soldep; Sotipox; Trichlorphene; Trichlorphon FN; Trinex; Tugon; Tugon Stable Spray; Tugon Fly Bait; Vermicide Bayer 2349; Volfartol; Votexit; WEC 50; Wotexit

1.2 Structural and molecular formulae and molecular weight



$C_4H_8Cl_3O_4P$ Mol. wt: 257.4

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point:* 83-84°C

(*c*) *Density*: d_4^{20} 1.73

(*d*) *Refractive index:* n_D^{20} 1.3439 (100 g/l aqueous solution)

(*e*) *Spectroscopy data:* Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1981) have been reported.

(*f*) *Solubility:* Soluble in water (154 g/l at 25°C), benzene, ethanol and most chlorinated hydrocarbons; poorly soluble in carbon tetrachloride and diethyl ether; insoluble in petroleum oils

(*g*) *Volatility:* Vapour pressure, 7.8×10^{-6} mm Hg at 20°C

(*h*) *Stability:* Stable at room temperature; decomposes at higher temperatures in water and at pH <5.5 to form dichlorvos (2,2-dichlorovinyl dimethyl phosphate) [see IARC, 1979]

1.4 Environmental chemistry

Ultra-violet irradiation of trichlorfon produced dichlorvos and a number of other decomposition products, including *O*-methyl-2,2-dichlorovinyl phosphate, dichlorovinyl alcohol, dichloroacetaldehyde, dichloroacetic acid, and 2,2-dichloroethanol (compounds that were also identified among the metabolites of dichlorvos) (Giovanoli-Jakubczak *et al.*, 1971). In acidic solution, trichlorfon was degraded into dimethyl phosphonic acid and trichloroethanol; in alkaline and neutral solutions, it was converted to dichlorvos, which was hydrolysed to dimethyl phosphate and dichlorovinyl alcohol. The latter was converted to dichloroacetaldehyde, a volatile compound (Bücklers & Eggensperger, 1975).

Trichlorfon has been reported to persist in soil for up to two weeks. Ammonifying soil microorganisms decomposed it (Molozhanova *et al.*, 1973). The enzymatic degradation of ^{14}C-labelled trichlorfon in buffered solutions of broad bean and clover, host plants of the microorganisms *Rhizobium leguminosarum* and *Rhizobium trifolii* (nodule-forming bacteria), produced mono- and dimethyl phosphates. The same metabolites were identified in culture media of these microorganisms. The liberation of $^{14}CO_2$ from cultures incubated with ^{14}C-trichlorfon, suggested that some of the methanol groups were degraded oxidatively by the two *Rhizobium* species (Salama *et al.*, 1975).

1.5 Technical products and impurities

In 1972, the composition of a technical grade of trichlorfon was reported to be: 98% minimum active ingredient, 0-0.2% dichlorvos, 0-0.05% trichloroacetaldehyde, 0-0.03% dichloroacetaldehyde, 0-0.3% demethyl trichlorfon and a maximum of 0.3% water (WHO, 1972).

Trichlorfon is available as a 50% active water-dispersible powder, as 50, 80 and 95% active soluble powders, as a 50% active soluble concentrate, as 25, 50, and 75% active ultra-low volume (ULV) concentrates, as a 5% active dust, as 2.5 and 5% active granules, as a 30% active stable spray, as a 1% active fly bait, and as a preparation for veterinary use (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Trichlorfon was introduced as a commercial chemical in 1952. It is made by the reaction of dimethyl hydrogen phosphite with trichloroacetaldehyde (Worthing, 1979).

It is believed to be produced by one company in the Federal Republic of Germany and one in Spain. Total western European production in 1977 is estimated to have been 2 million kg.

Production of trichlorfon by the sole Japanese producer is estimated to have been 1.1 million kg in 1980 and 1.2 million kg in 1979. Japanese imports of trichlorfon in 1976-1980 were only significant in 1978, when 185 thousand kg were imported. Exports of trichlorfon amounted to 180 thousand kg in 1980, none in 1979 and 392 thousand kg in 1978.

Trichlorfon is also believed to be produced in Argentina, Brazil, Israel, Mexico and South Korea and has probably been produced in the USSR.

It has not been produced commercially in the US, but it is believed to be imported from the Federal Republic of Germany.

(*b*) *Use*

Trichlorfon is used both as an agricultural insecticide for the control of insects on crops and animals, and as a forest insecticide.

In 1976, only 45 thousand kg of trichlorfon were used by US farmers on major crops, representing 0.1% of the total quantity of all active insecticide ingredients used on those crops in that year. Less than 230 kg of trichlorfon were used as a livestock insecticide (US Department of Agriculture, 1978). In 1978, a total of 454 thousand kg were used in the US, with 40% on miscellaneous field crops, 20% on alfalfa, 20% on forests, 10% on cotton and 10% on vegetables. The forestry usage included applications to control outbreaks of gypsy moth and eastern spruce budworm. It is also used to control botfly larvae and worms in horses and ectoparasites in beef cattle.

More than 6000 persons have been treated with trichlorfon for various parasitic infestations of the intestine and the body by administration of doses of up to 70 mg/kg bw per day over periods of up to 12 days (Commission of the European Communities, 1977).

The Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues in November 1971 established an acceptable daily intake of trichlorfon for humans of 0-0.01 mg/kg bw. The following temporary tolerances were recommended for residues of trichlorfon on commodities (mg/kg): cereals, fruits, vegetables, oil seeds, shelled peanuts and meat, fat and by-products of cattle and pigs, 0.1-0.2; and sugar beets and whole milk, 0.05 (WHO, 1972). In 1975, that Group recommended temporary maximum residue limits of 0.5 mg/kg on lettuce and spinach, 0.2 mg/kg on tomatoes and 0.1 mg/kg on raw cereals, including maize (WHO, 1976). In 1978, the Joint Meeting amended the recommendations to 2 mg/kg for apples, 1 mg/kg for strawberries and 0.5 mg/kg for cabbage, and the following new recommendations were made: grapes, 0.5 mg/kg; mutton and radishes, 0.1 mg/kg; and parsley, carrots and aubergines, 0.05 mg/kg (FAO, 1979).

The Council of the European Communities has fixed a maximum acceptable level for trichlorfon residues in and on fruit and vegetables at 0.5 mg/kg (Commission of European Communities, 1976).

Tolerances in the US for residues of trichlorfon in or on raw agricultural commodities are presently 0.1 (negligible residues)-240 ppm (mg/kg) for a variety of 65 commodities, including grains, grasses, vegetables, fruits, nuts and seeds, and animal meats, fats and by-products (US Environmental Protection Agency, 1980a). A tolerance is also established for residues of trichlorfon in dried citrus pulp used as animal feeds, when present as a result of application of the insecticide to growing citrus fruit (US Food & Drug Administration, 1980a).

Trichlorfon is approved in the US for use alone or in combination with atropine, fenbendazole or thiabendazole in anthelmintic preparations for horses (US Food & Drug Administration, 1980b,c, 1981).

Notification must be given to the US Environmental Protection Agency (1980b) of any discharge into waterways of 454 kg or more of trichlorfon. Shipments of this pesticide in the US are subject to a variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1981).

Two countries have established regulations for occupational exposure to trichlorfon as a skin irritant; maximum levels allowed in workplace air are 1 mg/m^3 in Bulgaria (1971) and 0.5 mg/m^3 in the USSR (1977) (International Labour Office, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Trichlorfon is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to trichlorfon, nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to trichlorfon,

namely, its production and its formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that 9.5 thousand US workers in the disinfecting and exterminating industry were exposed to products known to contain trichlorfon.

(*c*) *Water and sediments*

Residues of trichlorfon were detected in water samples during forest spraying monitoring programmes in Canada. In 1976, levels of 60-210 ng/ml were reported in water from the spray area during the 48 hours following application; a slight spray drift resulted in a level of 4.4 ng/ml in water from a neighbouring area two hours after spraying. In 1977, trichlorfon levels ranged from 'not detected'-58.0 ng/ml in water from the spray block 0-12 days following spraying and from 'not detected'-0.7 ng/ml in water from neighbouring areas 0-16 days after spraying (Sergeant & Zitko, 1979).

(*d*) *Soil and plants*

No trichlorfon residue was detected in soil samples from 33-34 tobacco farms in southern Ontario, Canada, in 1976-1978, although six of the farms in 1977 and 11 of the farms in 1978 were known to have used trichlorfon (Frank *et al.*, 1980).

Studies in the USSR have reported concentrations of $\leqslant$0.3 mg/kg trichlorfon in soil samples from an unidentified source and of $\leqslant$0.8 mg/kg in 9.3% of soil samples from cotton fields in the Tadzhik SSR (Baratov, 1978, 1980).

(*e*) *Food, beverages and animal feeds*

The US Department of Agriculture (1981) reported that no trichlorfon was found in 23 samples of liver tissues of food-producing animals in 1980. Trichlorfon was not detected in a total diet study of food composites from five Canadian regions in 1976-1978 (McLeod *et al.*, 1980).

In a study of grapes, 60% of trichlorfon residues were found in the skin; levels were higher in grape juice concentrate, raisins, and wine than in the grapes, and trichlorfon accumulated in wine (Hiramatsu & Furutani, 1978).

(*f*) *Tobacco and tobacco smoke*

Samples of tobacco leaf collected from cured commercial crops in three warehouses in Ontario, Canada, during 1976 and 1977 did not contain detectable amounts of trichlorfon. Residues were also not found in cured tobacco samples collected from 33-34 farms in southern Ontario in 1976-1978, although six and 11 of the farms in 1977 and 1978, respectively, were known to have used trichlorfon (Frank *et al.*, 1980).

2.3 Analysis

Standard methods used for the analysis of trichlorfon in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of trichlorfon

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract (ethyl acetate)	GC/TID	not given	Zweig & Sherma (1972)
Vegetables	Macerate; dialyse; extract	GC/MCD	0.1 mg/kg	Markus & Puma (1970)
Alfalfa	Proceed as above, using acetone for final dissolution	GC/TID	0.02 mg/kg	Zweig & Sherma (1972)
Milk	Blend (acetone and Super-Cel); filter; partition (benzene); concentrate	GC/ECD	0.01 mg/kg	Markus & Puma (1970)
Animal tissue	A sequence of extractions	GC/ECD	0.1 mg/kg	Markus & Puma (1970)

[a]Abbreviations: GC/TID, gas chromatography/thermionic flame ionization detection; GC/MCD, gas chromatography/microcoulometric detection; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) *Oral administration*

Mouse: A group of 30 male and 28 female eight-week-old AB/Jena strain mice received 30 mg/kg bw trichlorfon (purified by several recrystallizations) by gavage twice weekly for 75 weeks, with a two-week break after the 45th week (cumulative dose: males, 157.5 mg; females, 154 mg). All surviving animals were sacrificed at 80 weeks. A group of 30 male and 29 female mice served as controls. There was no significant difference in the incidence of tumours between treated and control mice (Teichmann & Hauschild, 1978). [The Working Group noted the short duration of the study].

Rat: A group of 30 male and 35 female 10-week-old albino rats received 22 mg/kg bw trichlorfon (purified by repeated recrystallizations) in saline by gavage twice weekly for 90 weeks; all surviving animals were killed at 118 weeks (cumulative dose: males 2.08 g; females, 1.98 g). A group of 25 male and 26 female control rats were given saline. There was no significant difference in the incidence of tumours between treated and control groups (Teichmann *et al.*, 1978).

[1]The Working Group was aware of a bioassay in progress in mice and rats in which trichlorfon was administered in drinking-water (IARC, 1981).

A group of 40 Wistar rats [numbers of males and females not specified], 10 weeks of age, were given 15 mg/kg bw trichlorfon (commercial product, ~98% pure: Gibel *et al.*, 1971) by gavage twice weekly for life. The average survival time was 743 days for the 40 controls and 654 days for the treated group. Of the treated rats, 7/28 developed malignant tumours in several tissues. No malignant tumour was reported in controls. In addition, benign tumours were found in 19/28 treated rats, compared with 3/36 controls (Gibel *et al.*, 1973). [The Working Group considered that the inadequate reporting of certain items, such as numbers of males and females in each group, as well as the amalgamation of tumour types regardless of the sex of the animals precluded a complete evaluation of this study.]

(*b*) *Intraperitoneal administration*

Mouse: A group of 30 male and 30 female eight-week-old AB/Jena strain mice received 28.2 mg/kg bw trichlorfon (purified by several recrystallizations; as a 0.94% solution in saline) by i.p. injection twice weekly for 75 weeks, with a two-week break at 45 weeks. The cumulative doses were 160.8 mg in males and 149.7 mg in females. All surviving animals were killed at 80 weeks. A group of 30 male and 30 female controls were given saline by i.p. injections. There was no significant difference in the incidence of tumours between treated and control mice (Teichmann & Hauschild, 1978). [The Working Group noted the short duration of the study.]

Rat: A group of 30 male and 35 female 10-week-old albino rats were given 12 mg/kg bw trichlorfon (purified by several recrystallizations) by i.p. injection twice weekly for 90 weeks. The average cumulative dose was 1.16 g in males and 1.1 g in females. A group of 25 male and 25 female controls received saline injections. All surviving animals were killed at 118 weeks. No statistically significant difference was found in the incidence of tumours between treated and control rats (Teichmann *et al.*, 1978).

Hamster: A group of 23 male and 25 female Syrian golden hamsters, seven to eight weeks of age, were given 20 mg/kg bw trichlorfon (purified by repeated recrystallizations) as a 2% solution in isotonic saline by i.p. injection once weekly for 90 weeks. A group of 22 male and 23 female controls received saline injections. All surviving animals were killed at 100 weeks. There was no significant difference in the incidence of tumours between treated and control hamsters (Teichmann & Schmidt, 1978).

(*c*) *Skin application*

Mouse: Groups of 40 AB strain mice [numbers of males and females per group not specified], eight weeks of age, received 15 mg/kg bw trichlorfon (commercial product, *~98%* pure: Gibel *et al.*, 1971) by skin application twice weekly for six weeks and were observed for life. Malignant tumours (myeloid leukaemia) developed in 5/14 treated mice by 406 days (Gibel *et al.*, 1973). [The Working Group considered that the inadequate reporting of certain items, such as numbers of males and females in each group, the amalgamation of tumour types regardless of the sex of the animals, and the lack of sufficient data on the control group precluded a complete evaluation of this study.]

A group of 30 male and 30 female, eight-week-old AB/Jena strain mice each received 0.25 ml of a 1% solution of trichlorfon (purified by several recrystallizations) in acetone twice weekly for 75 weeks (cumulative dose, 375 mg). All surviving animals were sacrificed at 80 weeks. A group of 30 male and 30 female mice served as controls. There was no significant difference in the incidence of tumours between treated and control mice

(Teichmann & Hauschild, 1978). [The Working Group noted the short duration of the study.]

(*d*) *Subcutaneous and/or intramuscular administration*

Rat: A group of 40 Wistar rats [numbers of males and females not specified], 10 weeks of age, were given i.m. injections of 15 mg/kg bw trichlorfon (commercial product, ~98% pure: Gibel *et al.*, 1971) twice weekly for life. The average survival time was 711 days for the 40 controls and 565 days for the treated group. Of the treated rats, 4/27 developed malignant tumours in several tissues; no malignant tumour was reported in controls. Benign tumours were found in 7/27 treated rats and in 4/35 controls (Gibel *et al.*, 1973). [The Working Group considered that the inadequate reporting of certain items, such as numbers of males and females in each group as well as the amalgamation of tumour types regardless of the sex of the animals precluded a complete evaluation of this study.]

3.2 Other relevant biological data

The toxicology of trichlorfon has been reviewed (Royal Swedish Academy of Sciences, 1981). (See also the section 'General Remarks on the Substances Considered'.)

(*a*) *Experimental systems*

Unless stated otherwise, the purity or impurities present in the material tested was not stated.

Toxic effects

The oral LD_{50} of trichlorfon was 630-800 mg/kg bw in mice (Vrbovskyé *et al.*, 1959; Belyaev, 1969; Haley *et al.*, 1975), 400-650 mg/kg bw in rats (DuBois & Cotter, 1955; Edson & Noakes, 1960; Gaines, 1969; Gibel *et al.*, 1973), 710 mg/kg bw in rabbits (Janda, 1975), >200 mg/kg bw in sheep, >10 mg/kg bw in calves and >100 mg/kg bw in cattle (Radeleff & Woodward, 1957). The i.p. LD_{50} was 500-630 mg/kg bw in mice (DuBois & Cotter, 1955; Vrbovskyé *et al.*, 1959; Gibel *et al.*, 1973), 190-400 mg/kg bw in rats (DuBois & Cotter, 1955; Arthur & Casida, 1957; Brodeur & DuBois, 1963) and 60 mg/kg bw in rabbits (Kadin, 1962). The s.c. LD_{50} was 267-320 mg/kg bw in mice (Commission of the European Communities, 1977) and 400 mg/kg bw in rats (Krueger & Casida, 1957). The dermal LD_{50} in rats was found to be >2000 mg/kg bw (Gaines, 1969) and >2800 mg/kg bw (Edson & Noakes, 1960).

The acute toxicity of trichlorflon is due to inhibition of acetylcholinesterase at nerve endings, leading to an accumulation of endogenous acetylcholine. The effects are manifested by muscarinic, nicotinic and central nervous system signs and symptoms: sweating, salivation, diarrhoea, bronchorrhoea, bradycardia, bronchoconstriction, muscle fasciculations and coma. The cause of death is primarily respiratory failure (Taylor, 1980).

Animals given sublethal doses recover extremely rapidly, suggesting that trichlorfon is detoxified faster than are many other cholinergic organophosphate compounds (DuBois & Cotter, 1955; Edson & Noakes, 1960). However, trichlorfon administered intraperitoneally to mice gives rise, non-enzymatically, to dichlorvos (acting as a slow-release formulation), so that the effect of trichlorfon was more prolonged than that of dichlorvos (Nordgren *et*

al., 1978). Trichlorfon potentiated the acute toxicity of some other organophosphorus insecticides (DuBois, 1958).

Symptoms of acute poisoning developed earlier and lethality was higher in mice administered trichlorfon and maintained at 40-41°C than in mice maintained at 20-22°C (Litvinenko *et al.*, 1973).

In rats given daily oral doses of 300 mg/kg bw technical trichlorfon for five days, brain oedema, congestion of organs, fatty degeneration and glycogen depletion of the liver, glycogen depletion of the heart muscle and emphysema and local inflammation in the lungs were observed (Karmilov, 1973).

At high doses, trichlorfon and dichlorvos are both capable of inducing delayed neuropathy in hens (Johnson, 1980; Caroldi & Lotti, 1981).

Trichlorfon has been reported to produce alterations in: the cardiac activity of dogs (Filchenko, 1976) and rabbits (Kossakowski & Patyra, 1977); renal tubules of rats (Bonashevskaya & Tabakova, 1972) and mice (Peziol-Laszczynska, 1978); gastric mucosa of rats (Kuchinsky *et al.*, 1977); pancreas of rats (Woroniecka *et al.*, 1977); and liver of rats (Wojcik, 1975). Immunological depression in rats (Olefir, 1971a), allergenic reactivity in rats and rabbits (Gavat *et al.*, 1978) and depressed antibody formation in rats (Olefir, 1971b) have also been reported.

Rats and mice exposed chronically to 15 mg/kg bw trichlorfon twice a week showed steatocryptosis and inflammatory changes in the liver, hyperplasia of the haematopoietic tissue of the bone marrow and leucocytosis in the peripheral blood (Gibel *et al.*, 1971, 1973). However, trichlorfon produced no pathological change in rats fed 500 mg/kg of diet for one year (Bücklers & Eggensperger, 1975).

Survival time and average body weight were considerably lower in male Syrian golden hamsters given weekly i.p. injections of 20 mg/kg bw trichlorfon for 90 weeks than in a control group (Teichmann & Schmidt, 1978).

Dogs fed trichlorfon for four years showed a depression of plasma and erythrocyte cholinesterase levels proportional to the dose (200, 800 or 3200 mg/kg of diet). Generally, the depression of cholinesterase activity was greater at the beginning of the experiment and tended to be less marked later on (Commission of the European Communities, 1977).

Effects on reproduction and prenatal toxicity

Doses of 60-360 mg/kg bw trichlorfon administered as a single or multiple i.p. doses during pregnancy produced no clear evidence of teratogenicity in three pure-bred strains of mice; embryotoxicity was observed in one strain (AB/Jena) (Scheufler, 1975). A dose of 500 or 600 mg/kg bw given to CD-1 mice daily by oral gavage on days 10-14 of pregnancy resulted in reduction of both food intake and body weight in dams, reduced foetal weight and a slightly but significantly increased incidence of cleft palate. Anomalies were seen in 7/205 foetuses exposed to 600 mg/kg bw, in 4/67 foetuses exposed to 500 mg/kg bw, 1/44 foetuses given 400 mg/kg bw, 2/91 exposed to 300 mg/kg bw and 2/267 and 1/135 in two control groups (Staples & Goulding, 1979). The foetuses of CD-1 mice treated during pregnancy had an increased incidence of extra ribs when exposed to 200 mg/kg bw, a reduced number of ribs when exposed to 400 mg/kg bw and a normal number of ribs at the intermediate dose of 300 mg/kg bw (Courtney & Andrews, 1980).

When albino rats were exposed to aerosols of 0.005, 0.02, 0.2 or 9 mg/m^3 trichlorfon over the entire period of pregnancy, no teratogenic effect was seen in their offspring and no change in placental histology occurred (Gofmekler & Tabakova, 1970). A single 80 mg/kg bw dose administered to rats orally by gavage on day 13 of pregnancy caused an increased number of embryonic deaths, a decreased number of live foetuses and increased foetal anomalies, such as exencephaly and failure of eyelids to close; administration of 8 mg/kg bw throughout pregnancy produced no teratogenic manifestation (Martson & Voronina, 1976). When trichlorfon (98.5% pure) was fed to rats on days 6-15 of pregnancy at a daily intake of 0, 76, 145, 375, 432 or 519 mg/kg bw, maternal food intake was reduced with doses $\geqslant$145 mg/kg bw, and both maternal and foetal body weights were reduced at doses $\geqslant$432 mg/kg bw. There was a dose-related increase in foetal malformations with concentrations $\geqslant$145 mg/kg; exencephaly, hydrocephaly, syndactyly and cleft palate were the predominant anomalies. No adverse effect was observed with 76 mg/kg bw (Staples *et al.*, 1976). In a three-generation reproduction study, rats administered a daily dose of 60 mg/kg bw in the drinking-water produced progeny with reduced viability and body weight (Rybak, 1973).

Low incidences (1 and 9%) of malformed foetuses were seen when hamsters were administered 300 and 400 mg/kg bw in three doses each day by gavage on days 7-11 of pregnancy. Both doses resulted in a reduction in maternal food intake. A dose of 200 mg/kg bw had no significant adverse effect (Staples & Goulding, 1979).

Absorption, distribution, excretion and metabolism

The absorption, distribution and excretion of trichlorfon in mammals is rapid: about 70-80% of a dose administered orally to mice was excreted during the first 12 hours after treatment. The biological half-life of trichlorfon was 80 min. The main metabolites detected in urine and tissues were dimethylphosphoric acid, phosphoric acid, demethyldichlorvos and monomethyl phosphoric acid (Miyata & Saito, 1973). Dichlorvos was detected in the brain of mice after i.p. injection of trichlorfon (Nordgren *et al.*, 1978). Following dermal and intragastric application of trichlorfon to cows, the parent compound and dichlorvos were detected in the milk up to 22 days after application (Fechner *et al.*, 1968; Juszkiewicz & Stec, 1970; Nepoklonov & Metelitsa, 1971; Filatov *et al.*, 1972; Todorov *et al.*, 1974).

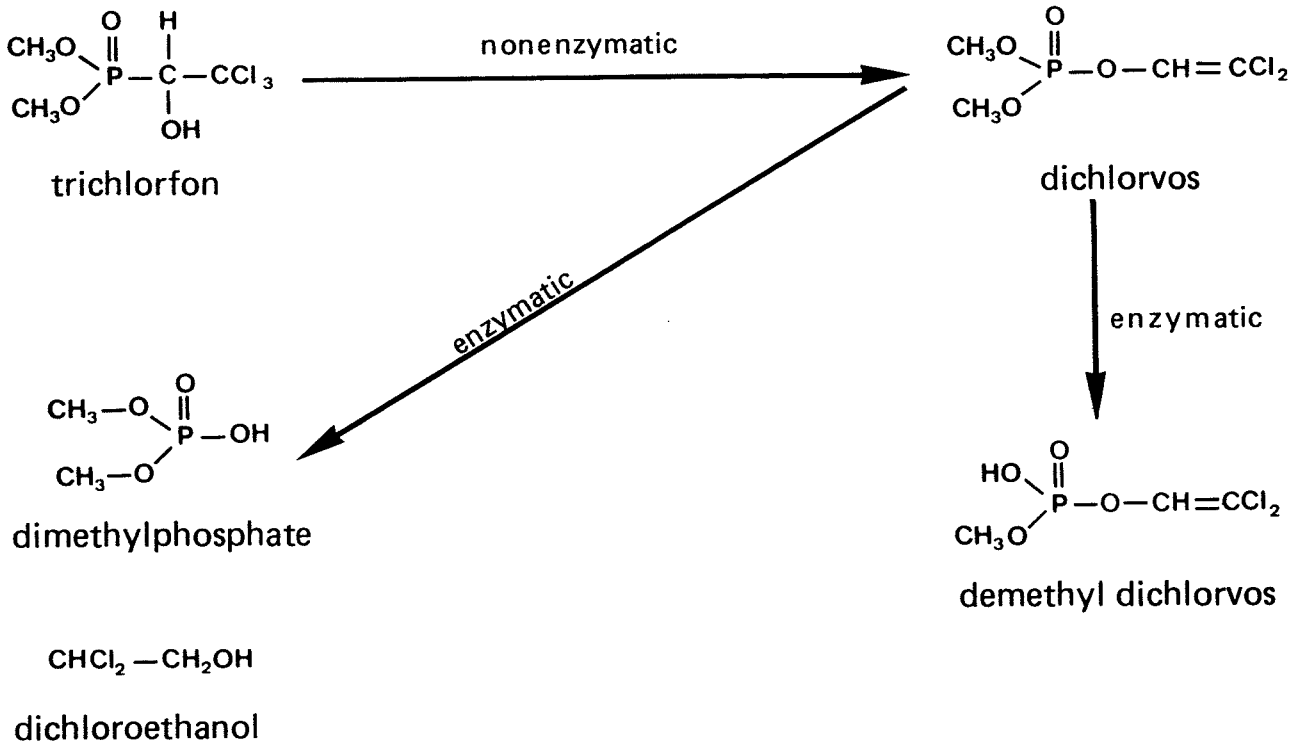
The major metabolic pathways of trichlorfon are shown in Figure 1. After an i.p. injection of 5 mg ^{32}P-trichlorfon to rats, trichlorfon (0.7%), dimethyl phosphate (35.7%), phosphoric acid and methyl phosphate (0.8%), *O*-demethyltrichlorfon (1.4%) and *O*-demethyldichlorvos (0.8%) were found in the urine (Bull & Ridgway, 1969). After i.p. administration of trichlorfon, ^{14}C-labelled at the two methyl groups, 24% of the dose was recovered as $^{14}CO_2$ in the expired air within 10 hours; 32% was recovered in urine as formate (7-15%) and dimethyl phosphate (65-75%) in the first 24 hours after the administration (Hassan & Zayed, 1965).

Three hours after an i.v. injection of [$^{14}CH_3O$] trichlorfon to rats, trace amounts of radioactivity were found in the liver, lungs, kidney, heart, spleen and blood. Glutathione and proteins were methylated (Dedek & Lohs, 1970a).

Mutagenicity and other short-term tests

Trichlorfon reacts *in vitro* with DNA to cause depurination and strand excision (Rosenkranz & Rosenkranz, 1972). The alkylating activity of ^{14}C-trichlorfon, labelled at the

Fig. 1 Major metabolic pathways of trichlorfon[a]



[a]From Bull & Ridgway (1969) and Huston & Hoadley (1972)

CH_3O group, toward guanine N-7 of nucleic acids *in vivo*, when given as an i.p. injection of 160 mg/kg bw to male AB Jena/Halle mice, was four times lower than that of dichlorvos (Dedek *et al.*, 1976).

Results with bacteria have not been consistent; the differences reported are probably due to differences in methodology. Trichlorfon was negative in the *rec* and *pol* assays (Shirasu *et al.*, 1976) and in some mutagenicity tests, e.g., in spot tests with *Escherichia coli hcr*$^+$ and *hcr*$^-$ (Nagy *et al.*, 1975) and with *Salmonella typhimurium* strains TA1535, TA1536, TA1537 and TA1538 at 2000 µg/plate (Carere *et al.*, 1978a). Others have reported mutagenicity in *S. typhimurium* and *E. coli* WP2 (Byeon *et al.*, 1976; Batzinger & Bueding, 1977; Simmon *et al.*, 1979; Kawachi *et al.*, 1980; Braun *et al.*, 1982; Shirasu *et al.*, 1982), *E. coli* WP2 *uvrA* (Hanna & Dyer, 1975) and *Streptomyces coelicolor* (Carere *et al.*, 1978a,b). In general, induction of base-pair substitution or mutation was observed and exogenous metabolic activation was not required.

According to Carere *et al.* (1978b) the negative result obtained with *S. typhimurium* TA1535 using the standard plate protocol is changed to a positive result if the trichlorfon solution is stored for 12 hours before application to the cells for one hour at 12 mg/ml. Mutagenicity following storage was also noted by Hanna and Dyer (1975). The likelihood that degradation products, such as dichlorvos, may be present must be considered in all studies with trichlorfon. The fact that the mutagenicity of trichlorfon or its degradation product does not require metabolic activation (Batzinger & Bueding, 1977; Kawachi *et al.*, 1980) is consistent with the activity of an alkylating agent.

In *Aspergillus nidulans*, 2 mg/plate trichlorfon [purity unspecified] did not induce point mutations but weakly stimulated somatic crossing over (Morpurgo *et al.*, 1977). Mitotic recombination was also stimulated by a technical grade of trichlorfon [purity unspecified] in the yeast *Saccharomyces cerevisiae* D3 system (Simmon, 1979; Waters *et al.*, 1982). Technical-grade trichlorfon [purity unspecified] induced mitotic crossing over and gene conversion in strain D7 of *Saccharomyces cerevisiae* with and without an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

Trichlorfon [purity unspecified] was more potent than ethyl methylsulphonate in inducing chromosomal damage in *Hordeum vulgare*. A dose-response effect was observed (Panda & Sharma, 1980).

Trichlorfon did not induce mutation in *Drosophila melanogaster* (Benes & Sram, 1969; Brzheskii, 1973; Lamb, 1977; Valencia, 1977; Waters *et al.*, 1980), but because of high toxicity only low doses could be tested.

Trichlorfon is genotoxic in cultured mammalian cells. It induced unscheduled DNA synthesis in a human epithelioid cell line (Benigni & Dogliotti, 1980) and in WI38 human fibroblasts with and without an uninduced mouse liver microsomal preparation (Waters *et al.*, 1982). Sister chromatid exchanges were induced in V79 Chinese hamster cells with 98% pure trichlorfon (Chen *et al.*, 1981) and in CHO cells with and without an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982). In a table summarizing work carried out in a Japanese cooperative programme [details not given] trichlorfon was reported to induce chromosomal aberrations in Chinese hamster cells without exogenous metabolic activation (Kawachi *et al.*, 1980). It had the same (weak) activity in human lymphocytes (Kurinniy & Pilinskaya, 1977).

Technical-grade trichlorfon [purity unspecified] induced presumed gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells with and without an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

No significant induction of micronuclei was found after six hours in mouse bone-marrow cells following two i.p. injections of 125 or 312.5 mg/kg bw trichlorfon [purity unspecified] (Paik & Lee, 1977). A similar negative result was obtained by Jones *et al.* (1982) and Waters *et al.* (1982) with two i.p. injections of 100, 200 or 400 mg/kg bw trichlorfon [technical grade, purity unspecified], sampling after 48, 72 and 96 hours. No evidence of cytogenetic damage was reported (in an abstract) in mouse bone marrow or spermatogonia following treatment with one i.p. injection of 100 mg/kg bw or five oral administrations of 20 mg/kg bw at 14-day intervals or 0.5 mg/l in water for seven weeks (Degraeve *et al.*, 1981).

Other workers have obtained positive results. A single oral dose of 8.5, 85 or 125 mg/kg bw trichlorfon to BALB/c mice increased the incidence of chromosomal aberrations in bone-marrow cells to 1.6%, 1.4% and 3.4%, respectively, *versus* 0.6% in controls, 24 hours after administration of the pesticide (Ryazanova & Gafurova, 1980). Induction of chromosomal aberrations in mouse bone marrow was also reported by Kurinniy (1975) and Kuzmenko *et al.* (1980); and increased numbers of chromosomal aberrations of many types were observed in spermatocytes from mice fed 0.15% trichlorfon for 50 or 100 days (Bulsiewicz *et al.*, 1976). [It may be noted that the source and purity of the trichlorfon used in the studies with positive results is likely to have been different from those in the negative studies.]

Post-implantation losses were not significantly elevated when seven male mice were given an i.p. injection of 56 mg/kg bw, nine were given 280 mg/kg bw intraperitoneally and 10 received five oral doses of 360 mg/kg bw (Epstein *et al.*, 1972). In an abstract describing a study of unspecified size, no dominant lethal mutation was induced in mice (Degraeve *et al.*, 1981). No effect was also reported (in another abstract) following a single i.p. injection of 4.5 or 3 x 10^{-2} M [volume not specified] to groups of 20 male NMRI mice (Becker & Schöneich, 1980). In contrast, post-implantation losses were noted after groups of 10 male mice were given i.p. injections of 405 mg/kg bw as a single dose or 54 mg/kg bw daily for three weeks (Dedek *et al.*, 1975). A positive effect was also reported following an i.p. injection of 405 mg/kg bw to male mice (Fischer *et al.*, 1977). Induction of dominant lethal mutations in mice was reported in another abstract after both high acute doses and chronic low doses (Schiemann, 1975).

Although the positive results found in studies with microorganisms may be attributed to the alkylating ability of the degradation product of trichlorfon, dichlorvos, this cannot be the case with the studies of whole animals and may not be so with cultured mammalian cells. Dedek *et al.* (1975) found a similar dominant lethal effect with trichlorfon and demethyltrichlorphon and concluded that the effect could not be due to alkylation. The most likely candidates for activity *in vivo* are dichloroacetaldehyde and 2,2-dichloro-1,1-dihydroxyethanephosphonic acid methyl ester, both degradation products of demethyltrichlorfon and metabolites of trichlorfon. I.p. injections of 1.6 mmol/kg bw of these compounds produced similar dominant lethal effects to those of trichlorfon (Fischer *et al.*, 1977). Persisting metabolites are probably also responsible for the positive result obtained in the mouse host-mediated assay with *S. typhimurium* TA100 and in an assay on mouse urine with TA100 and (weakly) with TA98 (Batzinger & Bueding, 1977).

(*b*) *Humans*

Toxic effects

Greenhouse workers exposed to dicofol and trichlorfon were reported to suffer frequently from allergic dermatitis (Zolotnikova & Somov, 1978).

Trichlorfon has been found to be effective in the treatment of helminthic diseases, particularly schistosomiasis, and has been used at various dosages: Those employed most commonly are 7-24 mg/kg bw administered for two or three days (Lebrun & Cerf, 1960; Beheyt *et al.*, 1961; Plestina *et al.*, 1972). Regardless of the dosing regimes, mild and reversible side effects have been observed occasionally in patients in western Europe and Africa (Cerf *et al.*, 1962; Titova & Badiugin, 1970); these were typical of anticholinesterase effects.

Severe cases of poisoning, sometimes resulting in polyneuropathy, have occurred in Poland (Cichecki, 1971; Dmochowska-Mroczek *et al.*, 1972; Eljasz & Kryszton-Przekop, 1975), Rumania (Vasilescu & Fluorescu, 1980), Hungary (Irányi, 1975), Japan (Ishihara *et al.*, 1974; Fukuhara *et al.*, 1977), the UK (Hierons & Johnson, 1978) and the USSR (Lobsin & Tsinovoy, 1969; Akimov *et al.*, 1975, 1977; Evseev, 1980). It is impossible to exclude the possibility that the preparations used in other countries were of Soviet origin; it has been suggested that at least some lots of trichlorfon produced in the USSR might have contained impurities that were highly toxic and had specific neurotoxic effects (Holmstedt *et al.*, 1978).

Delayed polyneuropathy following severe anticholinesterase poisoning always affected the legs most severely, but the hands, arms and apparently the cranial nerves were

sometimes affected to a lesser extent. Recovery was delayed and often incomplete (Vernik, 1971; Zhabin & Litvishenko, 1971; Petrova *et al.*, 1972; Fukuhara *et al.*, 1977).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

After administration of two doses of 600 mg (7.5 mg/kg bw) trichlorfon to two patients with schistosomiasis, trichlorfon and dichlorvos concentrations in the blood were monitored for eight hours. Dichlorvos was readily detected within a few minutes of trichlorfon administration, and the time course curves of blood concentrations increased then declined in roughly parallel fashion. Dichlorvos concentrations averaged about 1% of trichlorfon concentrations throughout, suggesting that metabolic disposition of dichlorvos proceeds at about the same rate as synthesis from trichlorfon. Both erythrocyte and plasma cholinesterase activities were strongly inhibited. The patients remained asymptomatic (Nordgren *et al.*, 1980).

Trichlorfon itself is not active as a cholinesterase inhibitor but is effective only by reason of its conversion to dichlorvos (Reiner *et al.*, 1975). It is rapidly converted nonenzymatically to dichlorvos in human plasma, with a half-life of about one hour (Arthur & Casida, 1958). This conversion has also been shown to occur *in vivo* (Arthur & Casida, 1957).

The major metabolites of trichlorfon in man are shown in Figure 1; metabolism is thought to be similar in humans to that in rats and mice (Hutson & Hoadley, 1972). Trichlorfon, dichlorvos, dimethylphosphate and demethyltrichlorfon were detected in human serum incubated with ^{14}C-trichlorfon (Dedek & Lohs, 1970b). The metabolism of [1-^{14}C-vinyl]-dichlorvos has also been studied *in vivo* following oral ingestion of 5 mg or inhalation of vapour. Eight hours after ingestion of labelled dichlorvos, 27% of the label was recovered as exhaled CO_2; 9% appeared in the urine within 48 hours of dosing. Identifiable ^{14}C-labelled substances in the urine were demethyldichlorvos, urea, hippuric acid and dichloroethanol glucuronide. Dichloroethanol glucuronide was also recovered from the urine of a man who inhaled dichlorvos vapour (38 µg/l) for 105 min (Hutson & Hoadley, 1972). Reductions in plasma and red-blood cell cholinesterase activities were well correlated with an inhaled dosage (Hunter, 1973).

Mutagenicity and chromosomal effects

van Bao *et al.* (1974) found a significant excess of chromatid aberrations and stable chromosomal aberrations in the lymphocytes of a group of five patients one month after acute intoxication with trichlorfon (Ditriphon-50) as compared with healthy controls. [The small numbers of subjects involved and the inappropriateness of the controls used do not permit the association to be established as causal.]

It was reported in an abstract that chromatid-type aberrations in peripheral lymphocytes were increased in 17 factory workers exposed to small doses of trichlorfon over a long period as compared with controls (Király *et al.*, 1977). In eight of these individuals, the level was described as a 'pathological value' (Király *et al.*, 1979). These authors noted that the level of chromatid-type aberrations was also elevated in workers from the same factory not specifically exposed occupationally, suggesting the possibility of airborne contamination by other chemicals.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Trichlorfon was tested for carcinogenicity by oral administration in mice and rats, by intraperitoneal administration in mice, rats and hamsters, by dermal application in mice and by intramuscular administration in rats. The studies in mice and two of the studies in rats were considered inadequate for evaluation. The other studies in rats and that in hamsters were not indicative of a carcinogenic effect.

Trichlorfon was teratogenic to mice, rats and hamsters when given at dose levels which also caused reductions in maternal food intake and maternal body weight gain.

There is sufficient evidence that trichlorfon or its degradation products is mutagenic in bacteria, mammalian cells and mice. Inconsistent results have been reported with many systems, however, and the instability of trichlorfon may be an important consideration in interpreting these data.

4.2 Human data

Trichlorfon was introduced in 1952. Its use as an insecticide in agricultural applications is a potential source of exposure, both of workers and of the general population. Its use in human medicine as an anthelmintic is another possible source of human exposure.

No data were available to evaluate the teratogenic effects of trichlorfon in humans. The available data were insufficient to evaluate the chromosomal effects of trichlorfon in humans.

No case report or epidemiological study of the carcinogenicity of trichlorfon alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Users and Formulators'.)

4.3 Evaluation

The available data, while providing no evidence that trichlorfon is carcinogenic to mice or rats, were considered inadequate to evaluate the carcinogenicity of this compound to experimental animals. In view of its mutagenicity, confirmed in several experimental systems, further studies on the carcinogenicity of this compound are warranted. The Working Group was aware that a long-term bioassay was in progress.

No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of trichlorfon to humans.

5. References

Akimov, G.A., Buchko, V.M. & Kremleva, R.V. (1975) Neurological disorders in chlorophos poisoning (Russ.). *Klin. Med.*, *5*, 65-69

Akimov, G.A., Buchko, V.M., Kremleva, R.V. & Kolesnichenko, I.P. (1977) Changes in the nervous system in acute peroral intoxications with chlorophos (clinical and pathomorphological data) (Russ.). *Zh. Nevropatol. Psikhiatr.*, *77*, 204-207

Arthur, B.W. & Casida, J.E. (1957) Metabolism and selectivity of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate and its acetyl and vinyl derivatives. *Agric. Food Chem.*, *5*, 186-192

Arthur, B.W. & Casida, J.E. (1958) Biological activity of several *O,O*-dialkyl alpha-acyloxyethyl phosphonates. *J. agric. Food Chem.*, *6*, 360-365

van Bao, T., Szabó, I., Ruzicska, P. & Czeizel, A. (1974) Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. *Humangenetik*, *24*, 33-57

Baratov, K.B. (1978) Data on the level of several pesticides in some environmental objects in the Tadzhik SSR (Russ.). *Izv. Akad. Neuk Tadzh. SSR, Otd. Biol. Nauk*, *2*, 89-92 [*Chem. Abstr.*, *90*, 67680y]

Baratov, K.B. (1980) Pesticides and the environment (Russ.). *Khlopkovodstvo*, *3*, 23 [*Chem. Abstr.*, *93*, 93678k]

Batzinger, R.P. & Bueding, E. (1977) Mutagenic activities *in vitro* and *in vivo* of five antischistosomal compounds. *J. Pharmacol. exp. Ther.*, *200*, 1-9

Becker, K. & Schöneich, J. (1980) Dominant lethal test with trichlorphon in male mice (Abstract no. 111). *Mutat. Res.*, *74*, 224

Beheyt, P., Lebrun, A., Cerf, J., Dierickx, J. & Degroote, V. (1961) Study of toxicity of an organophosphorus insecticide for man (Fr.). *Bull. World Health Organ.*, *24*, 465-473

Belyaev, V.I. (1969) Toxicological study of trichlorometaphos-3, trichlorfon and trolene in animals (Russ.). *Veterinariya*, *46*, 58-60

Benes, V. & Sram, R. (1969) Mutagenic activity of some pesticides in *Drosophila melanogaster*. *Ind. Med.*, *38*, 50-52

Benigni, R. & Dogliotti, E. (1980) UDS studies on selected environmental chemicals (Abstract no. 97). *Mutat. Res.*, *74*, 217

Bonashevskaya, T.I. & Tabakova, S.A. (1972) Morphological alterations occurring in albino rat organs following inhalation of chlorophos in microconcentrations (Russ.). *Farmakol. Toxikol.*, *35*, 240-241

Braun, R., Schöneich, J., Weissflog, L. & Dedek, W. (1982) Activity of organophosphorus insecticides in bacterial tests for mutagenicity and DNA repair - Direct alkylation vs.

metabolic activation and breakdown. I. Butonate, vinylbutonate, trichlorfon, dichlorvos, demethyl dichlorvos and demethyl vinylbutonate. *Chem.-biol. Interactions*, *39*, 339-350

Brodeur, J. & DuBois, K.P. (1963) Comparison of acute toxicity of anticholinesterase insecticides to weanling and adult male rats. *Proc. Soc. exp. Biol. Med.*, *114*, 509-511

Brzheskii, V.V. (973) Possibility of induction of mutations in *Drosophila melanogaster* with chlorophos (Russ.). *Med. Parazitol. Parazit. Bolezni.*, *42*, 703-706

Bücklers, L. & Eggensperger, H. (1975) One-step disinfection and insect control of feed storage containers (Ger.). *Tier*(aêrztliche *Umschau*, *30*, 621-628

Bull, D.L. & Ridgway, R.L. (1969) Metabolism of trichlorfon in animals and plants. *J. agric. Food Chem.*, *17*, 837-841

Bulsiewicz, H., Rózewicka, L., Januszewska, H. & Bajko, J. (1976) Aberrations of meiotic chromosomes induced in mice with insecticides. *Folia Morphol. (Warsz.)*, *35*, 361-368

Byeon, W.-H., Hyun, H.H. & Lee, S.Y. (1976) Mutagenicity of pesticides in the *Salmonella*/microsome system. *Korean J. Microbiol.*, *14*, 128-134

Carere, A., Ortali, V.A., Cardamone, G., Torracca, A.M. & Raschetti, R. (1978a) Microbiological mutagenicity studies of pesticides *in vitro*. *Mutat. Res.*, *57*, 277-286

Carere, A., Ortali, V.A., Cardamone, G. & Morpurgo, G. (1978b) Mutagenicity of dichlorvos and other structurally related pesticides in *Salmonella* and *Streptomyces*. *Chem.-biol. Interactions*, *22*, 297-308

Caroldi, S. & Lotti, M. (1981) Delayed neurotoxicity caused by a single massive dose of dichlorvos to adult hens. *Toxicol. Lett.*, *9*, 157-159

Cerf, J., Lebrun, A. & Dierichx, J. (1962) A new approach to helminthiasis control: The use of an organophosphorus compound. *Am. J. trop. Med. Hyg.*, *11*, 514-517

Chen, H.H., Hsueh, J.L., Sirianni, S.R. & Huang, C.C. (1981) Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. *Mutat. Res.*, *88*, 307-316

Cichecki, Z. (1971) Hallucinosis following intoxication with phoschlorine R-20 (Pol.). *Psychiatr. Pol.*, *5*, 607-609

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *L340*, 26-31

Commission of the European Communities (1977) *Organophosphorus Pesticides*, Oxford, Pergamon Press, pp. 55, 78, 95

Courtney, K.D. & Andrews, J.E. (1980) Extra ribs indicate fetotoxicity and maldevelopment (Abstract). *Teratology*, *21*, 35A

Dedek, W. & Lohs, K. (1970a) The alkylating effect of trichlorfon in warm blooded animals. II. Distribution of ^{14}C in organs and liver proteins in rats after administration of ^{14}C-trichlorfon (Ger.). *Z. Naturforsch., 25B,* 1110-1113

Dedek, W. & Lohs, K. (1970b) The alkylating effect of trichlorfon in warm blooded animals. I. Investigations *in vitro* in human serum with ^{14}C-trichlorfon (Ger.). *Z. Naturforsch., 25B*, 94-96

Dedek, W., Scheufler, H. & Fischer, G.W. (1975) Mutagenicity of desmethyltrichlorphon in the dominant lethal test in mice (Ger.). *Arch. Toxicol., 33*, 163-168

Dedek, W., Lohs, K., Fischer, G.W. & Schmidt, R. (1976) Alkylation of guanine in mice *in vivo* by organophosphorus insecticides. I. Trichlorphone and butonate. *Pestic. Biochem. Physiol., 6*, 101-110

Degraeve, N., Chollet, M., Moutschen, J., Moutschen-Dahmen, M., Gilot-Delhalle, J. & Colizzi, A. (1981) Genetic and cytogenetic effects of trichlorfon in acute, subacute and chronic treatment (Abstract). *Mutat. Res., 80*, 297

Dmochowska-Mroczek, H., Lebensztejn, W. & Tolwinéski, K. (1972) Severe intoxication with Dipterex in a pregnant woman (Pol.). *Pol. Tyg. Lek., 27*, 1406-1407

DuBois, K.P. (1958) Potentiation of the toxicity of insecticidal organic phosphates. *Arch. ind. Health, 18*, 488-496

DuBois, K.P. & Cotter, G.J. (1955) Studies on the toxicity and mechanisms of action of dipterex. *Arch. ind. Health, 11*, 53-60

Edson, E.F. & Noakes, D.N. (1960) The comparative toxicity of six organophosphorus insecticides in the rat. *Toxicol. appl. Pharmacol., 2*, 523-539

Eljasz, L. & Krzysztoné-Przekop, T. (1975) Polyneuropathy as the result of foschlor poisoning (Pol.). *Pol. Tyg. Lek., 30*, 1841-1842

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol., 23*, 288-325

Evseev, V.N. (1980) Neurological disturbances and vocational prognosis after acute poisoning with chlorophos (Russ.). *Zh. Nevropatol. Psikhiatr., 80*, 203-208

FAO (1979) *Pesticide Residues in Food: 1978 Evaluations*, Rome, pp. 239-255

Fechner, G., Führer, G. & Ackermann, H. (1968) Studies of milk contamination following trichlorfon treatment of milk cows (Ger.). *Monatschr. Veterinaermed., 23*, 529-531

Filatov, G.V., Sivokhin, P.A. & Metelitsa, V.K. (1972) Trichlorfon excretion in milk (Russ.) *Veterinariya, 5*, 102

Filchenko, A.S. (1976) Changes in the phasic structure of the cardiac cycle in dogs in acute chlorophos poisoning (Russ.). *Farmakol. Toksikol., 39*, 728-731

Fischer, G.W., Schneider, P. & Scheufler, H. (1977) Mutagenicity of dichloroacetaldehyde and 2,2-dichloro-1,1-dihydroxy-ethanephosphonic methyl ester, possible metabolites of the organophosphorus pesticide trichlorphon (Ger.). *Chem.-biol. Interactions*, *19*, 205-213

Frank, R., Braun, H.E., Stonefield, K.I., Elliot, J.M. & Zilkey, B.F. (1980) Insecticide residues and metal contents in flue-cured tobacco and tobacco soil of southern Ontario, 1976-1978. *Tob. int.*, *182*, 59-63

Fukuhara, N., Hoshi, M. & Mori, S. (1977) Core targetoid fibres and multiple cytoplasmic bodies in organophosphate neuropathy. *Acta neuropathol.*, *40*, 137-144

Gaines, T.B. (1969) Acute toxicity of pesticides. *Toxicol. appl. Pharmacol.*, *14*, 515-534

Gavat, V., Alexa, L., Filipiuc, M. & Mungiu, C. (1978) Toxicity of pesticides on laboratory animals (Rum.). *Rev. med. chir.*, *82*, 623-627

Gibel, W., Lohs, K., Wildner, G.-P. & Ziebarth, D. (1971) Experimental studies on hepatotoxic and cancerogenic activity of phophor-organic compounds. I. Trichlorphon (Ger.). *Arch. Geschwulstforsch.*, *37*, 303-312

Gibel, V.W., Lohs, K., Wildner, G.-P., Ziebarth, D. & Steiglitz, R. (1973) Experimental study on cancerogenic haematotoxic and hepatotoxic activity of phosphor-organic pesticides. *Arch. Geschwulstforsch.*, *41*, 311-328

Giovanoli-Jakubczak, T., Fitak, B. & Chodkowski, J. (1971) Photolysis of dipterex and DDVP under the influence of UV irradiation. *Rocz. Chem.*, *45*, 689-694

Gofmekler, V.A. & Tabakova, S.A. (1970) Chlorphos action on the embryogenesis of rats (Russ.). *Farmakol. Toksikol.*, *33*, 735-737

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem.*, *54*, 1040-1082

Haley, T.J., Farmer, J.H., Harmon, J.R. & Dooley, K.L. (1975) Estimation of the LD_1 and extrapolation of the $LD_{0.1}$ for five organophosphate pesticides. *Arch. Toxicol.*, *34*, 103-109

Hanna, P.J. & Dyer, K.F. (1975) Mutagenicity of organophosphorus compounds in bacteria and *Drosophila*. *Mutat. Res.*, *28*, 405-420

Hassan, A. & Zayed, S.M.A.D. (1965) Metabolism of organophosphorus insecticides. III. Fate of the methyl groups of dipterex *in vivo*. *Can. J. Biochem.*, *43*, 1271-1275

Hierons, R. & Johnson, M.K. (1978) Clinical and toxicological investigations of a case of delayed neuropathy in man after acute poisoning by an organophosphorus pesticide. *Arch. Toxicol.*, *40*, 279-284

Hiramatsu, R. & Furutani, F. (1978) Persistence of sprayed malathion and trichlorfon in grape berries and grape products (Jpn.). *Yamaguchi-ken Nogyo Shikenjo Kenkyu Hokoku*, *30*, 37-44 [*Chem. Abstr.*, *89*, 19244g]

Holmstedt, B., Nordgren, I., Sandoz, M. & Sundwall, A. (1978) Metrifonate. Summary of toxicological and pharmacological information available. *Arch. Toxicol.*, *41*, 3-29

Hunter, C.G. (1973) Dichlorvos: Human inhalation studies (Abstract no. 46). *Toxicol. appl. Pharmacol.*, *19*, 379

Hutson, D.G. & Hoadley, E.C. (1972) The comparative metabolism of [^{14}C-vinyl] dichlorvos in animals and man. *Arch. Toxicol.*, *30*, 9-18

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, Lyon, pp. 97-127

IARC (1981) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, No. 9, Lyon, p. 180

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 72, 73

Iranéyi, J. (1975) Organophosphate-induced polyneuropathy (Hung.). *Orv. Hetil.*, *116*, 1572-1575

Ishihara, O., Onuma, T. & Fukushima, H. (1974) A case of peripheral neuropathy by intoxication due to a pesticide, trichlorfon (Jpn.). *Clin. Neurol. (Tokyo)*, *14*, 57

Janda, J. (1975) Toxic effect of soldep insecticide on pheasants and rabbits (Slov.). *Agrochemia*, *15*, 120-123

Johnson, M.K. (1980) The mechanism of delayed neuropathy caused by some organophosphorus esters: Using the understanding to improve safety. *J. environ. Sci. Health*, *B15*, 823-841

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

Juszkiewicz, T. & Stec, J. (1970) Insecticide residues in the tissues and milk of cows following the dermal application of fenchlorphos and trichlorfon: A preliminary report (Pol.). *Med. Weterynar.*, *26*, 85-89

Kadin, M. (1962) Studies on the toxicity and effect of dipterex in rabbits. *Am. J. Ophthalmol.*, *53*, 512-517

Karmilov, V.A. (1973) Subacute experimental chlorophos poisoning (morphological investigation) (Russ.). *Farmakol. Toksikol.*, *36*, 727-728

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

Király, J., Czeizel, A. & Szentesi, I. (1977) Genetic study on workers producing organophosphate insecticides (Abstract no. 50). *Mutat. Res.*, *46*, 224

Király, J., Szentesi, I., Ruzicska, M. & Czeizel, A. (1979) Chromosome studies in workers producing organophosphate insecticides. *Arch. environ. Contam. Toxicol.*, *8*, 309-319

Kossakowski, S. & Patyra, S. (1977) Electrocardiogram of rabbits poisoned with foschlor (Pol.). *Med. Weterynar.*, *33*, 677-680

Kreuger, H.R. & Casida, J.E. (1957) Toxicity of fifteen organophosphorus insecticides to several insect species and to rats. *J. econ. Entomol.*, *50*, 356-358

Kuchinsky, M., Savitsky, B. & Voronetskaya, G. (1977) Morphological and histochemical changes in the gastric mucosa of rats undergoing subacute chlorofos poisoning (Russ.). *Farmakol. Toksikol.*, *40*, 451-454

Kurinniy, A.I. (1975) Comparative study of the cytogenetic effect of a series of organophosphorus pesticides (Russ.). *Genetika*, *11*, 64-69

Kurinniy, A.I. & Pilinskaya, M.A. (1977) Cytogenetic activity of the pesticides imidan, dipterex and gardona in cultured human lymphocytes (Russ.). *Genetika*, *13*, 337-339

Kuzmenko, N.M., Didenko, G.G., Kurinniy, A.I., Martson, L.V., Petrovskaya, O.G., Pilinskaya, M.A. & Shepelskaya, N.R. (1980) Long-term health effects of pesticides (Russ.). *Gig. Sanit.*, *45*, 88-89

Lamb, M.J. (1977) Mutagenicity tests with metrifonate in *Drosophila melanogaster*. *Mutat. Res.*, *56*, 157-162

Lebrun, A. & Cerf, C. (1960) Preliminary note on the toxicity of an organophosphorus insecticide (Dipterex) for man (Fr.). *Bull. World Health Organ.*, *22*, 579-582

Litvinenko, P.M., Kravtsov, B.N. & El'baum, L.Y. (1973) Effect of some vitamins on the process of chlorophos poisoning in a tropical climate (Russ.). *Med. Zh. Uzb.*, *4*, 19-21

Lobsin, V.S. & Tsinovoy, P.Y. (1969) Neurological disorders in chlorophos poisoning (Russ.). *Zh. Nevropatol. Pskhiatr.*, *69*, 679-683

Markus, J.R. & Puma, B., eds (1970) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.198

Martson, L.V. & Vononina, V.M. (1976) Experimental study of the effect of a series of phosphoroorganic pesticides (dipterex and imidan) on embryogenesis. *Environ. Health Perspect.*, *13*, 121-125

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Miyata, T. & Saito, T. (1973) Metabolism of NS 2662 in the mouse (Jpn.). *Botyu-kagaku*, *38*, 81-86

Molozhanova, E.G., Remizova, L.B. & Bransevich, L.G. (1973) Detoxication of chlorophos by soil microorganisms (Russ.). *Khim. Sel. Khoz.*, *11*, 761-762 [*Chem. Abstr.*, *80*, 116858s]

Morpurgo, G., Aulicino, F., Bignami, M., Conti, L. & Velcich, A. (1977) Relationship between structure and mutagenicity of dichlorvos and other pesticides. *Rend. Clas. Sci. fis. mat. nat., Serie 8, 62*, 692-701

Nagy, Z., Mile, I. & Antoni, F. (1975) The mutagenic effect of pesticides on *Escherichia coli* WP2 *try*. *Acta microbiol. acad. sci. hung., 22*, 309-314

National Institute for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards*, Cincinnati, OH, p. 58

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, p. 4795 (generics included), 3562 (generics excluded)

Nepoklonov, a.A. & Metelitsa, V.K. (1971) Metabolism and retention of chlorophos in cattle (Russ.). *Tr. Vses. Nauch. Issled. Inst. Vet. Sanit., 39*, 155-164 [*Chem. Abstr., 82*, 81416h]

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Nordgren, I., Bergström, M., Holmstedt, B. & Sandoz, M. (1978) Transformation and action of metrifonate. *Arch. Toxicol., 41*, 31-41

Nordgren, I., Holmstedt, B., Bengtsson, E. & Finkel, Y. (1980) Plasma levels of metrifonate and dichlorvos during treatment of schistosomiasis with Bilcarcil[R]. *Am. J. trop. Med., 29*, 426-430

Olefir, A.I. (1971a) The action of chlorophos on the immunobiological reactivity of experimental animals (Russ.). *Gig. Sanit., 36*, 104-105

Olefir, A.I. (1971b) A study of the effect of chemical substances on the formation of acquired immunity (Russ.). *Vrach. Delo, 10*, 125-127

Paik, S.G. & Lee, S.Y. (1977) Genetic effects of pesticides in the mammalian cells. I. Induction of micronucleus. *Korean J. Zool., 20*, 19-28

Panda, B.B. & Sharma, C.B.S.R. (1980) Cytogenetic hazards from agricultural chemicals. 3. Monitoring the cytogenetic activity of trichlorfon and dichlorvos in *Hordeum vulgare*. *Mutat. Res., 78*, 341-345

Petrova, N.I., Kogan, Y.M., Botsyurko, V.I. & Krekhovetskiy, Z.S. (1972) Acute trichlorfon poisoning, complicated by polyneuritis (Russ.). *Vrach. Delo, 12*, 114-115

Peziol-Laszczynska, M. (1978) Effect of fluid insecticides: Foschlor-50 and Metox-30 on histological and histoenzymatic picture of kidney in mice (Pol.). *Bromatol. Chem. Toksykol., 11*, 7-14

Plestina, R., Davis, A. & Bailey, D.R. (1972) Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull. World Health Organ., 46*, 747-759

Radeleff, R.D. & Woodard, G.T. (1957) The toxicity of organic phosphorus insecticides to livestock. *J. Am. vet. med. Assoc., 130*, 215-216

Reiner, E., Krauthacker, B., Simeon, V. & Skrinjaricé-Spoljar, M. (1975) Mechanism of inhibition *in vitro* of mammalian acetylcholinesterase and cholinesterase in solutions of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate (Trichlorfon). *Biochem. Pharmacol.*, *22*, 717-722

Rosenkranz, H.S. & Rosenkranz, S. (1972) Reaction of DNA with phosphoric acid esters: Gasoline additive and insecticides. *Experientia*, *28*, 386-387

The Royal Swedish Academy of Sciences (1981) Metrifonate and dichlorvos: Theoretical and practical aspects. *Acta pharmacol. toxicol.*, *49*, *Suppl. 5*

Ryazanova, R.A. & Gafurova, T.V. (1980) Mutagenic action of a binary mixture of the pesticides chlorophos and zineb (Russ.). *Gig. Sanit.*, *1*, 80-81

Rybak, M. (1973) Effect of phoschlor administered in water on the ontogenic development of white rats and their offspring (Pol.). *Rocz. Panstw. Zakl. Hig.*, *24*, 465-475

Salama, A.M., Mostafa, I.Y. & El-Zawahry, Y.A. (1975) Insecticides and soil microorganisms. III. Fate of carbon-14-labeled dipterex as affected by two nodule-forming *Rhizobium* species and roots of their respective leguminous host plants. *Acta biol. acad. sci. hung.*, *26*, 1-7 [*Chem. Abstr.*, *84*, 85567x]

Scheufler, H. (1975) Effects of relatively high doses of dimethoate and trichlorfon on the embryogenesis of laboratory mice (Ger.). *Biol. Rundsch.*, *13*, 238-240

Schiemann, S. (1975) Mutagenic effect of trichlorfon on the mouse with special regard to the dominant lethal tests (Ger.). *Wiss. Z. Martin-Luther-Univ., Halle-Wittenbergs, Math.-Naturwiss. Reihe*, *24*, 85-86

Sergeant, D.B. & Zitko, V. (1979) *The Determination of Trichlorfon, Dichlorvos, Fenitrothion and Phosphamidon in Water* (*Fish. Mar. Serv. Tech. Rep. 886*), St Andrews, New Brunswick, Department of Fisheries and Oceans, Biological Station, pp. 1-12

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.*, *40*, 19-30

Shirasu, Y., Moriya, M., Tezuka, H., Teramoto, S., Ohta, T. & Inoue, T. (1982) *Mutagenicity screening studies on pesticides*. In: Sugimura, T., Kondo, S. & Takebe, H., eds, *Environmental Mutagens and Carcinogens*, Tokyo, University of Tokyo Press, pp. 331-335

Simmon, V.F. (1979) *In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides* (*EPA-600/1-79-041*), Research Triangle Park, NC, Environmental Protection Agency, pp. 79-81, 87, 111

Staples, R.E. & Goulding, E.H. (1979) Dipterex teratogenicity in the rat, hamster, and mouse when given by gavage. *Environ. Health Perspect.*, *30*, 105-113

Staples, R.E., Kellam, R.G. & Haseman, J.K. (1976) Developmental toxicity in the rat after ingestion or gavage of organophosphate pesticides (dipterex, imidan) during pregnancy. *Environ. Health Perspect.*, *13*, 133-140

Taylor, P. (1980) *Anticholinesterase agents.* In: Gilman, A.G., Goodman, L.S. & Gilman, A., eds, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed., New York, MacMillan, pp. 100-119

Teichmann, B. & Hauschild, F. (1978) Test of *O,O*-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorfon) for carcinogenic activity in mice by oral (oesophageal-gastric intubation), intraperitoneal and dermal application (Ger.). *Arch. Geschwulstforsch.*, *48*, 301-307

Teichmann, B. & Schmidt, A. (1978) Test of *O,O*-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorfon) for carcinogenic activity in Syrian golden hamsters (*Mesocricetus auratus* Waterhouse) by intraperitoneal administration (Ger.). *Arch. Geschwulstforsch.*, *48*, 718-721

Teichmann, B., Hauschild, F. & Eckelmann, A. (1978) Test of *O,O*-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorfon) for carcinogenic activity in rats by oral (oesophageal-gastric intubation) and intraperitoneal application (Ger.). *Arch. Geschwulstforsch.*, *48*, 112-119

Titova, N.N. & Badiugin, I.S. (1970) Acute chlorophos poisoning (Russ.). *Kazan. med. Zh.*, *1*, 37-40

Todorov, D., Yotov, Y., Bratanov, V., Sergyeva, D. & Yurukov, M. (1974) Sevin and neguvon residues in milk during antiparasitic treatment of sheep and goats (Bulg.). *Vet. Med. Nauki*, *11*, 9-15

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976, Agricultural Economic Report No. 418*, Washington DC, Economics, Statistics and Cooperatives Service, pp. 16, 26

US Department of Agriculture (1981) *Monitoring Phase Biological Residue Report, January 1980 through December 1980*, Washington DC, Residue Evaluation and Surveillance Division

US Department of Transportation (1981) Listing of hazardous materials. *US Code Fed. Regul.*, *Title 49*, part 172; *Fed. Regist.*, *46*, 17738-17750

US Environmental Protection Agency (1980a) Protection of environment. *US Code Red. Regul.*, *Title 40*, part 180.198, pp. 565, 566

US Environmental Protection Agency (1980b) Protection of environment. *US Code Red. Regul.*, *Title 40*, parts 116, 117, pp. 35-50

US Food & Drug Administration (1980a) Food and drugs. *US Code Fed. Regul.*, *Title 21*, part 561.190, p. 513

US Food & Drug Administration (1980b) Food and drugs. *US Code Fed. Regul.*, *Title 21*, parts 520.2380, 520.2520, pp. 186-189

US Food & Drug Administration (1980c) Oral dosage form new animal drugs not subject to certification; trichlorfon boluses and granules. *US Code Fed. Regul.*, *Title 21*, part 520; *Fed. Regist.*, *45*, 48127, 48128

US Food & Drug Administration (1981) Oral dosage form new animal drugs not subject to certification; fenbendazole with trichlorfon. *US Code Fed. Regul., Title 21*, part 520; *Fed. Regist., 45*, 29464

Valencia, R. (1977) *Mutagenesis Screening of Pesticides Using* Drosophila (*Contract No. 68-01-2474*), Madison, WI, WARF Institute, Inc.

Vasilescu, C. & Fluorescu, A. (1980) Clinical and electrophysiological study of neuropathy after organophosphorus compounds poisoning. *Arch. Toxicol., 43*, 305-315

Vrbovskyé, L., Seleckyé, V. & Rosival, L. (1959) Toxicological and pharmacological studies of phosphoric ester insecticides (Ger.). *Arch. exp. Pathol. Pharmakol., 236*, 202-205

Vernik, A.Y. (1971) Polyneuritis from chlorophos (Russ.). *Sov. Med., 9*, 44-46

Waters, M.D., Simmon, V.F., Mitchell, A.D., Jorgenson, J.A. & Valencia, R. (1980) An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. *J. environ. Sci. Health, B15*, 867-906

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity*. In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

WHO (1972) *1971 Evaluations of Some Pesticide Residues in Food* (*World Health Organ. Pestic. Residues Ser., No. 1*), Geneva, pp. 183-230

WHO (1976) *1975 Evaluations of Some Pesticide Residues in Food* (*World Health Organ. Pestic. Residues Ser., No. 5*), Geneva, pp. 379-392

Wojcik, J. (1975) The effect of foschlor present in drinking water on the organs of three rat generations (Pol.). *Roczn. Panst. Zakl., 26*, 383-391

Woroniecka, G., Kuczynski, M. & Sawicki, B. (1977) Investigations of influence of subacute foschlor intoxication on morphology and histochemistry of rat pancreas (Abstract). *Folia Histochem. Cytochem., 15*, 167

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 531

Zhabin, V.A. & Litvishenko, F.L. (1971) A case of chlorophos poisoning (Russ.). *Vrach. Delo, 3*, 143-144

Zolotnikova, G.P. & Somov, B.A. (1978) On the role of pesticides in the occurrence of occupational dermatitis in workers of hothouses (Russ.). *Vestnik. Dermatol. Venerol., 4*, 76-79

Zweig, G. & Sherma, J. (1972) *Dylox*. In: Zweig, G., ed, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, New York, Academic Press, pp. 387-392

HERBICIDES

DIALLATE

This substance was considered by a previous Working Group, in June 1976 (IARC, 1976). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 2303-16-4

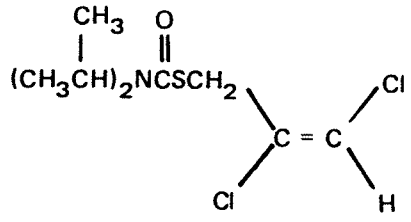
Chem. Abstr. Name: Carbamothioic acid, bis(1-methylethyl)-, *S*-(2,3-dichloro-2-propenyl)ester

IUPAC Systematic Name: *S*-2,3-Dichloroallyl diisopropylthiocarbamate

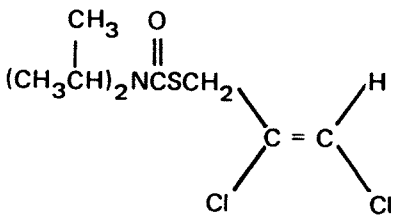
Synonyms: Bis(1-methylethyl)carbamothioic acid *S*-(2,3-dichloro-2-propenyl) ester; DATC; diallate; dichloroallyl diisopropylthiocarbamate; *S*-(2,3-dichloroallyl)-*N*,*N*-diisopropyl-monothiocarbamate; 2,3-dichloroallyl *N*,*N*-diisopropylthiocarbamate; *S*-(2,3-dichloroallyl)-*N*,*N*-diisopropylthiocarbamate; *S*-(2,3-dichloroallyl)diisopropylthiolcarbamate; 2,3-dichloro-2-propene-1-thiol diisopropylcarbamate; diisopropylthiocarbamic acid *S*-(2,3-dichloroallyl) ester

Trade Names: Avadex; CP 15336; 2,3-DCDT; Pyradex

1.2 Structural and molecular formulae and molecular weight



(E)



(Z)

$C_{10}H_{17}Cl_2NOS$

Mol. wt: 270.2

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Amber-coloured liquid

(*b*) *Boiling-point:* 150°C at 9 mm Hg

(*c*) *Melting-point:* 25-30°C (Weed Science Society of America, 1979)

(*d*) *Density:* $d_{15.6}^{25}$ 1.188 (Weed Science Society of America, 1979)

(*e*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*f*) *Solubility:* Slightly soluble in water (14 mg/l at 25°C); miscible with ethanol and other organic solvents

(*g*) *Volatility:* Vapour pressure, 1.5 x 10^{-4} mm at 25°C (Weed Science Society of America, 1979)

(*h*) *Stability:* Decomposition temperature is above 200°C; highly resistant to decomposition by ultra-violet irradiation (Weed Science Society of America, 1979)

1.4 Technical products and impurities

Commercial formulations of diallate have been reported to contain roughly equal amounts of the E and Z isomers (Rummens, 1975). Diallate is available as 40 and 48% active concentrates, as 10% active granules (Worthing, 1979), and in a combination with the herbicide chloridazon (pyrazon, 5-amino-4-chloro-2-phenylpyridazin-3-one) (Berg, 1981).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Diallate was introduced as a commercial chemical in 1960. It is made by the reaction of carbonyl sulphide with diisopropylamine and 1,2,3-trichloropropene (Worthing, 1979). Diallate was first produced commercially in the US in 1961 (US Tariff Commission, 1962), but commercial production has not been reported in the US since 1975, when one company produced it (US International Trade Commission, 1977). Separate data on US imports and exports of diallate are not available.

Diallate is produced by one company in Belgium. Annual production of diallate in western Europe in 1975 is estimated to have been in the range of 1-5 million kg. It is not produced commercially in Japan.

(*b*) *Use*

Diallate is used as a pre-emergence herbicide in agricultural applications, principally for the control of weeds such as wild oats in field crops.

The US Environmental Protection Agency (1980a) reported that there were eight federal registrations of products containing diallate. The major uses of diallate in US agriculture in 1976-1978 were (average quantity of active ingredient applied, in thousand kg/year): sugar beets, 125.4; flax, 17.5; lentils, 19.7; and peas, 13.8, for a total of 176.4 thousand kg/year. The amount of diallate used on other crops is quite small (e.g., only 0.5% of the total US potato acreage is treated with diallate).

The Council of the European Communities fixed a maximum acceptable level for residues of diallate in and on fruit and vegetables at 0.05 mg/kg (Commission of the European Communities, 1976).

Tolerances in the US for residues of diallate in or on raw agricultural commodities are presently 0.05 (negligible residue) mg/kg for a variety of 22 commodities, including grains, fodders and forages, seeds, beans and vegetables (US Environmental Protection Agency, 1980b). The US Environmental Protection Agency issued a notice of rebuttable presumption against registration and continued registration of pesticide products containing diallate in 1977; in 1980, it announced that it was initiating a regulatory action which would cancel the use of all diallate emulsifiable concentrate formulations two years after its decision became final. Use of diallate in granular form would not have been affected by this action (US Environmental Protection Agency, 1980c). In 1982, they concluded that it is possible to use the emulsifiable concentrate formulations without exposing applicators to unacceptable risk. The document requires changes of diallate labels to assure that applicator exposure (and therefore risk) is limited as much as possible through the use of protective clothing and that the material be used only by or under the direct supervision of trained and certified applicators (US Environmental Protection Agency, 1982).

2.2 Occurrence

(*a*) *Natural occurrence*

Diallate is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the numbers of workers exposed to diallate in the two nonagricultural activities most likely to involve exposure, namely its production and formulation into the products applied by agricultural workers. The US Environmental Protection Agency (1980c) has estimated that there are 2400 pesticide applicators exposed to diallate in the US. Exposure of unprotected spray applicators to this compound has been estimated as 0.048-0.156 mg/kg per year for dermal exposure and 0.0038-0.0061 mg/kg per year for inhalational exposure (US Environmental Protection Agency, 1982).

(*c*) *Food, beverage and animal feeds*

Diallate was not detected in any of the food composites analysed in the Canadian Total Diet Survey (limit of detection, 0.04 mg/kg) (McLeod *et al.*, 1980). None was detected in

samples of 13 crops in the US analysed in 1967 (limit of detection, 0.1-0.2 mg/kg) or in seven crops analysed in 1969 (limit of detection, 0.02 mg/kg) (Stewart, 1977).

2.3 Analysis

The diallate content of soil and sugar beets may be analysed by gas chromatography with electron capture detection after extraction with acetone; the limit of detection is 0.25 mg/kg (Nassar *et al.*, 1978). Thin-layer chromatography, with a limit of detection of 0.5 μg, has also been used (Ebing, 1972).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 and 18 male and 18 female (C57BL/6 x AKR)F_1 mice received Avadex, a commercial formulation of diallate [purity unspecified; b.p. 146-150°C at 9 mm] according to the following treatment schedule: 215 mg/kg bw in 0.5% gelatine at seven days of age by stomach tube; the same dose, not adjusted for increasing body weight, daily up to four weeks of age, when the animals were weaned; then 560 mg/kg of diet diallate until the experiment was terminated at 84-86 weeks of age, when all survivors were killed. [The maximum tolerated dose was that established for infant and young mice only; no experiment was done to establish the maximum tolerated dose for adult mice.] No treatment-related effect on survival was noted in either strain: at the end of the experiment, 31/36 males and 30/36 females were still alive; of control mice, 162/180 males and 158/180 females were still alive at that time. Tumour incidences were compared with those in 79-90 control mice of each sex and strain. Hepatomas were found in 13/16 male and 2/16 female treated necropsied mice of the (C57BL/6 x C3H/Anf)F_1 strain (compared with 8/79 and 0/87 in the respective controls) and in 10/18 male and 1/15 female treated necropsied mice of the (C57BL/6 x AKR)F_1 strain (compared with 5/90 and 1/82 in the respective controls). This increased incidence of hepatomas was statistically significant [$p < 0.01$] only for male mice of both strains. The incidence of pulmonary adenomas among male mice of the (C57BL/6 x C3H/Anf)F_1 strain was 4/16 compared with 5/79 in controls [$p < 0.01$] (National Technical Information Service, 1968; Innes *et al.*, 1969).

Rat: Groups of 26 Charles River CD rats of each sex, six weeks old, were fed 150 or 300 mg/kg commercial diallate (Avadex) in the diet for 18 months. (Examination of the compound by nuclear magnetic resonance and gas-liquid chromatography indicated purities of 92.5% and 94.3%, respectively.) The level of 300 mg/kg of diet was chosen on the basis of preliminary investigations of subchronic toxicity. Untreated controls consisted of 184 rats of each sex; and two groups of positive controls were fed fluorenylacetamide (FAA) at levels of 80 mg/kg diet (32 rats) or 250 mg/kg diet (20 rats). After 78 weeks' treatment, five rats of each sex in the group receiving 300 mg/kg of diallate were killed

and necropsied; these animals were taken into account when calculating the tumour incidence but not survival rates. All survivors were killed 24 months after the start of treatment. No treatment-related effect on survival was noted: after 52 weeks of treatment 100% of males and 96% of females were still alive; at 78 weeks at least 77% of the animals in each treated group were still alive. Of the controls, 97% of males and 99% of females were still alive at 52 weeks. All animals in the positive control group treated with the high dose of FAA (250 mg/kg diet) were killed at 52 weeks because of poor survival; the survival rates at 78 weeks in rats given the low dose of FAA were 75% for males and 88% for females. The mean body weights of all diallate-treated animals were less than those of their controls. No increase in the incidence of tumours was noted in diallate-treated rats of either sex (Weisburger *et al.*, 1981). [The Working Group noted the incomplete reporting of the experiment, in that no data were available on the tumour incidence of diallate-treated animals; the small size of the experimental groups; and the short duration of treatment.]

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 1000 mg/kg bw commercial diallate (Avadex) [purity unspecified; b.p., 146-150°C at 9 mm] in corn oil on the 28th day of life and were observed until they were about 78 weeks of age, at which time 17, 18, 18 and 15 mice in the four groups, respectively, were still alive. Tumour incidences were compared with those in groups of 141, 154, 161 and 157 untreated or vehicle-injected controls that were necropsied. Systemic reticulum-cell sarcomas developed in 4/18 necropsied male (C57BL/6 x C3H/Anf)F_1 mice, compared with 8/141 control males of that strain [$p = 0.032$]. Such tumours were not observed in treated males of the (C57BL/6 x AKR)F_1 strain (National Technical Information Service, 1968).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

Oral LD_{50} values for diallate in rats range from 393-1000 mg/kg bw; the dermal LD_{50} in rabbits is 2000-2500 mg/kg bw (Ben-Dyke *et al.*, 1970). In mice, rats and cats, injection of diallate caused central nervous system excitation (Pestova, 1966).

Repeated application of diallate to the eyes and skin of guinea-pigs and rabbits caused local irritation, weight loss, leucocytosis and anaemia; oral and subcutaneous administration produced similar effects (Doloshitskii, 1969; Gzhegotskii & Doloshitskii, 1971).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Rats administered either of the two [$^{14}C{=}O$] diallate isomers excreted the *S*-diisopropylcarbamoyl conjugates of mercapturic acid (62%), cysteine (7%), mercaptoacetic

acid (1.5%) and $^{14}CO_2$ (20%). The principal metabolic pathway in rodents thus appears to involve sulphoxidation, a nonenzymatic reaction of the sulphoxide with formation of glutathione and mercapturic acid (Chen *et al.*, 1979). Sulphoxidized metabolites undergo two distinct types of reaction important to their biological activity: (1) rearrangement-elimination to form 2-chloroacrolein; (2) carbamoylation of tissue thiols with liberation of 2,3-dichloroallylsulphonic acid (Schuphan & Casida, 1979).

Mutagenicity and other short-term tests

Diallate (technical grade; 96-99% pure) was mutagenic to *Salmonella typhimurium* strains TA100 and TA1535 in the presence of Aroclor-induced rat liver microsomal preparations (De Lorenzo *et al.*, 1978; Sikka & Florczyk, 1978; Jones *et al.*, 1982). From studies of a number of related compounds, De Lorenzo *et al.* (1978) concluded that the 2-chloroallyl group was necessary for mutagenic activity; the potent bacterial mutagen, 2-chloroacrolein, is formed from diallate on incubation with hepatic microsomal monooxygenases (Schuphan *et al.*, 1979). A slight increase was also reported in the induction of reverse mutations in *S. typhimurium* strain TA98, with similar metabolic activation (Schuphan *et al.*, 1979; Jones *et al.*, 1982). At very high doses of diallate (98% pure), weak mutagenic activity has been reported in the absence of metabolic activiation in *S. typhimurium* strains TA1535, TA98 and TA100 (Douglas *et al.*, 1981). Diallate [technical grade; purity unspecified] did not induce reverse mutations in *Escherichia coli* WP2 or WP2 *uvr* A, with or without an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

Forward mutations to streptomycin resistance in *Streptomyces coelicolor* were reported with 400 μg/plate diallate [purity unspecified] in the absence of metabolic activation (Carere *et al.*, 1978).

Diallate [technical grade; purity unspecified] induced mitotic recombination in *Saccharomyces cerevisiae* D3 in the presence, but not in the absence of an Aroclor-induced rat liver microsomal preparation but did not induce mitotic crossing over, gene conversion or reversion in strain D7, either with or without metabolic activation (Jones *et al.*, 1982; Waters *et al.*, 1982). A commercial form was mutagenic and induced forward recombination in *Aspergillus nidulans* (Morpurgo *et al.*, 1977).

Diallate [technical grade; purity unspecified] induced sex-linked recessive lethal mutations when fed to male *Drosophila melanogaster* at a concentration of 0.0004% for three days (Jones *et al.*, 1982; Waters *et al.*, 1982).

Diallate [purity unspecified] induced dose-related unscheduled DNA synthesis in human embryo EUE cells as measured by autoradiography (Benigni *et al.*, 1982), but the compound (98% pure) elicited no detectable DNA repair when measured by scintillation counting (Rocchi *et al.*, 1980; Benigni *et al.*, 1982).

It was reported in an abstract that diallate induced recessive mutations in haploid *Pelargonium* (Pohlheim *et al.*, 1977).

A 98% pure preparation induced sister chromatid exchanges in cultured Chinese hamster ovary cells in the presence of an Aroclor-induced rat liver microsomal preparation; DNA damage was detected using alkaline sucrose gradient sedimentation and similar conditions of metabolic activation (Douglas *et al.*, 1981).

Diallate [technical grade; purity unspecified] induced presumed gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells; an uninduced mouse liver microsomal preparation enhanced but was not required for mutagenic activity (Jones *et al.*, 1982; Waters *et al.*, 1982). Chromosomal aberrations were induced by diallate (98% pure) in Chinese hamster ovary cells in a dose-dependent manner in the presence of an Aroclor-induced rat liver microsomal preparation (Douglas *et al.*, 1981).

It was reported in an abstract that a commercial formulation of diallate (Avadex) did not induce dominant lethal mutations when male mice were given i.p. injections of 100 or 200 mg/kg bw (Johannsen *et al.*, 1978).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Diallate was tested for carcinogenicity in two strains of mice by oral and subcutaneous administration and in one strain of rats by oral administration. Following its administration in the diet, the incidence of hepatomas was increased in male mice of both strains, and the incidence of lung adenomas was increased in male mice of one strain. The study in rats was considered to be inadequate for evaluation.

No data were available to evaluate the teratogenicity of diallate to experimental animals.

Diallate was mutagenic in bacteria and yeasts. It induced mutations in *Drosophila melanogaster*, and unscheduled DNA synthesis, sister chromatid exchange, gene mutations and chromosomal aberrations in cultured mammalian cells. Exogenous metabolic activation was usually required to produce or enhance mutagenic activity. Diallate was ineffective in a dominant lethal test in mice. There is sufficient evidence that diallate is mutagenic in cellular systems, but insufficient evidence for its mutagenicity in mammals.

4.2 Human data

Diallate was introduced in 1960. Its production, formulation and use as a herbicide in agricultural applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of diallate in humans.

No case report or epidemiological study of the carcinogenicity of diallate alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

Results of experiments in mice provide *limited evidence* that diallate is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of diallate to humans.

5. References

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970). *World Rev. Pestic. Control.*, *9*, 119-127

Benigni, R., Dogliotti, E., Falcone, E. & Calcagnile, A. (1982) DNA repair studies on diallate, triallate and sulfallate in human cell cultures. *Mutat. Res.*, *103*, 385-390

Berg, G.L., ed. (1981) *Farm Chemicals Handbook, 1981*, Willoughby, OH, Meister Publishing Co., p. C27, C282

Carere, A., Ortali, V.A., Cardamone, G. & Morpurgo, G. (1978) Mutagenicity of dichlorvos and other structurally related pesticides in *Salmonella* and *Streptomyces*. *Chem.-biol. Interactions*, *22*, 297-308

Chen, Y.S., Schuphan, I. & Casida, J.E. (1979) *S*-Chloroallyl thiocarbamate herbicides: Mouse hepatic microsomal oxygenase and rat metabolism of *cis*- and *trans*-[^{14}C=O] diallate. *J. agric. Food Chem.*, *27*, 709-712

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Communities*, *L340*, 26-31

De Lorenzo, F., Saiano, N., Silengo, L. & Cortese, R. (1978) Mutagenicity of diallate, sulfallate, and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture. *Cancer Res.*, *38*, 13-15

Doloshitskii, S.L. (1969) Hygienic standardization of herbicide avadex containing chlorine in water. *Gig. Sanit.*, *34*, 21-25 [Translation in *Hyg. Sanit.* (1969), *34*, 356-360]

[1]This evaluation should be read in conjunction with p. 18 of the preamble.

Douglas, G.R., Nestmann, E.R., Grant, C.E., Bell, R.D.L., Wytsma, J.M. & Kowbel, D.J. (1981) Mutagenic activity of diallate and triallate determined by a battery of *in vitro* mammalian and microbial tests. *Mutat. Res.*, *85*, 45-56

Ebing, W. (1972) Routine method for identification by thin-layer chromatography of pesticides of the class of triazines, carbamates, ureas and uracils (Ger.). *J. Chromatogr.*, *65*, 533-545

Gzhegotskii, M.I. & Doloshitskii, S.L. (1971) The skin resorption effect of herbicides (Russ.). *Vrach. Delo*, *11*, 133-134

IARC (1976) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some Carbamates, Thiocarbamates and Carbazides*, Lyon, pp. 69-75

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst.*, *42*, 1101-1114

Johannsen, F.R., Levinskas, G.J., Wright, P.L. & Gordon, D.E. (1978) *Toxicological evaluation of Avadex and Avadex BW herbicides* (Abstract). In: Plaa, G.L. & Duncan, W.A.M., eds, *Proceedings of the First International Congress on Toxicology*, New York, Academic Press, p. 441

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Morpurgo, G., Aulicino, F., Bignami, M., Conti, L. & Velcich, A. (1977) Relationship between structure and mutagenicity of dichlorvos and other pesticides. *Rend. Cl. Sci. fis. mat. nat.*, *62*, 692-701

Nassar, A.R., Schuphan, I. & Ebing, W. (1978) Rapid method for determination of *cis*-, *trans*-diallate and triallate residues in sugar beets and soils by electron capture gas chromatography. *Egypt. J. Chem.*, *21*, 163-169

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study*, Washington DC, US Department of Commerce

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Pestova, A.G. (1966) Toxicity of diptal and avadex (Russ.). *Gig. Tiksikol. Pest. Klin. Otravlenii*, *4*, 166-169 [*Chem. Abstr.*, *70*, 2642e]

Pohlheim, E., Pohlheim, F. & Günther, G. (1977) Mutagenicity testing of herbicides with a haploid *Pelargonium* (Abstract no. 61). *Mutat. Res.*, *46*, 232

Rocchi, P., Perocco, P., Alberghini, W., Fini, A. & Prodi, G. (1980) Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. *Arch. Toxicol.*, *45*, 101-108

Rummens, F.H.A. (1975) Separation and structural assignment of the *cis* and *trans* isomers of *S*-(2,3-dichloroallyl) diisopropylthioacarbamate (diallate). *Weed Sci., 23,* 7-10

Schuphan, I. & Casida, J.E. (1979) *S*-Chloroallyl thiocarbamate herbicides: Chemical and biological formation and rearrangement of diallate and triallate sulfoxides. *J. agric. Food Chem.*, *27*, 1060-1067

Schuphan, I., Rosen, J.D. & Casida, J.E. (1979) Novel activation mechanism for the promutagenic herbicide diallate. *Science*, *205*, 1013-1015

Sikka, H.C. & Florczyk, P. (1978) Mutagenic activity of thiocarbamate herbicides in *Salmonella typhimurium*. *J. agric. Food Chem.*, *26*, 146-148

Stewart, J. (1977) *Diallate: Position Document 1* (*EPA/SPRD-80/26*), Arlington, VA, US Environmental Protection Agency, p. 2

US Environmental Protection Agency (1980a) *Diallate - Position Document 2/3* (*EPA/SPRD-80/27; PB80-216849*), Springfield, VA, National Technical Information Service, pp. I-1 - I-5, III-1 - III-3, III-9

US Environmental Protection Agency (1980b) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 180.277, p. 583

US Environmental Protection Agency (1980c) Diallate: Preliminary notice of determination concluding the rebuttable presumption against registration of pesticide products and notice of availability of position document. *Fed. Regist.*, *45*, 38437-38440

US Environmental Protection Agency (1982) Diallate position document. *Fed. Regist.*, *47*, 27109

US International Trade Commission (1977) *Synthetic Organic Chemicals, US Production and Sales, 1975* (*USITC Publ. 804*), Washington DC, US Government Printing Office, p. 188

US Tariff Commission (1962) *Synthetic Organic Chemicals, US Production and Sales, 1961* (*TC Publ. 72*), Washington DC, US Government Printing Office, p. 167

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity*. In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

Weed Science Society of America (1979) *Herbicide Handbook*, 4th ed., Champaign, IL, pp. 146, 147

Weisburger, E.K., Ulland, B.M., Nam, J.-M., Gart, J.J. & Weisburger, J.H. (1981) Carcinogenicity tests of certain environmental and industrial chemicals. *J. natl Cancer Inst.*, *67*, 75-88

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 161

FLUOMETURON

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 2164-17-2

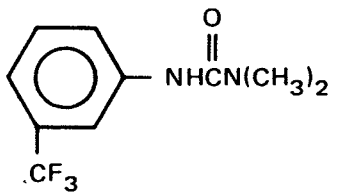
Chem. Abstr. Name: Urea, *N*,*N*-dimethyl-*N*′-[3-(trifluoromethyl)phenyl]-

IUPAC Systematic Name: 1,1-Dimethyl-3-(α,α,α-trifluoro-*meta*-tolyl)urea

Synonyms: 1,1-Dimethyl-3-(3-trifluoromethylphenyl)urea; NCI CO8695; *N*-(*meta*-trifluoromethylphenyl)-*N*,*N*′-dimethylurea; *N*-(3-trifluoromethylphenyl)-*N*,*N*′dimethylurea; 3-(*meta*-trifluoromethylphenyl)-1,1-dimethylurea; 3-(3-trifluoromethylphenyl)-1,1-dimethylurea

Trade Names: C 2059; Ciba 2059; Cotoran; Cotoran Multi 50WP; Cottonex; Herbicide C-2059; Lanex; Pakhtaran

1.2 Structural and molecular formulae and molecular weight



$C_{10}H_{11}F_3N_2O$ Mol. wt: 232.2

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 163-164.5°C

(*c*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*d*) *Solubility:* Slightly soluble in water (105 mg/l at 20°C); soluble in most organic solvents

(*e*) *Volatility*: Vapour pressure, 5 x 10^{-7} mm Hg at 20°C

1.4 Technical products and impurities

Technical fluometuron was reported to be about 96% pure and have a melting-point of approximately 155°C (Spencer, 1973). It is available as 50 and 80% active water-dispersible powders, in a 50% active 'flowable' formulation, in a combination with the herbicide metolachlor [2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl) acetamide] (Worthing, 1979), and in a combination with the herbicide monosodium methane arsonate (Berg, 1981).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Fluometuron was introduced as a commercial chemical in 1960. It is made by the reaction of dimethylamine with α,α,α-trifluoro-*meta*-tolyl isocyanate (Worthing, 1979). It was first produced commercially in the US in 1967 (US Tariff Commission, 1969). Commercial production of fluometuron has not been reported in the US since 1979 when one company produced it (US International Trade Commission, 1980); it is believed to be producing fluometuron currently.

Imports of fluometuron through the principal US customs districts amounted to only 500 kg in 1980 (US International Trade Commission, 1981), compared with the 550 thousand kg imported in 1976 (US International Trade Commission, 1977). Separate data on US exports of fluometuron are not available.

It is believed to be produced commercially by one company each in Israel, Mexico and Switzerland. It is not produced commercially in Japan.

(*b*) *Use*

Fluometuron is used exclusively as a herbicide. In 1976, 2.4 million kg of fluometuron were used on major crops in the US (US Department of Agriculture, 1978). In 1978, total US usage of fluometuron is estimated to have been 1.3 million kg, all of which was used as a herbicide to control broadleaf weeds and grasses in cotton (approximately 20% was applied as a combination with monosodium methane arsonate). The area of largest use in the US is reported to be the Mississippi delta (National Cancer Institute, 1980).

Tolerances in the US for negligible residues of fluometuron in or on the raw agricultural commodities, cottonseed and sugar cane, are established at 0.1 mg/kg and in or on sugar cane bagasse at 0.2 mg/kg (US Environmental Protection Agency, 1980a,b).

In 1977, the USSR established a regulation limiting maximum occupational exposure to fluometuron to 5 mg/m^3 maximum in workplace air (International Labour Office, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Fluometuron is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the numbers of workers exposed to fluometuron during its production and its formulation into products for use in agriculture.

Air samples taken over a field on a collective farm in Tashkent, USSR, indicated that tractor operators were exposed to 0.64-7.4 mg/m^3 fluometuron and seeders to 4.28-10.98 mg/m^3 (Kukanbaev, 1980).

2.3 Analysis

Standard methods for the analysis of fluometuron in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of fluometuron

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract (chloroform); heat with trifluoroacetic anhydride; centrifuge	GC/FID	not given	Hofberg *et al.* (1977); Horwitz (1980)
	Extract (dichloromethane); wash (hydrochloric acid); hydrolyse to dimethylamine; steam distill into water containing indicator	Titration	not given	Voss *et al.* (1974)
Water-dispersible powders and dusts; suspensions	Extract (chloroform)	IR spectroscopy	not given	US Environmental Protection Agency (1976)
Vegetables, cottonseed, sugar cane and soil	Hydrolyse (alkali); steam distill; extract (isooctane); extract (hydrochloric acid); diazotize; derivatize (*N*-ethyl-1-naphthyl-amine); chromatograph (cellulose)	Colorimetry and TLC confirmation	0.03-0.06 mg/kg	Markus & Puma (1971); Voss *et al.* (1974)
Plants and soil	Hydrolyse (alkali); steam distill; extract (isooctane); extract (hydrochloric acid); diazotize; iodinate	GC/ECD	0.05 mg/kg	Voss *et al.* (1974)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; IR, infra-red; TLC, thin-layer chromatography; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ hybrid mice, seven weeks old, were fed diets containing 500 or 1000 mg/kg fluometuron (99% pure; impurities not specified) mixed with corn oil for 103 weeks; 25 female and 25 male matched controls received a diet containing 2% corn oil. The mice were observed for another week before they were killed. Survival to the end of the study among male mice was 14/25 (56%) of the controls, 33/50 (66%) of the low-dose and 32/50 (64%) of the high-dose group; among females, 16/25 (64%) of the controls, 38/50 (76%) of the low-dose and 33/50 (66%) of the high-dose group were still alive at that time. Mean body weights of dosed and control mice were comparable throughout the study. Neoplastic and non-neoplastic lesions occurred in similar incidences among control and dosed mice, with the exception of tumours of the liver and of the haematopoietic system in male mice: there were 3/21 (14%) hepatocellular carcinomas in controls, 8/47 (17%) in the low-dose group, and 15/49 (31%) in the high-dose group. A trend analysis of this difference was not statistically significant. In addition, 1/21 adenomas of the liver was observed in control males, 5/47 at the low dose, and 6/49 at the high dose. When the incidence of the total number of liver tumours were compared, a difference of borderline statistical significance was noted using the Cochran-Armitage test ($p = 0.024$) and by the Fisher exact test ($p = 0.049$). In addition, a non-statistically significant increased incidence of lymphoma or leukaemia was seen among male mice: 0/21 of controls, 6/48 of the low-dose, and 7/49 of the high-dose group. Leukaemia or lymphoma was first noted 36 weeks after onset of exposure among low-dose male mice and 75 weeks after onset of exposure among high-dose mice (National Cancer Institute, 1980).

Rat: Groups of 50 male and 50 female Fischer 344 rats, seven weeks old, were fed diets containing 0, 125 or 250 mg/kg fluometuron (99% pure; impurities not specified) with corn oil for 103 weeks. Corn oil was also added to the control diet at a concentration of 2%. Animals were observed for an additional week. Mean body weights of dosed and control rats were comparable throughout the study. Of the male rats, 38/50 (76%) of the controls, 37/50 (74%) fed 125 mg/kg and 44/50 (88%) fed 250 mg/kg were still alive at 90 weeks; at that time, of the females, 44/50 (88%) of controls, 47/50 (94%) fed 125 mg/kg and 48/50 (96%) fed 250 mg/kg were still alive. Although a number of tumours were noted in control as well as dosed rats, no statistically significant difference was observed between exposed and control animals (National Cancer Institute, 1980).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The acute oral LD_{50} of fluometuron in male and female rats was 8900 mg/kg bw (Ben-Dyke *et al.*, 1970); it was 900 mg/kg bw in male mice, 2370 mg/kg bw in female mice and

>10 000 mg/kg bw in rabbits and dogs (Spencer, 1968). The dermal LD_{50} in rabbits was >10 000 mg/kg bw (Ben-Dyke *et al.*, 1970)

In 90-day feeding studies with Fischer 344 rats, a two-fold increase in the weight of the spleen was seen in males fed 4000 mg/kg of diet and in females fed 2000 or 4000 mg/kg of diet. A dose-related increase in the incidence of red-blood cells with polychromasia and anisocytosis was also observed. Mean body weight gain of females was depressed more than 10% by doses of 4000 mg/kg in the diet (National Cancer Institute, 1980).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

After incubation of ^{14}C-labelled fluometuron with cultured human embryonic lung cells for up to 72 h, 95% of the compound remained unchanged. Human embryonic lung cell homogenate metabolized small amounts of fluometuron through oxidative pathways to *N*-(3-trifluoromethylphenyl)-*N'*-formyl-*N'*-methylurea, *N*-(3-trifluoromethylphenyl)-*N'*-methylurea and *N*-(3-trifluoromethylphenyl) urea (Lin *et al.*, 1976).

Mutagenicity and other short-term tests

Fluometuron (commercial formulation) showed slight mutagenic activity in a bacterial spot test with *Salmonella typhimurium* strain *his* G46 (Seiler, 1977). A weak positive effect was observed when fluometuron [purity not specified] was tested in a plate assay and in a liquid fluctuation test in *S. typhimurium* strain TA1535 in the presence of a rat liver microsomal preparation (Seiler, 1978); however, Dunkel and Simmon (1980) observed no activity with 99% pure fluometuron in five *Salmonella* strains, either in the presence or absence of a metabolic activation system from non-induced or Aroclor-induced rats, mice or hamsters. [It cannot be excluded that the positive results obtained in some studies may be due to mutagenic impurities.]

A commercial formulation of fluometuron was ineffective in inducing mitotic gene conversion in *Saccharomyces cerevisiae* strain D4 without exogenous metabolic activation (Siebert & Lemperle, 1974).

Fluometuron [purity unspecified] given orally to mice at doses of up to 2000 mg/kg bw resulted in a strong inhibition of testicular DNA synthesis. Results obtained in a micronucleus test were inconclusive (Seiler, 1978).

Treatment of *Vicia faba* root tips with up to 90 mg/l of a commercial formulation for 24 and 72 hours induced low levels of mitotic aberration (Hakeem & Shehab, 1973). Treatment of cotton seeds with 0.01-1% of a commercial formulation resulted in dose- and time-dependent increases in chromosomal aberrations (Sultanov & Ergashev, 1981).

(*b*) *Humans*

Toxic effects

No data were available to the Working Group.

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

A frequency of 5.8% of aberrant metaphases was observed in peripheral leucocytes from sowers exposed to an air concentration of 4.28-10.90 mg/m^3 of a commercial formulation of fluometuron; a frequency of 4.3% was seen in leucocytes of tractor drivers exposed to concentrations of 0.64-7.4 mg/m^3, compared with 2.5% prior to exposure (Kukanbaev, 1980).

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Fluometuron was tested for carcinogenicity in mice and rats by administration in the diet. In male mice, an increased incidence of liver-cell tumours was found. In female mice and in rats of both sexes, the results were not indicative of a carcinogenic effect.

No data were available to evaluate the teratogenicity of fluometuron to experimental animals.

Fluometuron was weakly or nonmutagenic to *Salmonella typhimurium*. It was not active in inducing mitotic gene conversion in yeast. Mitotic chromosomal aberrations were observed in treated *Vicia faba* root tips and cotton seeds. In all studies that gave positive results, commercial formulations were known or suspected to have been used, suggesting that the observed activity may be attributable to other ingredients. There are insufficient data to evaluate the mutagenicity of pure fluometuron, but there is limited evidence that commercial formulations of this compound are mutagenic in experimental animals.

4.2 Human data

Fluometuron was introduced in 1960. Its production, formulation and use as a herbicide on cotton are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenicity of fluometuron to humans. The available data were insufficient to evaluate its chromosomal effects in humans.

No case report or epidemiological study of the carcinogenicity of fluometuron alone was available to the Working Group. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation

The available data are inadequate to evaluate the carcinogenicity of fluometuron to experimental animals. No data on humans were available.

No evaluation of the carcinogenicity of fluometuron to humans can be made.

5. References

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970). *World Rev. Pestic. Control, 9*, 119-127

Berg, G.L., ed. (1981) *Farm Chemicals Handbook 1981,* Willoughby, OH, Meister Publishing Co., p. C 151

Dunkel, V.C. & Simmon, V.F. (1980) *Mutagenicity of chemicals previously tested for carcinogenicity in the National Cancer Institute Bioassay Program.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 283-302

Hakeem, H. & Shehab, A. (1973) Cytological effects of Eptam and Cotoran on *Vicia faba. Egypt. J. Bot., 16*, 303-311

Hofberg, A.H., Jr, Henrichs, L.C., Barringer, V.M., Tin, M. & Gentry, G.A. (1977) Collaborative study of gas-liquid chromatographic method for determining fluometuron. *J. Assoc. off. anal. Chem., 60*, 716-719

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, p. 105

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 118, 119

Kukanbaev, R.U. (1980) Cytogenetic analysis of the peripheral blood of workers exposed to the herbicide cotoran (Russ.). *Med. Zh. Uzb., 10*, 65-67

Lin, T.H., Menzer, R.E. & North, H.H. (1976) Metabolism in human embryonic lung cell cultures of three phenylurea herbicides: Chlorotoluron, fluometuron, and metobromuron. *J. agric. Food Chem., 24*, 759-763

Markus, J.R. & Puma, B., eds (1971) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.229

National Cancer Institute (1980) *Bioassay of Fluometuron for Possible Carcinogenicity (NCI-CG-TR-195, NTP-80-11, NIH Publ. No. 80-1751)*, Bethesda, MD

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Seiler, J.P. (1977) Nitrosation *in vitro* and *in vivo* by sodium nitrite, and mutagenicity of nitrogenous pesticides. *Mutat. Res.*, *48*, 225-236

Seiler, J.P. (1978) Herbicidal phenylalkylureas as possible mutagens. 1. Mutagenicity tests with some urea herbicides. *Mutat. Res.*, *58*, 353-359

Siebert, D. & Lemperle, E. (1974) Genetic effects of herbicides: Induction of mitotic gene conversion in *Saccharomyces cerevisiae*. *Mutat. Res.*, *22*, 111-120

Spencer, E.Y. (1968) *Guide to the Chemicals Used in Crop Protection*, 5th ed. (*Research Branch Agriculture Canada Publ. 1093*), London, Ont., University of Western Ontario, p. 275

Spencer, E.Y. (1973) *Guide to the Chemicals Used in Crop Protection*, 6th ed. (*Research Branch Agriculture Canada Publ. 1093*), London, Ont., University of Western Ontario, p. 283

Sultanov, A.S. & Ergashev, A.K. (1981) Comparative studies of the mutagenic effects of the herbicides cotoran and toluidine on different species of cotton (Russ.). *Genetika*, *17*, 2057-2060

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976, Agricultural Economic Report No. 418*, Washington DC, Economics, Statistics and Cooperatives Service, p. 10

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Office of Pesticide Programs, Washington DC, Association of Official Analytical Chemists, Fluometuron EPA-1, pp. 1-3

US Environmental Protection Agency (1980a) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.229, p. 573

US Environmental Protection Agency (1980b) Food and drugs. *US Code Fed. Regul., Title 21*, part 561.240, p. 516

US International Trade Commission (1977) *Imports of Benzenoid Chemicals and Products, 1976 (USITC Publ. 828)*, Washington DC, US Government Printing Office, p. 102

US International Trade Commission (1980) *Synthetic Organic Chemicals, US Production and Sales, 1979 (USITC Publ. 1099)*, Washington DC, US Government Printing Office, p. 240

US International Trade Commission (1981) *Imports of Benzenoid Chemicals and Products, 1980* (*USITC Publ. 1163*), Washington DC, US Government Printing Office, p. 106

US Tariff Commission (1969) *Synthetic Organic Chemicals, US Production and Sales, 1967* (*TC Publ. 295*), Washington DC, US Government Printing Office, p. 162

Voss, G., Gross, D., Bucker, A. & Guth, J.A. (1974) *Fluometuron, Metobromuron, Chlorbromuron and Chloroxuron.* In: Sherma, J. & Zweig, G., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VII, New York, Academic Press, pp. 573-594

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 275

MCPA[1]

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 94-74-6

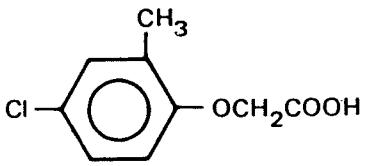
Chem. Abstr. Name: Acetic acid, (4-chloro-2-methylphenoxy)-

IUPAC Systematic Name: (4-Chloro-*ortho*-tolyloxy)acetic acid

Synonyms: 2M-4CH; 2M4KH; 4-chloro-*ortho*-cresoxyacetic acid; chlorotoloxyacetic acid; (4-chloro-*ortho*-toloxy)acetic acid; [(4-chloro-*ortho*-tolyl)oxy]acetic acid; MCP; 2,4-MCPA; 2-methyl-4-chlorophenoxyacetic acid; metaxon

Trade Names: Agritox; Agroxon; Agroxone; AK-2M; Anicon Kombi; Anicon M; Banlene Plus; Banvel M; Basagran-M; BH MCPA; Bordermaster; Brominal M & Plus; Bronate; B-Selektonon M; Cambilene; Cekherbex; Chiptox; Chwastox; Cornox M; Ded-Weed; Dicopur-M; Dicotex; Dikotes; Dow MCP Amine Weed Killer; Emcepan; Empal; Empral; Hedapur M52, Hedarex M; Hedonal M; Herbicide M; Hormotuho; Hormotuho X Super; Hornotuha; Kilsem; Krezone; Legumex DB; Leuna M; Leyspray; Linormore; M40; Mephanac; Methoxone; Netazol; Okultin M; Phenoxylene Plus; Phenoxylene Super; Raphone; Razol Dock Killer; Rhomenc; Rhomene; Rhonox; Seppic MMD; Trasan; U 46; U 46 M-Fluid 4 & 6; Ustinex; Vesakontuho MCPA; Verdone; Weedar; Weedar Sodium MCPA; Weedar MCPA Concentrate; Weedone MCPA Ester; Weed-Rhap; Zelan

1.2 Structural and molecular formulae and molecular weight



$C_9H_9ClO_3$ Mol. wt: 200.6

---

[1] Information relevant to this compound is included in the monographs on 2,4-D and 2,4,5-T (IARC, 1977).

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 118-119°C

(*c*) *Spectroscopy data*: Infra-red and ultra-violet spectral data (Gore *et al.*, 1971) and mass spectroscopy data (NIH/EPA Chemical Information System, 1981) have been reported

(*d*) *Density*: $d_{15.5}^{25}$ 1.56 (Weed Science Society of America, 1979)

(*e*) *Solubility*: Slightly soluble in water (825 mg/l at room temperature). Soluble in diethyl ether, ethanol, toluene and xylene; slightly soluble in *n*-heptane; essentially insoluble in carbon disulphide (Weed Science Society of America, 1979)

(*f*) *Reactivity*: Forms water-soluble salts with alkalis and amines

1.4 Technical products and impurities

Crude MCPA (approximately 85-95% pure) is a solid, with a melting-point of 100-115°C (Worthing, 1979). Technical MCPA has been reported to have the following typical composition: MCPA, 94-96%; 2-methyl-6-chlorophenoxyacetic acid (an isomer of MCPA), 1.5-3%; a mixture of 2-methyl-4,6-dichlorophenoxyacetic acid, 2-methylphenoxyacetic acid, 2- and 4-chlorophenoxyacetic acid and 2,6-dimethyl-4-chlorophenoxyacetic acid, 0.5-1.5%; chloro-*ortho*-cresol, 0.5%; and water, 1.0% (National Research Council, 1977). In 1979, a commercial product of MCPA was reported to contain approximately 4% of 4-chloro-*ortho*-cresol as an impurity (Hattula *et al.*, 1979a).

MCPA is available as aqueous concentrates of its metal and amine salts, as a powder (its sodium salt), as emulsifiable concentrates of its esters, and in numerous mixtures with other herbicides (Worthing, 1979). Formulations based on the potassium, sodium and dimethylamine salts and on the butyl, isooctyl and butoxyethyl esters are available (Berg, 1981). The dimethyl salt has been reported to contain <1-0.65 mg/kg *N*-nitroso-dimethylamine (Cohen *et al.*, 1978).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

MCPA was introduced as a commercial chemical in 1945. It is made by the reaction of 4-chloro-*ortho*-cresol with sodium chloroacetate or chloroacetic acid in alkaline solution (Worthing, 1979). MCPA was first produced commercially in the US in 1951 (US Tariff Commssion, 1952). Three US companies presently produce MCPA and/or its salts and esters. Commercial production of MCPA and its dimethylamine salt was reported by one company in 1980 (US International Trade Commission 1981a); production of the iso-octyl ester was last reported in the US in 1977 by one company (US International Trade Commission, 1978); and production of the potassium salt was last reported in the US in 1970 by one company (US Tariff Commission, 1972).

In I980, imports of MCPA through the principal US customs districts amounted to only 152 thousand kg (US International Trade Commission, 1981b), compared with 1.48 million kg imported in 1979 (US International Trade Commission, 1980). Separate data on US exports of MCPA are not available.

This compound is believed to be produced by three companies in the UK, two in France, two in the Federal Republic of Germany and one company each in The Netherlands, Denmark and Austria.

In 1980, the only Japanese company that makes MCPA produced 133 thousand kg; 256 thousand kg were produced in 1976. During 1976-1980, imports ranged from 11 thousand kg in 1979 to 127 thousand kg in 1980. Japanese exports of MCPA have been negligible.

MCPA is also believed to be produced in Canada (one company) and the Democratic Republic of Germany (two plants). It may also be produced in Czechoslovakia, Hungary, Poland and New Zealand.

(*b*) *Use*

MCPA is used as a postemergence herbicide for control of broadleaf weeds in agricultural applications.

Total use of MCPA in the US in 1973 was estimated to be 1.6-2.0 million kg (National Research Council, 1977). In 1978, a total of 1.6 million kg were used, with 69% on wheat, 17% on other grains and 14% on rice. In California, in 1979, 360 kg of the butoxyethanol ester were used, principally on barley; 243 thousand kg of the dimethylamine salt, 85% of which was used on rice; 4100 kg of the isooctyl ester, mainly on barley; and 9800 kg of the sodium salt, 90% on rice (California Department of Food & Agriculture, 1980).

In Japan, an estimated 260 thousand kg of MCPA were used in 1980, principally on rice.

Tolerances in the US for residues of MCPA and its salts and esters in or on raw agricultural commodities are presently 0.1 (negligible residues)-300 mg/kg for a variety of 34 raw agricultural commodities, including grains, grasses, vegetables and forage legumes and their hays. In addition, tolerances are established at 0.1 mg/kg (negligible) for combined residues of MCPA and its metabolite 2-methyl-4-chlorophenol in or on milk, cattle, goats, hogs, horses and sheep (US Environmental Protection Agency, 1980, 1982).

2.2 Occurrence

(*a*) *Natural occurrence*

MCPA is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of workers exposed to MCPA during its production, formulation and use as a herbicide.

(*c*) *Soil and plants*

The related herbicide, MCPB [4-(4-chloro-2-methylphenoxy)butanoic acid], is oxidized to MCPA by some plants (Worthing, 1979).

(*d*) *Water and sediments*

In Ontario, Canada, 11 agricultural watersheds which drain into the Great Lakes were surveyed for residues of MCPA: it was detected in trace amounts (0.3 μg/l) in six of 949 stream-water samples analysed (limit of detection, 0.1 μg/l). None was detected in 22 rainwater samples collected from six of the watersheds or in streambed sediments from all watersheds (Frank & Sirons, 1980). In another study in Ontario, 237 wells suspected of being contaminated were analysed for residues of a variety of herbicides. MCPA was detected in two of the wells at levels of 1.1-10 μg/l and 1-10 mg/l (limit of detection, 0.01 μg/l) (Frank *et al.*, 1979).

(*e*) *Food, beverages and animal feeds*

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration, MCPA was detected in food composites during 1965-1968 at a maximum concentration of less than 0.4 mg/kg (National Research Council, 1977). In the same programme, MCPA was not detected in food composites of adult total diet samples during 1971-1976 (Manske & Johnson, 1975; Johnson & Manske, 1976, 1977; Manske & Johnson, 1977; Johnson *et al.*, 1981) or in infant or toddler diet samples during 1974-1975 (Johnson *et al.*, 1979); limits of detection varied with the food composite analysed.

2.3 Analysis

Standard methods used for the analysis of MCPA in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of MCPA

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract (methyl isobutyl ketone)	Titration	not given	St John (1967)
	Extract (carbon disulphide)	IR spectroscopy	not given	St John (1967)
	Extract (chloroform); partition (sodium carbonate); acidify; extract (chloroform); evaporate; dissolve (methanol)	UV spectroscopy	not given	St John (1967)
Dimethylamine salt of formulation with Dicamba[b]	Precipitate (hydrochloric acid); extract (chloroform); evaporate; dissolve (acetone)	IR spectroscopy	not given	Horwitz (1980)
Amine salt and ester formulations	Dissolve (isopropanol/ aqueous potassium hydroxide)	HPLC/UV	not given	Association of Official Analytical Chemists (1980)
Salt and ester formulations	Reflux (sodium hydroxide); extract (diethyl ether); acidify (sulphuric acid); extract (carbon tetrachloride); dissolve (sodium hydroxide)	UV spectroscopy	not given	US Environmental Protection Agency (1976)
Ester and free acid formulations	Dissolve (methanol)	HPLC/UV	not given	US Environmental Protection Agency (1976)
Free acid formulations	Extract (diethyl ether); evaporate; dissolve (acetone); dry (sodium sulphate); derivatize (MSTFA) on column	GC/FID	not given	US Environmental Protection Agency (1976)
Forage crops and feed grains, milk and urine	Extract (acidified acetone); partition (diethyl ether/base); acidify; extract (diethyl ether); nitrate; dilute (aqueous sodium sulphate); equilibrate (diethyl ether); evaporate; methylate (methanol/boron trifluoride)	GC/ECD	0.1 mg/kg	St John (1967)
Urine	Hydrolyse (sulphuric acid); extract (chloroform)	HPLC/UV	0.2 mg/kg	Fjeldstad & Wannag (1977)

[a]Abbreviations: IR spectroscopy, infra-red spectroscopy; UV spectroscopy, ultra-violet spectroscopy; HPLC/UV, high-performance liquid chromatography/ultra-violet detection; MSTFA, *N*-methyl-*N*-trimethylsilyl-2,2,2-trifluoroacetamide; GC/FID, gas chromatography/ flame ionization detection; GC/ECD, gas chromatography/electron capture detecton

[b]Dicamba: 3,6-dichloro-2-methoxybenzoic acid

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Rat: Groups of five male and five female rats [age and strain unspecified] were administered diets containing 0, 100, 400, 1000 or 2500 mg/kg MCPA [purity unspecified] for seven months. Total survival was more than 74%; most deaths occurred in the highest dose group, which received a maximum tolerated dose. No abnormality was observed on histological examination of major tissues (Gurd *et al.*, 1965). [The Working Group considered this experiment inadequate for evaluation of carcinogenicity because of short dosage period, small group size and no statistical analysis of tumour incidence.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The oral LD_{50} of the free acid in rats was 800 mg/kg bw (Ben-Dyke *et al.*, 1970) or 700 mg/kg bw when fed to males in corn oil (Rowe & Hymas, 1954). The dermal LD_{50} of MCPA in rats was >1000 mg/kg bw (Jones *et al.*, 1968). The oral LD_{50} of sodium MCPA was 560 mg/kg bw in mice; the i.p. LD_{50} of the sodium salt was 500 mg/kg bw in mice and 400 mg/kg bw in rats (Gurd *et al.*, 1965). The s.c. LD_{50} of sodium MCPA in rats was 500 mg/kg bw (Hattula *et al.*, 1977). The oral LD_{50} of the amine salt in rats was 1200 mg/kg bw (Rowe & Hymas, 1954). The oral LD_{50} of 4-chloro-*ortho*-cresol, a metabolite or contaminant of MCPA, in rats was 1194 mg/kg bw and the i.p. LD_{50}, 794 mg/kg bw (Hattula *et al.*, 1979a).

Rats given sodium MCPA subcutaneously at doses of 250-700 mg/kg bw showed lethargy and severe myotonia within 0.5-1.5 hours of dosing (Elo & Ylitalo, 1977; Hattula *et al.*, 1977). Post mortem examination revealed extensive haemorrhages in the gastrointestinal and urinary tracts. Hyperaemic sinusoids and focal parenchymal-cell necrosis were seen in the liver. The splenic periarterial lymphoid tissue was diminished, and the germinal centres were reduced in number. The spleen contained necrotic foci (Hattula *et al.*, 1977).

Single oral doses of approximately 1000 mg/kg bw 4-chloro-*ortho*-cresol (believed to be a metabolite or contaminant of MCPA) to male Wistar rats produced mononuclear infiltration in kidney glomeruli, liver necrosis and enlarged centres of spleen follicles. Rats given 100 mg/kg bw per day 4-chloro-*ortho*-cresol in a subchronic experiment showed necrosis in the small intestine (Hattula *et al.*, 1979a). In rats given 250 mg/kg bw 5-chloro-3-methyl-catechol (a metabolite of MCPA) intragastrically for two weeks, slight hepatitis and slight inflammatory lesions were found in the small intestine (Hattula *et al.*, 1979b).

There was a significant increase in the size of peroxisomes and a slight increase in their frequency in liver cells of Chinese hamsters administered a single oral dose of 100 mg/kg bw Vesakontuho MCPA (a commercial product) (Vainio *et al.*, 1982).

In subacute dermal studies in rabbits, MCPA was applied at doses of 0.5, 1.0 or 2.0 g/kg bw for three weeks. The animals lost weight and showed slight erythema; microscopic examination of the skin showed hyperplasia and hyperkeratosis. Systemic manifestations of poisoning were also present. Food consumption and weight gain were significantly decreased in rats given 400 and 3200 mg/kg MCPA in the diet for 90 days (Verschuuren *et al.*, 1975).

Albino rats given 25 mg/kg bw aqueous technical-grade (80% pure) sodium MCPA intragastrically for six months showed peripheral blood changes by the end of the second month of exposure, and slight eosinophilia and impaired kidney function by the end of the sixth month (Gzhegotskii & Shtabskii, 1969).

Effects on reproduction and prenatal toxicity

The ethyl ester of MCPA (purity, 94.12%) was fed in the diet at concentrations of 40, 500, 1000 or 2000 mg/kg [about 2.7, 30, 60 and 100 mg/kg bw per day] to Wistar rats on days 8-15 of pregnancy. Maternal body weight was reduced with doses of 500 mg/kg and higher. The incidences of resorptions and foetal malformations were significantly increased and foetal body weight decreased with 2000 mg/kg; the mean weight of female foetuses was also decreased with 1000 mg/kg. The salient malformations were cleft palate and ventricular septal defects. No effect was observed with 40 or 500 mg/kg (Yasuda & Maeda, 1972).

When technical-grade MCPA (80% pure) was administered in a single dose equal to one-half the LD_{50} [acute oral LD_{50}, 700 mg/kg bw (Worthing, 1979)] by stomach intubation on day 9 of pregnancy, increased frequency of resorptions and reductions in foetal weight and length were seen. Encephalocele, defects in brain ventricles and haemorrhages in the internal organs and stomach cavity were also observed, but it was not stated whether the test dose was toxic to the dams (Buslovich *et al.*, 1979).

Absorption, distribution, excretion and metabolism

MCPA is readily absorbed from the gut but poorly through the skin of mice (Gurd *et al.*, 1965). After rats were exposed acutely or chronically to MCPA, it was detected in all organs tested (Elo, 1976; Elo & Ylitalo, 1976, 1979; Hattula *et al.*, 1977). In rabbits and cattle, MCPA is excreted rapidly largely unchanged (Bache *et al.*, 1964; Verschuuren *et al.*, 1975).

After intragastric administration of ^{14}C-labelled MCPA (about 11.5 mg/kg bw) to rats, 92.3% and 6.76% of the radioactivity was recovered in the urine and faeces, respectively, during the first 24 hours (Elo, 1976). When male rats were given s.c. injections of 250 or 500 mg/kg bw sodium MCPA followed by i.v. injection of ^{14}C-MCPA three hours later, the concentration of MCPA was markedly higher in the brain (11- and 18-fold) and in the cerebrospinal fluid (39- and 67-fold) than in the liver (4.5- and 5.6-fold) (Elo & Ylitalo, 1977).

MCPA binds to plasma proteins (Elo & Ylitalo, 1977).

4-Chloro-*ortho*-cresol was found in the liver of rats that received 0.1-3 g/l MCPA in their drinking-water for three months (Hattula *et al.*, 1977). [The possibility that the 4-chloro-*ortho*-cresol was a contaminant of MCPA and not a metabolite cannot be established unequivocally.]

Mutagenicity and other short-term tests

The mutagenicity of MCPA has been reviewed (Seiler, 1978).

MCPA (purity, 99.9%) was not mutagenic to *Salmonella typhimurium* strains TA1535, TA1537, TA98 or TA100 in either the presence or absence of Aroclor-induced rat liver microsomal preparations (Räsänen *et al.*, 1977). Similarly, the methyl ester (analytical grade) was not mutagenic to *Salmonella* strains TA98 and TA100 in the presence or absence of Aroclor-induced mouse liver microsomal preparations (Zetterberg, 1979). MCPA also failed to induce *S. typhimurium* strain *his* G46 and *Serratia marcescens* mutant a21 *leu* in the host-mediated assay in NMRI mice treated intraperitoneally with 1000 mg/kg bw of the compound [purity unspecified] (Buselmaier *et al.*, 1972). It gave negative results in the forward mutation assay to streptomycin resistance and to galactose protrophy in *Escherichia coli* as well as in the back mutation assay in *S. marcescens*. Exogenous metabolic activation was not employed (Fahrig, 1974).

No mitotic gene conversion at the *ade* 2 or *trp* 5 loci of *Saccharomyces cerevisiae* was observed in the absence of exogenous metabolic activation (Fahrig, 1974) [details not given]. However, MCPA and its methyl ester caused killing and induction of back mutations in a haploid, DNA-repair-defective strain, *rad* 18, of *S. cerevisiae* in the absence of exogenous metabolic activation; activity was observed only with concentrations of MCPA that resulted in extensive cell killing (Zetterberg, 1979).

A weak but significant effect in the sex-linked recessive lethal test was shown in *Drosophila melanogaster* males fed a 5 mM solution of MCPA [purity unspecified] (Vogel & Chandler, 1974). However, concentrations of 250 or 500 mg/kg of 94% pure compound in the feed produced no increase in chromosome loss, non-disjunction or induced X-Y recombination in males (Magnusson *et al.*, 1977).

MCPA did not induce chromosomal aberrations in human lymphocytes *in vitro* (Fahrig, 1974) [details not given].

(*b*) *Humans*

Toxic effects

A single oral dose of 5 mg MCPA [about 0.07 mg/kg bw] was without clinical effect (Fjeldstad & Wannag, 1977).

Three suicide attempts by ingestion of MCPA have been reported (Popham & Davies, 1964; Johnson & Koumides, 1965; Jones *et al.*, 1967). Doses taken in the two fatal cases were estimated to have been 440 and 250 mg/kg bw, and the post-mortem blood concentrations of MCPA were 230 and 180 mg/l, respectively. The manifestations of toxicity common to all three cases were coma, constricted, unreactive pupils, and diastolic hypotension. Deep-tendon reflexes were either depressed or hyperactive at various times in the clinical course of the poisonings. Pathological findings in the surviving case included proteinuria and glycosuria (which subsided during convalescence), elevated serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels (which soon returned to normal), anaemia (11.1 g Hb/100 ml) and transient thrombocytopenia. The two fatal cases were unconscious when found; in one, central nervous system disturbance progressed to tonic-clonic convulsions; in both, blood pressure fell gradually, and death occurred about 20 hours after admission to hospital.

Autopsy findings included venous congestion of the lungs and abdominal organs, and pulmonary oedema. There was no indication of a corrosive effect on the mouth, oesophagus, stomach or intestine. Some degree of gastrointestinal haemorrhage was observed in the surviving case, but no corrosive burns of the mouth were present.

A single case of severe erosive gastroduodenitis was reported in a 50-year-old farmer after spraying MCPA. Inhalation and dermal absorption of MCPA were presumed to have occurred (Huep & Hesselmann, 1979).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Autopsy specimens (obtained from one of the fatal cases described above) contained the following levels of MCPA: liver, 0.158 g [146 mg/kg]; heart, 0.037 g [154 mg/kg] and brain, 0.038 g [33 mg/kg] (Popham & Davies, 1964). In another case, in which death was due to a combination of MCPA and parathion, the concentration of MCPA in the blood was 7.75 mg% [77.5 mg/kg], and that in the tissues was 0.70-2.8 mg% [7-28 mg/kg] (De Beer *et al.*, 1980).

After each of four volunteers ingested 5 mg MCPA, about 50% of the total dose was detected in the urine within 48 hours. After an additional three days, the concentration in the urine was less than the detectable limit of 0.02 μg/ml (Fjeldstad & Wannag, 1977).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

Palva *et al.* (1975) described a case of aplastic anaemia in a 64-year-old farmer which developed a few weeks after he sprayed MCPA as a weed killer. His symptoms included muscular weakness, haemorrhagic gastritis and pancytopenia, associated with slightly impaired liver function. Following treatment with prednisone, methenolone and repeated blood transfusions, his condition improved, and he was asymptomatic five months after the exposure. Twelve months later he developed acute myelomonocytic leukaemia, from which he later died (Timonen & Palva, 1980).

Barthel (1976) found 30 cases of cancer on follow up of 316 men exposed to a variety of herbicides (2,4-D and MCPA), insecticides (DDT, hexachlorocyclohexane, toxaphene, parathion, DNOC [4,6-dinitro-*ortho*-cresol]), fungicides (copper-containing and other) and, to some extent, arsenic, in the German Democratic Republic. There were 11 cases of lung cancer, 4 of prostatic cancer, 3 of stomach cancer, 3 of skin cancer, 2 of bladder cancer, 2 of rectal cancer, one each of kidney, oesophagus, gall-bladder and epiglottis cancer and one lymphoma. The expected number of lung cancers was estimated to be 0.54. [The expected number would be higher if it were calculated correctly, by multiplication of the population annual incidence rate by the man-years at risk in each age group rather than by the number of men in each age group. Due to the fact that the

exposure was to many chemicals, including arsenic, it was not possible to determine the specific carcinogenic effect of any one pesticide.]

Eriksson *et al.* (1981) conducted a case-control study in Umegoa, Sweden, in which particular emphasis was paid to MCPA and 2,4-D, which are less likely to contain chlorinated dibenzo-*para*-dioxins than other phenoxyacetic acid herbicides. A group of 110 men [aged 25-75], diagnosed as having soft-tissue sarcomas between 1974-1978, were each matched for age, sex, place of residence and vital status with two controls. The soft-tissue sarcomas included 33 leiomyosarcomas, 19 malignant fibrous histiocytomas, 15 liposarcomas and 11 neurogenic sarcomas. Questions about present and previous smoking history were asked by questionnaire or by interviewers; employers, agricultural commissions and neighbours were also interviewed. Exposure to other chemicals, such as organic solvents, DDT and mercury, was also investigated to check for confounding factors. The relative risk for exposure to phenoxyacetic acids considered to be free from dioxins (including MCPA) was 4.2 [95% confidence limits, 1.2-14.9, calculated by Coggon and Acheson (1982)].

In a similar study of malignant lymphomas in relation to exposure to phenoxyacetic acids and chlorophenols, 5/169 lymphoma cases and 0/335 controls had been exposed to MCPA alone (Hardell *et al.*, 1981).

Exposure to phenoxyacetic acid herbicides, including MCPA, in relation to cancer, is also discussed in the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

No adequate study of the carcinogenicity of MCPA to animals was available to the Working Group.

MCPA and maternally toxic doses of its ethyl ester were teratogenic and embryotoxic to rats.

MCPA was not mutagenic in bacterial systems in plate or host-mediated assays. A questionable result was obtained with MCPA in yeast, but its methyl ester was mutagenic. Recessive lethal mutations, but no chromosome loss, non-disjunction or X-Y chromosome rearrangement, were induced in *Drosophila melanogaster*. No overall evaluation of the mutagenicity of MCPA could be made.

4.2 Human data

MCPA was introduced in 1945. The production and formulation of this compound and of its derivatives and their use as herbicides in agricultural applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of MCPA in humans.

Exposure to MCPA alone was reported for some cases in one of three case-control studies and in one case report. The case-control studies are also discussed in detail in the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.

4.3 Evaluation

No adequate data were available to evaluate the carcinogenicity of MCPA to experimental animals. The data on humans were also considered to be inadequate.

The available data are insufficent to evaluate the carcinogenicity to humans of MCPA alone.

5. References

Association of Official Analytical Chemists (1980) Changes in official methods of analysis made at the ninety-third annual meeting, October 15-18, 1979. 1st supplement to 13th edition Official Methods of Analysis. *J. Assoc. off. anal. Chem.*, *63*, 378

Bache, C.A., Lisk, D.J., Wagner, D.G. & Wagner, R.G. (1964) Elimination of 2-methyl-4-chlorophenoxyacetic acid and 4-(2-methyl-4-chlorophenoxybutyric)acid in the urine from cows. *J. Dairy Sci.*, *47*, 93-95

Barthel, E. (1976) High incidence of lung cancer in persons with chronic professional exposure to pesticides in agriculture (Ger.). *Z. Erkrank. Atm.-Org.*, *146*, 266-274

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides. *World Rev. Pestic. Control*, *9*, 119-127

Berg, G.L., ed. (1981) *Farm Chemicals Handbook, 1981*, Willoughby, OH, Meister Publishing Co., pp. C 206, C 207

Buselmaier, W., Röhrborn, G. & Propping, P. (1972) Mutagenicity investigations with pesticides in the host-mediated assay and the dominant lethal test in mice (Ger.). *Biol. Zentralbl.*, *91*, 311-325

Buslovich, S.Y., Aleksashina, Z.A. & Kolosovskaya, V.M. (1979) Effect of phenobarbital on the embryotoxic action of 2-methyl-4-cholophenoxyacetic acid (a herbicide). *Russ. Pharmacol. Toxicol.*, *42*, 57-61

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 157, 158

Coggon, D. & Acheson, E.D. (1982) Do phenoxy herbicides cause cancer in man? *Lancet*, *i*, 1057-1059

Cohen, S.Z., Zweig, G., Law, M., Wright, D. & Bontoyan, W.R. (1978) *Analytical determination of N-nitroso compounds in pesticides by the United States Environmental Protection Agency - A preliminary study.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of N-Nitroso Compounds (IARC Scientific Publications No. 19)*, Lyon, pp. 333-342

De Beer, J., Heyndrickx, A., Van Peteghem, C., Piette, M. & Timperman, J. (1980) Suicidal poisoning by MCPA and parathion. *J. anal. Toxicol., 4*, 91-98

Elo, H. (1976) Distribution and elimination of 2-methyl-4-chlorophenoxyacetic acid (MCPA) in male rats. *Acta pharmacol. toxicol., 39*, 58-64

Elo, H. & Ylitalo, P. (1976) Increase in permeability of blood-brain barrier in rats during 2-methyl-4-chlorophenoxyacetic acid (MCPA) poisoning (Abstract no. 112). *Acta physiol. scand., Suppl. 440,* 85

Elo, H. & Ylitalo, P. (1977) Substantial increase in the levels of chlorophenoxyacetic acids in the CNS of rats as a result of severe intoxication. *Acta pharmacol. toxicol., 41*, 280-284

Elo, H. & Ylitalo, P. (1979) Distribution of 2-methyl-4-chlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid in male rats: Evidence for the involvement of the central nervous system in their toxicity. *Toxicol. appl. Pharmacol., 51,* 439-446

Eriksson, M., Hardell, L., O'Berg, N., Möller, T. & Axelson, O. (1980) Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. *Br. J. ind. Med., 38*, 27-33

Fahrig, R. (1974) *Comparative mutagenicity studies with pesticides.* In: Montesano, R. & Tomatis, L., eds, *Chemical Carcinogenesis Essays (IARC Scientific Publications No. 10)*, Lyon, pp. 161-181

Fjeldstad, P. & Wannag, A. (1977) Human urinary excretion of the herbicide 2-methyl-4-chlorophenoxyacetic acid. *Scand. J. Work environ. Health, 3*, 100-103

Frank, R. & Sirons, G.J. (1980) Chlorophenoxy and chlorobenzoic acid herbicides: Their use in eleven agricultural watersheds and their loss to stream waters in southern Ontario, Canada, 1975-1977. *Sci. total Environ., 15*, 149-167

Frank, R., Sirons, G.J. & Ripley, B.D. (1979) Herbicide contamination and decontamination of well waters in Ontario, Canada, 1969-78. *Pestic. Monit. J., 13*, 120-127

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem., 54*, 1040-1082

Gurd, M.R., Harmer, G.L.M. & Lessel, B. (1965) Acute toxicity and 7-month feeding studies with mecoprop and MCPA. *Food Cosmet. Toxicol., 3*, 883-885

Gzhegotskii, M.I. & Shtabskii, B.M. (1969) The effect of Dicotex on white rat progeny (Russ.). *Gig. Sanit., 34*, 109-111

Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. *Br. J. Cancer, 43*, 169-176

Hattula, M.L., Elo, H., Reunanen, H., Arstila, A.U. & Sorvari, T.E. (1977) Acute and subchronic toxicity of 2-methyl-4-chlorophenoxyacetic acid (MCPA) in male rat. I. Light microscopy and tissue concentrations of MCPA. *Bull. environ. Contam. Toxicol.*, *18*, 152-158

Hattula, M.L., Reunanen, H. & Arstila, A.U. (1979a) Toxicity of 4-chloro-*o*-cresol in rats. I. Light microscopy and chemical observations. *Bull. environ. Contam. Toxicol.*, *21*, 492-497

Hattula, M.L., Reunanen, H., Krees, R., Arstilla, A.U. & Knuutinen, J. (1979b) Toxicity of 5-chloro-3-methyl-catechol to rat: Chemical observations and light microscopy of the tissue. *Bull. environ. Contam. Toxicol., 22,* 457-461

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, p. 103

Huep, W.W., & Hesselmann, J. (1979) Severe acute erosive haemorrhagic gastroduodenitis after spraying of the herbicide Banvel M (Ger.). *Dtsch. med. Wochenschr.*, *104*, 525

IARC (1977) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, pp. 111-138, 273-299

Johnson, H.R.M. & Koumides, O. (1965) A further case of MCPA poisoning. *Br. med. J.*, *ii*, 629-630

Johnson, R.D. & Manske, D.D. (1976) Pesticide residues in total diet samples (IX). *Pestic. Monit. J.*, *9*, 157-169

Johnson, R.D. & Manske, D.D. (1977) Pesticide and other chemical residues in total diet samples (XI). *Pestic. Monit. J.*, *11*, 116-131

Johnson, R.D., Manske, D.D., New, D.H. & Podrebarac, D.S. (1979) Pesticide and other chemical residues in infant and toddler total diet samples - (I) - August 1974-July 1975. *Pestic. Monit. J.*, *13*, 87-98

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975-July 1976. *Pestic. Monit. J.*, *15*, 54-69

Jones, D.I.R., Knight, A.G. & Smith, A.J. (1967) Attempted suicide with herbicide containing MCPA. *Arch. environ. Health*, *14*, 363-366

Jones, K.H., Sanderson, D.M. & Noakes, D.N. (1968) Acute toxicity data for pesticides (1968). *World Rev. Pestic. Control*, *7*, 135-143

Magnusson, J., Ramel, C. & Eriksson, A. (1977) Mutagenic effects of chlorinated phenoxyacetic acids in *Drosophila melanogaster*. *Hereditas*, *87*, 121-123

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII). *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

National Research Council (1977) *Drinking Water and Health*, Washington DC, National Academy of Sciences, pp. 509, 513

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Palva, H.L.A., Koivisto, O. & Palva, I.P. (1975) Aplastic anaemia after exposure to a weed killer, 2-methyl-4-chlorophenoxyacetic acid. *Acta haematol.*, *53*, 105-108

Popham, R.D. & Davies, D.M. (1964) A case of MCPA poisoning. *Br. med. J.*, *i*, 677-678

Räsänen, L., Hattula, M.L. & Arstila, A.U. (1977) The mutagenicity of MCPA and its soil metabolites, chlorinated phenols, catechols and some widely used slimicides in Finland. *Bull. environ. Contam. Toxicol.*, *18*, 565-571

Rowe, V.K. & Hymas, T.A. (1954) Summary of toxicological information on 2,4-D and 2,4,5-T type herbicides and an evaluation of the hazards to livestock associated with their use. *Am. J. vet. Res.*, *15*, 622-629

Seiler, J.P. (1978) The genetic toxicology of phenoxy acids other than 2,4,5-T. *Mutat. Res.*, *55*, 197-226

St John, L.E., Jr (1967) *MCPA*. In: Zweig, G. & Sherma, J., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. V, New York, Academic Press, pp. 441-454

Timonen, T.T.T. & Palva, I.P. (1980) Acute leukaemia after exposure to a weed killer, 2-methyl-4-chlorophenoxyacetic acid. *Acta haematol.*, *63*, 170-171

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Office of Pesticide Programs, Washington DC, Association of Official Analytical Chemists, Chlorophenoxy Herbicides EPA-2, EPA-3, EPA-5

US Environmental Protection Agency (1980) Protection of environment. *US Code Red. Regul.*, *Title 40*, part 180.339, p. 596

US Environmental Protection Agency (1982) Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities; MCPA. *Fed. Regist.*, *47*, 8013

US International Trade Commission (1978) *Synthetic Organic Chemicals, Production and Sales, 1977* (*USITC Publ. 920*), Washington DC, US Government Printing Office, p. 326

US International Trade Commission (1980) *Imports of Benzenoid Chemicals and Products, 1979* (*USITC Publ. 1083*), Washington DC, US Government Printing Office, p. 110

US International Trade Commission (1981a) *Synthetic Organic Chemicals, Production and Sales, 1980* (*USITC Publ. 1183*), Washington DC, US Government Printing Office, p. 236

US International Trade Commission (1981b) *Imports of Benzenoid Chemicals and Products, 1980 (USITC Publ. 1163)*, Washington DC, US Government Printing Office, p. 105

US Tariff Commission (1952) *Synthetic Organic Chemicals, Production and Sales, 1951 (Report No. 175, Second Series)*, Washington DC, US Government Printing Office, p. 135

US Tariff Commission (1972) *Synthetic Organic Chemicals, Production and Sales, 1970 (TC Publ. 479)*, Washington DC, US Government Printing Office, p. 201

Vainio, H., Nickels, J. & Linnainmaa, K. (1982) Phenoxy acid herbicides cause peroxisome proliferation in Chinese hamsters. *Scand. J. Work environ. Health, 8*, 70-73

Verschuuren, H.G., Kroes, R. & Den Tonkelaar, E.M. (1975) Short-term oral and dermal toxicity of MCPA and MCPP. *Toxicology, 3*, 349-359

Vogel, E. & Chandler, J.L.R. (1974) Mutagenicity testing of cyclamate and some pesticides in *Drosophila melanogaster. Experientia, 30*, 621-623

Weed Science Society of America (1979) *Herbicide Handbook*, 4th ed., Champaign, IL, p. 256

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, pp. 326, 327

Yasuda, M. & Maeda, H. (1972) Teratogenic effects of 4-chloro-2-methylphenoxyacetic acid ethylester (MCPEE) in rats. *Toxicol. appl. Pharmacol., 23*, 326-333

Zetterberg, G. (1979) Mechanism of the lethal and mutagenic effects of phenoxyacetic acids in *Saccharomyces cerevisiae. Mutat. Res., 60*, 291-300

NITROFEN

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 1836-75-5

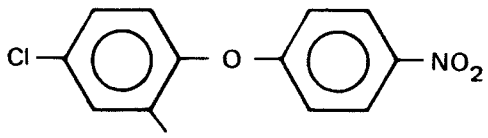
Chem. Abstr. Name: Benzene, 2,4-dichloro-1-(4-nitrophenoxy)-

IUPAC Systematic Name: 2,4-Dichlorophenyl 4-nitrophenyl ether

Synonyms: 2,4-Dichloro-4′-nitrodiphenyl ether; 2,4-dichloro-4′-nitrophenyl ether; 4-(2,4-dichlorophenoxy)nitrobenzene; 2,4-dichlorophenyl-*para*-nitrophenyl ether; NCI CO0420; 4′-nitro-2,4-dichlorodiphenyl ether; 4-nitro-2′,4′-dichlorophenyl ether; nitrofene; nitrophen

Trade Names: FW 925; Mezotox; Niclofen; Nip; Nitrafen; Nitraphen; Nitrochlor; Nitrophene; Tok; Tok 2, E, E25, & WP50; Tokkorn; Trizilin

1.2 Structural and molecular formulae and molecular weight



$C_{12}H_7Cl_2NO_3$ Mol. wt: 284.1

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Crystals

(*b*) *Melting-point*: 70-71°C

(*c*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*d*) *Solubility*: Slightly soluble in water (0.7-1.2 mg/l at 22°C). Soluble (approx. 25% at room temperature) in acetone, methanol and xylene (Weed Science Society of America, 1979)

(*e*) *Volatility*: Vapour pressure, 8 x 10^{-6} mm Hg at 40°C

(*f*) *Stability*: Darkens on exposure to light (Weed Science Society of America, 1979)

1.4 Environmental chemistry

Photolysis of nitrofen in aqueous methanol by sunlight involves photonucleophilic displacement of nitrophenate by the hydroxide ion of the water. In the presence of potassium cyanide, irradiation of nitrofen resulted in 2,4-dichlorobenzonitrile and related compounds. Photoreaction with piperidine produced *para*-nitrophenol as well as tarry products from the further reaction of the intermediate 2,4-dichlorophenol with the amine. 2,4-Dichlorophenol also reacted with potassium cyanide to form 2,4-dicyanophenol (4-hydroxyisophthalonitrile) (Nakagawa & Crosby, 1974a).

Photodecomposition of nitrofen in aqueous solution, under sunlight or simulated sunlight, was characterized by rapid cleavage of the ether linkage to form 2,4-dichlorophenol, *para*-nitrophenol, hydroquinone, 4-nitrocatechol, 2,4-dichlorophenyl-*para*-aminophenyl ether, 4,4′-bis(2,4-dichlorophenoxy)azobenzene and other products. Other pathways involved the replacement of the ring chlorines by hydroxyl or hydrogen, ring hydroxylation, denitration by hydroxide prior to cleavage of the ether linkage and possible intramolecular rearrangement of the nitrofen to a biphenyl. After four weeks of exposure to sunlight, approximately 10% of the initial nitrofen remained in the aqueous solution (Nakagawa & Crosby, 1974b).

1.5 Technical products and impurities

A sample reported by the manufacturer to be more than 98% pure was found by high-performance liquid chromatography to contain the following five impurities at unspecified levels: *para*-chloronitrobenzene, bis(*para*-nitrophenyl)ether, 2,4-dichloro-2,2-dinitrophenyl ether, 2-chloro-4-nitrodiphenyl ether and 4-chloro-4-nitrophenyl ether. Four other unidentified impurities were also observed in the mg/kg (ppm) range (Stone & Manson, 1981). Technical nitrofen may also contain 2,7-dichlorodibenzodioxin (Kimbrough *et al.*, 1974). [It is theoretically possible that other di- and trichlorodibenzodioxins may also be present; the only tetrachlorodibenzodioxin that has been suggested to occur is 1,3,6,8-tetrachlorodibenzodioxin. Nitrofen is made from 2,4-dichlorophenol, which contains 2,6-dichlorophenol, 2,4,6-trichlorophenol and 2-monochlorophenol as impurities; and the various chlorinated dibenzodioxins could be formed during the production process.]

Nitrofen is available as emulsifiable concentrates containing about 25% active ingredient, and as a 50% active water-dispersible powder (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Nitrofen was introduced as a commercial chemical in about 1964. It is made by the reaction of 1-chloro-4-nitrobenzene with a metal salt of 2,4-dichlorophenol (Worthing, 1979).

Nitrofen was first produced commercially in the US in 1963 (US Tariff Commission, 1964). In 1974, annual US production of this herbicide was estimated to have been 227-454 thousand kg (Kimbrough *et al.*, 1974). Only one US company presently produces it, in undisclosed quantities (see preamble, section 8(*b*)(ii)). US imports of nitrofen through the principal US customs districts were last reported in 1968, when they amounted to 10 thousand kg (US Tariff Commission, 1969).

The only company producing nitrofen in Japan ceased production in 1981. It had produced only 12 thousand kg in 1980, none in 1977 and 1978 and 34 thousand kg in 1976. In 1980, 27 thousand kg of nitrofen and an estimated 78 thousand kg of formulations containing nitrofen were imported; imports of nitrofen were 17 thousand kg in 1977 and 223 thousand kg in 1976. None was exported in 1980, but 10 thousand kg were exported in 1976 and 1977.

Nitrofen is believed to be produced by two companies in France, in one plant in the Democratic Republic of Germany and by two companies in Taiwan.

(*b*) *Use*

Nitrofen is used as a pre- and postemergence herbicide in agricultural applications.

In 1978, a total of 410 thousand kg nitrofen were estimated to have been used in the US, with almost 90% on vegetables and the remainder on sugar beets. Total use of nitrofen in California in 1979 was 286 thousand kg, over 50% of which was used on broccoli and 27% on cauliflower (California Department of Food & Agriculture, 1980).

In Japan, nitrofen is used mostly as a herbicide in rice fields.

Tolerances in the US for residues of nitrofen in or on raw agricultural commodities are presently 0.02-0.75 mg/kg for a variety of 24 commodities, including vegetables, milk, rice, poultry and meats (US Environmental Protection Agency, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Nitrofen is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the numbers of workers exposed to nitrofen during its production, formulation and use as a herbicide.

(*c*) *Water and sediments*

Nitrofen was detected in 1975-1977 at levels of <0.2-58.1 mg/m^3 (according to the season) in samples of natural running water taken in Belgium in areas where the herbicide had been applied commercially (Deleu & Copin, 1979).

(*d*) *Food, beverages and animal feeds*

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration during 1973-1974, nitrofen was detected in one of 30 composite samples of leafy vegetables at a level of 0.039 mg/kg (Manske & Johnson, 1977). It was found in kohlrabi, radish, rutabaga and turnip in the US at maximum levels of <0.1, >1, <0.1 and >0.5 mg/kg, respectively (Yu *et al.*, 1979).

Nitrofen was not detected in rice samples (Miyaube *et al.*, 1977) or in fish or shellfish (Ishikawa *et al.*, 1981) from Japan. It was not detected in broccoli or cauliflower from Finland (limit of detection, 0.02 mg/kg) (Siltanen & Rosenberg, 1978).

2.3 Analysis

Standard methods used for the analysis of nitrofen in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of nitrofen

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Plants, fruits and vegetables, rice kernels and soil	Extract (solvent system specific for matrix); chromatograph (Florisil); reduce (zinc-mercury amalgam/hexane hydrochloric acid); diazotize (potassium nitrite); couple (*N*-α-naphthyl-*N'*-diethylpropylene diamine)	Colorimetry	0.05 mg/kg	Markus & Puma (1973)
Green succulent crops, dry crops, oily grains and soil	Add magnesium sulphate; extract with dichloromethane (isopropanol-benzene for soil); evaporate; dissolve (petroleum ether); partition (acetonitrile) to remove oils if required; chromatograph (Florisil); evaporate; dissolve (hexane)	GC/ECD	0.01 mg/kg	Markus & Puma (1973)
Non-oily, dry crops	Same as above without magnesium sulphate	GC/ECD	0.01 mg/kg	Markus & Puma (1973)
Vegetables	Macerate (methanol); Soxhlet extract (methanol); add hexane; partition (aqueous potassium hydroxide); chromatograph (silica gel)	GC/ECD	not given	Yu *et al.* (1979)
Human or animal adipose tissue	Macerate (sand and sodium sulphate); extract (petroleum ether); extract (acetonitrile); dilute (water); partition (petroleum ether); concentrate; chromatograph (Florisil); concentrate	GC/ECD	not given	Watts (1980)
Human milk, human and animal tissue	Macerate (acetonitrile); partition (aqueous sodium sulphate/hexane); concentrate; chromatograph (Florisil); concentrate	GC/ECD	not given	Watts (1980)

[a]Abbreviation: GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female young B6C3F$_1$ mice [age not specified] were fed diets containing technical nitrofen [stated to be >80% pure; impurities unspecified] dissolved in corn oil for 78 weeks at levels of 1775-2500 mg/kg (low dose) or 3550-5000 mg/kg (high dose), to give time-weighted average concentrations of 2348 and 4696 mg/kg of diet. A group of 20 male and 20 female controls received the basal diet containing 2% corn oil. All mice were observed for a further 12 weeks after treatment. Weight gain was depressed in both groups of treated females and in the males exposed to the high dose. Beginning at week 54, pronounced abdominal distension was displayed by increasing numbers of treated mice. By the end of the study, 10% of the control male mice, 34% of the high-dose group and 54% of the low-dose group were still alive; and, of the female mice, 62% were still alive in the high-dose group, 54% in the low-dose group and 85% of the controls. For neither sex could a positive association be established between dosage of nitrofen and mortality. A high incidence of hepatocellular carcinomas was found in exposed male and female mice: in 4/20 control males, 36/49 low-dose males and 46/48 high-dose males, in none of the control female mice (both matched and pooled controls), in 36/41 low-dose females and in 43/44 high-dose females. A few of these tumours metastasized to other sites. The difference in incidence between control and exposed male and female mice was statistically significant ($p < 0.001$) at both dose levels. Haemangiosarcomas of the spleen were found in 2/47 of high-dose males, and haemangiosarcoma of the liver in 1/49 low-dose males and 2/48 high-dose males. In female mice, haemangiosarcomas were seen in the spleen in 1/18 controls, in the liver in 4/44 high-dose animals and in the abdominal cavity in 1/43 of the high-dose group. The Cochran- Armitage test showed a significant positive association between increased dose and elevated incidence of haemangiosarcomas for male ($p = 0.01$) and female mice ($p = 0.032$) when compared with pooled controls. The Fisher exact test showed a significantly ($p = 0.022$) higher incidence of haemangiosarcoma in the high-dose males than in the pooled controls but no statistically significant difference in the incidence among females (National Cancer Institute, 1978).

Groups of 50 male and 50 female six-week-old B6C3F$_1$ mice were fed diets containing 3000 or 6000 mg/kg technical-grade nitrofen [purity not specified] for 78 weeks. The 20 male and 20 female controls received the basal diet. All animals received acidulated (pH 2.5) water *ad libitum*. After exposure to nitrofen, animals were observed for a further 13 weeks. Consistent dose-related depressions in mean body weight were noted in male and female mice, reaching about 25% in high-dose males by the end of the study. At that time, 40/50 of the high-dose males, 48/50 of the low-dose males and 19/20 of the control males were still alive; and of the females, 48/50 of the high-dose and 43/50 of the low-dose group and 12/20 of the controls survived until the end of the study. Although a variety of tumours were noted, only the incidence of liver tumours seemed to be related to nitrofen exposure: Hepatocellular adenomas were seen in 1/20 control males, 18/49 low-dose males and 20/48 high-dose males, and hepatocellular carcinomas in 0/20 controls, 13/49 low-dose males and 20/48 of the high-dose group. In addition, none of the controls, but 3/49 of the low-dose group and 4/48 of the high-dose group had hepatoblastoma [a very rare tumour in this strain of mice]. Of the females, 0/18 controls,

9/48 low-dose and 17/50 high-dose mice had hepatocellular adenomas; and hepatocellular carcinomas were observed in 0/18 control, 5/48 low-dose and 13/50 high-dose female mice. In addition, a hepatoblastoma was found in 1/48 females in the low-dose group. The incidences in male and female mice of hepatocellular adenomas and of hepatocellular carcinomas were statistically significantly different for the low- and high-dose groups by the Cochran-Armitage and the Fisher exact tests (National Cancer Institute, 1979).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats [age not specified] were fed diets containing technical-grade nitrofen [stated to be >80% pure; impurities unspecified] in 2% corn oil for 78 weeks. The dietary concentration for males was 2300 mg/kg (low dose) or 2300-4600 mg/kg (high dose), to give a time-weighted average of 3627 mg/kg. The dietary concentrations for female rats were 1300 mg/kg (low dose) or 2600 mg/kg (high dose). The low-dose males, the control animals and the high- and low-dose females were observed for an additional 32 weeks, during which they were maintained on basal laboratory diet plus corn oil; the high-dose males were observed for an additional five weeks after dosing was stopped. Groups of 20 male and 20 female controls received the basal diet plus 2% corn oil. A dose-related decrease in body weight was noted; by 75 weeks after onset of dosing, the high-dose females weighed roughly one-third less than the controls. Fifty percent of the high-dose males were dead by week 45, and only 15 survived to week 83; 60% of the low-dose and 45% of the control group survived until the end of the study. Of the females, 56% at the high dose, 74% at the low dose and 80% of the controls survived until the end of the study. Anaplastic adenocarcinomas of the pancreas (exocrine, not further specified) [a very unusual lesion in rats (Milman *et al.*, 1978)] were seen in 2/50 females at the low dose and in 7/50 at the high dose. All tumours showed local invasion and had metastasized to the lungs. No such tumour was seen in the 20 matched controls or in the 110 pooled controls. The difference was statistically significant for high-dose animals. No other tumour showed a statistically significant difference in incidence between control and exposed rats. Poor survival precluded the evaluation of carcinogenicity in male rats (National Cancer Institute, 1978). [The Working Group noted the short duration of exposure.]

Groups of 50 male and 50 female six-week-old Fischer 344 rats were fed diets containing 3000 or 6000 mg/kg technical-grade nitrofen [not further specified] for 78 weeks. A group of 20 male and 20 female rats were given the control diet. All animals received acidified water (pH 2.5). The animals were followed for an additional 26 weeks, when all surviving rats were killed. A dose-related depression in mean body weight was noted in animals of both sexes, reaching 15% for those given the high dose for 60 to 75 weeks. Of the male rats, 45/50 given the high dose, 42/50 given the low dose and 17/20 of the controls survived until termination of the study; of the females, 38/50, 42/50 and 17,20, respectively, survived. No statistically significant difference in the incidence of tumours was observed between the exposed and control groups (National Cancer Institute, 1979). [The Working Group noted the short duration of exposure.]

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD_{50} by intragastric administration was 450 mg/kg bw in mice and 740 mg/kg bw in rats; the percutaneous LD_{50} was >5000 mg/kg bw in rabbits (Ivanova, 1967). The

oral LD_{50} by feeding in the diet ranged from 410-3580 mg/kg bw in rats (Ambrose *et al.*, 1971; Shardina, 1972; Kimbrough *et al.*, 1974; Wiswesser, 1976) and from 780-1620 mg/kg bw in rabbits (Shardina, 1972; Wiswesser, 1976). The dermal LD_{50} in rats was 5000 mg/kg bw (Kimbrough *et al.*, 1974).

Nitrofen is toxic when administered orally, percutaneously or by inhalation (Ivanova, 1967). The symptomatology of acute intoxication in laboratory animals was mainly neurological and respiratory (Ivanova, 1967; Shardina, 1972).

Significantly higher liver:body weight ratios were noted in young albino rats exposed to dietary levels of nitrofen of up to 12 500 mg/kg and in six-month-old beagle dogs given 2000 mg/kg (Ambrose *et al.*, 1971).

Rat liver homogenates incubated with amino derivatives of nitrofen, an NADPH-generating system and erythrocytes from rats or humans metabolized the amino derivatives to methaemoglobin-forming metabolites (Miyauchi *et al.*, 1979).

Effects on reproduction and prenatal toxicity

Nitrofen [purity unspecified] administered by gavage at a dose of 100 mg/kg bw per day on days 7-17 of pregnancy to CD-1 mice produced hydrocephaly and microphthalmia during postnatal development of the progeny (Gray *et al.*, 1981, 1982).

Nitrofen (>99% pure or 89% technical-grade) was administered at doses of 10, 20 or 50 mg/kg bw daily by stomach intubation on days 7-15 of pregnancy to Sherman rats. The 20 mg/kg bw dose increased the number of stillbirths and reduced pup viability postnatally, but the 10 mg/kg bw produced none of these effects. Term foetuses from dams treated daily with 50 mg/kg bw on days 7-18 of pregnancy were found to have poorly expanded lungs (Kimbrough *et al.*, 1974). Prenatal exposure of rats to nitrofen reduced foetal lung weight without inhibiting its surfactant activity (Stone, 1979). Purified nitrofen (containing traces of impurities) administered orally at a dose of 150 mg/kg bw to Long Evans rats, either as a single dose on day 9, 10, 11 or 12 of pregnancy or as three doses at one-day intervals for different periods between 7-14 days of pregnancy, caused reduction in pup weight at birth and high postnatal mortality. Administration of this dose on day 11 of pregnancy produced foetal malformations, including cardiac deformities, hydronephrosis and diaphragmatic hernia (Costlow & Manson, 1981).

Three generations of albino rats, allowed to mate twice in each generation, were fed diets containing 0, 10, 100 or 1000 mg/kg technical-grade nitrofen (purity 95%). With the highest dose, there was an increased number of stillbirths and practically no pup survival in F_{1a} and F_{1b}, and with 100 mg/kg there was an increased number of stillbirths (Ambrose *et al.*, 1971). [Decreased incidence of pregnancy occurred in F_{2b}, F_{3a} and F_{3b} exposed to 10 mg/kg.] In a two-generation reproduction study, Sherman rats were fed dietary levels of 0, 20, 100 or 500 mg/kg nitrofen of 89% purity. The survival of progeny was reduced with 100 mg/kg and severely reduced with 500 mg/kg (Kimbrough *et al.*, 1974).

Absorption, distribution, excretion and metabolism

^{14}C-Labelled nitrofen was administered orally to a sheep at a dose of 40 mg/kg bw. After 99 hours, 76.2% of the applied dose was accounted for in the excreta. After 100 hours, radioactivity was highest in fat (23 mg/kg); the liver, thyroid, mammary gland, adrenal gland, kidney, lung, muscle, skin and spleen contained levels of 1-3 mg/kg. The

predominant metabolites were 2,4-dichlorophenyl 4-aminophenyl ether, 2,4-dichloro-5-hydroxyphenyl-4-nitrodiphenyl ether, 2,4-dichlorophenol, 2-chlorophenyl-4-nitrophenyl ether and conjugates (Hunt *et al.*, 1977).

Mutagenicity and other short-term tests

Nitrofen [purity unspecified] was negative in the *rec*-assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*), in the absence of exogenous metabolic activation (Shirasu *et al.*, 1976), but induced mutations in *Salmonella typhimurium* TA100 both in the presence and absence of an Aroclor-induced rat liver microsomal preparation (Shirasu *et al.*, 1982). In another study, nitrofen [purity unspecified] was mutagenic in TA98 and TA100, but not in TA1535 or TA1538; it was mutagenic in TA100 only in the presence of an Aroclor-induced rat liver microsomal preparation (Byeon *et al.*, 1976).

Oral administration of 1/15 or 1/200 of the LD_{50} [doses unspecified] to rats for six days caused no significant increase in the frequency of chromosomal aberrations in bone-marrow cells (Kiryushin, 1975); i.p. administration of 500 to 1000 mg/kg bw [purity unspecified] induced no micronuclei in mouse bone marrow (Paik & Lee, 1977).

(*b*) *Humans*

Toxic effects

Nitrofen has been reported to have irritating effects on the skin and eye in occupationally exposed subjects (Imaizumi et al., 1972; Suga, 1972; Tsyrkunov, 1978).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Nitrofen (technical grade) was tested for carcinogenicity in one strain of mice and in two strains of rats by administration in the diet. In two studies in mice, it significantly increased the incidence of hepatocellular carcinomas. In one study, haemangiosarcomas at various anatomical sites occurred in a significantly higher incidence among male mice given a higher dose. In rats of one strain, adenocarcinomas of the pancreas were produced in females.

Nitrofen was teratogenic to mice and rats when given at very high doses. It decreased neonatal and postnatal viability in three-generation reproduction studies in rats.

Nitrofen was mutagenic to *Salmonella typhimurium*. In two studies, there was no evidence for chromosomal damage in mammals. The data are insufficient to evaluate the mutagenicity of nitrofen in mammals.

4.2 Human data

Nitrofen was introduced in about 1964. Its production, formulation and use as a herbicide in agricultural applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of nitrofen in humans.

No case report or epidemiological study of the carcinogenicity of nitrofen alone was available to the Working Group; however, it should be noted that the period since introduction of this compound may be too short for a carcinogenic effect to be detected in humans. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

No data on humans were available.

There is *sufficient evidence*[2] that technical-grade nitrofen is carcinogenic to experimental animals.

---

[1] This evaluation should be read in conjunction with p. 18 of the preamble.

[2] In the absence of data on humans, nitrofen should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

5. References

Ambrose, A.M., Larson, P.S., Borzelleca, J.F., Blackwell Smith, R., Jr & Hennigar, G.R., Jr (1971) Toxicologic studies on 2,4-dichlorophenyl-*p*-nitrophenyl ether. *Toxicol. appl. Pharmacol.*, *19*, 263-275

Byeon, W., Hyun, H.H. & Lee, S.Y. (1976) Mutagenicity of pesticides in the *Salmonella*/microsomal enzyme activation system. *Korean J. Microbiol.*, *14*, 128-134 (Translation)

California Department of Food & Agriculture (1980) *Pesticide Use Report, Annual 1979*, Sacramento, CA, pp. 186, 187

Costlow, R.D. & Manson, J.M. (1981) The heart and diaphragm: Target organs in the neonatal death induced by nitrofen (2,4-dichlorophenyl-*p*-nitrophenyl ether). *Toxicology*, *20*, 209-227

Deleu, R. & Copin, A. (1979) Extraction and gas chromatographic determination of the herbicides nitrofen and Neburon. Application to natural waters (Fr.). *J. Chromatogr.*, *171*, 263-268

Gray, L.E., Jr, Kavlock, R.J. & Chernoff, N. (1981) A research protocol for postnatal evaluation of teratogenic effects (Abstract). *Teratoloty*, *21*, 41A

Gray, L.E., Jr, Kavlock, R.J., Chernoff, N., Ferrell, J., McLamb, J. & Ostby, J. (1982) Prenatal exposure to the herbicide 2,4-dichlorophenol-*p*-nitrophenyl ether destroys the rodent Harderian gland. *Science*, *215*, 293-294

Hunt, L.M., Chamberlain, W.F., Gilbert, B.N., Hopkins, D.E. & Gingrich, A.R. (1977) Absorption, excretion and metabolism of nitrofen by a sheep. *J. agric. Food Chem.*, *25*, 1062-1065

Imaizumi, K., Atsumi, K., Tanifuji, Y., Ishikawa, Y. & Hoshi, H. (1972) Clinical observation of ophthalmic disturbances due to agricultural chemicals (Jpn.). *Folia Ophthalmol. Jpn.*, *22*, 154-156

Ishikawa, K., Suzuki, S., Sato, N., Takatsuki, K. & Sakai, K. (1981) Studies on residual diphenyl ether herbicides in foods. II. Analytical method for diphenyl ether herbicides in fish and shellfish (Jpn.). *Shokuhin Eiseigaku Zasshi*, *22*, 56-59 [*Chem. Abstr.*, *95*, 5223w]

Ivanova, T.P. (1967) The maximum permissible concentration of nitrophen in the air of the working zone. *Hyg. Sanit.*, *32*, 20-26

Kimbrough, R.D., Gaines, T.B. & Linder, R.E. (1974) 2,4-Dichlorophenyl-*p*-nitrophenyl ether (TOK). Effects on the lung maturation of rat fetus. *Arch. environ. Health.*, *28*, 316-320

Kiryushin, V.A. (1975) Mutagenic action of various pesticides in case of their successive entry into the body of albino rats (Russ.). *Gig. Sanit.*, *9*, 43-46

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 180.223

Milman, H.A., Ward, J.M. & Chu, K.C. (1978) Pancreatic carcinogenesis and naturally occurring pancreatic neoplasms of rats and mice in the NCI carcinogenesis testing program. *J. environ. Pathol. Toxicol.*, *1*, 829-840

Miyabe, M., Maruyama, Y. & Sakabe, Y. (1977) Studies on pesticide residues in foods. VIII. Analysis of CNP, NIP and their degradation products in unpolished rice (Jpn.). *Nagoya-shi Eisei Kenkyusho Ho 1976*, *23*, 33-55 [*Chem. Abstr.*, *90*, 85411r]

Miyauchi, M., Takagi, M. & Uematsu, T. (1979) Studies on toxicities of biphenyl ether herbicides and their analogues to fish. II. Production of methemaglobin-forming metabolites of the amino-derivatives by white-spotted char, *Salvelinus leucomaenis*, liver homogenate. *Bull. Jpn. Soc. Sci. Fish.*, *45*, 1569-1574

Nakagawa, M. & Crosby, D.G. (1974a) Photoneucleophilic reaction of nitrofen. *J. agric. Food Chem.*, *22*, 930-933

Nakagawa, M. & Crosby, D.G. (1974b) Photodecomposition of nitrofen. *J. agric. Food Chem.*, *22*, 849-853

National Cancer Institute (1978) *Bioassay of Nitrofen for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 26; DHEW Publ. No. (NIH) 78-826*), Washington DC

National Cancer Institute (1979) *Bioassay of Nitrofen for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 184; DHEW Publ. No. (NIH) 79-1740*), Washington DC

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Paik, S.G. & Lee, S.Y. (1977) Genetic effects of pesticides in the mammalian cell. I. Induction of micronucleus. *Korean J. Zool.*, *20*, 19-28

Shardina, R.A. (1972) Hygienic and toxicological assessment of nitrofen in water reservoirs (Russ.). *Med. Zh. Uzb.*, *5*, 26-28

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res.*, *40*, 19-30

Shirasu, Y., Moriya, M., Tezuka, H., Teramoto, S., Ohta, T. & Inoue, T. (1982) *Mutagenicity screening studies on pesticides.* In: Sugimura, T., Kondo, S. & Takebe, H., eds, *Environmental Mutagens and Carcinogens*, Tokyo, University of Tokyo Press, pp. 331-335

Siltanen, H. & Rosenberg, C. (1978) *Residue Analysis of the Official Testing of Pesticides 1977*, No. 15, Helsinki, State Institute of Agricultural Chemistry, p. 66

Stone, L.C. (1979) Effects of the herbicide 2,4-dichlorophenyl-*p*-nitrophenyl ether (TOK^{R}) on lung maturation (Abstract). *Diss. Abstr. Int. B, 39*, 4273

Stone, L.C. & Manson, J.M. (1981) Effects of the herbicide 2,4-dichlorophenyl-*p*-nitrophenyl ether (nitrofen) on fetal lung development in rats. *Toxicology, 20*, 195-207

Suga, K. (1972) Environmental pollution and eye damage (Jpn.). *Jpn. Rev. clin. Ophthalmol., 66*, 537-539

Tsyrkunov, L.P. (1978) Chemical dermatosis due to the action of nitrofen (Russ.). *Gig. Tr. prof. Zabol., 7*, 48-49

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.223, p. 572

US Tariff Commission (1964) *Synthetic Organic Chemicals, US Production and Sales, 1963* (*TC Publ. 143*), Washington DC, US Government Printing Office, p. 171

US Tariff Commission (1969) *Imports of Benzenoid Chemicals and Products, 1968* (*TC Publ. 290*), Washington DC, US Government Printing Office, p. 92

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, Sections 5A(1)(a), 5A(2)(a)(b)

Weed Science Society of America (1979) *Herbicide Handbook*, 4th ed., Champaign, IL, p. 307

Wiswesser, W.J., ed. (1976) *Pesticide Index*, 5th ed., College Park, MD, The Entomological Society of America, p. 166

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 386

Yu, T.C., Johnson, E.R. & Montgomery, M.L. (1979) Simultaneous extraction and analysis of trifluralin and nitrofen residues in crucifers. *J. agric. Food Chem., 27*, 1413-1414

SULFALLATE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 95-06-7

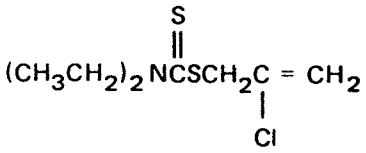
Chem. Abstr. Name: Carbamodithioic acid, diethyl-, 2-chloro-2-propenyl ester

IUPAC Systematic Name: 2-Chloroallyl diethyldithiocarbamate

Synonyms: CDEC; chloroallyl diethyldithiocarbamate; 2-chloroallyl *N,N*-diethyldithiocarbamate; 2-chloro-2-propene-1-thiol diethyldithiocarbamate; diethylcarbamodithioic acid 2-chloro-2-propenyl ester; diethyldithiocarbamic acid 2-chloroallyl ester; NCI CO0453

Trade Names: CP 4742; CP 4572; Thioallate; Vegadex; Vegdex Super

1.2 Structural and molecular formulae and molecular weight



$C_8H_{14}ClNS_2$ Mol. wt: 223.8

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Amber oil

(*b*) *Boiling-point:* 128°C at 1 mm Hg

(*c*) *Density*: d^{25} 1.088

(*d*) *Refractive index*: n_D^{25} 1.5822

(*e*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981)

(*f*) *Solubility:* Very slightly soluble in water (92 mg/l at 25°C); soluble in most organic solvents

(*g*) *Volatility:* Vapour pressure, 2.2 x 10^{-3} mm Hg at 20°C

(*h*) *Stability:* Hydrolysed by alkalis

1.4 Technical products and impurities

One sample of technical grade sulfallate was found by gas-liquid chromatography to be over 90% pure and to contain 14 minor components (National Cancer Institute, 1978). Sulfallate is available as a 48% active emulsifiable concentrate and as 20% active granules (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Sulfallate was introduced as a commercial chemical in 1954. It is made by the reaction of 2,3-dichloropropene-1 with sodium diethyldithiocarbamate (Worthing, 1979).

Sulfallate was first produced commercially in the US in 1955 (US Tariff Commission, 1956). Only one US company has produced it, and production data are not available (see preamble, section 8(*b*)(ii)); that company is believed to have stopped production in 1981. Separate data on US imports and exports of sulfallate are not available.

This compound is not produced commercially in western Europe or Japan.

(*b*) *Use*

Sulfallate is used as a herbicide in agricultural applications. In 1976, total usage of 'other carbamates' (which includes a number of carbamates as well as thiocarbamates such as sulfallate) by US farmers on major crops was reported to have been 2.1 million kg (US Department of Agriculture, 1978). In 1978, a total of 45 thousand kg is estimated to have been used, essentially all as a herbicide on vegetables.

Tolerances in the US for negligible residues of sulfallate in or on raw agricultural commodities are established at 0.2 mg/kg for a variety of 31 fruits and vegetables (US Environmental Protection Agency, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Sulfallate is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the numbers of workers exposed to sulfallate during its production, formulation and use as a herbicide.

(*c*) *Air*

Sulfallate has been reported to be present in the air emissions from sulfallate manufacture at a level of 0.5 kg/1000 kg pesticide produced (Archer *et al.*, 1978).

2.3 Analysis

Standard methods used for the analysis of sulfallate in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of sulfallate

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Technical	Dilute (methanol)	UV spectroscopy	not given	Conkin & Gleason (1964)
Liquid or granular formulations	Reflux (isobutanol/sodium); quench (methanol); heat with hydrogen peroxide; acidify (nitric acid)	Potentiometric titration	not given	Conkin & Gleason (1964)
Crops	Extract (chloroform); wash (hydrochloric acid); hydrolyse to amine sulphate (sulphuric acid); distill from aqueous sodium hydroxide into aqueous hydrochloric acid; extract (chloroform); add colour reagent (copper-ammonia reagent/chloroform-carbon disulphide) to form cupric dithiocarbamate complex	Colorimetry	[5 µg]	Conkin & Gleason (1964)
Vegetables	Grind; extract (acetone); filter; partition (hexane); dry (sodium sulphate)	GC/ECD	0.01 mg/kg	Zweig & Sherma (1972)
Ambient air	Soxhlet extract (hexane/diethyl ether/acetone); concentrate	GC/ElCD[b]	not given	Watts (1980)
	Soxhlet extract (hexane/diethyl ether/acetone); concentrate; derivatize (-bromo-2,3,4,5,6-pentafluorotoluene); chromatograph (deactivated silica gel); concentrate	GC/ECD[b]	not given	Watts (1980)

[a]Abbreviations: UV spectroscopy, ultra-violet spectroscopy; GC/ECD, gas chromatography/electron capture detection; GC/ElCD, gas chromatography/electrolytic conductivity detection

[b]Confirmation by extraction *p* values

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks old, were fed diets containing technical-grade sulfallate (purity, >90%; 7-14 minor components; analyses not performed) by various schedules. Males were fed 1000 mg/kg (low dose) or 2000 mg/kg (high dose) for 62 weeks and were then given the compound cyclically during 12 weeks, with a pattern of one dose-free week followed by four weeks of treatment (5 days/week). Subsequently the mice were observed for 13 weeks before they were killed. This dosage resulted in time-weighted average concentrations of 949 mg/kg of diet for the low-dose group and 1897 mg/kg for the high-dose group over a 78-week treatment period. Females were given 600 mg/kg (low dose) or 1200 mg/kg (high dose) for eight weeks; the dose was then increased to 1000 mg/kg (low dose) or 2000 mg/kg (high dose) and administered for 54 weeks; after this point, dietary exposure to sulfallate was the same as for the males. This dosage resulted in time-weighted average concentrations of 908 mg/kg of diet for the low-dose group or 1815 mg/kg for the high-dose group. Groups of 20 male and 20 female untreated controls were observed for 91 weeks. A dose-related depression in mean body weight was noted; and, among females, a significant ($p < 0.001$) positive association between dosage and mortality was also observed: By 75 weeks, 46/50 males at the high dose, 43/50 at the low dose and 16/20 of the controls were still alive; at that time, 22/50 females at the high dose, 37/50 at the low dose and 20/20 of the control mice were still alive. Mammary adenocarcinomas occurred in 0/20 controls, 33/48 low-dose females and 27/46 high-dose females, and some of these tumours metastasized to other sites. This incidence was statistically significantly different for the low- and high-dose groups when compared with the controls by the Fisher exact test ($p < 0.001$). Squamous-cell carcinomas of the skin or subcutaneous tissue occurred in a few low- and high-dose males and in a few low-dose females. Occasional papillomas or squamous-cell carcinomas of the forestomach were observed in low- and high-dose males and females. None of these types of tumours were observed in the controls, but in each instance the incidence was very low, ranging from 1-7%. Alveolar/bronchiolar adenomas occurred in 0/20 controls, 11/43 low-dose males, 9/45 high-dose males, 1/19 control females, 11/45 low-dose females and 2/37 high-dose females. Alveolar/bronchiolar carcinomas were observed in 0/20 control males, 3/43 low-dose males, 9/45 high-dose males, 0/19 control females, 4/45 low-dose females and 2/37 high-dose females. When the incidences of alveolar/bronchiolar adenoma and carcinoma in males were combined, the Cochran-Armitage test indicated a significant ($p = 0.004$) positive association betwen dosage and incidence. The Fisher exact test supported these findings, showing significant associations between both high dose ($p = 0.001$) and low dose ($p = 0.002$) and control. A statistically significant difference using the Fisher exact test was noted only for females given the low dose ($p = 0.032$) (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, six weeks old, were fed diets containing 250 mg/kg technical-grade sulfallate (purity, >90%; 7-14 minor components; analysis not performed) for a total of 78 weeks (low-dose groups) or 500 mg/kg for the first seven (females) and 11 weeks (males) (high-dose groups). The animals received these high doses for four weeks, followed by a dose-free week, over a total of 53-

56 weeks, resulting in time-weighted average concentrations of 404 mg/kg for females and 410 mg/kg for males. Animals were observed for 25-26 weeks after dosing. Groups of 50 male and 50 female untreated controls were observed for 111 weeks. A distinct dose-related depression in mean body weight was observed throughout the study, and, by the end, the high-dose females weighed almost a third less than the controls. By 90 weeks, 27/50 high-dose males, 37/50 low-dose males and 42/50 controls were still alive; at that time, 30/50 high-dose females, 43/50 low-dose females and 45/50 female controls were still alive. Squamous-cell carcinomas of the forestomach were seen in 0/46 of male controls, 0/30 low-dose males and 2/25 high-dose males; no papilloma of the forestomach was noted in the controls or in the low-dose group, but the high-dose group had an incidence of 3/25 papillomas. In addition, one papilloma and one squamous-cell carcinoma of the oesophagus were found in the high-dose group. Of the females, only 1/28 rats in the high-dose group had a squamous-cell carcinoma of the oesophagus and 2/35 a papilloma of the forestomach. When the incidences of squamous-cell carcinomas and papillomas of the forestomach in males were combined, the difference between the controls and the high-dose group was statistically significantly different by the Fisher exact test ($p = 0.004$). No significant difference was found for females. However, adenocarcinomas of the mammary gland were observed among females, in 0/50 controls, 7/50 low-dose and 11/48 high-dose rats, thus showing a dose-related trend. The incidence was statistically significantly different between the controls and the low-dose group ($p = 0.006$) and between the controls and the high-dose group ($p < 0.001$) by the Fisher exact test. Occasional (incidence, 2-4%) squamous-cell carcinomas of the integument and thyroid were noted in high-dose males and of the integument, thyroid and external ear in high-dose female rats (National Cancer Institute, 1978).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The acute oral LD_{50} of sulfallate in rats was 850 mg/kg bw. It is weakly irritating to the skin and eye (Worthing, 1979).

In the chronic feeding studies described in section 3.1, a dose-related increase in the incidence of toxic tubular nephropathy was observed in male rats and in mice of both sexes (National Cancer Institute, 1978).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

2-Chloroacrolein is formed from sulfallate when it is incubated with rat liver microsomes (Rosen *et al.*, 1980a).

Mutagenicity and other short-term tests

Sulfallate gave negative results in both the *Escherichia coli pol* and *Bacillus subtilis rec* differential killing tests in bacteria, in the absence of metabolic activation (Jones *et al.*, 1982; Waters *et al.*, 1982).

Although in early work in which metabolic activation was not used, no mutagenicity was observed in *Salmonella typhimurium* [strains unspecified] or T4 phage (Andersen *et al.*, 1972), other workers have detected mutagenicity in *S. typhimurium* strains TA1535 and TA100 (e.g., Bignami *et al.*, 1977). Some authors (De Lorenzo *et al.*, 1978; Sikka & Florczyk, 1978; Jones *et al.*, 1982; Waters *et al.*, 1982), using a technical- or analytical-grade preparation of sulfallate or 96-99% pure sulfallate, found that the presence of rat liver supernatant was absolutely necessary for mutagenicity; however, Carere *et al.* (1978) found a weak effect of high doses in its absence. Of 20 related compounds, only the three possessing the 2-chloroallyl group (including sulfallate) were mutagenic (De Lorenzo *et al.*, 1978). It has been suggested that rat liver supernatant converts sulfallate to 2-chloroacrolein, a potent directly acting mutagen (Rosen *et al.*, 1980a,b).

In contrast, neither mutagenicity nor toxicity was seen in the analogous *Escherichia coli* base-pair substitution strain WP2 *uvr*A, either with or without a microsomal supernatant fraction from Aroclor-induced rat liver (Jones *et al.*, 1982; Waters *et al.*, 1982).

Sulfallate [purity unspecified] was also mutagenic to *Aspergillus nidulans* (8-azaguanine resistance) (Bignami *et al.*, 1977, 1982) and *Streptomyces coelicolor* (streptomycin resistance) (Carere *et al.*, 1978) in the absence of exogenous metabolic activation. It is reported to be a powerful inducer of mitotic crossing over (Bignami *et al.*, 1977) in *Aspergillus* in the absence of exogenous metabolic activation. It was negative in the *Saccharomyces cerevisiae* D3 assay for enhanced mitotic recombination, in the presence or absence of an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

No unscheduled DNA synthesis was detected in human lymphocytes in short-term culture (Rocchi *et al.*, 1980) or in human EUE cells, using a scintillation counting technique, although a possible effect of 5×10^{-4} M ($p = 0.024$) was found with a more sensitive autoradiographic technique (Benigni *et al.*, 1982).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Sulfallate (technical grade) was tested for carcinogenicity in one strain of mice and in one strain of rats by administration in the diet. It was carcinogenic in mice, inducing mammary gland tumours in females and lung tumours in males. It was also carcinogenic

in rats, inducing mammary gland tumours in females and benign and malignant tumours of the forestomach in males.

No data were available to evaluate the teratogenicity of sulfallate to experimental animals.

Sulfallate was mutagenic to *Salmonella typhimurium* in the presence of exogenous metabolic activation and to *Aspergillus* and *Streptomyces* but not to *Saccharomyces cerevisiae* with or without metabolic activation. There is sufficient evidence for the mutagenicity of sulfallate in bacterial systems but insufficient evidence for its mutagenicity in mammalian cells or in mammals.

4.2 Human data

Sulfallate was introduced in 1954. Its production and use as a herbicide in agricultural applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of sulfallate in humans.

No case report or epidemiological study of the carcinogenicity of sulfallate alone was available to the Working Group. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

No data on humans were available.

There is *sufficient evidence*[2] that sulfallate is carcinogenic to experimental animals.

5. References

Andersen, K.J., Leighty, E.G. & Takahashi, M.T. (1972) Evaluation of herbicides for possible mutagenic properties. *J. agric. Food Chem.*, *20*, 649-656

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization* (*EPA-600/2/78-004d*), Washington DC, US Environmental Protection Agency, p. 134

---

[1] This evaluation should be read in conjunction with p. 18 of the preamble.

[2] In the absence of data on humans, sulfallate should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

Benigni, R., Dogliotti, E., Falcone, E. & Calcagnile, A. (1982) DNA repair studies on diallate, triallate and sulfallate in human cell cultures. *Mutat. Res.*, *103*, 385-390

Bignami, M., Cardamone, G., Comba, P., Ortali, V.A., Morpurgo, G. & Carere, A. (1977) Relationship between chemical structure and mutagenic activity in some pesticides: The use of *Salmonella typhimurium* and *Aspergillus nidulans* (Abstract no. 79). *Mutat. Res.*, *46*, 243-244

Bignami, M., Cardamone, G., Carere, A., Comba, P., Dogliotti, E., Morpurgo, G. & Ortali, V.A. (1982) Mutagenicity of chemicals of industrial and agricultural relevance in *Salmonella*, *Streptomyces* and *Aspergillus*. *Chem.-biol. Interactions* (in press)

Carere, A., Ortali, V.A., Cardamone, G. & Morpurgo, G. (1978) Mutagenicity of dichlorvos and other structurally related pesticides in *Salmonella* and *Streptomyces*. *Chem.-biol. Interactions*, *22*, 297-308

Conkin, R.A. & Gleason, L.S. (1964) *Vegadex*. In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. IV, New York, Academic Press, pp. 251-257

De Lorenzo, F., Staiano, N., Silengo, L. & Cortese, R. (1978) Mutagenicity of diallate, sulfallate, and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture. *Cancer Res.*, *38*, 13-15

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

National Cancer Institute (1978) *Bioassay of Sulfallate for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 115; DHEW Publ. No. (NIH) 78-1370*), Washington DC

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Rocchi, P., Perocco, P., Alberghini, W., Fini, A. & Prodi, G. (1980) Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. *Arch. Toxicol.*, *45*, 101-108

Rosen, J.D., Schuphan, I., Segall, Y. & Casida, J.E. (1980a) Mechanism for the mutagenic activation of the herbicide sulfallate. *J. agric. Food Chem.*, *28*, 880-881

Rosen, J.D., Segall, Y. & Casida, J.E. (1980b) Mutagenic potency of haloacroleins and related compounds. *Mutat. Res.*, *78*, 113-119

Sikka, H.C. & Florczyk, P. (1978) Mutagenic activity of thiocarbamate herbicides in *Salmonella typhimurium*. *J. agric. Food Chem.*, *26*, 146-148

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976, Agricultural Economic Report No. 418*, Washington DC, p. 10

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 180.274, p. 577

US Tariff Commission (1956) *Synthetic Organic Chemicals, US Production and Sales, 1955 (Report No. 198, Second Series)*, Washington DC, US Government Printing Office, p. 138

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity*. In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, sect. 8A; 12C

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 483

Zweig, G. & Sherma, J. (1972) *Vegadex*. In: Zweig, G., ed., *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, New York, Academic Press, pp. 704-707

FUNGICIDES

CAPTAN

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 133-06-2

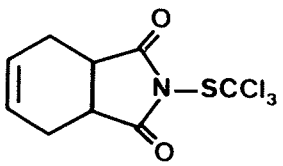
Chem. Abstr. Name: 1*H*-Isoindole-1,3(2*H*)-dione, 3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-

IUPAC Systematic Name: 1,2,3,6-Tetrahydro-*N*-(trichloromethylthio-phthalimide

Synonyms: Captane; ENT 26538; 3a,4,7,7a-tetrahydro-*N*-(trichloromethanesulphenyl)phthalimide; *N*-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide; *N*-trichloromethylmercapto-tetrahydrophthalimide; *N*-(trichloromethylmercapto)-Δ^4-tetrahydrophthalimide; *cis*-*N*-[(trichloromethyl)thio]-4-cyclohexene-1,2-dicarboximide: *N*-[(trichloromethyl)thio]-4-cyclohexene-1,2-dicarboximide; *N*-(trichloromethylthio)-cyclohex-4-ene-1,2-dicarboximide; *N*-trichloromethylthiocyclohex-4-ene-1,2-dicarboxyimide; *N*-[(trichloromethyl)thio]tetrahydrophthalimide; *N*-[(trichloromethyl)thio]-Δ(4)-tetrahydrophthalimide; *N*-trichloromethylthio-3a,4,7,7a-tetrahydrophthalimide

Trade Names: Aacaptan; Agrosol S; Agrox 2-Way and 3-Way; Amercide; Bangton; Bean Seed Protectant; Captaf, Captan 50W; Captan-Streptomycin 7.5-0.1 Potato Seed Piece Protectant; Captex; Esso Fungicide 406; Flit 406; Fungus Ban Type II; Glyodex 37-22; Granox PFM; Gustafson Captan 30-DD; Hexacap; Isotox Seed Treater "D" and "F"; Kaptan; Malipur; Merpan; Micro-Check 12; Neracid; Orthocide; Orthocide 7.5, 50, 75 & 83; Osocide; SR 406; Stauffer Captan; Vancide P-75, 89 and 89 RE; Vangard K; Vanguard K; Vanicide; Vondcaptan

1.2 Structural and molecular formulae and molecular weight



$C_9H_8Cl_3NO_2S$ Mol. wt: 300.6

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 178°C (decomposes)

(*c*) *Density*: 1.74 (Weast, 1977)

(*d*) *Spectroscopy data*: Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*e*) *Solubility*: Very slightly soluble in water (3.3 mg/l at 25°C); soluble at 25°C in acetone (21 g/kg), chloroform (70 g/kg), cyclohexanone (23 g/kg), isopropanol (1.7 g/kg) and xylene (20 g/kg); insoluble in petroleum oils

(*f*) *Volatility*: Vapour pressure, $<1 \times 10^{-5}$ mm Hg at 25°C

(*g*) *Stability*: Rapidly hydrolysed in water (half-life is a matter of hours) to 4-cyclohexene-1,2-dicarboximide, carbon dioxide, hydrochloric acid and sulphur (Consultative Committee on Industrial Bio-Test Pesticides, 1982). Decomposes at or near its melting-point

1.4 Technical products and impurities

Technical captan is a colourless-to-beige amorphous solid with a pungent odour; it is 90-95% pure and has a melting-point of 160-170°C (Worthing, 1979). One sample of technical-grade captan was 96% pure, with the remainder consisting of sodium chloride, water and tetrahydrophthalimide (FAO/WHO, 1970).

Captan is available as 50, 80 and 83% active water-dispersible powders, 5 and 10% active dusts, 60-75% active dusts for seed treatment, and combinations with other fungicides or insecticides (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Synthesis of captan was first reported in 1949 (Consultative Committee on Industrial Bio-Test Pesticides, 1982). It is made commercially by the reaction of perchloromethyl-mercaptan with tetrahydrophthalimide in the presence of sodium hydroxide (US Environmental Protection Agency, 1975).

Captan was first produced commercially in the US in 1951 (US Tariff Commission, 1952). Two US companies presently produce it in a unit which they operate jointly. Data on annual production are not published, but production in 1972 was estimated to have been 7.7 million kg (US Environmental Protection Agency, 1975); the production of one of the two companies in 1977 was in the range of 4.54-22.7 million kg (NIH/EPA Chemical Information System, 1982). Total production in 1978 is estimated to have been approximately 6 million kg. Imports of captan through the principal US customs districts amounted to 60 thousand kg in 1980 (US International Trade Commission, 1981). Separate data on US exports are not available.

This compound is believed to be produced by one company in France and by one company each in Israel, Mexico and South Korea. It is not produced commercially in Japan; imports totalled 785 thousand kg in 1980 and 335 thousand kg in 1976.

(*b*) *Use*

Captan is used principally as an agricultural fungicide on food crops and plant seeds, although it also finds use as a fungicide in nonagricultural applications and as a preservative in cosmetics.

In 1975, captan was registered and recommended in the US for use on more than 80 crops. Tolerances for residues on 67 raw agricultural commodities ranged from 2-100 mg/kg (US Environmental Protection Agency, 1975). More recently, the US Environmental Protection Agency (1980a) reported that there were approximately 600 federally-registered pesticide products containing captan, 100 applications were pending for federal registration of state-registered products, and 33 other products had been registered in states. Preliminary data reported for usage of captan in US agriculture in 1978-1979 are shown in Table 1.

Nonagricultural (industrial) usage, estimated on the basis of a telephone survey done by the US Environmental Protection Agency (1980a) in the autumn of 1979 and on data available from industry, was as follows (thousand kg/year): 22.7-68.1 in pastes, principally for wallpaper; 4.5-22.7 in paint for greenhouses, medical facilities, food-packaging, plants, etc; 22.7-68.1 in textiles such as vinyl-coated fabrics, vinyl car roofs and synthetic turf; <0.45 in lacquers, in paper and in rubber stabilizers; and 0.45-4.5 in plasticizers, in polyethylene (used for garbage bags and pond liners) and in vinyl resins used as precursors of vinyl.

Although captan has reportedly been used as a plant regulator on citrus fruit, no evidence was found that it is currently used for this purpose in the US.

Captan has been reported to be present as a preservative in 15 of the 82 cosmetic product categories included in the US Food and Drug Administration (1981) programme. The level of captan in the 36 products in these 15 categories ranged from <0.1% to 1%. It was found most frequently in non-colouring hair conditioners (14 products contained captan) and in non-colouring shampoos (three products).

In Japan, captan is widely used as a fungicide on fruits, vegetables and flowers. In Canada, about 300 thousand kg captan are used annually, with 82% on leaves and fruit, 10% for seed treatment, 5% for home and garden uses and 3% for nonagricultural applications. Annual usage of captan in Sweden in 1980 and 1981 was 27 thousand kg. About 13 million kg of captan are used annually throught the world (Consultative Committee on Industrial Bio-Test Pesticides, 1982).

Table 1. Use of captan in US agriculture, 1978-1979

Crop	Active ingredient applied (thousand kg/year)
Pome fruits	
Apples	1124-1144
Pears	9-26
Stone fruits	
Cherries	26-70
Peaches/nectarines, apricots	298-343
Plums/prunes	27-71
Other fruits and nuts	
Almonds	351-419
Grapes	282-294
Lemons/limes	44-57
Strawberries	95-106
Seed treatments	
Corn (field)	500-506
Corn (sweet)	0.4-0.5
Cotton	155-157
Potatoes	366-504
All other field crops	313-329
All other vegetables	130-150
Vegetables	
Lettuce	9-36
Tomatoes	19-46
Other vegetables	16-38
Commercial greenhouses and ornamental plants	20-23
All other agricultural uses (including post-harvest)	20-23
Home and garden	48-73
Total	3856-4417

The Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues in November 1978 established an acceptable daily intake of captan for humans of 0-0.1 mg/kg bw (FAO, 1979).

In 1969, that Group recommended the following tolerances for residues of captan on commodities (mg/kg): apples and cherries, 40; pears, 30; apricots, 20; citrus fruits, peaches, plums, rhubarb and tomatoes, 15; strawberries, cranberries, raspberries, cucumbers, lettuce, green beans and peppers, 10; and raisins (dried vine fruits), 5 (WHO, 1970). In 1977, the Joint Meeting recommended a maximum residue limit on apples and pears of 25 mg/kg (FAO, 1978). In 1978, they recommended a maximum residue limit on potatoes of 0.1 mg/kg (FAO, 1979).

The Council of the European Communities has fixed a maximum acceptable level for residues of captan in and on fruit and vegetables at 15 mg/kg (Commission of the European Communities, 1976). In 1981, a proposal was submitted to amend the Council Directive and to fix maximum levels for captan residues at 20 mg/kg in strawberries, apricots and cherries; 10 mg/kg in cucumbers, green beans, lettuce, peppers and raspberries; and 15 mg/kg in other products (Commission of the European Communities, 1982).

The US Environmental Protection Agency (1980a) reported that tolerances had been established for captan residues in or on 62 raw agricultural commodities at levels ranging from 0.25-100 mg/kg. Tolerances had also been established at levels from 2-100 mg/kg for the transmission of captan residues to meat, milk, and eggs from feeding cattle or poultry with 11 captan-treated products or their by-products. At the same time, that Agency issued a rebuttable presumption against registration (RPAR) and continued registration of all pesticide products containing captan. This action was based on a finding that such products exceed the risk criteria relating to oncogenicity and mutagenicity.

Captan is approved in the US as a component of paper and paperboard as a mould- and mildew-proofing agent in coatings intended for contact with certain types of foods (US Food & Drug Administration, 1980).

Use of captan by amateurs in homes and gardens and all use on various berries was banned in Sweden in December 1981. It may still be used by professionals on a variety of fruits, seeds and trees (Consultative Committee on Industrial Bio-Test Pesticides, 1982).

Permissible levels of captan in the working environment have been established in at least five countries by regulation or recommended guidelines. These standards are listed in Table 2.

The US Environmental Protection Agency (1980b) effluent guidelines and standards require that the average daily effluent value of all regulated organic active ingredients manufactured at a captan production plant for 30 consecutive days not exceed 0.0018 kg/1000 kg of organic pesticide chemical.

Table 2. National occupational exposure limits for captan[a]

Country	Year	Air concentration (mg/m^3)	Interpretation[b]	Status
Australia	1978	5	Ceiling	Guideline
Belgium	1978	5	Ceiling	Regulation
The Netherlands	1978	5	Ceiling	Guideline
Switzerland	1978	5	TWA	Regulation
US	1981	5[c,d]	TWA	Guideline
		15	STEL	Guideline

[a]From International Labour Office (1980)
[b]TWA - time-weighted average; STEL-short-term exposure limit
[c]From American Conference of Governmental Industrial Hygienists (1981)
[d]The ACGIH guideline is used in the US for both agricultural and nonagricultural workers.

In Canada, the maximum residue limit in a wide variety of fruits and vegetables is currently 25 or 40 mg/kg; for certain vegetables, a maximum of 2 mg/kg is allowed (Department of National Health & Welfare, 1980). In May 1982, it was proposed to reduce the limits of 25 and 40 mg/kg on 12 fruits to 5 mg/kg (Department of National Health & Welfare, 1982).

2.2 Occurrence

(*a*) *Natural occurrence*

Captan is not reported to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to captan, nor were separate data available on the numbers of workers exposed in the two nonagricultural activities most likely to involve exposure to captan, namely, its production and formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that 50 thousand US workers in 15 nonagricultural industries were exposed to captan, including horticultural services, canning of fruits and vegetables, fabrication of rubber products and manufacture of surgical appliances and supplies.

Blenders and packers in a plant producing captan in Ontario, Canada, were exposed to pesticide dust in the air at levels of 2.54-5.15 mg/m^3. Air dust concentrations of 0.87-2.59 mg/m^3 were reported in a plant producing gammasant, a seed-treatment fungicide mixture which contains 10% captan, 50% lindane and 6% benomyl (Elguindi & Rajhans, 1979). Captan was detected at a level of 0.01 mg/m^3 in one of eight air samples taken from the seed treatment areas of a wholesale seed-producing plant in California, USA; it was not detected (<0.1 μg/m^3) in 10 air samples taken from other areas of the plant (Okawa & Bodner, 1973).

Potential hourly exposure rates of US workers involved in various aspects of planting treated seed potatoes were calculated to be 0.33-15 mg/hour (dermal) and 0.027-1.7 mg/hour (respiratory) (Stevens & Davis, 1981).

Exposure to captan during orchard spraying operations has been studied in Michigan, USA, where respiratory exposure levels of 0.8-9.4 μg/min for mixers and 0.07-0.66 μg/min for sprayers were detected (Oudbier *et al.*, 1974). In a similar report of farm workers in Maryland, USA, respiratory exposures averaged 0.032 mg/hour (maximum, 0.08 mg/hour) for tractor drivers and sprayer operators; and the average dermal exposure was calculated to be 1.96 mg/person per hour (maximum, 3.3 mg/person per hour), based on an assumed exposed area of 0.294 m^3 when no protective clothing was worn (Hansen *et al.*, 1978).

Air emissions during captan manufacture have been reported to include 0.066 kg captan particulate per 1000 kg of pesticide produced (Archer *et al.*, 1978).

(*c*) *Water and sediments*

No captan was found in liquid effluents discharged from one US plant producing it (Lawless *et al.*, 1972).

(*d*) *Soil and plants*

Studies monitoring for captan in soil and seeds have been reviewed (US Environmental Protection Agency, 1975). It was detected in the soils of vegetable patches in Japan (Mishima *et al.*, 1979).

(*e*) *Food, beverages and animal feeds*

Studies monitoring for captan in crops and seeds have been reviewed (US Environmental Protection Agency, 1975).

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration, captan was detected in food composites from 20-32 cities during the years 1971-1976. In 1971-1972 and 1975-1976, captan was found in fruits at levels in the range of trace-0.040 mg/kg; in 1973-1974, it was detected in oils, fats and shortening at a level of 0.178 mg/kg (Manske & Johnson, 1975, 1977; Johnson *et al.*, 1981). The highest dietary exposure to captan has been estimated to be 0.117 mg/kg bw (7.01 mg/1.5 kg diet per day) (US Environmental Protection Agency, 1980).

In a total diet study of food composites from five Canadian geographical regions in 1976-1978, captan residues were detected in fruits at levels of 0.8-1.5 μg/person (expressed as daily intake) and the average dietary intake of captan by Canadians was calculated to be 0.004 μg/kg bw. In the Vancouver, British Columbia, area, an average intake of 0.024 μg/kg bw captan was reported in 1970. Fruits from Halifax, Nova Scotia, Montreal, Quebec and Toronto, Ontario were found to contain 10 μg/kg captan, while fruits from Winnipeg, Manitoba contained 20 μg/kg captan (McLeod *et al.*, 1980).

Captan was detected in a study of nonpurified extracts of fruits, vegetables and mushrooms in Poland at levels of 0.1-0.5 mg/kg (Zadrozinska, 1979). In a study in Sweden of imported and Swedish grapes, strawberries and apples for fungicide residues in 1974-1975, captan residues were found in none of the eight grape samples, in four of 50 Swedish strawberry samples, in 10 of 39 imported strawberry samples, in 25 of 56 Swedish apple samples, and in four of 30 imported apple samples (Johansson, 1976). The total mean captan residue in strawberries in Belgium was 3.09 mg/kg, with 44.9 mg/kg in the sepals and 1.49 mg/kg in the berries (Dejonckheere *et al.*, 1980).

Captan was detected in two of 10 cucumber samples produced in Shimane Prefecture, Japan, at levels of 0.034-0.065 mg/kg (Takeshita *et al.*, 1976); it was not found in any sample of tomatoes, cucumbers, strawberries, spinach, cabbage, apples, pears and peaches marketed in Tokyo (Koseki *et al.*, 1980).

(*f*) *Other*

Process wastes and losses from captan manufacture are reported to include approximately 1.8 kg/day of captan as particulates; disposal methods for this discharge were not reported (Lawless *et al.*, 1972).

2.3 Analysis

Standard methods used for the analysis of captan in a variety of matrices are listed in Table 3.

Table 3. Methods for analysis of captan

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract (methanol/acetone); reflux (sodium hydroxide)	Titration	not given	Ospenson *et al.* (1964); US Environmental Protection Agency (1976)
	Extract (dioxane)	GC/TCD or GC/FID	not given	Horwitz (1980)
	Extract (dichloromethane)	HPLC/UV	not given	Association of Official Analytical Chemists (1980); Carlstrom (1980)
	Extract (chloroform); dry (sodium sulphate)	IR spectroscopy	not given	US Environmental Protection Agency (1976)
Fruits and vegetables	Extract (acetonitrile); partition (dichloromethane/petroleum ether); chromatograph (Florisil)	GC/ECD	0.1-2 mg/kg	Zweig & Sherma (1972); Markus & Puma (1973)
Fruits, treated seeds and soil	Extract (solvent specific to matrix); decolourize; react with pyridine/tetra-ethylammonium hydroxide	Colorimetry	50 mg/kg	Ospenson *et al.* (1964)
Fruits and vegetables, milk, meat, fat, blood and biological fluids	Extract and partition (solvent specific to matrix); dissolve (benzene); react with hot resorcinol/acetic acid	Colorimetry	10 mg/kg	Ospenson *et al.* (1964); Horwitz (1980)
Human or animal adipose tissue	Macerate (sand); extract (petroleum ether, acetonitrile); partition (petroleum ether); chromatograph (Florisil)	GC/ECD[b]	not given	Watts (1980)
Water	Extract (dichloromethane); concentrate; chromatograph (deactivated silica gel)	GC/ECD[b]	6 µg/l	Watts (1980)

[a]Abbreviations: GC/TCD, gas chromatography/thermal conductivity detection; GC/FID, gas chromatography/flame ionization detection; HPLC/UV, high-performance liquid chromatography/ultra-violet absorbance detection; IR spectroscopy, infra-red spectroscopy; GC/ECD, gas chromatography/electron capture detection

[b]Confirmation by thin-layer chromatography

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 mice were treated with captan [technical grade; impurities unspecified] as follows: at the age of seven days, they received a single dose of 215 mg/kg bw captan in 0.5% gelatine by gavage. Without taking into account subsequent weight gains, this treatment was repeated daily until the animals were weaned at the age of four weeks. Then captan was fed in the diet, at a final concentration of 560 mg/kg, until the end of the experiment at 18 months. [The dose was the maximum tolerated dose for infant and young mice, but not necessarily that for adults.] Appropriate negative (vehicle and untreated) and positive (using six known carcinogens) controls were also included in the study. No significant increase in tumour incidence was seen (National Technical Information Service, 1968; Innes *et al.*, 1969).

Groups of 50 male and 50 female weanling B6C3F_1 mice were fed diets containing captan (pure on the basis of gas chromatographic analysis), to give final concentrations of 8000 (low dose) or 16 000 (high dose) mg/kg of diet, for 80 weeks. The animals were observed for a further 11 weeks. Ten mice of each sex served as controls and received a diet with 2% corn oil during the entire 91-week duration of the study; 80 additional mice of each sex, used as pooled controls in other bioassays run concurrently at the same testing facility, were also included in the evaluation. A positive dose-related trend in the incidence of duodenal adenocarcinoma was revealed by the Cochran-Armitage test in animals of both sexes; in males, 0/68 pooled controls, 1/43 low-dose, and 3/46 high-dose animals ($p = 0.033$); in females, 0/68 pooled controls, 0/49 low-dose and 3/48 high-dose animals ($p = 0.022$). The combined incidence of duodenal tumours (adenocarcinomas and adenomatous polyps) in male mice receiving the high dose was significantly elevated as revealed by the Fisher exact test: 0/68 pooled controls, 5/46 treated ($p = 0.009$). No statistical significance was seen with the Fisher exact test in the incidences of tumours in females at either dose level or in males maintained on the low-dose diet, nor in any group in the incidence of duodenal adenocarcinomas without adenomatous polyps (National Cancer Institute, 1977).

Rat: Groups of 50 male and 50 female weanling Osborne-Mendel rats were fed diets containing captan (pure on the basis of gas chromatographic analysis). Since satisfactorily tolerable dose levels could not be established beforehand, the concentration of captan in the feed was changed repeatedly or entirely new groups were started during the course of the study. There were two exposure levels: low-dose groups were maintained on feed containing 4000 mg/kg of diet for 21 weeks and 2000 mg/kg for the subsequent 59 weeks; high-dose groups were fed dietary concentrations of 8000 mg/kg of diet for 41 weeks and 4000 mg/kg for the following 39 weeks. During the remaining 33-34 weeks of the study, basal diet without captan was fed. Groups of 10 control animals of each sex received the basal diet during the entire assay period of 114 weeks; 75 additional rats of each sex, used as controls in other bioassays run concurrently at the same testing facility, were also included in the evaluation of this study as pooled controls. Survival rate was considered adequate for a meaningful evaluation. No statistically significant difference in tumour incidence was found by the Fisher exact test. In female

rats only, the Cochran-Armitage test revealed a positive dose-related trend in the incidence of C-cell adenomas of the thyroid gland (pooled control, 1/66; low dose, 1/49; high dose, 4/44; p = 0.035) and of the combined incidence of adrenocortical adenomas and carcinomas (pooled control, 0/64; low dose, 2/50; high dose, 3/47; p = 0.047) (National Cancer Institute, 1977). [The Working Group noted the short duration of treatment. In agreement with the authors of the report, the Working Group concluded that the tumours in the thyroid glands and the adrenals were apparently not related to the treatment.]

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 1000 mg/kg bw technical captan [impurities unspecified] in 0.5% gelatin on the 28th day of life and were observed until they were about 78 weeks of age, at which time 15, 17, 16 and 17 mice were still alive in the four groups, respectively. A group of negative controls comprised untreated animals and animals treated with gelatin, corn oil or dimethyl sulphoxide. No increased incidence of tumours was observed (National Technical Information Service, 1968). [The Working Group noted that a negative result obtained following a single s.c. injection is not an adequate basis for discounting carcinogenicity.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The oral and i.p. LD_{50}s of captan in Swiss-Webster mice are about 7500 and 500 mg/kg bw, respectively; the two-hour inhalational LC_{50} is 1.7-3.7 mg/l [about 300 mg/kg bw] (Stevens *et al.*, 1978). The oral and i.p. LD_{50}s in rats range from 8400 to 15 000 mg/kg bw and from 25 to 100 mg/kg bw, respectively (Spector, 1956; Ben-Dyke *et al.*, 1970; Alnot *et al.*, 1974).

An i.p. LD_{50} dose of captan to Wistar rats caused fibrinous peritonitis and lesions in the small intestine, lung, liver and kidney (Alnot *et al.*, 1974). Toxic signs, evident within two to three days after oral administration to rats, included vasodilatation, loss of organ weight and meningocerebral congestion (Boyd & Krijnen, 1968).

Rats fed a low-protein diet were reported to be much more sensitive to the acute oral toxicity (LD_{50} = 480 mg/kg bw) of captan than rats receiving a normal diet (LD_{50} = 12 500 mg/kg bw) (Boyd & Krijnen, 1968).

Effects on reproduction and prenatal toxicity

[A number of studies on the teratogenicity of captan were available, but since questions have been raised concerning the validity of the data reported, the Working Group chose not to include them among the studies evaluated.]

It was reported in an abstract that no malformation was observed in term foetuses of CD-1 mice following daily oral or s.c. administration of 100 mg/kg bw captan [purity

unspecified] on days 6-15 of pregnancy or following inhalation (by whole-body exposure to air containing 488 mg/m^3 per hour; <5 μm particle size) for four hours per day on days 6-13 of pregnancy (Courtney *et al.*, 1978).

Male DBA/2J mice, treated by gavage with 50 or 100 mg/kg bw per day for five days [purity unspecified], were each placed with two untreated females of the same strain for three weeks, and the females were allowed to litter. The latter, when adult, were bred across litters but within each experimental group to produce two litters, F_{2a} and F_{2b}. Reductions in pup survival between birth and four days of age were seen in F_1 and F_{2a}, and reductions in weaning weight occurred in F_{2a} in the 100 mg/kg bw group. The number of liveborn and the average weaning weight were decreased in F_1 of both the 50 and 100 mg/kg bw groups. Litter size per pregnancy and the number of pup survivors at weaning were not affected (Collins, 1972b).

Captan (90.5% pure) dissolved in olive oil was injected as a single i.p. dose of 25 mg/kg bw on day 6 or 7 of pregnancy to eight Wistar rats and on day 13 or 14 of pregnancy to six Wistar rats. Half of the dams died with acute peritonitis and ascites, and the rest were killed at term. There was an increased number of resorptions and a decreased mean foetal weight; of 40 foetuses, two were deformed: one had shortened forelimbs and the other had a cleft palate. None of the 80 control foetuses was deformed (Alnot *et al.*, 1974). [It is not clear whether the embryonal and foetal effects resulted directly from administration of captan or were due to maternal toxicity.]

Technical-grade captan suspended in carboxymethylcellulose was administered in total doses ranging from 200-2500 mg/kg bw to 2-10 hamsters per group, either as a single treatment on day 7 or 8 of pregnancy or once daily on days 6-10 of pregnancy. Doses tolerated by the mothers - up to 400 mg/kg bw by a single treatment and 1000 mg/kg bw in a five-day treatment - caused foetal mortality and weight reduction but no teratogenicity. A single treatment with doses of 600, 750 or 1000 mg/kg bw killed some dams; foetuses from the surviving dams showed anomalies, including exencephaly and fused ribs (Robens, 1970).

Doses of 37.5, 75 or 150 mg/kg bw per day captan [purity not specified] were administered in gelatin capsules on days 6-16 of pregnancy to New Zealand white rabbits. Nine malformed foetuses were observed from 75 implantations of nine pregnant dams that received 75 mg/kg bw, and one malformed foetus from 49 implantations of six dams that received 37.5 mg/kg bw (McLaughlin *et al.*, 1969). [No mention was made of whether malformations occurred in the concurrent controls.]

Absorption, distribution, excretion and metabolism

After an oral dose to rats of ^{35}S-captan, more than 90% of the radioactivity was excreted in the faeces and urine within 24 hours, and almost 100% within three days; 0.01-0.05% of the radioactivity was detected in organs or incorporated in proteins and nucleic acids (Seidler *et al.*, 1971). Following oral administration of 100 mg/kg bw ^{14}C-captan to rats, 50% of the radioactivity was excreted within nine hours; 50% excretion of an i.p. dose (20 mg/kg bw) was not achieved until two days after injection; 80-90% of the oral dose was excreted within 96 hours in the faeces (16%), urine (52%) and expired air (23%) (DeBaun *et al.*, 1974).

Degradation in the gut appears to play a major role in the metabolism of captan. The toxic metabolite thiophosgene is produced from the trichloromethylthio moiety of the

molecule in the presence of cellular thiol compounds. It is further metabolized to thiazolidine-2-thione-4-carboxylic acid, which is excreted in the urine of orally dosed rats; carbon dioxide is also a product of the metabolism of thiophosgene with the intermediate formation of carbonyl sulphide (23% of the administered radiocarbon is expired as $^{14}CO_2$). Thiophosgene is also detoxified by sulphites present in the gut and is excreted in the urine of orally dosed rats to yield dithiobis(methanesulphonic acid) and its disulphide monooxide derivative (DeBaun *et al.*, 1974).

Captan is metabolized *in vitro* by liver mixed-function oxidases to carbonyl sulphide, suggesting a pathway similar to that which occurs *in vivo*. A single oral dose to rats inhibited aniline hydroxylase activity and decreased the level of cytochrome P-450 in liver microsomes (Peeples & Dalvi, 1978).

Mutagenicity and other related short-term tests

The mutagenicity of captan has been reviewed (Bridges, 1975; US Environmental Protection Agency, 1980a).

Captan alkylates DNA at the N^7-position of guanine, producing 7-(trichloromethylsulphenyl)guanine (Bridges, 1975).

Positive results have been obtained in growth inhibition assays using the following DNA repair-deficient bacteria: *Escherichia coli* WP2 *uvrA* and WP2 *uvrA exrA* (Bridges *et al.*, 1972), *E. coli* WP2 (Bridges *et al.*, 1973), *Bacillus subtilis* H17 *rec*$^+$ and M45 *rec*$^-$ (Shirasu *et al.*, 1976; Waters *et al.*, 1982) and *E. coli pol A*$^+$ and *pol A*$^-$ (Waters *et al.*, 1982; Rosenkranz & Leifer, 1980).

Captan induced reverse mutations in *Salmonella typhimurium* strains TA100 and TA1535 (McCann *et al.*, 1975; Marshall *et al.*, 1976; Shirasu *et al.*, 1976; Simmon *et al.*, 1977; Carere *et al.*, 1978), TA98, TA1537 and TA1538 (McCann *et al.*, 1975; Marshall *et al.*, 1976; Jones *et al.*, 1982) in the absence of metabolic activation. Addition of Aroclor- or benzo[*a*]pyrene-induced rat liver microsome preparations in the *Salmonella* test resulted in total or partial suppression of mutagenic activity (Marshall *et al.*, 1976; Ficsor *et al.*, 1977; De Flora, 1978), while pretreatment of the compound with human gastric juice has been reported to enhance mutagenicity (De Flora & Boido, 1980). In another study, the mutagenic activity of captan in *S. typhimurium* strain TA1950 was significantly decreased by pretreatment with human or rat blood, while only weak inactivation was seen with rat plasma. A possible role of red-blood cell glutathione in the inactivation of captan was proposed (Ficsor *et al.*, 1977).

Captan has been reported to induce reverse mutations in *E. coli* WP *uvrA*, WP2 and SD4-73 (Legator *et al.*, 1969; Nagy *et al.*, 1975; Shirasu *et al.*, 1976; Simmon *et al.*, 1977; Waters *et al.*, 1982) and forward mutations to colicin E2 and streptomycin resistance in *E. coli* WP2 and in *Streptomyces coelicolor*, respectively (Bridges *et al.*, 1973; Carere *et al.*, 1978). Evidence has been produced that there is a volatile degradation product of captan that also possesses mutagenic activity and which differs from captan in being independent of the error-prone repair systems in *E. coli* (Bridges *et al.*, 1972).

Captan was negative in a host-mediated assay using *S. typhimurium his* G46 as the indicator organism (Legator, 1970; Kennedy *et al.*, 1975). A different experimental procedure, in which more bacteria were collected, resulted in a significant increase in the number of reverse mutations in *S. typhimurium his* G46 and *Serratia marcescens* a21

leu after s.c. injection of 500 mg/kg bw captan to NMRI mice (Buselmaier *et al.*, 1972, 1973). However, Ficsor *et al.* (1977) failed to detect any mutagenic effect in *S. typhimurium* in three host-mediated assays: (1) after three hourly s.c. injections of 500 mg/kg bw or after a single 1000 mg/kg bw oral dose in Upjohn Swiss albino mice with strain *his* G46; (2) after a single 2000 mg/kg bw oral dose in Upjohn Sprague-Dawley rats with strain TA1950; and (3) in fluid (urine and blood)-mediated assays after a single oral dose of 250 mg/kg bw in mice with strain *his* G46, and in blood after a single 1000 mg/kg bw i.p. injection or a 2000 mg/kg bw oral dose in rats with strain TA1950. Pockets of undissolved captan were visible at s.c. injection sites [which could explain the failure to duplicate Buselmaier's results].

Captan induced forward mutations in the ad-3 region of *Neurospora crassa* (Bridges, 1975).

Purified captan induced forward mutations to 8-azaguanine resistance and mitotic crossing-over, but not mitotic non-disjunction, in *Aspergillus nidulans* (Bignami *et al.*, 1977). Mitotic gene conversion has been observed (de Bertoldi *et al.*, 1980). It was reported in an abstract that induction of forward mutations to methionine independence in *Aspergillus* was suppressed by rat liver microsome preparations (Kappas & Demopoulos, 1981).

Captan [purity unspecified] induced mitotic gene conversion in strain D4 of *Saccharomyces cerevisiae*, but activity was abolished in the presence of a mouse liver microsomal preparation (Siebert *et al.*, 1970; de Bertoldi *et al.*, 1980). Mitotic recombination was also observed in strain D3 of *S. cerevisiae*; addition of an Aroclor-induced rat liver microsomal preparation reduced the mutagenic activity (Simmon *et al.*, 1977).

Captan (pure and 83% pure commercial formulate) administered to *Drosophila melanogaster*, as a single injection (up to 1 mg/ml) to adult males or by feeding (up to 1% in the culture medium) to larvae, did not significantly increase complete and mosaic sex-linked lethal mutations, II and III translocations or dominant lethal mutations, although a very weak effect in inducing recessive lethals was not excluded (Kramers & Knaap, 1973). Negative results in a sex-linked recessive test were also obtained following administration by injection (99.5% pure) or by topical application (Mollet, 1973). A weak positive response in the sex-linked recessive lethal test was reported with addition of 2000 mg/l captan [technical grade, purity unspecified] to the feeding solution (Valencia, 1977; Waters *et al.*, 1980).

Concentrations of up to 10 µg/ml captan (recrystallized commercial formulate 'Orthocide') failed to induce an absolute increase in forward mutations to 8-azaguanine resistance in V79 Chinese hamster cells, although an increased frequency of mutations per surviving cell was noted; a clear positive effect was observed, however, for the induction of ouabain-resistant mutants. Mutagenic activity was abolished in the presence of foetal calf serum. Exposure to captan in the vapour phase also led to an absolute increase in the number of 8-azaguanine- and ouabain-resistant mutants (Arlett *et al.*, 1975). Thioguanine resistance has been induced in CHO-K_1-BH_4 cells by captan [details not given] (Hsie *et al.*, 1979).

Unambiguous induction of presumptive gene mutations at the thymidine kinase location was observed in L5178Y mouse lymphoma cells following treatment with captan [technical grade, purity unspecified] both in the presence and absence of an Aroclor-induced rat liver microsomal preparation (Jones *et al.*, 1982; Waters *et al.*, 1982).

Addition of 10 μg/ml captan [purity unspecified] for five hours to human embryonic lung cells L-132 resulted in a 50% reduction of DNA synthesis and a 40% increase in chromosomal breaks, mainly of the chromatid type (Legator *et al.*, 1969). Chinese hamster cells treated with up to 0.06 mM captan (99.9% pure) for 26.5 hours had a strong dose-related increase in chromosomal aberrations, mainly of the chromatid type, and in sister chromatid exchanges (Tezuka *et al.*, 1980); induction of chromosomal aberrations in Chinese hamster cells was also reported by Kawachi *et al.* (1980) [details not given].

Tests for chromosomal aberrations and sister chromatid exchange in human fibroblasts were negative (Tezuka *et al.*, 1978; Kawachi *et al.*, 1980 [details not given]). [Attention is drawn to the low dose of captan (4 μg/ml) used by by Tezuka *et al.*, 1978.]

Captan induced unscheduled DNA synthesis in SV-40 transformed human VA-4 cells at concentrations ranging from 0.001 to 1 mM, in the presence or absence of uninduced rat liver microsomal preparations (Ahmed *et al.*, 1977). Negative results were obtained when human lung WI38 fibroblasts were exposed to 0.003-1 mM captan [technical grade, purity unspecified] in the presence or absence of uninduced mouse liver microsomal preparations (Jones *et al.*, 1982; Waters *et al.*, 1982). A small increase in unscheduled DNA synthesis was observed in human lymphocytes treated with 5 μg/ml captan (91.5% pure) (Rocchi *et al.*, 1980); and captan failed to induce unscheduled DNA synthesis in rat hepatocyte primary cultures (Probst & Hill, 1980) [details not given].

DNA damage, measured by the DNA alkaline elution technique, was induced in cultured Chinese hamster V79 cells with concentrations ranging from 0.03 to 1 mM captan [technical grade, purity unspecified]; however, the dose of 3 mM was ineffective in the presence of rat liver metabolic activation (Swenberg *et al.*, 1976).

Negative results were obtained in the micronucleus test in the bone-marrow cells of ICR female mice treated either by i.p. injection or by stomach intubation with up to 12 mg/kg bw captan [purity unspecified] (Seiler, 1975). [Attention is drawn to low doses tested.]

Captan (commercial formulate containing 50% technical grade) injected as an i.p. dose of 250 mg/kg bw to Swiss albino male mice failed to induce a significant increase in chromosomal aberrations in bone-marrow cells, although three metacentric chromosomes were observed among 1001 metaphases from captan-treated animals (Fry & Ficsor, 1978); negative results were also reported in rat bone-marrow cells (Kawachi *et al.*, 1980) [details not given].

Generally negative results were obtained in the dominant lethal assay. Male Swiss CD-1 mice, treated intraperitoneally with 9 or 500 mg/kg bw captan showed no significant mutation of this type (Epstein & Shafner, 1968). No significant increase in dominant lethal mutations was reported in a later study in which groups of five to nine ICR/Ha Swiss mice were given either a single i.p. injection of up to 30 mg/kg bw captan (commercial formulation 'Orthocide'), or single doses of up to 800 mg/kg bw, or five daily doses of up to 50 mg/kg bw by oral intubation; however, actual experimental values were not reported (Epstein *et al.*, 1972). [Attention is drawn to the low doses used.] Captan [purity unspecified], given by a single i.p. dose of 3 or 6 mg/kg bw to groups of 12 male albino mice, was also negative in a dominant lethal assay (Kennedy *et al.*, 1975). [Attention is drawn to the absence of positive controls and to the low dose used.] Negative results were also obtained in studies in which groups of 20 male ICR/SIM mice were fed up to 5000 mg/kg bw per day in the diet for seven weeks (Simmon *et al.*, 1977; Waters *et al.*,

1982) or two groups of 15 male C3H mice were given five daily oral doses of 200 or 600 mg/kg bw captan (>98% pure) (Tezuka *et al.*, 1978). However, increases in early foetal deaths were seen in both rats and mice following oral or i.p. administration in a study in which groups of 15 male Osborne-Mendel rats and groups of 15 male CBA-J mice were treated with either five i.p. injections of up to 10 mg/kg bw per day or by oral intubation in five doses of up to 200 mg/kg bw per day captan [technical grade, purity unspecified] and mated with untreated females (Collins, 1972b).

Two generations of offspring were studied after treatment of male DBA-J mice with 50 or 100 mg/kg bw per day captan for five days [technical grade, purity unspecified] administered by gavage. Exposed animals showed only a slight decrease in the fertility index; however, a significant reduction in survival from birth to day 4 and in average weight in the F_2 generation was reported, which was attributed to polygenic effects on reproductive fitness (Collins, 1972a).

The heritable translocation test was performed in 200 progeny of 60 ICR/SIM male mice fed up to 5000 mg/kg bw captan [technical grade, purity unspecified] in the diet for eight weeks. One translocation was found in the high-dose group; however, as one translocation was also seen in the negative control group (the only one seen in over 1600 control males in that laboratory) it was difficult to evaluate the significance of the results (Simmon *et al.*, 1977).

(*b*) *Humans*

Toxic effects

Despite extensive worker contact in the course of agricultural operations, no systemic poisoning by captan has been reported. It has apparently induced severe sensitization in some workers (Jung, 1979). When tested systematically, however, the proportion of individuals who become sensitized to captan was relatively low (3-5%) (Marzulli & Maibach, 1974; Jordan & King, 1977).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Captan was tested for carcinogenicity in mice and rats by administration in the diet. It was carcinogenic to one strain of mice, inducing duodenal tumours (adenocarcinoma and adenomatous polyp). No evidence of carcinogenicity was found in rats.

Captan has shown little, if any, embryotoxic or teratogenic potential in mice or rats at maternally tolerated doses. Results obtained in tests with rabbits and hamsters were considered inconclusive.

Captan was mutagenic to bacteria and yeast. Both positive and negative results were obtained in the host-mediated assay in mice. Weak or negative effects were observed in *Drosophila melanogaster*. Captan induced chromosomal aberrations, sister chromatid exchange and mutations at several loci, but not unscheduled DNA synthesis, in cultured mammalian cells. No increase in micronucleated erythrocytes or chromosomal aberrations was detected in treated mice or rats; positive results obtained in dominant lethal tests in mice and rats were not confirmed by other studies. Thus, there is sufficient evidence to establish the mutagenicity of captan in cellular systems, but the data were insufficient to establish its mutagenicity in mammals.

4.2 Human data

Captan was introduced commercially in 1951. Its production, formulation and use as a fungicide in agricultural and industrial applications and in cosmetics are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of captan in humans.

No case report or epidemiological study of the carcinogenicity of captan alone was available to the Working Group. (See, however, the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

Results of the experiments in mice provide *limited evidence* that captan is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of captan to humans.

---

[1]This evaluation should be read in conjunction with p. 18 of the preamble.

5. References

Ahmed, F.E., Hart, R.W. & Lewis, N.J. (1977) Pesticide induced DNA damage and its repair in cultured human cells. *Mutat. Res.*, *42*, 161-174

Alnot, M.-O., Lefevre, H., Pfister, A. & Da Lage, C. (1974) Preliminary observations on the toxicity and teratogenicity of captan in the Wistar rat (Fr.). *C.R. Séances Soc. Biol.*, *168*, 1173-1177

American Conference of Governmental Industrial Hygienists (1981) *TLVs*^{R} *Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981*, Cincinnati, OH, p. 12

Archer, S.R., McCurley, W.R. & Rawlings, G.D. (1978) *Source Assessment: Pesticide Manufacturing Air Emissions - Overview and Prioritization* (*EPA-600/12-78-004d*) Washington DC, US Environmental Protection Agency, pp. 53, 134

Arlett, C.F., Turnbull, D., Harcourt, S.A., Lehmann, A.R. & Colella, C.M. (1975) A comparison of the 8-azaguanine and ouabain-resistance systems for the selection of induced mutant Chinese hamster cells. *Mutat. Res.*, *33*, 261-278

Association of Official Analytical Chemists (1980) Changes in official methods of analysis made at the ninety-third annual meeting, October 15-18, 1979. 1st supplement to 13th edition Official Methods of Analysis. *J. Assoc. off. anal. Chem.*, *63*, 376-377

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970) *World Rev. Pestic. Control*, *9*, 119-127

de Bertoldi, M., Griselli, M., Giovannetti, M. & Barale, R. (1980) Mutagenicity of pesticides evaluated by means of gene-conversion in *Saccharomyes cerevisiae* and in *Aspergillus nidulans*. *Environ. Mutagenesis*, *2*, 359-370

Bignami, M., Aulicino, F., Velcich, A., Carere, A. & Morpurgo, G. (1977) Mutagenic and recombinogenic action of pesticides in *Aspergillus nidulans*. *Mutat. Res.*, *46*, 395-402

Boyd, E.M. & Krijnen, C.J. (1968) Toxicity of captan and protein-deficient diet. *J. clin. Pharmacol.*, *8*, 225-234

Bridges, B.A. (1975) The mutagenicity of captan and related fungicides. *Mutat. Res.*, *32*, 3-34

Bridges, B.A., Mottershead, R.P., Rothwell, M.A. & Green, M.H.L. (1972) Repair-deficient bacterial strains suitable for mutagenicity screening: Tests with the fungicide captan. *Chem.-biol. Interactions*, *5*, 77-84

Bridges, B.A., Mottershead, R.P. & Collela, C. (1973) Induction of forward mutations to colicin E2 resistance in repair deficient strains of *Escherichia coli*: Experiments with ultraviolet light and captan. *Mutat. Res.*, *21*, 303-313

Buselmaier, W., Röhrborn, G. & Propping, P. (1972) Study of the mutagenicity of pesticides in the host-mediated assay and the dominant lethal test in the mouse (Ger.). *Biol. Zentralbl.*, *91*, 311-325

Carere, A., Ortali, V.A., Cardamone, G., Torracca, A.M. & Raschetti, R. (1978) Microbiological mutagenicity studies of pesticides *in vitro*. *Mutat. Res.*, *57*, 277-286

Carlstrom, A.A. (1980) High pressure liquid chromatography of captan in formulations: Collaborative study. *J. Assoc. off. anal. Chem.*, *63*, 1231-1237

Collins, T.F.X. (1972a) Effects of captan and triethylenemelanine (TEM) on reproductive fitness of DBA/2J mice. *Toxicol. appl. Pharmacol.*, *23*, 277-287

Collins, T.F.X. (1972b) Dominant lethal assay. I. Captan. *Food Cosmet. Toxicol.*, *10*, 353-361

Commission of the European Communities (1976) Council Directive of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Comm.*, *L340*, 26-31

Commission of the European Communities (1982) Proposal for a Council Directive amending Annex II to the Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables. *Off. J. Eur. Comm.*, *C95*, 6-10

Consultative Committee on Industrial Bio-Test Pesticides (1982) *Captan*, Ottawa

Courtney, K.D., Andrews, J.E. & Stevens, J.T. (1978) Inhalation teratology studies with captan and folpet (Abstract no. 167). *Toxicol. appl. Pharmacol.*, *45*, 292

DeBaun, J.R., Miaullis, J.B., Knarr, J., Mihailovski, A. & Menn, J.J. (1974) The fate of *N*-trichloro[^{14}C]methylthio-4-cyclohexene-1,2-dicarboximide [^{14}C captan] in the rat. *Xenobiotica, 4,* 101-119

De Flora, S. (1978) Metabolic deactivation of mutagens in the *Salmonella*-microsome test. *Nature*, *271*, 455-456

De Flora, S. & Boido, V. (1980) Effect of human gastric juice on the mutagenicity of chemicals. *Mutat. Res.*, *77*, 307-315

Dejonckheere, W., Steurbaut, W., Verstraeten, R., Melkebeke, G. & Kips, R.H. (1980) Simplified method for the analysis of chlorinated pesticide residues on lettuce and strawberries. *Med. Fac. Landbouww. Rijksuniv. Gent*, *45*, 929-934

Department of National Health & Welfare (1980) Agricultural chemicals. *Canada Gazette*, June 26, 65C-65C1

Department of National Health & Welfare (1982) Food and drugs act. *Canada Gazette*, Part I, 4687-4688

Elguindi, K. & Rajhans, G.S. (1979) *Occupational health hazards and their control in the manufacturing and handling of pesticides in Ontario.* In: *Report of the 6th*

International Symposium on the Prevention of Occupational Risks in the Chemical Industry, Frankfurt-am-Main, Federal Republic of Germany, International Section of the ISSA for the Prevention of Occupational Risks in the Chemical Industry, pp. 441-466

Epstein, S.S. & Shafner, H. (1968) Chemical mutagens in the human environment. *Nature*, *219*, 385-387

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol.*, *23*, 288-325

FAO (1978) *Pesticide Residues in Food: 1977 Evaluations*, Rome, pp. 39-45

FAO (1979) *Pesticide Residues in Food: 1978 Evaluations*, Rome, pp. 17-25

FAO/WHO (1970) *1969 Evaluations of Some Pesticide Residues in Food* (*WHO/Food Add./70.38*), Geneva, p. 33

Ficsor, G., Bordás, S., Wade, S.M., Muthiani, E., Wertz, G.F. & Zimmer, D.M. (1977) Mammalian host- and fluid-mediated mutagenicity assays of captan and streptozotocin in *Salmonella typhimurium*. *Mutat. Res.*, *48*, 1-16

Fry, S.M. & Ficsor, G. (1978) Cytogenetic test of captan in mouse bone marrow. *Mutat. Res.*, *58*, 111-114

Hansen, J.D., Schneider, B.A., Olive, B.M. & Bates, J.J. (1978) Personnel safety and foliage residue in an orchard spray program using azinphosmethyl and captan. *Arch. environ. Contam. Toxicol.*, *7*, 63-71

Horwitz, W., ed. (1980) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 13th ed., Washington DC, Association of Official Analytical Chemists, pp. 96-97, 483

Hsie, A.W., O'Neill, J.P., San Sebastien, J.R., Couch, D.B., Brimer, P.A., Sun, W.N.C., Fuscoe, J.C., Forbes, N.L., Machanoff, R., Riddle, J.C. & Hsie, M.H. (1979) Quantitative mammalian cell genetic toxicity: Study of the cytotoxicity and mutagenicity of seventy individual environmental agents related to energy technologies and three subfractions of a crude synthetic oil in the CHO/HGPRT system. *Environ. Sci. Res.*, *15*, 291-315

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst.*, *42*, 1101-1114

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 64-65

Johansson, C.E. (1976) Residues of certain fungicides in strawberries, grapes and apples 1974-1975 (Swed.). *Var Foeda*, *28*, 156-159 [*Chem. Abstr.*, *86*, 28548j]

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975-July 1976. *Pestic. Monit. J.*, *15*, 54-69

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) *In vitro Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

Jordan, W.P., Jr & King, S.E. (1977) Delayed hypersensitivity in females. The development of allergic contact dermatitis in females during the comparison of two predictive patch tests. *Contact Dermatitis*, *3*, 19-26

Jung, H.D. (1979) Occupational dermatosis after pesticides (Ger.). *Allgemeinmedizin*, *34*, 1144-1148

Kappas, A. & Domopoulos, N. (1981) The effect of microsomes on the mutagenicity of captan (Abstract). *Mutat. Res.*, *80*, 273

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan*. In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

Kennedy, G.L., Jr, Arnold, D.W. & Keplinger, M.L. (1975) Mutagenicity studies with captan, captofol, folpet and thalidomide. *Food Cosmet. Toxicol.*, *13*, 55-61

Koseki, M., Shimamura, Y., Maki, T., Tamara, Y. & Naoi, Y. (1980) Residues of TPN (tetrachloroisophthalonitrile), captan, diazinon, and chinomethionate in vegetables and fruits (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, (31-1), 170-173 [*Chem. Abstr.*, *94*, 173005z]

Kramers, P.G.N. & Knaap, A.G.A.C. (1973) Mutagenicity tests with captan and folpet in *Drosophila melanogaster*. *Mutat. Res.*, *21*, 149-154

Lawless, E.W., von Rumker, R. & Ferguson, T.L. (1972) *The Pollution Potential in Pesticide Manufacturing* (*Tech. Studies Rep.: TS-00-72-04*), US Environmental Protection Agency, Office of Water Programs, Applied Technology Division, Rural Wastes Branch, Washington DC, US Government Printing Office, pp. 157-162

Legator, M.S. (1970) *The host-mediated assay, a practical procedure for evaluating potential mutagenic agents*. In: Vogel, F. & Röhrborn, G., eds, *Chemical Mutagenesis in Mammals and Man*, Springer, Berlin, pp. 260-270

Legator, M.S., Kelly, F.J., Green, S. & Oswald, E.J. (1969) Mutagenic effects of captan. *Ann. N.Y. Acad. Sci.*, *60*, 344-351

Manske, D.D. & Johnson, R.D. (1975) Pesticide residues in total diet samples (VIII) *Pestic. Monit. J.*, *9*, 94-105

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

Markus, J.R. & Puma, B., eds (1973) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.103

Marshall, T.C., Dorough, H.W. & Swin, H.E. (1976) Screening of pesticides for mutagenic potential using *Salmonella typhimurium* mutants. *J. agric. Food Chem.*, *24*, 560-563

Marzulli, F.N. & Maibach, H.I. (1974) Antimicrobials: Experimental contact sensitization in man. *J. Soc. Cosmet. Chem.*, *24*, 399-421

McCann, J., Choi, E., Yamasaki, E. & Ames, B.N. (1975) Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc. natl Acad. Sci. USA*, *72*, 5135-5139

McLaughlin, J., Jr, Reynaldo, E.F., Lamar, J.K. & Marliac, J.-P. (1969) Teratology studies in rabbits with captan, folpet, and thalidomide (Abstract no. 72). *Toxicol. appl. Pharmacol.*, *14*, 641

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

Mishima, Y., Sugano, T. & Konishi, T. (1979) Survey on pesticidal residues. 5. Organochlorine pesticides in soil, fruits, and vegetables (Jpn.). *Senda-shi Eisei Shikenshoho 1977, 7,* 143-146 [*Chem. Abstr., 93,* 68827a]

Mollet, P. (1973) Mutagenicity and toxicity tests with captan in *Drosophila* (Ger.). *Mutat. Res.*, *21*, 137-148

Nagy, Z., Mile, I. & Antoni, F. (1975) The mutagenic effect of pesticides on *Escherichia coli* WP2 *try*$^-$. *Acta microbiol. acad. sci. hung.*, *22*, 309-314

National Cancer Institute (1977) *Bioassay of Captan for Possible Carcinogenicity, CAS No. 133-06-2* (*Tech. Rep. Ser. No. 15; DHEW Publ. No. (NIH) 77-815*), Washington DC

National Institue for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards,* Cincinnati, OH, p. 82

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, p. 4013 (generics included) and 2913 (generics excluded)

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study*, Washington DC, US Department of Commerce, p. 80

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

NIH/EPA Chemical Information System (1982) *TSCA - Plant and Production*, Washington DC, Information Sciences Corporation

Okawa, M.T. & Bodner, A. (1973) *Health Hazard Evaluation/Toxicity Determination. Ferry Morse Seed Company, Mountain View, CA, PB-229 644*, Cincinnati, OH, National Institute for Occupational Safety & Health

Ospenson, J.N., Pack, D.E., Kohn, G.K., Burchfield, H.P. & Storrs, E.E. (1964) *Captan*. In: Zweig, G., ed., *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives*, Vol. 3, New York, Academic Press, pp. 9-12, 15-17, 19-25

Oudbier, A.J., Bloomer, A.W., Price, H.A. & Welch, R.L. (1974) Respiratory route of pesticide exposure as a potential health hazard. *Bull. environ. Contam. Toxicol., 12*, 1-9

Peeples, A. & Dalvi, R.R. (1978) Toxicologic studies of *N*-trichloromethylthio-4-cyclohexene-1,2-dicarboximide (captan): Its metabolism by rat liver drug metabolizing enzyme system. *Toxicology, 9*, 341-351

Probst, G.S. & Hill, L.E. (1980) Chemically-induced DNA repair synthesis in primary rat hepatocytes: A correlation with bacterial mutagenicity. *Ann. N.Y. Acad. Sci., 249*, 405-406

Robens, J.F. (1970) Teratogenic activity of several phthalimide derivatives in the golden hamster. *Toxicol. appl. Pharmacol., 16*, 24-34

Rocchi, P., Perocco, P., Alberghini, W., Fini, A. & Prodi, G. (1980) Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. *Arch. Toxicol., 45*, 101-108

Rosenkranz, H.S. & Leifer, Z. (1980) *Determining the DNA-modifying activity of chemicals using DNA-polymerase-deficient* Escherichia coli. In: de Serres, F.J. & Hollaender, A., eds, *Chemical Mutagens. Principles and Methods for Their Detection*, Vol. 6, New York, Plenum, pp. 109-147

Seidler, H., Härtig, H., Schnaak, W. & Engst, R. (1971) Studies on the metabolism of certain insecticides and fungicides in the rat. II. Excretion, distribution and degradation of [^{35}S]-labelled captan (Ger.). *Nahrung, 15*, 177-185

Seiler, J.P. (1975) Evaluation of some pesticides for mutagenicity. *Proc. Eur. Soc. Toxicol., 17*, 398-404

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res., 40*, 19-30

Siebert, D., Zimmermann, F.K. & Lemperle, E. (1970) Genetic effects of fungicides. *Mutat. Res., 10*, 533-543

Simmon, V.F., Mitchell, A.D. & Jorgenson, T.A. (1977) *Evaluation of Selected Pesticides as Chemical Mutagens. In vitro and in vivo Studies (EPA-600/1-77-028)*, Research Triangle Park, NC, Environmental Protection Agency, p. 239

Spector, W.S. (1956) *Handbook of Toxicology*, Vol. 1, Philadelphia and London, W.B. Saunders Co., p. 58

Stevens, E.R. & Davis, J.E. (1981) Potential exposure of workers during seed potato treatment with captan. *Bull. environ. Contam. Toxicol.*, *26*, 681-688

Stevens, J.T., Farmer, J.D. & Dipasquale, L.C. (1978) The acute inhalation toxicity of technical captan and folpet (Abstract no. 234). *Toxicol. appl. Pharmacol.*, *45*, 320

Swenberg, J.A., Petzold, G.L. & Harbach, P.R. (1976) *In vitro* DNA damage/alkaline elution assay for predicting carcinogenic potential. *Biochem. biophys. Res. Commun.*, *72*, 732-738

Takeshita, T., Inuyama, Y., Yoneda, T. & Goto, M. (1976) Environmental pollutants in foods (Jpn.). *Shimane-ken Eisei Kogai Kenkyusho Ho*, *18*, 124-131 [*Chem. Abstr.*, *90*, 4563s]

Tezuka, H., Teramoto, S., Kaneda, M., Henmi, R., Murakami, N. & Shirasu, Y. (1978) Cytogenetic and dominant lethal studies on captan. *Mutat. Res.*, *57*, 201-207

Tezuka, H., Ando, N., Suzuki, R., Terahata, M., Moriya, M. & Shirasu, Y. (1980) Sister-chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells treated with pesticides positive in microbial reversion assays. *Mutat. Res.*, *78*, 177-191

US Environmental Protection Agency (1975) *Initial Scientific and Minieconomic Review of Captan* (*Substitute Chemical Program, EPA-540/1/75-012*), Washington DC, Office of Pesticide Programs, Criteria and Evaluation Division, pp. 12-14, 111-113, 144

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Office of Pesticide Programs, Washington DC, Association of Official Analytical Chemists, Captan EPA-1, Captan EPA-2

US Environmental Protection Agency (1980a) Pesticide programs; Rebuttable presumption against registration (RPAR) and continued registration of pesticide products containing captan. *Fed. Regist.*, *45*, 54938-54986

US Environmental Protection Agency (1980b) Protection of environment. *US Code Fed. Regul.*, *Title 40*, part 455-20, pp. 285, 286

US Food & Drug Administration (1980) Food and drugs. *US Code Fed. Regul.*, *Title 21*, part 176.170(b)(2), pp. 158, 159

US Food & Drug Administration (1981) *Products Containing Captan*, Washington DC, Division of Cosmetics Technology

US International Trade Commission (1981) *Imports of Benzenoid Chemicals and Products, 1980* (*USITC Publ. 1163*), Washington DC, US Government Printing Office, p. 108

US Tariff Commission (1952) *Synthetic Organic Chemicals, Production and Sales, 1951* (*Report No. 175, Second Series*), Washington DC, US Government Printing Office, p. 135

Valencia, R. (1977) *Mutagenesis Screening of Pesticides Using* Drosophila (*Contract No. 68-01-2474*), Madison, WI, WARF Institute, Inc.

Waters, M.D., Simmon, V.F., Mitchell, A.D., Jorgenson, J.A. & Valencia, R. (1980) An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. *J. environ. Sci. Health, B15*, 867-906

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (1982) *Study of pesticide genotoxicity.* In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology - An Agricultural Perspective*, New York, Plenum (in press)

Watts, R.R., ed. (1980) *Analysis of Pesticide Residues in Human and Environmental Samples*, Research Triangle Park, NC, US Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, sect.5A(1)(a); 10A; 12B

Weast, R.C., ed. (1977) *CRC Handbook of Chemistry and Physics*, 58th ed., Cleveland, OH, CRC Press, p. C-266

WHO (1970) *1969 Evaluation of Some Pesticide Residues in Food (WHO/Food Add./70.38)*, Geneva, pp. 33-44

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 78

Zadrozinska, J. (1979) The use of fungi as a biological test for determination of residues of certain fungicides in plant material. Part II. Determination of benomyl, dichlofluanid, folpet, captan, carbendazim, methyl thiophanate, and thiuram, in fruits, vegetables, and mushrooms (Pol.). *Rocz. Panstw. Zakl. Hig., 30*, 433-440 [*Chem. Abstr., 92*, 179184n]

Zweig, G. & Sherma, J. (1972) *Captan and phaltan.* In: Zweig, G., ed., *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VI, New York, Academic Press, pp. 546-549

CHLOROTHALONIL

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 1897-45-6

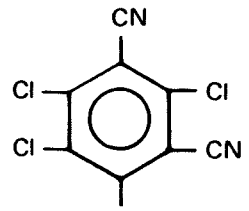
Chem. Abstr. Name: 1,3-Benzenedicarbonitrile, 2,4,5,6-tetrachloro-

IUPAC Systematic Name: Tetrachloroisophthalonitrile

Synonyms: Chloroalonil; 1,3-dicyanotetrachlorobenzene; NCI CO0102; TCIN; *meta*-TCPN; tetrachlorisophthalonitrile; 2,4,5,6-tetrachloro-3-cyanobenzonitrile; 2,4,5,6-tetrachloroisophthalonitrile; *meta*-tetrachlorophthalodinitrile; tetrachloro-*meta*-phthalodinitrile; TPN[pesticide]

Trade Names: Bravo; Bravo 6F, 500 & W-75; DAC 2787; Daconil; Daconil 2787, 2787 W-75, 2787 WP; Daconil 2787 Flowable Fungicide; Daconil 2787 Fungicide; Dacosoil; Exotherm; Exotherm Termil; Forturf; Nopcocide; Nopcocide N40D & N96; Sweep; Termil

1.2 Structural and molecular formulae and molecular weight



$C_8Cl_4N_2$ Mol. wt: 265.9

1.3 Chemical and physical properties of the pure substance

From Martin and Worthing (1977), unless otherwise specified

(*a*) *Description*: Colourless, odourless crystals

(*b*) *Boiling-point:* 350°C

(*c*) *Melting-point*: 250-25l°C

(*d*) *Density*: 1.8 (for the 96% pure compound) (Diamond Shamrock Corp., 1980)

(*e*) *Spectroscopy data:* Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, l981)

(*f*) *Solubility*: Very slightly soluble in water (0.6 mg/kg); soluble in acetone (20 g/kg), cyclohexanone (30 g/kg), dimethylformamide (30 g/kg), dimethyl sulph-

oxide (20 g/kg), kerosine (<10g/kg), butanone (20 g/kg) and xylene (80 g/kg); readily soluble in benzene (Satoh, 1979)

(*g*) *Volatility*: Vapour pressure, <0.01 mm Hg at 40°C. 9.2 mm Hg at 170.4°C

(*h*) *Stability:* Thermally stable under normal storage conditions, stable to alkaline and acid aqueous solutions and to ultra-violet light; non-inflammable; may decompose at high temporatures to emit hydrogen chloride; when stored in benzene and exposed to light, forms 3,5,6-trichlorobiphenyl-2,4-dicarbonitrile (Satoh, 1979)

1.4 Technical products and impurities

Technical-grade chlorothalonil is about 98% pure (Martin & Worthing, 1977); it contains a minimum of 96% tetrachloroisophthalonitrile and a maximum of 4% inert ingredients (Diamond Shamrock Corp., 1980). One sample of technical-grade chlorothalonil was reported to contain the following compounds (average %): chlorothalonil, 97.6; tetrachlorophthalonitrile, <0.1%; tetrachloroterephthalonitrile, 0.5; pentachlorobenzonitrile, 1.2; partially chlorinated dicyanobenzenes (all isomers), 0.4; unchlorinated dicyanobenzenes (all isomers), 0.3; matter insoluble in xylene, 0.2 (WHO, 1975).

Chlorothalonil is available as a 75% active water-dispersible powder and in 'flowable' formulations with varying levels of active ingredient (Berg, 1981).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Chlorothalonil was introduced for experimental use in 1963 (Spencer, 1973). It can be produced by the chlorination of isophthalonitrile (Martin & Worthing, 1977) or by treatment of tetrachloroisophthaloyl amide with phosphorus oxychloride.

Chlorothalonil was first produced commercially in the US in 1969 (US Tariff Commission, 1971). Only one US company presently produces it, and no production data are available (see preamble, section 8(*b*)(ii)); the company is estimated to have an annual production capacity of 5 million kg. Imports of chlorothalonil through the principal US customs districts amounted to 175 thousand kg in 1980 (US International Trade Commission, 1981); 1.65 million kg were imported in 1976 (US International Trade Commission, 1978). Separate data on US exports of chlorothalonil are not available.

It is not produced commercially in western Europe. One company, with an estimated annual production capacity of 3 million kg, produces chlorothalonil in Japan.

(*b*) *Use*

Chlorothalonil is used as a fungicide in both agricultural and nonagricultural applications.

In 1976, 2 million kg of chlorothalonil were used by US farmers on major crops, representing 54.3% of the total quantity of all active fungicide ingredients used on those crops in that year (US Department of Agriculture, 1978). In 1980, total US agricultural usage is estimated to have been 5.0 million kg, with approximately 53% on peanuts, 31% on vegetables, 12% on lawns and turf, and 5% on potatoes.

Chlorothalonil is also used as a mildewicide in aqueous emulsion/latex paints, and 300 thousand kg were used for this purpose in 1978 (Trotz & Pitts, 1981).

The Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues in December 1981 set a temporary acceptable daily intake of chlorothalonil for humans of 0-0.005 mg/kg bw (FAO, 1982). In 1974, that Group recommended the following tolerances for residues of chlorothalonil on commodities (mg/kg): peaches, 30; currants, 25; celery, 15; 22 assorted fruits and vegetables, 5 or 10; carrots, sweet corn and sugar beets, 1; lima beans and whole peanuts, 0.5; and peanuts (kernel) and potatoes, 0.1 (WHO, 1975). In 1977, the Joint Meeting recommended tolerances of 25 mg/kg on peaches, 5 mg/kg on citrus fruits, 4 mg/kg on whole bananas and 0.1 mg/kg on banana pulp (FAO, 1978). In 1978, they recommended a temporary maximum residue level on cereals of 0.2 mg/kg (FAO, 1979). In 1979, the Joint Meeting recommended temporary maximum residue levels of 5 mg/kg on grapes, 0.2 mg/kg on whole bananas and 0.05 mg/kg on banana pulp (FAO, 1980).

Tolerances in the US for residues of chlorothalonil in or on raw agricultural commodities are established at levels of 0.1-15 mg/kg for a variety of 21 fruits and vegetables (US Environmental Protection Agency, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

Chlorothalonil is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group on the numbers of workers exposed to chlorothalonil during its production, formulation and use as a fungicide.

(*c*) *Food, beverages and animal feeds*

Fruits and vegetables imported into Finland were analysed for residues of chlorothalonil, and levels of 0.02-0.15 mg/kg were detected in strawberries, 0.01-0.86 mg/kg in Chinese lettuce, and 0.12-1.2 mg/kg in peaches (FAO, 1980).

In the Total Diet Study (a sampling of US food consumption) conducted by the US Food and Drug Administration, no residue of chlorothalonil was detected (limit of detection, <0.01 mg/kg) during 1976 and 1977. In Sweden, no residue of chlorothalonil was detected (limit of detection, 0.005 mg/kg) in samples of Swedish potatoes in 1979 (FAO, 1980).

Chlorothalonil was detected at levels of 0.001-1.35 mg/kg in most samples of apples, cabbages, Chinese cabbages, cucumbers, peaches, pears, spinach, strawberries and tomatoes marketed in Tokyo, Japan (Koseki *et al.*, 1980). In the Canadian Total Diet

Survey, chlorothalonil was detected in one of six composite samples of garden fruits; the minimum detectable level was 20 μg/kg. On the basis of the level measured in one sample, daily dietary intake was calculated to be 0.04 μg/person (McLeod *et al.*, 1980).

2.3 Analysis

Standard methods used for the analysis of chlorothalonil in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of chlorothalonil

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Formulations	Extract (1,4-dioxane or methyl ethyl ketone/ carbon disulphide/ 1,2-dimethoxyethane)	GC/TCD or GC/FID	not given	Ballee *et al.* (1976)
Emulsifiable concentrates and "flowables"	Extract (dichloromethane/ anhydrous sodium sulphate) ; concentrate	IR spectro-scopy	not given	US Environmental Protection Agency (1976)
Potatoes	Extract (acidified acetone) ; chromatograph (Florisil) ; derivatize (diazomethane)	GC/ECD GC/MCD	0.01 mg/kg 0.02 mg/kg	Markus & Puma (1973)
Fruit and vegetable surfaces	Strip (dichloromethane) ; evaporate ; dilute (benzene)	GC/ECD	0.01 mg/kg	Ballee *et al.* (1976)
Green leafy vegetables	extract (acidified acetone) ; evaporate ; dissolve (aqueous sodium bicarbonate) ; adjust pH ; extract (diisopropyl ether) ; evaporate ; dilute (benzene) ; chromatograph (alumina), if necessary to remove interferences	GC/ECD	0.01 mg/kg	Ballee *et al.* (1976)
Soil	Extract (acidified acetone) ; extract (acetonitrile/hexane) ; dilute lower layer (aqueous sodium bicarbonate) ; adjust pH to 4.5 (sulphuric acid or sodium bicarbonate) ; extract (diisopropyl ether) ; concentrate ; dilute (benzene) ; chromatograph (alumina), if necessary to remove interferences	GC/ECD	0.01 mg/kg	Ballee *et al.* (1976)
Water	Adjust pH to 4.5 (sulphuric acid) ; extract (diisopropyl ether) ; concentrate ; dilute (benzene)	GC/ECD	0.01 mg/kg	Ballee *et al.* (1976)

[a]Abbreviations: GC/TCD, gas chromatography/thermal conductivity detection; GC/FID, gas chromatography/flame ionization detection; IR spectroscopy, infra-red spectroscopy; GC/ECD, gas chromatography/electron capture detection; GC/MCD, gas chromatography/ microcoulometric detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female weanling B6C3F$_1$ mice were fed *ad libitum* a diet containing chlorothalonil (technical grade; 98-98.5% pure; impurities consisted of 0.6 or 1.24% pentachlorobenzonitrile, 0.06 or 1.2% other tetrachlorodicyanobenzene isomers and traces of other partially chlorinated dicyanobenzenes) for 80 weeks. Males recieved 10 000 mg/kg for two weeks and 2500 mg/kg for 78 weeks (low dose; time-weighted average dose, 2688 mg/kg of diet) or 20 000 mg/kg for two weeks and 5000 mg/kg for 78 weeks (high dose; time-weighted average dose, 5375 mg/kg of diet). Females received 10 000 mg/kg for two weeks, 5000 mg/kg for 10 weeks and 2500 mg/kg for 68 weeks (low dose; time-weighted average dose, 3000 mg/kg of diet) or 20 000 mg/kg for two weeks, 10 000 mg/kg for 10 weeks and 5000 mg/kg for 68 weeks (high dose; time-weighted average dose, 6000 mg/kg of diet). All surviving animals were killed at 91 or 92 weeks. A matched control group consisted of 10 male and 10 female mice; statistical comparisons were based on both matched controls and on a pooled control group consisting of 60 mice of each sex. Survival rates were similar in all groups. Although variations in tumour incidences were observed, no significant difference attributable to treatment was encountered for any tumour type (National Cancer Institute, 1978). [The Working Group noted the short duration of treatment (80 weeks) and of the period of observation preceding sacrifice (11-12 weeks).]

Rat: Groups of 50 male and 50 female weanling Osborne-Mendel rats were fed diets containing chlorothalonil (technical grade, 98-98.5% pure; impurities as described above) for 80 weeks. Low-dose groups were fed 10 000 mg/kg of diet for one week and 5000 mg/kg for 79 weeks (time-weighted average dose, 5063 mg/kg); and the high-dose groups, 20 000 mg/kg of diet for one week and 10 000 mg/kg for 79 weeks (time-weighted average dose, 10 126 mg/kg). All surviving animals were killed at 110-111 weeks. A matched control group consisted of 10 male and 10 female mice; statistical comparisons were based both on matched controls and on a pooled control group consisting of 65 rats of each sex. Adenomas and adenocarcinomas of the renal tubular epithelium developed in 3/46 males and 1/48 females in the low-dose group and in 4/49 males ($p = 0.035$) and 5/50 females ($p = 0.016$) in the high-dose group, compared with 0/62 males and 0/62 females in the pooled controls. There was a statistically significant dose-related trend in both the males ($p = 0.030$) and the females ($p = 0.007$) (National Cancer Institute, 1978). [The Working Group noted the short duration of treatment (80 weeks) and of the period of observation preceding termination of the experiment (30-31 weeks).]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The single oral and i.p. LD_{50}s of chlorothalonil in ICR female mice were 6000 and 2.5 mg/kg bw, respectively (Yoshikawa & Kawai, 1966). The oral LD_{50} in rats is more than

10 000 mg/kg bw (Spencer, 1973). In two-year chronic feeding studies (see section 3.1), male mice became hyperexcitable from week 62 (National Cancer Institute, 1978).

Effects on reproduction and prenatal toxicity

No published data were available[1].

Absorption, distribution, excretion and metabolism

Following administration of 1 mg/kg bw ^{14}C-chlorothalonil to male Sprague-Dawley rats by endotracheal instillation, gavage or dermal application, <6% of the administered dose was recovered in the blood or urine within 48 hours after dosing (Chin *et al.*, 1981).

Chlorothalonil reacts with cellular sulphhydryl compounds; binding to calf thymus histones and rat liver nuclei, but not to DNA, *in vitro* has been reported (Rosanoff & Siegel, 1981).

Mutagenicity and other short-term tests

Chlorothalonil [purity unspecified] did not induce reverse mutations in *Salmonella typhimurium* strains TA98 or TA100 when tested in the presence or absence of rat liver microsomal preparations (Kawachi *et al.*, 1980) [details not given]. A commercial formulation did not induce mitotic gene conversion in two eukaryotic microorganisms, *Saccharomyces cerevisiae* and *Aspergillus nidulans*, in the presence of a mouse liver microsomal preparation (de Bertoldi *et al.*, 1980). Purified chlorothalonil did not cause sectoring of the heterozygous diploid fungal strain colonies of *Aspergillus nidulans* (Georgopoulos *et al.*, 1976). It also failed to induce mutations in silkworms (Kawachi *et al.*, 1980) [details not given].

Concentrations of up to 1500 mg/l chlorothalonil (75% pure) failed to induce chromosomal aberrations in barley shoot tips (Tomkins & Grant, 1972; Kahlon & Banerjee, 1979). It did not induce chromosomal aberrations in hamster lung fibroblasts (Kawachi *et al.*, 1980) [details not given].

(*b*) *Humans*

Toxic effects

Patch testing indicated that 10-28% of 88 Japanese farmers were sensitive to chlorothalonil and other pesticides; 35 had acute dermatitis. In some cases, photosensitization was involved (Horiuchi & Ando, 1980a). Highly positive reactions were also seen in 66 greenhouse workers, 51 vegetable farmers and 25 other patients with pesticide-induced dermatitis (Horiuchi & Ando, 1980b). Four cases of severe, recurrent contact dermatitis were reported in workers exposed to wood preservatives containing chlorothalonil (Bach & Pedersen, 1977; Spindeldreier & Deichmann, 1980).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

---

[1] A three-generation reproduction study on chlorothalonil in the rat was reviewed by WHO (1975).

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chlorothalonil was tested for carcinogenicity in mice and rats by administration in the diet; it produced adenomas and adenocarcinomas of the kidney in rats. No evidence of carcinogenicity was found in mice.

No published data were available to evaluate the teratogenicity of this compound to experimental animals.

Chlorothalonil was not mutagenic in two fungal systems and was reported to be nonmutagenic in *Salmonella typhimurium*. Available data on other systems are inadequate, and no overall evaluation of the mutagenicity of chlorothalonil could be made.

4.2 Human data

Chlorothalonil was introduced commercially in 1969. Its production, formulation and use as a fungicide in agricultural and industrial applications are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of chlorothalonil in humans.

No case report or epidemiological study of the carcinogenicity of chlorothalonil alone was available to the Working Group; however, it should be noted that the period since introduction of this compound may be too short for a carcinogenic effect to be detected in humans. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulations and Users'.)

4.3 Evaluation[1]

Results of one experiment in rats provide *limited evidence* that chlorothalonil is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of chlorothalonil to humans.

5. References

Bach, B. & Pedersen, N.B. (1977) Contact dermatitis from a wood preservative containing tetrachloroisophthalonitrile. *Contact Dermatitis*, *3*, 142

Ballee, D.L., Duane, W.C., Stallard, D.E. & Wolfe, A.L. (1976) *Chlorothalonil.* In: Zweig, G. & Sherma, J., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. VIII, New York, Academic Press, pp. 266-274

Berg, G.L., ed. (1981) *Farm Chemicals Handbook, 1981*, Willoughby, OH, Meister Publishing Co., pp. C49-C50

de Bertoldi, M., Griselli, M., Giovannetti, M. & Barale, P. (1980) Mutagenicity of pesticides evaluated by means of gene-conversion in *Saccharomyces cerevisiae* and in *Aspergillus nidulans*. *Environ. Mutagenesis*, *2*, 359-370

Chin, B.H., McGloin, J.E., Spangler, N.L. & Heilman, R.D. (1981) Chlorothalonil equivalents in the blood and urine of rats following oral, endotracheal and dermal administration of ^{14}C-chlorothalonil. *Bull. environ. Contam. Toxicol.*, *26*, 258-261

Diamond Shamrock Corp. (1980) *Technical Chlorothalonil Fungicide* (*Material Safety Data Sheet*), Cleveland, OH, Agricultural Chemicals Division

FAO (1978) *Pesticide Residues in Food: 1977 Evaluations*, Rome, pp. 87-99

FAO (1979) *Pesticide Residues in Food: 1978 Evaluations*, Rome, pp. 79-83

FAO (1980) *Pesticide Residues in Food: 1979 Evaluations*, Rome, pp. 137-148

FAO (1982) *Pesticide Residues in Food - 1981*, Rome, pp. 17-18

Georgopoulos, S.G., Kappas, A. & Hastie, A.C. (1976) Induced sectoring in diploid *Aspergillus nidulans* as a criterion of fungitoxicity by interference with hereditary processes. *Phytopathology*, *66*, 217-220

Horiuchi, N. & Ando, S. (1980a) Contact dermatitis due to pesticides for agricultural use (Jpn.). *Jpn. J. Dermatol.*, *90*, 289 [*Pestic. Abstr.*, *3*, 80-1644]

---

[1] This evaluation should be read in conjunction with p. 18 of the preamble.

Horiuchi, N. & Ando, S. (1980b) Dermatitis due to pesticides for agricultural use. *Jpn. J. Dermatol.*, *90*, 277-279

Kahlon, P.S. & Banerjee, M.R. (1979) Evaluation of Bravo, Phosdrin and Telvar as possible environmental mutagens. *Bull. environ. Contam. Toxicol.*, *22*, 365-370

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

Koseki, M., Shimamura, Y., Maki, T., Tamura, Y. & Naoi, Y. (1980) Residues of TPN (tetrachloroisophthalonitrile), captan, diazinon, and chinomethionate in vegetables and fruits (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, *31-1*, 170-173 [*Chem. Abstr.*, *94*, 173005z]

Markus, J.R. & Puma, B., eds (1970) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.275

Martin, H. & Worthing, C.R., eds (1979) *Pesticide Manual.*, 5th ed., Croydon, UK, British Crop Protection Council, p. 113

McLeod, H.A., Smith, D.C. & Bluman, N. (1980) Pesticide residues in the total diet in Canada, V: 1976 to 1978. *J. Food Saf.*, *2*, 141-164

National Cancer Institute (1978) *Bioassay of Chlorothalonil for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 41; DHEW Publ. No. (NIH) 78-841*), Washington DC, US Government Printing Office

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Rosanoff, K.A. & Siegel, M.R. (1981) Mechanism of action and fate of the fungicide chlorothalonil (2,4,5,6-tetrachloroisophthalonitrile) in biological systems. 3. Interaction with mammalian DNA, histones, and isolated rat liver nuclei. *Pestic. Biochem. Physiol.*, *6*, 120-128

Satoh, M. (1979) Photochemical reaction of chlorothalonil in organic solvents. *Bull. environ. Contam. Toxicol.*, *22*, 598-602

Spencer, E.Y. (1973) *Guide to the Chemicals Used in Crop Protection* (*Research Branch, Agriculture Canada, Publ. 1093*), 6th ed., London, Ont., University of Western Ontario, p. 120

Spindeldreier, A. & Deichmann, B. (1980) Contact dermatitis against a wood preservative with a new fungicidal agent (Ger.). *Dermatosen*, *28*, 88-90

Tomkins, D.J. & Grant, W.F. (1972) Comparative cytological effects of the pesticides menazon, metrobromuron and tetrachloroisophthalonitrile in *Hordeum* and *Tradescantia*. *Can. J. Genet. Cytol.*, *14*, 245-256

Trotz, S.I. & Pitts, J.J. (1981) *Industrial antimicrobial agents.* In: Kirk, R.E. & Othmer, D.F., eds, *Encylopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley & Sons, pp. 223, 249, 253

US Department of Agriculture (1978) *Farmers' Use of Pesticides in 1976 (Agricultural Economic Report No. 418)*. Washington DC, Economics, Statistics, and Cooperatives Service, p. 21

US Environmental Protection Agency (1976) *Manual of Chemical Methods for Pesticides and Devices*, Washington DC, Office of Pesticides Programs, Association of Official Analytical Chemists, Chlorothalonil EPA-1

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.275, p. 583

US International Trade Commission (1978) *Imports of Benzenoid Chemicals and Products, 1977 (USITC Publ. 900)*, Washington DC, US Government Printing Office, p. 97

US International Trade Commission (1981) *Imports of Benzenoid Chemicals and Products, 1980 (USITC Publ. 1163)*, Washington DC, US Government Printing Office, p. 108

US Tariff Commission (1971) *Synthetic Organic Chemicals, US Production and Sales, 1969 (TC Publ. 412)*, Washington DC, US Government Printing Office, p. 192

WHO (1975) *1974 Evaluations of Some Pesticide Residues in Food (World Health Organ. Pestic. Residue Ser., No. 4)*, Geneva, pp. 101-148

Yoshikawa, H. & Kawai, K. (1966) Toxicity of phthalodinitrile and tetrachlorophthalodinitrile. I. Acute toxicity in mice. *Ind. Health, 4,* 11-15

ortho-PHENYLPHENOL AND ITS SODIUM SALT

1. Chemical and Physical Data

ortho-*Phenylphenol*

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 90-43-7

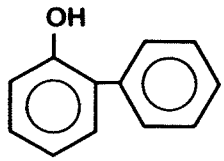
Chem. Abstr. Name: (1,1′-Biphenyl)-2-ol

IUPAC Systematic Name: 2-Biphenylol

Synonyms: *ortho*-Biphenylol; *ortho*-diphenylol; *ortho*-hydroxybiphenyl; 2-hydroxybiphenyl; *ortho*-hydroxydiphenyl; 2-hydroxydiphenyl; orthoxenol; 2-phenylphenol; *ortho*-xenol

Trade Names: Dowicide 1; Preventol O Extra; Remol TRF; Tetrosin OE; Tumescal OPE

1.2 Structural and molecular formulae and molecular weight



$C_{12}H_{10}O$ Mol. wt: 170.2

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: White flakes (Dow Chemical Co., 1976a)

(*b*) *Boiling-point*: 286°C

(*c*) *Melting-point*: 57°C (freezing-point)

(*d*) *Density*: d_{25}^{25} 1.217

(*e*) *Spectroscopy data*: Infra-red and ultra-violet spectral data have been reported (Gore *et al.*, 1971).

(*f*) *Solubility*: Very slightly soluble in water (0.7 g/kg at 25°C); soluble in 95% ethanol, ethylene glycol, isopropanol and various glycol ethers and polyglycols (Dow Chemical Co., 1976a)

(*g*) *Volatility*: Vapour pressure, 7 mm Hg at 140°C (Dow Chemical Co., 1976a)

(*h*) *Reactivity*: Reacts with aqueous sodium hydroxide to form sodium *ortho*-phenylphenate (Dow Chemical Co., 1976a)

1.4 Technical products and impurities

ortho-Phenylphenol is available as a technical product containing a minimum of 99% pure compound in the form of white or light-tan-to-pink flakes or in molten form (Dow Chemical Co., 1976a). The specifications for one technical product in 1970 were: melting-point, 56-58°C; a minimum of 99% *ortho*-phenylphenol; maxima of 0.3% biphenyl ether, 0.1% *para*-phenylphenol, 0.01% α-naphthol and 0.05% sulphate after ashing (WHO, 1970).

Sodium ortho-*phenylphenate*

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 132-27-4

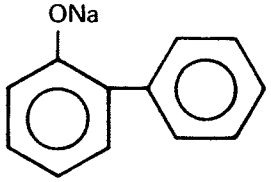
Chem. Abstr. Name: (1,1′-Biphenyl)-2-ol, sodium salt

IUPAC Systematic Name: Sodium 2-biphenylolate

Synonyms: 2-Biphenylol, sodium salt; biphenyl-2-ol, sodium salt; 2-hydroxybiphenyl sodium salt; 2-hydroxydiphenyl sodium; *ortho*-phenylphenol sodium salt; 2-phenylphenol sodium salt; sodium [1,1′-biphenyl]-2-olate; sodium 2-hydroxydiphenyl; sodium phenylphenate;, sodium 2-phenylphenate; sodium *ortho*-phenylphenol; sodium *ortho*-phenylphenolate; sodium *ortho*-phenylphenoxide; sodium *ortho*-phenylphenylolate; SOPP

Trade Names: Dowicide; Dowicide A & A Flakes; Dowizid A; Mystox WFA; Natriphene; Preventol ON & ON Extra; Stopmold B; Topane

1.2 Structural and molecular formulae and molecular weights



$C_{12}H_9ONa$ Mol. wt: 192.3

$C_{12}H_9ONa.4H_20$ (tetrahydrate) Mol. wt: 264.3

1.3 Chemical and physical properties of the pure substance

From Windholz (1976), unless otherwise specified

(*a*) *Description*: White flakes (tetrahydrate)

(*b*) *Solubility:* The tetrahydrate is soluble in water (1220 g/kg), acetone (1560 g/kg), methanol (1380 g/kg), denatured alcohol formula no. 30 (3350 g/kg) and propylene glycol (280 g/kg); practically insoluble in petroleum fractions and pine oil

1.4 Technical products and impurities

In 1970, the specifications for one technical grade of sodium *ortho*-phenylphenate were given as: melting-point, 56-58°C; pH, 11.1-11.8 for a 2% water solution; a minimum of 95% sodium 2-phenylphenate tetrahydrate; maxima of 0.3% biphenyl ether, 0.1% *para*-phenylphenol and 0.01% α-naphthol (WHO, 1970). The tetrahydrate is available as 97% active flakes (Dow Chemical Co., 1976b), as aqueous solutions with various levels of active ingredient, as 0.5-5% active wax emulsions, and as a 0.2% paste (Thomson, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

ortho-Phenylphenol (and *para*-phenylphenol) is produced as a by-product in the hydrolysis of chlorobenzene with aqueous sodium hydroxide (Weaver *et al.*, 1979). The sodium salt is made by treating the free phenol with sodium hydroxide.

ortho-Phenylphenol was first produced commercially in the US in 1934 (US Tariff Commission, 1936), and the sodium salt was first produced in 1941-1943 (US Tariff Commission, 1945). In 1977, two US companies reported production of a total of 0.46-4.6 million kg *ortho*-phenylphenol, and six US companies reported production of 5.9-59.9 thousand kg sodium *ortho*-phenylphenate (NIH/EPA Chemical Information System, 1982). Since only one US company currently produces these chemicals, no production data are available (see preamble, section 8(*b*)(ii)).

Imports of *ortho*-phenylphenol through the principal US customs districts were last reported in 1979, when 68.2 thousand kg were imported (US International Trade Commission, 1980). Imports of sodium *ortho*-phenylphenate were last reported in 1973 when 5 thousand kg were imported (US Tariff Commission, 1974). Separate data on US exports of *ortho*-phenylphenol and sodium *ortho*-phenylphenate are not available.

ortho-Phenylphenol is believed to be produced commercially by one company in the Federal Republic of Germany and by one in Italy, and sodium *ortho*-phenylphenate by one company in the Federal Republic of Germany. Although these compounds have

apparently been produced commercially in Japan in the past, no evidence was found that they are produced there now.

(*b*) *Use*

ortho-Phenylphenol and sodium *ortho*-phenylphenate are used as fungicides and antibacterial agents in a wide variety of agricultural and nonagricultural applications. Agricultural use is believed to be largely in post-harvest treatment of fruits and vegetables. In 1978, 2.2 million kg of the sodium salt and free phenol were used for industrial purposes in the US (Trotz & Pitts, 1981).

The free phenol is a component of hard-surface cleaners, metal-working fluids, automotive gaskets, finished leather, paint and polishes (Trotz & Pitts, 1981). It is used in ceramic glazes, clay slips and phenolic disinfectants used in hospitals, households and industry (Dow Chemical Co., 1976a) and in the rubber industry (Windholz, 1976).

The sodium salt is used in adhesives, ceramic glazes, chemical toilets, clay slips, colloidal graphite, construction materials, feathers, floor waxes, metal-working fluids, paints and textiles (Trotz & Pitts, 1981). It is used in the leather industry, in the pulp and paper industry, and as a preservative in fire extinguisher solutions, water-colour printing inks, polyvinyl alcohol solutions and in a variety of household products (Dow Chemical Co., 1976b).

The Joint Meeting of the FAO Working Party of Experts and the WHO Expert Committee on Pesticide Residues in December 1969 established an acceptable daily intake of *ortho*-phenylphenol and of sodium *ortho*-phenylphenate for humans at 0-1.0 mg/kg bw. That Group also recommended the following tolerances for residues of *ortho*-phenylphenol and sodium *ortho*-phenylphenate on commodities (mg/kg): cherries and nectarines, 3; citrus, cucumbers, peppers (bell), pineapples and tomatoes, 10; sweet potatoes, apples and plums (fresh prunes), 15; carrots and peaches, 20; pears, 25; whole cantaloup melons, 120; and the edible part of cantaloups, 10 (WHO, 1970). In 1975, the Joint Committee recommended that the maximum residue limit for apples be increased to 25 mg/kg (WHO, 1976).

Tolerances in the US for residues of *ortho*-phenylphenol and sodium *ortho*-phenylphenate in or on raw agricultural commodities are established at 5-125 mg/kg, expressed as *ortho*-phenylphenol, for a variety of 21 fruits and vegetables (US Environmental Protection Agency, 1981). Sodium *ortho*-phenylphenate is exempt from a maximum level of 0.1% in preservative formulations applied to growing crops when used in accordance with 'good agricultural practice' (US Environmental Protection Agency, 1980).

ortho-Phenylphenol and sodium *ortho*-phenylphenate are approved for use in the US as preservatives in adhesives and glues in articles used in food packaging, and as components of defoaming agents used in the manufacture of paper and paperboard (US Food & Drug Administration, 1980). In addition, *ortho*-phenylphenol is permitted for use in the US as an antioxidant or antiozonant in rubber articles for repeated use in contact with food (total antioxidant or antiozonant content $\leqslant$5% by weight) and as a component of an aqueous sanitizing solution for use in food-contact articles at a level of 400 ppm (mg/l) (US Food & Drug Administration, 1980). Sodium *ortho*-phenylphenate is approved for use as a preservative in animal glues in articles used in food packaging and as a component (0.05% max) in closure-sealing gaskets for food containers (US Food & Drug Administration, 1980), and as a disinfectant for use in livestock markets and facilities for control of hog cholera and other communicable swine diseases, and to eradicate tuberculosis during insterstate transportation of animals (US Department of Agriculture, 1980).

2.2 Occurrence

(*a*) *Natural occurrence*

ortho-Phenylphenol and sodium *ortho*-phenylphenate are not known to occur as natural products.

(*b*) *Occupational exposure*

No data were available to the Working Group on the number of agricultural workers exposed to *ortho*-phenylphenol and its sodium salt, nor were separate data available on the number of workers exposed in the nonagricultural activities most likely to involve exposure to these compounds, namely, their production and their formulation into the products applied by agricultural workers. However, on the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that 544 thousand US workers in 67 nonagricultural industries were exposed to *ortho*-phenylphenol and 81 thousand US workers in 42 nonagricultural industries were exposed to sodium *ortho*-phenylphenate.

(*c*) *Water and sediments*

ortho-Phenylphenol was detected in one sample of groundwater during a survey in 1978 of treated waters in the UK. It was not detected in an initial survey of raw and treated waters (Fjelding *et al.*, 1981). It was also found in groundwater samples collected in the western suburbs of Melbourne, Australia, in 1978 (Stepan *et al.*, 1981). This compound was detected in sewage samples from Phoenix, Arizona, at concentrations of $\leqslant$0.008 μg/l, but was not detected in groundwater following sewage treatment by a rapid infiltration system (Tomson *et al.*, 1981).

ortho-Phenylphenol was detected in discharges from two of five US leather tanning plants in 1978 (Thruston & McGuire, 1981), and in raw waste from an unidentified textile finishing plant in the south-eastern US where it was reportedly used as a dye carrier (Gordon & Gordon, 1981). It was also detected in effluent and sludge from a water treatment plant in Putnam, Connecticut (Collins, 1976).

In a study carried out over four years in the Federal Republic of Germany, *ortho*-phenylphenol was detected in water samples from a water filtration plant at levels of 0.1-10 μg/l, in wastewater from sanitoria (includes *ortho*-phenylphenol and/or 6-chlorothymol) at levels of <1-95 μg/l, in the Ruhr River at levels of <0.1-1 μg/l, and in drinking-water at a concentration of 0.02 μg/l (Dietz & Traud, 1978).

(*d*) *Food, beverages and animal feeds*

In the Total Diet Program (a sampling of US food consumption) of the US Food and Drug Administration, *ortho*-phenylphenol was detected in food composites from 10-30 US cities during 1973-1976 at levels ranging from traces to 0.2 mg/kg in fruits and sugars and adjuncts from adult diet samples. In 1975-1976, it was not detected in infant diet samples, but it was found at a trace level in fruits and fruit juices from 'toddler' diet samples (Johnson & Manske, 1977; Manske & Johnson, 1977; Johnson *et al.*, 1981a,b).

Lemons used as raw material of marmalade in Japan contained 2.3 mg/kg *ortho*-phenylphenol on a whole basis (Ito *et al.*, 1979). No *ortho*-phenylphenol was detected in domestic Japanese citrus fruit samples (detection limit, 1 mg/kg), but residues were found

in samples of foreign citrus fruit (Ishiki *et al.*, 1980). Imported citrus fruits being sold in Kyoto, Japan, contained concentrations of 0.1-3.2 mg/kg; *ortho*-phenylphenol was not detected in imported bananas (Chikamoto *et al.*, 1981).

Residues of *ortho*-phenylphenol were detected in various varieties of Spanish oranges; in 86% of the samples, the levels were <10 mg/kg (Camps Alemany *et al.*, 1980).

(*e*) *Human tissues and secretions*

The serum of 10 infants with hyperbilirubinaemia who had been exposed to a germicidal phenolic solution containing 9.8% *ortho*-phenylphenol was analysed for the presence of three germicidal phenols. *ortho*-Phenylphenol was detected in the serum of seven infants in the range of 500-1900 ng/ml (Needham *et al.*, 1980).

2.3 Analysis

Standard methods used for the analysis of *ortho*-phenylphenol and sodium *ortho*-phenylphenate in a variety of matrices are listed in Table 1.

Table 1. Methods for the analysis of *ortho*-phenylphenol and sodium *ortho*-phenylphenate

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Citrus fruit	Reflux (dilute acid) ; steam distill	HPLC	not given	Farrow *et al.* (1977)
	Steam distill ; extract (heptane) ; derivatize (pentafluorobenzoic acid)	GC/ECD	0.13 mg/kg	Tanaka *et al.* (1978)
Citrus peel	Extract (acetone/dichloro-methane); chromatograph (Florisil)	GC/FID	not given	Bertling *et al.* (1978)
	Extract (dichloromethane) ; chromatograph (Florisil)	LC/UV	< 1 mg/kg	Ott (1978)
Citrus fruit wrappers	Extract (chloroform) ; extract (dilute aqueous sodium hydroxide); react with sulphuric acid, ferric iron and formaldehyde	Colorimetry	1 µg	Rajzman (1970)
Tomatoes	Extract (aqueous phosphoric acid) ; derivatize (4-amino-antipyrine)	Colorimetry	< 0.7 mg/kg	Markus & Puma (1971)
Urine	Automated acid hydrolysis; steam distill	LC/UV	1-2 mg/l	Ott (1979)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; HPLC, high-performance liquid chromatography; LC/UV, liquid chromatography/ultra-violet detection; GC/ECD, gas chromatography/electron capture detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were treated with *ortho*-phenylphenol [Dowicide 1, purity unspecified] as follows: At the age of seven days, they received a single dose of 100 mg/kg bw in 0.5% gelatine by gavage. Not taking into account subsequent weight gains, this treatment was repeated daily until the animals were weaned at the age of four weeks. Then 280 mg/kg of diet were fed until the end of the experiment, at 18 months. [The dose was the maximum tolerated dose for infant and young mice but not necessarily that for adults.] Appropriate negative (vehicle and untreated) and positive (using six known carcinogens) controls were also included in the study. No significant increase in tumour incidence was observed (National Technical Information Service, 1968; Innes *et al.*, 1969).

Rat: Groups of 25 male and 25 female 28-day-old Wistar-derived rats (Rochester strain) received a commercial diet supplemented with meat and containing 0, 0.02, 0.2 or 2% *ortho*-phenylphenol (Dowicide 1, with an assumed purity of at least 98%). Survival at the end of the two-year feeding period was 12-32%, allegedly unrelated to treatment [no break-down by individual group is given]. Apart from a significant growth retardation and increased testicular weight in the groups receiving the diet containing 2%, no treatment-related change was reported. The authors maintained that the pathological changes found, e.g., 'occasional tumours', 'chronic low grade nephritis' [incidence not given], were unrelated to treatment. According to the report, kidney and urinary bladder were among the tissues collected for histological examination (Hodge *et al.*, 1952). [The Working Group noted insufficiencies in reporting the details of the study.]

Groups of five-week-old Fischer 344/DuCrj rats were fed pelleted diet containing 0, 0.125, 0.25, 0.5, 1.0, 2.0 or 4.0% sodium *ortho*-phenylphenate (purity, at least 95%). In a preliminary experiment, using nine or 10 males and nine or 10 females per group, feeding was continued for 13 weeks, at which time the animals were killed; the estimated daily intake of sodium *ortho*-phenylphenate was about 85, 180, 350, 700, 1400 or 2500 mg/kg bw, respectively. No mortality occurred during this experiment, but tumours of the urinary bladder were found: papillomas occurred in 1/10 males fed 1%, in 4/10 at 2% and in 2/10 females at 2%; and transitional-cell carcinomas occurred in 5/10 males fed 2% and in 1/10 fed 4%. No such tumour was detected in other groups. In a further study, groups of 20 or 21 male rats received the same dietary concentrations described above, but for 91 weeks; the estimated daily intake of sodium *ortho*-phenylphenate was 62, 125, 250, 500, 1000 or 2000 mg/kg bw, respectively. Survival in the control and lower dose groups was about 90%, while survival was 57% and 71% in those receiving the diets with 2% and 4% of sodium *ortho*-phenylphenol, respectively. In this study, only malignant tumours were detected: transitional-cell carcinoma of the renal papilla in 1/21 rats at 0.5%, 1/21

[1]The Working Group was aware of a study in progress on *ortho*-phenylphenol by skin application to mice and by oral administration to rats and of a study planned in mice and hamsters by oral administration of sodium *ortho*-phenylphenate (IARC, 1981).

at 2%, and 10/20 at 4%; transitional-cell carcinoma of the renal pelvis in 1/21 at 0.5%, in 1/21 at 1% and in 3/20 at 4%; transitional-cell carcinoma of the urinary bladder in 6/21 at 1%, in 18/21 at 2% and in 8/20 at 4%; and one carcinosarcoma of the urinary bladder in a rat fed 2% sodium *ortho*-phenylphenate. Starting at the 45th week of treatment, haematuria was seen sporadically in all treated groups. Urinary bladder calculi were observed in eight out of 34 tumour-bearing animals, and tumours of the testes, adrenals and pituitary were also seen; the incidence of neoplasms at these sites [not specified] was not thought to be related to treatment (Hiraga & Fujii, 1981).

[The Working Group noted that in another 90-day experiment using groups of 30 male Fischer rats, eight to 11 weeks old, fed diets containing 2% *ortho*-phenylphenol (99.8% pure) or 2% sodium *ortho*-phenylphenate (at least 98.7% pure) no neoplastic lesion of the urinary tract was reported (Reitz *et al.*, 1982).]

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 1000 mg/kg bw *ortho*-phenylphenol [purity unspecified] in corn oil on the 28th day of life and were observed until they were about 78 weeks of age, at which time 15, 18, 18 and 16 mice were still alive. A group of negative controls comprised untreated animals and animals treated with gelatine, corn oil or dimethyl sulphoxide. No statistically significant increase in the incidence of tumours was observed in treated compared with control mice (National Technical Information Service, 1968). [The Working Group noted that a negative result following a single s.c. injection is not an adequate basis for discounting carcinogenicity.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

The oral LD_{50} of *ortho*-phenylphenol was about 2000 mg/kg bw in mice (Yanagisawa *et al.*, 1978) and 2700 mg/kg bw in male rats (Hodge *et al.*, 1952); the intragastric LD_{50} of *ortho*-phenylphenol in acacia suspension or nut oil solution was about 3000 mg/kg bw in rats and about 500 mg/kg bw in cats. The i.p. LD_{50} in rats of the acacia formulation was about 500 mg/kg bw and that of the nut oil formulation about 1500 mg/kg bw (Macintosh, 1945). The oral LD_{50} of sodium *ortho*-phenylphenate was 683-1018 and 812-857 mg/kg bw in male and female mice, respectively (Ogata *et al.*, 1979), and 1096 and 1049 in male and female rats, respectively (Tayama *et al.*, 1979).

Acute intoxication after oral administration of *ortho*-phenylphenol to rats and cats consisted of respiratory failure and haemorrhages in the lung, liver, gastrointestinal lumen and myocardium (Macintosh, 1945). The compound caused dermal damage when painted on rats and rabbits (Hanada, 1977).

Rats maintained for two years on a diet containing 2% *ortho*-phenylphenol showed slight growth retardation and acute and chronic inflammation of the kidney (Hodge *et al.*, 1952). The mean growth rate of rats given up to 200 mg/kg bw per day in nut oil for 32 days was similar to that of a control group. No sign of intoxication occurred in these

animals (Macintosh, 1945). Focal tubular necrosis was noted in the kidneys of rats fed 2% *ortho*-phenylphenol in the diet for 90 days. Thickening of the bladder epithelium was observed in rats fed similar doses of sodium *ortho*-phenylphenate (Reitz *et al.*, 1982).

Effects on reproduction and prenatal toxicity

Reductions in maternal and foetal body weight were noticed, but no malformation occurred when pregnant mice were administered 1450, 1740 or 2100 mg/kg bw per day *ortho*-phenylphenol or 100, 200 or 400 mg/kg bw per day sodium *ortho*-phenylphenate orally on days 7-15 of pregnancy (Ogata *et al.*, 1978a).

No embryotoxicity or teratogenicity was observed in Sprague-Dawley rats given 100, 300 or 700 mg/kg bw per day *ortho*-phenylphenol by gavage on days 6-15 of pregnancy (John *et al.*, 1981).

Absorption, distribution, excretion and metabolism

In dogs and cats, *ortho*-phenylphenol is excreted in the urine as the parent compound and as the glucuronide and sulphate conjugates (Savides & Oehme, 1980). In rats, *ortho*-phenylphenol and sodium *ortho*-phenylphate are excreted in the urine mainly as the glucuronide and sulphate conjugates; the parent compounds, 2,5-dihydroxybiphenyl and dihydroxybiphenyl conjugates have also been detected (Ernst, 1965; Reitz *et al.*, 1982)

Mutagenicity and other short-term tests

Sodium *ortho*-phenylphenate (Kawachi *et al.*, 1980 [details not given]) and *ortho*-phenylphenol (Shirasu *et al.*, 1978 [abstract]) were reported to be negative in the *rec* assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*) with and without exogenous metabolic activation. Positive results were obtained, however, with *ortho*-phenylphenol in an analogous repair test with *Escherichia coli* strains WP2, WP2 *uvrA*, CM571 (*recA*) and WP100 (*uvrA recA*) (Nishioka & Ogasawara, 1978 [abstract]).

ortho-Phenylphenol failed to induce mutations in *Escherichia coli* WP2 *hcr*$^-$. *ortho*-Phenylphenol (Shirasu *et al.*, 1978, Abstract) and its salt (Kawachi *et al.*, 1980 [details not given]; Reitz *et al.*, 1982) failed to induce reverse mutations in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 when tested with or without metabolic activation. It was reported that *ortho*-phenylphenol produced an ambiguous weak positive effect with strain TA98, both in the presence and absence of metabolic activation (Nishioka & Ogasawara, 1978 [abstract]). *ortho*-Phenylphenol was negative in a gradient assay in eight strains of *Salmonella* (*his* G46, TA1535, TA100, *his* C3076, TA1537, *his* D3052, TA1538 and TA95) and in *E. coli* WP2 and WP2 *uvrA* in the presence or absence of an Aroclor-induced rat liver preparation (Cline & McMahon, 1977). *ortho*-Phenylphenol was also negative in a host-mediated assay in mice treated orally with 200 or 600 mg/kg bw for five days (Shirasu *et al.*, 1978 [abstract]).

In *Aspergillus nidulans*, sodium *ortho*-phenylphenate [purity unspecified] increased homozygosis through incompletely defined mechanisms, including non-disjunction (Kappas & Georgopoulos, 1975 [abstract]).

No dominant lethal or specific locus mutation was induced by sodium *ortho*-phenylphenate in silkworms (Fukase *et al.*, 1978). Concentrations of 1-75 μg/ml failed to induce sister chromatid exchange in CHO-K1 cells (Nawai *et al.*, 1979 [abstract]) and there

was no evidence for the induction of unscheduled DNA synthesis in primary rat hepatocytes treated with concentrations of up to 10^{-4} M (Reitz *et al.*, 1982). No chromosomal aberration was induced by purified sodium *ortho*-phenylphenate in cultured Chinese hamster (CHO) cells (without exogenous metabolic activation) or in bone marrow from rats fed diets containing 1-4% of the compound for 13 weeks. Chromosomal aberrations were, however, reported to be induced in CHO cells by two commercial preparations (5-100 μg/ml) (Yoshida *et al.*, 1979).

ortho-Phenylphenol (technical grade) did not induce unscheduled DNA synthesis in primary cultures of adult rat hepatocytes (Probst *et al.*, 1981). Sister chromatid exchange was not induced in CHO cells cells by 5-50 μg/ml *ortho*-phenylphenol (Nawai *et al.*, 1979 [abstract]). No chromosomal abnormality was observed in bone-marrow cells from mice treated orally for five days with up to 800 mg/kg bw *ortho*-phenylphenol or with single oral doses of up to 4000 mg/kg bw (Shirasu *et al.*, 1978 [abstract]).

No dominant lethal mutation was induced in the offspring of male mice treated for two months with 4, 2, 1 or 0.5% sodium *ortho*-phenylphenate in the diet (Ogata *et al.*, 1978b [abstract]), nor in offspring of male rats treated for three months with 4, 2 or 1% sodium *ortho*-phenylphenate in the diet (Ogata *et al.*, 1980 [abstract]). Negative results were also obtained with male mice treated for five days with 100 or 500 mg/kg bw *ortho*-phenylphenol (Kaneda *et al.*, 1978 [abstract]; Shirasu *et al.*, 1978 [abstract]).

There was no evidence for the binding of ^{14}C-labelled sodium *ortho*-phenylphenate or *ortho*-phenylphenol to DNA in the urinary bladder of rats when measured 16 hours after oral administration of 500 mg/kg bw (Reitz *et al.*, 1982).

(*b*) *Humans*

Toxic effects

Solutions of 1 or 5% sodium *ortho*-phenylphenate caused irritation in a patch test in 100 men and 100 women, while 5% *ortho*-phenylphenol caused neither primary irritation nor sensitization (Hodge *et al.*, 1952).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

ortho-Phenylphenol was tested for carcinogenicity in mice and rats by administration in the diet. Sodium *ortho*-phenylphenate was tested in rats by administration in the diet. No evidence of carcinogenicity of *ortho*-phenylphenol was found in mice or rats, but both studies had some limitations. In rats, sodium *ortho*-phenyphenate is carcinogenic to the urinary tract, producing both benign and malignant tumours.

The available data were insufficient to evaluate the teratogenicity of sodium *ortho*-phenylphenate to experimental animals.

ortho-Phenylphenol and sodium *ortho*-phenylphenate have been subjected to a variety of mutagenicity tests, including those using rodents, without demonstrating any unambiguous mutagenic or DNA damaging effect. Commercial preparations have been reported to contain uncharacterized impurities capable of inducing chromosomal aberrations in cultured mammalian cells.

4.2 Human data

ortho-Phenylphenol was first made in commercial quantities in 1934, and sodium *ortho*-phenylphenate was introduced commercially in 1941-1943. Their production, formulation and use as fungicides and as antibacterial agents in agricultural applications and in a wide variety of industrial and household products are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of *ortho*-phenylphenol or sodium *ortho*-phenylphenate in humans.

No case report or epidemiological study of the carcinogenicity of *ortho*-phenylphenol or sodium *ortho*-phenylphenate alone was available to the Working Group. (See also the section 'Cancer Epidemiology of Pesticide Manufacturers, Formulators and Users'.)

4.3 Evaluation[1]

The available data are inadequate to evaluate the carcinogenicity of *ortho*-phenylphenol to experimental animals. Results of the experiments in rats provide *limited evidence* that sodium *ortho*-phenylphenate is carcinogenic to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of *ortho*-phenylphenol or sodium *ortho*-phenylphenate to humans.

---

[1] This evaluation should be read in conjunction with p. 18 of the preamble.

5. References

Bertling, L., Delventhal, J. & Tietz, I. (1978) Determination of diphenyl and *o*-phenylphenol in citrus fruits (Ger.). *Dtsch. Lebensm. Rundsch.*, *74*, 41-42

Camps Alemany, A., Alberola Matoses, J. & Cunat Broseta, P. (1980) Residual levels of fungicides used in orange and mandarin treatments following harvest (Span.). *EFCE Publ. Ser.*, *12* (Proceedings Congress Nacional de Quimica, 3rd, 1980, Vol. 2), 37-44 [*Chem. Abstr.*, *95*, 23054w]

Chikamoto, T., Tsuzuki, H., Konishi, T. & Kometani, T. (1981) Survey on the preservatives in imported citrus fruit and banana (Jpn.). *Kyoto-fu Eisei Kogai Kenkyusho Nempo*, *26*, 163-166 [*Chem. Abstr.*, *96*, 179607k]

Cline, J.C. & McMahon, R.E. (1977) Detection of chemical mutagens: Use of concentration gradient plates in a high capacity screen. *Res. Commun. Chem. Pathol. Pharmacol.*, *16*, 523-533

Collins, R.P. (1976) *Identification of Stable Organic Compounds in Waste Effluents*, prepared for the Office of Water Research and Technology, PB-256 562, Springfield, VA, National Technical Information Service

Dietz, F. & Traud, J. (1978) The trace analysis of phenols, especially chlorophenols, in water by gas chromatography - methods and results (Ger.). *Vom Wasser*, *51*, 235-257

Dow Chemical Co. (1976a) *Antimicrobial Agents*, Section I-1 Revised, Midland, MI, Dowicide 1 Antimicrobial

Dow Chemical Co. (1976b) *Antimicrobial Agents*, Section I-9 Revised, Midland, MI, Dowicide A Antimicrobial

Ernst, W. (1965) Conversion and elimination of 2-hydroxybiphenyl by rats (Ger.). *Arzneimittel Forsch.*, *15*, 632-636

Farrow, J.E., Hoodless, R.A., Sargent, M. & Sidwell, J.A. (1977) Fungicide residues. VI. Determination of residues of post-harvest fungicides on citrus fruit by high-performance liquid chromatography. *Analyst*, *102*, 752-758

Fjelding, M., Gibson, T.M., James, H.A., McLoughlin, K. & Steel, C.P. (1981) *Organic Micropollutants in Drinking Water*, Technical Report TR 159, Medmenham, UK, WRC Environmental Protection, Water Research Centre

Fukase, Y., Nisijima, H. & Murakami, A. (1978) Genetic effect of *ortho*-phenylphenol sodium salt on silkworm germ-cells. *Nippon Sanshigaku Zasshi*, *47*, 375-381

Gordon, A.W. & Gordon, M. (1981) Analysis of volatile organic compounds in a textile finishing plant effluent. *Trans. Ky. Acad. Sci.*, *42*, 149-157

Gore, R.C., Hannah, R.W., Pattacini, S.C. & Porro, T.J. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. *J. Assoc. off. anal. Chem.*, *54*, 1040-1082

Hanada, S. (1977) Studies on food additives, diphenyl (biphenyl) and *o*-phenylphenol from the view point of public health. Part 2. On the toxicities of diphenyl and *o*-phenylphenol (Jpn.). *J. Nagoya City Univ. med. Sch., 28,* 983-995 [*Chem. Abstr., 89,* 161662v]

Hiraga, K. & Fujii, T. (1981) Induction of tumours of the urinary system in F344 rats by dietary administration of sodium *o*-phenylphenate. *Food Cosmet. Toxicol., 19,* 303-310

Hodge, H.C. Maynard, E.A., Blanchet, H.J., Jr, Spencer, H.C. & Rowe, V.K. (1952) Toxicological studies or orthophenylphenol (Dowicide 1). *J. Pharmacol. exp. Ther., 104,* 202-210

IARC (1981) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity,* No. 9, Lyon, pp. 84, 133

Innes, J.R.M. Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Palotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst., 42,* 1101-1114

Ishiki, K., Tsumura, S. & Watanabe, T. (1980) Simultaneous analysis of food additives in foods. Part III. Determination of diphenyl, *o*-phenylphenol and thiabendazole in citrus fruits (Jpn.). *Nippon Nogei Kagaku Kaishi, 54,* 1045-1050 [*Chem. Abstr., 94,* 137876a]

Ito, Y., Toyoda, M., Ogawa, S., Iwaida, M. & Yanagida, F. (1979) Occurrence of orthophenylphenol during manufacture of lemon marmalade. *J. Food. Prot., 42,* 292-293

John, J.A., Murray, F.J., Ras, K.S. & Schwetz, B.A. (1981) Teratological evaluation of orthophenylphenol in rats. *Fundam. appl. Toxicol., 1,* 282-285

Johnson, R.D. & Manske, D.D. (1977) Pesticide and other chemical residues in total diet samples (XI). *Pestic. Monit. J., 11,* 116-131

Johnson, R.D., Manske, D.D. & Podrebarac, D.S. (1981a) Pesticide, metal, and other chemical residues in adult total diet samples - (XII) - August 1975-July 1976. *Pestic. Monit. J., 15,* 54-69

Johnson, R.D., Manske, D.D., New, D.H. & Podrebarac, D.S. (1981b) Pesticide, heavy metal, and other chemical residues in infant and toddler total diet samples - (II) - August 1975-July 1976. *Pestic. Monit. J., 15,* 39-50

Kaneda, M., Teramoto, S., Shingu, A. & Shirasu, Y. (1978) Teratogenicity and dominant lethal studies with *o*-phenylphenol. *J. Pestic. Sci., 3,* 365-370

Kappas, A. & Georgopoulos, S.G. (1975) Fungicides causing mitotic segregation in *Aspergillus* diploids (Abstract no. 31). *Mutat. Res., 29,* 236

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests* (*IARC Scientific Publications No. 27*), Lyon, pp. 323-330

Macintosh, F.C. (1945) The toxicity of diphenyl and *o*-phenyl-phenol. *Analyst*, *70*, 334-335

Manske, D.D. & Johnson, R.D. (1977) Pesticide and other chemical residues in total diet samples (X). *Pestic. Monit. J.*, *10*, 134-148

Markus, J.R. & Puma, B., eds (1971) *Pesticide Analytical Manual: Methods for Individual Pesticide Residues*, Vol. 2, Washington DC, US Food & Drug Administration, Pesticide Reg. Sec. 120.129

National Institute for Occupational Safety & health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards,* Cincinnati, OH, pp. 67, 81

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, pp. 1369, 9487-9491 (generics included); 900, 6939, 6940 (generics excluded)

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study*, Washington DC, US Department of Commerce, p. 87

Nawai, S., Yoshida, S., Nakao, T. & Hiraga, K. (1979) Examination of mutagens by induced sister chromatid exchange (SCE). II. Test of two fungicides by induced SCE *in vitro* (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, *30*, 51-53 [*Chem. Abstr.*, *94*, 25909g]

Needham, L.L., Hill, R.H., Jr, Paschal, D.C. & Sirmans, S.L. (1980) Determination of three germicidal phenols in serum of infants with hyperbilirubinemia. *Clin. chim. Acta*, *107*, 261-266

NIH/EPA Chemical Information System (1982) *TSCA - Plant and Production*, Washington DC, Information Sciences Corporation

Nishioka, J. & Ogasawara, H. (1978) Mutagenicity testing for diphenyl derivatives in bacterial systems (Abstract no. 22). *Mutat. Res.*, *54*, 248-249

Ogata, A., Ando, H., Kubo. Y. & Hiraga, K. (1979) Acute oral oxicity study of sodium *o*-phenylphenate (OPP-Na) in mice (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo, 30,* 54-56 [*Chem. Abstr., 93,* 126712x]

Ogata, A., Yoshida, S., Nawai, S., Ando, H., Kubo, Y., Hiraga, K. & Masubuchi, M. (1978b) Dominant lethal tests of long-term administration with sodium *o*-phenylphenol in mice (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, *29*, 99-103 [*Chem. Abstr.*, *93*, 108374j]

Ogata, A., Ando, H., Kubo. Y. & Hiraga, K. (1979) Acute oral toxicity study of sodium *o*-phenylphenate (OPP-Na) in mice (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo, 30,* 54-56 [*Chem. Abstr., 93,* 126712x]

Ogata, A., Ando, H., Kubo, Y. & Hiraga, K. (1980) Dominant lethal tests of long-term administration with sodium *o*-phenylphenol in rats (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, *31*, 17-19 [*Chem. Abstr.*, *95*, 1565m]

Ott, D.E. (1978) Evaluation of amperometric detector for liquid chromatographic determination of 2-phenylphenol residues in orange rind. *J. Assoc. off. anal. Chem.*, *61*, 1465-1468

Ott, D.E. (1979) Mechanized system for liquid chromatographic determination of 4-nitrophenol and some other phenolic pesticide metabolites in urine. *J. Assoc. off. anal. Chem.*, *62*, 93-99

Probst, G.S., McMahon, R.E., Hill, L.E., Thompson, C.Z., Epp, J.K. & Neal, S.B. (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. *Environ. Mutagenesis*, *3*, 11-32

Rajzman, A. (1970) A colorimetric method for the microdetermination of 2-phenylphenol. *Analyst*, *95*, 490-497

Reitz, R.H., Fox, T.R., Quast, J.F., Hermann, E.A. & Watanabe, P.G. (1982) Molecular mechanisms involved in the toxicity and carcinogenicity of orthophenylphenol and its sodium salt. *Chem.-biol. Interactions* (in press)

Savides, M.C. & Oehme, F.W. (1980) Urinary metabolism of orally administered *ortho*-phenylphenol in dogs and cats. *Toxicology*, *17*, 355-363

Shirasu, Y., Moriya, M., Kato, K., Tezuka, H., Henmi, R., Shingu, A., Kaneda, M. & Teramoto, S. (1978) Mutagenicity testing on *o*-phenylphenyl (Abstract no. 31). *Mutat. Res.*, *54*, 227

Stepan, S., Smith, J.F. & Riha, M. (1981) Movement and chemical change of organic pollutants in an aquifer. *Aust. Water Resour. Counc. Conf. Ser.*, *1*, 415-424

Tanaka, A., Nose, N., Suzuki, T., Hirose, A. & Watanabe, A. (1978) Application of an improved steam distillation procedure in residue analysis. I. Determination of biphenyl and 2-phenylphenol in citrus fruits. *Analyst*, *103*, 851-855

Tayama, K., Iguchi, S. & Hiraga, K. (1979) Acute oral toxicity of sodium *o*-phenylphenate (OPP-Na) in rats (Jpn.). *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo*, *30*, 57-65 [*Chem. Abstr.*, *93*, 162099m]

Thomson, W.T. (1979) *Agricultural Chemicals*, Book IV, *Fungicides*, Fresno, CA, Thomson Publications, p. 102

Thruston, A.D., Jr & McGuire, J.M. (1981) Characterization of organics in tannery effluents by liquid chromatography mass spectrometry. *Biomed. Mass Spectrom.*, *8*, 47-50

Tomson, M.B., Dauchy, J., Hutchins, S., Curran, C., Cook, C.J. & Ward, C.H. (1981) Groundwater contamination by trace level organics from a rapid infiltration site. *Water Res.*, *15*, 1109-1116

Trotz, S.I. & Pitts, J.J. (1981) *Industrial antimicrobial agents.* In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley & Sons, pp. 225-229, 249-253

US Department of Agriculture (1980) Animals and animal products. *US Code Fed. Regul., Title 9*, part 71.12, pp. 118-123; part 76.32, pp. 164-175

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul., Title 40*, part 180.129, pp. 546, 547; part 180.1001, pp. 605-607, 613, 618

US Environmental Protection Agency (1981) *o*-Phenylphenol; tolerances for pesticide chemicals in or on raw agricultural commodities. *US Code Fed. Regul., Title 40*, part 180; *Fed. Regist., 46*, pp. 27938, 27939

US Food & Drug Administration (1980) Food and drugs. *US Code Fed. Regul., Title 21*, part 175.105, pp. 111, 118, 122, 123; part 176.210, pp. 147, 173, 174; part 177.1210, pp. 191-194; part 177.2600, pp. 249-253; part 178.1010, pp. 255-259; part 178.3120, pp. 267, 268

US International Trade Commission (1980) *Imports of Benzenoid Chemicals and Products, 1979* (*USITC Publ. 1083*), Washington DC, US Government Printing Office, p. 112

US Tariff Commission (1936) *Dyes and Other Synthetic Organic Chemicals in the United States, 1934* (*Report No. 101, Second Series*) Washington DC, US Government Printing Office, p. 13

US Tariff Commission (1945) *Synthetic Organic Chemicals, Production and Sales, 1941-43* (*Report No. 153, Second Series*), Washington DC, US Government Printing Office, p. 79

US Tariff Commission (1974) *Imports of Benzenoid Chemicals and Products, 1973* (*TC Publ. 688*), Washington DC, US Government Printing Office, p. 93

Weaver, W.C., Simmons, P.B. & Thompson, Q.E. (1979) *Diphenyl and terphenyls*. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 7, New York, John Wiley & Sons, pp. 789-793

WHO (1970) *1969 Evaluations of Some Pesticide Residues in Food* (*WHO/Food Add./70.38*), Geneva, pp. 185-194

WHO (1976) 1975 Evaluations of some pesticide residues in foods. *WHO Pestic. Residue Ser., No. 5*, Geneva, pp. 351-354

Windholz, M., ed. (1976) *The Merck Index*, 9th ed., Rahway, NJ, Merck & Co., Inc., p. 7106

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, pp. 417, 419

Yanagisawa, F., Ueda, Y. & Tsuchida, M. (1978) Acute intoxication by *o*-phenylphenol (Jpn.). *Jpn. J. rural Med., 27*, 632-633 [*Pestic. Abstr.*, 79-0701]

Yoshida, S., Nawai, S. & Hiraga, K. (1979) Cytogenetic studies of sodium *o*-phenylphenate (Jpn.).*Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo, 30*, 44-47

RODENTICIDE

1-NAPHTHYLTHIOUREA (ANTU)

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 86-88-4

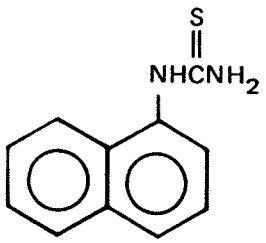
Chem. Abstr. Name: Thiourea, 1-naphthalenyl-

IUPAC Systematic Name: 1-(1-Naphthyl)-2-thiourea

Synonyms: Krysid; α-naphthothiourea; α-naphthylthiocarbamide; Antu; Chemical 109; α-naphthylthiourea; *N*-1-naphthylthiourea; *N*-(1-naphthyl)-2-thiourea; 1-(1-naphthyl)thiourea; U5227

Trade Names: Alrato; Anturat; Bantu; Chemical 109; Dirax; Kill Kantz; Kripid; Krysid PI; Naphtox; Rattrack; Rat-tu; Smeesana

1.2 Structural and molecular formulae and molecular weight



$C_{11}H_{10}N_2S$ Mol. wt: 202.3

1.3 Chemical and physical properties of the pure substance

From Worthing (1979), unless otherwise specified

(*a*) *Description*: Colourless crystals

(*b*) *Melting-point*: 198°C

(*c*) *Spectroscopy data*: Mass spectroscopy data have been reported (NIH/EPA Chemical Information System, 1981).

(*d*) *Solubility*: The technical product is slightly soluble in water (600 mg/l); soluble in acetone (24.3 g/l) and triethylene glycol (86 g/l)

(*e*) *Stability*: Stable on exposure to sun and air

1.4 Technical products and impurities

Technical 1-naphthylthiourea is a blue-grey powder (Worthing, 1979). It has been reported to have contained approximately 2% of 2-naphthylamine as an impurity (WHO, 1973). 1-Naphthylthiourea is available as 10% active baits in suitable protein- or carbohydrate-rich materials and as a 20% active tracking powder (Worthing, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

1-Naphthylthiourea was introduced as a commercial chemical in 1946 (Thomson, 1978). It is made by the reaction of 1-naphthyl isothiocyanate with ammonia (Worthing, 1979); 1-naphthyl isothiocyanate can be made by reacting 1-naphthylamine with thiophosgene.

1-Naphthylthiourea was first produced commercially in the US in 1946 (US Tariff Commission, 1948), but production has not been reported since 1953, when one company produced it (US Tariff Commission, 1954). Separate production data were reported only for 1947, when four companies produced a total of 64 thousand kg (US Tariff Commission, 1949). Imports through the principal US customs districts were last reported in 1975 when they amounted to 901 kg (US International Trade Commission, 1977); 3753 kg were imported in 1972 (US Tariff Commission 1973). Separate data on US exports are not available.

1-Naphthylthiourea is believed to be produced by one company each in France and the Federal Republic of Germany. It is not produced commercially in Japan.

(*b*) *Use*

1-Naphthylthiourea is used as a rodenticide for the control of adult Norway rats. It was widely used in the 1940s but has subsequently been replaced by other compounds in most countries (Thomson, 1978). It reportedly was withdrawn from use in the UK in 1967 (Davies *et al.*, 1982).

Since the US Environmental Protection Agency (1980) has determined 1-naphthylthiourea to be a hazardous waste, persons who discard or intend to discard it or products containing it must comply with the regulations of a Federal hazardous waste management

programme. Shipments of 1-naphthylthiourea in the US are subject to a wide variety of labelling, packaging, quantity and shipping restrictions consistent with its designation as a hazardous material (US Department of Transportation, 1981).

Permissible levels of 1-naphthylthiourea in the working environment have been established in at least 10 countries by regulation or recommended guidelines. These standards are listed in Table 1.

Table 1. National occupational exposure limits for 1-naphthylthiourea[a]

Country	Year	Air concentration (mg/m^3)	Interpretation[b]	Status
Australia	1978	0.3	Ceiling	Guideline
Belgium	1978	0.3	Ceiling	Regulation
Finland	1975	0.3	Ceiling	Regulation
Federal Republic of Germany	1979	0.3	TWA	Guideline
The Netherlands	1978	0.3	Ceiling	Guideline
Romania	1975	0.2	Average	Regulation
		0.6	Maximum	Regulation
Switzerland	1978	0.3	TWA	Regulation
USA OSHA[c]	1980	0.3	TWA	Regulation
USSR	1977	0.1	Maximum	Regulation
Yugoslavia	1971	0.3	Ceiling	Regulation
ACGIH[c,d]	1981	0.3	STEL	Guideline

[a]From International Labour Office (1980)
[b]TWA - time-weighted average; STEL - short-term exposure limit
[c]The OSHA regulation and the ACGIH guideline are used in the US for both agricultural and nonagricultural workers.
[d]From American Conference of Governmental Industrial Hygienists (1981)

2.2 Occurrence

(*a*) *Natural occurrence*

1-Naphthylthiourea is not known to occur as a natural product.

(*b*) *Occupational exposure*

On the basis of the 1974 National Occupational Hazard Survey, the National Institute for Occupational Safety and Health (1980, 1981) estimated that approximately 1100 US workers were exposed to 1-naphthylthiourea.

2.3 Analysis

Standard methods used for the analysis of 1-naphthylthiourea in a variety of matrices are listed in Table 2.

Table 2. Methods for the analysis of 1-naphthylthiourea

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Technical-grade and mixtures	Soxhlet extract (acetone)	Kjeldahl digestion and titration	not given	Horwitz (1965)
Air	Collect (Teflon filter) ; extract (methanol)	HPLC/UV	[0.1 mg/m^3]	Taylor (1979)

[a]Abbreviation: HPLC/UV, high-performance liquid chromatography/ultra-violet detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and female (C57BL/6 x AKR)F_1 mice received commercial 1-naphthylthiourea [purity unspecified] according to the following dose schedule: 2.15 mg/kg bw in 0.5% gelatine by stomach tube at seven days of age and the same amount (not adjusted for increasing body weight) daily up to 28 days of age; subsequently, the mice were given 6 mg/kg of diet. [The dose was the maximum tolerated dose for infant and young mice but not necessarily that for adults.] The experiment was terminated when the mice were about 18 months of age. Histological examinations of major organs and of all grossly visible lesions were carried out, however, neither the cranium nor the thyroid glands were dissected. No statistically significant elevation of the incidence of any type of tumour in any sex-strain subgroup or combination of groups occurred (National Technical Information Service, 1968; Innes *et al.*, 1969).

Rat: Groups of 18 male Osborne-Mendel rats, 21 days of age, received diets containing 0, 50, 100, 200, 400, 600 or 800 mg/kg 1-naphthylthiourea [purity unspecified] for two years. At histopathology, slight hyperplasia of the thyroid was seen in an increasing dose-related trend. No tumour was reported (Fitzhugh & Nelson, 1947). [The Working Group considered this study inadequate for evaluation of carcinogenicity because of limited group size and incomplete data on survival and tumours].

(*b*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice were given single s.c. injections of 4.64 mg/kg bw 1-naphthylthiourea [purity unspecified] in dimethyl sulphoxide on the 28th day of life

and were observed until they were about 78 weeks of age, at which time 16, 18, 17 and 15 mice were still alive. A group of negative controls comprised untreated animals and animals treated with gelatine, corn oil or dimethyl sulphoxide. No increase in tumour incidence was observed in treated mice in comparison with controls (National Technical Information Service, 1968). [The Working Group noted that a negative result obtained following a single s.c. injection is not an adequate basis for discounting carcinogenicity.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

Acute LD_{50} values for 1-naphthylthiourea are given in Table 3. There is remarkable variation in species susceptibility to i.p. administration, ranging from 2.5-10.00 mg/kg bw in rats (except for the Alexandrine strain) to 2500 mg/kg bw in chicken. The Norway rat is exceptionally vulnerable to parenteral and intragastric administration of this compound. Young Norway rats and dogs are more resistant to its toxic effects than adult animals (Dieke & Richter, 1946a,b).

Table 3. Acute LD_{50}s of 1-naphthylthiourea in various species[a]

Species	Route	LD_{50} (mg/kg bw)	
Mouse	i.p.	56.00	
Rat	i.p.	10.0	(Boyd Neal, 1976)
	i.p.	7.0	(Lisella *et al.*, 1971)
	i.p.	5.0	(DuBois *et al.*, 1947)
Norway, domestic I	i.p.	2.50	
Norway, domestic II	i.p.	6.25	
Norway, wild, adult	i.p.	6.20-8.10	
young	i.p.	16-58	
Alexandrine	i.p.	250.0	
Norway, wild	i.g.	6.90	
Guinea-pig	i.p.	140.0	(DuBois *et al.*, 1947)
	i.p.	350.0	
Rabbit	i.p. or i.g.	> 400.0	
Cat	i.g.	500.0	
Dog	i.p.	< 16.0	
	i.g.	38.0	
Chicken	i.p.	2500.0	
	i.g.	4250.0	
Monkey	i.p.	175	
	i.g.	4250	

[a]From Dieke & Richter (1946a,b), unless otherwise specified

The principal causes of death in susceptible rats are pleural effusion (McClosky & Smith, 1945; Richter, 1952) and pulmonary oedema (Richter, 1945, 1952; Cunningham & Hurley, 1972; Meyrick *et al.*, 1972; Böhm, 1973; Boyd, 1980). Symptoms appear in one-half to six hours, and death occurs within six to 36 hours (McClosky & Smith, 1945; Richter, 1952; Cunningham & Hurley, 1972). Laboured respiration and muscular weakness are the principal manifestations of toxic action (McClosky & Smith, 1945). Damage to the endothelial cells of the lung capillaries and the alveolar epithelium, allowing plasma leakage, is the apparent mechanism of the pulmonary oedema (Meyrick *et al.*, 1972).

Tolerance to 1-naphthylthiourea can be induced in susceptible animals by repeated sublethal doses (McClosky & Smith, 1945); multiple biochemical mechanisms appear to operate in the development of such tolerance (Boyd & Neal, 1976).

Toxic symptoms observed in laboratory animals given repeated sublethal doses of 1-naphthylthiourea include impaired weight gain and deformities of the legs and feet (Fitzhugh & Nelson, 1947); inhibition of hair growth and defective hair pigmentation (Dieke, 1947); thyroid hyperplasia (Fitzhugh & Nelson, 1947) and hypercholesterolaemia (Chanutin *et al.*, 1947); and fatty degeneration of the liver and bile-duct proliferation (McClosky & Smith, 1945). Other symptoms that have been reported are inhibition of pulmonary aniline hydroxylase activity, increased pulmonary aminopyrine demethylase activity (Heimann *et al.*, 1979) and inhibition of Na^+/K^+ ATPases in erythrocyte membranes and kidney microsomes (Patil & Radhakrishnamurty, 1978).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Absorption of 1-naphthylthiourea from the gut is rapid, especially in the presence of fat (Richter, 1945). Differences between oral and parenteral LD_{50} values suggest that gut absorption of this compound may be incomplete in some species.

1-Naphthylthiourea was metabolized by lung and liver microsomal preparations into α-naphthylurea and atomic sulphur. Available evidence indicates that the toxicity of this compound to the lung requires its activation by mixed-function oxidases at the thiocarbonyl moiety. It has been suggested that covalent binding of atomic sulphur or of a compound containing the carbonyl carbon of 1-naphthylthiourea to macromolecules of critical organs is responsible for its toxicity (Boyd & Neal, 1976; Lee *et al.*, 1980).

Mutagenicity and other short-term tests

1-Naphthylthiourea induced reverse mutations in *Salmonella typhimurium* strain TA1538 in the presence but not in the absence of Aroclor- or phenobarbital-induced rat liver microsomal preparations. A preparation purified by thin-layer chromatography was as active as a technical-grade preparation, thus excluding the attribution of activity to contaminating 2-naphthylamine (Kawalek *et al.*, 1979). When products of the reaction of 1-naphthylthiourea with nitrate were tested in *S. typhimurium* strain G46, no mutagenic activity was observed, even though nitrosation products were identified in the mixture by thin-layer chromatography and mass spectrometry (Seiler, 1977). [Attention is drawn, however, to the limited sensitivity and specificity of strain G46.]

A transformed phenotype was induced in Syrian hamster embryo cells *in vitro*, without the addition of a metabolizing system, by a preparation of 1-naphthylthiourea purified by thin-layer chromatography. A fraction containing several impurities of a commercial preparation (but not 1-naphthylthiourea itself) was also positive in this test (Kawalek *et al.*, 1979).

(*b*) *Humans*

Toxic effects

A number of cases of acute, nonfatal poisoning have been reported in association with the accidental or suicidal ingestion of a commercial mixture of 1-naphthylthiourea with chloralose used for killing rats (Favarel-Garrigues & Boget, 1968; Tempé & Kurtz, 1972). The symptoms observed, which resembled those due to chloralose alone, included some degree of coma combined with motor agitation and respiratory difficulty due to excessive secretion from the trachea and bronchi (Favarel-Garrigues & Boget, 1968). After deliberate ingestion of about 15 g 1-naphthylthiourea together with beverage alcohol, vomiting followed; 75 min later, the patient was severely dyspnoeic and cyanotic (Cimbal, 1952).

One case of eczema was attributed to occupational exposure to 1-naphthylthiourea (Laubstein, 1962).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No relevant data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1-Naphthylthiourea was tested for carcinogenicity in mice and rats by administration in the diet. The studies were considered to be inadequate for evaluation.

No data were available to evaluate the teratogenicity of 1-naphthylthiourea to experimental animals.

1-Naphthylthiourea was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic activation system. It induced a transformed phenotype in Syrian hamster embryo cells *in vitro*. There is limited evidence that 1-naphthylthiourea is mutagenic in cellular systems. No data were available to evaluate its mutagenicity to mammals.

4.2 Human data

1-Naphthylthiourea was introduced in 1946. Its production, formulation and use as a rodenticide are potential sources of exposure, both of workers and of the general population.

No data were available to evaluate the teratogenic or chromosomal effects of 1-naphthylthiourea in humans.

No case report or epidemiological study of the carcinogenicity of 1-naphthylthiourea was available to the Working Group.[1]

4.3 Evaluation

The available data were inadequate to evaluate the carcinogenicity of 1-naphthylthiourea to experimental animals. No data on humans were available.

The available data are insufficient to evaluate the carcinogenicity of 1-naphthylthiourea to humans.

5. References

American Conference of Governmental Industrial Hygienists (1981) *TLVs*^{R} *Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981*, Cincinnati, OH, p. 10

Böhm, G.M. (1973) Changes in lung arterioles in pulmonary oedema induced in rats by alpha-naphthylthiourea. *J. Pathol.*, *110*, 343-345

Boyd, M.R. (1980) Biochemical mechanisms in chemical-induced lung injury: Roles of metabolic activation. *CRC crit. Rev. Toxicol.*, *7*, 103-176

Boyd, M.R. & Neal, R.A. (1976) Studies on the mechanism of toxicity and of development of tolerance to the pulmonary toxin, α-naphthylthiourea (ANTU). *Drug Metab. Disposition*, *4*, 314-322

---

[1]Subsequent to the meeting, the Working Group became aware of a study by Davies *et al.* (1982) in which 12 cases of urothelial tumour were reported among rodent operatives in England who used 1-naphthylthiourea which contained up to 0.2% 2-naphthylamine.

Chanutin, A., Gjessing, E.C. & Ludewig, S. (1947) Alpha naphthylthiourea (ANTU) in dogs: Electrophoretic and cholesterol studies on blood plasma and pleural effusion. *Proc. Soc. exp. Biol. Med.*, *64*, 174-179

Cimbal, G. (1952) α-Naphthylthiourea poisoning in humans (Ger.). *Samml. Vergiftungsfällen (Arch. Toxicol.), 14,* 2-6

Cunningham, A.L. & Hurley, J.V. (1972) Alpha-naphthyl-thiourea-induced pulmonary oedema in the rat: A topographical and electron-microscope study. *J. Pathol.*, *106*, 25-35

Davies, J.M., Thomas, H.F. & Manson, D. (1982) Bladder tumours among rodent operatives handling ANTU. *Br. med. J.*, *285*, 927-931

Dieke, S.H. (1947) Pigmentation and hair growth in black rats, as modified by the chronic administration of thiourea, phenyl thiourea and alpha-naphthyl thiourea. *Endocrinology*, *40*, 123-136

Dieke, S.H. & richter, C.P. (1946a) Age and species variations in the acute toxicity of alpha-naphthyl thiourea. *Proc. Soc. exp. Biol. Med.*, *62*, 22-25

Dieke, S.H. & Richter, C.P. (1946b) Comparative assays of rodenticides on wild Norway rats. I. Toxicity. *Public Health Rep.*, *61*, 672-679

DuBois, K.P., Herrmann, R.G. & Erway, W.F. (1947) Studies on the mechanism of action of thiourea and related compounds. III. The effect of acute poisoning on carbohydrate metabolism. *J. Pharmacol. exp. Ther., 89,* 186-195

Favarel-Garrigues, J.-C. & Boget, J.C. (1968) Acute intoxications by raticides based on chloralose and ANTU (Fr.). *Concours méd.*, *90*, 2289-2298

Fitzhugh, O.G. & Nelson, A.A. (1947) Chronic oral toxicity of alpha-naphthyl thiourea. *Proc. Soc. exp. Biol. Med.*, *64*, 305-310

Heimann, R., Skornik, W. & Jaeger, R.J. (1979) Biochemical changes in guinea pig lungs following exposure to plastic combustion products, paraquat, or ANTU (Abstract no. 115). *Toxicol. appl. Pharmacol.*, *48*, A 58

Horwitz, W., ed. (1965) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 10th ed., Washington DC, Association of Official Analytical Chemists, pp. 16, 53-54

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natl Cancer Inst., 42,* 1101-1114

International Labour Office (1980) *Occupational Expousre Limits for Airborne Toxic Substances*, 2nd rev. ed. (*Occupational Safety & Health Series No. 37*), Geneva, pp. 46-47

Kawalek, J.C., Andrews, A.W. & Pienta, R.J. (1979) 1-Naphthylthiourea: A mutagenic rodenticide that transforms hamster embryo cells. *Mol. Pharmacol.*, *15*, 678-684

Laubstein, H. (1962) Contact eczema from a rodenticide (Ger.). *Berufdermatosen, 10*, 154-160

Lee, P.W., Arnau, T. & Neal, R.A. (1980) Metabolism of α-naphthylthiourea by rat liver and rat lung microsomes. *Toxicol. appl. Pharmacol., 53*, 164-173

Lisella, F.S., Long, K.R. & Scott, H.G. (1971) Toxicology of rodenticides and their relation to human health. Part II. *J. environ. Health, 33*, 361-365

McClosky, W.T. & Smith, M.I. (1945) Studies on the pharmacologic action and the pathology of alphanaphthylthiourea (ANTU). I. Pharmacology. *Public Health Rep., 60*, 1101-1113

Meyrick, B., Miller, J. & Reid, L. (1972) Pulmonary oedema induced by ANTU or by high or low oxygen concentration in rat - an electron microscopic study. *Br. J. exp. Pathol., 53*, 347-358

Muir, C.S. & Wagner, G., eds (1981) *Directory of On-Going Research in Cancer Epidemiology* (*IARC Scientific Publications No.38*), Lyon, p. 258

National Institute for Occupational Safety & Health (1980) *Projected Number of Occupational Exposures to Chemical and Physical Hazards*, Cincinnati, OH, p. 66

National Institute for Occupational Safety & Health (1981) *National Occupational Hazard Survey* (microfiche), Cincinnati, OH, p. 8387

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study*, Washington DC, US Department of Commerce, p. 85

NIH/EPA Chemical Information System (1981) *Mass Spectral Search System*, Washington DC, Information Sciences Corporation

Patil, T.N. & Radhakrishnamurty, R. (1978) Effect of alpha-naphthylthiourea on (Na^+ + K^+)-ATPases in albino rats. *Indian J. Biochem. Biophys., 15*, 294-298

Richter, C.P. (1945) The development and use of alpha-naphthyl thiourea (ANTU) as a rat poison. *J. Am. med. Assoc., 129*, 927-931

Richter, C.P. (1952) The physiology and cytology of pulmonary oedema and pleural effusion produced in rats by alpha-naphthylthiourea (ANTU). *J. thoracic Surg., 23*, 66-91

Seiler, J.P. (1977) Nitrosation *in vitro* and *in vivo* by sodium nitrite, and mutagenicity of nitrogenous pesticides. *Mutat. Res., 48*, 225-236

Taylor, D.G. (1979) *NIOSH Manual of Analytical Methods*, Vol. 5, *Method S276 DHEW (NIOSH)*, Washington DC, US Government Printing Office, pp. S276-1 - S276-6

Tempé, J.-D. & Kurtz, D. (1972) Acute intoxication by chloralose (Fr.). *Concours méd., 94*, 801-811

Thomson, W.T. (1978) *Agricultural Chemicals*, Book III, *Miscellaneous Chemicals*, Fresno, CA, Thomson Publications, p. 143

US Department of Transportation (1981) Use of United Nations shipping descriptions. *US Code Fed. Regul., Title 49*, part 172, pp. 29392, 29421

US Environmental Protection Agency (1980) Protection of environment. *US Code Fed. Regul., Title 40*, part 261.33, pp. 918-921

US International Trade Commission (1977) *Imports of Benzenoid Chemicals and Products, 1975* (*USITC Publ. 806*), Washington DC, US Government Printing Office, p. 99

US Tariff Commission (1948) *Synthetic Organic Chemicals, Production and Sales, 1946* (*Report No. 159, Second Series*), Washington DC, US Government Printing Office, p. 134

US Tariff Commission (1949) *Synthetic Organic Chemicals, Production and Sales, 1947* (*Report No. 162, Second Series*), Washington DC, US Government Printing Office, pp. 57, 138

US Tariff Commission (1954) *Synthetic Organic Chemicals, Production and Sales, 1953* (*Report No. 194, Second Series*), Washington DC, US Government Printing Office, p. 134

US Tariff Commission (1973) *Imports of Benzenoid Chemicals and Products, 1972* (*TC Publ. 601*), Washington DC, US Government Printing Office, p. 96

WHO (1973) *Safe Use of Pesticides* (*WHO tech. Rep. Ser., 513*), Geneva, p. 40

Worthing, C.R., ed. (1979) *The Pesticide Manual. A World Compendium*, 6th ed., Croydon, UK, British Crop Protection Council, p. 19

APPENDIX: GENERAL CONSIDERATIONS ON *N*-NITROSATABLE PESTICIDES

Introduction

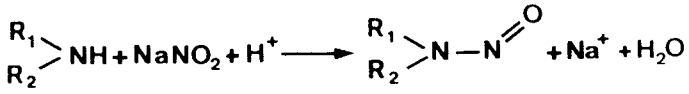
Many *N*-nitroso compounds (nitrosamines and nitrosamides) have been shown to be carcinogenic in experimental animals (IARC, 1978). Formation of *N*-nitroso compounds is theoretically possible from all compounds that contain amino groups, and the significance of this possibility for humans is discussed in detail in a recent review on nitrates and nitrites (National Academy of Sciences, 1981). Secondary amines react directly; tertiary and, in some cases, primary amines may react by more complicated mechanisms. Figure 1 shows the reaction products of the *N*-nitrosation of a primary, secondary and tertiary amine with R_1, R_2 and R_3, which may be virtually any organic group.

Figure 1. Formation of *N*-nitroso compounds by the *N*-nitrosation of primary, secondary and tertiary amine compounds

Amine	N-Nitrosamine
RNH_2	R_2N-NO
R_1R_2NH	R_1R_2N-NO
$R_1R_2R_3N$	R_1R_2N-NO, R_2R_3N-NO, R_1R_3N-NO

Chemistry of *N*-nitrosation

The formation of nitrosamines from secondary amines and nitrite at acid pH can be described by the following equation:



In reality, the chemistry of this reaction is much more complicated (Ridd, 1961; Challis & Butler, 1968; Fridman *et al.*, 1971). For amines, the effective nitrosating agent is N_2O_3, which is formed from nitrite in acidic aqueous media. Only the free, unprotonated amine, and not the amine salt, is available for nitrosation. As a result, the reaction rate is heavily dependent on pH: low pH favours formation of N_2O_3 from nitrite, but also favours protonation of the amine; at higher pH, free amine is available, but N_2O_3 formation is reduced. It follows that the nitrosation of basic amines shows a pH optimum (usually pH 3.0-3.5) and is dependent on the basicity (pK_a) of the amine. The data in Table 1 demonstrate that less basic amines are much more easily nitrosated at the pH optimum than are strongly basic amines.

Table 1. Rate constants of nitrosation of amines with nitrite at optimal pH and 25°C[a]

Amine	pK_a	pH optimum	Rate constant K_2 ($mol^{-2} \times sec^{-1}$)
Piperidine	11.2	3.0	0.00045
Dimethylamine	10.7	3.4	0.0017
N-Methylbenzylamine	9.5	3.0	0.013
Morpholine	8.7	3.4	0.42
Mononitrosopiperazine	6.8	3.0	6.7
Piperazine	5.6	3.0	83

[a]From Mirvish (1975)

The nitrosation of weakly basic secondary amines has in general no pH optimum: as the pH changes from 3 to 1, nitrosation increases by a factor of 10 per pH unit. The nitrosating agent is usually the nitrosyl cation NO^+.

Tertiary amines may also undergo nitrosation (Hein, 1963; Smith & Loeppky, 1967). The reaction rate is, however, usually appreciably lower than that of the nitrosation of secondary amines and is maximal at weakly acid pH (pH 3-6). The nitrosative cleavage of a C-N-bond probably leads to immonium intermediates, which either hydrolyse to form a secondary amine (Smith & Loeppky, 1967) or react directly with nitrite to form nitrite esters, which rearrange to form the nitrosamine (Lijinsky *et al.*, 1972).

Catalysis

Nitrosation reactions can be catalysed by a variety of chemicals. Chloride and thiocyanate ions are simple inorganic catalysts (Boyland *et al.*, 1971; Fan & Tannenbaum, 1973), which probably act by forming highly reactive nitrosyl halides or analogous

compounds, such as nitrosyl thiocyanates (Challis & Butler, 1968). Chloride ion is a normal component of the stomach fluid, and thiocyanate ion is present in saliva. These ions play a role in nitrosation only under acid conditions.

Aldehydes such as formaldehyde, chloral (Keefer & Roller, 1973), benzaldehyde and pyridoxal (vitamin B_6) (Archer *et al.*, 1976) catalyse nitrosation reactions, probably by the formation of nitrite esters *via* methylene-immonium intermediates. The esters then rearrange to form nitrosamine and aldehyde. It is important to note that formaldehyde catalysis also leads to formation of nitrosamines in neutral and even in strongly alkaline media (Keefer & Roller, 1973).

Diphenols, such as 4-methylcatechol, are also effective catalysts (Challis & Bartlett, 1975; Davies *et al.*, 1978; Pignatelli *et al.*, 1980), as are micelle-forming surface-active compounds, such as lecithin (Okun & Archer, 1976). Bacteria have also been shown to catalyse nitrosation reactions (Archer *et al.*, 1978).

Inhibition

Competition by inhibitors for a nitrosating agent may prevent nitrosamine formation or decrease reaction yields. Ascorbic acid is probably the most effective inhibitor (Mirvish *et al.*, 1972); a reaction between ascorbic acid and a nitrosating agent forms NO from N_2O_3 and dehydroascorbic acid (Dahn *et al.*, 1960). Another important nitrosation inhibitor is α-tocopherol (vitamin E) (Mergens *et al.*, 1978).

Examples of other compounds that compete with nitrosatable amines for available nitrite are amino acids, urea, amidosulphonic acids and primary amines. The simultaneous presence, for example, of primary and secondary amino groups in a nitrosation mixture usually favours *N*-nitrosation over deamination (Paulsen & Mäckel, 1969; Mirvish, 1971).

N-Nitrosation *in vivo*

Many experiments in animals, and some observations in humans, have shown that nitrosation reactions can occur *in vivo*, mainly in the stomach. The extent to which they occur depends, however, on the relative concentrations of substrates, catalysts and inhibitors, and is influenced by the inhomogeneity of the stomach contents, by pH and by many other factors. Thus, quantitative prediction of nitrosation rates and yields *in vivo* is at present impossible.

One reactant, nitrite, is a normal constituent of human saliva; it is also a common constituent of many diets because sodium nitrite is used in meat curing. Its concentration in saliva depends largely on the nitrate intake in food and drinking-water. After reabsorption from the gut, dietary nitrate is partially secreted *via* the salivary glands into the mouth, where about 20% is reduced to nitrite by bacteria (Tannenbaum *et al.*, 1974; Spiegelhalder *et al.*, 1976; Tannenbaum *et al.*, 1976).

N-Nitrosation in chemical systems

Pesticides containing secondary amino groups form the corresponding *N*-nitroso compounds by interaction with nitrite in acidic solution. Eisenbrand *et al.* (1974) investigated possible endogenous nitrosamine formation in animals, but exogenous formation might also occur if nitrogen oxides are present in the environment. It has been shown that nitrogen oxides, even in low concentrations, are powerful nitrosating agents for secondary amines in solution (Challis *et al.*, 1978); moreover, they also react easily with solid substances (Eisenbrand *et al.*, 1979). This kind of reaction has been shown to occur during storage and application of pesticides (Ross *et al.*, 1977; Janzowski *et al.*, 1980).

Nitrosation of pesticides

Elespuru and Lijinsky (1973), Eisenbrand *et al.* (1974), Elespuru *et al.* (1974), Sen *et al.* (1975) and Mirvish (1975) showed that pesticides containing secondary and tertiary amine groups may react with nitrite to form *N*-nitroso compounds. As would be expected, reaction rate varies considerably and depends on the type of amino compound, pH and temperature. Such reactions could provide a significant source of exposure of humans to *N*-nitroso derivatives of pesticides, some of which are carcinogenic. The *N*-nitroso derivatives formed from several pesticides are listed in Table 2.

Table 2. *N*-Nitroso compounds formed from pesticides

Pesticide	*N*-Nitroso compound formed	References
Aldicarb	*N*-nitrosoaldicarb	Seiler (1977a) ; Lijinsky & Schmähl (1978)
Atrazine	*N*-nitrosoatrazine	Eisenbrand *et al.* (1975b) ; Kearney *et al.* (1977) ; Cohen *et al.* (1978) ; Janzowski *et al.* (1980)
Benfluralin	*N*-nitrosobutylethylamine	Cohen *et al.* (1978)
Benomyl	*N*-nitrosobenomyl	Börzsönyi & Pintér (1977)
Benzthiazuron	*N*-nitrosobenzthiazuron	Ungerer *et al.* (1974) ; Eisenbrand *et al.* (1975b) ; Seiler (1977a)
Butralin	*N*-nitrosobutralin	Cohen *et al.* (1978) ; Oliver & Konston (1978) ; Zweig *et al.* (1980)
Bux-Ten	*N*-nitrosobux-ten	Lijinsky & Schmähl (1978)
Carbaryl	*N*-nitrosocarbaryl	Elespuru & Lijinsky (1973) ; Eisenbrand *et al.* (1975b) ; Uchiyama *et al.* (1975) ; Egert & Greim (1976a) ; Seiler (1977a) ; Lijinsky & Schmähl (1978)
Carbendazim	*N*-nitrosocarbendazim	Börzsönyi & Pintér (1979)

Pesticide	*N*-Nitroso compound formed	References
Carbofuran	*N*-nitrosocarbofuran	Seiler (1977a) ; Lijinsky & Schmähl (1978)
Chloroxuron	*N*-nitrosodimethylamine	Egert & Greim (1976b)
Cycluron	*N*-nitrosodimethylamine	Egert & Greim (1976b)
Daminozide	*N*-nitrosodimethylamine	Sen *et al.* (1975)
Dimefox	*N*-nitrosodimethylamine	Egert & Greim (1976b)
Dinitralin	*N*-nitrosodiethylamine	Zweig *et al.* (1980)
Dodine	*N*-nitrosododine	Egert & Greim (1976a) ; Seiler (1977a)
Ethiofencarb	*N*-nitrosoethiofencarb	Seiler (1977a)
Fenuron	*N*-nitrosodimethylamine	Börzsönyi & Pintér (1979)
Ferbam	*N*-nitrosodimethylamine	Sen *et al.* (1975)
Fluchloralin	*N*-nitroso-*N*-(2-chloro-ethyl) propylamine	Zweig *et al.* (1980)
Glyphosate	*N*-nitrosoglyphosate	Khan & Young (1977) ; Seiler (1977a)
Isopropalin	*N*-nitrosodipropylamine	Cohen *et al.* (1978) ; Zweig *et al.* (1980)
Landrin	*N*-nitrosolandrin	Lijinsky & Schmähl (1978)
MCPA (as an amine salt)	*N*-nitrosodimethylamine	Cohen *et al.* (1978)
Methomyl	*N*-nitrosomethomyl	Lijinsky & Schmähl (1978)
Oryzalin	*N*-nitrosodipropylamine	Cohen *et al.* (1978)
Pendimethalin	*N*-nitrosopendimethalin	Bontoyan *et al.* (1979) ; Zweig *et al.* (1980)
Prometryn	*N*-nitrosoprometryn	Egert & Greim (1976a)
Propoxur	*N*-nitrosopropoxur	Eisenbrand *et al.* (1975b) ; Seiler (1977a) ; Lijinsky & Schmähl (1978)
Simazine	*N*-nitrososimazine	Eisenbrand *et al.* (1975b) ; Janzowski *et al.* (1980)
Thiram	*N*-nitrosodimethylamine	Sen *et al.* (1975) ; Egert & Greim (1976b)
Trifluralin	*N*-nitrosodipropylamine	Cohen *et al.* (1978) ; Fanelli *et al.* (1978) ; Zweig *et al.* (1980)
Triforin	1,4-dinitrosopiperazine	Börzsönyi & Pintér (1979)
Ziram	*N*-nitrosodimethylamine	Eisenbrand *et al.* (1974, 1975b)

Contamination by nitrosamines has been reported in two classes of herbicides - amine salts and dinitroaniline compounds (Ross *et al.*, 1977; Cohen *et al.*, 1978). The concentration of *N*-nitrosodimethylamine (NDMA) in herbicides formulated as dimethylamine salts ranged between 187 and 640 ppm. This contamination was thought to have resulted from the reaction of dimethylamine with sodium nitrite added as a rust inhibitor in the drums used for distribution. *N*-Nitrosodipropylamine (NDPA) was found in the herbicide trifluralin at concentrations ranging from 11 to 202 ppm. The actual mechanism of formation of the NDPA found in the dinitroaniline compounds is not completely understood; proposed mechanisms are transnitrosation and a synthetic route which involves ring nitrosation with nitric and sulphuric acids followed by the addition of dipropylamine. *N*-Nitrosodipropylamine is formed from the reaction of the residual nitrosating agents with dipropylamine (Von Rumker *et al.*, 1975).

Pesticides with reactive amino groups can react with a source of nitrosation to yield the corresponding nitrosamine. The reaction yield of NDMA from thiram was 5.7%, that from ziram, 2%, that from ferbam, 1.6% and that from daminozide, 1.4% (Sen *et al.*, 1975). The yield of NDMA from ziram increases from 1.6% of theoretical to approximately 8% as the concentration of sodium nitrite increases by a 20 molar excess. The conditions for this yield were a reaction time of 10 min at pH 2 and at 37°C. The rate of formation of NDMA is dependent on pH, the yield decreasing with increasing pH. The pH optimum for formation of NDMA from ziram is 1.5-2.0 (Eisenbrand *et al.*, 1974).

N-Nitrosation in a 10^{-3} molar solution for 15 min with a 5:1 molar ratio of sodium nitrite at pH 1 and 37°C was within the theoretical yield: 7.9% for atrazine, 7.1% for simazine, 8.1% for benzthiazuron, 5.2% for propoxur and 1.2% for carbaryl. The yield of *N*-nitroso compounds is reduced significantly at lower concentrations, according to the laws of chemical kinetics (Eisenbrand *et al.*, 1975a).

Certain classes of chemical compounds have a greater probability of forming *N*-nitroso compounds than others. These are: dialkyl thiocarbamates and thiocarbamoyl disulphides, dimethylamine salts of phenoxyacetic acid herbicides, substituted dinitroaniline derivatives, di- and triethanolamine salts of several pesticides and some morpholine derivatives (National Academy of Sciences, 1981). A list of pesticides (excluding those listed in Table 2) that possibly contain *N*-nitroso compounds is given in Table 3 (Zweig *et al.*, 1980; National Academy of Sciences, 1981).

Table 3. Other pesticides that possibly contain *N*-nitroso compounds[a]

Chemical class	Pesticide	Use	Reference
Amides	Alachlor	herbicide	Zweig *et al.* (1980)
	Chlorothiamid	herbicide	Seiler (1977a)
	Diphenamid	herbicide	Zweig *et al.* (1980)
	Niclosamide	molluscicide	Zweig *et al.* (1980)
	Propyzamid	herbicide	Seiler (1977a)
Carbamates and thiocarbamates	BPMC	insecticide	Uchiyama *et al.* (1975)
	Cypendazole	fungicide	Seiler (1977a)
	Dimethoate	insecticide	Seiler (1977a)
	Dioxacarb	insecticide	Seiler (1977a)
	Ethiofencarb	insecticide	Zweig *et al.* (1980)
	Formelanate	insecticide	Seiler (1977a)
	Isoprocarb	insecticide	Uchiyama *et al.* (1975)

Chemical class	Pesticide	Use	Reference
	Methiocarb	insecticide	Zweig *et al.* (1980)
	Phenmedipham	herbicide	Seiler (1977a)
	Propham	herbicide	Seiler (1977a)
	Sulfallate[b]	herbicide	Zweig *et al.* (1980)
	Swep	herbicide	Seiler (1977a)
	Triallate	herbicide	Zweig *et al.* (1980)
Triazines	Ametryne	herbicide	Zweig *et al.* (1980)
	Anilazine	fungicide	Zweig *et al.* (1980)
	Cyanazine	herbicide	Zweig *et al.* (1980)
	Metribuzin	herbicide	Zweig *et al.* (1980)
	Propazine	herbicide	Zweig *et al.* (1980)
Organophosphates	Acephate	insecticide	Zweig *et al.* (1980)
	Azinphos-methyl	insecticide	Zweig *et al.* (1980)
	Dialifos	insecticide	Zweig *et al.* (1980)
	Dicrotophos	insecticide	Zweig *et al.* (1980)
	Fenamiphos	nematicide	Zweig *et al.* (1980)
	Isofenphos	insecticide	Zweig *et al.* (1980)
	Methamidophos	insecticide	Zweig *et al.* (1980)
	Monocrotophos	insecticide	Zweig *et al.* (1980)
Substituted ureas	Buturon	herbicide	Seiler (1977a)
	Chlorobromuron	herbicide	Seiler (1977a)
	Chlorotoluron	herbicide	Seiler (1977a)
	Diuron	herbicide	Zweig *et al.* (1980)
	Fluometuron[b]	herbicide	Seiler (1977a)
	Linuron	herbicide	Zweig *et al.* (1980)
	Methabenzthiazuron	herbicide	Seiler (1977a)
	Metoxuron	herbicide	Seiler (1977a)
	Monolinuron	herbicide	Seiler (1977a)
	Monuron	herbicide	Seiler (1977a)
	1-Naphthylthiourea (ANTU)[b]	rodenticide	Seiler (1977a)
Miscellaneous	Chlorothalonil[b]	fungicide	Zweig *et al.* (1980)
	Fenaminosulf	fungicide	Zweig *et al.* (1980)
	Maleic hydrazide	growth retarder	Zweig *et al.* (1980)
	Quinomethionate	insecticide/ fungicide	Zweig *et al.* (1980)

[a]Excluding compounds listed in Table 2
[b]Compounds evaluated in this volume

Some selected methods for analysis of *N*-nitrosamines have been described in IARC publications (Walker *et al.*, 1980; Bartsch *et al.*, 1982).

Experimental evidence of carcinogenic and mutagenic effects of *N*-nitrosatable pesticides

N-Nitroso compounds may be formed *in vivo* by the reaction of a pesticide with nitrous acid. References to reports of available carcinogenicity tests on selected *N*-nitrosatable pesticides, administered alone or in conjunction with sodium nitrite, and on the *N*-nitrosation products of some pesticides are given in Tables 4 and 5.

References to reports of short-term assays of *N*-nitrosatable pesticides and/or their *N*-nitrosated products are tabulated in Table 6. None of these studies was critically reviewed by the Working Group. The entries in the table were selected to show the diversity of assay systems and genetic endpoints used. They show that this group of pesticides has been tested predominantly in non-mammalian cellular systems which detect genetic or chromosomal effects; few studies are currently available in which this group of compounds has been evaluated in whole animals. It is also evident from the table that the nitrosated forms of these pesticides have not been extensively studied in any system. The nitrosated forms listed were obtained after reaction with sodium nitrite. The nitrosated product was detected, in most instances, by thin-layer chromatography and/or mass spectrometry. Complete information regarding strain designations is included when available.

The structural formulae, synonyms and trade names and production figures for some pesticides that react with nitrite are given in Table 7.

Table 4. Carcinogenicity studies of some *N*-nitrosatable pesticides (by oral administration unless otherwise specified)[a]

Compound	Species	Tested alone	Tested with nitrite	Reference
Aldicarb	rat	yes	no	National Cancer Institute (1979)
	mouse	yes	no	National Cancer Institute (1979)
Atrazine	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)
Benzthiazuron	rat	yes	yes	Ungerer *et al.* (1974)
Carbaryl[b]	rat	yes	no	Carpenter *et al.* (1961) ; Andrianova & Alekseev (1970)
	rat (transplacental)	yes	yes	Lijinsky & Taylor (1977a)
	mouse (i.p.)	yes	no	Shimkin *et al.* (1969)
Carbendazim	rat	yes	yes	Syrowatka *et al.* (1980)
	mouse (transplacental)	yes	yes	Börzsönyi *et al.* (1976)
	mouse	yes	yes	Börzsönyi & Csik (1975) ; Börzsönyi & Pintér (1977)
Dodine	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)
	mouse (transplacental	yes	yes	Börzsönyi *et al.* (1978b)
	rat	yes	no	Levinskas *et al.* (1961)
Fenuron	rat	yes	yes	Lijinsky & Taylor (1977b)

Compound	Species	Tested alone	Tested with nitrite	Reference
Ferbam[c]	rat	yes	no	Hodge *et al.* (1956) ; Lee *et al.* (1978)
	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)
Methomyl	rat	yes	no	Kaplan & Sherman (1977)
	dog	yes	no	Kaplan & Sherman (1977)
Simazine	rat	yes	no	Pliss & Zabezhinsky (1970)
	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)
Thiram[d]	rat	yes	no	Lehman (1965) ; Lee *et al.* (1978)
	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)
Trifluralin[e]	rat	yes	no	National Cancer Institute (1978)
	mouse	yes	no	National Cancer Institute (1978)
Triforin	mouse	yes	yes	Börzsönyi *et al.* (1978a)
Ziram[f]	rat	yes	no	Hodge *et al.* (1956) ; Andrianova & Alekseev (1970)
	mouse	yes	no	National Technical Information Service (1968) ; Innes *et al.* (1969)

[a]Subsequent to the meeting of the Working Group, the Secretariat became aware of another study of benomyl alone and with nitrite (Börzsönyi & Pintér, 1977).
[b]See also IARC (1976a).
[c]See also IARC (1976b).
[d]See also IARC (1976c).
[e]The sample tested was contaminated with 84-88 ppm *N*-nitrosodipropylamine.
[f]See also IARC (1976d).

Table 5. Carcinogenicity studies of *N*-nitroso derivatives of pesticides

Compound	Species	Reference
N-Nitrosoaldicarb	rat	Lijinsky & Schmähl (1978)
N-Nitrosobenzthiazuron	rat	Ungerer *et al.* (1974); Preussmann *et al.* (1976)
N-Nitrosobux-ten	rat	Lijinsky & Schmähl (1978)
N-Nitrosocarbaryl	rat	Eisenbrand *et al.* (1975a, 1976) ; Lijinsky & Taylor (1976) ; Preussmann *et al.* (1976) ; Lijinsky & Schmähl (1978)
N-Nitrosocarbofuran	rat	Lijinsky & Schmähl (1978)
N-Nitrosolandrin	rat	Lijinsky & Schmähl (1978)
N-Nitrosomethomyl	rat	Lijinsky & Schmähl (1978)
N-Nitrosopropoxur	rat	Lijinsky & Schmähl (1978)

Table 6. Summary of the genotoxic testing of non-nitrosated and nitrosated products of several pesticides[a]

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
Aldicarb (116-06-3)	DNA damage	*Bacillus subtilis* H17*rec*$^+$, M45 *rec*$^-$	Jeang & Li (1978)
		Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Dunkel & Simmon (1980)
		Salmonella typhimurium TA98, TA100	Jeang & Li (1978)
		Salmonella typhimurium TA1535, TA100, TA1537, TA1538, TA98	Mayberry & Savage (1978)
		Saccharomyces cerevisiae 632/4	Guerzoni *et al.* (1976)
		Tradescantia clone 02 and 4430	Sparrow & Schairer (1974)
	Mitotic recombination	*Saccharomyces cerevisiae* D3	Mayberry & Savage (1978)
N-Nitrosoaldicarb (57644-85-6)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA1535	Lijinsky & Andrews (1979)
		Salmonella typhimurium G46	Seiler (1977a)
		Escherichia coli	Lijinsky & Elespuru (1976)
Atrazine (1912-24-9)	DNA damage	DNA from calf thymus, salmon sperm and pea seedlings	Penner & Early (1972)
		Escherichia coli repair-deficient strains (unspecified)	Plewa (1978)
		Bacillus subtilis H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976)
	Unscheduled DNA synthesis	Human skin fibroblasts (EUE cells)	Adler (1980)
	Gene mutation	*Aspergillus nidulans*	Benigni *et al.* (1979) ; Adler (1980)
		Drosophila melanogaster	Murnik & Nash (1977) ; Adler (1980)

	Bacteriophage T4, AP72, N17 ; *Salmonella typhimurium*, eight *his*⁻ strains (unspecified)	Andersen *et al.* (1972)
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Eisenbeis *et al.* (1981)
	Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976)
	Salmonella typhimurium TA98, TA100	Plewa (1978)
	Salmonella typhimurium TA98, TA100, TA1535, TA1538	Lusby *et al.* (1979)
	Salmonella typhimurium TA1535, TA1537, TA1538, TA100	Simmon *et al.* (1977)
	Salmonella typhimurium his⁻ strains (unspecified)	Adler (1980)
	Tradescantia clone 4430	Schairer *et al.* (1979)
	Zea mays	Plewa & Gentile (1976) ; Plewa (1978)
	Escherichia coli	Adler (1980) ; Plewa (1978)
	Escherichia coli WP2	Nagy *et al.* (1975) ; Shirasu (1975) ; Shirasu *et al.* (1976) ; Simmon *et al.* (1977)
	Schizosaccharomyces pombe	Barale *et al.* (1979) ; Adler (1980)
	Streptomyces coelicolor	Adler (1980)
	Chinese hamster lung cells (V79)	Adler (1980)
Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Lemperle (1974) ; Plewa & Gentile (1976) ; Gentile *et al.* (1977) ; Plewa (1978) ; Adler (1980) ; de Bertoldi *et al.* (1980) ; Singh *et al.* (1982)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
		Aspergillus nidulans paba A1, paba A6	de Bertoldi *et al.* (1980)
	Mitotic recombination	*Aspergillus nidulans*	Benigni *et al.* (1979) ; Adler (1980)
		Saccharomyces cerevisiae D3	Simmon *et al.* (1977)
	Aneuploidy	*Neurospora crassa*	Griffiths (1979)
		Aspergillus nidulans	Benigni *et al.* (1979)
		Drosophila melanogaster	Murnik & Nash (1977)
	Chromosomal aberrations	*Hordeum vulgare*	Wuu & Grant (1967a) ; Stroev (1968, 1970)
		Vicia faba	Wuu & Grant (1967b)
		Mouse (strain unspecified) bone marrow ; Chinese hamster ovary cells (CHO)	Adler (1980)
		Rat (strain unspecified) bone marrow	Kulakov (1970)
		Vicia faba ; Hordeum vulgare ; Sorghum vulgare	Müller *et al.* (1972)
		Sorghum sp.	Liang & Liang (1972)
		Allium sp.	Khubutiya & Uguluva (1973)
		Hordeum sp.	Sharma (1973)
	Dominant lethal mutations	*Drosophila melanogaster*	Murnik & Nash (1977)
		Mouse (strain unspecified)	Adler (1980)
	Sister chromatid exchange	Chinese hamster ovary cells (CHO)	Adler (1980)
N-Nitrosoatrazine (56525-09-8)	No information available		
Benfluralin (1861-40-1)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976)

	Gene mutation	*Salmonella typhimurium* eight *his*$^-$ strains (unspecified)	Andersen *et al.* (1972)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli WP2, WP2, *try hcr*	Shirasu (1975) ; Shirasu *et al.* (1976)
N-Nitrosobenflurabin[b]	No information available		
Benzthiazuron (1929-88-0)	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974) ; Siebert & Lemperle (1974)
N-Nitrosobenzthiazuron (51542-33-7)	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
		Neurospora crassa	Brockman (1976)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974)
Bux-ten (8065-36-9)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535 TA1536, TA1537	Blevins *et al.* (1977b)
Nitrosobux-ten (62573-59-5)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535 TA1537, TA1538	Blevins *et al.* (1977b)
		Escherichia coli	Lijinsky & Elespuru (1976)
Carbaryl (63-25-2)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Uchiyama *et al.* (1975) ; Shirasu (1975) ; Shirasu *et al.* (1976)
		Human skin fibroblasts	Regan *et al.* (1976)
		Escherichia coli polA$^+$, *polA*$^-$	Rosenkranz & Leifer (1980)
		Human lymphocytes ; rat (Wistar) thymocytes	Rocchi *et al.* (1980)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
	Testicular DNA synthesis	Mouse (strain unspecified)	Seiler (1977b)
	Unscheduled DNA synthesis	Primary rat (Fischer 344) hepatocytes	Probst *et al.* (1981)
	Gene mutation	*Escherichia coli* WP2	Uchiyama *et al.* (1975)
		Salmonella typhimurium TA1538	Egert & Greim (1976a)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Marshall *et al.* (1976)
		Salmonella typhimurium TA98, TA100, TA1535 TA1537	Jaszczuk *et al.* (1979)
		Salmonella typhimurium TA100, TA1535	De Lorenzo *et al.* (1978)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Blevins *et al.* (1977b)
		Salmonella typhimurium G46	Seiler (1977a) ; Rani *et al.* (1980)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli WP2, WP2 *try hcr*	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli WP2	Nagy *et al.* (1975)
		Drosophila melanogaster	Brzeskii (1972) ; Brzeskii & Vaskov (1972)
		Chinese hamster lung cells (V79)	Ahmed *et al.* (1977)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974) ; Jaszczuk & Syrowatka (1979)
	Chromosomal aberrations	*Hordeum vulgare*	Wuu & Grant (1967a)
		Vicia faba	Wuu & Grant (1967b)

		Drosophila melanogaster	Hoque (1972)
		Chinese hamster fibroblasts	Ishidate & Odashima (1977)
	Dominant lethal mutations	Mouse (Swiss ICR/Ha)	Epstein *et al.* (1972)
	Micronucleus test	Mouse (strain unspecified) bone-marrow cells	Rani *et al.* (1980)
	Aneuploidy	*Aspergillus nidulans*	Morpurgo *et al.* (1979)
Nitrosocarbaryl (7090-25-7)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, 45T *rec*$^-$	Uchiyama *et al.* (1975)
		Human skin fibroblasts	Regan *et al.* (1976)
		Haemophilus influenzae Rd	Kimball *et al.* (1977)
		Escherichia coli R15 *polA*$^-$, NG30 *recA*$^-$	Yoshikawa *et al.* (1978)
	Gene mutation	*Haemophilus influenzae*	Beattie & Kimball (1974) ; Elespuru *et al.* (1974) ; Beattie (1975) ; Lijinsky & Elespuru (1976) ; Elespuru (1979)
		Salmonella typhimurium TA1535	Lee *et al.* (1977) ; Lijinsky & Andrews (1979)
		Salmonella typhimurium TA1535, TA1538	Greim *et al.* (1977)
		Salmonella typhimurium TA1538	Egert & Greim (1976a)
		Salmonella typhimurium TA98, TA100	Eya & Talcott (1980)
		Salmonella typhimurium G46	Seiler (1977a)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Marshall *et al.* (1976)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537	Jaszczuk *et al.* (1979)
		Escherichia coli K-12	Egert & Greim (1976a)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
		Escherichia coli WP2	Uchiyama *et al.* (1975)
		Escherichia coli H/r30R, H/r30R *uvr*A$^-$	Yoshikawa *et al.* (1978)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974)
	Mitotic recombination	*Saccharomyces cerevisiae* D3	Eya & Talcott (1980)
	Chromosomal aberrations	Chinese hamster lung cells (V79-E)	Thust *et al.* (1980)
		Human lymphocytes	Greim *et al.* (1977)
	Sister chromatid exchange	Chinese hamster lung cells (V79-E)	Thust *et al.* (1980)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1977a)
Carbendazim (10605-21-7)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Jeang & Li (1978)
	Testicular DNA synthesis	Mouse (strain unspecified)	Seiler (1977b)
	Gene mutation	*Aspergillus nidulans*	Speakman & Nirenberg (1981)
		Cladosporium cucumerium	Speakman & Nirenberg (1981)
		Salmonella typhimurium G46, TA100, TA1530, TA1950	Ficsor *et al.* (1978)
		Salmonella typhimurium G46	Seiler (1977a)
		Salmonella typhimurium TA1535	Seiler (1975)
		Salmonella typhimurium TA98, TA100	Jeang & Li (1978)
		Salmonella typhimurium LT-2, G46, TA1530, TA1531, TA1532, TA1534, D3052	Seiler (1972)

	Mouse spot test	Mouse (C57BL) embryos	Fahrig & Seiler (1978)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D7	Singh (1978)
	Mitotic recombinaion	*Saccharomyces cerevisiae* D7	Singh (1978)
		Drosophila melanogaster	Mollet (1976)
	Chromosomal aberrations	Mouse (strain unspecified) bone-marrow cells	Pilinskaya *et al.* (1980)
		Hunan adult liver cells (Chang)	Styles & Garner (1974)
		Rat (Wistar) bone-marrow cells	Styles & Garner (1974)
		Drosophila melanogaster	Lamb & Lilly (1980)
	Aneuploidy	*Aspergillus nidulans*	Kappas *et al.* (1974) ; Morpurgo *et al.* (1979)
		Microtus oeconomus	Tates (1979)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1975, 1976)
Nitrosocarbendazim[b]	Gene mutation	*Salmonella typhimurium* G46	Seiler (1967a)
Carbofuran (1563-66-2)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
		Escherichia coli W3110, P3478	Waters *et al.* (1982)
		Bacillus subtilis H17 *rec*$^+$, 45 *rec*$^-$	Jeang & Li (1978) ; Nelson *et al.* (1982)
	Unscheduled DNA synthesis	Human diploid fibroblasts (WI38 cells)	Waters *et al.* (1982)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Waters *et al.* (1982)
		Salmonella typhimurium G46	Seiler (1977a)
		Salmonella typhimurium TA98, TA100	Jeang & Li (1978) ; Nelson *et al.* (1981)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
		Nostoc muscorum	*Kar & Singh* (1979)
		Drosophila melanogaster	Valencia (1977)
	Mitotic recombination	*Saccharomyces cerevisiae* D3	Waters *et al.* (1982)
	Chromosomal aberrations	Chinese hamster ovary cells (CHO)	Nelson *et al.* (1981)
		Hordeum vulgare	Singh *et al.* (1977, 1979)
	Dominant lethal mutation	*Drosophila melanogaster*	Sathaiah *et al.* (1974) ; Valencia (1977)
	Aneuploidy	*Drosophila melanogaster*	Valencia (1977)
	Sister chromatid exchange	Chinese hamster ovary cells (CHO)	Nelson *et al.* (1981)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1977a)
Nitrosocarbofuran (62593-23-1)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA1535	Lijinsky & Andrews (1979)
		Salmonella typhimurium TA98, TA100, TA1535	Richard (1980)
		Salmonella typhimurium TA98, TA100	Nelson *et al.* (1981)
		Salmonella typhimurium G46	Seiler (1977a)
		Escherichia coli	Lijinsky & Elespuru (1976)
	Chromosomal aberrations	Chinese hamster ovary cells (CHO)	Nelson *et al.* (1981)
	Sister chromatid exchange	Chinese hamster ovary cells (CHO)	Nelson *et al.* (1981)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1977a)

Chloroxuron (1982-47-4)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976)
	Gene mutation	*Escherichia coli* WP2	Nagy *et al.* (1975) ; Shirasu (1975); Shirasu *et al.* (1976)
		Salmonella typhimurium, eight *his*$^-$ strains (unspecified)	Andersen *et al.* (1972)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976)
	Chromosomal aberrations	*Hordeum vulgare*	Pusztai & Vegh (1978) ; Kahlon (1980)
Nitrosochloroxuron[b]	No information available		
Cycluron (2163-69-1)	Gene mutation	*Escherichia coli* K-12	Egert & Greim (1976b)
		Salmonella typhimurium, eight strains	Andersen *et al.* (1972)
Nitrosocycluron[d]	No information available		
Dimefox (115-26-4)	Gene mutation	*Escherichia coli* K-12	Egert & Greim (1976b)
Nitrosodimefox[b]	No information available		
Dodine (2439-10-3)	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
		Saccharomyces cerevisiae 632/4	Guerzoni *et al.* (1976)
		Aspergillus nidulans	Bignami *et al.* (1977)
	Mitotic recombination	*Aspergillus nidulans*	Georgopoulos *et al.* (1976) ; Bignami *et al.* (1977)
	Aneuploidy	*Aspergillus nidulans*	Bignami *et al.* (1977); Morpurgo *et al.* (1979)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
Nitrosododine[b]	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
Ethiofencarb (29973-13-5)	Gene mutation	*Salmonella typhimuriun* G46	Seiler (1977a)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1977a)
Nitrosoethiofencarb[b]	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
	Micronucleus test	Mouse (ICR) bone-marrow cells	Seiler (1977a)
Fenuron (101-42-8)	DNA damage	*Escherichia coli polA*$^+$, *polA*$^-$	Rosenkranz & Leifer (1980)
	Gene mutation	*Salmonella typhimurium,* eight *his*$^-$ strains (unspecified)	Andersen *et al.* (1972)
	Micronucleus test	Mouse (strain unspecified) bone-marrow cells	Seiler (1978)
Ferbam (14484-64-1)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976)
	Gene mutation	*Aspergillus niger*	Prasad & Pramer (1968)
		Escherichia coli WP2	Nagy *et al.* (1975) ; Shirasu (1975)
		Salmonella typhimuriun TA1535, TA1536, TA1537, TA1538	Shirasu (1975)
		Salmonella typhimurium TA100, TA1535	De Lorenzo *et al.* (1978)
	Chromosomal aberrations	*Allium cepa*	Prasad & Pramer (1968)
		Vicia faba	Zutshi & Kaul (1975)
		Hordeum vulgare	Zutshi & Kaul (1975)
Nitrosoferbam[b]	No information available		

Glyphosate (1071-83-6)	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
	Chromosomal aberrations	*Secale cereale*	Boyle & Evans (1974)
	Sister chromatid exchange	Human lymphocytes	Vigfusson & Vyse (1980)
Nitrosoglyphosate (56516-72-5)	Gene mutation	*Salmonella typhimurium* G46	Seiler (1977a)
Ispropalin (33820-53-0)	No information available		
Nitrosoisopropalin[b]	No information available		
Landrin (12407-86-2)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1536, TA1537	Blevins *et al.* (1977b)
Nitrosolandrin (64521-09-1)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1536, TA1537	Blevins *et al.* (1977b)
		Salmonella typhimurium TA1535	Lijinsky & Andrews (1979)
		Escherichia coli	Lijinsky & Elespuru (1976)
Methomyl (16752-77-5)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
		Escherichia coli W3110, P3478	Jones *et al.* (1982) ; Waters *et al.* (1982)
		Bacillus subtilis H17 *rec*$^+$, M45 *rec*$^-$	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Unscheduled DNA synthesis	Human diploid fibroblasts (W138 cells)	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Blevins *et al.* (1977b) ; Jones *et al.* (1982) ; Waters *et al.* (1982)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
		Salmonella typhimurium G46	Seiler (1977a)
		Escherichia coli WP2 *uvrA*$^-$	Jones *et al.* (1982) ; Waters *et al.* (1982)
		Drosophila melanogaster	Valencia (1977)
	Mitotic recombination	*Saccharomyces cerevisiae* D3	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Dominant lethal mutation	Mice (ICR)	Waters *et al.* (1982)
	Aneuploidy	*Drosophila melanogaster*	Valencia (1977)
Nitrosomethomyl (57117-24-5)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
		Escherichia coli	Lijinsky & Elespuru (1976)
		Salmonella typhimurium G46	Seiler (1977a)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Blevins *et al.* (1977b)
		Salmonella typhimurium TA1535	Lijinsky & Andrews (1979)
	Micronucleus test	Mouse (ICR) bone marrow	Seiler (1977a)
Nitralin (4762-14-1)	Mitotic effects	*Gossypium* sp.	Rizk (1973)
		Tradescantia paludosa	Sawamura & Jackson (1968)
		Vicia faba	Sawamura & Jackson (1968)
Nitrosonitralin[b]	No information available		
Oryzalin (19044-88-3)	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Eisenbeis *et al.* (1981)

	Mitotic effects	*Triticum aestivum*	Bartels & Hilton (1973)
		Zea mays	Bartels & Hilton (1973)
Nitrosooryzalin[b]	No information available		
Propoxur (114-26-1)	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
		Escherichia coli polA$^+$, *polA*$^-$	Rosenkranz & Leifer (1980)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Blevins *et al.* (1977b)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537	Jaszczuk *et al.* (1979)
		Salmonella typhimurium TA1535, TA1537	Byeon *et al.* (1976)
		Salmonella typhimurium TA100, TA1535	De Lorenzo *et al.* (1978)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974) ; Jaszczuk & Syrowatka (1979)
Nitropropoxur (38777-13-8)	Dominant lethal mutation	Mouse (BALB/c × C57BL)	Tyrkiel (1977)
	DNA damage	Human skin fibroblasts	Blevins *et al.* (1977a)
		Bacillus subtilis H17 *rec*$^+$, M45 *rec*$^-$	Uchiyama *et al.* (1975)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA535, TA1537	Jaszczuk *et al.* (1979)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Blevins *et al.* (1977b)
		Escherichia coli	Lijinsky & Elespuru (1976)
		Escherichia coli WP2	Uchiyama *et al.* (1975)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Siebert & Eisenbrand (1974)

Pesticide (CAS Reg. No)	Genetic endpoint evaluated or test system	Test object	Reference
Simazine (122-34-9)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976)
	Testicular DNA damage	Mouse (strain unspecified)	Seiler (1977b)
	Unscheduled DNA synthesis	Human skin fibroblasts WI38	Waters *et al.* (1982)
	Gene mutation	*Salmonella typhimurium* TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976) ; Waters *et al.* (1982)
		Salmonella typhimurium G46, TA1530, TA1531, TA1532, TA1534	Seiler (1973)
		Escherichia coli WP2	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli	Fahrig (1974)
		Saccharomyces cerevisiae 632/4	Guerzoni *et al.* (1976)
		Serratia marcescens	Fahrig (1974)
		Drosophila melanogaster	Valencia (1977)
		Tradescantia reflexa	Sawamura (1965)
	Aneuploidy	*Neurospora crassa*	Griffiths (1979)
	Chromosomal aberrations	*Vicia faba*	Hakeem Shehab (1974)
		Hordeum vulgare	Wuu & Grant (1967a)
	Sister chromatid exchange	Chinese hamster ovary cells	Waters *et al.* (1982)
	Micronucleus test	Mouse bone-marrow cells	Waters *et al.* (1982)
Nitrososimazine[b]	No information available		

Thiram (137-26-8)	DNA damage	*Escherichia coli polA*$^+$, *polA*$^-$	Rosenkranz & Leifer (1980)
		Bacillus subtilis H17 *rec*$^+$, M45 *rec*$^-$	Shirasu *et al.* (1976, 1977) ; Kawachi *et al.* (1980)
	DNA synthesis	Rat (Wistar) thymocytes	Rocchi *et al.* (1980)
	Unscheduled DNA synthesis	Human lymphocytes	Rocchi *et al.* (1980)
	Prophage induction	Prophage lambda ; host, *Escherichia coli* K-12	Zdzienicka *et al.* (1981)
	Gene mutation	*Salmonella typhimurium* TA1538, TA1978	Zdzienicka *et al.* (1981)
		Salmonella typhimurium TA98, TA100	Kawachi *et al.* (1980)
		Salmonella typhimurium TA100, TA1535	Hedenstedt *et al.* (1979)
		Salmonella typhimurium TA98, TA100, TA1535, TA1538	Byeon *et al.* (1976)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu *et al.* (1977)
		Salmonella typhimurium G46	Seiler (1977a)
		Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Andrews *et al.* (1980)
		Escherichia coli WP2	Nagy *et al.* (1975)
		Escherichia coli WP2, WP2 *uvrA*	Shirasu *et al.* (1977)
		Aspergillus nidulans	Zdzienicka *et al.* (1981)
	Chromosomal aberrations	Hamster (strain unspecified) fibroblasts	Kawachi *et al.* (1980)
		Rat (strain unspecified) bone marrow	Kawachi *et al.* (1980)
		Vicia faba	Zutshi & Kaul (1975)
		Hordeum vulgare	George *et al.* (1970) ; Zutshi & Kaul (1975)

Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
	Dominant lethal mutations	*Bombyx mori*	Kawachi *et al.* (1980)
	Micronucleus test	Mouse (strain unspecified) bone marrow	Paik & Lee (1977)
		Mouse (ICR) bone marrow	Seiler (1977a)
Nitrosothiram[b]	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Andrews *et al.* (1980)
Trifluralin (1582-09-8)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$, M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976) ; Jones *et al.* (1982) ; Waters *et al.* (1982)
		Escherichia coli W3110, P3478	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Unscheduled DNA synthesis	Human diploid fibroblasts (WI38 cells)	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Eisenbeis *et al.* (1981)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975)
		Salmonella typhimurium TA100, TA1535, TA1537, TA1538	Jones *et al.* (1982) ; Waters *et al.* (1982)
		Escherichia coli WP2	Shirasu (1975)
		Escherichia coli WP2 *uvr*A$^-$	Waters *et al.* (1982)
	Mitotic recombination	*Saccharomyces cerevisiae* D3	Jones *et al.* (1982) ; Waters *et al.* (1982)
	Chromosomal aberrations	Mouse (CFLP) germ cells	Nehez *et al.* (1980)

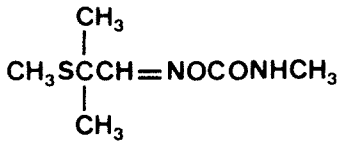
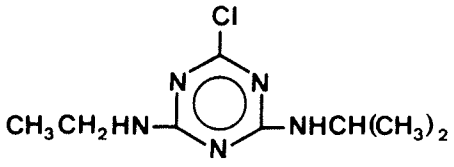
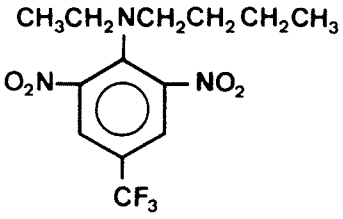
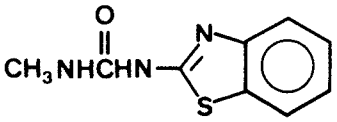
		Mouse (CFLP) bone-marrow cells	Nehez *et al.* (1979)
		Allium cepa	Petrovska *et al.* (1981)
		Gossypium herbaceum	Musalevski *et al.* (1981)
		Pisum sativum	Suruzhiu *et al.* (1978)
		Hordeum vulgare	Oku (1976)
	Dominant lethal mutations	Mouse (ICR)	Waters *et al.* (1982)
		Mouse (CFLP)	Nehez *et al.* (1980)
		Drosophila melanogaster	Valencia (1977)
	Heritable translocation	Mouse (CFLP) F_1 embryos	Nehez *et al.* (1980)
	Aneuploidy	*Sordaria brevicollis*	Bond & McMillan (1979)
		Neurospora crassa	Griffiths (1979)
		Drosophila melanogaster	Valencia (1977)
Nitrosotrifluralin[b]	No information available		
Ziram (137-30-4)	DNA damage	*Bacillus subtilis* H17 *rec*$^+$ M45 *rec*$^-$	Shirasu (1975) ; Shirasu *et al.* (1976, 1977)
		Escherichia coli polA$^+$, *polA*$^-$	Rosenkranz & Leifer (1980)
	Gene mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Hedenstedt *et al.* (1979) ; De Lorenzo *et al.* (1978)
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli WP2	Shirasu (1975) ; Shirasu *et al.* (1976)
		Escherichia coli Gal Rs, Str A	Fahrig (1974)

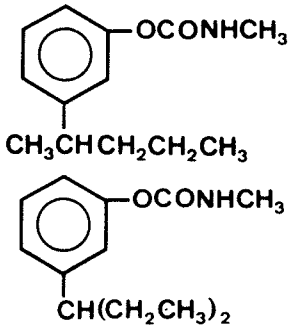
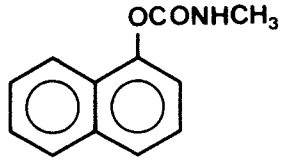
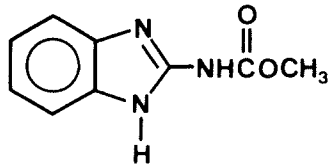
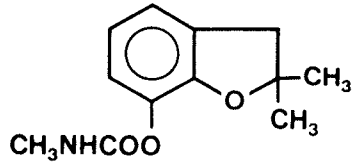
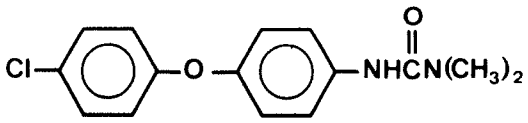
Pesticide (CAS Reg. No.)	Genetic endpoint evaluated or test system	Test object	Reference
		Serratia marcescens a21, a742	Fahrig (1974)
		Verticillium dahliae	Kas'yanenko *et al.* (1977)
		Drosophila melanogaster	Benes & Sram (1969)
	Mitotic gene conversion	*Saccharomyces cerevisiae* D4	Fahrig (1974) ; Siebert *et al.* (1970)
	Chromosomal aberrations	*Hordeum vulgare*	Zutshi & Kaul (1975)
Nitrosoziram[b]	No information available		

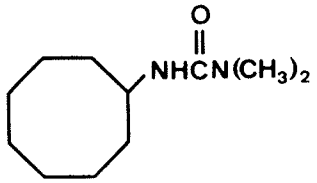
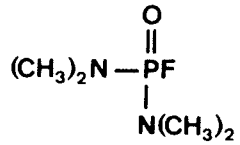
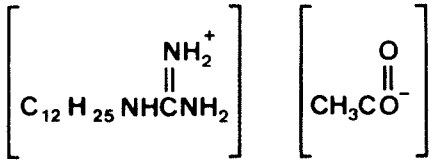
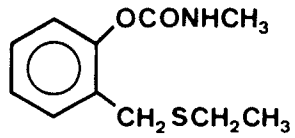
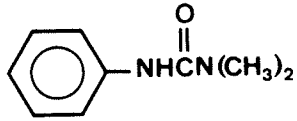
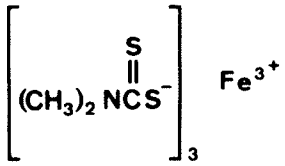
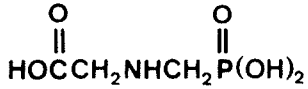
[a]Readers who would like a complete listing on the compounds cited may obtain it by request from the Environmental Mutagen Information Center, P.O. Box Y, Bldg 9224, Oak Ridge, TN 37830, USA.

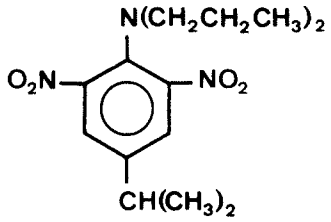
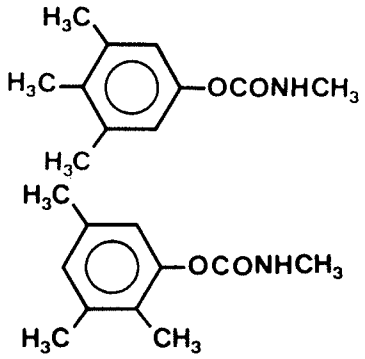
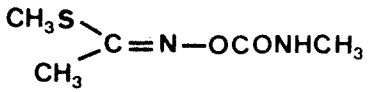
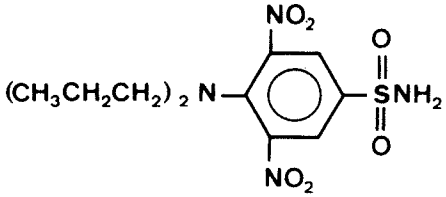
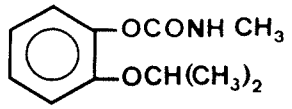
[b]No Chemical Abstracts Services (CAS) Registry Number available.

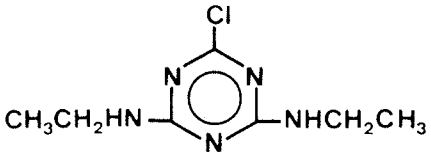
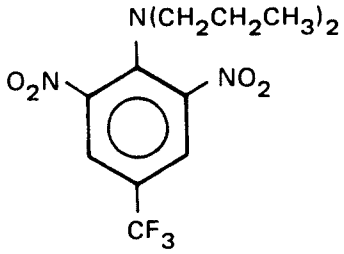
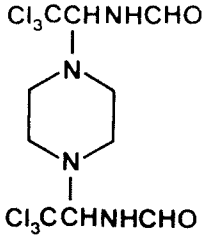
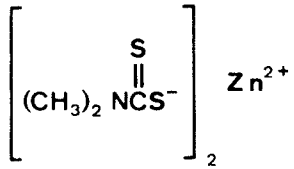
Table 7. Some pesticides that react with nitrite

Chemical name, CAS Reg. No. and principal use	Common synonyms and trade names	Structural formula	Production[a] (thousand kg)
Aldicarb 116-06-3 Insecticide - cotton; acaricide and nematicide - sugar beets	2-Methyl-2-(methylthio)propionaldehyde *O*-methylcarbamoyloxime 2-Methyl-2-(methylthio)propanal *O*-[(methylamino)carbonyl]oxime Temik		US - 1320 (1978U) Western Europe - 200-300 (1981E) Japan - NP India - ND Brazil - ND
Atrazine 1912-24-9 Herbicide - corn	2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine 6-Chloro-*N*-ethyl-*N'*-(1-methylethyl)-1,3,5-triazine-2,4-diamine Gesaprim; Primatol A		US - 38 300 (1978U) Western Europe - ND Japan - NP South Africa - ND Mexico - ND Brazil - ND Israel - ND
Benfluralin 1861-40-1 Herbicide - peanuts	*N*-Butyl-*N*-ethyl-α,α,α-trifluoro-2,6-dinitro-p-toluidine *N*-Butyl-*N*-ethyl-2,6-dinitro-4-(trifluoromethyl)benzenamine Balan; Bonalan		US - 772 (1978U) Western Europe - ND Japan - NP Israel - ND
Benzthiazuron 1929-88-0 Herbicide - sugar beets	1-(Benzothiazol-2-yl)-3-methylurea *N*-2-Benzothiazoyl-*N'*-methylurea Gatnon		US - NP Western Europe - negligible Japan - NP

Chemical name, CAS Reg. No. and principal use	Common synonyms and trade names	Structural formula	Production[a] (thousand kg)
Bux-Ten 8065-36-9 Insecticide - corn	3-(1-Ethylpropyl)phenyl methylcarbamate mixt. with 3(1-methylbutyl)phenyl methylcarbamate Bufencarb; Bux		US - discontinued Western Europe - ND Japan - NP
Carbaryl 63-25-2 Insecticide - corn, soya beans	1-Naphthyl methylcarbamate 1-Naphthalenyl methylcarbamate Sevin		US - 10 600 (1978U) Western Europe - ND Japan - NP Israel - 4545 (1980E) India - ND
Carbendazim 10605-21-7 Fungicide - numerous crops	Methyl benzimidazol-2-ylcarbamate Methyl 1*H*-benzimidazol-2-ylcarbamate Derosal; Bavistin; Delsene		US - NP Western Europe - 10 (1981E) Japan - NP Taiwan - ND
Carbofuran 1563-66-2 Insecticide - corn; acaricide and nematicide - corn	2,3-Dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate 2,3-Dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate Furadan; Curaterr		US - 849 (1978U) Western Europe - ND Japan - NP
Chloroxuron 1982-47-4 Herbicide - soya beans	3[4-(4-Chlorophenoxy)phenyl]-1,1-dimethylurea *N'*-[4-(4-Chlorophenoxy)phenyl]-*N,N*-dimethylurea Tenoran		US - 272 (1978U); discontinued Western Europe - ND Japan - NP

Cycluron 2163-69-1 Herbicide - sugar beets	3-Cyclooctyl-1,1-dimethylurea *N'*-Cyclooctyl-*N,N*-dimethylurea Component of Alipur		US - NP Western Europe - discontinued Japan - NP
Dimefox 115-26-4 Insecticide and acaricide - hops	Tetramethylphosphorodiamidic fluoride Bis(dimethylamido)fluoro-phosphine oxide Terra-Sytam		US - NP Western Europe - ND Japan - NP
Dodine 2439-10-3 Fungicide - apples	Dodecylguanidinium acetate Dodecylguanidine monoacetate Cyprex; Melprex		US - 636 (1978U) Western Europe - 1363 (1980E) Japan - NP
Ethiofencarb 29973-13-5 Insecticide - various crops	α-(Ethylthio)-*o*-tolyl methyl-carbamate 2-[(Ethylthio)methyl]phenyl methylcarbamate Croneton		US - NP Western Europe - ND Japan - NP
Fenuron 101-42-8 Herbicide - fruits, vegetables	1,1-Dimethyl-3-phenylurea *N-N*-Dimethyl-*N'*-phenylurea Dybar		US - discontinued Western Europe - ND Japan - NP
Ferbam 14484-64-1 Fungicide - apples	Iron tris(dimethyldithio-carbamate (OC-6-11)-Tris(dimethylcarbamo-dithioato-*S,S'*)iron Fermate		US - 45 (1978U) Western Europe - 500 (1981E) Japan - NP
Glyphosate 1071-83-6 Herbicide - industrial/ commercial applications	*N*-(Phosphonomethyl)glycine Phosphonomethyliminoacetic acid Roundup		US - 772 (1978U) Western Europe - ND Japan - NP

Chemical name, CAS Reg. No. and principal use	Common synonyms and trade names	Structural formula	Production[a] (thousand kg)
Isopropalin 33820-53-0 Herbicide - vegetables, tobacco	4-Isopropyl-2,6-dinitro-*N,N*-dipropylaniline 4-(1-Methylethyl)-2,6-dinitro-*N,N*-dipropylbenzenamine Paarlan		US - 136 (1978C) Western Europe - NP Japan - NP
Landrin 12407-86-2 Insecticide - corn	3,5,2 or 4-Trimethylphenyl methylcarbamate 2,3,5-Trimethylphenyl methylcarbamate mixt. with 3,4,5-trimethylphenyl methylcarbamate		US - discontinued Western Europe - ND Japan - NP
Methomyl 16752-77-5 Insecticide and nematicide - vegetables	*S*-Methyl *N*-(methylcarbamoyloxy)-thioacetimidate *N*-[[(Methylamino)carbonyl]oxy]-ethanimidothioate Lannate		US - 381 (1978U) Western Europe - NP Japan - NP
Oryzalin 19044-88-3 Herbicide - soya beans	3,5-Dinitro-N^4, N^4-dipropylsulphanilamide 4-(Dipropylamino)-3,5-dinitrobenzenesulfonamide Dirimal; Surflan		US - 454 (1978U) Western Europe - NP Japan - NP
Propoxur 114-26-1 ° Insecticide - commercial/household/industrial applications	2-Isopropoxyphenyl methylcarbamate 2-(1-Methylethoxy)phenyl methylcarbamate Baygon; Blattanex; Unden		US - 590 (1978U) Western Europe - 1000 (1980E) Japan - NP

Simazine 122-34-9 Herbicide - corn	6-Chloro-*N,N'*-diethyl-1,3,5-triazine-2,4-diamine 2-Chloro-4,6-bis(ethylamino)-1,3,5-triazine Aquazine; Gesatop; Princep		US - 4200 (1978U) Western Europe - 1000-5000 (1981E) Japan - NP
Thiram 137-26-8 Fungicide - apples, field crops, lawn, turf	Tetramethylthiuram disulphide Tetramethylthioperoxydicarbonic diamide Arasan; Tersan; Pomarsol; Ferna-Col; Fernasan		US - 136 (1978U) Western Europe - 9000 (1981E) Japan - 120 (1979E)
Trifluralin 1582-09-8 Herbicide - soya beans	2,6-Dinitro-*N, N*-dipropyl-4-(trifluoromethyl)benzenamine α,α,α-Trifluoro-2,6-dinitro-*N,N*-dipropyl-*para*-toluidine Elancolan; Trefanocide; Treflan		US - 13 100 (1978U) Western Europe - 1000-3000 (1980E) Japan - NP
Triforine 226644-46-2 Fungicide - ornamentals	1,4-Bis(2,2,2,-trichloro-1-formamido-ethyl)piperazine *N,N'*-[1,4-Piperazinediylbis(2,2,2-trichloroethylidene)]bisformamide Funginex; Saprol		US - negligible (1978U) Western Europe - ND Japan - NP
Ziram 137-30-4 Fungicide - deciduous fruits	Zinc dimethyldithiocarbamate Bis(dimethyldithiocarbamato)zinc Milbam; Zerlate; Fuklasin; Aaprotect		US - 182 (1978U) Western Europe - 4000-6000 (1981E) Japan - NP

[a]The year for which data were reported is given in parentheses. U = data on use; E = estimate from industry; ND = no data available; NP = not produced

[b]Production of thiram in Japan has not been reported since 1979.

References

Adler, I.-D. (1980) A review of the coordinated research effort on the comparison of test systems for the detection of mutagenic effects, sponsored by the E.E.C. *Mutat. Res.*, *74*, 77-93

Ahmed, F.E., Lewis, N.J. & Hart, R.W. (1977) Pesticide induced ouabain resistant mutants in Chinese hamster V79 cells. *Chem.-biol. Interactions*, *19*, 369-374

Andersen, K.J., Leighty, E.G. & Takahashi, M.T. (1972) Evaluation of herbicides for possible mutagenic properties. *J. agric. Food Chem.*, *20*, 649-656

Andrews, A.W., Fornwald, J.A. & Lijinsky, W. (1980) Nitrosation and mutagenicity of some amine drugs. *Toxicol. appl. Pharmacol.*, *52*, 237-244

Andrianova, M.M. & Alekseev, I.A. (1970) On the carcinogenous properties of the pesticides sevine, maneb, ciram and cineb (Russ.). *Vopr. Pitan.*, *29*, 71-74

Archer, M.C., Tannenbaum, S.R. & Wishnok, J.S. (1976) *Nitrosamine formation in the presence of carbonyl compounds*. In: Walker, E.A., Bogovski, P. & Griciute, L., eds, *Environmental* N-*Nitroso Compounds: Analysis and Formation* (*IARC Scientific Publications No. 14*), Lyon, International Agency for Research on Cancer, pp. 141-145

Archer, M.C., Yang, H.S. & Okun, J.D. (1978) *Acceleration of nitrosamine formation at pH 3.5 by microorganisms*. In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N-*Nitroso Compounds* (*IARC Scientific Publications No. 19*), Lyon, International Agency for Research on Cancer, pp. 239-246

Barale, R., Presciuttini, S. & Rossi, A.M. (1979) Schizosaccharomyces pombe - *Forward mutations* (Ital.). In: Magni, G.E., ed., *Mutagenesi Ambientale; Metodiche di Analisi*, Vol. 1, *Test* in vitro, pp. 105-121

Bartels, P.G. & Hilton, J.L. (I973) Comparison of trifluralin, oryzalin, pronamide, propham, and calchicine treatment on microtubules. *Pestic. Biochem. Physiol.*, *3*, 462-472

Bartsch, H., O'Neill, I.K., Castegnaro, M. & Okada, M., eds (1982) N-*Nitroso Compounds: Occurrence and Biological Effects* (*IARC Scientific Publications No. 41*), Lyon, International Agency for Research on Cancer

Beattie, K.L. (1975) *N*-Nitrosocarbaryl-induced mutagenesis in *Haemophilus influenzae* strains deficient in repair and recombination. *Mutat. Res.*, *27*, 201-217

Beattie, K.L. & Kimball, R.F. (1974) Involvement of DNA replication and repair in mutagenesis of *Haemophilus influenzae* induced by *N*-nitrosocarbaryl. *Mutat. Res.*, *24*, 105-115

Benes, V. & Sram, R. (1969) Mutagenic activity of some pesticides in *Drosophila melanogaster*. *Ind. Med. Surg.*, *38*, 442-444

Benigni, R., Bignami, M., Camoni, I., Carere, A., Conti, G., Iachetta, R., Morpurgo, G. & Ortali, V.A. (1979) A new *in vitro* method for testing plant metabolism in mutagenicity studies. *J. Toxicol. environ. Health, 5*, 809-819

de Bertoldi, M., Griselli, M., Giovannetti, M. & Barale, R. (1980) Mutagenicity of pesticides evaluated by means of gene-conversion in *Saccharomyces cerevisiae* and in *Aspergillus nidulans. Environ. Mutagenesis, 2*, 359-370

Bignami, M., Aulicino, F., Velcich, A., Carere, A. & Morpurgo, G. (1977) Mutagenic and recombinogenic action of pesticides in *A. nidulans. Mutat. Res., 46*, 395-402

Blevins, R.D., Lijinsky, W. & Regan, J.D. (1977a) Nitrosated methylcarbamate insecticides: Effect on the DNA of human cells. *Mutat. Res., 44*, 1-7

Blevins, R.D., Lee, M. & Regan, J.D. (1977b) Mutagenicity screening of five methylcarbamate insecticides and their nitroso derivatives using mutants of *Salmonella typhimurium* CT_2. *Mutat. Res., 56*, 1-6

Bond, D.J. & McMillan, L. (1979) Meiotic aneuploidy: Its origins and induction following chemical treatment in *Sordaria brevicollis. Environ. Health Perspect., 31*, 67-74

Bontoyan, W.R., Law, M.W. & Wright, D.P. (1979) Nitrosamines in agricultural and home-use pesticides. *J. agric. Food Chem., 27*, 631-635

Börzsönyi, M. & Csik, M. (1975) Induction of malignant lymphomas in Swiss mice by *N*-nitroso compounds formed *in vivo. Int. J. Cancer, 15,* 830-838

Börzsönyi, M. & Pintér, A. (1977) The carcinogenicity of *N*-nitroso compounds formed endogenously in mice from benzimidazole carbamate pesticides. *Neoplasma, 24*, 119-122

Börzsönyi, M. & Pintér, A. (1979) The formation of carcinogenic *N*-nitroso compounds in the living organism and in the environment (Hung.). *Magyar Onkol., 23*, 171-179

Börzsönyi, M., Pintér, A., Surján, A. & Farkas, I. (1976) Transplacental induction of lymphomas in Swiss mice by carbendazim and sodium nitrite. *Int. J. Cancer, 17*, 742-747

Börzsönyi, M., Pintér, A., Török, G. & Surján, A. (1978a) *Formation and biological effect of* N-*nitroso compound from piperazine pesticide triforine.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N-*Nitroso Compounds* (*IARC Scientific Publications No. 19*), Lyon, International Agency for Research on Cancer, pp. 477-484

Börzsönyi, M., Pintér, A., Surján, A. & Török, G. (1978b) Carcinogenic effect of a guanidine pesticide administered with sodium nitrite on adult mice and on the offspring after prenatal exposure. *Cancer Lett., 5*, 107-113

Boyland, E., Nice, E. & Williams, K. (1971) The catalysis of nitrosation by thiocyanate from saliva. *Food Cosmet. Toxicol., 9*, 639-643

Boyle, W.S. & Evans, J.O (1974) Effects of glyphosate and ethephon on meiotic chromosomes of *Secale cereale* L. *J. Hered., 65*, 250-252

Brockman, H.E. (1976) *Report on NO-Benzthiazuron (BTZ) Using the ad-3 Test System (Heterocaryon-12) of* Neurospora crassa (NIH-75-C-I73CC), Research Triangle Park, NC

Brzeskii, V.V. (1972) Study of the mutagenic properties of an insecticide from the carbamate group - sevin. *Sov. Genet., 8*, 798-800

Brzeskii, V.V. & Vaskov, V.I. (1972) Studies on mutation and calculation of fertility in *Drosophila melanogaster* under the effect of carbaryl (Ger.). *Angew. Parasitol., 13*, 23-28

Byeon, W.-H., Hyun, H.H. & Lee, S.Y. (1976) Mutagenicity of pesticides in the *Salmonella*/microsome system (Korean). *Misaengmul Hakhoe Chi (Korean J. Microbiol.), 14*, 128-134

Carpenter, C.P., Weil, C.S., Palm, P.E., Woodside, M.W., Nair, J.H., III & Smyth, H.F., Jr (1961) Mammalian toxicity of 1-naphthyl-*N*-methylcarbamate (Sevin insecticide). *J. agric. Food Chem., 9*, 30-39

Challis, B.C. & Bartlett, C.D. (1975) Possible cocarcinogenic effects of coffee constituents. *Nature, 254*, 532-533

Challis, B.C. & Butler, A.R. (1968) *Substitution at an amino nitrogen.* In: Patai, S., ed., *The Chemistry of the Amino Group*, Vol. 1, New York, Interscience, pp. 305-320

Challis, B.C., Edwards, A., Hunma, R.R., Kyrtopoulos, S.A. & Outram, J.R. (1978) *Rapid formation of* N*-nitrosamines from nitrogen oxides under neutral and alkaline conditions.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N*-Nitroso Compounds (IARC Scientific Publications No. 19)*, Lyon, International Agency for Research on Cancer, pp. 127-142

Cohen, S.Z., Sweig, G., Law, M., Wright, D. & Bontoyan, W.R. (1978) *Analytical determination of* N*-nitroso compounds in pesticides by the United States Environmental Protection Agency - A preliminary study.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N*-Nitroso Compounds (IARC Scientific Publications No. 19)*, Lyon, International Agency for Research on Cancer, pp. 333-342

Dahn, H., Loewe, L. & Bunton, C.A. (1960) Oxidation of ascorbic acid by nitrous acid. VI. Review and discussion of the results. 18. Note on reduction and 1,2,3-tricarbonyl compounds (Ger.). *Helv. chim. Acta, 43*, 320-333

Davies, R., Dennis, M.J., Massey, R.C. & McWeeny, D.J. (1978) *Some effects of phenol- and thiol-nitrosation reactions on* N*-nitrosamine formation.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N*-Nitroso Compounds (IARC Scientific Publications No. 19)*, Lyon, International Agency for Research on Cancer, pp. 183-197

De Lorenzo, F., Staiano, N., Silengo, L. & Cortese, R. (1978) Mutagenicity of diallate, sulfallate, and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture. *Cancer Res., 38*, 13-15

Dunkel, V.C. & Simmon, V.F. (1980) *Mutagenic activity of chemicals previously tested for carcinogenicity in the National Cancer Institute bioassay program.* In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests (IARC Scientific Publications No. 27)*, Lyon, International Agency for Research on Cancer, pp. 283-302

Egert, G. & Greim, H. (1976a) Formation of mutagenic *N*-nitroso compounds from the pesticides prometryne, dodine and carbaryl in the presence of nitrite at pH 1. *Mutat. Res., 37*, 179-186

Egert, C. & Greim, H. (1976b) Formation of dimethylnitrosamine from chloroxuron, cycluron, dimefox and thiram in the presence of nitrite (Abstract No. 61) *Mutat. Res., 38*, 136-137

Eisenbeis, S.J., Lynch, D.L. & Hampel, A.E. (1981) The Ames mutagen assay tested against herbicides and herbicide combinations. *Soil Sci., 131*, 44-47

Eisenbrand, G., Ungerer, O. & Preussmann, R. (1974) Rapid formation of carcinogenic *N*-nitrosamines by interaction of nitrite with fungicides derived from dithiocarbamic acid *in vitro* under simulated gastric conditions and *in vivo* in the rat stomach. *Food Cosmet. Toxicol., 12*, 229-232

Eisenbrand, G., Ungerer, O. & Preussmann, R. (1975a) *Formation of* N-*nitroso compounds from agricultural chemicals and nitrite.* In: Bogovski, P. & Walker, E.A., eds, N-*Nitroso Compounds in the Environment (IARC Scientific Publications No. 9),* Lyon, International Agency for Research on Cancer, pp. 71-74

Eisenbrand, G., Ungerer, O. & Preussmann, R. (1975b) The reaction of nitrite with pesticides. II. Formation, chemical properties and carcinogenic activity of the *N*-nitroso derivative of *N*-methyl-1-naphthyl carbamate (carbaryl). *Food Cosmet. Toxicol., 13,* 356-367

Eisenbrand, G., Schmähl, D. & Preussmann, R. (1976) Carcinogenicity in rats of high oral doses of *N*-nitrosocarbaryl, a nitrosated pesticide. *Cancer Lett., 1*, 281-284

Eisenbrand, G., Spiegelhalder, B., Kann, J., Klein, R. & Preussmann, R. (1979) Carcinogenic *N*-nitrosodimethylamine as a contamination in drugs containing 4-dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (amidopyrine, aminophenazone). *Arzneim.-Forsch./Drug Res., 29*, 867-869

Elespuru, R.K. (1979) Mutagenicity of nitrosocarbaryl and other methylating nitrosamides as related to uptake in *Haemophilus influenzae. Environ. Mutagenesis, 1*, 249-257

Elespuru, R.K. & Lijinsky, W. (1973) The formation of carcinogenic nitroso compounds from nitrite and some types of agricultural chemicals. *Food Cosmet. Toxicol., 11*, 807-817

Elespuru, R.K., Lijinsky, W. & Setlow, J.K. (1974) Nitrosocarbaryl as a potent mutagen of environmental significance. *Nature, 247*, 386-387

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol., 23*, 288-325

Eya, B.K. & Talcott, R.E. (1980) Effect of *N*-alkyl chain length on the mutagenicity of *N*-nitrosated 1-naphthyl *N*-alkylcarbamates. *Environ. Mutagenesis, 2,* 395-404

Fahrig, R. (1974) *Comparative mutagenicity studies with pesticides.* In: Montesano, R. & Tomatis, L., eds, *Chemical Carcinogenesis Essays* (*IARC Scientific Publications No. 10*), Lyon, International Agency for Research on Cancer, pp. 161-178

Fahrig, R. & Seiler, J.P. (1979) Dose and effect of methyl-2-benzimidazolylcarbamate in the 'mammalian spot test', an *in vivo* method for the detection of genetic alterations in somatic cells of mice. *Chem.-biol. Interactions*, *26*, 115-120

Fan, T.-Y. & Tannenbaum, S.R. (1973) Factors influencing the rate of formation of nitrosomorpholine from morpholine and nitrite: Acceleration by thiocyanate and other anions. *J. agric. Food Chem.*, *21*, 237-240

Fanelli, R., Chiabrando, C. & Airoldi, L. (1978) Determination of volatile *N*-nitrosamines as pesticide contaminants by gas chromatography-mass fragmentography. *Anal. Lett.*, *A11*, 845-854

Ficsor, G., Bordas, S. & Stewart, S.J. (1978) Mutagenicity testing of benomyl, methyl-2-benzimidazole carbamate, streptozotocin and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in *Salmonella typhimurium in vitro* and in rodent host-mediated assays. *Mutat. Res.*, *51*, 151-164

Fridman, A.L., Mukhametshin, F.M. & Novikov, S.S. (1971) Advances in the chemistry of aliphatic *N*-nitrosamines. *Russ. chem. Rev.*, *40*, 34-50

Gentile, J.M., Wagner, E.D. & Plewa, M.J. (1977) The detection of weak recombinogenic activities in the herbicides alachlor and propachlor using a plant-activation bioassay. *Mutat. Res., 48,* 113-116

George, M.K., Aulakh, K.S. & Dhesi, J.S. (1970) Morphological and cytological changes induced in barley (*Hordeum vulgare*) seedlings following seed treatment with fungicides. *Can. J. Genet. Cytol.*, *12*, 415-419

Georgopoulos, S.G., Kappas, A. & Hastie, A.C. (1976) Criterion of fungitoxicity by interference with hereditary processes. *Phytopathology*, *66*, 217-220

Greim, H., Bimboes, D., Egert, G., Göggelmann, W. & Krämer, M. (1977) Mutagenicity and chromosomal aberrations as an analytical tool for *in vitro* detection of mammalian enzyme-mediated formation of reactive metabolites. *Arch. Toxicol.*, *39*, 159-169

Griffiths, A.J.F. (1979) *Neurospora* prototroph selection system for studying aneuploid production. *Environ. Health Perspect.*, *31*, 75-80

Guerzoni, M.E., Del Cupolo, L. & Ponti, I. (1976) Mutagenic activity of pesticides (Ital.) *Riv. Sci. Tecn. Alim. Nutr. Um.*, *6*, 161-165

Hakeem, H. & Shehab, A. (1974) Cytological effects of simazine on *Vicia faba*. *Proc. Egypt. Acad. Sci.*, *25*, 61-66

Hedenstedt, A., Rannug, U., Ramel, C. & Wachtmeister, C.A. (1979) Mutagenicity and metabolism studies on 12 thiuram and dithiocarbamate compounds used as accelerators in the Swedish rubber industry. *Mutat. Res.*, *68*, 313-325

Hein, G.E. (1963) The reaction of tertiary amines with nitrous acid. *J. chem. Educ.*, *40*, 181-184

Hodge, H.C., Maynard, E.A., Downs, W.L., Coye, R.D., Jr & Steadman, L.T. (1956) Chronic oral toxicity of ferric dimethyldithiocarbamate (ferbam) and zinc dimethyldithiocarbamate (ziram). *J. Pharmacol. exp. Ther.*, *118*, 174-181

Hoque, M.Z. (1972) Carbaryl, a new chemical mutagen. *Curr. Sci.*, *41*, 855-856

IARC (1976a) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some carbamates, thiocarbamates and carbazides*, Lyon, International Agency for Research on Cancer, pp. 37-53

IARC (1976b) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some carbamates, thiocarbamates and carbazides*, Lyon, International Agency for Research on Cancer, pp. 121-129

IARC (1976c) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some carbamates, thiocarbamates and carbazides*, Lyon, International Agency for Research on Cancer, pp. 225-236

IARC (1976d) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 12, *Some carbamates, thiocarbamates and carbazides*, Lyon, International Agency for Research on Cancer, pp. 259-270

IARC (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 17, *Some* N-*Nitroso Compounds*, Lyon, International Agency for Research on Cancer

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. & Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary note. *J. natl Cancer Inst.*, *42*, 1101-1114

Ishidate, M., Jr & Odashima, S. (1977) Chromosome tests with 134 compounds on Chinese hamster cells *in vitro* - a screening for chemical carcinogens. *Mutat. Res.*, *48*, 337-354

Janzowski, C., Klein, R. & Preussmann, R. (1980) *Formation of* N-*nitroso compounds of the pesticides atrazine, simazine and carbaryl with nitrogen oxides.* In: Walker, E.A., Griciute, L., Castegnaro, M. & Borzsonyi, M., eds, N-*Nitroso Compounds: Analysis, Formation and Occurrence* (*IARC Scientific Publications No. 31*), Lyon, International Agency for Research on Cancer, pp. 329-339

Jaszczuk, E. & Syrowatka, T. (1979) Induction of mitotic conversion in *Saccharomyces cerevisiae* D4 with propoxur, carbaryl, dimethylnitrosamine and products of their metabolic activation. *Rocz. Panstw. Zakl. Hig.*, *30*, 323-330

Jaszczuk, E., Syrowatka, T. & Cybulski, J. (1979) Mutagenic activity of propoxur, carbaryl and their nitroso derivatives: Induction of reversion in *Salmonella typhimurium*. *Rocz. Panstw. Zakl. Hig.*, *30*, 81-88

Jeang, C.-L. & Li, G.-C. (1978) Screening of pesticides for mutagenicity in the microbial system. *K'o Hsueh Fa Chan Yueh K'an*, *6*, 780-788

Jones, D.C.L., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Evans, E.L., Jotz, M.M., Riccio, E.S., Robinson, D.E. & Kirkhart, B.A. (1982) In vitro *Mutagenicity Studies of Environmental Chemicals*, Washington DC, National Technical Information Service (in press)

Kahlon, P.S. (1980) Seedling injury and chromosome aberrations induced by bladex, dowpon, princep and tenoran. *J. Tenn. Acad. Sci.*, *55*, 17-19

Kaplan, A.M. & Sherman, H. (1977) Toxicity studies with methyl *N*-[[(methylamino)carbonyl]oxy]ethanimidothioate. *Toxicol. appl. Pharmacol.*, *40*, 1-17

Kappas, A., Georgopoulos, S.G. & Hastie, A.C. (1974) On the genetic activity of benzimidazole and thiophanate fungicides on diploid *Aspergillus nidulans*. *Mutat. Res.*, *26*, 17-27

Kar, S. & Singh, P.K. (1979) Mutagenicity of pesticides carbofuran and hexachlorocyclohexane to blue-green alga *Nostoc muscorum*. *Microbios Lett.*, *12*, 79-82

Kas'yanenko, A.G., Kordleva, N.S., Ryabova, I.M. & Shevtsova, V.M. (1977) *Verticillium* mutation induced by pesticides (Russ.). *Izv. Akad. Nauk. Tadzh. SSR Otd. Biol. Nauk.*, *1*, 22-27

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980) *Cooperative programme on short-term assays for carcinogenicity in Japan*. In: Montesano, R., Bartsch, H. & Tomatis, L., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests (IARC Scientific Publications No. 27)*, Lyon, International Agency for Research on Cancer, pp. 323-330

Kearney, P.C., Oliver, J.E., Helling, C.S., Isensee, A.R. & Kontson, A. (1977) Distribution, movement, persistence and metabolism of *N*-nitrosatrazine in soil and a model aquatic ecosystem. *J. agric. Food Chem.*, *25*, 1177-1181

Keefer, L.K. & Roller, P.P. (1973) *N*-Nitrosation by nitrite ion in neutral and basic medium. *Science*, *181*, 1245-1247

Khan, S.U. & Young, J.C. (1977) *N*-Nitrosamine formation in soil from the herbicide glyphosate. *J. agric. Food Chem.*, *25*, 1430-1432

Khubutiya, R.A. & Uguluva, N.A. (1973) Cytogenetic effect of herbicides (Georg.). *Tr. Nauchno-Issled, Inst. Zashch. Rast.* (*Tiflis*), *25*, 97-99

Kimball, R.F., Boling, M.E. & Perdue, S.W. (1977) Evidence that UV-inducible error-prone repair is absent in *Haemophilus influenzae* Rd, with a discussion of the relation to error-prone repair of alkylating-agent damage. *Mutat. Res.*, *44*, 183-196

Kulakov, A.E. (1970) Cytogenetic analysis of bone marrow cells of rats exposed to symm-triazine herbicides (Russ.). *Farmakol. Toksikol. (Moscow), 33*, 224-227

Lamb, M.J. & Lilly, L.J. (1980) An investigation of some genetic toxicological effects of the fungicide benomyl. *Toxicology, 17*, 83-95

Lee, C.-C., Russell, J.Q. & Minor, J.L. (1978) Oral toxicity of ferric dimethyldithiocarbamate (ferbam) and tetramethylthiuram disulfide (thiram) in rodents. *J. Toxicol. environ. Health, 4*, 93-106

Lee, K., Gold, B. & Mirvish, S.S. (1977) Mutagenicity of 22 *N*-nitrosamides and related compounds for *Salmonella typhimurium* TA1535. *Mutat. Res., 48*, 131-138

Lehman, A.J. (1965) *Summaries of Pesticide Toxicity*, Topeka, KS, Association of Food and Drug Officials of the US, pp. 81-82

Levinskas, G.J., Vidone, L.B., O'Grady, J.J. & Shaffer, C.B. (1961) Acute and chronic toxocity of dodine (*n*-dodecylguanidine acetate). *Toxicol. appl. Pharmacol., 3*, 127-142

Liang, G.H. & Liang, Y.T.S. (1972) Effects of atrazine on chromosomal behaviour in sorghum. *Can. J. Genet. Cytol., 14*, 423-427

Lijinsky, W. & Andrews, A.W. (1979) The mutagenicity of nitrosamides in *Salmonella typhimurium*. *Mutat. Res., 68*, 1-8

Lijinsky, W. & Elespuru, R.K. (1976) *Mutagenicity and carcinogenicity of* N-*nitroso derivatives of carbamate insecticides*. In: Walker, E.A., Bogovski, P. & Griciute, L., eds, *Environmental* N-*Nitroso Compounds: Analysis and Formation* (*IARC Scientific Publications No. 14*), Lyon, International Agency for Research on Cancer, pp. 425-428

Lijinsky, W. & Schmêahl, D. (1978) Carcinogenicity of *N*-nitroso derivatives of *N*-methylcarbamate insecticides in rats. *Ecotoxicol. environ. Saf., 2*, 413-419

Lijinsky, W. & Taylor, H.W. (1976) Carcinogenesis in Sprague-Dawley rats of *N*-nitroso-*N*-alkylcarbamate esters. *Cancer Lett., 1*, 275-279

Lijinsky, W. & Taylor, H.W. (1977a) Transplacental chronic toxicity test of carbaryl with nitrite in rats. *Food Cosmet. Toxicol., 15*, 229-232

Lijinsky, W. & Taylor, H.W. (1977b) Feeding tests in rats on mixtures of nitrite with secondary and tertiary amines of environmental importance. *Food Cosmet. Toxicol., 15*, 269-274

Lijinsky, W., Keefer, L., Conrad, E. & Van de Bogart, R. (1972) Nitrosation of tertiary amines and some biologic implications. *J. natl Cancer Inst., 49*, 1239-1249

Lusby, A.F., Simmons, Z. & McGuire, P.M. (1979) Variation in mutagenicity of S-triazine compounds tested on four *Salmonella* strains. *Environ. Mutagenesis, 1*, 287-290

Marshall, T.C., Dorough, H.W. & Swim, H.E. (1976) Screening of pesticides for mutagenic potential using *Salmonella typhimurium* mutants. *J. agric. Food Chem., 24*, 560-563

Mayberry, R.M. & Savage, J. (1978) Mutagenic activity of several pesticides using the *Salmonella* test and *Saccharomyces* D3 system. *Abstr. Ann. Meet. Am. Soc. Microbiol.*, *78*, 125

Mergens, W.J., Kamm, J.J., Newmark, H.L., Fiddler, W. & Pensabene, J. (1978) *Alpha-tocopherol: Uses in preventing nitrosamine formation.* In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N-*Nitroso Compounds* (*IARC Scientific Publications No. 19*), Lyon, International Agency for Research on Cancer, pp. 199-212

Mirvish, S.S. (1971) Kinetics of nitrosamide formation from alkylureas, *N*-alkylurethans, and alkylguanidines: Possible implications for the etiology of human gastric cancer. *J. natl Cancer Inst.*, *46*, 1183-1193

Mirvish, S.S. (1975) Formation of *N*-nitroso comounds: Chemistry, kinetics, and *in vivo* occurrence. *Toxicol. appl. Pharmacol.*, *31*, 325-351

Mirvish, S.S., Wallcave, L., Eagen, M. & Shubik, P. (1972) Ascorbate-nitrite reaction: Possible means of blocking the formation of carcinogenic *N*-nitroso compounds. *Science*, *177*, 65-68

Mollet, P. (1976) Lack of proof of induction of somatic recombination and mutation in *Drosophila* by methyl-2-benzimidazole carbamate, dimethyl sulfoxide and acetic acid. *Mutat. Res.*, *40*, 383-388

Morpurgo, G., Bellincampi, D., Gualandi, G., Baldinelli, L. & Serlupi Crescenzi, O. (1979) Analysis of mitotic nondisjunction with *Aspergillus nidulans*. *Environ. Health Perspect.*, *31*, 81-95

Müller, A., Ebert, E. & Gast, A. (1972) Cytogenetic studies with atrazine (2-chloro-4-ethyl-amino-6-isopropylamino-*s*-triazone) on plants. *Experientia*, *28*, 704-705

Murnik, M.R. & Nash, C.L. (1977) Mutagenicity of the triazine herbicides atrazine, cyanazine, and simazine in *Drosophila melanogaster*. *J. Toxicol. environ. Health*, *3*, 691-697

Musalevski, A., Shopova, M., Shange, T., Petrovska, D.,, Najchevska, C., Stojkovski, C. & Sekovski, Z. (1981) The effect of herbicide trifluralin on root mitosis and meiosis in *Gossypium herbaceum* (Abstract) *Mutat. Res.*, *80*, 229

Nagy, Z., Mile, I. & Antoni, F. (1975) Mutagenic effect of pesticides on *Escherichia coli* WP2 *try*. *Acta microbiol. acad. sci. hung.*, *22*, 309-314

National Academy of Sciences (1981) *The Health Effects of Nitrate, Nitrite, and* N-*Nitroso Compounds*, Washington DC, National Academy Press

National Cancer Institute (1978) *Bioassay of Trifluralin for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 343; DHEW Publ. No. (NIH) 78-834*), Bethesda, MD, Department of Health, Education & Welfare

National Cancer Institute (1979) *Bioassay of Aldicarb for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 136; NIH Publ. No. 79-1391*), Bethesda, MD, National Institutes of Health

National Technical Information Service (1968) *Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals*, Vol. 1, *Carcinogenic Study*, Bethesda, MD, Bionetics Research Laboratories

Nehez, M., Páldy, A., Selypes, A., Körösfalvi, M., Lörinczi, I. & Berencsi, G. (1979) The mutagenic effect of trifluralin-containing herbicide on mouse bone marrow *in vivo*. *Ecotoxicol. environ. Saf.*, *3*, 454-457

Nehez, M., Páldy, A., Selypes, A., Körösfalvi, M., Lörinczi, I. & Berencsi, G. (1980) The mutagenic effect of trifluralin-containing herbicide on mouse germ cells *in vivo*. *Ecotoxicol. environ. Saf.*, *4*, 263-266

Nelson, J., MacKinnon, E.A., Mower, H.F. & Wong, L. (1981) Mutagenicity of *N*-nitroso derivatives of carbofuran and its toxic metabolites. *J. Toxicol. environ. Health*, *7*, 519-531

Oku, K. (1976) Effects of some herbicides on somatic division in barley (Jpn.). *Senshokutai (Kromosoma)*, *2*, 63-68

Okun, J.D. & Archer, M.C. (1976) *Micellar catalysis of nitrosamine formation*. In: Walker, E.A., Bogovski, P. & Griciute, L., eds, *Environmental N-Nitroso Compounds: Analysis and Formation* (*IARC Scientific Publications No. 14*), Lyon, International Agency for Research on Cancer, pp. 147-151

Oliver, J. & Konston, A. (1978) Formation and persistence of *N*-nitrosobutralin in soil. *Bull. environ. Contam. Toxicol.*, *20*, 170-173

Paik, S.G. & Lee, S.Y. (1977) Genetic effects of pesticides in the mammalian cells. 1. Induction of micronucleus. *Tongmul Hakhow Chi* (*Korean J. Zool.*), *20*, 19-28

Paulsen, H. & Mäckel, E. (1969) Monosaccharides with ring containing nitrogen. XXIV. Competition between nitrosation of neighbouring primary and secondary amino groups. Synthesis of nitrosamino sugars (Ger.). *Chem. Ber.*, *102*, 3844-3853

Penner, D. & Early, R.W. (1972) Role pf pH in the observed effect of plant growth regulators on DNA. *Phytochemistry*, *11*, 3135-3138

Petrovska, D., Shopova, M., Musalevski, C., Najchevska, C., Sekovski, Z. & Stojkovski, C. (1981) Some cytological effects of herbicide trifluralin in *Allium cepa* L. (Abstract). *Mutat. Res.*, *85*, 229-230

Pignatelli, B., Friesen, M. & Walker, E.A. (1980) *The role of phenols in catalysis of nitrosamine formation*. In: Walker, E.A., Griciute, L., Castegnaro, M. & Börzsönyi, M., eds, *N-Nitroso Compounds: Analysis, Formation and Occurrence* (*IARC Scientific Publications No. 31*), Lyon, International Agency for Research on Cancer, pp. 95-109

Pilinskaya, M.A., Kurrinyi, A.I., L'vova, T.S. & German, I.V. (1980) Primary evaluation of cytogenetic activity and potential mutagenic hazard of 22 pesticides. *Tsitol. Genet.*, *14*, 41-47

Plewa, M.J. (1978) Activation of chemicals into mutagens by green plants: A preliminary discussion. *Environ. Health Perspect.*, *27*, 45-50

Plewa, M.J. & Gentile, J.M. (1976) Mutagenicity of atrazine: A maize-microbe bioassay. *Mutat. Res.*, *38*, 287-292

Pliss, G.B. & Zabezhinsky, M.A. (1970) On carcinogenic properties of symmetrical triazine derivatives (Russ.). *Vopr. Onkol.*, *16*, 82-85

Prasad, I. & Pramer, D. (1968) Genetic effects of ferbam on *Aspergillus niger* and *Allium cepa*. *Phytopathology*, *58*, 1188-1189

Preussmann, R., Eisenbrand, G. & Schmähl, D. (1976) *Carcinogenicity testing of low doses of nitrosopyrrolidine and of nitrosobenzthiazuron and nitrosocarbaryl in rats.* In: Walker, E.A., Bogovski, P. & Griciute, L., eds, *Environmental N-Nitroso Compounds: Analysis and Formation* (*IARC Scientific Publications No. 14*), Lyon, International Agency for Research on Cancer, pp. 429-433

Probst, G.S., McMahon, R.E., Hill, L.E., Thompson, C.Z., Epp, J.K. & Neal, S.B. (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. *Environ. Mutagenesis*, *3*, 11-32

Pusztai, T. & Vegh, A. (1978) Mutagenic effects of pesticides. I. Cytological effects on some substituted urea herbicides in barley. *Acta bot. acad. sci. hung.*, *24*, 327-342

Rani, M.V.U., Reddi, O.S. & Reddy, P.P. (1980) Mutagenicity studies involving aldrin, endosulfan, dimethoate, phosphamidon, carbaryl and ceresan. *Bull. environ. Contam. Toxicol.*, *25*, 277-282

Regan, J.D., Setlow, R.B., Francis, A.A. & Lijinsky, W. (1976) Nitrosocarbaryl: Its effect on human DNA. *Mutat. Res.*, *38*, 293-301

Richard, R.W. (1980) Chemical properties and potential toxicological significance of *N*-nitrosocarbamates. *Diss. Abstr. Int. B, 40,* 5595

Ridd, J.H. (1961) Nitrosation, diazotisation, and deamination. *Q. Rev. Chem. Soc. (Lond.)*, *15*, 418-441

Rizk, T.Y. (1973) Anatomical and cytological changes in excised cotton roots in response to trifluralin or nitralin treatments. *Egypt. J. Bot.*, *16*, 281-289

Rocchi, P., Perocco, P., Alberghini, W., Fini, A. & Prodi, G. (1980) Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. *Arch. Toxicol.*, *45*, 101-108

Rosenkranz, H.S. & Leifer, Z. (1980) *Determining the DNA-modifying activity of chemicals using DNA-polymerase-deficient* Escherichia coli. In: de Serres, F.J. & Hollaender, A., eds, *Chemical Mutagens. Principles and Methods for Their Detection*, Vol. 6, New York, Plenum Press, pp. 109-147

Ross, R.D., Morrison, J., Rounbehler, D.P., Fan, S. & Fine, D.H. (1977) N-Nitroso compound impurities in herbicide formulations. *J. agric. Food Chem.*, *25*, 1416-1418

Sathaiah, V., Sastry, G.A. & Reddy, P.V. (1974) Cytological effects of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methyl carbamate 'carbofuran'. *Curr. Sci.*, *43*, 53-54

Sawamura, S. (1965) Studies on the effect of herbicides on plant cells *in vivo*. II. Non-hormonic herbicides. *Cytologia, 60*, 325-348

Sawamura, S. & Jackson, W.T. (1968) Cytological studies *in vivo* of picloram, pyriclor, trifluralin, 2,3,6-TBA, 2,3,5,6-TBA and nitralin. *Cytologia, 33*, 545-554

Schairer, L.A., Van't Hof, J., Hayes, C.G., Burton, R.M. & de Serres, F.J. (1979) Measurement of biological activity of ambient air mixtures using a mobile laboratory for *in situ* exposures: Preliminary results from the *Tradescantia* plant test system. *Environ. Sci. Res., 15*, 419-440

Seiler, J.P. (1972) The mutagenicity of benzimidazole and benzimidazole derivatives. I. Forward and reverse mutations in *Salmonella typhimurium* caused by benzimidazole and some of its derivatives. *Mutat. Res., 15*, 273-276

Seiler, J.P. (1973) A survey of the mutagenicity of various pesticides. *Experientia, 29*, 622-623

Seiler, J.P. (1975) Evaluation of some pesticides for mutagenicity. *Proc. Eur. Soc. Toxicol., 17*, 398-404

Seiler, J.P. (1976) The mutagenicity of benzimidazole and benzimidazole derivatives. VI. Cytogenetic effects of benzimidazole derivatives in the bone marrow of the mouse and the Chinese hamster. *Mutat. Res., 40*, 339-348

Seiler, J.P. (1977a) Nitrosation *in vitro* and *in vivo* by sodium nitrite, and mutagenicity of nitrogenous pesticides. *Mutat. Res., 48*, 225-226

Seiler, J.P. (1977b) Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. *Mutat. Res., 46*, 305-310

Seiler, J.P. (1978) Herbicidal phenylalkylureas as possible mutagens. I. Mutagenicity tests with some urea herbicides. *Mutat. Res., 58*, 353-359

Sen, N.P., Donaldson, B.A. & Charbonneau, C. (1975) *Formation of nitrosodimethylamine from the interaction of certain pesticides and nitrite.* In: Bogovski, P. & Walker, E.A., eds, N-*Nitroso Compounds in the Environment* (*IARC Scientific Publications No. 9*), Lyon, International Agency for Research on Cancer, pp. 75-79

Sharma, G.S. (1973) Chromosomal aberrations induced by herbicides in meitotic cells of huskless barley. *Univ. Udaipur Res. Stud., 8*, 55-56

Shimkin, M.B., Wieder, R., McDonough, M., Fishbein, L. & Swern, D. (1969) Lung tumor response in strain A mice as a quantitative bioassay of carcinogenic activity of some carbamates and aziridines. *Cancer Res., 29*, 2184-2190

Shirasu, Y. (1975) Significance of mutagenicity testing on pesticides. *Environ. Qual. Saf., 4*, 226-231

Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A. & Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat. Res., 40*, 19-30

Shirasu, Y., Moriya, M., Kato, K., Lienard, F., Tezuka, H., Teramoto, S. & Kada, T. (1977) *Mutagenicity screening on pesticides and modification products: A basis of carcinogenicity evaluation.* In: Hiatt, H.H., Watson, J.D. & Winsten, J.A., eds, *Origins of Human Cancer*, Book A, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 267-285

Siebert, D. & Eisenbrand, G. (1974) Induction of mitotic gene conversion in *Saccharomyces cerevisiae* by *N*-nitrosated pesticides. *Mutat. Res.*, *22*, 121-126

Siebert, D. & Lemperle, E. (1974) Genetic effects of herbicides: Induction of mitotic gene conversion in *Saccharomyces cerevisiae*. *Mutat. Res.*, *22*, 111-120

Siebert, D., Zimmermann, F.K. & Lemperle, E. (1970) Genetic effects of fungicides. *Mutat. Res.*, *10*, 533-543

Simmon, V.F., Kauhanen, K. & Tardiff, R.G. (1977) Mutagenic activity of chemicals identified in drinking water. *Dev. Toxicol. environ. Sci.*, *2*, 249-258

Singh, B.D., Singh, Y., Singh, R.B., Singh, R.M., Sarma, N.D.R.K. & Singh, J. (1977) Cytogenetic aberrations and morphological changes induced by insecticide treatments of barley seeds. *Indian J. exp. Biol.*, *15*, 688-691

Singh, B.D., Singh, R.B., Singh, R.M., Singh, Y. & Singh, J. (1979) Effect of insecticides on germination, early growth and cytogenetic behaviour of barley (*Hordeum vulgare*). *Environ. exp. Bot.*, *19*, 127-132

Singh, I. (1978) Induction of mitotic crossing over and gene conversion by the fungicide bavistin in *Saccharomyces cerevisiae*. *Indian J. exp. Biol.*, *16*, 393-394

Singh, I., Lusby, A.F. & McGuire, P.M. (1982) Mutagenicity of HPLC fractions from extracts of Atrex-treated corn. *Environ. Mutagenesis*, *4*, 45-53

Smith, P.A.S. & Loeppky, R.N. (1967) Nitrosative cleavage of tertiary amines. *J. Am. chem. Soc.*, *89*, 1147-1157

Sparrow, A.H. & Schairer, L.A. (1974) Mutagenic response of *Tradescantia* to treatment with X-rays, EMS, DBE, ozone, SO_2, N_2O and several insecticides (Abstract no. 2). *Mutat. Res.*, *26*, 445

Speakman, J.B. & Nirenberg, H.I. (1981) Mutagenicity of methyl benzimidazol-2-yl carbamate (MBC) towards *Aspergillus nidulans* (Eidam) winter and *Cladosporium cucmerinum* Ellis & Arth. *Mutat. Res.*, *88*, 45-51

Spiegelhalder, B., Eisenbrand, G. & Preussmann, R. (1976) Influence of dietary nitrate on nitrite content of human saliva: Possible relevance to *in vivo* formation of *N*-nitroso compounds. *Food Cosmet. Toxicol.*, *14*, 545-548

Stroev, V.S. (1968) The mutagenic effect by the action of herbicides on the barley (Russ.). *Genetika*, *4*, 164-167

Stroev, V.S. (1970) Cytogenetic activity of the herbicides atrazine, chloro-IPC, and paraquat (Russ.). *Genetika*, *6*, 31-37

Styles, J.A. & Garner, R. (1974) Benzimidazolecarbamate methyl ester - evaluation of its effects *in vivo* and *in vitro*. *Mutat. Res.*, *26*, 177-187

Suruzhiu, A.I., Chebotar', A.A., Bukhar, B.I. & Bezrukova, T.A. (1978) Polyploidizing effect of herbicides as exemplified by *Pisum sativum* L. *Dokl. Biol. Sci.*, *239*, 98-100

Syrowatka, T., Tyrkiel, E., Wiadrowska, B. & Nazarewicz, T. (1980) Investigations on the effects of simultaneous administration of sodium nitrite on the toxic and cancerogenic activity of carbendazyme in long-term experiments (Pol.). *Roczn. Pzh.*, *31*, 117-124

Tannenbaum, S.R., Sinskey, A.J., Weisman, M. & Bishop, W. (1974) Nitrite in human saliva. Its possible relationship to nitrosamine formation. *J. natl Cancer Inst.*, *53*, 79-84

Tannenbaum, S.R., Weisman, M. & Fett, D. (1976) The effect of nitrate intake on nitrite formation in human saliva. *Food Cosmet. Toxicol.*, *14*, 549-552

Tates, A.D. (1979) *Microtus oeconomus* (rodentia), a useful mammal for studying the induction of sex-chromosome nondisjunction and diploid gametes in male germ cells. *Environ. Health Perspect.*, *31*, 151-159

Thust, R., Mendel, J., Schwarz, H. & Warzok, R. (1980) Nitrosated urea pesticide metabolites and other nitrosamides. Activity in clastogenicity and SCE assays, and aberration kinetics in Chinese hamster V79-E cells. *Mutat. Res.*, *79*, 239-248

Tyrkiel, E. (1977) Mutagenic action of *o*-isopropoxyphenyl *N*-methylcarbamate (propoxur) on mouse gametes (Pol.). *Rocz. Panstw. Zakl. Hig.*, *28*, 601-613

Uchiyama, M., Takeda, M., Suzuki, T. & Yoshikawa, K. (1975) Mutagenicity of nitroso derivatives of *N*-methylcarbamate insecticides in microbiological method. *Bull. environ. Contam. Toxicol.*, *14*, 389-394

Ungerer, O., Eisenbrand, G. & Preussmann, R. (1974) Formation, chemical properties and carcinogenic activity of the *N*-nitroso compound of the herbicide *N*-methyl-*N'*-(2-benzothiazolyl)-urea (Benzthiazuron) (Ger.). *Z. Krebsforsch.*, *81*, 207-224

Valencia, R. (1977) *Mutagenesis Screening of Pesticides Using* Drosophila, Madison, WI, WARF Institute, Inc.

Vigfusson, N.V. & Vyse, E.R. (1980) The effect of the pesticides, dexon, captan and roundup, on sister-chromatid exchanges in human lymphocytes *in vitro*. *Mutat. Res.*, *79*, 53-57

Von Rumker, R., Lawless, E.W. & Meiners, A.F. (1975) *Production, Distribution, Use and Environmental Impact Potential of Selected Pesticides*, Washington DC, Office of Pesticide Programs, Office of Water and Hazardous Materials, US Environmental Protection Agency

Walker, E.A., Griciute, L., Castegnaro, M. & Börzsönyi, M., eds (1980) *N-Nitroso Compounds: Analysis, Formation and Occurrence* (*IARC Scientific Publications No. 31*), Lyon, International Agency for Research on Cancer

Waters, M.D., Sandhu, S.S., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T.A., Jones, D.C.L., Valencia, R. & Garrett, N.E. (I982) *Study of pesticide genotoxicity.* In: Fleck, R. & Hollaender, A., eds, *Genetic Toxicology. An Agricultural Perspective*, New York, Plenum Press (in press)

Wuu, K.D. & Grant, W.F. (1967a) Chromosomal aberrations induced by pesticides in meiotic cells of barley. *Cytologia*, *32*, 31-41

Wuu, K.D. & Grant, W.F. (1967b) Chromosomal aberrations induced in somatic cells of *Vicia faba* by pesticides. *Nucleus*, *10*, 37-46

Yoshikawa, K., Uchino, H. & Kurata, H. (1978) Differential mutagenicity of *N*-methyl-*N*-nitrosocarbamate insecticides in *Escherichia coli* strains having different DNA repair capacities. *Mutat. Res.*, *54*, 283-288

Zdzienicka, M., Zielenéska, M., Trojanowska, M., Szymczyk, T., Bignami, M. & Carere, A. (1981) Microbial short-term assays with thiram *in vitro*. *Mutat. Res.*, *89*, 1-7

Zutshi, U. & Kaul, B.L. (1975) Cytogenetic activity of some common fungicides in higher plants. *Cytobios*, *12*, 61-67

Zweig, G., Selim, S., Hummel, R., Mittelman, A., Wright, D.P., Jr, Law, C., Jr & Regelman, E. (1980) *Analytical survey of* N-*nitroso contaminants in pesticide products.* In: Walker, E.A., Griciute, L., Castegnaro, M. & Börzönyi, M., eds, N-*Nitroso Compounds: Analysis, Formation and Occurrence* (*IARC Scientific Publications No. 31*), Lyon, International Agency for Research on Cancer, pp. 555-564

SUPPLEMENTARY CORRIGENDA TO VOLUMES 1-29

Corrigenda covering volumes 1-6 appeared in volume 7, others appeared in volumes 8, 10-13 and 15-27.

Volume 4		
p. 119	1.1 Synonyms and trade names	*replace* 49-40-31 *by* 494-03-1
Volume 7		
p. 147	1.1 Synonyms and trade names	*replace* 259-62-77-0 *by* 25962-77-0
Volume 9		
p. 245	1.1 Synonyms and trade names	*replace* 778-24-92 *by* 7782-49-2
Volume 16		
p. 179	*Mouse*:	*delete* paragraph
p. 182	4.1 Animal data	*delete* It also produced an increased incidence of kidney tumours in mice after its oral administration.
p. 185	5. References	*delete reference* Rowland *et al.*, *since paper will not be published*
Volume 20		
p. 283	1.1 Synonyms and trade names	*delete* Dechlorane Plus; Dechlorane Plus 515′
Volume 24		
p. 212	1.2 Structural and molecular formulae and molecular weight	*replace* CH_3COO *by* CH_3OOC
p. 301	Table 2 (contd) Disulfiram Niketamide	 *delete* and *N*-nitrosopiperidine *delete* and *N*-nitrosopiperidine
Volume 28		
p. 1		*replace* February *by* June
Volume 29		
p. 59	4.3 Evaluation, 2nd paragraph, last line	*replace* 'benzoyl' *by* 'benzyl'

CUMULATIVE INDEX TO IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Numbers in bold indicate volume, and other numbers indicate page. References to corrigenda are given in parentheses. Compounds marked with an asterisk (*) were considered by the working groups, but monographs were not prepared because adequate data on carcinogenicity were not available.

A
Acetamide — *7*, 197
Acetylsalicylic acid*
Acridine orange — *16*, 145
Acriflavinium chloride — *13*, 31
Acrolein — *19*, 479
Acrylic acid — *19*, 47
Acrylic fibres — *19*, 86
Acrylonitrile — *19*, 73
Acrylonitrile-butadiene-styrene copolymers — *19*, 91
Actinomycin C*
Actinomycins — *10*, 29 (corr. *29*, 399)
Adipic acid*
Adriamycin — *10*, 43
Aflatoxins — *1*, 145 (corr. *7*, 319) (corr. *8*, 349) *10*, 51
Aldrin — *5*, 25
Amaranth — *8*, 41
5-Aminoacenaphthene — *16*, 243
2-Aminoanthraquinone — *27*, 191
para-Aminoazobenzene — *8*, 53
ortho-Aminoazotoluene — *8*, 61 (corr. *11*, 295)
para-Aminobenzoic acid — *16*, 249
4-Aminobiphenyl — *1*, 74 (corr. *10*, 343)
1-Amino-2-methylanthraquinone — *27*, 199
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole — *7*, 143
4-Amino-2-nitrophenol — *16*, 43
2-Amino-4-nitrophenol*
2-Amino-5-nitrophenol*
6-Aminopenicillanic acid*
Amitrole — *7*, 31
Amobarbital sodium*
Anaesthetics, volatile — *11*, 285
Aniline — *4*, 27 (corr. *7*, 320) *27*, 39

Aniline hydrochloride	*27*, 40
ortho-Anisidine and its hydrochloride	*27*, 63
para-Anisidine and its hydrochloride	*27*, 65
Anthranilic acid	*16*, 265
Apholate	*9*, 31
Aramite	*5*, 39
Arsenic and arsenic compounds	*1*, 41 *2*, 48 *23*, 39
Arsanilic acid	
Arsenic pentoxide	
Arsenic sulphide	
Arsenic trioxide	
Arsine	
Calcium arsenate	
Dimethylarsinic acid	
Lead arsenate	
Methanearsonic acid, disodium salt	
Methanearsonic acid, monosodium salt	
Potassium arsenate	
Potassium arsenite	
Sodium arsenate	
Sodium arsenite	
Sodium cacodylate	
Asbestos	*2*, 17 (corr. 7, 319) *14* (corr. *15*, 341) (corr. *17*, 351)
Actinolite	
Amosite	
Anthophyllite	
Chrysotile	
Crocidolite	
Tremolite	
Asiaticoside*	
Auramine	*1*, 69 (corr. *7*, 319)
Aurothioglucose	*13*, 39
5-Azacytidine	*26*, 37
Azaserine	*10*, 73 (corr. *12*, 271)
Azathioprine	*26*, 47
Aziridine	*9*, 37
2-(1-Aziridinyl)ethanol	*9*, 47
Aziridyl benzoquinone	*9*, 51
Azobenzene	*8*, 75
B	
Benz[*c*]acridine	*3*, 241
Benzal chloride	*29*, 65
Benz[*a*]anthracene	*3*, 45
Benzene	*7*, 203 (corr. *11*, 295) *29*, 93
Benzidine and its salts	*1*, 80 *29*, 149

Benzo[*b*]fluoranthene *3*, 69
Benzo[*j*]fluoranthene *3*, 82
Benzo[*a*]pyrene *3*, 91
Benzo[*e*]pyrene *3*, 137
para-Benzoquinone dioxime *29*, 185
Benzotrichloride *29*, 73
Benzoyl chloride *29*, 83
Benzyl chloride *11*, 217 (corr. *13*, 243)
29, 49 (corr. 30, 407)
Benzyl violet 4B *16*, 153
Beryllium and beryllium compounds *1*, 17
23, 143 (corr. *25*, 391)
Bertrandite
Beryllium acetate
Beryllium acetate, basic
Beryllium-aluminium alloy
Beryllium carbonate
Beryllium chloride
Beryllium-copper alloy
Beryllium-copper-cobalt alloy
Beryllium fluoride
Beryllium hydroxide
Beryllium-nickel alloy
Beryllium oxide
Beryllium phosphate
Beryllium silicate
Beryllium sulphate and its tetrahydrate
Beryl ore
Zinc beryllium silicate
Bis(1-aziridinyl)morpholinophosphine sulphide *9*, 55
Bis (2-chloroethyl)ether *9*, 117
N,N-Bis(2-chloroethyl)-2-naphthylamine *4*, 119 (corr. *30*, 407)
Bischloroethyl nitrosourea (BCNU) *26*, 79
Bis-(2-chloroisopropyl)ether*
1,2-Bis(chloromethoxy)ethane *15*, 31
1,4-Bis(chloromethoxymethyl)benzene *15*, 37
Bis(chloromethyl)ether *4*, 231 (corr. *13*, 243)
Bleomycins *26*, 97
Blue VRS *16*, 163
Boot and shoe manufacture and repair *25*, 249
Brilliant blue FCF diammonium and disodium salts *16*, 171 (corr. *30*, 407)
1,4-Butanediol dimethanesulphonate (Myleran) *4*, *247*
Butyl benzyl phthalate *29*, 194
Butyl-*cis*-9,10-expoxystearate*
ß-Butyrolactone *11*, 225
γ-Butyrolactone *11*, 231

C
Cadmium and cadmium compounds *2*, 74
11, 39 (corr. *27*, 321)
Cadmium acetate
Cadmium chloride
Cadmium oxide

Cadmium sulphate	
Cadmium sulphide	
Calcium cyclamate	*22*, 58 (corr. *25*, 391)
Calcium saccharin	*22*, 120 (corr. *25*, 391)
Cantharidin	*10*, 79
Caprolactam	*19*, 115
Captan	*30*, 295
Carbaryl	*12*, 37
Carbon tetrachloride	*1*, 53
	20, 371
Carmoisine	*8*, 83
Carpentry and joinery	*25*, 139
Carrageenans (native)	*10*, 181 (corr. *11*, 295)
Catechol	*15*, 155
Chloramben*	
Chlorambucil	*9*, 125
	26, 115
Chloramphenicol	*10*, 85
Chlordane	*20*, 45 (corr. *25*, 391)
Chlordecone (Kepone)	*20*, 67
Chlordimeform	*30*, 61
Chlorinated dibenzodioxins	*15*, 41
Chlormadinone acetate	*6*, 149
	21, 365
Chlorobenzilate	*5*, 75
	30, 73
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)	*26*, 137
Chloroform	*1*, 61
	20, 401
Chloromethyl methyl ether	*4*, 239
4-Chloro-*ortho*-phenylenediamine	*27*, 81
4-Chloro-*meta*-phenylenediamine	*27*, 82
Chloroprene	*19*, 131
Chloropropham	*12*, 55
Chloroquine	*13*, 47
Chlorothalonil	*30*, 319
para-Chloro-*ortho*-toluidine and its hydrochloride	*16*, 277
	30,
5-Chloro-*ortho*-toluidine*	
Chlorotrianisene	*21*, 139
Chlorpromazine*	
Cholesterol	*10*, 99
Chromium and chromium compounds	*2*, 100
	23, 205
Barium chromate	
Basic chromic sulphate	
Calcium chromate	
Chromic acetate	
Chromic chloride	
Chromic oxide	
Chromic phosphate	
Chromite ore	

Chromium carbonyl	
Chromium potassium sulphate	
Chromium sulphate	
Chromium trioxide	
Cobalt-chromium alloy	
Ferrochromium	
Lead chromate	
Lead chromate oxide	
Potassium chromate	
Potassium dichromate	
Sodium chromate	
Sodium dichromate	
Strontium chromate	
Zinc chromate	
Zinc chromate hydroxide	
Zinc potassium chromate	
Zinc yellow	
Chrysene	*3*, 159
Chrysoidine	*8*, 91
C.I. Disperse Yellow 3	*8*, 97
Cinnamyl anthranilate	*16*, 287
Cisplatin	*26*, 151
Citrus Red No. 2	*8*, 101 (corr. *19*, 495)
Clofibrate	*24*, 39
Clomiphene and its citrate	*21*, 551
Conjugated oestrogens	*21*, 147
Copper 8-hydroxyquinoline	*15*, 103
Coumarin	*10*, 113
meta-Cresidine	*27*, 91
para-Cresidine	*27*, 92
Cycasin	*1*, 157 (corr *7*, 319) *10*, 121
Cyclamic acid	*22*, 55 (corr. *25*, 391)
Cyclochlorotine	*10*, 139
Cyclohexylamine	*22*, 59 (corr. *25*, 391)
Cyclophosphamide	*9*, 135 *26*, 165
D	
Dacarbazine	*26*, 203
2,4-D and esters	*15*, 111
D and C Red No. 9	*8*, 107
Dapsone	*24*, 59
Daunomycin	*10*, 145
DDT and associated substances	*5*, 83 (corr. *7*, 320)
DDD (TDE)	
DDE	
Diacetylaminoazotoluene	*8*, 113
N,N'-Diacetylbenzidine	*16*, 293
Diallate	*12*, 69 *30*, 235
2,4-Diaminoanisole and its sulphate	*16*, 51 *27*, 103

2,5-Diaminoanisole*	
4,4'-Diaminodiphenyl ether	*16*, 301 *29*, 203
1,2-Diamino-4-nitrobenzene	*16*, 63
1,4-Diamino-2-nitrobenzene	*16*, 73
2,4-Diaminotoluene	*16*, 83
2,5-Diaminotoluene and its sulphate	*16*, 97
Diazepam	*13*, 57
Diazomethane	*7*, 223
Dibenz[*a,h*]acridine	*3*, 247
Dibenz[*a,j*]acridine	*3*, 254
Dibenz[*a,h*]anthracene	*3*, 178
7*H*-Dibenzo[*c,g*]carbazole	*3*, 260
Dibenzo[*h,rst*]pentaphene	*3*, 197
Dibenzo[*a,e*]pyrene	*3*, 201
Dibenzo[*a,h*]pyrene	*3*, 207
Dibenzo[*a,i*]pyrene	*3*, 215
Dibenzo[*a,l*]pyrene	*3*, 224
1,2-Dibromo-3-chloropropane	*15*, 139 *20*, 83
ortho-Dichlorobenzene	*7*, 231 *29*, 213
para-Dichlorobenzene	*7*, 231 *29*, 215
3,3'-Dichlorobenzidine and its dihydrochloride	*4*, 49 *29*, 239
trans-1,4-Dichlorobutene	*15*, 149
3,3'-Dichloro-4,4'-diaminodiphenyl ether	*16*, 309
1,2-Dichloroethane	*20*, 429
Dichloromethane	*20*, 449
Dichlorvos	*20*, 97
Dicofol	*30*, 87
Dicyclohexylamine	*22*, 60 (corr. *25*, 391)
Dieldrin	*5*, 125
Dienoestrol	*21*, 161
Diepoxybutane	*11*, 115 (corr. *12*, 271)
Di-(2-ethylhexyl) adipate	*29*, 257
Di-(2-ethylhexyl) phthalate	*29*, 269
1,2-Diethylhydrazine	*4*, 153
Diethylstilboestrol	*6*, 55 *21*, 173 (corr. *23*, 417)
Diethylstilboestrol dipropionate	*21*, 175
Diethyl sulphate	*4*, 277
Diglycidyl resorcinol ether	*11*, 125
Dihydrosafrole	*1*, 170 *10*, 233
Dihydroxybenzenes	*15*, 155
Dihydroxymethylfuratrizine	*24*, 77
Dimethisterone	*6*, 167 *21*, 377
Dimethoate*	
Dimethoxane	*15*, 177

3,3'-Dimethoxybenzidine (*ortho*-Dianisidine) *4*, 41
para-Dimethylaminoazobenzene *8*, 125
para-Dimethylaminobenzenediazo sodium sulphonate *8*, 147
trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole *7*, 147 (corr. *30*, 407)
3,3'-Dimethylbenzidine (*ortho*-Tolidine) *1*, 87
Dimethylcarbamoyl chloride *12*, 77
1,1-Dimethylhydrazine *4*, 137
1,2-Dimethylhydrazine *4*, 145 (corr. *7*, 320)
Dimethyl sulphate *4*, 271
Dimethylterephthalate*
Dinitrosopentamethylenetetramine *11*, 241
1,4-Dioxane *11*, 247
2,4'-Diphenyldiamine *16*, 313
Diphenylthiohydantoin*
Direct Black 38 *29*, 295
Direct Blue 6 *29*, 311
Direct Brown 95 *29*, 321
Disulfiram *12*, 85
Dithranol *13*, 75
Dulcin *12*, 97

E
Endrin *5*, 157
Enflurane*
Eosin and its disodium salt *15*, 183
Epichlorohydrin *11*, 131 (corr. *18*, 125) (corr. *26*, 387)
1-Epoxyethyl-3,4-epoxycyclohexane *11*, 141
3,4-Epoxy-6-methylcyclohexylmethyl-3,4-epoxy-6-methylcyclohexane carboxylate *11*, 147
cis-9,10-Epoxystearic acid *11*, 153
Ethinyloestradiol *6*, 77 *21*, 233
Ethionamide *12*, 83
Ethyl acrylate *19*, 57
Ethylene *19*, 157
Ethylene dibromide *15*, 195
Ethylene oxide *11*, 157
Ethylene sulphide *11*, 257
Ethylenethiourea *7*, 45
Ethyl methanesulphonate *7*, 245
Ethyl selenac *12*, 107
Ethyl tellurac *12*, 115
Ethynodiol diacetate *6*, 173 *21*, 387
Evans blue *8*, 151

F
Fast green FCF *16*, 187
Ferbam *12*, 121 (corr. *13*, 243)

Fluometuron	*30*, 245
Fluorescein and its disodium salt*	
Fluorides (inorganic, used in drinking-water and dental preparations)	*27*, 237
Fluorspar	
Fluosilicic acid	
Sodium fluoride	
Sodium monofluorophosphate	
Sodium silicofluoride	
Stannous fluoride	
5-Fluorouracil	*26*,217
Formaldehyde	*29*, 345
2-(2-Formylhydrazino)-4(5-nitro-2-furyl)-thiazole	*7*, 151 (corr. *11*, 295)
The furniture and cabinet-making industry	*25*, 99
Fusarenon-X	*11*, 169
G	
Glycidaldehyde	*11*, 175
Glycidyl oleate	*11*, 183
Glycidyl stearate	*11*, 187
Griseofulvin	*10*, 153
Guinea green B	*16*, 199
H	
Haematite	*1*, 29
Haematoxylin*	
Hair dyes, epidemiology of	*16*, 29 *27*, 307
Halothane*	
Heptachlor and its epoxide	*5*, 173 *20*, *129*
Hexachlorobenzene	*20*, 155
Hexachlorobutadiene	*20*, 179
Hexachlorocyclohexane (α-,ß-,δ-,ε-, technical HCH and lindane)	*5*, 47 *20*, 195
Hexachloroethane	*20*, 467
Hexachlorophene	*20*, 241
Hexamethylenediamine*	
Hexamethylphosphoramide	*15*, 211
Hycanthone and its mesylate	*13*, 91
Hydralazine and its hydrochloride	*24*, 85
Hydrazine	*4*, 127
Hydroquinone	*15*, 155
4-Hydroxyazobenzene	*8*, 157
17α-Hydroxyprogesterone caproate	*21*, 399
8-Hydroxyquinoline	*13*, 101
Hydroxysenkirkine	*10*, 265
I	
Indeno[1,2,3-*cd*]pyrene	*3*, 229
Iron-dextran complex	*2*, 161

Iron-dextrin complex *2*, 161 (corr. *7*, 319)
Iron oxide *1*, 29
Iron sorbitol-citric acid complex *2*, 161
Isatidine *10*, 269
Isoflurane*
Isonicotinic acid hydrazide *4*, 159
Isophosphamide *26*, 237
Isoprene*
Isopropyl alcohol *15*, 223
Isopropyl oils *15*, 223
Isosafrole *1*, 169
10, 232

J
Jacobine *10*, 275

L
Lasiocarpine *10*, 281
Lead and lead compounds *1*, 40 (corr. *7*, 319)
2, 52 (corr. *8*, 349)
2, 150
23, 39, 205, 325
Lead acetate and its trihydrate
Lead carbonate
Lead chloride
Lead naphthenate
Lead nitrate
Lead oxide
Lead phosphate
Lead subacetate
Lead tetroxide
Tetraethyllead
Tetramethyllead
The leather goods manufacturing industry (other than boot and shoe manufacture and tanning) *25*, 279
The leather tanning and processing industries *25*, 201
Ledate *12*, 131
Light green SF *16*, 209
Lindane *5*, 47
20, 196
The lumber and sawmill industries (including logging) *25*, 49
Luteoskyrin *10*, 163
Lynoestrenol *21*, 407
Lysergide*

M
Magenta *4*, 57 (corr. *7*, 320)
Malathion *30*, 103
Maleic hydrazide *4*, 173 (corr. *18*, 125)
Maneb *12*, 137
Mannomustine and its dihydrochloride *9*, 157
MCPA *30*, 255

Medphalan	*9*, 168
Medroxyprogesterone acetate	*6*, 157
	21, 417 (corr. *25*, 391)
Megestrol acetate	*21*, 431
Melphalan	*9*, 167
6-Mercaptopurine	*26*, 249
Merphalan	*9*, 169
Mestranol	*6*, 87
	21, 257 (corr. *25*, 391)
Methacrylic acid*	
Methallenoestril*	
Methotrexate	*26*, 267
Methoxsalen	*24*, 101
Methoxychlor	*5*, 193
	20, 259
Methoxyflurane*	
Methyl acrylate	*19*, 52
2-Methylaziridine	*9*, 61
Methylazoxymethanol	*10*, 121
Methylazoxymethanol acetate	*1*, 164
	10, 131
Methyl bromide*	
Methyl carbamate	*12*, 151
N-Methyl-*N*,4-dinitrosoaniline	*1*, 141
4,4'-Methylene bis(2-chloroaniline)	*4*, 65 (corr. *7*, 320)
4,4'-Methylene bis (*N*,*N*-dimethyl)benzenamine	*27*, 119
4,4'-Methylene bis(2-methylaniline)	*4*, 73
4,4'-Methylenedianiline	*4*, 79 (corr. *7*, 320)
4,4'-Methylenediphenyl diisocyanate	*19*, 314
Methyl iodide	*15*, 245
Methyl methacrylate	*19*, 187
Methyl methanesulphonate	*7*, 253
2-Methyl-1-nitroanthraquinone	*27*, 205
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine	*4*, 183
Methyl parathion	*30*, 131
Methyl protoanemonin*	
Methyl red	*8*, 161
Methyl selenac	*12*, 161
Methylthiouracil	*7*, 53
Metronidazole	*13*, 113
Mirex	*5*, 203
	20, 283 (corr. 30, 407)
Mitomycin C	*10*, 171
Modacrylic fibres	*19*, 86
Monocrotaline	*10*, 291
Monuron	*12*, 167
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone	*7*, 161
Mustard gas	*9*, 181 (corr. *13*, 243)

N

Nafenopin *24*, 125
1,5-Naphthalenediamine *27*, 127
1,5-Naphthalene diisocyanate *19*, 311
1-Naphthylamine *4*, 87 (corr. *8*, 349)
(corr. *22*, 187)
2-Naphthylamine *4*, 97
1-Naphthylthiourea (ANTU) *30*, 347
Nickel and nickel compounds *2*, 126 (corr. 7, 319)
11, 75
Nickel acetate and its tetrahydrate
Nickel ammonium sulphate
Nickel carbonate
Nickel carbonyl
Nickel chloride
Nickel-gallium alloy
Nickel hydroxide
Nickelocene
Nickel oxide
Nickel subsulphide
Nickel sulphate
Niridazole *13*, 123
5-Nitroacenaphthene *15*, 319
5-Nitro-*ortho*-anisidine *27*, 133
4-Nitrobiphenyl *4*, 113
Nitrofen *30*, 271
5-Nitro-2-furaldehyde semicarbazone *7*, 171
1[(5-Nitrofurfurylidene)amino]-2-imidazolidinone *7*, 181
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide *1*, 181
7, 185
Nitrogen mustard and its hydrochloride *9*, 193
Nitrogen mustard *N*-oxide and its hydrochloride *9*, 209
2-Nitropropane *29*,
N-Nitrosatable drugs *24*, 297 (corr. *30*, 407)
N-Nitrosatable pesticides *30*,
N-Nitrosodi-*n*-butylamine *4*, 197
17, 51
N-Nitrosodiethanolamine *17*, 77
N-Nitrosodiethylamine *1*, 107 (corr. *11*, 295)
17, 83 (corr. *23*, 419)
N-Nitrosodimethylamine *1*, 95
17, 125 (corr. *25*, 391)
N-Nitrosodiphenylamine *27*, 213
para-Nitrosodiphenylamine *27*, 227
N-Nitrosodi-*n*-propylamine *17*, 177
N-Nitroso-*N*-ethylurea *1*, 135
17, 191
N-Nitrosofolic acid *17*, 217
N-Nitrosohydroxyproline *17*, 304
N-Nitrosomethylethylamine *17*, 221
N-Nitroso-*N*-methylurea *1*, 125
17, 227

N-Nitroso-*N*-methylurethane *4*, 211
N-Nitrosomethylvinylamine *17*, 257
N-Nitrosomorpholine *17*, 263
N'-Nitrosonornicotine *17*, 281
N-Nitrosopiperidine *17*, 287
N-Nitrosoproline *17*, 303
N-Nitrosopyrrolidine *17*, 313
N-Nitrososarcosine *17*, 327
N-Nitrososarcosine ethyl ester*
Nitroxoline*
Nivalenol
Norethisterone and its acetate *6*, 179
21, 441
Norethynodrel *6*, 191
21, 461 (corr. *25*, 391)
Norgestrel *6*, 201
21, 479
Nylon 6 *19*, 120
Nylon 6/6*

O
Ochratoxin A *10*, 191
Oestradiol-17ß *6*, 99
21, 279
Oestradiol 3-benzoate *21*, 281
Oestradiol dipropionate *21*, 283
Oestradiol mustard *9*, 217
Oestradiol-17ß-valerate *21*, 284
Oestriol *6*, 117
21, 327
Oestrone *6*, 123
21, 343 (corr. *25*, 391)
Oestrone benzoate *21*, 345
Oil Orange SS *8*, 165
Orange I *8*, 173
Orange G *8*, 181
Oxazepam *13*, 58
Oxymetholone *13*, 131
Oxyphenbutazone *13*, 185

P
Panfuran S (Dihydroxymethylfuratrizine) *24*, 77
Parasorbic acid *10*, 199 (corr. *12*, 271)
Parathion *30*, 153
Patulin *10*, 205
Penicillic acid *10*, 211
Pentachlorophenol *20*, 303
Pentobarbital sodium*
Phenacetin *13*, 141
24, 135
Phenazopyridine (2,6-Diamino-3-(phenylazo)pyridine) and its hydrochloride *8*, 117
24, 163 (corr. *29*, 399)

Phenelzine and its sulphate	*24*, 175
Phenicarbazide	*12*, 177
Phenobarbital and its sodium salt	*13*, 157
Phenoxybenzamine and its hydrochloride	*9*, *223* *24*, 185
Phenylbutazone	*13*, 183
ortho-Phenylenediamine*	
meta-Phenylenediamine and its hydrochloride	*16*, 111
para-Phenylenediamine and its hydrochloride	*16*, 125
N-Phenyl-2-naphthylamine	*16*, 325 (corr. *25*, 391)
ortho-Phenylphenol and its sodium salt	*30*, 329
N-Phenyl-*para*-phenylenediamine*	
Phenytoin and its sodium salt	*13*, 201
Piperazine oestrone sulphate	*21*, 148
Piperonyl butoxide	*30*, 183
Polyacrylic acid	*19*, 62
Polybrominated biphenyls	*18*, 107
Polychlorinated biphenyls	*7*, 261 *18*, 43
Polychloroprene	*19*, 141
Polyethylene (low-density and high-density)	*19*, 164
Polyethylene terephthalate*	
Polyisoprene*	
Polymethylene polyphenyl isocyanate	*19*, 314
Polymethyl methacrylate	*19*, 195
Polyoestradiol phosphate	*21*, 286
Polypropylene	*19*, 218
Polystyrene	*19*, 245
Polytetrafluoroethylene	*19*, 288
Polyurethane foams (flexible and rigid)	*19*, 320
Polyvinyl acetate	*19*, 346
Polyvinyl alcohol	*19*, 351
Polyvinyl chloride	*7*, 306 *19*, 402
Polyvinylidene fluoride*	
Polyvinyl pyrrolidone	*19*, 463
Ponceau MX	*8*, 189
Ponceau 3R	*8*, 199
Ponceau SX	*8*, 207
Potassium bis(2-hydroxyethyl)dithiocarbamate	*12*, 183
Prednisone	*26*, 293
Procarbazine hydrochloride	*26*, 311
Proflavine and its salts	*24*, 195
Progesterone	*6*, 135 *21*, 491
Pronetalol hydrochloride	*13*, 227 (corr. *16*, 387)
1,3-Propane sultone	*4*, 253 (corr. *13*, 243) (corr. *20*, 591)
Propham	*12*, 189
ß-Propiolactone	*4*, 259 (corr. *15*, 341)
n-Propyl carbamate	*12*, 201
Propylene	*19*, 213

Propylene oxide	*11*, 191
Propylthiouracil	*7*, 67
The pulp and paper industry	*25*, 157
Pyrazinamide*	
Pyrimethamine	*13*, 233
Pyrrolizidine alkaloids	*10*, 333
Q	
Quinoestradol*	
Quinoestrol*	
para-Quinone	*15*, 255
Quintozene (Pentachloronitrobenzene)	*5*, 211
R	
Reserpine	*10*, 217
	24, 211 (corr. *26*, 387) (corr. *30*, 407)
Resorcinol	*15*, 155
Retrorsine	*10*, 303
Rhodamine B	*16*, 221
Rhodamine 6G	*16*, 233
Riddelliine	*10*, 313
Rifampicin	*24*, 243
Rotenone*	
The rubber industry	*28* (corr. *30*, 407)
S	
Saccharated iron oxide	*2*, 161
Saccharin	*22*, 111 (corr. *25*, 391)
Safrole	*1*, 169
	10, 231
Scarlet red	*8*, 217
Selenium and selenium compounds	*9*, 245 (corr. *12*, 271) (corr. *30*, 407)
Semicarbazide hydrochloride	*12*, 209 (corr. *16*, 387)
Seneciphylline	*10*, 319
Senkirkine	*10*, 327
Simazine*	
Sodium cyclamate	*22*, 56 (corr. *25*, 391)
Sodium diethyldithiocarbamate	*12*, 217
Sodium equilin sulphate	*21*, 148
Sodium oestrone sulphate	*21*, 147
Sodium saccharin	*22*, 113 (corr. *25*, 391)
Soot, tars and minerals oils	*3*, 22
Spironolactone	*24*, 259
Sterigmatocystin	*1*, 175
	10, 245
Streptozotocin	*4*, 221
	17, 337
Styrene	*19*, 231
Styrene-acrylonitrile copolymers	*19*, 97
Styrene-butadiene copolymers	*19*, 252

Styrene oxide	*11*, 201
	19, 275
Succinic anhydride	*15*, 265
Sudan I	*8*, 225
Sudan II	*8*, 233
Sudan III	*8*, 241
Sudan brown RR	*8*, 249
Sudan red 7B	*8*, 253
Sulfafurazole (Sulphisoxazole)	*24*, 275
Sulfallate	*30*, 283
Sulfamethoxazole	*24*, 285
Sunset yellow FCF	*8*, 257
T	
2,4,5-T and esters	*15*, 273
Tannic acid	*10*, 253 (corr. *16*, 387)
Tannins	*10*, 254
Terephthalic acid*	
Terpene polychlorinates (Strobane®)	*5*, 219
Testosterone	*6*, 209
	21, 519
Testosterone oenanthate	*21*, 521
Testosterone propionate	*21*, 522
2,2',5,5'-Tetrachlorobenzidine	*27*, 141
1,1,2,2,-Tetrachloroethane	*20*, 477
Tetrachloroethylene	*20*, 491
Tetrachlorvinphos	*30*, 197
Tetrafluoroethylene	*19*, 285
Thioacetamide	*7*, 77
4,4'-Thiodianiline	*16*, 343
	27, 147
Thiouracil	*7*, 85
Thiourea	*7*, 95
Thiram	*12*, 225
2,4-Toluene diisocyanate	*19*, 303
2,6-Toluene diisocyanate	*19*, 303
ortho-Toluenesulphonamide	*22*, 121
ortho-Toluidine and its hydrochloride	*16*, 349
	27, 155
Toxaphene (Polychlorinated camphenes)	*20*, 327
Treosulphan	*26*, 341
Trichlorphon	*30*, 207
1,1,1-Trichloroethane	*20*, 515
1,1,2-Trichloroethane	*20*, 533
Trichloroethylene	*11*, 263
	20, 545
2,4,5-and 2,4,6-Trichlorophenols	*20*, 349
Trichlorotriethylamine hydrochloride	*9*, 229
Trichlorphon*	
Triethylene glycol diglycidyl ether	*11*, 209
Trifluralin*	
2,4,5-Trimethylaniline and its hydrochloride	*27*, 177

2,4,6-Trimethylaniline and its hydrochloride	*27*, 178
Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)	*9*, 67
Tris(1-aziridinyl)phosphine oxide	*9*, 75
Tris(1-aziridinyl)phosphine sulphide (Thiotepa)	*9*, 85
2,4,6-Tris(1-aziridinyl)-*s*-triazine	*9*, 95
1,2,3-Tris(chloromethoxy)propane	*15*, 301
Tris(2,3-dibromopropyl) phosphate	*20*, 575
Tris(2-methyl-1-aziridinyl)phosphine oxide	*9*, 107
Trypan blue	*8*, 267
U	
Uracil mustard	*9*, 235
Urethane	*7*, 111
V	
Vinblastine sulphate	*26*, 349
Vincristine sulphate	*26*, 365
Vinyl acetate	*19*, 341
Vinyl bromide	*19*, 367
Vinyl chloride	*7*, 291 *19*, 377
Vinyl chloride-vinyl acetate copolymers	*7*, 311 *19*, 412
4-Vinylcyclohexene	*11*, 277
Vinylidene chloride	*19*, 439
Vinylidene chloride-vinyl chloride copolymers	*19*, 448
Vinylidene fluoride*	
N-Vinyl-2-pyrrolidone	*19*, 461
X	
2,4-Xylidine and its hydrochloride	*16*, 367
2,5-Xylidine and its hydrochloride	*16*, 377
2,6-Xylidine*	
Y	
Yellow AB	*8*, 279
Yellow OB	*8*, 287
Z	
Zectran	*12*, 237
Zineb	*12*, 245
Ziram	*12*, 259

LIVER CANCER	No. 1, 1971; 176 pages US$ 10.000; Sw. fr. 30.—
Oncogenesis and Herpesviruses	No. 2, 1972; 515 pages US$ 25.00; Sw. fr. 100.—
N-Nitroso Compounds, Analysis and Formation	No. 3, 1972; 140 pages US$ 6.25; Sw. fr. 25.—
Transplacental Carcinogenesis	No. 4, 1973; 181 pages US$ 12.00; Sw. fr. 40.—
Pathology of Tumours in Laboratory Animals—Volume I—Tumours of the Rat, Part 1	No. 5, 1973; 214 pages US$ 15.00; Sw. fr. 50.—
Pathology of Tumours in Laboratory Animals—Volume I—Tumours of the Rat, Part 2	No. 6, 1976; 319 pages US$ 35.00; Sw. fr. 90.— (OUT OF PRINT)
Host Environment Interactions in the Etiology of Cancer in Man	No. 7, 1973; 464 pages US$ 40.00; Sw. fr. 100.—
Biological Effects of Asbestos	No. 8, 1973; 346 pages US$ 32.00; Sw. fr. 80.—
N-Nitroso Compounds in the Environment	No. 9, 1974; 243 pages US$ 20.00; Sw. fr. 50.—
Chemical Carcinogenesis Essays	No. 10, 1974; 230 pages US$ 20.00; Sw. fr. 50.—
Oncogenesis and Herpesviruses II	No. 11, 1975; Part 1, 511 pages US$ 38.00; Sw. fr. 100.— Part 2, 403 pages US$ 30.00; Sw. fr. 80.—
Screening Tests in Chemical Carcinogenesis	No. 12, 1976; 666 pages US$ 48.00; Sw. fr. 120.—
Environmental Pollution and Carcinogenic Risks	No. 13, 1976; 454 pages US$ 20.00; Sw. fr. 50.—
Environmental *N*-Nitroso Compounds–Analysis and Formation	No. 14, 1976; 512 pages US$ 45.00; Sw. fr. 110.—
Cancer Incidence in Five Continents—Volume III	No. 15, 1976; 584 pages US$ 40.00; Sw. fr. 100.—
Air Pollution and Cancer in Man	No. 16, 1977; 331 pages US$ 35.00; Sw. fr. 90.—
Directory of On-going Research in Cancer Epidemiology 1977	No. 17, 1977; 599 pages US$ 10.00; Sw. fr. 25.— (OUT OF PRINT)
Environmental Carcinogens—Selected Methods of Analysis, Vol. 1: Analysis of Volatile Nitrosamines in Food	No. 18, 1978; 212 pages US$ 45.00; Sw. fr. 90.—
Environmental Aspects of *N*-Nitroso Compounds	No. 19, 1978; 566 pages US$ 50.00; Sw. fr. 100.—
Nasopharyngeal Carcinoma: Etiology and Control	No. 20, 1978; 610 pages US$ 60.00; Sw. fr. 100.—
Cancer Registration and Its Techniques	No. 21, 1978; 235 pages US$ 25.00; Sw. fr. 40.—
Environmental Carcinogens—Selected Methods of Analysis, Vol. 2: Methods for the Measurement of Vinyl Chloride in Poly (vinyl chloride), Air, Water and Foodstuffs	No. 22, 1978; 142 pages US$ 45.00; Sw. fr. 75.—
Pathology of Tumours in Laboratory Animals—Volume II—Tumours of the Mouse	No. 23, 1979; 669 pages US$ 60.00; Sw. fr. 100.—
Oncogenesis and Herpesviruses III	No. 24, 1978; Part I, 580 pages US$ 30.00; Sw. fr. 50.— Part 2, 522 pages US$ 30.00; Sw. fr. 50.—
Carcinogenic Risks—Strategies for Intervention	No. 25, 1979; 283 pages US$ 30.00; Sw. fr. 50.—
Directory of On-Going Research in Cancer Epidemiology 1978	No. 26, 1978; 550 pages Sw. fr. 30.—
Molecular and Cellular Aspects of Carcinogen Screening Tests	No. 27, 1980; 371 pages US$ 40.00; Sw. fr. 60.—
Directory of On-Going Research in Cancer Epidemiology 1979	No. 28, 1979; 672 pages Sw. fr. 30.— (OUT OF PRINT)
Environmental Carcinogens—Selected Methods of Anlysis, Vol. 3: Analysis of Polycyclic Aromatic Hydrocarbons in Environmental Samples	No. 29, 1979; 240 pages US$ 30.00; Sw. fr. 50.—
Biological Effects of Mineral Fibres	No. 30, 1980; Volume 1, 494 pages US$ 35.00; Sw. fr. 60.— Volume 2, 513 pages US$ 35.00; Sw. fr. 60.—
N-Nitroso-Compounds: Analysis, Formation and Occurrence	No. 31, 1980; 841 pages US$ 40.00; Sw. fr. 70.—
Statistical Methods in Cancer Research, Vol. 1: The Analysis of Case-Control Studies	No. 32, 1980; 338 pages US$ 30.00; Sw. fr. 50.—
Handling Chemical Carcinogens in the Laboratory—Problems of Safety	No. 33, 1979; 32 pages US$ 8.00; Sw. fr. 12.—
Pathology of Tumours in Laboratory Animals—Volume III—Tumours of the Hamster	No. 34, 1982; 461 pages US$ 40.00; Sw. fr. 80.—
Directory of On-Going Research in Cancer Epidemiology 1980	No. 35, 1980; 660 pages Sw. fr. 35.—
Cancer Mortality by Occupation and Social Class 1851-1971	No. 36, 1982; 253 pages US$ 30.00; Sw. fr. 60.—
Laboratory Decontamination and Destruction of Aflatoxins B_1, B_2, G_1, G_2 in Laboratory Wastes	No. 37, 1980; 59 pages US$ 10.00; Sw. fr. 18.—
Directory of On-Going Research in Cancer Epidemiology 1981	No. 38, 1981; 696 pages Sw. fr. 40.—
Host Factors in Human Carcinogenesis	No. 39, 1982; 583 pages US$ 50.00; Sw. fr. 100.—
Environmental Carcinogens—Selected Methods of Analysis, Vol. 4: Some Aromatic Amines and Azo Dyes in the General and Industrial Environment	No. 40, 1981; 347 pages US$ 30.00; Sw. fr. 60.—
N-Nitroso Compounds: Occurrence and Biological Effects	No. 41, 1982; 755 pages US$ 55.00; Sw. fr. 110.—
Cancer Incidence in Five Continents—Volume IV	No. 42, 1982; 811 pages US$ 50.00; Sw. fr. 100.—
Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some	No. 43, 1982; 73 pages US$ 10.00; Sw. fr. 18.—

Environmental Carcinogens—Selected Methods of Analysis, Vol. 5: Mycotoxins	No. 44, 1983; 455 pages US$ 30.00; Sw. fr. 60.—
Environmental Carcinogens—Selected Methods of Analysis, Vol. 6: *N*-Nitroso Compounds	No. 45, 1983 (in press)
Directory of On-Going Research in Cancer Epidemiology 1982	No. 46, 1982; 722 pages Sw. fr. 40.—
Cancer Incidence in Singapore	No. 47, 1982; 174 pages US$ 15.00; Sw. fr. 30.—
Cancer Incidence in the USSR	No. 48, 1982; 111 pages US$ 15.00; Sw. fr. 30.—

NON-SERIAL PUBLICATIONS

ALCOOL ET CANCER (FRENCH ONLY)	1978; 42 pages Fr. fr. 35.—; Sw. fr. 14.—
INFORMATION BULLETIN ON THE SURVEY OF CHEMICALS BEING TESTED FOR CARCINOGENICITY	No. 8, 1979; 604 pages US$ 25.00; Sw. fr. 40.—
INFORMATION BULLETIN ON THE SURVEY OF CHEMICALS BEING TESTED FOR CARCINOGENICITY	No. 9, 1981; 294 pages US$ 20.00; Sw. fr. 41.—
INFORMATION BULLETIN ON THE SURVEY OF CHEMICALS BEING TESTED FOR CARCINOGENICITY	No. 10, 1983 (in press)
CANCER MORBIDITY AND CAUSES OF DEATH AMONG DANISH BREWERY WORKERS	1980; 145 pages US$ 25.00; Sw. fr. 45.—

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds, and Natural Products	Volume 1, 1972; 184 pages US$ 4.20; Sw. fr. 12.— (out of print)
Some Inorganic and Organometallic Compounds	Volume 2, 1973; 181 pages US$ 3.60; Sw. fr. 12.—
Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds	Volume 3, 1973; 271 pages US$ 5.40; Sw. fr. 18.— (out of print)
Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents	Volume 4, 1974; 286 pages US$ 7.20; Sw. fr. 18.—
Some Organochlorine Pesticides	Volume 5, 1974; 241 pages US$ 7.20; Sw. fr. 18.—
Sex Hormones	Volume 6, 1974; 243 pages US$ 7.20; Sw. fr. 18.—
Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals	Volume 7, 1974; 326 pages US$ 12.30; Sw. fr. 32.—
Some Aromatic Azo Compounds	Volume 8, 1975; 357 pages US$ 14.40; Sw. fr. 36.—
Some Aziridines, *N*-, *S*-, and *O*-Mustards and Selenium	Volume 9, 1975; 268 pages US$ 10.80; Sw. fr. 27.—
Some Naturally Occuring Substances	Volume 10, 1976; 353 pages US$ 15.00; Sw. fr. 38.—
Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics	Volume 11, 1976; 306 pages US$ 14.00; Sw. fr. 34.—
Some Carbamates, Thiocarbamates and Carbazides	Volume 12, 1976; 282 pages US$ 14.00; Sw. fr. 34.—
Some Miscellaneous Pharmaceutical Substances	Volume 13, 1977; 255 pages US$ 12.00; Sw. fr. 30.—
Asbestos	Volume 14, 1977; 106 pages US$ 6.00; Sw. fr. 14.—
Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals	Volume 15, 1977; 354 pages US$ 20.00; Sw. fr. 50.—
Some Aromatic Amines and Related Nitro Compounds—Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals	Volume 16, 1978; 400 pages US$ 20.00, Sw. fr. 50.—
Some *N*-Nitroso Compounds	Volume 17, 1978; 365 pages US$ 25.00; Sw. fr. 50.—
Polychlorinated Biphenyls and Polybrominated Biphenyls	Volume 18, 1978; 140 pages US$ 13.00; Sw. fr. 20.—
Some Monomers, Plastics and Synthetic Elastomers, and Acrolein	Volume 19, 1979; 513 pages US$ 35.00; Sw. fr. 60.—
Some Halogenated Hydrocarbons	Volume 20, 1979; 609 pages US$ 35.00; Sw. fr. 60.—
Sex Hormones (II)	Volume 21, 1979; 583 pages US$ 35.00; Sw. fr. 60.—
Some Non-Nutritive Sweetening Agents	Volume 22, 1980; 208 pages US$ 15.00; Sw. fr. 25.—
Some Metals and Metallic Compounds	Volume 23, 1980; 438 pages US$ 30.00; Sw. fr. 50.—
Some Pharmaceutical Drugs	Volume 24, 1980; 337 pages US$ 25.00; Sw. fr. 40.—
Wood, Leather and Some Associated Industries	Volume 25, 1981; 412 pages US$ 30.00; Sw. fr. 60.—
Some Antineoplastic and Immunosuppressive Agents	Volume 26, 1981; 411 pages US$ 30.00; Sw. fr. 62.—
Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations	Volume 27, 1982; 341 pages US$ 25.00; Sw. fr. 40.—
The Rubber Industry	Volume 28, 1982; 486 pages US$ 35.00; Sw. fr. 70.—
Some Industrial Chemicals and Dyestuffs	Volume 29, 1982; 416 pages US$ 30.00; Sw. fr. 60.—
Miscellaneous Pesticides	Volume 30, 1983; 424 pages US$ 30.00; Sw fr. 60.—
Chemicals and Industrial Processes Associated with Cancer in Humans. IARC Monographs, Volumes 1 to 20	Suppl. 1, 1979; 71 pages US$ 6.00; Sw. fr. 10.— (out of print)
Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal	Suppl. 2, 1980; 426 pages US$ 25.00; Sw. fr. 40.—
Cross Index of Synonyms and Trade Names in Volumes 1 to 26	Suppl. 3, 1982; 199 pages US$ 30.00; Sw. fr. 60.—
Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC	Suppl. 4, 1982; 292 pages US$ 30.00; Sw. fr. 60.—