Environmental Health Criteria 178

Methomyl

UNEP

...under the joint sponsorship of the United Nations Environment Programme, ...International Labour Organisation, and the World Health Organization

WORLD HEALTH ORGANIZATION

Acetaldehyde (No. 167, 1995)
Acetonitrile (No. 154, 1993)
Acrolein (No. 127, 1991)
Acrylamide (No. 49, 1985)
Acrylonitrile (No. 28, 1983)
Aged population, principles for evaluating the effects of chemicals (No. 144, 1992)
Aldicarb (No. 121, 1991)
Aldrin and dieldrin (No. 91, 1989)
Allethrins (No. 87, 1989)
Amitrole (No. 158, 1994)
Ammonia (No. 54, 1986)
Anticoagulant rodenticides (No. 175, 1995)
Arsenic (No. 18, 1981)
Asbestos and other natural mineral fibres (No. 53, 1986)
Barium (No. 107, 1990)
Benomyl (No. 148, 1993)
Benzene (No. 150, 1993)
Beryllium (No. 106, 1990)
Biomarkers and risk assessment: concepts and principles (No. 155, 1993)
Biotoxins, aquatic (marine and freshwater) (No. 37, 1984)
Brominated diphenylethers (No. 162, 1994)
Butanols - four isomers (No. 65, 1987)
Cadmium (No. 134, 1992)
Cadmium - environmental aspects (No. 135, 1992)
Camphechlor (No. 45, 1984)
Carbamate pesticides: a general introduction (No. 64, 1986)
Carbaryl (No. 153, 1994)
Carbendazim (No. 149, 1993)
Carbon disulfide (No. 10, 1979)
Carbon monoxide (No. 13, 1979)
Carcinogens, summary report on the evaluation of short-term *in vitro* tests (No. 47, 1985)
Carcinogens, summary report on the evaluation of short-term *in vivo* tests (No. 109, 1990)
Chlordane (No. 34, 1984)
Chlordecone (No. 43, 1984)
Chlorine and hydrogen chloride (No. 21, 1982)
Chlorobenzenes other than hexachlorobenzene (No. 128, 1991)
Chlorofluorocarbons, fully halogenated (No. 113, 1990)
Chlorofluorocarbons, partially halogenated (ethane derivatives) (No. 139, 1992)
(methane derivatives) (No. 126, 1991)
Chloroform (No. 163, 1994)
Chlorophenols (No. 93, 1989)
Chromium (No. 61, 1988)
Cresols (No. 168, 1995)
Cyhalothrin (No. 99, 1990)
Cypermethrin (No. 82, 1989)
Cypermethrin, alpha- (No. 142, 199
DDT and its derivatives (No. 9, 1979)
DDT and its derivatives - environmental aspects (No. 83, 1989)
Deltamethrin (No. 97, 1990)
Diaminotoluenes (No. 74, 1987)
1,2-Dichloroethane
(No. 62, 1987, 1st edition)
(No. 176, 1995, 2nd edition)
2,4-Dichlorophenoxyacetic acid (2,4-D) (No. 29, 1984)
2,4-Dichlorophenoxyacetic acid - environmental aspects (No. 84, 1989)
1,3-Dichloropropene, 1,2-dichloropropane and mixtures (No. 146, 1993)
Dichlorvos (No. 79, 1988)
Diethylhexyl phthalate (No. 131, 1992)
Dimethoate (No. 90, 1989)
Dimethylformamide (
Dimethyl sulfate (No.
Diseases of suspect
and their preventio
studies on (No. 72,
Dithiocarbamate pesticides, ethyl
and propylenethiourea: a ger
introduction (No. 78, 198
Electromagnetic fields (
Endosulfan (No. 40, 1
Endrin (No. 130, 1992
Environmental epider
studies in (No. 27, 1
Epichlorohydrin (No.
Ethylene oxide (No.
Extremely low freque
(No. 35, 1984)
Fenitrothion (No. 13
Fenvalerate (No. 95,
Fluorine and fluoride

1991)
1992)
ogy, guideline
3)
3, 1984)
5, 1985)
cy (ELF) fields
1992)
1990)
(No. 36, 1984)

end of book

continued at end

Environmental Health Criteria 178

METHOMYL

First draft prepared by Dr M.L. Litchfield, Arundel, United Kingdom

Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

World Health Organization
Geneva, 1996

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

WHO Library Cataloguing in Publication Data

Methomyl.

(Environmental health criteria ; 178)

1.Methomyl - toxicity 2.Insecticides, Carbamate
I.Series

ISBN 92 4 157178 0 (NLM Classification: WA 240)
ISSN 0250-863X

PRINTED IN FINLAND
95/10758 - VAMMALA 5500

CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR METHOMYL

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

* * *

This publication was made possible by grant number 5 U01 ES02617-15 from the National Institute of Environmental Health Sciences, National Institutes of Health, USA, and by financial support from the European Commission.

Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new 14

partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation

of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary - a review of the salient facts and the risk evaluation of the chemical
- Identity - physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the

substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

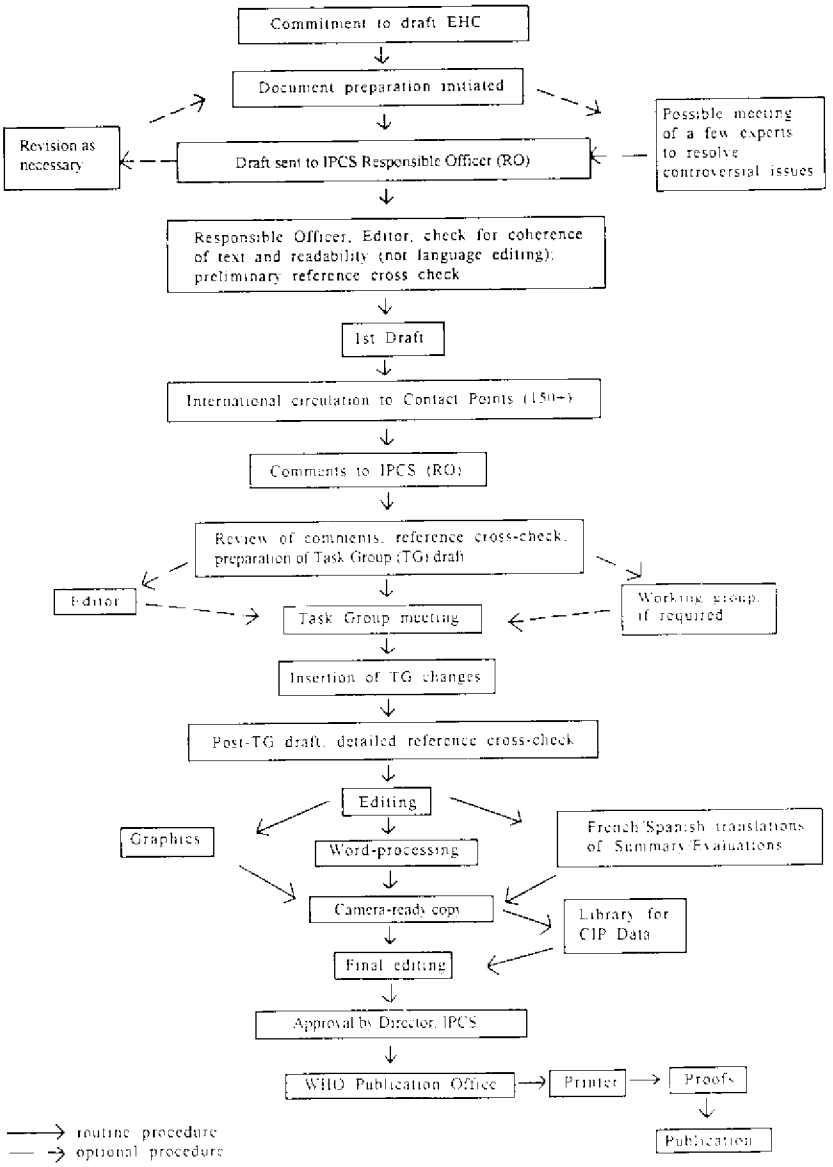
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task

EHC PREPARATION FLOW CHART



Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are

briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR METHOMYL

Members

Dr T. Bailey, US Environmental Protection Agency, Washington DC, USA

Dr A.L. Black, Dept. of Human Services and Health, Canberra, Australia

Mr D.J. Clegg, Carp, Ontario, Canada

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom *(Vice-Chairman)*

Dr P.E.T. Douben, Her Majesty's Inspectorate of Pollution, London, United Kingdom

Dr P. Fenner-Crisp, US Environmental Protection Agency, Washington DC, USA

Dr R. Hailey, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, USA

Ms K. Hughes, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr D. Kanungo, Central Insecticides Laboratory, Government of India, Ministry of Agriculture & Cooperation, Directorate of Plant Protection, Quarantine & Storage, Faridabad, Haryana, India

Dr L. Landner, MFG, European Environmental Research Group Ltd, Stockholm, Sweden

Dr M.H. Litchfield, Melrose Consultancy, Denmans Lane, Fontwell, Arundel, West Sussex, United Kingdom *(Rapporteur)*

Professor M. Lotti, Institute of Occupational Medicine, University of Padua, Padua, Italy *(Chairman)*

Professor D.R. Mattison, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA

Dr Jun Sekizawa, National Institute of Health Sciences, Tokyo, Japan

Dr Palarp Sinhaseni, Chulalongkorn University, Bangkok, Thailand

Dr Salah A. Soliman, King Saud University, Bureidah, Saudi Arabia

Dr M. Tasheva, National Centre of Hygiene, Medical Ecology and Nutrition, Sofia, Bulgaria

Mr J.R. Taylor, Pesticides Safety Directorate, Ministry of Agriculture Fisheries and Food, York, United Kingdom

Dr H.M. Temmink, Wageningen Agricultural University, Wageningen, The Netherlands

Dr M.I. Willems, TNO Nutrition and Food Research Institute, Zeist, The Netherlands

Observers

Dr R. Gardiner, GIFAP, Brussels, Belgium (Representative of GIFAP)

Dr B. Julin, Du Pont de Nemours (Belgium), Brussels, Belgium (Representative of GIFAP)

Dr S.M. Kennedy, Du Pont de Nemours (Belgium), Brussels, Belgium (Representative of GIFAP)

Dr Ronald L. Mull, Du Pont Agricultural Products, Wilmington, DE, United States of America (Representative of GIFAP)

Secretariat

Ms A. Sundén Byléhn, International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Châtelaine, Switzerland

Dr P. Chamberlain, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr J. Herrman, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr K. Jager, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr W. Kreisel, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Mercier, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M.I. Mikheev, Occupational Health, World Health Organization, Geneva, Switzerland

Dr G. Moy, Food Safety, World Health Organization, Geneva, Switzerland

Mr I. Obadia, International Labour Office, Geneva, Switzerland

Dr R. Pleština, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland *(Secretary)*

Dr E. Smith, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr J. Wilbourn, International Agency for Research on Cancer, Lyon, France

ENVIRONMENTAL HEALTH CRITERIA FOR METHOMYL

The Core Assessment Group (CAG) of the Joint Meeting on Pesticides (JMP) met in Geneva from 25 October to 3 November 1994. Dr W. Kreisel, Executive Director, welcomed the participants on behalf of WHO, and Dr M. Mercier, Director, IPCS on behalf of the three IPCS cooperating organizations (UNEP/ILO/WHO). The CAG reviewed and revised the draft monograph and made an evaluation of the risks for human health and the environment from exposure to methomyl.

The first draft of the monograph was prepared by Dr M.L. Litchfield, Arundel, United Kingdom. Extensive scientific comments were received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria monographs and these comments were incorporated into the second draft by the Secretariat.

The fact that E.I. Du Pont de Nemours and Co. made available to IPCS and the Core Assessment Group proprietary toxicological information on their products is gratefully acknowledged. This allowed the Group to make its evaluation on a more complete data base.

Dr R. Pleština and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively. The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

ABBREVIATIONS

ADI	Acceptable Daily Intake
ALC	Approximate Lethal Concentration
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
E_bC_{50}	median effective concentration for inhibition of growth based on comparison of areas under the growth curves after "b" hours
ECD	electron capture detector
FID	flame ionization detector
FSD	flame photometric detector selective for sulfur
GC	gas chromatography
GLC	gas-liquid chromatography
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HPLC	high performance liquid chromatography
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
MATC	maximum acceptable toxicant concentration
MHTA	*S*-methyl-*N*-hydroxythioacetimidate (a metabolite of methomyl)
mPa	millipascal (7.5×10^{-6} mmHg)
MRL	maximum residue limit
NOEC	no-observed-effect concentration
P2S	*N*-methyl-pyridium-2-aldoxime methane-sulphonate (antidote)
PAM	pyridine-2-aldoxime methiodiode (antidote)
RTECS	Registry of Toxic Effects of Chemical Substances
TEAC	tetraethylammonium chloride
TOCP	tri-*o*-cresyl phosphate
TOD	total oxygen demand
UV	ultraviolet

1. Summary

1.1 Identity, physical and chemical properties, and analytical methods

Methomyl is a white crystalline solid with a melting point of 77 °C and a vapour pressure of 0.72 mPa (25 °C). Its solubility in water is 54.7 g/litre and its octanol/water partition coefficient (K_{ow}) is 1.24. It is stable in sterile water at pH 7, but is broken down at higher pH values, the half-life being 30 days at pH 9 and 25 °C.

The analytical procedure for the determination of methomyl in different samples is extraction followed by clean-up and analysis by HPLC or GLC. In some cases methomyl is converted to its oxime derivative or a fluorophore derivative (post-column) prior to analytical determination.

1.2 Sources of human and environmental exposure

Methomyl is produced by reacting *S*-methyl *N*-hydroxythioacetimidate (MHTA) in methylene chloride with gaseous methyl isocyanate at 30-50 °C. It is a carbamate insecticide used on a wide range of crops throughout the world. Crops protected include fruit, vines, hops, vegetables, grain, soya bean, cotton and ornamentals. Indoor uses include the control of flies in animal houses and dairies.

The main formulations are water soluble powders and water miscible liquids, which are diluted with water for ground or aerial spraying of crops. Typical active ingredient rates are 0.15 to 1.0 kg/ha. The main sources of human exposure are during the preparation and application of these products and from the ingestion of crop residues in foodstuffs (see section 5.3.1.4).

1.3 Environmental transport, distribution and transformation

In laboratory studies, methomyl adsorbs poorly to soil. Weak adsorption to clay minerals, particularly illite, has been demonstrated; adsorption to soil organic matter is 50 times greater but still relatively weak. Hardly any desorption of bound residue is seen. With these characteristics, methomyl would be expected to be mobile in soil.

Under natural environmental conditions, abiotic degradation of methomyl by hydrolysis or photolysis is slow or absent.

Aerobic degradation in soil is about twice as fast as anaerobic degradation. Reported half-lives of methomyl in soil vary from a few days to more than 50 days; dry conditions delay breakdown. In practice in the field most applications should lead to a half-life of around one week.

In field conditions, methomyl does not leach to levels below 20 to 30 cm into the soil and does not contaminate ground water.

When ^{14}C-methomyl is applied to plant leaves it is absorbed but not translocated to other parts of the plant. When applied to the root system it is absorbed into the plant where the principle residue component is methomyl itself. Volatile breakdown products are CO_2 and acetonitrile. The remainder of the activity is incorporated into natural plant components such as lipids and Krebs cycle acids and sugars. The half-life of methomyl in plant foliage is a few days.

There was no evidence for accumulation of methomyl in rainbow trout exposed to the compound for 28 days in a flow-through system.

1.4 Environmental levels and human exposure

Methomyl levels are likely to be either very low or undetectable (< 0.02 mg/litre) in ground water on the evidence of analyses of various water sources after the application of the compound at recommended rates.

Low residue levels of methomyl are present in food and other crops at harvesting, the levels depending upon factors such as the applied rate, time interval after the last application and the type of crop. The residue is composed primarily of methomyl.

Residues of methomyl in dairy products are either undetectable or very low. Lactating cows given methomyl by capsule at a rate equivalent to 80 mg/kg in their feed for 28 days showed no detectable residues of methomyl or the metabolite MHTA in milk or tissues (< 0.02 mg/kg). No methomyl was detected in eggs or tissues of laying hens given 1 or 10 mg/kg in the diet for 4 weeks.

In total diet or individual food analyses in the USA, the concentrations of methomyl in sample surveys were either undetectable or very low. Residue levels are further reduced by processes such as washing, peeling and cooking.

Re-entry exposure studies, specifically for California desert conditions, showed that, when workers returned to vineyards where dislodgeable foliar residues had fallen to 0.1 $\mu g/cm^2$, the highest exposure occurred on the upper body and head during grape girdling and on the upper body and hands during raisin harvesting. Harvesting and packing table grapes resulted in the lowest exposure. Inhalation exposure was minimal.

After methomyl was sprayed on cucumber and tomato plants, ambient air concentrations in the greenhouse ranged up to 4.7 $\mu g/m^3$ on the day after spraying. Three and 7 days after spraying, breathing zone methomyl concentrations ranged up to 14.5 and 0.7 $\mu g/m^3$, respectively. Hand-wash methomyl values ranged from 10 to 322 μg per h work in a greenhouse. This indicated that dermal exposure was a more important route of exposure than inhalation and that re-entry intervals should be based on dermal exposure data.

1.5 Kinetics and metabolism in laboratory animals

The absorption, metabolism and excretion of methomyl after oral administration to rats are very rapid, the processes being completed within a few days. When rats were given radiolabelled methomyl (5 mg/kg body weight), 54% of the dose was excreted in urine and 2-3% in faeces within 7 days, and 34% in expired air within 5 days. After 7 days, 8-9% of the ^{14}C dose remained in the tissues and carcass, which was incorporated into endogenous constituents. The highest concentration of radioactivity was in the blood (representing 2% of the dose).

The major metabolic components in expired air of rats were carbon dioxide and acetonitrile in the ratio of about 2:1. The major metabolite in urine was the mercapturic acid derivative of methomyl, which was equal to 17% of the dose. Neither methomyl nor its oxime derivative was detected.

The proposed metabolic pathway includes displacement of the *S*-methyl grouping by glutathione followed by enzymic transformation to give the mercapturic acid derivative. Another

pathway is by hydrolysis to give MHTA, which is rapidly broken down to carbon dioxide. A further possible route is conversion of *syn*-methomyl (the insecticidal form) to its *anti*-isomer, which undergoes hydrolysis, rearrangement and elimination reactions to give acetonitrile. Methomyl is similarly metabolized in the monkey, except that the mercapturic acid derivative is a minor component in the urine.

The penetration of ^{14}C-methomyl was estimated to be 85% within one hour after dermal application in acetone to mice. At that time 3% of the dose had appeared in blood, 5% in liver and 13% had been excreted. Within 8 h the total excretion was 54.5%.

The rapid breakdown and elimination of methomyl in the rat, together with its lack of accumulation in tissues, are comparable to that seen in ruminants.

Methomyl is completely broken down when cows or goats are dosed. No methomyl or its oxime derivative was detected in milk or tissues. It was shown that the compound was metabolized and incorporated into natural constituents of milk and liver.

No nitrosomethomyl was detected when ^{14}C-methomyl was incubated under simulated stomach conditions with sodium nitrite in a cured meat macerate.

1.6 Effects on laboratory mammals and *in vitro* test systems

Methomyl has high acute oral toxicity, with an oral LD_{50} in the rat of 17-45 mg/kg body weight. It is also highly toxic to rats by the inhalation route, with a 4-h LC_{50} of 0.26 mg/litre in aerosol form. Dermal toxicity is very low, with the LD_{50} exceeding 2000 mg/kg body weight in the rabbit (intact skin) and > 1000 mg/kg body weight in the rat (abraded skin). Signs of acute toxic action are those expected of a cholinesterase inhibitor and include among others profuse salivation, lacrimation, tremor and pupil constriction. Recovery from the effects was rapid. No gross pathological effects due to treatment were seen in the organs examined. Methomyl is not a skin irritant or sensitizer and is a mild eye irritant.

Repeated dietary administration over longer periods did not lead to accumulation or increase in toxic effect. Rats and dogs fed diets containing methomyl up to 250 mg/kg and 400 mg/kg in the

diet, respectively, for 13 weeks did not show any toxic signs or mortality. Rats fed at the 250 mg/kg level showed small decreases in body weight gain, lower haemoglobin levels and moderate erythroid hyperplasia in the bone marrow. The NOEL in rats was 50 mg/kg in the diet (equivalent to 3.6 mg/kg body weight per day). Rabbits given repeated dermal applications of methomyl at doses up to 500 mg/kg body weight per day for 21 days showed hyperactivity and depressed plasma and brain cholinesterase activity at the top dose. The NOAEL was 50 mg/kg body weight per day in this study.

Long-term studies were carried out on rats at methomyl dietary levels of 0, 50, 100 or 400 mg/kg and on mice at 0, 50, 75 or 200 mg/kg. Effects on rats at the top dose included depressed body weight gain and lowered haemoglobin and haematocrit values. The NOEL was 100 mg/kg in the diet, equivalent to 5 mg/kg body weight per day. In the study in mice, an increased mortality rate and decreased haemoglobin and red blood cell counts were seen at the two higher dose levels. The NOEL was 50 mg/kg in the diet, equivalent to 8.7 mg/kg body weight per day. In a 2-year toxicity study in dogs (0, 50, 100, 400 or 1000 mg/kg in the diet), clinical signs of toxicity were noted in some animals at the top dose together with slight to moderate anaemia. The NOEL was 100 mg/kg in the diet, equivalent to 3 mg/kg body weight per day.

There was no evidence of treatment-related increases in tumour incidences in 2-year studies on rats and mice, indicating that methomyl is not carcinogenic. It was not genotoxic in bacterial or mammalian cells *in vitro* and was negative in tests for primary DNA damage in bacterial and mammalian cells *in vitro* and in an *in vivo* rat bone marrow chromosomal study. It showed cytogenetic potential in human lymphocytes *in vitro*, as shown by increases in micronuclei and chromosome aberrations. Methomyl did not produce embryotoxic or teratogenic effects in rats or rabbits at doses up to 400 mg/kg in the diet or 16 mg/kg body weight per day by gavage, respectively, at which levels toxic effects were present in the dams. In a 3-generation reproduction study in rats at dose levels of 50 or 100 mg/kg in the diet (equivalent to 5 or 10 mg/kg body weight per day) methomyl did not affect fertility, gestation or lactation indices and there were no treatment-related gross abnormalities.

Methomyl did not show delayed neurotoxicity after single or repeated administration. Rats fed 800 mg/kg in the diet showed significant depression of blood cholinesterase activity only in the early stages of a 5-month study. In a 28-day dietary study, brain cholinesterase activity was only slightly depressed at this dose level. This indicated the rapid reversibility of methomyl-inhibited cholinesterase activity in the animals during the feeding periods. *In vitro*, human erythrocyte cholinesterase activity was six times more sensitive to the inhibitory action of methomyl than that of the rat, although the rates of spontaneous reactivation were similar.

Atropine was shown to be the most consistently effective antidote for methomyl poisoning based upon the results of studies in several species.

1.7 Effects on humans

Reports on accidental and suicidal poisonings with methomyl provide some information on effect levels and recovery. Three out of five victims of accidental poisoning from a contaminated meal died within 3 h of the ingestion. It was estimated that the victims had consumed about 12–15 mg methomyl/kg body weight. A 31-year-old woman and her 6-year-old son, both of whom died as a result of deliberate poisoning, showed concentrations of methomyl in the liver of 15.4 and 56.5 mg/kg, respectively. The estimated doses were 55 mg/kg body weight for the mother and 13 mg/kg body weight for the son. Six hours after ingesting approximately 2.25 g methomyl, a woman's blood contained 1.6 mg methomyl/kg. Methomyl could not be detected 22 h after ingestion, when the woman was recovering.

A pesticide operator, who did not take any precautions when mixing a powdered methomyl formulation for spraying vegetables, displayed poisoning symptoms within one hour and showed a blood cholinesterase activity 40% of normal after 12 h, with recovery to 80% of normal activity within 36 h. Other operators, following the recommended precautions, did not show any symptoms or effects on red blood cell or plasma cholinesterase activity during activities with the aerial application of methomyl.

1.8 Effects on non-target organisms in the laboratory and field

Methomyl showed no effects on soil fungal or bacterial populations, nitrification or dehydrogenase activity when applied at recommended rates.

An NOEC for algal growth of 6.5 mg/litre was established for methomyl in laboratory studies.

Methomyl is moderately to highly toxic to fish, the 96-h LC_{50} values being in the range of 0.5–2 mg/litre for a variety of species. In a longer-term (21 days) study the LC_{50} for fingerling trout was 1.3 mg/litre methomyl when tested as a Lannate 20L (21.5% methomyl) formulation. In an early-life-stage toxicity study over 28 days with fathead minnows, the MATC was estimated to be > 57 and < 117 µg/litre.

In acute toxicity tests with other aquatic organisms, *Daphnia magna* was one of the most susceptible species to methomyl, the 48-h LC_{50} being 0.032 mg/litre. In a 21-day study on the survival, growth and reproductive capacity of *Daphnia magna*, the maximum acceptable toxicant concentration for methomyl was > 1.6 and < 3.5 µg/litre.

Methomyl is toxic to honey-bees, the reported contact LD_{50} being 1.29 µg/bee and the oral LD_{50} 0.2 µg/bee.

The acute toxicity of methomyl has been assessed in several bird species, typical acute oral LD_{50} values being 10 mg/kg body weight for pigeons and 34 mg/kg body weight for Japanese quail. It is relatively less toxic by the dietary route, the 8-day dietary LC_{50} being 1100 mg/kg methomyl in the diet for bobwhite quail and 2883 mg/kg methomyl in the diet for mallard ducks. In 18- to 20-week one-generation studies, the NOEC was 150 mg/kg methomyl in the diet in bobwhite quail and mallard ducks.

No effects were seen on bobwhite quail when they were exposed to serial spray applications of methomyl at recommended rates. Two studies on wild bird populations, after methomyl was sprayed over forest land or hop fields at recommended rates, did not reveal any apparent changes in bird activity and caused no treatment-related effect or mortality. Fat deposits of song birds in treated forests were reduced relative to controls; this was

considered to be an indirect effect through reduction in insect food.

1.9 Evaluation of human health risks and effects on the environment

Methomyl is a carbamate cholinesterase inhibitor with a well-known mechanism of toxic action. It is particularly toxic by the acute oral and inhalation routes in animal studies, but it has low dermal toxicity. Acute toxic signs in animals are typical of those of a cholinesterase inhibitor. The reversibility of acute toxic action is rapid, with survivors showing quick recovery from toxic signs and reversal of cholinesterase inhibition in the blood and brain. The quick recovery from toxic effects is due to the rapid reversibility of methomyl-inhibited cholinesterase, which is facilitated by the rapid clearance of the compound from the body. Data from accidental and intentional human poisonings show that the level of acute methomyl toxicity in humans is similar to that found in laboratory animals.

Because of the rapid reversibility of the action of methomyl during periods of feeding, acute toxic signs and blood cholinesterase inhibition were rarely seen in dietary studies. The most consistent findings in longer-term studies at the higher dietary levels were decreases in body weight gain in rodents and reduced red blood cell indices in rodents and dogs. There was no evidence for carcinogenic potential from three long-term studies in rodents. The compound was negative in *in vitro* genotoxicity tests that investigated several end-points, but methomyl showed cytogenetic potential in human lymphocytes. It was negative in an *in vivo* rat bone marrow chromosomal study.

NOELs were identified in each of the long-term animal studies, based upon depression of body weight gain and red blood cell indices. These were 5 mg/kg body weight per day in rats, 8.7 mg/kg body weight per day in mice and 3 mg/kg body weight per day in dogs. In the absence of any marked species differences in toxic effect in these studies, the NOEL in the dog of 3 mg/kg body weight per day should be used for the purpose of human risk estimation.

The adsorption of methomyl to soil is low to moderate with hardly any desorption. Aerobic degradation in soil (with a half-

life of around one week) is about twice as fast as anaerobic degradation.

Application of methomyl to plant leaves results in rapid absorption of about half the amount applied (the other half being adsorbed), and there is no indication of translocation. Absorbed methomyl concentrations in food crops decline rapidly to about 5% within one week.

Several aquatic invertebrates, and particularly daphnids, are very sensitive to methomyl with LC_{50} values in the order of 10 to 100 µg/litre.

Fish, both freshwater and estuarine, are less sensitive, the LC_{50} values ranging from 0.5 to 7 mg/litre. Given the low persistence of methomyl and its relatively low acute toxicity to fish, the risk is expected to be low.

At recommended application rates, methomyl does not adversely affect microbial activity in temperate soil.

Methomyl is classified as highly toxic to honey-bees with a topical LD_{50} of around 0.1 µg/bee.

Acute oral LD_{50} values for various bird species range between 10 and 40 mg/kg body weight. Dietary LC_{50} values (5 days) range from 1100 to 3700 mg/kg diet. Methomyl poses an acute risk to birds, particularly from granules; dietary intake from contaminated food is not expected to kill birds.

The high acute toxicity of methomyl to laboratory mammals indicates a similar hazard to wild mammals.

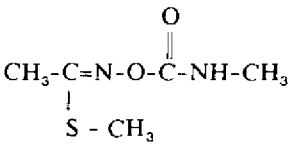
1.10 Conclusion

Considering the qualitative and quantitative characteristics of methomyl toxicity, the Task Group concluded that 0.03 mg/kg body weight per day will probably not cause adverse effects in humans by any route of exposure.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Used in the syn-isomer form

Molecular formula:	$C_5H_{10}N_2O_2S$
Relative molecular mass:	162.2
ISO common name:	methomyl
IUPAC chemical name:	*S*-methyl-*N*-[(methyl-carbamoyl)oxy] thio-acetimidate
CAS chemical name:	methyl N[[(methyl-amino)carbonyl]-oxy] ethanimidothioate
CAS registry number:	16752-77-5
RTECS number:	AK 2975000
Synonyms:	metomil, mesomil, OMS 1196
Trade names (manufacturers and suppliers):	Flytek (Zoecon), Golden Fly Bait (Sorex), Lannate (Du Pont), Methomex (Makhteshim), Methomyl (various), Nudrin (Shell), Pillarmate (Pillar)
Technical product purity:	> 98% w/w
Technical product impurities:	*S*-methyl-*N*-hydroxy-thioacetimidate (0.2%), 1,3-dimethylurea (0.4%)

2.2 Physical and chemical properties

The physical properties of methomyl are listed in Table 1.

Table 1. Physical properties of methomyl (Silveira, 1990)

Physical state	crystalline solid
Colour	white
Odour	slight sulfurous
Melting point	77 °C
Vapour pressure	0.72 mPa (at 25 °C)
Henry's Law constant	2.1×10^{-11} atm-m^3/mole
Octanol-water partition coefficient (K_{ow})	1.24
Solubility:	
water	54.7 g/litre
toluene	30 g/litre
isopropanol	220 g/litre
ethanol	420 g/litre
acetone	720 g/litre
methanol	1000 g/litre

Methomyl is stable at temperatures up to 140 °C. It is not sensitive to impact, but dusts may form explosive mixtures in air. The autoignition temperature is 265 °C. Methomyl is stable to sunlight; it does not decompose when exposed for 120 days. It is stable in sterile buffered water at 25 °C (at pH 5 or 7 no breakdown occurred within 30 days), but it is increasingly decomposed with increasing pH and temperature. The half-life in water at pH 9 is 30 days. Methomyl at concentrations of 10 or 100 mg/litre in water is decomposed by artificial sunlight with half-lives of 5.5 and 2 days, respectively. Methomyl itself is not corrosive but aqueous solutions may be mildly corrosive to iron (Silveira, 1990). Irradiation of methomyl in aqueous solution at 254 nm for 10 h gave rise to acetonitrile (40%), dimethyl disulfide (30%), acetone

(15%) and *N*-ethylideneme-thylamine (5%); the rest was unidentified products (Freeman & Ndip, 1984).

2.3 Conversion factors

1 ppm = 6.62 mg/m^3
1 mg/m^3 = 0.151 ppm

2.4 Analytical methods

Analytical methods for the detection and determination of methomyl in a variety of substrates are shown in Table 2. In general, methomyl is extracted from the sample followed by clean-up and HPLC or GLC analysis. In some cases the methomyl is converted to its oxime derivative or a fluorophore derivative (post-column) prior to analytical determination.

2.4.1 *Sample preparation*

Solid samples are extracted with organic solvents followed by solvent partition and then, usually, a column clean-up. Water samples are mainly submitted directly to solid phase extraction.

2.4.2 *Analytical determination*

The cleaned-up samples are submitted to either HPLC or GLC analysis, in some cases after conversion to the oxime derivative. HPLC analysis is coupled with UV detection, sometimes after conversion to a fluorescent derivative. GLC detection is provided by FID, FSD, ECD or microcoulometric detectors. A GC-mass spectrometric detection method has been described (Brodsky, 1991).

Table 2. Methods for the determination of methomyl

Sample type	Sample preparation extraction/clean-up	Analytical method	Limit of detection	Reference
Technical methomyl and formulations	Reverse phase HPLC	254 nm UV detector	not applicable	Du Pont (1982)
Plant, animal or soil residues	Extract (ethyl acetate), add water, evaporate, acidify, extract & discard (hexane), extract (chloroform), concentrate, derivatize by alkaline hydrolysis	GLC with S-microcoulometer detector or flame photometric detector	0.02 mg/kg (25 g sample, 93% recovery)	Pease & Kirkland (1968); Leitch & Pease (1973)
Crop residues	extract (acetonitrile), partition (hexane), Florisil clean-up	HPLC, UV detector at 233 nm	0.02 mg/kg (10 g sample, 98% recovery)	Clark & Kennedy (1990)
Non-fatty matrix residues	extract (methanol), 3-step solvent partition Celite/charcoal column clean-up, concentrate, filter	HPLC, post column derivatization, fluorescent detector at 254 nm	< 0.05 mg/kg (150 g sample, 89% recovery)	Labare (1990)
Vegetables	Homogenized (20 g sample) with methylene chloride. Clean-up 10 ml of the extract by passing through SEP-PAK silica cartridge. Wash with 2 ml CH_2Cl_2. Elute with CH_2Cl_2:CH_3OH (1:1 v/v). Evaporate eluate to dryness. Redissolve in 1 ml of CH_3CN:H_2O(1:1 v/v)	HPLC/UV (μ Baudpac C_{18} column)	µg/kg range	Ivie (1980)

Table 2 (contd).

Sample type	Sample preparation extraction/clean-up	Analytical method	Limit of detection	Reference
Body fluids	derivatize by alkaline hydrolysis, extract (ethyl acetate), concentrate, convert to trimethysilyl ether derivative	GC/chemical ionization mass spectroscopy	0.01 mg/kg (2 g sample, 95% recovery)	Miyazaki et al. (1989)
Soil	samples extracted with ethyl acetate; filtered; evaporated to 5 ml; silica gel clean-up used when cleaner extract needed for HPLC	HPLC, UV detector at 233 nm	0.020 mg/kg (5 ml sample, 94-102% recovery)	Kennedy (1989)
Groundwater	extract (solid phase adsorbent), elute (acetonitrile), concentrate	HPLC, UV detector	< 0.1 µg/litre (1 litre sample, 53-62% recovery)	Batelle (1991)
Well water	Filter, automated sample injection, HPLC, post-column alkaline hydrolysis and conversion to a fluorophore	flurometric detector at 230 nm excitation and 418 nm emission cut-off filter	1 µg/litre (0.5 ml sample, 95% recovery)	Hill et al. (1984)
Drinking-water	as above	as above	0.7 µg/litre (0.4 ml sample, 90% recovery)	Foerst & Moye (1985)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Methomyl does not occur naturally in the environment.

3.2 Anthropogenic sources

3.2.1 Production processes and levels

Methomyl is produced by reacting *S*-methyl-*N*-hydroxythioacetimidate (MHTA) in methylene chloride with gaseous methyl isocyanate at 30-50 °C. The unreacted MHTA is recovered and the remaining reaction product is subjected to solvent exchange into water followed by crystallization and centrifugation. The ensuing wet cake is dried to give technical methomyl (Council of the European Communities, 1991).

The worldwide production has been estimated to be less than 7000 tonnes (SRI, 1988).

There are no data available on possible releases to the environment from production processes and transportation.

3.2.2 Uses

Methomyl was introduced as an insecticide in 1966. It is used for the control of a large variety of insects on a wide range of crops throughout the world. It is particularly active on many lepidopterous insects. It acts by direct contact and following ingestion, through the stomach. Treated crops include fruit, vines, hops, vegetables, grain, soya beans, cotton and ornamentals. Indoor uses include the control of flies in animal houses and dairies.

A global estimate of the amount of methomyl used annually for the above purposes is not available. However, the annual amount used in the USA was estimated to be approximately 1300 tonnes in 1987 and 1992. The major crops treated in that country are sweet corn, apples, lettuce, soya beans, peanuts, tomatoes, cotton, corn, alfalfa, and grapes, accounting for nearly 80% of the total amount used (US EPA, 1988; Gianessi & Puffer, 1992).

The main formulated products are water-soluble powders (25-90% methomyl) and water-miscible liquids (12.5-29% methomyl). These products are diluted with water and applied by ground or aerial spray equipment. Typical methomyl concentrations in the spray solutions are 200-500 mg/litre. Typical active ingredient rates are 0.15-1.0 kg/ha although higher rates, up to 2 kg/ha, may be used for some purposes. Repeat applications, as directed on the label, may be required to maintain control of insect infestations. Examples of crops treated and methomyl use rates for the USA and Australia are given by FAO/WHO (1990a,b). Methomyl formulations are compatible in use with many other insecticides and fungicides, and combined formulations are registered and available for use in many countries. Methomyl is often used with one or more other products in a tank-mix. Possible potentiation by other cholinesterase inhibitors should be considered when assessing the safety of use of the tank-mix formulations.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Water

The transference of methomyl from greenhouse plants to soil and to water was assessed on chrysanthemums, grown three times per annum, with methomyl applied over a 6-month period at 1-week to 2-month intervals at a rate of 1.4 kg/ha. The three soils investigated were frequently irrigated and the drainage water was collected at a depth of 0.8 m. The adsorption isotherms for the three soils indicated that the adsorption of methomyl was weak to moderate. The concentration of methomyl in the drainage water was undetectable (< 0.1 μg/litre) in 60% of the samples and was below 1 μg/litre in the remainder (Leistra et al., 1984).

Methomyl was applied at a high rate of 2.2 kg/ha to a loamy sand soil on a farm site with a 10% slope. No methomyl was detected (< 0.01 mg/litre) at the base of the site after a total of about 80 mm of natural and artificial rain had fallen on the site over a period of 15 days (Harvey & Pease, 1973).

^{14}C-Methomyl was applied at a very high rate of 5 kg/ha to cylinders (38 cm deep) containing a fine sand soil or a loamy sand soil. No radioactivity was found in the eluate collected after the columns had been subjected to heavy rain (Harvey & Pease, 1973).

In natural waters, pesticides can be photochemically degraded by direct (the pesticide absorbs sunlight) and indirect (other chemicals in the water absorb sunlight, and transfer the energy to the pesticide) mechanisms. Current regulatory studies only address the direct mechanism, and thus neglect an important degradative process. This can result in unrealistically high estimates of persistence of a pesticide in surface water.

These data would suggest that any methomyl residues present in agricultural waters would be rapidly degraded, and that methomyl would not be expected to have an impact on non-target aquatic organisms.

4.1.2 Soil

Batch equilibrium studies were carried out with ^{14}C-methomyl on two sandy loams and two silt loams. Aqueous solutions containing 0.2-6 mg methomyl/litre of were mixed with the soils and shaken for 24 h. A separate study was also undertaken on each soil using TLC. Methomyl was shown to be weakly adsorbed on one of the silt loams (K_a=1.4), and poorly adsorbed on the other three soils. Desorption was related to soil organic matter content and indicated that methomyl is not readily desorbed. In the TLC assessment the R_f values (0.46-0.82) indicated methomyl as Class 4 (mobile) on a sandy loam and Class 3 (intermediate mobility) on the other three soils (Priester, 1984).

A silty clay loam, a silt loam and two sandy loams were made up as slurries and spread on TLC plates. Methomyl and a minor soil metabolite, *S*-methyl-*N*-hydroxy-thioacetimidate (MHTA) were applied at 1 μg/spot and the plates developed. Methomyl and its metabolite were considered to be very mobile, with R_f values of 0.64-0.79 and 0.86-0.93, respectively, in the four soils (US EPA, 1988).

In a field study on a sandy loam in California, methomyl was applied to cabbage by back-pack sprayers at a very high rate of 10 kg/ha (single application). Samples of the soil were taken at 0 and 6 h and then at intervals from 3 to 272 days after application. Analysis showed that methomyl residues remained mostly in the top 15 cm of soil with deepest penetration into the 15-30 cm layer after 48 cm rainfall/irrigation. On this basis the mobility of methomyl was considered to be low to moderate under field conditions in this soil (Kennedy, 1989).

In another field study on a soil characterized as a loam and silt loam, methomyl was applied to cabbage by back-pack sprayers at the high rate of 4.4 kg/ha (single application). Soil samples were taken at 0 and 6 h and then at intervals over a 91-day period after application. Methomyl residues were found only in the top 15 cm of soil after 28 cm rainfall/irrigation. On this basis methomyl was considered to be of low mobility in these field conditions (Kennedy, 1991).

Cox et al. (1993) studied methomyl adsorption to 14 soils from southern Spain. These varied in pH from 5.3 to 7.9, in percentage of organic matter from 0.59 to 2.5 %, in cation exchange capacity

from 4.2 to 28.5, and in the percentage of clay minerals. The methomyl concentration in soil and water components following shaking for 24 h was measured by HPLC. Simple and multiple regression analysis was used to evaluate which factors affected methomyl adsorption. Soils were equilibrated with both 20 and 50 μM methomyl (high purity); there was no significant difference between concentration at the same soil/solution ratio, indicating poor affinity of methomyl for the soils. Both simple and multiple regression indicated soil organic matter, clay content and clay minerals, methomyl in soil and illite content as the major features of soil affecting adsorption of methomyl. Further studies examined adsorption to individual soil components. Humic acid showed by far the highest affinity for methomyl with K_d values 50 times greater than for clay minerals. Montmonillonites showed a similar K_d to illite in these studies, contrary to findings with whole soils. The authors suggest, on the basis of maturation studies, that adsorption to clay may occur in the interlamellar space of the minerals.

4.1.3 Vegetation

When ^{14}C-methomyl was applied to the surface of tobacco plant leaves the compound was absorbed in the leaf but not translocated to other parts of the plant (Harvey & Reiser, 1973).

In a study by Fung et al. (1978), each tobacco seedling received 250 ml of water containing 500 μg methomyl/litre (equivalent to about 0.5 kg active ingredient per hectare of 17 000 plants) after transplantation. The concentration of methomyl peaked at 15 mg/kg in the leaves and at 2.5 mg/kg in the growing tips 2 weeks after treatment. Subsequently, the concentration decreased, which could be explained almost entirely by growth dilution. At 9 weeks after transplantation, the plants were sprayed with a solution of 500 mg methomyl/litre. Three weeks after this (i.e. 12 weeks after transplantation), another similar application was made. Some plants received an additional application of 250 ml of a 500 mg methomyl/litre solution on each side of the row of plants. Concentrations increased sharply after these treatments and dropped afterwards: levels in the leaves of plants with both foliar application peaked at 9 and 6 mg/kg; levels in leaves which received foliar and root applications peaked at 18 and 11 mg/kg. Part of the decrease after application could again be explained by growth dilution. It appears, therefore, that

translocation of methomyl from roots to leaves can occur (Fung et al., 1978).

A sandy loam soil was treated with ^{14}C-methomyl at a rate of 4.4 kg/ha and, 30-120 days later, cabbage, red beet and sunflower seeds were sown and the plants grown to maturity. Thirty days after treatment the soil contained 26% of the original methomyl whereas after 120 days it contained only 8%. All crops, sown at 30 or 120 days, contained only very small residues of methomyl and/or metabolites, equivalent to 0.01 mg/kg or less at harvest (Harvey, 1978).

4.2 Transformation

4.2.1 *Biodegradation*

In a study by Harvey (1972a), ^{14}C-methomyl (1 mg/litre) in river water (pH 6.3) was exposed for 8 weeks from July-September in the USA. The compound degraded with a half-life of about one week. The initial degradation product was MHTA followed by breakdown to carbon dioxide, which accounted for 65% of the original radioactivity after 8 weeks. The S-oxide of MHTA was also detected in small amounts. At termination, 9% of the original activity was present in sediment and the biological film on the walls of the container.

Laboratory studies were carried out on a non-sterile silt loam at its natural pH of 4.7 and at an adjusted pH of 7.9; an alkaline soil (pH 7.9) was also evaluated. All soils were treated with ^{14}C-methomyl at a high rate equivalent to 4.4-6.1 kg/ha and the breakdown was assessed over 42 days. Methomyl degraded (52-69%) in 42 days, carbon dioxide (31-45%) being the main decomposition product. Small amounts of MHTA (1-2%) were present in the soil at termination. It was shown that the $^{14}CO_2$ could be reincorporated into soil organic matter (Harvey & Pease, 1973) (J. Harvey, Jnr (1976): supplement to "Decomposition of methomyl in soil"; personal communication by Du Pont to IPCS, dated 28 July 1976).

Under field conditions the decomposition of methomyl was more rapid, with a 71% loss from a silt loam soil within one month; none was detected after one year. MHTA was present in trace amounts at 1 and 3 months but was not present at one year. Most of the residual application was found in the top 75 mm of

soil, and none was found below 200 mm. Decomposition was rather more rapid in fine sand and loamy sand soils (Harvey & Pease, 1973).

When applied at a concentration of 4.1 mg/kg to a microbially active loam soil (equivalent to a very high rate of 9 kg/ha), ^{14}C-methomyl was metabolized with a half-life of approximately 11 days. The decomposition followed first-order kinetics and the main end product was $^{14}CO_2$ (Zwick & Malik, 1990a). These results were in agreement with the studies described above and with other aerobic soil metabolism studies conducted on soils of high or low organic matter content and various pHs (Harvey, 1972b; 1977a,b).

Dissipation studies of methomyl in loam soils in California and Mississippi resulted in half-lives of 8 weeks and 5 days, respectively (Kennedy, 1989; 1991). In addition to differences in temperature, field moisture differences during the experiment seem largely responsible for these differences in half-life, because adjusting field moisture of the California soil to 75% of its capacity in the laboratory reduced the half-life to 11 days (Kennedy, 1991). Field moisture conditions greatly decrease the air content of the soil. In anaerobic soils it has been shown that ferrous ions facilitate the rapid degradation of methomyl (Bromilow et al., 1986).

Methomyl is also degraded under anaerobic soil conditions. An alkaline soil with low organic matter content was incubated with methomyl (4.1 mg/kg) aerobically for 14 days and then anaerobically for 60 days. The half-life under anaerobic conditions was approximately 14 days and $^{14}CO_2$ was a major breakdown product, equivalent to 23.4% of the applied activity during the 60 days of anaerobic incubation. Unextractable activity was 30% of the total at 7 days and 24% after 60 days of anaerobic treatment. Most of this was associated with soil organic matter (Zwick & Malik, 1990b).

Anaerobic degradation (Eh 80-310 mV) was studied in samples of sand, loamy sand and fine sand, taken from below the soil water table at four locations in the Netherlands (Smelt et al., 1983). In each case, methomyl was incubated at 10 °C and when pH was between 7.4 and 7.7 the half-life was less than 0.2 day (one hour after the start of the experiment, 38-63% of the applied dose was recovered, and after 24 h, 0.15-5% of the applied dose was recovered. When the fine sand sample was incubated at 10 °C

and pH 5.0, methomyl could be detected for 3 days, and the rate of decrease corresponded to a half-life of 7 h.

The role of microbial action was shown by perfusing two soil samples (fine sandy loam at pH 6.1 and fine sandy clay loam at pH 5.87 with organic matter content in both of 2.1-2.3 %) with methomyl solution (6 mg/litre) with and without sodium azide (Fung & Uren, 1977). The contribution of adsorption or dissipation of methomyl from solutions was small when compared with that of microbial transformation. The latter amounted to 25-45% in 42 days after a lag phase of 7-14 days. When previously perfused soil was re-exposed to fresh methomyl solution, 60-75% was lost in 42 days without any lag phase.

The metabolic fate of methomyl has been investigated in tobacco, corn and cabbage (Harvey & Reiser, 1973). Tobacco was grown from seedlings, and when the plants were 18 cm high the roots were treated with ^{14}C-methomyl (10 mg/litre solution). Cabbage (42 days old) and corn (28 cm high) plants were treated with ^{14}C-methomyl via foliar application. Each plant was placed in a glass metabolism apparatus for radioactivity measurement of volatile products and plant material. Tobacco absorbed 20-25% of the available activity over a 4-week period. One quarter of this was retained in plant tissue and the remainder volatilized. The principal component of plant tissue activity was methomyl. The volatile components were carbon dioxide and acetonitrile in equal proportions. Of the applied activity, 47% was lost from the growing shoots of young corn as volatile components within 10 days. This was composed of CO_2 and acetonitrile in the ratio of 1:4. One week after treatment of cabbage leaves, 20% of the activity was lost as CO_2 and acetonitrile in equal proportions. The extracts of the treated plants were investigated for the presence of three possible metabolites, MHTA and the S-oxide and S,S-dioxide derivatives of methomyl. There was no evidence for the presence of these compounds. The only terminal residue specifically detected was methomyl. The remainder of the radioactivity was incorporated into natural plant components such as lipids and Krebs cycle acids and sugars.

The biodegradation of methomyl was also studied in corn and cabbage under field conditions after the application of the radiolabelled compound. The outer leaves of cabbage contained most of the radioactive residue of which a small proportion (3-4%) was identified as methomyl. In corn, the outer portions contained

most of the radioactive residue with about 2 mg methomyl/kg being present (Harvey & Reiser, 1973).

The half-life of methomyl was determined in cotton leaves sampled during periods without rainfall after a single application at 0.75 kg/ha, the maximum label rate. The foliar half-life was estimated to be between 0.6 and 2.2 days, with an average of 1.1 days (Eble & Tomic, 1991). Bull (1974) applied radiolabelled ^{14}C-methomyl to leaves of tobacco in aqueous solution. Almost half of the applied methomyl penetrated the leaves within the first few hours. Surface residues were largely lost within 48 h and the parent compound was the only radioactive component of the unabsorbed dose. The absorbed methomyl was degraded within 8 days (mostly within 48 h). No S-oxide, S,S-dioxide or oxime derivatives were found in the plants, the methomyl being degraded to acetonitrile and CO_2. After methomyl was applied directly to tobacco leaves, its half-life was 3-7 days (Harvey & Reiser, 1973). Studies describing the decline of dislodgeable foliar residues on various crops are reviewed in section 5.3.

4.2.2 Abiotic degradation

When a 3% solution of methomyl in distilled water was stored for 168 days, 90% of the compound was recovered at the end of the period. The remainder was recovered as MHTA (Harvey, 1967).

The hydrolysis of methomyl was studied at pH 5, 7 and 9, at concentrations of 10 and 100 mg/litre, and at 25 °C. The compound was stable for 30 days at pH 5 and 7 but broke down at pH 9 with a half-life of about 30 days. The hydrolysis product was MHTA (Friedman, 1983).

The photolysis of methomyl was studied at initial concentrations of 10 and 100 mg/litre and at pH 5 under UV light. Methomyl photolysed rapidly at both concentrations with a half-life of 2-3 days at 100 mg/litre. The principal photo-product was acetonitrile (Harvey, 1983).

In a study by Swanson (1986), ^{14}C-methomyl was applied to a thin layer of a silt loam soil on glass plates and exposed to natural sunlight for 30 days at 24-28 °C. The compound decomposed with an estimated half-life of 34 days. The principal decomposition

product was acetonitrile. Duplicate preparations, kept in the dark, did not decompose.

Methomyl degraded rapidly in slightly alkaline solution (pH 8.85) with a chlorine/methomyl ratio of 10. The degradation rate increased with increasing temperature, increasing chlorine concentration, and decreasing pH. The reaction rate with free chlorine was 1000-fold faster than with chloramine. Methomyl degraded to acetic acid, methanesulfonic acid and dichloromethyl-amine after forming methomyl sulfoxide and *N*-chloromethomyl (Miles & Oshiro, 1990). Mason et al. (1990) also reported that the removal of methomyl can be effectively achieved by some disinfectants (Cl_2, O_3) but not by ClO_2.

4.2.3 Bioaccumulation

Rainbow trout were exposed to 0.075 and 0.75 mg methomyl per litre in a flow-through test system for up to 28 and 21 days, respectively, and then placed in clean water (pH 7.3, total hardness 25 mg $CaCO_3$/litre at 18 °C). At the higher concentration, fish tissue contained 0.36–0.45 mg methomyl/kg during the exposure period and, at the lower concentration, 0.04–0.07 mg/kg. Within one day of depuration the methomyl tissue levels fell to below 0.02 mg/kg in both exposure groups. There was therefore no indication of bioaccumulation of methomyl in these studies (Sleight, 1971).

4.3 Interaction with other physical, chemical or biological factors

When ^{14}C-methomyl was incubated with a rumen microorganism culture at a level of 1 mg/kg and at 38 °C for 24 h, 90% was metabolized to a volatile component which was identified as acetonitrile by gas chromatography. Less than 0.1% of the total activity was recovered as methomyl or MHTA (Belasco, 1972b).

No nitrosomethomyl was detected (< 1 µg/kg) when ^{14}C-methomyl (1 mg/kg) was incubated under simulated stomach conditions (pH 2) with sodium nitrite (16–20 mg/kg) in a macerate of cured meat for 1 or 3 h at 37 °C (Han, 1975).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 Water

In 60% of drain water samples from greenhouses containing treated plants in an area south of The Hague, The Netherlands, methomyl could not be detected (< 0.1 μg/litre). In the remaining 40% samples its concentration was < 1 μg/litre (Leistra et al., 1984).

Out of 22 404 wells sampled and analysed for methomyl in the US EPA pesticide monitoring programme, 85 showed detectable methomyl concentrations within the range of trace to 20 μg/litre, i.e. within the lifetime health advisory figure of 200 μg/litre (US EPA, 1991).

After a cedar swamp had been sprayed with Lannate LV formulation (29% a.i.) at a rate of 0.28 kg methomyl/ha, no methomyl could be detected (< 0.02 mg/litre) in surface water at any time between 1 and 58 days after treatment (Du Pont, 1978).

5.1.2 Soil

Soil samples taken from a tobacco farm in Maryland, USA, after a single application of methomyl (Lannate 90% a.i.; 13.4 kg/ha) contained 0.6 mg methomyl/kg at 0–15 cm depth after 8 days. At a depth of 15–30 cm, 0.1 mg/kg was detected after 17 days. No methomyl (< 0.02 mg/kg) was detected after 47 days at either level. Lannate is applied as an incorporation to a depth of 10 cm (Pease, 1968).

Levels of methomyl in soil after an upland forest and a cedar swamp had been sprayed with Lannate LV at a rate of 0.28 kg methomyl/ha were either very low (≤ 0.07 mg/kg) or undetectable (< 0.02 mg/kg) . No residues were detected (< 0.02 mg/kg) at an application of half the above rate (Du Pont, 1978).

5.1.3 Food crops

Methomyl is used as a broad spectrum insecticide on many food crops, hence low residues may be present at harvesting. The amount of residue at harvest depends upon factors such as the

application rate, time interval between the last application and harvest, and the type of crop. The residue is composed mainly of methomyl itself. The residue levels expected in food crops at harvest can be derived from the numerous supervised trials which have been carried out on many crops in countries worldwide (FAO/WHO, 1988a,b; 1990a,b). Pre-harvest intervals are also set on the basis of the results of supervised trials, e.g. 7 days for lettuce and onions in USA, 1 day for brassicas and tomatoes in Australia (FAO/WHO, 1990a,b).

The decline of methomyl residues on food crops after application was demonstrated by the field treatment of broccoli followed by harvesting at intervals thereafter. The results of treatment at 0.55 kg/ha (6 applications) are shown in Table 3 (Du Pont, 1973).

Table 3. The decline of surface and absorbed methomyl residues in broccoli (Du Pont, 1973)

Days after treatment	Residue (mg/kg)
1	1.0
3	0.15
7	0.04
10	0.02

Similar examples of the decline of methomyl residues have been shown for lettuce and cauliflower (Braun et al., 1980), celery (Braun et al., 1982), wheat (Du Pont, 1973; FAO/WHO, 1988a,b) and tomatoes (FAO/WHO, 1990a,b).

Treated food crops processed after harvesting generally do not show a concentration of methomyl residues in the processed fractions. Unwashed whole oranges were found to contain 0.96 mg/kg at harvest and 0.88 mg/kg after washing. The dried peel contained 2.8 mg/kg whereas the pulp, juice, cold process oil and molasses contained no detectable residue (< 0.02 mg/kg). Similarly, tomatoes analysed after harvest contained 0.38 mg/kg while the

processed fractions, wet pomace, dry pomace, juice and puree contained < 0.02 mg/kg (Kennedy & Hay, 1991a; Marxmiller & Hay, 1991). Mint oil produced from the distillation of methomyl-treated plants and wine produced from treated grapes contained no detectable residues (< 0.04 and < 0.02 mg/kg, respectively) of methomyl (Kiigemagi et al., 1973; Brodsky, 1991).

5.1.4 Other crops

Environmental levels of methomyl on treated crops such as cotton and tobacco may be deduced from supervised trials.

After 14 applications of methomyl at 0.5 kg/ha and two at the high rate of 1.65 kg/ha, cotton contained 0.17 mg methomyl/kg 15 days after the last application. Processed fractions showed < 0.02 mg/kg in oil, 0.065 mg/kg in meal and 0.14 mg/kg in hulls (Kennedy & Hay, 1991b).

The residue levels in tobacco leaves immediately after the application of methomyl at the recommended rate of 0.56 kg/ha were 44 and 88 mg/kg at two sites in the USA. After five days these levels had dropped to 0.7 and 1.4 mg/kg. Approximately 96% of the methomyl was lost during flue-curing (Leidy et al., 1977).

5.1.5 Dairy products

There are no reports of methomyl residues in dairy produce.

Groups of lactating cows (three/group) were dosed methomyl by capsule at a rate equivalent to 8, 24 or 80 mg/kg in their feed for 28 days. Milk collected during the dosing period and tissues taken at termination contained no detectable residues of methomyl or its metabolite MHTA. Acetonitrile was detected in the milk of cows dosed with methomyl at 8 mg/kg, the milk concentration of acetonitrile reaching a plateau of 0.04-0.1 mg/kg by day 4. This component was also present in liver (0.08 mg/kg) and kidney and muscle (0.04 mg/kg) at this dose level. Acetamide concentrations in milk and tissue of cows dosed with 80 mg/kg were the same as those found in control animals. Radiolabel assessment showed that the acetamide derived from methomyl was < 1% of the total dose (Powley, 1991). In another study, methomyl was fed to cows at 2 or 20 mg/kg in feed and no methomyl (< 0.02 mg/kg) was detected

in milk over a 30-day period nor in meat tissue at termination (Du Pont, 1967).

The ^{14}C-residue in milk was equivalent to 0.13 mg/kg 4 days after two goats had been fed ^{14}C-methomyl at 8 mg/kg diet. Methomyl itself could not be detected. Total ^{14}C-residues in a range of tissues were very low (< 0.001-0.003 mg/kg) (Osman et al., 1983).

5.1.6 Animal feed

Some indication of methomyl residues expected in those portions of treated crops used for animal feed can be deduced from the following studies. Methomyl concentrations were 0.35 mg/kg in forage, 0.14 mg/kg in cannery waste and < 0.02 mg/kg in kernels from sweet corn treated with methomyl at 0.9 kg/ha and harvested 9 days after the last of four applications (Harvey & Yates, 1967). Methomyl residues on sweet corn forage harvested immediately after the last of nine foliar applications at 0.5 or 1 kg/ha were 0.15-0.60 mg/kg and 0.2-0.72 mg/kg, respectively (US EPA, 1988). The residues on samples of wheat straw taken 7 days after foliar application of 0.55 kg methomyl/ha were < 0.02-6.5 mg/kg, and after 14-18 days they were < 0.02-0.8 mg/kg (US EPA, 1988).

5.2 General population exposure

Information available on general population exposure is limited and derives primarily from only one country. More complete exposure information via various routes specific to regions and countries is required to assess the risk of occupational exposure and intake of residues.

5.2.1 Food

The market baskets collected for the US FDA total diet study prior to 1991 consisted of 234 food items. Of these, a total of 72 items (69 adult foods, 2 baby foods and water) were analysed by methodology known to be capable of determining methomyl. Methomyl was detected only in 11 food items collected from 1987 to April 1991 (20 market basket studies): watermelon, pear, strawberries, grapes, cantaloupe, raisins, lettuce, celery, cauliflower, cucumber, and green sweet peppers. The levels detected in these

food samples ranged from trace to 0.630 mg/kg, well below the tolerances established by US EPA (US FDA, 1993a).

The total number of domestic and imported food samples analysed by methodology known to be capable of determining methomyl in US FDA regulatory monitoring programmes during the period 1988-1992 was 7765. Of these, methomyl residues were detected only in 112 samples. Four samples were found to be violative: one domestic sample of strawberry (4.53 mg/kg) and one imported cantaloupe (0.28 mg/kg) exceeded the USA tolerances and there were two imported samples for which no USA tolerances have been established (okra, 0.05 mg/kg and pepino, 0.46 mg/kg) (US FDA, 1993b).

Residues in foodstuffs are reduced by domestic processing such as washing, peeling and cooking. For example, 50-90% of methomyl residues on celery was removed by trimming (FAO/WHO, 1986). Methomyl residues declined by 70-93% in tomatoes, peas or cabbage after 30 min cooking in boiling water in open containers (Holt, 1971). Methomyl was added to spinach puree to give a concentration of 50 mg/kg and then processed in closed cans for 40 min at 122 °C. No methomyl was detected (< 0.05 mg/kg) at the end of this period (Niven, 1971).

Methomyl has not been detected in wine or mint oil prepared from crops previously treated with methomyl (see section 5.1.3).

No methomyl could be detected (< 0.02 mg/kg) in eggs or tissues of laying hens given 1 or 10 mg methomyl/kg diet for 4 weeks (Sherman, 1972).

5.3 Occupational exposure

A series of studies was carried out to determine worker re-entry times after the application of methomyl to grape vines in California, USA (Dong et al., 1992; Reeve et al., 1992). These studies were specific to the desert conditions found in California and should not be compared to studies on other crops or in other climates. Methomyl was applied at different times of the growing season at 1 kg/ha and the dislodgeable foliar residues were measured at time intervals after application to estimate how long it would take to reach the desired level of 0.1 $\mu g/cm^2$ on the leaves. Under desert conditions with water supplied only by furrow or drip irrigation, it was found that it required about

5 days to reach this level in June, when grape girdling was carried out, and about 10 days in September, at harvesting (Powley, 1989, 1990a,b).

A worker re-entry study was undertaken to estimate exposure after entry into vineyards when dislodgeable foliar residues had fallen to 0.1 μg methomyl/cm^2 or less. Each worker wore ankle length tights (except raisin grape harvesters) and long sleeved T-shirt, both worn under normal work clothes. Each wore a personal air sampling pump and two patches were attached to work hats. Sample patches were worn on the thigh and ankle on the normal work clothes by most workers during girdling operations. Work continued for 3-4 h. Methomyl exposure when girdling field grapes ranged from 315-1214 μg/h with highest values on the upper body and head. Exposure was highest to the upper body and hands of raisin harvesters where overall daily exposure was 463-865 μg/h. Harvesting and packing table grapes resulted in the lowest methomyl exposures of 219 and 102 μg/h, respectively. Inhalation exposure was minimal (Merricks, 1990).

It should be emphasized that the rate of decay of methomyl in the Californian studies described above is not representative of the situation in grape culture in other areas of the world or for other crops, as, due to irrigation and other cultural practices, Californian grape vines are quite large and have lush foliage which maximizes exposure. Methomyl does not hydrolyse readily in the hot dry desert-like conditions and this gives rise to atypical transfer rates.

Dislodgeable foliar residue from cotton plants was the subject of three studies in Arizona, USA (Cahill et al., 1975; Ware et al, 1978, 1980). In each case, methomyl was applied at 0.55 kg/ha and leaf samples were taken for analysis of dislodgeable residues up to 96 h after. In each study the methomyl residues had declined to 0.1 μg/cm^2 or less within 48 h.

Dislodgeable foliar residues were determined after spraying mint to estimate possible exposure to workers moving irrigation pipes. After spraying methomyl at 1 kg/ha from the air, dislodgeable residues were 1.5 μg/cm^2 at 4 h and 0.32 μg/cm^2 at 48 h, and, after applying 2 kg/ha, residues were 2.3 μg/cm^2 at 4 h and 0.6 μg/cm^2 at 48 h (Kiigemagi & Deinzer, 1979).

A pilot study was undertaken in Thailand with a methomyl 90% soluble powder formulation to assess the use of food dyes as

markers for pesticide exposure. Pesticide operators prepared and sprayed the diluted methomyl formulation containing the dyes on low (broccoli, chinese kale), medium (tobacco) or tall (citrus) crops with knapsack or high pressure power sprayers. Measurement of dye content of the outer garments showed that exposure occurred mainly to the lower body and legs when spraying low crops and mainly to the upper body and arms when spraying tall crops. Some correlation was shown between the amounts of methomyl and dye deposited on the outer garments. However, the number of participants (two per group) was too small to draw definite conclusions, and more work needs to be done to establish these correlations (Ambridge, 1992).

Methomyl was not detected in air samples from the working zones of operators during normal closed transfer, mixing-loading operations. During application, methomyl air concentrations of up to 7.5 $\mu g/m^3$ were found in applicator working zones (Knaak et al., 1980).

In order to establish a post-application re-entry interval for workers employed in greenhouse operations, methomyl dislodgeable foliar residue data were collected from rose foliage. It was shown that after a single high rate of application of 3.2 kg/ha it took nearly 5 days for the dislodgeable residue to decline to the required level of 0.1 $\mu g/cm^2$. It was estimated that for the application rate of 1 kg/ha, the highest normally used for rose treatment, a re-entry interval of 48 h would be required (Oswald et al., 1991).

The concentration of methomyl in greenhouse air was measured directly by an atmospheric pressure chemical ionization mass spectrometer system. The atmosphere was monitored during spraying of roses and for 26 h thereafter. Samples taken at head height during spraying showed methomyl levels of about 33.1-39.7 $\mu g/m^3$ (5-6 ppb). A few hours later, at the end of the day's operations, concentrations were about 19.9-26.5 $\mu g/m^3$ (3-4 ppb). When monitoring resumed the following morning the air concentrations were still at about the same level indicating that methomyl, deposited in aerosol droplets on the roses, had not fully evaporated (Williams et al., 1982).

Ambient air and breathing zone samples were analysed in four greenhouses 1 day before and 7 days after methomyl was sprayed on cucumber and tomato plants. Ambient air methomyl concen-

trations ranged up to 4.7 $\mu g/m^3$ on the first day after spraying. Three and seven days after spraying, breathing zone methomyl concentrations ranged up to 14.5 and 0.7 $\mu g/m^3$, respectively. Hand-wash methomyl values ranged from 10 to 322 $\mu g/h$ of work in a greenhouse. The authors considered that dermal exposure, as indicated by the hand-wash data, was a more important factor than air exposure and that re-entry intervals should be set according to information derived from the former (Boleij et al., 1991).

Ambient air in a pesticide storage building was monitored over a 3-h period using high volume air samplers and absorption on XAD-4 or XE-340 resins. Methomyl was stored in the building as a liquid concentrate along with other pesticide formulations. The average methomyl air concentration over the sampling period was 13.7 ng/m^3. This represents a value of 0.18 $\mu g/m^3$ when converted to a 40-h working week and can be compared with the ACGIH TLV of 2500 $\mu g/m^3$ (Yeboah & Kilgore, 1984).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS

The term ^{14}C-methomyl in this section refers to S-methyl-[1-^{14}C]-N-[(methylcarbamoyl)oxy] thioacetimidate, unless otherwise stated.

6.1 Absorption

The absorption of ^{14}C-methomyl was very rapid after oral dosing of 5 mg/kg to male or female rats. About 80% of the activity was excreted within 24 h as metabolic products in urine and expired air. Only 2-3% was found in faeces (Harvey et al., 1973; Hawkins et al., 1991).

A similar pattern was seen in the cynomolgus monkey following a single 5 mg/kg oral dose. More than 60% of the dose was eliminated in expired air and urine within 24 h as metabolic products. Only about 3% of the dose was found in faeces over a period of 168 h after dosing (Hawkins et al., 1992).

In an assessment of dermal penetration, ^{14}C-methomyl was applied in acetone to a 1 cm^2 shaved area of skin of mice (7-8 weeks old) at a rate of 1 mg/kg. The mice were then placed in metabolism chambers and killed for radioactivity measurements at intervals up to 48 h. Within 5 min, ^{14}C activity was detected in blood and liver. In 60 min, 2.9% of the original ^{14}C dose was present in blood, 5% was in the liver, and 12.9% had been excreted (urine plus CO_2 plus faeces). Very little methomyl remained at the application site after 60 min, when penetration was estimated to be approximately 85%. The half-life, as a measure of penetration rate, was approximately 13 min (Shah et al, 1981).

6.2 Distribution

After 5 mg ^{14}C-methomyl/kg had been dosed orally to five male and five female rats, 8-9% of the initial activity was found in the tissues and carcass 7 days later. The highest concentration of activity was found in blood (2 mg/kg equivalents) with a distribution of 3-4 mg/kg in red cells and 0.7-0.9 mg/kg in plasma. The radioactivity concentrations were lower in other tissues (< 1 mg per kg). As a proportion of the original dose, blood contained approximately 2%, liver 0.4%, gastrointestinal tract 0.6% and other

individual tissues < 0.1% each. There was no significant difference in distribution between males and females (Hawkins et al., 1991).

^{14}C activity was distributed among a range of tissues after two rats had been fed 200 mg methomyl/kg diet for 8 days and then given 5 mg ^{14}C-methomyl/kg orally. Of the ^{14}C dose, 9% was found in the tissues and carcass within one day and 10% within 3 days (Harvey et al., 1973).

When cynomolgus monkeys were given a single oral dose of 5 mg ^{14}C-methomyl/kg, approximately 5% of the radioactivity was retained in the tissues after 168 h. The highest concentrations of activity were in the liver (0.7-0.9 mg/kg equivalents), fat (0.4-0.7 mg/kg equivalents) and kidney (0.4-0.5 mg/kg equivalents). Lower concentrations found in other tissues were generally higher than blood levels of 0.1-0.2 mg/kg equivalents (Hawkins et al., 1992).

One hour after the dermal applications of ^{14}C-methomyl to mice (see section 6.1), 2.9% of the dose was present in blood, 5% in liver and 56% in the remaining carcass. After 8 h the distribution was 6.1% in blood, 3.3% in liver, 3.8% in the gastrointestinal tract and smaller amounts (< 1%) in other individual tissues. The remaining carcass contained 15% of the original dose (Shah et al., 1981).

6.3 Metabolic transformation

In an initial investigation, two male rats were fed a diet containing 200 mg methomyl/kg for 8 days, followed by intragastric intubation of 1.2 mg ^{14}C-methomyl (=5 mg/kg). One male rat was treated similarly except that the ^{14}C-methomyl was given after 19 days. Urinary and volatile metabolite identification was carried out 1 or 3 days after the ^{14}C dose. Volatile products, trapped in caustic soda solution or in cold traps, were identified as carbon dioxide and acetonitrile, the latter confirmed by mass spectroscopy. Countercurrent distribution of the urine showed that nearly all the radioactivity was present as polar material. Methomyl, its S,S-dioxide and MHTA were not detected. The methomyl S-oxide could not be detected by TLC (Harvey et al., 1973).

A more detailed study (Hawkins et al., 1991), with five male and five female rats receiving single oral doses of ^{14}C-methomyl

(5 mg/kg), confirmed that the expired metabolites (over 120 h) were carbon dioxide (22%) and acetonitrile (12%). The radioactive components of the 0-24 h urine were separated by reverse phase HPLC, ion partition chromatography and TLC. The major metabolite in urine was identified by NMR and mass spectroscopy as the mercapturic acid derivative of methomyl, equivalent to about 17% of the ^{14}C-dose. There were 10 minor components which included, on tentative identification, acetonitrile, acetate and methomyl oxime sulfate. Methomyl, MHTA and the anti-isomer form of methomyl were not detected.

Metabolic pathways for methomyl in the rat include the displacement of the S-methyl moiety by glutathione and enzymic transformation to give the mercapturic acid derivative. Another pathway involves hydrolysis to give MHTA which is rapidly broken down to carbon dioxide (Fig. 1).

Another proposed pathway involves the conversion of the syn-isomer of methomyl (the insecticide form) to its anti-isomer. The latter has been shown to produce acetonitrile as the main volatile metabolite when given orally to rats (see section 6.4). It is proposed that the anti-isomer hydrolyses to the anti-MHTA, which then undergoes a Beckmann re-arrangement and elimination reaction to form acetonitrile (Huhtanen & Dorough, 1976).

It is also likely that certain metabolic products such as acetonitrile undergo further reactions, with the carbon components being incorporated into natural body constituents such as fatty acids, neutral lipids and glycerol, as shown in ruminants (see section 4.2.1).

It is probable that two of the main metabolic pathways also operate in the monkey. When an oral dose of ^{14}C-methomyl (5 mg/kg body weight) was given to cynomolgus monkeys, the major metabolites were CO_2 (32-38%) and acetonitrile (4-7%) in the expired air. These were derived, presumably, by the same processes as described for the rat above. A combination of HPLC and TLC characterized 18 radioactive metabolites in urine, with no metabolite representing more than 4% of the dose. Small amounts of acetonitrile, acetate, acetamide and MHTA sulfate were among the products found. The mercapturic acid derivative of methomyl (a major rat urinary metabolite) accounted for about 1% of the dose. The presence of these minor metabolites are

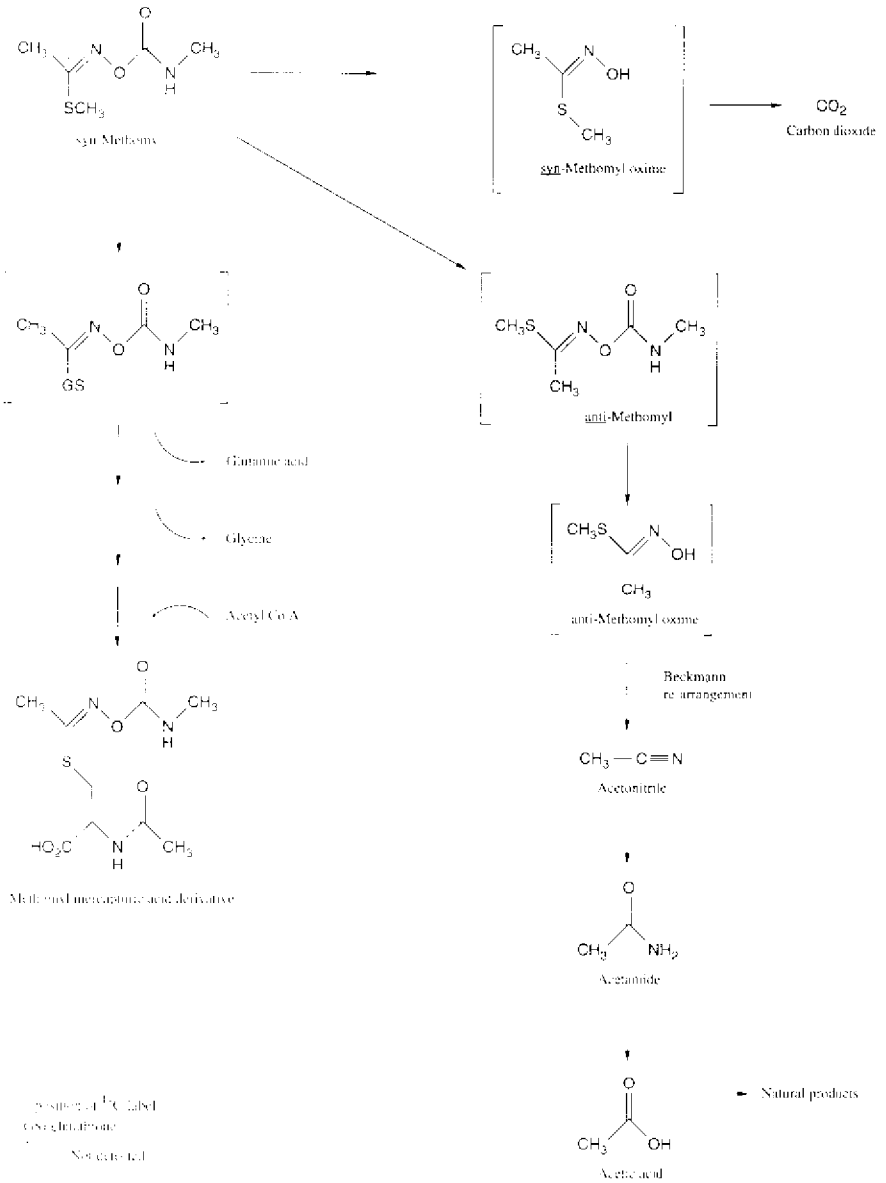


Fig. 1. Proposed metabolic pathway of methomyl in mammalian species

presumably the result of extensive metabolism of primary metabolites (Hawkins et al., 1992).

A lactating cow was dosed twice daily by capsule for 28 days with ^{14}C-methomyl at a rate equivalent to 8 mg/kg in feed. Milk samples were collected each day and selected tissues were taken within 24 h of the last dose. Radioactivity appeared in milk within one day and reached a plateau of 0.5 mg/kg (equivalents) within 6 days. This activity was mostly due to the reincorporation of the radiolabel into fatty acids, lactose and other acetate derived products. No methomyl or MHTA was detected; acetonitrile accounted for about 25% of the radioactivity. The liver showed the greatest concentration of radioactivity, equivalent to 9.23 mg/kg; kidney contained only 2.01 mg/kg and there were lower concentrations in fat and muscle. No methomyl was detected in tissue; most of the radioactivity was considered to be the result of reincorporation of the radiolabel as acetate into natural constituents (Monson & Ryan, 1991).

A lactating goat was given ^{14}C-methomyl by capsule, twice a day, for 10 days at a dose rate equivalent to 20 mg/kg in feed. Milk, blood, urine and faeces were sampled daily and selected tissues taken within one day of the last dose. No methomyl or the metabolite MHTA was detected in any of the samples. Approximately 16% and 7% of the activity was excreted in urine and faeces, respectively, and about 8% appeared in the milk and 17% in expired air. The milk activity reached a plateau after 3 days and was equivalent to approximately 2 mg/kg. At this time the lactose component contained about 11-13% of the milk activity. Hexane extracts, containing the triglyceride components, contained 26-37% of the milk activity and the casein component 8-9%. This indicates that methomyl had been completely broken down and incorporated into natural constituents of milk. Acetonitrile was identified as a volatile metabolite in milk and blood (Harvey, 1980).

The examination of the liver fractions showed that the radioactivity derived from methomyl was found in glycerol, glycerol-3-phosphate, fatty acids, neutral lipids and insoluble protein. This indicates a metabolic pathway via acetonitrile and acetate into the natural occurring constituents in the liver. The breakdown of methomyl and distribution of metabolic products in the liver was shown to be similar in the cow (Monson, 1989).

Acetonitrile, CO_2 and reincorporation products derived from acetate found after the application of methomyl to plants (section 4.2.1) are similar to those identified in the above animal studies.

The proposed metabolic pathway for methomyl in animals is shown in Fig. 1.

6.4 Elimination and excretion

Rat and monkey studies show that methomyl is very rapidly metabolized and eliminated, the processes being largely completed within 24 h.

Rats fed 200 mg methomyl/kg in diet and then given 5 mg ^{14}C-methomyl/kg orally (see section 6.3 for detail) showed a 50% elimination of ^{14}C in expired air in 3 days in the form of carbon dioxide and acetonitrile in the proportion of 1:2. Urinary excretion of ^{14}C was 27% in one day (Harvey et al, 1973).

In a more detailed study, where male and female rats were given 5 mg ^{14}C-methomyl/kg orally (see section 6.3), approximately 53% of the radioactivity was excreted in urine over 7 days, 45% of the dose being excreted in the first 6 h. Faecal excretion contributed only 2-3% over 7 days. The other major path of elimination (over 5 days) was via expired air as carbon dioxide (22% of dose) and acetonitrile (12% of dose). Of this, 18% of the dose was expired as CO_2 within 6 h and 10% as acetonitrile in 24 h. Overall, most of the radiolabelled dose (80%) had been eliminated in 24 h with an estimated half-life of 5 h. There was no obvious difference in the amount or rate of excretion between males and females. The single oral dose given to these animals (5 mg/kg) produced mild clinical signs of cholinesterase inhibition which disappeared within 2 h of dosing (Hawkins et al., 1991).

When methomyl was radiolabelled on the carbonyl group, the elimination of $^{14}CO_2$ was very rapid and equivalent to about 85% of the oral dose in male and female rats. When the labelling was at the -^{14}C=N group, the overall elimination in expired air in 24 h was 30% in the form of CO_2 and acetonitrile (in the proportion of 2:1). When ^{14}C-MHTA was administered in the same way the expired component was mainly $^{14}CO_2$, equivalent to 22% of the dose. The anti-isomer of methomyl mainly produced acetonitrile in the expired air, equivalent to 28% of the dose given orally to rats. Rats given the anti-MHTA by intraperitoneal injection

produced ten times more acetonitrile than those given the syn-MHTA. The urine from rats treated orally with ^{14}C-methomyl or MHTA contained 25-35% of the radioactivity over a 24-h period (Huhtanen & Dorough, 1976).

In monkeys given 5 mg ^{14}C-methomyl/kg orally, approximately 32% of the dose was excreted in urine in 7 days, with 34% as CO_2 and 5% as acetonitrile in the expired air. Most of this was excreted in the first 24 h. Faecal excretion amounted to only 3-4% (Hawkins et al., 1992).

After dermal application of ^{14}C-methomyl to mice (see section 6.1), the total excretion (urine plus CO_2 plus faeces), as a proportion of the applied dose, was 0.2% in 15 min, 12.9% in 60 min and 54.5% in 480 min (Shah et al., 1981).

6.5 Retention and turnover

The absorption, metabolism and excretion of methomyl in the rat are very rapid. No methomyl can be detected within the tissues or excretory products within a few hours of dosing. Most of the dose is eliminated within 24 h with an estimated half-life of 5 h (Hawkins et al., 1991). Metabolic products, mainly in urine and expired air, are also eliminated rapidly; tissue concentrations are very small and lower than blood levels. There is no evidence for accumulation in tissues. A similar picture exists for the metabolism of methomyl in ruminant species.

6.6 Reaction with body components

Methomyl is a potent direct inhibitor of acetylcholinesterase in both insects and mammals. The carbamylated enzymes undergo rapid spontaneous reactivation (see section 7.8.1).

7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single exposure

The results of the single exposure of technical methomyl by the oral, dermal and inhalation routes in various species are shown in Table 4.

Methomyl is very toxic by the oral route. In the rat, the signs of toxicity are those expected from a cholinesterase inhibitor and include profuse salivation, lacrimation, tremor, abnormal posture, pupil constriction, diarrhoea and prostration. At lethal doses the rats died within hours. Survivors began to recover within several hours and had fully recovered within days. No compound-related changes were seen in organs subjected to histopathological examination.

The acute dermal toxicity of methomyl is very low. No deaths occurred in rats or rabbits at the doses shown in Table 4. The compound has high toxicity by the inhalation route in the rat, with affected animals showing typical signs of cholinesterase inhibition. No target organ effect was seen upon histopathological examination. An LD_{50} of approximately 8 mg/kg was obtained when methomyl was injected intraperitoneally in rats (Dashiell, 1972).

The acute oral toxicity of methomyl formulations is in proportion to the amount of a.i. present and, therefore, they are less toxic than methomyl itself (Table 5). The same pattern is seen with the results of acute inhalation studies. The signs of toxicity in the oral and inhalation studies are those shown by the active ingredient. The dermal toxicity of the formulations is very low.

Ocular toxicity was shown by a solid formulation containing 92.4% methomyl when 10 mg was introduced into rabbits' eyes. Typical anticholinesterase effects were seen up to 20 min after treatment, including pupillary constriction of the treated eyes, incoordination, tremors and profuse salivation. All of the effects had disappeared by the next day (Sarver, 1991g).

Table 4. Acute toxicity of technical grade methomyl

Species	Sex	Route	Vehicle	Test[a]	Result	Reference
Rat	M	oral	peanut oil	LD_{50}	17 mg/kg	Sherman (1966)
Rat	F	oral	peanut oil	LD_{50}	23.5 mg/kg	Sherman (1968a)
Rat	M	oral	water	LD_{50}	45 mg/kg	Trivits (1979)
Rat	M	oral	water	LD_{50}	34 mg/kg	Sarver (1991a)
Rat	F	oral	water	LD_{50}	30 mg/kg	Sarver (1991a)
Rat	M	dermal	water	LD_{50} abraded skin	> 1000 mg/kg	Morrow (1972)
Rat	M	inhalation	aerosol	4-h ALC	0.30 mg/litre	Foster (1966a)
Rat	M	inhalation	vapour	4-h ALC	0.04 mg/litre	Foster (1966b)
Rat	M	inhalation	spray	4-h LC_{50}	0.45 mg/litre	Hornberger (1967)
Rat	M/F	inhalation	aerosol	4-h LC_{50}	0.258 mg/litre	Panepinto (1991a)

Table 4 (contd).

Species	Sex	Route	Vehicle	Test[a]	Result	Reference
Rabbit	M	oral	acetone/peanut oil	ALD	30 mg/kg	Sherman (1968c)
Rabbit	M/F	dermal	water	LD_{50} intact skin	> 2000 mg/kg	Sarver (1991b)
Dog	M	oral	capsule	ALD	20 mg/kg	Sherman (1968d)
Guinea-pig	M	oral	acetone/peanut oil	ALD	15 mg/kg	Kaplan & Sherman (1977)
Monkey	M/F	oral	water	ALD	40 mg/kg	Kaplan & Sherman (1977)

[a] ALC = approximate lethal concentration; ALD = approximate lethal dose

Table 5. Acute toxicity of some methomyl formulations

Formulation (% a.i.)	Species	Route	Vehicle	LD_{50} (mg/kg) or LC_{50} (mg/litre)[a]	Reference
Lannate 40 SP (41.6%)	rat	oral	water	61 (male) 73 (female)	Sarver (1992a)
Lannate 20 L (21.5%)	rat	oral	methanol	129	Lheritier (1991a)
Lannate 12.5 L (12.7%)	rat	oral	water	208	Sarver (1991c)
Lannate 40 SP (41.6%)	rabbit	dermal (intact skin)	water	> 2000	Sarver (1992b)
Lannate 20 L (21.5%)	rat	dermal (intact skin)	methanol	> 4000	Lheritier (1991b)
Lannate 40 SP	rat	inhalation (4 h)	aerosol	0.66	Kelly (1992)
Lannate 20 L (21.5%)	rat	inhalation (4 h)	aerosol	1.3	Jackson et al. (1991)
Lannate 12.5 L (12.7%)	rat	inhalation (4 h)	aerosol	3.7	Panepinto (1991b)

[a] Results are for both sexes, unless stated otherwise

7.2 Short-term exposure

Six male rats were given methomyl in peanut oil by gavage at a dose of 5.1 mg/kg body weight per day, 5 times per week for 2 weeks. The signs of toxicity were the same as those exhibited in acute oral studies (section 7.1) but they regressed during the second week of dosing. All animals survived, and there were no compound-related histopathological changes (Kaplan & Sherman, 1977).

Groups of 10 male and 10 female rats were fed diets containing 0, 10, 50, 125/500 (125 mg/kg for 6 weeks, 500 mg/kg for remaining period) or 250 mg methomyl/kg for 13 weeks. Assessments included haematological, biochemical and histopathological examinations. There were no mortalities nor clinical signs due to treatment in any group. A slight decrease in body weight was seen in males at the two higher dose levels and in females at 125/500 mg/kg. This was accompanied by lower food consumption. The only change attributed to methomyl on histopathological examination was moderate erythroid hyperplasia in the bone marrow of males fed 250 mg/kg. Lower haemoglobin values in the males of this group at two months could be linked to this effect. Histopathological examination of animals in the 125/500 mg/kg group did not reveal any changes due to treatment. The no-observed-effect level based upon body weight change was considered to be 50 mg/kg diet, equivalent to 3.56 mg methomyl/kg body weight per day (Paynter, 1966; Busey, 1966).

When groups of four male and four female one-year-old dogs were fed diets containing 0, 50, 100 or 400 mg methomyl/kg for 3 months, no effects were seen in a range of clinical, haematological, biochemical and histopathological assessments (Kaplan & Sherman, 1977).

A dose of 200 mg methomyl/kg body weight was applied as a 5% aqueous solution once a day 5 times per week for 3 weeks to the intact or abraded skin of five male, five female rabbits. Each dose was occluded for 6 h and then the site washed with water. There were no mortalities in animals with intact skin; clinical signs included nasal discharge, wheezing and diarrhoea. With abraded skin, signs of toxicity, including laboured respiration, salivation and tremors, appeared within one hour of dosing, and three animals died, one after the first application and the other after the

eighth application. No treatment-related changes were seen upon histopathological examination (Kaplan & Sherman, 1977).

Groups of rabbits were treated dermally (intact clipped skin) with doses of 0 (10 males, 10 females), 5, 50 (5 males 5 females) or 500 (10 males, 10 females) mg methomyl/kg body weight per day for 21 days. The doses were applied in water each day and occluded for 6 h. Half the males and females in the control and highest dose groups were killed at the end of the dosing regime, together with all animals in the other groups. The remaining animals in the control and highest dose groups were allowed to recover over a 14-day period and then killed. The only change noted clinically was a greater incidence of hyperactivity at 500 mg/kg. There were no effects on body weight gain, haematology, blood biochemistry, organ weights or organ histopathology. Plasma cholinesterase activity was depressed to 36% and 55% of normal at day 21 in highest dose males and females, respectively. Brain cholinesterase activity was depressed to 48% and 68%, respectively, in males and females at this dose, but red cell cholinesterase activity, although slightly decreased, was considered to be biologically insignificantly affected. In males, at 50 mg/kg, the plasma cholinesterase activity was depressed to 77% and there was no inhibition of red blood cell cholinesterase activity of either sex. All the depressed cholinesterase activities had returned to control values at the end of the 14-day recovery period. The no-observed-effect level, based upon changes in plasma cholinesterase activity, was 5 mg/kg body weight per day in males and 50 mg/kg in female rabbits (Brock, 1989).

Formulations of methomyl have also been tested by repeated dermal application to rabbits at doses equivalent to 50 or 100 mg methomyl/kg. No effects were seen after ten daily doses of Lannate L (25.5% methomyl). Ten daily doses of Lannate LV (30% methomyl) produced mild skin irritation at the higher dose level. Plasma cholinesterase activity was somewhat depressed at both dose levels but returned to normal over a 14-day recovery period (McAlack, 1973, Edwards, 1980).

A Lannate dust containing 45% methomyl was the subject of a 3-month inhalation study in male rats. Exposure was at 14.8 mg/m^3 for 4 h/day, 5 days/week; the mass median dynamic diameter of the dust was 4.4 μm. There were no effects on body weight, organ weight, histopathology or red cell cholinesterase activity. Plasma cholinesterase activity was depressed to about

29% of the pre-treatment activity in samples taken 4 h after the last exposure (Ta'Naka et al., 1987).

7.3 Long-term exposure

Groups of 35 male and 35 female rats were fed diets containing methomyl at 0 (2 groups), 50, 100, 200 or 400 mg/kg for 22 months. Five males and 5 females per group were killed at 12 months for gross and histopathological examination. Assessments were made throughout the study for clinical condition, body weight, food consumption, haematology, blood and urine biochemistry, organ weight and histopathology. Growth of males at the highest dose was significantly lower than that of controls over the first year. Growth of males at 200 mg/kg and females at 400 mg/kg was also lower at this time, but not significantly. Food consumption over the first 26 weeks was significantly lower than that of controls for the males fed 200 and 400 mg/kg. At 18 and 22 months there was a trend towards lower haemoglobin values in treated female groups. Compound-related increases in the incidence and severity of extra medullary haematopoiesis were observed in the spleen of females fed 200 or 400 mg/kg. Compound-related changes were also seen in the kidneys of both sexes at 400 mg/kg, characterized by vacuolization of epithelial cells and hypertrophy of the proximal convoluted tubules. On the basis of the body weight and haematopoietic findings in this study, the long-term no-observed-effect level for methomyl in rats was considered to be 100 mg/kg diet (Kaplan & Sherman, 1977).

In a 2-year study on rats, methomyl was fed in the diet to groups of 80 males and 80 females at levels of 0, 50, 100 or 400 mg/kg. The animals were observed and weighed regularly, and haematological and blood and urine biochemical measurements were made at 3, 6, 12, 18 and 24 months. Red cell cholinesterase activity was assayed in additional groups at 1, 2 and 4 weeks and 3, 6, 12 and 20 months. Brain cholinesterase activity was assayed at 12 and 20 months. Extensive histopathological examination was performed on animals killed at scheduled intervals, on animals dying and on animals killed at the end of the study.

There was a significant reduction in body weight gain in both sexes at 400 mg/kg over the first 12 months but not during the subsequent 12 months. There were no clinical signs attributable to treatment. Survival rate was the same among the groups and there was an acceptable number of animals at termination (40-

50%). Erythrocyte counts, haemoglobin values and haematocrits were significantly lower in females at 400 mg/kg. There were no compound-related changes for red cell or brain cholinesterase activity nor for other biochemical parameters. Organ weights were unaffected by treatment. The incidence of bone marrow hyperplasia, focal hyperplasia in the adrenal medulla and focal degeneration in the adrenal cortex was slightly increased in males at 400 mg/kg. The no-observed-effect level in the rat was therefore confirmed as 100 mg methomyl/kg diet, equivalent to about 5 mg/kg body weight per day (Kaplan, 1981).

A comprehensive long-term (2 years) study on the mouse was initiated with 80 males and 80 females per group at levels of 0, 50, 100 and 800 mg methomyl/kg diet. Because of early high mortality, the level of the highest dose group was reduced to 400 mg/kg at week 28 and then to 200 mg/kg at week 39. The level of the mid-dose group was also reduced to 75 mg/kg at week 39. Regular clinical observations and body weight and food consumption measurements were undertaken. Haematological analysis was carried out at 4, 13, 26, 52, 78 and 104 weeks. Organ weights were measured and an extensive histopathological examination carried out on all animals dying or killed. The mortality rate was higher than that of controls at the highest and medium dose levels throughout the study, and was slightly higher, in male mice only, at the low dose level in the latter stage of the study. There were no clinical findings due to treatment and no effects on body weight gain or food consumption. Some effects were noted on red cell parameters such as haemoglobin values and red cell counts during the first 26 weeks at the medium and highest dose levels. However, these were not apparent during the remainder of the study, after these dose levels had been decreased. No effects were observed on organ weights or microscopic findings. The no-observed-effect level was considered to be 50 mg/kg in diet, equivalent to approximately 10 mg/kg body weight per day (Serota et al, 1981).

A 2-year dog study was initiated with dietary levels of methomyl of 0, 50, 100, 400 and 1000 mg/kg with four males and four females per group. After one year, one male and one female from each group was killed for interim examination. Clinical condition was regularly observed and routine measurements made on body weight, food consumption, and haematological and biochemical parameters. After 2 years the surviving animals were

killed, organs were weighed and a histopathological examination was undertaken.

No clinical signs due to treatment were seen in animals at 50, 100 and 400 mg/kg. One highest dose female died after 8 weeks and its replacement also died within 18 days after showing compound-related toxic signs. Two males at this dose level exhibited tremors, salivation and incoordination during week 13. Slight to moderate anaemia was noted in the highest dose animals at 13 weeks and this persisted in one of the males. No effects were seen on body weight or biochemical parameters. Histopathological effects were noted in the kidneys and spleens of animals at 400 and 1000 mg/kg. Changes in kidneys were characterized by increased pigmentation and epithelial swelling, and in the spleen as extra-medullary haematopoiesis and increased pigmentation. A minimal to slight increase in bile duct proliferation was seen in livers of dogs at 1000 mg/kg, and bone marrow activity was also slightly increased in animals at this dose level. The no-observed-effect level was therefore 100 mg/kg diet, equivalent to about 3 mg methomyl/kg body weight per day (Kaplan & Sherman, 1977).

7.4 Skin and eye irritation; sensitization

7.4.1 Skin irritation

The skin irritation potential of methomyl was evaluated in six male rabbits with 0.5 g of the test material, moistened with deionized water, applied to the back of each animal. Each site was covered with a semi-occlusive dressing and exposure continued for 4 h. The skin was examined and evaluated 1, 24, 48 and 72 h after the end of the exposure period. No dermal irritation was seen in any of the animals during the study and, therefore, methomyl is classified as non-irritant to skin (Sarver, 1991d).

Methomyl formulations were also evaluated for skin irritation potential using the same test method as described above. The substances tested were a solid formulation containing 92.4% methomyl (Sarver, 1991e) and two liquid formulations containing approximately 20% and 12.7% methomyl (Clement, 1987a; Sarver, 1991f). None of the formulations irritated rabbit skin.

In a test on 10 guinea-pigs, methomyl was applied as a 60% paste in propylene glycol or as a 26% solution in Cellosolve and the

24-h reaction was noted as being mildly irritating (Kaplan & Sherman, 1977).

7.4.2 Eye irritation

Methomyl, either as 10 mg dry powder or 0.1 ml of a 10% solution in propylene glycol, was tested in rabbits' eyes (2 per group). One of each pair was washed after 20 sec and examination of each eye made at 1, 2, 3, 4 and 6 h after treatment and for up to 6 days thereafter. Only mild conjunctivitis was seen on the day of treatment but no corneal injury was noted (Kaplan & Sherman, 1977).

A solid formulation containing 92.4% methomyl was tested in the eyes of six male rabbits. A quantity of 10 mg was introduced into one eye of each rabbit and evaluations of the reaction were undertaken after 1, 24, 48 and 72 h. Pupillary constriction was evident after one hour but was not present the next day (see also section 7.1). Only very mild conjunctival chemosis and redness was seen at 24 h after treatment and the formulation was considered to be non-irritant (Sarver, 1991g).

Two liquid formulations, containing approximately 20% and 12.7% methomyl, respectively, were tested for eye irritancy using the method described in the previous paragraph. In both cases, the formulation produced ocular irritation in the form of conjunctival redness and chemosis, iritis and corneal opacity within one hour and were classified as irritant. These effects had disappeared after 21 days. (Clement, 1987b; Sarver, 1991h).

7.4.3 Skin sensitization

In a test to evaluate the skin sensitization potential of methomyl, the material was applied as a paste to the abraded skin of five guinea-pigs 3 times a week for 3 weeks; five other guinea-pigs received four intradermal injections of 0.1 ml of a 1% solution. The animals were then challenged after a 2-week rest period. Methomyl was shown not to be a skin sensitizer in this test (Kaplan & Sherman, 1977).

A closed-patch repeated insult dermal sensitization evaluation (Beuhler test) was undertaken in guinea-pigs with technical methomyl. The test compound (300 mg), moistened with water, was applied to the intact skin of each of 10 males and 10 females

for 6 h once a week for 3 weeks. Two weeks after the last induction treatment, the animals were challenged with another 300 mg methomyl for 6 h. No erythema was observed in either the induction or challenge phases, and therefore methomyl did not produce delayed contact sensitivity in the guinea-pig. Positive control animals treated with DNCB produced the expected sensitization responses (Armondi, 1991a).

A solid formulation containing 94.2% methomyl, subjected to the evaluation described in the previous paragraph, also failed to produce delayed contact hypersensitivity in guinea-pigs (Armondi, 1991b). The same result was obtained with a liquid formulation containing 21.5% methomyl when given at 0.5 ml per application (Mercier, 1991). Another liquid formulation containing 12.7% methomyl was tested in the Magnusson-Kligman guinea-pig sensitization maximization procedure and was found to be a moderate skin sensitizer under the conditions of the test (Armondi, 1992).

7.5 Reproductive toxicity, embryotoxicity and teratogenicity

7.5.1 Embryotoxicity and teratogenicity

Teratogenicity studies have been undertaken in the rat and rabbit.

Pregnant rats (25 per group) were fed 0, 50, 100 or 400 mg methomyl/kg diet during days 6-15 of gestation. The dams were observed and weighed regularly and then killed on day 21 of gestation. At that time the uterus was removed, and the number of corpora lutea, implantation sites, live and dead fetuses, resorptions and weight of live fetuses were recorded. About one half of the fetuses from each litter were taken for skeletal examination and the remainder for soft tissue examination. The pregnant rats at 400 mg/kg had significantly lower body weight and ate less food than those in the control group. There were no clinical signs of toxicity and all rats survived the test period. Parameters of pregnancy and fetal development, such as the number of litters with partial or total resorptions and fetal weight, were not affected in the test groups compared to controls. There were no treatment-related abnormalities in the fetuses. Methomyl was therefore not embryotoxic or teratogenic in the rat at levels up to 400 mg/kg diet, equivalent to 34 mg/kg body weight per day (Rogers et al., 1978).

Groups of 20 pregnant rabbits were given 0, 2, 6 or 16 mg methomyl/kg body weight per day by gavage on days 7-19 of gestation. The animals were observed and weighed regularly and killed on day 29. The uteruses were then examined for pregnancy, number of implantations, early and late resorptions and live or dead fetuses. Delivered pups were weighed and examined for visceral or skeletal abnormality. One pregnant rabbit at 6 mg/kg died, probably due to gavage error. At 16 mg/kg there were seven deaths during the test period due to the compound. Clinical signs at the highest dose level included tremors, hyperactivity, excessive salivation, aggression and convulsions. The no-observed-effect level for maternal toxicity was therefore 6 mg/kg body weight per day. There was no effect on pregnancy rate or on the average numbers of corpora lutea, implantations, resorptions or live fetuses per dam in treated groups compared to controls. There were no gross external visceral or skeletal variations due to treatment. Methomyl is therefore not embryotoxic or teratogenic to the rabbit at doses up to 16 mg/kg, at which dose maternal toxicity occurred (Christian et al., 1983).

In another study, pregnant rabbits (12 per group) were fed diets containing up to 100 mg methomyl/kg. The pregnancy rate was low in all groups, including controls. No effects were noted on a range of parameters including reproductive indices, fetal body weight or visceral and skeletal abnormalities. However, due to experimental inadequacies the results are difficult to assess (FAO/WHO, 1987).

7.5.2 Reproduction studies

A three-generation (two litters per generation) rat study was undertaken to test the potential reproductive effects of methomyl (Lu, 1983). The compound was fed at levels of 0, 50 or 100 mg/kg diet to 10 males and 20 females for approximately 90 days post weaning prior to first mating to produce the F_{1a} litter. Test diets were fed through to subsequent re-mating to produce the F_{1b} litter. Ten males and 20 females per group were then selected from the F_{1b} litter and continued on their respective diets for approximately 90 days to produce F_{2a} and then F_{2b} litters. The same procedure was used to produce subsequent litters of the next generation. Records were kept of all matings, number of pregnancies, number of young in each litter born alive or dead, the body weight of offspring at weaning, and the respective reproduction and lactation indices. Ten males and 10 female offspring were selected

from each group of the F_{3b} litter for histopathological examination. Methomyl did not affect the reproductive performance of rats in this study. There were no effects on fertility, gestation or lactation and no compound-related abnormalities on gross examination. No treatment related changes were seen upon histopathological examination of tissues from the offspring in the F_{3b} litter (Kaplan & Sherman, 1977).

A two-generation rat study was also carried out using high dietary levels of methomyl (600 and 1200 mg/kg) as well as a lower level of 75 mg/kg. The F_0 parents (13 males, 26 females) were mated after 100 days treatment and the F_1 parents (20 males, 40 females) after a minimum of 120 days. Spermatogenesis (based on sperm count) was measured on adult males in both generations after breeding, in addition to the standard assessments of reproductive performance. Histopathological examination was undertaken on a selection of tissues from parents and pups in both generations. Body weight depression in parents, seen at all or some stages during treatment at 600 and 1200 mg/kg in both generations and at 75 mg/kg in the F_1 generation, was probably related to lower food intake. Reduced red blood cell counts were seen in females at the highest dose level, together with a small (15-25%) depression in plasma cholinesterase activity in both sexes at this level. Decreases in litter size and live births were shown for the highest dose F_0 group and for all F_1 groups for which a clear no-observed-effect level was not established. Survival during lactation in F_1 pups (from F_0 parents) was reduced at the highest dose level, as was survival in highest dose F_2 pups during early lactation up to day 4. Pup body weight was slightly reduced at 75 mg/kg, significantly reduced at the two higher levels in the F_1 generations and reduced at the 600 and 1200 mg/kg levels in the F_2 generation. No histopathological changes due to treatment were seen in any of the tissues examined in parents or offspring. No effects on the reproductive parameters of fertility indices, gestation length or male sperm counts were seen at dose levels up to and including 1200 mg methomyl/kg in diet (Lu, 1983).

7.6 Mutagenicity

Numerous *in vitro* mutagenicity assays, to various end-points, have been carried out on methomyl by several investigators (Table 6). Methomyl did not show mutagenicity or cause primary DNA damage in bacterial or mammalian cells *in vitro*. It showed cyto-

Table 6. Summary of results of *in vitro* mutagenicity assays and related end-point studies on methomyl

Test	Organism	Activation + and/or -[c]	Dose range	Mutagenic potential	Reference
Prokaryotes					
Point mutation	*Salmonella typhimurium* (5 strains)[a]	-	50 nM	negative	Blevins et al. (1977a)
Point mutation	*S. typhimurium* (5 strains) *Escherichia coli* (WP2hcr)	+ and - + and -	up to 5000 µg/plate	negative negative	Moriya et al. (1983)
Point mutation	*S. typhimurium* (5 strains)	+ and -	up to 1 mg/plate	negative	Waters et al. 1982
Point mutation	*E. coli*, WP2uvr A	+ and -	up to 1 mg/plate	negative	Waters et al. 1982
DNA damage	*E. coli* pol A W3100, p 3478	-	1 mg/disc	negative	Waters et al. 1982
DNA damage	*Bacillus subtil rec*M45	-	1 mg/disc	negative	Waters et al. 1982
Yeast					
DNA damage	*Saccharomyces cerevisiae* D3	+ and -	1-3.5%	negative	Waters et al. 1982
Mammalian cells					
DNA damage	Human lung fibroblast WI-38	+ and -	10^{-7}-10^{-3}M	negative	Waters et al. 1982
DNA damage	Rat hepatocytes (UDS)	-	1 µM-75 mM	negative	Vincent (1985)
DNA damage	Human skin cell DNA	-	10^{-5}M	negative	Blevins et al. (1977b)

Table 6 (contd).

Test	Organism	Activation + and/or -[c]	Dose range	Mutagenic potential	Reference
Gene mutation	Chinese hamster V79 cells	+ and -	1-10 mM	negative	Wojciechowski et al. (1982)
Gene mutation	Chinese hamster ovary (CHO) cells, HGPRT	- +	10-55 mM 100-350 mM	negative	McCooey et al. (1984)
Chromosome aberrations	Human lymphocytes[b] (whole blood culture)	NA	0.02-0.54 mM	positive	Bonatti et al. (1994)
Sister-chromatid exchange	Human lymphocytes[b] (whole blood culture)	NA	0.02-0.54 mM	negative	Bonatti et al. (1994)
Micronuclei	Human lymphocytes[b] (whole blood culture)	NA	0.01-0.09 mM	positive	Bonatti et al. (1994)
DNA single strand breaks	Human lymphocytes[b] (whole blood culture)	NA	0.06-2 mM	negative	Bonatti et al. (1994)
DNA oxidative damage	Human lymphocytes[b] (whole blood culture)	NA	0.25 - 1 mM	negative	Bonatti et al (1994)

[a] Plate incorporation and spot tests
[b] The metabolic activity of the cell cultures was demonstrated by the positive control response
[c] NA = not applicable

genetic potential in human lymphocytes *in vitro* as indicated by an increase in micronuclei and chromosomal aberrations.

In an *in vivo* study, the clastogenic potential of methomyl was assessed by its ability to cause numerical and structural chromosomal aberrations in rat bone marrow cells. Single doses of methomyl were given by gavage to groups of 15 male and 15 female rats at doses of 2, 6 or 20 mg/kg body weight; five males and five females were killed at 6, 24 and 48 h after dosing and the bone marrow cells harvested. These were examined for chromatid and chromosome breaks and for gaps and other aberrations. The results showed that there was no significant increase in the frequency of chromosomal aberrations and no significant differences between the chromosome numbers and the mitotic indices of the dosed groups and the controls (Farrow et al, 1984).

Methomyl was tested in the sex-linked recessive lethal assay with *Drosophila melanogaster* at concentrations of 4 and 10 mg per litre in the test medium. No increase in mutation rate was observed in this assay (Waters et al., 1982).

A formulation (Lannate 20) containing 20% methomyl, but of otherwise unstated composition, caused an increase in the number of sex-linked recessive lethals, but with no observed translocations. The same formulation increased the incidence of abnormal sperm and frequency of chromosomal aberrations in mice (Hemavathy & Krishnamurthy, 1987a,b).

7.7 Carcinogenicity

The carcinogenic potential of methomyl was assessed in the long-term rat and mouse studies already described in section 7.3.

In the earliest study, groups of 35 male and 35 female rats were fed 0 (2 groups), 50, 100, 200 or 400 mg methomyl/kg diet for 22 months. No differences were seen in the incidence of neoplastic lesions between control and treated groups (Kaplan & Sherman, 1977).

In the more recent rat study, groups of 80 males and 80 females were fed 0, 50, 100 or 400 mg methomyl/kg diet for 2 years. The mortality rates were similar in all groups and there was an overall survival of 40-50% by the end of the study. More than 30 tissues/rat were examined microscopically from animals killed

or dying during the study and at interim and terminal sacrifice. There was no indication of any differences between groups in the appearance of any individual tumour nor were there any differences between groups for the number of tumour-bearing rats or those with benign or malignant tumours (Kaplan, 1981).

The 2-year mouse study was initiated at dietary levels of 0, 50, 100 and 800 mg/kg with groups of 80 males and 80 females. By week 39 the highest dose level had been reduced to 200 mg/kg and the 100 mg/kg level to 75 mg/kg (see section 7.3 for details). Mortality was higher in the highest dose male and female groups than in controls throughout the study and was also somewhat higher in the mid-dose group. Adequate numbers of mice survived to the termination of the study (30-50% for female groups and 38-68% for male groups). Histopathological examination on more than 30 tissues per mouse was undertaken on animals killed or dying during the study and at terminal sacrifice. There were no differences between groups for the numbers of tumour-bearing mice or those with benign or malignant tumours (Serota et al., 1981).

Methomyl did not transform hamster embryo cells in a transplacental host-mediated assay, nor did the cultured cells from this assay induce tumours when injected subcutaneously into young adult nude mice (Quarles et al., 1979).

7.8 Other special studies

7.8.1 *Cholinesterase studies* in vivo *and* in vitro

Due attention must be given to the measurement of cholinesterase activity in blood and brain samples because of the fast spontaneous reactivation of the methomyl-inhibited enzyme. It is important to analyse samples in the minimum possible time after sampling and to use an analytical method which requires the minimum of sample dilution and shortest assay time. If these criteria are not followed then cholinesterase inhibition due to methomyl can be misinterpreted.

In groups of rats fed 0, 50, 100, 200, 400 or 800 mg methomyl per kg diet for 79 days, only those fed the highest dose showed blood acetylcholinesterase activity inhibition as assayed by the Ellman method. Males showed blood cholinesterase activity inhibition of 25-40% early in the study (by 11 days) while females

showed this inhibition towards the end of the study period (Singles, 1970a). In an extension of this study, the blood acetylcholinesterase activity of rats fed 400 or 800 mg/kg was assayed by the Ellman method and a pH stat method after 5 months of feeding. In neither group was there an effect on blood acetylcholinesterase activity (Singles, 1970b).

Methomyl was fed to groups of rats in the diet at levels of 0, 100, 400 or 800 mg/kg, and blood was taken for red cell and plasma acetylcholinesterase activity assay at 1, 7, 14, 21 and 28 days. Brain acetylcholinesterase activity was also measured on rats at 14 and 29 days. All assays were undertaken by the Ellman method. There were small depressions of acetylcholinesterase activity (up to 20%) in red cells and plasma of males and females at 800 mg/kg. Brain acetylcholinesterase activity was also slightly depressed (≤17%) at this dose level. There were no consistent findings of acetylcholinesterase inhibition at the two lower levels of 100 and 400 mg/kg (Barnes, 1978).

Lannate, containing 90% methomyl, was given to 14 male rats at 41 mg/kg body weight by oral intubation each day for 8 successive days. The animals were killed 24 h after the last dose and blood was taken for the assay of serum cholinesterase activity by a colorimetric method. The activity was depressed by 40% compared to controls (Borady et al., 1983).

Cholinesterase activity in plasma and red cells of rats was assayed after the dermal application of methomyl. Four groups of rats were treated dermally with 200 mg methomyl per rat and blood samples were collected 2, 4, 6 and 24 h after treatment. Plasma cholinesterase activity was markedly reduced at each time interval compared to controls (22–50% of control value) while red cell cholinesterase activity was less affected (80–91% of control value). Groups of rats were also treated dermally with 25 or 100 mg per rat and blood was collected at 24 and 72 h after treatment. Plasma cholinesterase activity was depressed at both levels and at both time intervals, but red cell acetylcholinesterase was unaffected (Henry, 1981).

Lannate powder, containing 45% methomyl, was the subject of inhalation studies using a single 4-h exposure to 9.9 mg/m^3 or repeated exposures to 14.8 mg/m^3 (see section 7.2 for details). Plasma cholinesterase activity was markedly depressed (by 50%) for 4 h after the single exposure, but showed recovery almost to

the control value within 20 h. Red cell cholinesterase activity was not inhibited. Plasma cholinesterase activity was less affected (29% depression) 4 h after the last of the repeat exposures than after the single exposure (Ta'Naka et al., 1987).

The I_{50} value (the molar concentration of inhibitor giving 50% reduction in enzyme activity in given experimental conditions) for methomyl was determined *in vitro* for human and rat red blood cell acetylcholinesterase activity using a modified Ellman method. Human acetylcholinesterase was approximately six times more sensitive to methomyl's action than rat acetylcholinesterase (I_{50} values of 0.265×10^{-5} mol/litre and 1.56×10^{-5} mol/litre, respectively). Regeneration studies using a gel filtration method showed that methomyl-inhibited rat acetylcholinesterase regenerates at a faster rate than the human enzyme, with half-lives of 26.6 and 38.0 min, respectively (Carakostas, 1987).

7.8.2 Neurotoxicity

Hens given a single oral (LD_{50}) dose of 28 mg methomyl/kg either died within 10 min or survived. Survivors showed toxic signs of lacrimation and salivation, but no evidence of wing or leg paralysis. After a 21-day recovery period, no abnormalities were observed upon histopathological examination of the sciatic nerve. Doses much higher than the oral LD_{50} (up to 200 mg/kg) were given to hens without causing mortality after they had been pretreated with atropine sulfate subcutaneously at 10 mg/kg. Wing or leg paralysis was not observed and there were no histopathological abnormalities in the sciatic nerve after a 21-day recovery period. Birds treated with tri-*o*-cresyl phosphate (TOCP) at 500 mg/kg showed the leg paralysis and sciatic nerve degeneration expected of a positive control substance (Krauss & Stula, 1967).

7.8.3 Potentiation studies

Potentiating properties were determined by administering one-half the oral LD_{50} of methomyl to rats, followed immediately by one-half the LD_{50} of another anticholinesterase pesticide, and then recording the resultant mortality over 14 days. Out of 18 pesticides tested, only Sevin and Ronnel showed the ability to increase mortality indicative of a potentiation effect (Sherman, 1967). In another study, the inhibition of cholinesterase activity in rat blood after the oral administration of methomyl alone or in combination with another anticholinesterase pesticide was used to

measure potentiating effects. Methomyl in combination with methyl parathion or phosdrin was shown to be potentiating, while antagonism occurred when it was combined with dimethoate (Henry, 1975).

Rats (10 per sex and per group) were given methomyl at 200 mg/kg diet and ethanol as a 10% aqueous solution, either separately or together, for a period of 12 weeks. There was some evidence of increased effects as a result of the combined administration resulting in decreased body weights from weeks 2 (females) and 4 (males) and increased relative organ weights for adrenals (males) and kidneys (females). In male rats, the combination of the two compounds increased hepatic triglycerides and free fatty acids and decreased brain acetylcholinesterase activity more than that expected from either compound alone (Antal et al., 1979). Ethanol administered in the diet to rats, at a level equivalent to 25% of the calorie intake, did not potentiate erythrocyte acetylcholinesterase inhibition by methomyl co-administration at 200 mg/kg in the diet (Bracy et al., 1979).

In female rats only, the combination of methomyl and caffeine retarded growth, increased the relative weight of kidneys, spleen, adrenals, liver and heart, depressed glucose-6-phosphate dehydrogenase activity, and increased aniline hydroxylase and glucose-6-phosphatase activity (Bedő & Cieleszky, 1980).

7.8.4 Antidote studies

The antidotal properties of several agents against the toxicity of methomyl have been examined in a number of species.

Potential antidotes were administered within one minute after oral lethal doses of methomyl (30 or 60 mg/kg) were given to rats. Of the agents used, atropine sulfate given intraperitoneally as a single dose of 50 mg/kg proved to be the most effective antidote. Other agents used which were less effective or ineffective were pyridine-2-aldoxime methiodide (PAM) and tetra-ethylammonium chloride (TEAC) (Sherman, 1968a). Rats were also used in a study of the effectiveness of obidoxime or *N*-methyl-pyridinium-2-aldoxime methane-sulfonate (P2S) as antidotes alone or in combination with atropine sulfate. Methomyl was injected subcutaneously as solutions of logarithmically graded concentrations (1 ml/kg body weight), and at the onset of signs of toxicity atropine sulfate (17.4 mg/kg), P2S (50 mg/kg) and obidoxime

(90 mg/kg) were injected subcutaneously either alone or in a combination. Lethality was reduced by atropine sulfate or P2S but obidoxime was ineffective. Atropine sulfate in combination with P2S also was effective (Natoff & Reiff, 1973).

Mice fed a lethal dose of 100 mg methomyl/kg in pellets and then given TEAC by injection 10 min later survived, and resumed normal activity within another 10 min (Andrews & Miskus, 1968). Atropine sulfate (50 mg/kg intraperitoneal) was shown to have antidotal activity in guinea-pigs given methomyl orally at lethal single doses of 15-60 mg/kg (Sherman, 1968b). Dogs given a single oral dose of 10 or 20 mg methomyl/kg by capsule were protected against the toxic effects if atropine sulfate was given very quickly, i.e. within a few minutes. The antidote was more effective when given intravenously than when given intramuscularly or orally (Sherman, 1968c).

The antidotal effectiveness of atropine administered intravenously or orally at 1 or 10 mg/kg and hexamethonium or TEAC given intravenously at 10 mg/kg was evaluated in rhesus monkeys dosed with 20 or 40 mg methomyl/kg orally. Atropine at 1 mg/kg, given intravenously or orally, was effective as an antidote for the sublethal dose of 20 mg methomyl/kg. Atropine at 10 mg/kg orally, administered immediately after the appearance of toxic signs, was an effective antidote for the lethal dose of 40 mg methomyl/kg. Recovery occurred within 2-5 h of the methomyl dose. TEAC at 10 mg/kg (intravenous) also prevented the death of one monkey after a lethal dose of methomyl, although recovery took longer than after atropine. Hexamethonium did not appear to be very effective (Teeters, 1968).

7.8.5 Other studies

Lannate (90% methomyl) was given to 14 male rats at the high dose level of 41 mg/kg by intubation each day for 8 days and the animals were killed 24 h after the last dose for hepatic and serum assays. Liver weight was not increased, nor was there histopathological evidence of fatty deposit, but total lipids including cholesterol and phospholipids were increased. The treatment also increased the level of serum triglycerides, phospholipids and free fatty acids and increased the activity of GOT, GPT and alkaline phosphatase enzymes (Borady et al., 1983). Lung triglyceride, cholesterol and phospholipid contents were not affected when rats were exposed to Lannate (45% methomyl) dust at 14.8 mg/m^3 by

inhalation for 4 h/day, 5 days/week for 3 months (Ta'Naka et al, 1987).

Single oral doses of 2 or 10 mg methomyl/kg increased pancreatic chymotrypsin, lipase and amylase activities in male and female rats. Rats fed 100, 400 or 800 mg/kg diet for 10 days showed elevated serum cholesterol in females only. Hepatic aminopyrine demethylase and aniline hydroxylase activities were increased in female rats at 400 and 800 mg/kg. When rats were given 100 or 200 mg/kg diet, females fed 200 mg/kg showed elevation of total serum lipids and cholesterol. The females also showed decreased hepatic glucose-6-phosphatase activity and vitamin A at this level (Bedö & Cieleszky, 1980).

The effect of methomyl on a number of serum constituents was studied in rats given oral doses of 6.8 mg/kg per day, 6 days/week for 4 weeks. Increases were seen over the 4-week period for serum glucose, cholesterol, GOT and GPT, while decreases were seen for serum total protein albumin, globulin and cholinesterase activity. However, since control values did not seem to be available for the 4-week period, it was difficult to evaluate the significance of the results for methomyl (Saleh, 1990a,b,c).

7.9 Factors modifying toxicity

It has been shown that synthesized nitrosomethomyl is mutagenic *in vitro* and is capable of producing stomach tumours in rats (Blevins et al., 1977a,b; Lijinsky & Schmahl, 1978). However, when methomyl is incubated with nitrite and macerated meat under simulated stomach conditions, there is no evidence that nitrosomethomyl is formed (see section 4.3).

7.10 Mechanisms of toxicity - mode of action

As a member of the carbamate class of compounds, methomyl has a well-known mode of action via inhibition of the enzyme acetylcholinesterase at nerve junctions. A detailed description of the mechanism of action of carbamates on cholinesterases is given in Environmental Health Criteria 64: Carbamate pesticides: a general introduction (IPCS, 1986). Studies with methomyl show that the onset of toxic action is rapid and that, in common with many other carbamates, the toxic effect is rapidly reversible. Because of this, it is important to use appropriate assay methods when measuring cholinesterase activities during toxicity studies.

Failure to allow for the rapid reversibility of the action can lead to underestimation of enzyme inhibition.

The acute toxic action of methomyl is characterized by signs of poisoning typical of anticholinesterase action, i.e. lacrimation, profuse salivation, tremor and pupil constriction. Surviving animals quickly show signs of recovery, often within hours. The toxic action can be countered by the anticholinergic antidote atropine sulfate. The potency of methomyl is greatest when given by the oral or inhalation routes of administration. It has very low acute toxicity when given dermally, presumably because during the slower absorption phase there is time for recovery from toxic action and thus the effect is never fully exerted.

8. EFFECTS ON HUMANS

8.1 General population

8.1.1 Accidental and suicidal poisoning

Five Jamaican fishermen prepared a meal to which they accidentally added methomyl instead of salt. Within minutes of eating the meal, three of the men were badly affected, twitching, trembling and frothing at the mouth, and died within 3 h. One of the other two also showed toxic symptoms, while the other was unaffected. Both survivors were given atropine and the symptomatic patient recovered within 2 h after treatment. Postmortem examination of the dead men revealed highly congested stomach lining, lungs, trachea and bronchi. Analysis showed that part of the meal (roti) contained about 1% methomyl. It was estimated that the victims had consumed about 12-15 mg methomyl/kg (Liddle et al., 1979).

A 31-year-old woman committed suicide, using a methomyl preparation, together with her three children, one of whom (a 9-year-old son) survived. Postmortem examination showed congestion of the stomach mucous membranes and the lungs. Analysis of organs of the mother and a 6-year-old son showed highest methomyl concentrations in the liver (15.4 and 56.5 mg/kg, respectively). Large amounts of methomyl were present in the stomach contents and it was estimated that the doses were 55 mg/kg for the mother and 13 mg/kg for the son (Araki et al., 1982).

A woman attempted suicide by ingesting about 2.25 g methomyl. After 6 h, methomyl was present in the blood at a concentration of 1.61 mg/kg and in the urine at 10.9 mg/litre; at 15 h the levels were 0.04 mg/kg and 0.25 mg/litre, respectively, and at 22 h methomyl could not be detected (Noda, 1984).

Symptoms and treatment were described for 11 patients who had suffered methomyl poisoning in Spain over a 5-year period. Intoxication was accidental in six cases and suicidal in the other five. The time interval between exposure and admission for treatment averaged 2.8 h. All of the subjects showed cholinergic symptoms; plasma cholinesterase activity was normal in four cases and moderately reduced in the others. Treatments applied included gastric lavage, washing the skin, administration of activated

charcoal and small doses of atropine, according to the symptoms involved. All the patients recovered within 24-48 h (Martinez-Chuecos et al., 1990).

A blood level of 0.57 mg methomyl/litre was measured in a pilot who had died as a result of a crash while spraying a solution of methomyl and chlorothalonil in methanol. Analysis was not undertaken for chlorothalonil and methanol (Driskell et al., 1991).

A 79-year-old man and his 73-year-old wife attempted suicide by ingesting methomyl powder. The woman died within 19 h but the husband survived after treatment by gastrolavage, followed by administration of atropine sulfate. The serum methomyl concentration in the woman was 44 mg/kg 1 h after ingestion and 0.2 mg/kg in the blood at autopsy. The methomyl blood concentration of the man was 0.01-0.1 mg/kg 28 h after ingestion (Miyazaki et al., 1989).

8.2 Adverse effects of occupational exposure

Pesticide operators were reported to be affected after handling powder formulations of methomyl. In one case, an operator mixed a powder formulation and sprayed vegetables without taking any special precautions. He displayed poisoning symptoms within 1 h. His blood cholinesterase activity had decreased to 40% of normal after 12 h but had recovered to within 80% of normal after 36 h. Other operators, a mixer-loader, pilot and markers, using recommended safety precautions, did not show any effects on their red cell or plasma cholinesterase activities after handling liquid formulations and subsequent aerial application of methomyl (Simpson & Bermingham, 1977).

In a survey of agricultural applicators in California, USA, in 1982-1989, methomyl was reported to be involved in 129 out of 5371 exposure-related illnesses due to pesticides. For the period 1982-1985 and for the same area, methomyl was considered responsible for 47 illnesses out of 238 reported cases. Exposure was described as either short term ($\leq$ 3 days), longer term (> 3 days) or accidental (Brown et al., 1989). In 1986, in a summary of reported pesticide-related illnesses and injuries in California, methomyl was identified as the probable causative agent in 7 out of 1065 confirmed occupational cases. These cases were described as "..having some likelihood of being pesticide related" (Edmiston & Maddy, 1987).

An investigation of workers in a pesticide formulation plant revealed that 11 out of 102 workers had been hospitalized due to work-related illness. Most frequent were symptoms of exposure to methomyl and methaemoglobinaemia due to 3,4-dichloroaniline (Morse et al., 1979).

Significant T-wave changes (decreased height, inversion, and leftward deviation of T-wave axis) were shown in 10 out of 22 spraymen applying methomyl for five days under field conditions. These changes reverted to pre-exposure levels within one week. Sufficient information was not available to evaluate the significance of these findings for operator exposure, and further studies are required to fully understand their significance (Saiyed et al., 1992).

Two case reports of allergic contact dermatitis with exposure to methomyl have been described. In the first case, a 26-year-old woman had gradually worsening itchy hand eczema for six months when working in a plant nursery, pollinating, pricking out and potting plants sprayed with methomyl (Lannate) solution. After she avoided touching the sprayed plants or used polyvinyl gloves she became free of eczema. She also reacted positively to a 1% aqueous Lannate solution, indicating that Lannate was a cause of the hand eczema. The second patient had already had hand eczema for 14 years with recent worsening. As soon as she changed her job and no longer had contact with Lannate her eczema disappeared (Bruynzeel, 1991).

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Microorganisms

The effect of methomyl on sewage microorganisms was assessed indirectly by monitoring total oxygen demand (TOD) over a 24-h period. A mixture of activated sludge, phosphate buffer and a simulated waste consisting of Bactopeptone and meat extract was incubated with methomyl at concentrations of 0, 1, 5, 10, 50 and 90 mg/litre. Only at 90 mg/litre was there a slight effect on TOD (<10%), indicative of a minor effect on microorganism activity (Belasco, 1972a).

A fine sand and two silt loam soils were treated with 18 mg methomyl/kg, and the soil fungi and bacteria populations counted after 11 days. The effect on total microbial activity was determined by measuring the CO_2 evolved periodically over 56 days. Neither soil microorganism populations nor CO_2 production was affected by the high level of methomyl in the soils, when compared to controls (Peeples, 1977).

When methomyl was incorporated into a silt loam sand at 0.5 mg/kg together with ammonium sulfate, no effect on nitrification occurred over a 6-week period. This level of incorporation represented the recommended field treatment of 0.56 kg/ha. At ten times this level of incorporation there was some delay (8-9 days) in reaching the 50% nitrification level, but by 4 weeks the level was the same as that in the control soil (Han, 1972).

Methomyl, in the form of Lannate 20L (20% a.i.), was incorporated into a sandy and a loamy soil at rates of 1.87 and 18.7 mg a.i./kg and incubated at 20 °C for 28 days. Dehydrogenase activity, measured at 14 and 28 days, was unaffected by either rate of incorporation in both soils. Ammonia nitrogen and nitrate nitrogen declined by about the same extent in both soils over the 28-day period. This could have been due to stimulation of nitrogen assimilation by the product (Danneberg, 1991).

9.2 Aquatic organisms

9.2.1 Algae

The effect of methomyl on algal growth was assessed using *Selenastrum capricornutum* as test species. The organism was cultured under continuous illumination at 24 °C with methomyl at concentrations of 6.25-100 mg/litre for 120 h. Algal growth was monitored at intervals over the exposure period by measuring the absorbency of light at 665 nm. The E_bC_{50}, (median effective concentration for inhibition of growth based on a comparison of areas under the growth curves after "b" hours) after 72 and 120 h was 60 mg/litre. The E_rC_{50} (median effective concentration for growth inhibition based on a comparison of maximum growth rates from "x" to "y" hours) from 24-48 h was 140 mg/litre (extrapolated value). The no-observed-effect concentration was 6.25 mg/litre (Douglas & Handley, 1988).

A similar study was carried out using Lannate 20L (20% methomyl) as test substance at concentrations of 6.25-200 mg/litre. The E_bC_{50} (72 h) was 68 mg/litre, E_bC_{50} (120 h) was 116 mg/litre and the E_rC_{50} (0-24 h) was 67 mg/litre. A no-observed-effect concentration of 6.25 mg/litre was established (Douglas & Halls, 1991).

9.2.2 Fish

The acute toxicities (96-h LC_{50}, etc.) for several species of fish are shown in Table 7. The 96-h LC_{50} values lie mostly within the range of 0.5-2 mg/litre. The most resistant species tested were the cutthroat trout with a 96-h LC_{50} of 4-7 mg/litre. Generally, within a species, the higher the water temperature the higher the acute toxicity. Results for some methomyl formulations are shown in Table 8. These show lower acute toxicity, corresponding to the lower methomyl content. There are few descriptions of toxic signs in affected fish. In an acute study with carp and tilapia, the fish sank to the bottom of the tank and moved sluggishly, then became highly excited 10 min before death (El-Refai et al., 1976). Shrimps became lethargic before dying (Bentley, 1973; Sleight, 1973).

Two longer-term studies have been undertaken with methomyl and a formulation. This included a 21-day flow-through study on fingerling rainbow trout with Lannate 20L (21.5% methomyl) at

Table 7. The acute toxicity of methomyl to fish (static test)

Species	Temperature (°C)	LC_{50} (mg/litre) 96 h	48 h	24 h	Reference
Atlantic salmon (*Salmo salar*) (0.48 g)	12	1.12			USDI (1978)
	17	0.56			USDI (1978)
Bluegill sunfish (*Lepomis macrochirus*)	12	2.00			USDI (1978)
	22	0.86			USDI (1978)
	23	2.00			Carter & Graves (1973)
	22	1.00			USDI (1975)
Brook trout (*Salvelinus fontinalis*)	12	1.50			USDI (1978)
Carp (*Cyprinus carpio*) (5 cm)	25		2.8		Yoshida & Nishiuchi (1972)
Channel catfish (*Ictalurus punctatus*) (1.8 g)	22	0.53			USDI (1978)
	26			0.92	Carter & Graves (1973)
Cutthroat trout (*Salmo clarkie*)	10	6.8			USDI (1978)
	10	4.05			USDI (1975)
Fathead minow (*Pimephales promelas*) (0.75 g)	-	2.8			Mayer & Ellersieck (1986)
Japanese goldfish (*Carassius auratus*) (4 cm)	25		2.7		Yoshida & Nishiuchi (1972)

Table 7 (contd).

Killifish (*Oryzias latipes*) (2.5 cm)	25		0.87	Yoshida & Nishiuchi (1972)
Largemouth bass (*Micropterus salmoides*) (3 g)	22	1.25		USDI (1978)
Loach (10 cm)	25		1.5	Yoshida & Nishiuchi (1972)
Rainbow trout (*Salmo gairdneri*)	7	2.00		USDI (1978)
	12	1.60		USDI (1978)
	17	0.86		Mayer & Ellersieck (1986)
Sheepshead minnow (*Cyprinodon variegatus*)	21.6	1.16		Boeri & Ward (1989)

Table 8. The acute toxicity of some methomyl formulations to fish (static test)

Species	Formulation	Temperature (°C)	LC_{50} (mg/litre) 96 h	LC_{50} (mg/litre) 48 h	Reference
Bluegill sunfish (*Lepomis macrochirus*)	24% kg a.i.	-	0.7		USDI (1978)
Bluegill sunfish (*Lepomis macrochirus*)	Lannate 20 L	21.5	5.1		Baer (1991a)
Bluegill sunfish (*Lepomis macrochirus*)	Lannate 90% WDP	-	2.1		USDI (1978)
Carp (*Cyprinus carpio*)	Lannate 25 WP	22	4.7 - 12.5		Ökolimna (1980)
Carp (*Cyprinus carpio*) (1.75 g)	Lannate 24 EC	22-25		2.96	El-Refai et al. (1976)
Carp (*Cyprinus carpio*) (31.5 g)	Lannate 24 EC			1.21	El-Refai et al. (1976)
Rainbow trout (*Salmo gairdneri*)	Lannate 20 L	12.6	18		Baer (1991b)
	Lannate 90% WDP	13	3.4		McCain (1971)
Tilapia (*Tilapia nilocita*) (1.5 g)	Lannate 24EC	22-25	0.92		El-Refai et al. (1976)
Tilapia (*Tilapia nilocita*) (13.8 g)			0.88		
Channel catfish (*Ictaurus punctalus*)	24% liquid form	-	0.3		USDI (1978)
Channel catfish (*Ictaurus punctalus*)	29% liquid form		0.3		USDI (1978)
Brook trout (*Salvelinus fontinalis*)	24% liquid form	-	2.2		USDI (1978)

Table 8 (contd).

Killifish (*Oryzias latipes*) (2.5 cm)	25		0.87	Yoshida & Nishiuchi (1972)
Largemouth bass (*Micropterus salmoides*) (3 g)	22	1.25		USDI (1978)
Loach (10 cm)	25		1.5	Yoshida & Nishiuchi (1972)
Rainbow trout (*Salmo gairdneri*)	7	2.00		USDI (1978)
	12	1.60		USDI (1978)
	17	0.86		Mayer & Ellersieck (1986)
Sheepshead minnow (*Cyprinodon variegatus*)	21.6	1.16		Boeri & Ward (1989)

13 °C. The concentrations tested were 0.63, 1.3, 2.5, 5.0, 10 and 20 mg/litre, equivalent to 0.14-4.3 mg methomyl/litre. No effects on fish length or weight were noted throughout the study. Some increase in mortality occurred, from day 12 onwards, in the 5 mg/litre group, and greater dose-related increases were seen at the two higher concentrations throughout most of the study. Surviving fish at these concentrations showed increasing incidence of one or more of the signs of discoloration, lying on the tank bottom, gasping, bloated stomach, loss of equilibrium. The 21-day LC_{50} was calculated to be 6.1 mg/litre formulation (≡ 1.3 mg methomyl/litre) and the no-observed-effect concentration was 2.5 mg/litre formulation (Baer, 1991c).

In an early life-stage toxicity study, fathead minnow embryos and larvae were exposed for 28 days to methomyl at concentrations of 27-491 μg/litre. The water was changed at the rate of 10 aquarium volumes each 24 h and was maintained at a temperature of 25 °C. Embryo hatch and larval survival and growth was evaluated. The percentage embryo hatch was not affected at any concentration. Larval survival was significantly reduced at concentrations down to 117 μg/litre and growth reduced at 243 and 491 μg/litre. The maximum acceptable toxicant concentration was estimated to be >57 μg/litre and <117 μg/litre (Driscoll & Muska, 1982).

9.2.3 Other aquatic organisms

The acute toxicity results for a variety of other aquatic organisms are shown in Table 9. *Daphnia magna* appears to be one of the most susceptible species to the acute toxic action of methomyl, and the Eastern oyster the least susceptible. This difference was further emphasized in two other studies. The 48-h EC_{50} for the Lannate 20L formulation (21.5% methomyl) was 0.033 mg/litre (≡0.007 mg methomyl/litre) for *Daphnia magna* neonates (Baer, 1991d). The 96-h EC_{50} for the Eastern oyster was > 140 mg/litre, as measured by the effect of methomyl on shell deposition in a flow-through test at 21.2 to 23.7 °C (Ward & Boeri, 1991).

The effect of methomyl or its formulation on *Daphnia magna* was studied in longer-term tests on survival, growth and reproductive capacity. A study was initiated with < 24-h-old daphnids exposed to measured methomyl concentrations of 0.7, 1.0, 1.6, 3.5, 7.5 or 13.8 μg/litre. The test was conducted over a 21-day period at 20 °C under semi-static conditions with 2-day renewal of the

Table 9. The acute toxicity of methomyl to other aquatic organisms (static test)

Species	Stage	Methomyl product	Temperature (°C)	LC_{50} (mg/litre) 48 h	LC_{50} (mg/litre) 96 h	Reference
Midge (*Chironomus plumosus*)	mature	95% technical	22	0.088 (EC_{50})		USDI (1978)
		24% conc		0.032		USDI (1978)
Eastern oyster (*Crassostrea virginica*)	embryo/ larvae	technical	20	4.0 (EC_{50})		Ward & Boeri (1990)
Fiddler crab (*Uca pugilator*)	20 mm	Lannate L (24%)	21		2.38	Bentley (1973)
Grass shrimp (*Palaemonetes vulgaris*	18 mm	Lannate 90	21		0.049	Sleight (1973)
	18 mm	Lannate L (24%)	21		0.130	Bentley (1973)
Gammarus pseudolimnaeus	mature	technical	17		0.92	USDI (1978)
Mud crab (*Neopanope texana*)	15 mm	Lannate 90	21		0.41	Sleight (1973)
Mysid shrimp (*Mysidopsis bahia*)	10 day	99% technical	21.5		0.22	Ward & Boeri (1989)
Pink shrimp (*Panaeus duorarum*)	55 mm	Lannate 90	21		0.019	Sleight (1973)

Table 9 (contd).

Species	Stage	Methomyl product	Temperature (°C)	LC_{50} (mg/litre) 48 h	LC_{50} (mg/litre) 96 h	Reference
Stonefly (*Pteronarcys dorsarta*)	naiad	technical	7		0.034	USDI (1975)
Stonefly (*Pheronarcella badia*)	Year Class 1	99% technical			0.069	Mayer & Ellersieck (1986)
Stonefly (*Pheronarcella badia*)	Year Class 1	24% a.i.			0.06	Mayer & Ellersieck (1986)
Stonefly (*Slewala sp.*)	Year Class 1	95% technical			0.034	Mayer & Ellersieck (1986)
Stonefly (*Slewala sp.*)	Year Class 1	24% a.i.			0.92	Mayer & Ellersieck (1986)
Stonefly (*Isogenus sp.*)	Year Class 1	95% a.i.			0.343	Mayer & Ellersieck (1986)
Stonefly (*Isogenus sp.*)	Year Class 1	24% a.i.			0.029	Mayer & Ellersieck (1986)
Scud (*Gammarus pseudolimneus*)	adult	99% technical			0.92	Mayer & Ellersieck (1986)
Scud (*Gammarus pseudolimneus*)	adult	24% a.i.			0.72	Mayer & Ellersieck (1986)
Scud (*Gammarus pseudolimneus*)	adult	24% a.i. (flowthrough)			1.05	Mayer & Ellersieck (1986)

Table 9 (contd).

Water flea (*Daphnia magna*)	neonate	95% technical	18	0.032	Goodman (1978)
Water flea (*Daphnia magna*)	1st instar	95% technical	21	0.009 (EC_{50})	USDI (1978)
Water flea (*Daphnia magna*)	-	24% conc		0.0076	USDI (1978)
Water flea (*Daphnia magna*)	-	Lannate 20L (21.5)	20.4	0.033	Baer (1991e)
Water flea (*Daphnia magna*)	1st instar	95% technical		0.088	Mayer & Ellersieck (1986)

test solutions. Methomyl was found to be stable in these solutions for up to 72 h. Daphnid survival and growth were not affected at any concentration. The number of young produced and number of young per adult were reduced at 3.5, 7.5 and 13.8 μg/litre. There was some delay in the first day of reproduction at all levels, but this was considered to be biologically significant only at 3.5 μg/litre or more, where the number of young was affected. The maximum acceptable toxicant concentration was estimated to be between 1.6 and 3.5 μg/litre (Brittelli, 1982).

In another 21-day study, *Daphnia magna* were exposed to Lannate 20 (21.5% methomyl) at nominal concentrations of 0.63, 1.5, 3.4, 8. 18, 43, 100 or 232 μg/litre. The test conditions and parameters measured were as described above. At 232 μg/litre all daphnids died early in the study, but there was no effect on survival at the lower concentrations nor was growth affected. The 21-day EC_{50}, based upon adult survival, was estimated to be 160 μg/litre (equivalent to 26 μg methomyl/litre). The total young produced and number of young per adult were decreased at 3.4 μg/litre but not at 8 μg/litre. The 21-day no-observed-effect concentration was therefore considered to be 8 μg/litre, equivalent to 2.1 μg methomyl/litre (Baer, 1991e).

9.3 Terrestrial organisms

9.3.1 Terrestrial invertebrates

The acute toxicity of a liquid (Lannate 20L) and a solid (Lannate 25WP) methomyl formulation to earthworms (*Eisenia foetida andrei*) was determined over a 14-day period. The formulations were mixed with artificial soil (70% industrial sand, 20% kaolite and 10% moss peat) at six concentrations of 0-500 mg/kg (Lannate 20L) and 0-1000 mg/kg (Lannate 25WP), with 40 earthworms per concentration. The 7-day LC_{50} values were estimated to be 165 mg/kg and 147 mg/kg, respectively, and the 14-day LC_{50} values 102 mg/kg and 87 mg/kg, respectively (Armstrong et al., 1991; Caley et al., 1991).

Laboratory tests were undertaken to determine the broadcast dosage of methomyl, as a 90% SP, required to kill 50% of earthworms (night crawlers, *Lumbricus terrestris L*). The test substance was mixed with moistened potting soil at six rates from 0 to 35 kg/ha with 40 worms per rate. The estimated rate causing 50% mortality was 11.4 kg methomyl/ha (Ruppel & Laughlin, 1977).

The biochemical changes in experimental snails, *Eubania vermiculata* (Müller), were studied after treatment with 0.2% methomyl in bran bait (w/w) for periods of 1, 3, 5, 7 and 10 days. There was a significant reduction in total soluble proteins, lipids and glycogenic content, and significant increase of glutamic oxalocetic transaminase, glutamic pyruvic transaminase and catalase activities (El-Wakil & Radwan, 1991).

A bran methomyl bait (0.5% w/w) was tested for its molluscicidal activity on the white garden snail (*Theba pisana*) and compared with that of four other oxime carbamate pesticides (aldicarb, aldoxycarb, oxamyl and thiofanox). Methomyl had the most potent molluscicidal activity. The time for 50% mortality of snails (LT_{50}) for methomyl, oxamyl, aldoxycarb, aldicarb and thiofanox was 2.31, 3.97, 4.69, 5.77 and 6.67 days, respectively. The activities of acetylcholine esterase, acid phosphatase and alkaline phosphatase were inhibited by the pesticides in line with their potency. GOT and GPT activities were significantly increased by methomyl (Radwan et al., 1992).

Juvenile (4-week-old) laboratory reared earthworms (*Allolobophora caliginosa*) were kept individually in soil treated with methomyl for 7 days. Relative toxicity, i.e. concentration in soil (mg/kg) causing zero growth, compared to the standard, carbofuran, (0.10) was 0.54 (Martin, 1986).

The acute toxicity of methomyl to bees has been reported by several investigators using different types of test. In one such test groups of 20 bees were treated individually with a range of doses, the methomyl being applied to the thorax of each bee in a 1 μl acetone solution. The mortality was determined after 48 h and the LD_{50} was calculated as 0.1 μg/bee (Meade, 1984). The acute toxicity of methomyl by topical application to the honey-bee (*Apis mellifera*) was compared to that of the Western Yellow jacket (*Vespula pensylvanica*) after the pleural application of a 1 μl solution in acetone to each insect. Methomyl was less toxic to the honey-bee, with a 48-h LD_{50} of 12 μg/g, than to the Yellow jacket (0.9 μg/g) (Johansen & Davis, 1972). A contact LD_{50} of 1.29 μg per bee has been reported by Atkins et al., (1976) and an oral LD_{50} of 0.2 μg/bee by Clinch & Ross (1970).

The speed of action of methomyl on honey-bees was assessed in a special laboratory trial. A commercial formulation (90% DP) was diluted in 33% sucrose solution to give concentrations equal to

1.5, 2 or 4 x LD_{90}. These were fed to bees and the effects observed as two stages; the first was characterized by very fast and erratic movement and the second by the bees being unable to walk or fly. The time intervals to reach each stage were recorded (20 bees), as were the times taken for 50% and 90% bees to be affected. Methomyl was the fastest acting of 10 pesticides tested, taking about 3-5 min to give a 50% effect level. It was suggested that this type of information was needed when interpreting the results of field trials (Clinch & Ross, 1970).

In a tent trial, a methomyl formulation (35% methomyl) was applied to *Phacelia* at a 0.3% concentration in the evening after bees had finished flying and then rewetted early next morning prior to the start of flight. Observations were made later that day and during the following two days. Fewer bees visited the trial tent during this day than visited the control tent. Large numbers of bees were found dead in front of the hive and at the trial tent edges (about one order of magnitude higher) on the first day. On the second day about three times the number of dead bees were found when compared to the control. Fewer bees were found dead when the trial was repeated with the spray deposit left dry (Stute, 1983).

Methomyl was among 400 pesticides assessed in honey-bee laboratory and field studies by the University of California over 20 years. The compound was placed in the highly toxic category, i.e. severe losses should be expected if the pesticide is used when bees are present at treatment or within a day thereafter. It was shown that the contact LD_{50} of 1.29 μg/bee can be converted directly to 1.29 kg/ha, this being the application rate expected to cause a 50% mortality among foraging bees in a treated field crop, at the time of application or shortly thereafter. Several recommendations were included to help minimize bee losses when spraying with insecticides, including early morning or night applications, since there is less risk to honey-bees at these times (Atkins et al., 1976).

9.3.2 Birds

The results for methomyl in acute oral and short-term dietary studies in birds are shown in Tables 10 and 11. In an acute toxicity study on the bobwhite quail, a dose of 5.62 mg/kg produced lethargy, reduced reaction to external stimuli, loss of coordination and

Table 10. Acute toxicity studies on birds

Species	Test	Acute oral LD_{50} (mg/kg)	Reference
Bobwhite quail (*Colinus virginianus*)	intubation, suspended in corn oil	24.2	Beavers (1983)
Japanese quail (*Coturnix japonica*)	intubation, suspended in carboxymethylcellulose	34	Smith (1982)
Chicken (White Leghorn-Cornish)	capsule	minimum toxic dose 25	Palmer & Schlinke (1978)
Mallard duck (*Anas platyrhynchos*)		15.9	Tucker & Crabtree (1970)
Pheasant (*Phasianus colchicus*)		15.4	Tucker & Crabtree (1970)
Common pigeon (*Columba livia*)	in polyethylene glycol	10.0	Schafer (1975)[a]
Common grackle (*Quiscalus quiscala*)	in polyethylene glycol	13.3	Schafer (1975)[a]
Starling (*Sturnus vulgaris*)	in polyethylene glycol	31.6	Schafer (1975)[a]
House sparrow (*Passer domesticus*)	in polyethylene glycol	13.3	Schafer (1975)[a]
Starling (*Sturnus vulgaris*)	gavage in propylene glycol	42	Schafer (1972)
Redwing (*Agelaius phoeniceus*)	gavage in propylene glycol	10	Schafer (1972)

[a] Schafer EW Jr (1975) Avian toxicity tests - letter to Dr HJ Thome, April 28 1975 (unpublished report submitted to WHO by Du Pont)

Table 11. Dietary toxicity studies on birds

Species	8-day Test (5 days feeding, 3 days observation)	Dietary LC_{50} (mg/kg)	Reference
Bobwhite quail (*Colinus virginianus*)	4 concentrations	1100	Heath et al. (1972)
Japanese quail (*Coturnix japonica*)	6 concentrations	3124	Heath et al. (1972)
Mallard duck (*Anas platyrhynchas*)	6 concentrations	2883	Heath et al. (1972)
Bobwhite quail	7 concentrations	3680	Busey (1967)
Pekin duck	7 concentrations	1890	Busey (1967)

lower limb weakness within 30 min of dosing. The birds recovered within 2 h. The effects increased at higher doses and included salivation and wing droop, but recovery in survivors was rapid, within hours to one day. There were no mortalities at 10 mg/kg or less (Beavers, 1983). Chickens given methomyl by capsule at 25 or 50 mg/kg showed muscle tremor, ataxia, salivation, convulsions and death within 30 min (Palmer & Schlinke, 1978).

In a one-generation study, 20-week-old bobwhite quail, 16 male and 16 female per group, were fed diets containing 0, 50, 150 or 500 mg methomyl/kg for 20 weeks in their first breeding season. Assessments included adult clinical health, weight gain and food consumption and the reproductive parameters for numbers of eggs laid, development of eggs, viability of embryos, percent hatchability, offspring survival and eggshell thickness. There were no signs of toxicity in the adults or of treatment-related mortality. There was a slight decrease in body weight gain in males at 500 mg/kg up to week 8. No effects on reproductive parameters were seen at the two lower dietary levels. No treatment-related effects were observed for egg shell thickness at methomyl concentrations of 50, 150 or 500 mg/kg. Mean thicknesses of bobwhite quail eggs were 0.221 (± 0.02), 0.216 (± 0.01) and 0.214 (± 0.01) mm, respectively. Treatment groups did not differ significantly from the control (0.212 ± 0.02 mm). A small but biologically significant reduction in the numbers of eggs laid per hen and a subsequent reduction in the numbers of offspring were seen at 500 mg/kg. A clear no-observed-effect concentration of 150 mg methomyl/kg diet was therefore determined (Beavers et al., 1991a).

A one-generation study of similar design and the same dietary concentrations was undertaken with the mallard duck for a period of 18 weeks. There were no signs of toxicity or treatment-related mortalities in the adults. No effect was seen on body weight at the two lower levels but a decrease in weight gain occurred in hens fed 500 mg/kg over the last 10 weeks of the study. Egg shell thickness was not affected by methomyl. Mean shell thicknesses of eggs from exposed ducks were 0.378 (±0.03), 0.379 (±0.07) and 0.370 (±0.03) mm for 50, 150 and 500 mg/kg, respectively. No significant differences from the control (0.378 ± 0.03 mm) were detected. A slight reduction in the percentage of viable embryos was observed at 500 mg/kg. A clear no-observed-effect concentration was therefore established at 150 mg/kg (Beavers et al., 1991b).

Methomyl did not give any indication of a teratogenic effect in a chick embryo test when it was injected into the yolk (Proctor et al., 1976).

9.4 Field studies

Bobwhite quails, 6 males and 6 females, were exposed to sprays of Lannate formulations, equivalent to a field application of 1 kg methomyl/ha, once every 48 h for a total of four applications. The birds were killed 14 days after the last application. There were no observable effects due to exposure and no treatment-related changes in tissues on gross examination (Aftosmis, 1973a,b).

A simulated field trial was carried out on two groups of bobwhite quail (three males and three females per group). One group was fed prior to treatment, the other group was fed 12 h after treatment. The treatment consisted of spraying methomyl over the test area at the rate of 1.1 kg/ha. In all, six sprayings were made, each 5 days apart, with a 15-day observation period after the last application. Some weight loss occurred in the group fed prior to treatment; otherwise there were no observable effects on surviving birds compared to controls and no changes due to treatment upon gross examination of tissues (Hinkle & Cameron, 1980).

In 1978, 400 ha of Maine (USA) forest land was treated with the formulation Lannate LV at the rate of 0.28 kg methomyl/ha to control spruce budworm. Monitoring of more than 30 species of songbirds was undertaken over 6-day census periods pre-spray, immediately post-spray and 2 weeks post-spray. The census was carried out firstly by individual bird counts and then by territorial counts. Searches were made for dead birds. Spray deposit cards were used to ensure that the insecticide was present in the census plots. A concurrent sampling and analytical programme determined the residue levels of methomyl in trees and other plants, leaf litter, soil and water. The maximum level detected was 15 mg/kg in foliage from the top third of the trees. Underbrush had initial residues of 6 mg/kg, low levels were found in leaf litter, negligible amounts in soil and none in water. These levels dissipated rapidly apart from leaf litter where low levels lasted 34-61 days. The study revealed no evidence of changes in the activity levels among songbirds. No dead or intoxicated birds were found and there was no disruption of nesting birds (Brown, 1978).

A study of brain cholinesterase activity was undertaken on wild mice (*Mus musculus*) trapped over a period of 3 days after a soya bean field had been sprayed with Lannate 1.8 L at 0.5 kg methomyl/ha. Some inhibition of brain cholinesterase activity occurred at a level of about 10% over the study period indicating the possibility of a small effect (Montz et al., 1983).

A census of birds was undertaken before and after spraying a field of hops in Kent, United Kingdom, with 0.56 kg methomyl per ha. Records were made of birds seen, feeding in the hop field, singing and nesting. Monitoring was carried out 1, 3 and 10 days after spraying. Principal species observed feeding upon the sprayed area included blackbird, song thrush, various tits and finches, robin, wren and hedge sparrow. There was no apparent difference in feeding habits before or after spraying and no unhealthy or dead birds were found over the total observation period (Orpin, 1971).

Methomyl (90% SP), applied at 3.4 kg/ha pasture, produced decreases in population and biomass of three species of earthworms of 28.5% and 14%, respectively. The compound was considered to be the least active of the seven pesticides tested (Tomlin & Gore, 1974).

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

Methomyl is a carbamate cholinesterase inhibitor with a well-known mechanism of toxic action. It is particularly toxic by the acute oral and inhalation routes in animal studies, but it has low dermal toxicity. Acute toxic signs in animals are typical of those of a cholinesterase inhibitor. The reversibility of acute toxic action is rapid, with survivors showing quick recovery from toxic signs and reversal of cholinesterase inhibition in the blood and brain. The quick recovery from toxic effects is due to the rapid reversibility of methomyl-inhibited cholinesterase, which is facilitated by the rapid clearance of the compound from the body. Data from accidental and intentional human poisonings show that the level of acute methomyl toxicity in humans is similar to that found in laboratory animals.

Because of the rapid reversibility of the action of methomyl during periods of feeding, acute toxic signs and blood cholinesterase inhibition were rarely seen in dietary studies. The most consistent findings in longer-term studies at the higher dietary levels were decreases in body weight gain in rodents and reduced red blood cell indices in rodents and dogs. There was no evidence for carcinogenic potential from three long-term studies in rodents. The compound was negative in *in vitro* genotoxicity tests that investigated several end-points, but methomyl showed cytogenetic potential in human lymphocytes. It was negative in an *in vivo* rat bone marrow chromosomal study.

NOELs were identified in each of the long-term animal studies, based upon depression of body weight gain and red blood cell indices. These were 5 mg/kg body weight per day in rats, 8.7 mg/kg body weight per day in mice and 3 mg/kg body weight per day in dogs. In the absence of any marked species differences in toxic effect in these studies, the NOEL in the dog of 3 mg/kg body weight per day should be used for the purpose of human risk estimation.

The proposed toxicological criteria for setting guidance values are presented in Table 12.

Table 12. Proposed toxicological criteria for setting guidance values

Exposure scenario	Relevant route/effect	Result/remarks
Short-term (1-7 days)	oral, acute, several species including human	highly toxic; rat LD_{50} = 17 mg/kg body weight; LOEL[a] = 5 mg/kg body weight
	eye, irritation, rabbit	mild irritant
	inhalation, acute, rat	highly toxic; LC_{50} = 0.26 mg/litre (4-h aerosol); NOEL[b] = 0.14 mg/litre
	dermal, acute, rat and rabbit	low toxicity; intact skin - LD_{50} > 2000 mg/kg body weight; NOEL[c] = 2000 mg/kg body weight in the rabbit
Medium-term (1-26 weeks)	repeat dermal, rabbit	21-day study; no toxicologically significant effects at 50 mg/kg body weight per day
	repeat oral, rat	13-week study; NOEL = 3.6 mg/kg body weight per day
	maternal oral, rabbit	teratology study; NOEL = 6 mg/kg body weight per day
Long-term	repeat oral, dog	2-year study; NOEL = 3 mg/kg body weight per day

[a] mild cholinergic signs of toxicity in guinea-pig
[b] no-observed-effect level for clinical signs and death
[c] no clinical symptoms noted except signs of skin irritation

10.2 Evaluation of effects on the environment

Adsorption of methomyl to soil is low to moderate with hardly any desorption. Aerobic degradation in soil (with a half-life of around one week) is about twice as fast as anaerobic degradation. A relative increase in soil organic matter delays degradation.

Despite the above adsorption characteristics, leaching of methomyl in soil to levels deeper than 20 to 30 cm has not been observed. The concentrations of methomyl in both surface and well water are below the limit of detection. Methomyl is degraded rapidly with a half-life of about one week in water and sediment. In sterile water, methomyl is stable for at least 30 days at normal environmental pH.

Application of methomyl to plant leaves results in rapid absorption of about half the amount applied (the other half being adsorbed), and there is no indication of translocation. In contrast, when applied to soil, uptake through the roots occurs readily with rapid translocation to the leaves. Adsorbed foliar residues degrade with a half-life in the order of 4 days. Absorbed methomyl concentrations in food crops decline rapidly to about 5% within one week; this may be due to growth dilution.

Bioaccumulation by rainbow trout did not occur in a flow-through study. Depuration occurred within one day of transfer to clean water. Trout were discoloured when exposed to levels between 0.075 and 0.75 mg/litre, an effect that disappeared within 5 days, the time depending on original exposure concentration.

At recommended application rates, methomyl does not adversely affect microbial activity in temperate soil; nitrification can be delayed at applications 10 times higher. An aquatic green alga showed a NOEC for growth of 6.25 mg/litre.

Several aquatic invertebrates, and particularly daphnids, are very sensitive to methomyl, the LC_{50}s being of the order of 10 to 100 μg/litre. MATC values from two 21-day *Daphnia* studies were estimated to be around 2 μg/litre. Kills of aquatic invertebrates are expected following overspray.

Fish, both freshwater and estuarine, are less sensitive, the LC_{50}s ranging from 0.5 to 7 mg/litre. Two longer-term studies gave an NOEC of 0.5 mg/litre for lethality of fingerling rainbow

trout and an MATC of > 0.06 and > 0.12 mg litre for survival of embryo larval stages of fathead minnow. Given the low persistence of methomyl and its relatively low acute toxicity to fish, the risk is expected to be low.

Laboratory tests in artificial soil with methomyl formulations (25% WP) established a 14-day LC_{50} of 90-100 mg formulation/kg for earthworms. It was estimated that 11 kg a.i./ha of methomyl would kill 50% of earthworms. A field application of 3 kg a.i./ha caused reduced earthworm population (28%) and biomass (14%). The TER for earthworms is around 40 indicating low risk.

Methomyl is classified as highly toxic to honey-bees, the topical LD_{50} being approximately 0.1 μg/bee. Field (tent) trials showed dead bees both at the treatment tent and hive when residues from spraying the previous day were wetted. Less effect was seen with dry residues. Methomyl has not been implicated in bee incidents in the field; this probably reflects advice to restrict spraying times to protect bees.

Acute oral LD_{50}s for various bird species range between 10 and 40 mg/kg body weight. Dietary LC_{50}s (5 days) range from 1100 to 3700 mg/kg diet. Methomyl poses an acute oral risk to birds, particularly from granules; dietary intake from contaminated food is not expected to kill birds. An example of a toxicity exposure ratio for birds and fish is shown in Table 13.

The NOEC for reproduction was established at 150 mg/kg diet for both the bobwhite quail and mallard duck. Field studies following spraying of methomyl formulations in forests showed no mortality of songbirds and no changes in feeding behaviour or general activity. Reduced fat deposits of songbirds reflect reduced insect prey. It was not considered that methomyl poses a threat to birds after recommended applications.

The high acute toxicity of methomyl to laboratory mammals indicates a similar hazard to wild mammals.

Table 13. Toxicity exposure ratios for birds, fish and aquatic invertebrates based on application rates of 2.5 kg a.i./ha methomyl to soybeans (worst case)

Risk category	LC_{50} (mg/litre or mg/kg diet)	Estimated exposure (mg/litre or mg/kg diet)[a,b]	Toxicity/exposure ratio (TER)[c]
Acute bird	10	50-364	02-0.027
Acute fish (stream)	0.5	0.2	2.5
Acute fish (pond)	0.5	0.04	12.3
Acute aquatic invertebrate (stream)	0.009	0.2	0.045
Acute aquatic invertebrate (pond)	0.009	0.04	0.225

[a] Estimated environmental concentration in the terrestrial environment (for bird exposure) is based on the stated application rate and the assumption of deposition on short grass using the US EPA monogram

[b] Aquatic exposure concentrations were taken from the STREAM model based on a single application and estimated run-off into water; no direct overspray is included

[c] TER is the toxicity (as LC_{50}) divided by the exposure; values at or below 1.0 indicate likely exposure to toxic concentrations by organisms in the different risk categories

11. CONCLUSIONS AND RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

Considering the toxicological characteristics of methomyl, both qualitatively and quantitatively, it is concluded, on the basis of the no-observed-effect level of 3 mg/kg body weight per day in the 2-year toxicity study on dogs and applying a 100-fold uncertainty factor, that 0.03 mg/kg body weight per day will probably not cause adverse effects in humans by any route of exposure.

12. FURTHER RESEARCH

No further studies were thought to be necessary.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The Joint FAO/WHO Meeting on Pesticide Residues has discussed and evaluated methomyl on several occasions since 1975. Residue aspects were discussed in 1975, 1976, 1977, 1978, 1986, 1987, 1988, 1989, 1990 and 1991 (FAO/WHO, 1976, 1977, 1978, 1979, 1986, 1987, 1988a,b, 1990a,b,c, 1991). Toxicological evaluations took place in 1978, 1986 and 1989, when an Acceptable Daily Intake (ADI) of 0-0.03 mg/kg body weight was established (FAO/WHO, 1979, 1987, 1990a,b).

The Joint FAO/WHO Codex Alimentarius Commission has established maximum residue limits (MRLs) for methomyl in various commodities (FAO/WHO, 1993).

It should be noted that the 1992 CCPR meeting decided to combine MRLs for thiodicarb and methomyl into a single list. In the cases of different MRLs the higher limit would prevail.

Methomyl is listed in Class IB ("Highly Hazardous") in the WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification (1994-1995) on the basis of its rat acute oral LD_{50} value of 17 mg/kg body weight (IPCS, 1994).

The time-weighted average (TWA) adopted by the American Conference of Governmental Industrial Chemists (ACGIH) is 2.5 mg/m^3 (ACGIH, 1994-1995).

REFERENCES

* Report submitted to WHO by E.I. Du Pont de Nemours and Co., Wilmington, Delaware, USA

Aftosmis JG (1973a) Carbamic acid, methyl ester with oxime function of thiolacetohydroxamine acid, S-methyl ester (25% a.i.) (Lannate L methomyl insecticide). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-354-73*).

Aftosmis JG (1973b) Carbamic acid, methyl ester with oxime function of thiolacetohydroxamic acid, S-methyl ester (30% a.i.) (non-flammable Lannate L methomyl insecticide), Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-606-73*).

Ambridge EM (1992) Report on field trials to assess operator contamination during application of two different pesticides to crops of varying heights in Thailand, November/December 1991 (NRI Contract No. 00195) (Unpublished report*).

ACGIH (1994-1995) Threshold limit values for chemical substances in the work environment. Cincinnati, Ohio, American Conference of Governmental Industrial Hygienists, p 28.

Andrews TL & Miskus RP (1968) Tetraethylammonium chloride as an antidote for certain insecticides in mice. Science, **159**: 1367-1368.

Antal M, Bedö M, Constantinovits G, Nagy K, & Szépvölgyi J (1979) Studies on the interaction of methomyl and ethanol in rats. Food Cosmet Toxicol, **17**: 333-338.

Araki M, Yonemitsu K, Kambe T, Idaka D, Tsunenari S, Kanda M, & Kambara T (1982), [Forensic toxicological investigations in fatal cases of carbamate pesticide methomyl (Lannate®) poisoning.] Nippon Hoigaku Zasshi, **36**: 584-588 (in Japanese).

Armondi S (1991a) Closed-patch repeated insult dermal sensitization study (Buehler method) with DPX-X1179-394 in Guinea pigs. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLO-345-91*).

Armondi S (1991b) Closed-patch repeated insult dermal sensitization study (Buehler method) with DPX-X1179-425 in Guinea pigs. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report HLO 346-91*).

Armondi S (1992) Closed-patch repeated insult dermal sensitization study (maximization method) with DPX-X1179-424 in Guinea pigs. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLO-659-91*).

Armstrong K, Caley CY, Hall BE, & Knight B (1991) Lannate 20L: Determination of acute toxicity (LC_{50}) in earthworms. Tranent, Scotland, Inveresk Research International Ltd (Unpublished report No. 8546*).

Atkins EL, Anderson LD, Kellum DD, & Neuman KW (1976) Protecting honey bees from pesticides. Berkeley, California, University of California, Division of Agricultural Sciences, 15 pp (Leaflet 2883).

Baer KN (1991a) Static, acute, 96-hour LC_{50} of DPX-X1179-423 to bluegill sunfish (*Lepomis macrochirus*). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-30-91*).

Baer KN (1991b) Static, acute, 96-hour LC_{50} of DPX-X1179-423 (Lannate^R 20L) to rainbow trout (*Oncorhynchus mykiss*). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-29-91*).

Baer KN (1991c) Flow-through, 21-day toxicity of DPX-X1179-423 (Lannate^R 20L) to rainbow trout (*Oncorhynchus mykiss*). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-34-91*).

Baer KN (1991d) Static, acute, 48-hour EC_{50} of DPX-X1179-423 (Lannate^R 20L) to *Daphnia magna*. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-150-91*).

Baer KN (1991e) Chronic toxicity of DPX-X1179-423 (Lannate^R 20L) to *Daphnia magna*. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-292-91*).

Barnes JR (1978) Cholinesterase tests with methomyl. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-280-78*).

Battelle (1991) Method for determination of oxamyl and methomyl in groundwater. Columbus, Ohio, Battelle Institute (Unpublished report No. AMR-1392-89*).

Beavers JB (1983) An acute oral toxicity study in the Bobwhite with H-15,000. Easton, Maryland, Wildlife International Ltd (Unpublished report No. HLO-464-83*).

Beavers JB, Hawrot R, Lynn SP, & Jaber M (1991a) A one-generation reproduction study with the Northern Bobwhite (*Colinus virginianus*). Easton, Maryland, Wildlife International Ltd (Unpublished report No. HLO-337-91*).

Beavers JB, Hawrot R, Lynn SP, & Jaber M (1991b) A one-generation reproduction study with the mallard (*Anas platyrhynchos*). Easton, Maryland, Wildlife International Ltd (Unpublished report No. HLO-336-91*).

Bedö M & Cieleszky V (1990) Nutritional toxicology in the evaluation of pesticides. Bibl Nutr Dieta, **29**: 20-31.

Belasco IJ (1972a) Effect of methomyl on the activity of sewage microorganisms (Unpublished report No. ML/ME15*).

Belasco IJ (1972b) Methomyl: Incubation with rumen microorganisms (Unpublished report No. ML/ME26*).

Bentley RE (1973) Acute toxicity of H-8385 to grass shrimp (*Palaemonetes vulgaris*) and fiddler crab (*Uca pugilator*). Wareham, Massachusetts, Bionomics Inc. (Unpublished report No. HLO-504-73*).

Blevins RD, Lee M, & Regan JD (1977a) Mutagenicity screening of five methyl carbamate insecticides and their nitroso derivatives using mutants of *Salmonella typhimurium* LT2. Mutat Res, **56**: 1-6.

Blevins RD, Lijinsky W, & Regan JD (1977b) Nitrosated methylcarbamate insecticides: Effect on the DNA of human cells. Mutat Res, **44**: 1-7.

Boeri RL & Ward TJ (1989) Static acute toxicity of methomyl to the sheepshead minnow, *Cyprinodon variegatus*. Hampton, New Hampshire, Resource Analysts Inc., EnviroSystems Division (Unpublished report No. HLO-700-89*).

Boleij JSM, Kromhout H, Fleuren M, Tieleman W, & Verstappen G (1991) Re-entry after methomyl application in greenhouses. Appl Occup Environ Hyg, **6**(8): 672-676.

Bonatti S, Bolognesi C, Degan P, & Abbondandolo A (1994) Genotoxic effects of the carbamate insecticide methomyl. 1. *In vitro* studies with pure compound and the technical formulation Lannate 25. Environ Mol Mutagen, **23**: 306-311.

Borady AMA, Mikhail TH, Awadallah R, Ibrahim KA, & Kamar GAR (1983) Effect of some insecticides on fat metabolism and blood enzymes in rats. Egypt J Anim Prod, **23**: 33-44.

Boulton JJK, Boyce CBC, Jewess PJ, & Jones RF (1971) Comparative properties of N-acetyl derivatives of oxime N-methylcarbamates & aryl N-methyl carbamates as insecticides and acetylcholinesterase inhibitors. Pestic Sci, **2**: 10-15.

Bracy OL, Doyle RS, Kennedy M, McNally SM, Weed JD, & Thorne BM (1979) Effects of methomyl and ethanol on behaviour in the Sprague-Dawley rat. Pharmacol Biochem Behav, **10**: 21-25.

Braun HE, Ritcey GM, Frank R, McEwen FL, & Ripley BD (1980) Dissipation rates of insecticides in six minor vegetable crops grown on organic soils in Ontario, Canada. Pestic Sci, **11**: 605-616.

Braun HE, Ritcey GM, Ripley BD, McEwen FL, & Frank R (1982) Studies of the disappearance of nine pesticides on celery and lettuce grown on muck soils in Ontario 1977-1980. Pestic Sci, **13**: 119-128.

Brittelli MR (1982) Chronic toxicity of methomyl to *Daphnia magna*. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-46-82*).

Brock WJ (1989) Repeated dose dermal toxicity: 21-day study with DPX-X1179-394 (methomyl) in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-387-89*).

Brodsky J (1991) Determination of residues of methomyl in grapes, wine & wine processing fractions by GC-MS following treatment with "Lannate", season 1990, France. Frankfurt, Germany, Battelle-Europe (Unpublished report No. BE-A-11-91-10-BF*).

Bromilow RH, Briggs G, Williams MR, Smelt JH, Tuinstra LGMT, & Traag WA (1986) The role of ferrous ions in the rapid degradation of oxamyl, methomyl and aldicarb in anaerobic soils. Pestic Sci, **17**: 535-547.

Brown HL (1978) The effects of Lannate LV on singing male songbirds in Maine in 1978 (Unpublished report No. ML/FW-12 report*).

Brown SK, Ames RG, & Mengle DC (1989) Occupational illnesses from cholinesterase-inhibiting pesticides among agricultural applicators in California, 1982-1985. Arch Environ Health, 44: 34-39.

Bruynzeel DP (1991) Contact sensitivity to Lannate®. Contact Dermatitis, 25: 60-61.

Bull DL (1974) Fate of methomyl on cotton. Environ Entomol, 3: 723-724.

Busey WM (1966) Three-month dietary administration - Rats: Insecticide 1179. Supplement to final report. Falls Church, Virginia, Hazleton Laboratories Inc. (Unpublished report No. MRO-848*).

Busey WM (1967) Acute aqueous exposure - Goldfish, Bluegill, and Rainbow trout. Acute dietary administration - Peking ducks & Bobwhite quail: Insecticide 1179. Falls Church, Virginia, Hazleton Laboratories Inc. (Unpublished report No. MRO-888-1*).

Cahill WP, Estesen B, & Ware GW (1975) Foliage residues of insecticides on cotton. Bull Environ Contam Toxicol, 13: 334-337.

Caley CY, Cameron BD, Hall BE, & Knight B (1991) Lannate 25 WP: Determination of acute toxicity (LC_{50}) in earthworms. Tranent, Scotland, Inverest Research International Ltd (Unpublished report No. 8455*).

Carakostas MC (1987) Inhibition and regeneration kinetics for human and rat acetylcholinesterase exposed to methomyl *in vitro*. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-379-88*).

Carbonnel E, Puig M, Xamena N, Creus A, & Marco R. (1990) Sister chromatid exchange in lymphocytes of agricultural workers exposed to pesticides. Mutagenesis, 5(4): 403-405.

Carter FL & Graves JB (1973) Measuring effects of insecticides on aquatic animals. La Agric, 16: 14-15.

Christian MS, Hoberman AM, & Fuessner EL (1983) Embryo-fetal toxicity and teratogenicity study of methomyl in the rabbit. Horsham, Pennsylvania, Argus Research Laboratories Inc. (Unpublished report No. HLO-331-83*).

Clark S & Kennedy SM (1990) Analytical method for the quantification of methomyl in grapes. Sacramento, California, Morse Laboratories (Unpublished report No. AMR-1806-90*).

Clement C (1987a) Test to evaluate the acute cutaneous primary irritation and corrosivity in the rabbit. L'Arbresle, France, Hazleton France, 16 pp (Unpublished report No. 702408*).

Clement C (1987b) Test to evaluate acute ocular irritation and corrosivity in the rabbit. L'Arbresle, France, Hazleton France, 26 pp (Unpublished report No. 703313*).

Clinch PG & Ross IGM (1970) Laboratory assessment of the speed of action on honey bees of orally dosed insecticides. N Z J Agric Res, 13: 717-725.

Council of the European Communities (1991) Council directive of 15 July 1991 concerning the placing of plant protection products on the market (91/414/EEC). Off J Eur Communities, L230: Part II.

Cox L, Hermosin MC, & Comejo J (1993) Adsorption of methomyl by soils of southern Spain and soil components. Chemosphere, 27: 837-849.

Danneberg G (1991) Investigation of the effects of Lannate 20L on the activity of the microflora of soil. Frankfurt, Germany, Battelle Institute (Unpublished report No. BE-S-11-91-01-DEH-01*).

Dashiell OL (1972) Intraperitoneal LD_{50} test in rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-518-72*).

Debuyst B & Van Larebeke N (1983) Induction of sister-chromatid exchanges in human lymphocytes by aldicarb, thiofanox and methomyl. Mutat Res, **113**: 242-243.

Dong MH, Krieger RI, & Ross JH (1992) Calculated re-entry interval for table rape harvesters working in California vineyards treated with methomyl. Bull Environ Contam Toxicol, **49**: 708-714.

Douglas MT & Halls RWS (1991) The algistatic activity of Lannate 20L. Huntingdon, United Kingdom, Huntingdon Research Centre (Unpublished report No. DPC-16(f) 91399*).

Douglas MT & Handley JW (1988) The algistatic activity of methomyl Tech. (DPX-X1179-00620-06). Huntingdon, United Kingdom, Huntingdon Research Centre (Unpublished report No. DPT-171(j) 871676*).

Driscoll RR & Muska CF (1982) Early life stage toxicity of methomyl to fathead minnow. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-528-82*).

Driskell WJ, Groce DF, Hill RH Jr, & Birky MM (1991) Methomyl in the blood of a pilot who crashed during aerial spraying. J Anal Toxicol, **15**: 339-340.

Du Pont (1967) Methomyl - Livestock feeding studies: Milk and meat. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Industrial and Biochemicals Department (Unpublished report No. ML/ME27*).

Du Pont (1973) Petition for residue tolerance - methomyl: Broccoli, brussel sprouts, cauliflower, spinach, celery. Pesticide Petition 4F 1448, Section D, 1973. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report*).

Du Pont (1978) Ecosystem residue study: Spruce/fir forest and cedar swamp, Princeton, Maine 1978. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. ML/PC-25*).

Du Pont (1982) Lannate® insecticide formulations and technical methomyl - Determination of methomyl (INX-1179) - Reversed-phase liquid chromatography (RPLC) assay method (Method No. L30.4662/(E). Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report [Second issue]*).

Eble JE & Tomic DM (1991) Foliar half-life of methomyl in cotton leaves. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1871-90*).

Edmiston S & Maddy KT (1987) Summary of illnesses and injuries reported in California by physicians in 1986 as potentially related to pesticides. Vet Hum Toxicol, 29: 391-397.

Edwards DF (1980) 10 Day subacute skin absorption test on rabbits. Mewark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-166-80*).

El-Refai A, Fahmy FA, Mahmound FA, Abdel-Lateef, & Imam AKE (1976) Toxicity of three insecticides to two species of fish. Int Pest Control, Nov/Dec: 4-8.

El-Wakil HB & Radwan MA (1991) Biochemical studies on the terrestrial snail *Eubania vermiculata* (Müller) treated with some pesticides. J Environ Sci Health, B26(5/6): 479-489.

FAO (1985) Guidelines for the disposal of waste pesticide containers on the farm. Rome, Food and Agriculture Organization of the United Nations.

FAO/WHO (1976) Pesticide residues in food. Report of the 1975 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. Geneva, World Health Organization (WHO Technical Report Series No. 592; FAO Plant Production and Protection Series No. 1).

FAO/WHO (1977) 1976 Evaluations of some pesticide residues in food: The monographs. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Series No. 8; AGP:1976/M/14).

FAO/WHO (1978) Pesticide residues in food. 1977 Evaluations: The monographs. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 10 Sup).

FAO/WHO (1979) Pesticide residues in food. 1978 Evaluations: The monographs. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 15 Sup).

FAO/WHO (1986) Pesticide residues in food - 1986. Evaluations: Part I - Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 78).

FAO/WHO (1987) Pesticide residues in food - 1986. Evaluations: Part II - Toxicology. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 78/2).

FAO/WHO (1988a) Pesticide residues in food - 1987. Evaluations: Part I - Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 86/1).

FAO/WHO (1988b) Pesticide residues in food - 1988. Evaluations: Part I - Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 93/1).

FAO/WHO (1990a) Pesticide residues in food - 1989. Evaluations: Part I - Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 100).

FAO/WHO (1990b) Pesticide residues in food - 1989. Evaluations: Part II - Toxicology. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 100/2).

FAO/WHO (1990c) Pesticide residues in food - 1990. Evaluations: Part I - Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 103/1).

FAO/WHO (1991) Pesticide residues in food - 1991. Report. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper No. 111).

FAO/WHO (1993) Codex Alimentarius - Volume two: Pesticide residues in food. Rome, Food and Agriculture Organization.

Farrow MG, Cortina T, & Padilla-Nash H (1984) *In vivo* bone marrow chromosome study in rats, H15,000. Final Report. Vienna, Virginia, Hazleton Biotechnologies Corporation (Unpublished report No. HLO-63-84*).

Fayez V & Baig MRE (1991) Short-term toxicity of methomyl in rats. Chemosphere, 23(3): 375-382.

Foerst DL & Moye HA (1985) Aldicarb and related compounds in drinking water via direct aqueous injection HPLC with post column derivatisation. Cincinnati, Ohio, US Environmental Protection Agency (EPA/600/D-85/051).

Fossi MC, Leonzio C, Massi A, Lari L, & Casini S (1992) Serum esterase inhibition in birds: A nondestructive biomarker to assess organophosphorus and carbamate contamination. Arch Environ Contam Toxicol, 23: 99-104.

Foster GV (1966a) Acute inhalation LC_{50} test in rats using technical methomyl (>98% methomyl) progress report. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-73-66*).

Foster GV (1966b) Acute inhalation LC_{50} test in rats using technical methomyl (>98% methomyl). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-214-66*).

Friedman PL (1983) Hydrolysis of [1-^{14}C] methomyl. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report No. AMR-109-83*).

Freeman PK & Ndip EMN (1984) Photochemistry of oxime carbamates 2. Phototransformations of methomyl. J Agric Food Chem, 32(4): 877-881.

Fung KH & Uren NC (1977) Microbial transformation of S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate (methomyl) in soils. J Agric Food Chem, 25(4): 966-969.

Fung KH, Luke RKJ, & Uren NC (1978) Concentrations of methomyl in Australian tobacco plants following transplant, foliar and soil treatments. Tob Sci, 22: 24-26.

Gianessi LP & Puffer CA (1992) Insecticide used in US crop production. Resources for the Future. Washington, DC.

GIFAP (1987) Guidelines for the avoidance, limitation and disposal of pesticide waste on the farm. Brussels, International Group of National Associations of Agrochemical Manufacturers.

Goodman NC (1978) 48-Hour LC_{50} to *Daphnia magnia*. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-165-78*).

Gordon M & Richter ED (1991) Hazards associated with aerial spraying of organophosphate insecticides in Israel. Rev Environ Health, 9(4): 229-238.

Gupta RC, Goad JT, & Kadel WL (1992) Characteristic changes in LDH and its isoenzymes as biomarkers under the influence of acute methomyl toxicity. Fed Am Soc Exp Biol J, 6(4): A1307.

Han JCY (1972) Evaluation of possible effects of methomyl on nitrifying bacteria in soil (Unpublished report ML/ME16*).

Han JCY (1975) Absence of nitroso formation from [^{14}C] methomyl and sodium nitrite under simulated stomach conditions. J Agric Food Chem, 23: 892-896.

Harvey J Jr (1967) Exposure of S-methyl N-[(methyl carbomoyl)oxy] thioacetimidate in sunlight, water and soil (Unpublished report No. ML/ME-10*).

Harvey J Jr (1972a) Decomposition of ^{14}C-methomyl in aerated river water exposed to sunlight (Unpublished report No. ML/ME-13*).

Harvey J Jr (1972b) Decomposition of ^{14}C-methomyl in a high organic matter soil (Unpublished report No. ML/ME-18*).

Harvey J Jr (1977a) Decomposition of ^{14}C-methomyl in a sandy loam soil in the greenhouse (Unpublished report No. ML/ME-19*).

Harvey J Jr (1977b) Degradation of ^{14}C-methomyl in Flanagan silt loam in biometer flasks (Unpublished report No. ML/ME-20*).

Harvey J Jr (1978) Crop rotation study with ^{14}C-methomyl in the greenhouse. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report No. ML/ME-22*).

Harvey J Jr (1980) Metabolism of ^{14}C-methomyl in the lactating goat. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report No. AMR-22-80*).

Harvey J Jr (1983) Photolysis of [1-^{14}C] methomyl. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Chemicals Department (Unpublished report No. AMR-121-83*).

Harvey J Jr & Pease HL (1973) Decomposition of methomyl in soil. J Agric Food Chem, 21(5): 784-786.

Harvey J Jr & Reiser RW (1973) Metabolism of methomyl in tobacco, corn and cabbage. J Agric Food Chem, 21: 775-783.

Harvey J Jr & Yates RA (1967) Metabolism of methomyl in the corn plant. I. Plant growth chamber - Carbon 14 studies (Unpublished report No. ML/ME2*).

Harvey J Jr, Jelinek AG, & Sherman H (1973) Metabolism of methomyl in the rat. J Agric Food Chem, **21**(5): 769-775.

Hashimoto Y & Fukami J (1969) Toxicity of orally and topically applied pesticide ingredients to Carp *Cyprinus carpio Linné*. Botuy Kagaku, **34**: 63-66.

Hawkins DR, Mayo BC, Pollard AD, & Haynes LM (1991) The metabolism of [1-^{14}C] methomyl in rats. Huntingdon, United Kingdom, Huntingdon Research Centre and Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1584-90*).

Hawkins DR, Mayo BC, Pollard AD, & Haynes LM (1992) The metabolism of [1-^{14}C] methomyl in male cynomolgus monkeys. Huntingdon, United Kingdom, Huntingdon Research Centre (Unpublished report No. AMR-1902-90*).

Heath RG, Spann JW, Hill EF, & Kreitzer JF (1972) Comparative dietary toxicities of pesticides to birds. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Special Scientific Report-Wildlife No. 152).

Hemavathy KC & Krishnamurthy NB (1987a) Mutagenicity studies in *Drosophila melanogaster* with Lannate 20. Mutat Res, **191**: 41-43.

Hemavathy KC & Krishnamurthy NB (1987b) Evaluation of Lannate 20, a carbamate pesticide in the germ cells of male rice. Environ Res, **42**: 362-365.

Henry NW III (1975) Lannate® L methomyl insecticide potentiation studies. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-278-75*).

Henry JE (1981) Acute dermal methomyl-cholinesterase response study in male rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-303-81*).

Hill KM, Hollowell RH, & Dal Cortivo LA (1984) Determination of N-methylcarbamate pesticides in well water by liquid chromatography with postcolumn fluorescence derivatization. Anal Chem, **56**: 2465-2468.

Hinkle S & Cameron JT (1980) Simulated field trial in Bobwhite quail, H-13 099. Final report. Vienna, Virginia, Hazleton Laboratories America Inc. (Unpublished report No. HLO-97-80*).

Holt RF (1971) Lannate® residue cooking studies. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Industrial and Biochemicals Department (Unpublished report*).

Hornberger CS (1967) Acute inhalation toxicity of aqueous spray mist. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-171-67*).

Hosling GC (1969) Dietary administration - Cotornix Quail: INX-1179 (Unpublished report No. HLO-238-69*).

Huhtanen K & Dorough HW (1976) Isomerization and Beckmann rearrangement reactions in the metabolism of methomyl in rats. Pestic Biochem Physiol, **6**: 571-583.

IPCS (1986) Environmental Health Criteria 64: Carbamate pesticides - A general introduction. Geneva, World Health Organization.

IPCS (1994) The WHO recommended classification of pesticides by hazard and guidelines to classification 1994-1995. Geneva, World Health Organization (Unpublished document WHO/PCS/94.2).

Ivie KF (1980) High performance liquid chromatography (HPLC) in pesticide residue analysis. In: Zweig G & Sherman J ed. Updated general techniques and additional pesticides. New York, London, Academic Press, pp 55-58.

Jackson GC, Hardy CJ, Gregson RL, Offer JM, & Gopinath C (1991) Lannate 20L: Acute inhalation toxicity in rats 4-hour exposure. Huntingdon, United Kingdom, Huntingdon Research Centre (Unpublished report No. DPT-247/91521*).

Johansen CA & Davis HG (1972) Toxicity of nine insecticides to the Western yellowjacket. J Econ Entomol, **65**: 40-42.

Kaplan AM (1981) Long-term feeding study in rats with S-methyl N-[(methylcaramoyl)oxy]thioacetimidate (methomyl, INX-1179). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-235-81*).

Kaplan AM & Sherman H (1977) Toxicity studies with methyl N-[[(methylamino) carbonyl]oxy]-ethanimidothioate. Toxicol Appl Pharmacol, **40**: 1-17.

Kelly DP (1992) Acute inhalation toxicity study with DPX-X1179-440 in rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-326-92*).

Kennedy SM (1989) Field soil dissipation of Lannate® L insecticide. Sacramento, California, Morse Laboratories Inc. (Unpublished report No. AMR-1215-88*).

Kennedy CM (1991) Field soil dissipation of Lannate® L insecticide - A 1991 study. Sacramento, California, Morse Laboratories Inc. and Lincoln, Nebraska, Harris Environmental Technologies Inc. (Unpublished report No. AMR-1921-91*).

Kennedy CM & Hay RJ (1991a) Magnitude of residues of methomyl insecticide in citrus and its processed fractions. Wilington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1361-89*).

Kennedy CM & Hay RJ (1991b) Magnitude of residues of methomyl insecticide in cottonseed and its processed fractions. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1355-89*).

Kiigemagi U & Deinzer ML (1979) Dislodgeable and total residues of methomyl on mint foliage. Bull Environ Contam Toxicol, **22**: 517-521.

Kiigemagi U, Wellman D, Cooley EJ, & Terriere LC (1973) Residues of the insecticides phorate and methomyl in mint hay and oil. Pestic Sci, **4**: 89-99.

Knaak JE, Jackson T, Fredrickson AS, Rivera L, Maddy KT, & Akesson NB (1980) Safety effectiveness of closed transfer, mixing, loading and application equipment in preventing exposure to pesticides. Arch Environ Contam Toxicol, **9**: 231.

Krauss WC & Stula EF (1967) Oral LD_{50} and delayed paralysis tests (Hens). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-161-67*).

Labare A (1990) Testing of DPX-X1179 through FDA multi-residue protocols A-E. Beltsville, Maryland, Biospherics Inc. (Unpublished report No. AMR-1405-89*).

Leidy RB, Domanski JJ, Haire PL, & Sheets TJ (1977) Effects of weathering and flue-curing on methomyl residues on tobacco. Arch Environ Contam Toxicol, **5**: 199-206.

Leistra M, Dekker A, & Van Der Burg AMM (1984) Computed and measured leaching of the insecticide methomyl from greenhouse soils into water courses. Water Air Soil Pollut, **23**: 155-167.

Leitch RE & Pease HL (1973) Lannate®-methomyl. In: Sherma J & Zweig G ed. Analytical methods for pesticides and plant growth regulators, 7th ed. New York, London, Academic Press, pp 331-338.

Lheritier M (1991a) Test to evaluate the acute toxicity following a single oral administration (LD_{50}) in the rat. L'Arbresle, France, Hazleton France (Unpublished report No. 104367*).

Lheritier M (1991b) Test to evaluate the acute toxicity following a single cutaneous application (limit test) in the rat. L'Arbresle, France, Hazleton France (Unpublished report No. 106393*).

Liddle JA, Kimbrough RD, Needham LL, Cline RE, Smrek AL, Yert LW, & Bayse DD (1979) A fatal episode of accidental methomyl poisoning. Clin Toxicol, **15**(2): 159-167.

Lijinsky W & Schmahl D (1978) Carcinogenicity of N-nitroso derivatives of N-methylcarbamate insecticides in rats. Ecotoxicol Environ Saf, **2**: 413-419.

Lu CC (1983) Nudrin®: Two-generation reproduction study in rats (Protocol No. RA-274). Houston, Texas, Shell Development Co., Westhollow Research Center (Unpublished report*).

McAlack JW (1973) Ten-day subacute exposure of rabbit skin to Lannate® L insecticide. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report HLR 24-73*).

McCain JC (1971), Acute fish toxicity study - static freshwater: Lannate, MR-581, H-6854. Falls Church, Virginia, Hazleton Laboratories Inc. (Unpublished report No. HLO-71-71*).

McConnel R, Pacheco Anton AF, & Magnotti R (1990) Crop duster aviation mechanics: High risk for pesticide poisoning. Am J Public Health, **80**(10): 1236-1239.

McCooey KT, Chromey NC, Sarrif AM & Hemingway RE (1984), CHO/HGPRT assay for gene mutation. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-556-83*).

Macieira OJD & Hebling Beraldo MJA (1989) Laboratory toxicity of insecticides to workers to *Trigona spinipes*. J Apic Res, **28**(1): 3-6.

Martin NA (1986) Toxicity of pesticides to *Allolobophora caliginosa* (*Oligochaeta; Lumbricidae*). N Z J Agric Res, **29**: 699-706.

Martinez-Chuecos J, Molinero-Somolinos F, Solé-Violan J, & Rubio-Sanz R (1990) Management of methomyl poisoning. Hum Exp Toxicol, **9**: 251-254.

Marxmiller RL & Hay RJ (1991) Magnitude of residues of methomyl insecticide in tomatoes and their processed fractions. Wilington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1360-69*).

Mason Y, Choshen E, & Rav-Acha C (1990) Carbamate insecticides: Removal from water by chlorination and ozonation. Water Res, **24**(1): 11-21.

Mayer FL & Ellersieck MR (1986) Manual of acute toxicity: Interpretation and data base for 410 chemicals and 66 species of freshwater animals. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication No. 160).

Meade AB (1984) Methomyl toxicity to honey bee. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Chemicals Department (Unpublished report No. METH/ECO 9*).

Mercier O (1991) Test to evaluate the sensitising potential by topical applications in the Guinea-pig. "The Buehler Test". L'Arbresle, France, Hazleton France (Unpublished report No. 106348*).

Merricks DL (1990) Lannate insecticide - Field worker exposure study in grape girdling and harvesting operations. Frederick, Maryland, Agrisearch Incorporated, Sacramento, California, Morse Laboratories Inc. and Fresno, California, Siemer and Associates Inc. (Unpublished report No. AMR-1442-89*).

Miles CJ & Oshiro WC (1990) Degradation of methomyl in chlorinated water. Environ Toxicol Chem, **9**: 535-540.

Miyazaki T, Yashiki M, Kojima T, Chikasue F, Ochiai A, & Hidani Y (1989) Fatal and non-fatal methomyl intoxication in an attempted double suicide. Forensic Sci Int, **42**: 263-270.

Monson KD (1989) Metabolism of ^{14}C-methomyl in the lactating goat. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-22-80*).

Monson KD & Ryan DL (1991) [^{14}C] Methomyl cow metabolism study. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1675-90*).

Montz WE, Scanlon PF, & Kirkpatrick RL (1983) Effects of field application of the anti-cholinesterase insecticide methomyl on brain acetylcholinesterase activities in wild *Mus musculus*. Bull Environ Contam Toxicol, **31**: 158-163.

Moriya M, Ohta T, Watanabe K, Miyazawa T, Kato K, & Shirasu Y (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res, **116**: 185-216.

Morrow RW (1972) Acute skin absorption study on rats using technical methomyl and a 25% methomyl formulation (Lannate® 25W). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-438-72*).

Morse DL, Baker EL, Kimbrough RD, & Wiseman CL (1979) Propanil-chloracne and methomyl toxicity in workers of a pesticide manufacturing plant. Clin Toxicol, **15**(1): 13-21.

Natoff IL & Reiff B (1973) Effect of oximes on the acute toxicity of anticholinesterase carbamates. Toxicol Appl Pharmacol, **25**: 569-575.

Niven CF Jr (1971) Thermal destruction of Lannate in spinach processing. Walnut Creek, California, Del Monte Corporation Research Center (Unpublished report*).

Noda J (1984) [Determination of methomyl by using chemical ionization mass fragmentography. A case report of methomyl poisoning and the animal experiment of its poisoning.] Nippon Hoigaku Zasshi, **38**: 71-82 (in Japanese).

Ökolimna (1980) [Fish toxicity, carps, Lannate 25 WP.] Burgwedel, Germany, Ökolimna (Unpublished report*) (in German).

Orpin R (1971) Methomyl - Study of effects on wild life. Glaston, United Kingdom, Farm Protection Ltd (Unpublished report*).

Osman AZ, Hazza A, Nagwa I, & Awad TM (1983) Fate and metabolism of the insecticide ^{14}C-Lannate in farm animals. Isot Rad Res, **15**(2): 111-120.

Oswald T, Adams J & Hicks SC (1991), Lannate® insecticide - Dislodgeable foliar residue study in Rose Greenhouse operations. Fresno, California, Siemer and Associates Inc. (Unpublished report No. AMR-1909-90*).

Owens CB, Owens EW, & Zahn D (1978) The extent of exposure of migrant workers to pesticide and pesticide residues (Abstract). Int J Chronobil, **5**(2): 428-429.

Palmer JS & Schlinke JC (1978) Preliminary toxicological evaluations of six pesticide compounds in cattle, sheep and chickens (Unpublished report METH/TOX5*).

Panepinto AS (1991a) Acute inhalation toxicity study with DPX-X1179-427 in rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-678-91*).

Panepinto AS (1991b) Acute inhalation toxicity study with DPX-X1179-424 in rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-560-91*).

Paynter OE (1966) Three-month dietary administration - Rats. Insecticide 1179. Falls Church, Virginia, Hazleton Laboratories Inc. (Unpublished report*).

Pease HL (1968) Methomyl residue analysis - Soils. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Industrial and Biochemicals Department (Unpublished report*).

Pease HL & Kirkland JJ (1968) Determination of methomyl residues using microcolourmetric gas chromatography. J Agric Food Chem, **16**: 554-557.

Peeples JL (1977) Effect of methomyl on soil microorganisms (Unpublished report No. ML/ME21*).

Powley CR (1989) Methomyl foliar dislodgeable residues on grapes in California. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. BMP/DFR-189*).

Powley CR (1990a) Lannate® insecticide: Dislodgeable foliar residue study in grape girdling and harvesting operations. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1445-89*).

Powley CR (1990b) Lannate® insecticide: Dislodgeable foliar residue study on grapes grown in California. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-1515-89*).

Powley CR (1991) Determination of possible bioaccumulation of ^{14}C-methomyl in lactating dairy cows. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products (Unpublished report No. AMR-898-87*).

Priester TM (1984) Batch equilibrium (adsorption/desorption) and soil thin-layer chromatography studies with methomyl. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Chemicals Department (Unpublished report No. AMR-174-84*).

Proctor NH, Moscioni AD, & Casida JE (1976) Chicken embryo NAD levels lowered by teratogenic organophosphorus and methylcarbamate insecticides. Biochem Pharmacol, **25**: 757-762.

Quarles JM, Sega MW, Schenley CK, & Lijinsky W (1979) Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res, **39**: 4525-4533.

Radwan MA, El-Wakil HB, & Osman KA (1992) Toxicity and biochemical impact of certain oxime carbamate pesticides against terrestrial snail, *Theba psiana* (Müller). J Environ Sci Health, **B27**: 759-773.

Reeve MW, O'Connell LP, Bissell S, & Ross J (1992) Characterization of methomyl dissipation on grape foliage. Bull Environ Contam Toxicol, **49**: 105-111.

Rogers AS, Culik R, Kaplan AM, & Aftosmis JG (1978) Oral teratogenic study in rats with Lannate (INX-1179). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-498-78*).

Ruppel RF & Laughlin CW (1977) Toxicity of some soil pesticides to earthworms. J Kansas Entomol Soc, **50**: 113-118.

Saiyed HN, Sadhu HG, Bhatnagar VK, Dewan A, Venkaiah K, & Kashyap SK (1992) Cardiac toxicity following short-term exposure to methomyl in spraymen and rabbits. Hum Exp Toxicol, **11**(2): 93-97.

Saleh F (1990a) Metabolic effects of the carbamate insecticide (methomyl) on rats. I. Levels of glucose, lipids and cholesterol in serum after administration of the insecticide. Egypt J Physiol Sci, **14**(1-2): 45-54.

Saleh F (1990b) Metabolic effects of the carbamate insecticide (methomyl) on rats. II. Changes in serum cholinesterase and transaminases following treatment of the insecticide. Egypt J Physiol Sci, **14**(1-2): 55-64.

Saleh F (1990c) Metabolic effects of the carbamate insecticide (methomyl) on rats. II. Changes in some blood biochemical indices in the rats poisoned with the insecticide. Egypt J Physiol Sci, **14**(1-2): 65-74.

Sarver JW (1991a) Acute oral toxicity study with DPX-X1179-394 in male and female rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-661-91*).

Sarver JW (1991b) Acute dermal toxicity study of DPX-X1179-394 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-455-91*).

Sarver JW (1991c) Acute oral toxicity study with DPX-X1179-424 in male and female rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-171-91*).

Sarver JW (1991d) Primary dermal irritation study with DPX-X1179-394 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-165-91*).

Sarver JW (1991e) Primary dermal irritation study with DPX-X1179-425 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-166-91*).

Sarver JW (1991f) Primary dermal irritation study with DPX-X1179-424 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-162-91*).

Sarver JW (1991g) Primary eye irritation study with DPX-X1179-425 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-280-91*).

Sarver JW (1991h) Primary eye irritation study with DPX-X1179-424 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-279-91*).

Sarver JW (1992a) Acute oral toxicity study with DPX-X1179-439 in male and female rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-858-91*).

Sarver JW (1992b) Acute dermal toxicity study of DPX-X1179-439 in rabbits. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-825-91*).

Schafer EW (1972) The acute oral toxicity of 369 pesticidal pharmaceuticals and other chemicals to wild birds. Toxicol Appl Pharmacol, 21: 315-330.

Serota DG, Machotka SV, Hastings TF, Alsaker RD, & Lane Fezio W (1981) 104-Week chronic toxicity and carcinogenicity study in mice. Methomyl; H-11,135. Vienna, Virginia, Hazleton Laboratories America Inc. (Unpublished report No. HLO-253-81*).

Shah PV, Monroe RJ, & Guthrie FE (1981) Comparative rates of dermal penetration of insecticides in mice. Toxicol Appl Pharmacol, **59**: 414-423.

Sherman H (1966) Acute oral LD_{50} test in rats using technical methomyl (>98% methomyl). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-210-66*).

Sherman H (1967) Acute oral potentiation studies with S-methyl N-[(methylcarbamoyl)oxy] thioacetimidate [INX-1179). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-160-67*).

Sherman H (1968a) Antidote studies with rats. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-251-68*).

Sherman H (1968b) Acute oral and antidote tests with guinea pigs. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-252-68*).

Sherman H (1968c) Acute oral toxicity and antidote tests in rabbits using technical methomyl (>98%). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-250-68*).

Sherman H (1968d) Acute oral toxicity and antidote tests in dogs using technical methomyl (>98%). Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-279-68*).

Sherman H (1972) Chicken & egg study. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-55-72*).

Silveira EJ (1990) Technical methomyl - physical and chemical characteristics. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products Department (Unpublished report No. AMR-1753-90*).

Simpson GR & Bermingham S (1977) Poisoning by carbamate pesticides. Med J Aust, 2: 148-149.

Singles GH (1970a) INX-1179 and cholinesterase activity. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-186-70*).

Singles GH (1970b) INX-1179 and cholinesterase activity. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-327-70*).

Sleight BH (1971) Continuous exposure of rainbow trout (*Salmo gairdneri*) to Lannate® in water. Wareham, Massachusetts, Bionomics Inc. (Unpublished report*).

Sleight BH (1973) Acute toxicity of H-7946 to grass shrimp (*Palaemonetes vulgaris*), pink shrimp (*Penaeus duorarum*) and mud crab (*Neopanope texana*). Wareham, Massachusetts, Bionomics Inc. (Unpublished report No. HLO-186-73*).

Smelt JH, Dekker A, Leistra M, & Houx NWH (1983) Conversion of four carbamoyloximes in soil samples from above and below the soil water table. Pestic Sci, **14**: 173-181.

Smith LW (1982) Wildlife toxicity studies with methomyl. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Biochemicals Department (Unpublished report No. ML/FW20*

SRI International (1988) Pesticides and intermediates, Supplement C. Menlo Park, California, SRI International (Report No. 171C).

Stute K (1983) Results of the registration trials on bee toxicity - 1983. Celle, Germany, Du Pont de Nemours (Germany) GmbH (Unpublished report No. METH/ECO14*).

Swanson MB (1986) Photodegradation of [1-^{14}C] methomyl in soil. Wilmington, Delaware, E.I. Du Pont de Nemours and Co., Agricultural Products Department (Unpublished report No. AMR-611-86*).

Ta'Naka I, Igisu H, Haratake J, Cho S, Mori K, Fujishiro K, Inoue N, Horie A, & Akiyama T (1987) Cumulative toxicity potential of methomyl aerosol by repeated inhalation. Am Ind Hyg Assoc J, 48(4): 330-334.

Teeters WR (1968) Lannate antidotal study - monkeys. Falls Church, Virginia, Hazleton Laboratories Inc. (Unpublished report No. 201-219*).

Tomlin AD & Gore FL (1974) Effects of six insecticides and a fungicide on the numbers and biomass of earthworms in pasture. Bull Environ Contam Toxicol, 12(4): 487-492.

Trivits R (1979) Acute oral LD_{50} test in rats using technical methomyl. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-496-79*).

Tucker RK & Crabtree DG (1970) Handbook of toxicity of pesticides to wildlife. Washington, DC, US Department of the Interior, Fish and Wildlife Service, pp 74-75 (Resource Publication No. 84).

USDI (1975) Acute toxicity studies. Cutthroat trout and stonefly larvae. Columbia, Missouri, US Department of the Interior, Fish and Wildlife Service, Columbia National Fishery Research Laboratory (Unpublished report No. ML/FW-1*).

USDI (1978) Methomyl - Summary of acute toxicity. Columbia, Missouri, US Department of the Interior, Fish and Wildlife Service, Columbia National Fishery Research Laboratory (Unpublished report No. ML/FW-3*).

USEPA (1988) Methomyl science chapters - June 1988: Parts I and II. Washington, DC, US Environmental Protection Agency, Office of Pesticides and Toxic Substances.

USEPA (1991) Pesticides in ground water database. Washington, DC, US Environmental Protection Agency, Pesticides and Toxic Substances.

US FDA (1993a) Food and Drug Administration total diet study: 20 market basket studies, October 1986 - April 1991: Findings of methomyl in food collected for total diet study. Washington, DC, US Food and Drug Administration.

US FDA (1993b) FDA-Regulatory monitoring data: FY 1988-1992 - Findings of methomyl in samples of domestic and imported foods. Washington, DC, US Food and Drug Administration.

US FDA (1993c) FDA-Regulatory monitoring data: FY 1988-1992 - Counts of samples of domestic and imported foods and feeds analyzed by methodology known to be capable of determining methomyl. Washington, DC, US Food and Drug Administration.

Vincent DR (1985) Assessment of methomyl (INX-1179-255) in the *in vitro* unscheduled DNA synthesis assay in primary rat hepatocytes. Newark, Delaware, E.I. Du Pont de Nemours and Co., Haskell Laboratory (Unpublished report No. HLR-149-85*).

Ward TJ & Boeri RL (1989) Static acute toxicity of methomyl to the mysid, *Mysidopsis bahia*. Hampton, New Hampshire, Resource Analysts Inc., EnviroSystems Division (Unpublished report No. HLO-675-89*).

Ward TJ & Boeri RL (1990) Static acute toxicity of methomyl to bivalve mollusc embryos and larvae. Hampton, New Hampshire, Resource Analysts Inc., EnviroSystems Division (Unpublished report No. HLO-422-90*).

Ward TJ & Boeri RL (1991) Acute flow-through mollusc shell deposition test with DPX-X1179-394 (methomyl). Hampton, New Hampshire, Resource Analysts Inc., EnviroSystems Division (Unpublished report No. HLO-710-91*).

Ware GW, Estesen B, & Cahill WP (1978) Dislodgeable insecticide residues on cotton (1975). Bull Environ Contam Toxicol, **20**: 17-19.

Ware GW, Estesen BJ, & Buck NA (1980) Dislodgeable insecticide residues on cotton foliage: Acephate, AC222705, EPN, fenvalerate, methomyl, methyl parathion, permethrin and thiodicarb. Bull Environ Contam Toxicol, **25**: 608-615.

Waters MD, Sandhu SS, Simmon VF, Mortelmans KE, Mitchell AD, Jorgenson TA, Jones DCL, Valencia R, & Garrett NE (1982) Study of pesticide genotoxicity. In: Fleck RA & Hollaender A ed. Genetic toxicology: An agricultural perspective. New York, London, Plenum Press, pp 275-324.

Williams DT, Denley HV, Lane DA, & Quan ESK (1982) Real time monitoring of methomyl air levels during and after spraying in a greenhouse. Am Ind Hyg Assoc J, **43**: 190-195.

Wojciechowski JP, Kaur P, & Sabharwal PS (1982) Induction of ouabain resistance in V-79 cells by four carbamate pesticides. Environ Res, **29**: 48-53.

Yeboah PO & Kilgore WW (1984) Analysis of airborne pesticides in a commercial pesticide storage building. Bull Environ Contam Toxicol, **32**: 629-634.

Yoshida K & Nishiuchi Y (1972) Toxicity of pesticides to some water organisms. Jpn Bull Agric Chem Insp Stn, **12**: 122-128.

Zwick TC & Malik N (1990a) Aerobic metabolism of [1-^{14}C] methomyl in Madera, California soil. Columbus, Ohio, Battelle Memorial Institute, Environmental Sciences Department (Unpublished report No. AMR-1543-89*).

Zwick TC & Malik N (1990b) Anaerobic metabolism of [1-^{14}C] methomyl in Madera, California soil. Columbus, Ohio, Battelle Memorial Institute, Environmental Sciences Department (Unpublished report No. AMR-1544-89*).

RESUME

1. Identité, propriétés physiques et chimiques, et méthodes d'analyse

Le méthomyl est un solide cristallin blanc dont le point de fusion est de 77 °C et la tension de vapeur de 0,72 mPa à 25 °C. Sa solubilité dans l'eau est de 54,7 g/litre et son coefficient de partage octanol/eau (K_{ow}) est de 1,24. Il est stable dans l'eau stérile à pH 7 mais il se décompose à pH plus élevé, sa demi-vie étant de 30 jours à pH 9 et 25 °C.

Le dosage du méthomyl dans divers échantillons consiste en une extraction suivie d'une purification, l'analyse finale s'effectuant par chromatographie en phase liquide à haute performance ou chromatographie gaz/liquide. Dans certains cas, avant le dosage proprement dit, on transforme le méthomyl en oxime ou en fluorophore (post-colonne).

2. Sources d'exposition humaine et environnementale

Le méthomyl est préparé en faisant réagir le *N*-hydroxy-thioacétimidate de *S*-méthyle (MHTA) en solution dans le chlorure de méthylène, sur l'isocyanate de méthyle gazeux à 30-50 °C. Il s'agit d'un carbamate à propriété insecticide que l'on utilise partout dans le monde sur toutes sortes de cultures. Il sert notamment à protéger les fruits, les vignes, le houblon, les légumes, les céréales, le soja, le coton et les plantes ornementales. A l'intérieur des bâtiments, on l'utilise aussi pour détruire les mouches dans les animaleries et les laiteries.

Il est principalement présenté sous forme de poudre hydrosoluble ou encore de liquide miscible à l'eau que l'on dilue pour le traitement des cultures au sol ou en pulvérisations aériennes. Les doses d'emploi vont habituellement de 0,15 à 1,0 kg de matière active par hectare. C'est essentiellement au cours de la préparation et de l'épandage de ces produits ou par suite de l'ingestion de résidus subsistant sur des cultures vivrières qu'il peut y avoir exposition humaine (voir section 5.3.1.4).

3. Transport, distribution et transformation dans l'environnement

Les études de laboratoire montrent que le méthomyl est faiblement adsorbé aux particules du sol. On a ainsi montré que l'adsorption était faible sur les minéraux argileux en particulier l'illite; sur les matières organiques du sol, elle est multipliée par 50 tout en restant encore relativement faible. Une fois adsorbés, les résidus ne se désorbent pratiquement pas. Du fait de ses propriétés, on peut penser que le méthomyl doit être doté d'une certaine mobilité dans le sol.

Dans l'environnement naturel, la décomposition abiotique du méthomyl par hydrolyse ou photolyse est lente ou nulle.

Dans le sol, la décomposition aérobie est environ deux fois plus rapide que la décomposition anaérobie. On a fait état de valeurs de la demi-vie dans le sol qui vont de quelques jours à plus de 50 jours; la sécheresse retarde la décomposition. Dans la pratique, on peut considérer que dans la plupart des cas, on aura après épandage, une demi-vie d'environ une semaine.

Dans les conditions de plein champ, le méthomyl ne pénètre pas dans le sol, par lessivage, à une profondeur de plus de 20-30 cm et il n'y a pas de contamination des eaux souterraines.

Lorsqu'on épand du méthomyl marqué au ^{14}C sur les feuilles de végétaux, il y absorption, mais le produit n'est pas transporté dans d'autres parties de la plante. Lorsqu'on l'applique sur le système radiculaire, le composé est fixé par la plante, le principal résidu étant le méthomyl lui-même. Les produits de décomposition volatils du méthomyl sont le CO_2 et l'acétonitrile. Le reste de la fraction radio-active se retrouve dans les constituants naturels de la plante tels que les lipides ainsi que les acides et les sucres du cycle de Krebs. Dans le feuillage, la demi-vie du méthomyl est de l'ordre de quelques jours.

Après exposition de truites arc-en-ciel à ce composé pendant 28 jours dans un système à courant d'eau, on n'a trouvé aucun signe d'accumulation.

4. Concentrations dans l'environnement et exposition humaine

Si l'on en croit les analyses effectuées sur diverses sources d'eau après épandage du composé aux doses recommandées, il est probable que les concentrations de méthomyl dans les eaux souterraines sont soit très faibles, soit inférieures à la limite de détection (< 0,02 mg/litre).

De faibles résidus de méthomyl se retrouvent sur les cultures, notamment vivrières, lors de la récolte, les quantités dépendant de facteurs tels que la dose d'emploi, le laps de temps écoulé depuis le dernier épandage et le type de culture. Ces résidus sont essentiellement constitués du produit initial.

Dans les produits laitiers, les résidus de méthomyl sont soit inférieurs à la limite de détection, soit très faibles. Après administration de méthomyl à des vaches laitières sous forme de capsules, pendant 28 jours à une dose équivalant à 80 mg/kg de nourriture, on n'a pas retrouvé de résidus décelables de ce composé ou de son métabolite (le MHTA) dans la lait ou les tissus de ces animaux (< 0,02 mg/kg). Aucune trace de méthomyl n'a été non plus décelée dans les oeufs ou dans les tissus de poules pondeuses qui en avaient reçu 1 ou 10 mg/kg dans leur nourriture pendant quatre semaines.

Des analyses effectuées par sondage aux Etats-Unis sur la ration totale ou sur certains types d'aliments, ont montré que la concentration de méthomyl était soit très faible, soit inférieure à la limite de détection. Par ailleurs, un certain nombre d'opérations tels que le lavage, l'épluchage ou la cuisson, réduisent encore la teneur en résidus.

Des études effectuées lors du retour des ouvriers agricoles sur les vignobles après épandage, notamment dans les conditions du désert de Californie, ont montré que pour un résidu foliaire mobile tombé à 0,1 $\mu g/cm^2$, l'exposition était maximale au niveau du torse et de la tête lorsque les ouvriers agricoles pratiquaient l'incision annulaire, le torse et les mains étant les plus touchés lors de la cueillette du raisin. En ce qui concerne le raisin de table, c'est lors de la cueillette et de l'emballage que l'exposition était la plus faible. L'exposition par inhalation était minime.

Après pulvérisation de méthomyl sur des plants de concombres et de tomates, on a mesuré dans l'air de la serre qui les abritait, des concentrations d'insecticide allant jusqu'à 4,7 $\mu g/m^3$ dans la journée qui a suivi l'épandage. Trois, puis sept jours après ce traitement, les concentrations de méthomyl dans la zone de respiration allaient respectivement jusqu'à 14,5 ou 0,7 $\mu g/m^3$. Dans l'eau de lavage des mains des jardiniers d'une serre, on a retrouvé des quantités de méthomyl allant de 10 à 300 μg/heure de travail. Cela montre que l'exposition cutanée est une voie d'exposition plus importante que l'inhalation et que la durée de l'attente à observer avant de retourner sur les lieux doit être basée sur les données d'exposition cutanée.

5. Cinétique et métabolisme chez les animaux de laboratoire

Après administration à des rats par voie orale, le méthomyl est rapidement absorbé, métabolisé et excrété, l'ensemble du processus étant achevé en quelques jours. Une semaine après avoir administré à des rats du méthomyl radio-marqué à raison de 5 mg/kg de poids corporel, on a constaté que 54% de la dose était excrétés dans l'urine, 2 à 3% dans les matières fécales et 34% dans l'air expiré (en l'espace de cinq jours). Au bout de sept jours, il restait dans les tissus et la carcasse 8 à 9% de la radioactivité, le carbone-14 étant incorporé dans les constituants endogènes. C'est dans le sang que la fraction radioactive était la plus importante (2% de la dose).

Chez ces rats, les principaux métabolites présents dans l'air expiré étaient du dioxyde de carbone et l'acétonitrile dans le rapport d'environ 2:1. Dans les urines, le principal métabolite était constitué par un dérivé mercapturique du méthomyl, à hauteur de 17% de la dose. On n'a pas décelé la présence de méthomyl ni de son oxime.

On pense que la métabolisation du méthomyl s'effectue selon le schéma suivant: déplacement du groupe *S*-méthyle par le glutathion, puis transformation enzymatique en dérivé de l'acide mercapturique. Il existe une autre voie métabolique, à savoir l'hydrolyse en MHTA qui est ensuite rapidement décomposé pour donner du dioxyde de carbone. Il pourrait y avoir aussi conversion du *syn*-méthomyl (qui est la forme insecticide) en isomère *anti*, lequel serait ensuite décomposé en acétonitrile par des réactions d'hydrolyse, de transposition et d'élimination. Chez le singe, le

métabolisme est analogue, à cela près que le dérivé de l'acide mercapturique ne constitue qu'un métabolite urinaire mineur.

Une heure après application cutanée à des souris d'une solution acétonique de méthomyl marqué au ^{14}C, on a constaté que le taux de pénétration était de l'ordre de 85%. A ce moment, 3% de la dose étaient présents dans le sang, 5% dans le foie et 13% avaient été excrétés. Au bout de huit heures, l'excrétion totale était de 54,5%.

La décomposition et l'élimination rapides du méthomyl chez le rat ainsi que son absence d'accumulation tissulaire, est comparable à ce que l'on observe chez les ruminants.

Du méthomyl administré à des vaches et à des chèvres a subi une dégradation totale. Ni le composé initial, ni son oxime n'ont été retrouvés dans le lait ou les tissus. On a montré que le méthomyl était métabolisé et incorporé dans les constituants naturels du lait et du foie.

Après avoir fait incuber du méthomyl marqué au ^{14}C avec du nitrite de sodium dans un macérat de viande séchée, dans des conditions simulant le milieu gastrique, on n'a pas mis en évidence la formation de nitrosométhomyl.

6. Effets sur les mammifères de laboratoire et les systèmes d'épreuves *in vitro*

Le méthomyl présente une forte toxicité aiguë par voie orale, sa DL_{50} chez le rat allant de 17 à 45 mg/kg de poids corporel. Il présente également une forte toxicité inhalatoire chez cet animal, la CL_{50} à 4 heures étant de 0,26 mg/litre lorsque le composé est inhalé sous forme d'aérosol. La toxicité cutanée est très faible, la DL_{50} dépassant 2000 mg/kg de poids corporel chez le lapin (peau intacte) et 1000 mg/kg de poids corporel chez le rat (peau abrasée). Les signes d'intoxication aiguë sont ceux que l'on peut attendre d'un inhibiteur de la cholinestérase et consistent, entre autres, en une hypersalivation, une lacrimation, des tremblements et un myosis. On a constaté que les animaux récupéraient rapidement et l'examen de leurs organes n'a pas révélé la présence de lésions anatomopathologies visibles qui soient imputables au traitement. Le méthomyl ne provoque pas d'irritation ou d'hypersensibilisation cutanée et il est légèrement irritant pour la muqueuse oculaire.

L'administration répétée de méthomyl dans la nourriture pendant des périodes prolongées n'a pas conduit à une accumulation ou à un accroissement des effets toxiques. Des rats et des chiens à qui on avait administré une nourriture contenant jusqu'à 250 mg/kg et 400 mg/kg respectivement de méthomyl, pendant 13 semaines, n'ont présenté ni signes d'intoxication ni surmortalité. Chez des rats qui en avaient reçu dans leur nourriture à la dose de 250 mg/kg, on a observé une légère diminution du gain de poids, une réduction du taux d'hémoglobine et une hyperplasie modérée de la lignée érythroblastique au niveau de la moelle osseuse. Chez le rat, la dose sans effets observables était de 50 mg/kg de nourriture (soit l'équivalent d'une dose quotidienne de 3,6 mg/kg de poids corporel). Des lapins, qui avaient subi des applications cutanées répétées de méthomyl à des doses quotidiennes allant jusqu'à 500 mg/kg de poids corporel, pendant 21 jours, ont présenté une hyperactivité ainsi qu'une réduction de l'activité cholinestérasique plasmatique et cérébrale à la dose la plus élevée. La dose sans effets nocifs observables était égale, selon cette étude, à 50 mg/kg de poids corporel par jour.

Au cours d'études à long terme, des rats ont reçu du méthomyl dans leur nourriture à raison de 0, 50, 100 ou 400 mg/kg et des souris en ont reçu de la même manière, 0, 50, 75 ou 200 mg/kg. Chez les rats, les effets observés à la dose la plus élevée consistaient en une réduction du gain de poids ainsi qu'en une diminution du taux d'hémoglobine et de la valeur de l'hématocrite. La dose sans effets observables était de 100 mg/kg de nourriture, soit l'équivalent d'une dose quotidienne de 5 mg/kg de poids corporel. Chez les souris, on a constaté aux deux doses les plus élevées, une augmentation du taux de mortalité ainsi qu'une diminution du taux d'hémoglobine et du nombre de globules rouges. La dose sans effets observables a été évaluée à 50 mg/kg de nourriture, soit l'équivalent d'une dose quotidienne de 8,7 mg/kg de poids corporel. Lors d'une étude toxicologique de deux ans chez des chiens (doses de 0, 50, 100, 400 ou 1000 mg/kg de nourriture), on a observé des signes d'intoxication chez certains animaux à la dose la plus forte, avec une anémie légère à modérée. La dose sans effets observables était de 100 mg/kg de nourriture, soit l'équivalent d'une dose quotidienne de 3 mg/kg de poids corporel.

Des études de deux ans sur des rats et des souris n'ont révélé aucun signe d'accroissement de l'incidence des tumeurs qui soient

imputables à l'administration de méthomyl, ce qui indique que le méthomyl n'est pas cancérogène. Il se s'est pas révélé non plus génotoxique lors d'épreuves *in vitro* sur des cellules bactériennes ou mammaliennes et la recherche de lésions primaires de l'ADN sur des cellules bactériennes ou mammaliennes *in vitro* ou encore d'aberrations chromosomiques médullaires lors d'épreuves *in vivo* chez le rat, a donné des résultats négatifs. On a cependant observé la possibilité d'effets cytogénétiques sur des lymphocytes humains *in vivo*, attestée par l'augmentation du nombre de micronoyaux et d'aberrations chromosomiques. Chez des rats et des lapins qui en avaient reçu par gavage des doses allant jusqu'à 400 mg/kg de nourriture (soit une dose quotidienne de 16 mg/kg de poids corporel), le méthomyl n'a pas produit non plus d'effets embryotoxiques ou tératogènes, alors qu'à ces doses, des effets toxiques pouvaient être constatés chez les femelles gravides. Lors d'une étude de reproduction portant sur trois générations de rats, qui avaient reçu 50 ou 100 mg de méthomyl/kg de nourriture (soit l'équivalent quotidien de 50 ou 10 mg/kg de poids corporel), on n'a pas constaté d'effets sur la fécondité, la gestation ou la lactation qui soient imputables au méthomyl et aucune anomalie visible résultant de ce traitement n'a été observée.

Après administration unique ou répétée de méthomyl, on n'a pas observé de neurotoxicité retardée. Des rats qui en avaient reçu dans leur nourriture à raison de 800 mg/kg, n'ont présenté une diminution sensible de leur activité cholinestérasique sanguine qu'au début d'une étude de cinq mois. Une étude d'alimentation de 28 jours n'a révélé qu'une légère diminution de l'activité cholinestérasique cérébrale à cette dose. Il y a donc eu réversibilité rapide de l'effet anticholinestérasique du méthomyl chez les animaux au cours de la période d'expérimentation. *In vitro*, l'activité cholinestérasique érythrocytaire humaine s'est révélée six fois plus sensible à l'action inhibitrice du méthomyl que celle du rat, mais la réactivation spontanée s'est produite sensiblement à la même vitesse.

Des études menées sur diverses espèces ont montré que l'atropine est le meilleur antidote d'une intoxication par le méthomyl.

7. Effets sur l'homme

La lecture des rapports sur les intoxications accidentelles et les suicides par empoisonnement avec du méthomyl éclaire quelque

peu sur la gravité des effets et les possibilités de récupération. Sur cinq victimes d'une intoxication accidentelle due à la consommation d'aliments contaminés, trois sont décédées dans les trois heures suivant le repas. On estime que les victimes avaient ingéré environ 12 à 15 mg de méthomyl/kg de poids corporel. Une femme âgée de 31 ans et son fils de six ans, qui étaient tous les deux décédés par suite d'un empoisonnement volontaire, présentaient des concentrations hépatiques de méthomyl respectivement égales à 15,4 et 56,5 mg/kg. Les doses ont été estimées à 55 mg/kg de poids corporel pour la mère et 13 mg/kg de poids corporel pour l'enfant. Chez une femme qui avait ingéré environ 2,25 g de méthomyl, on a retrouvé dans son sang six heures plus tard une quantité de méthomyl égale à 1,6 mg/kg. Vingt-deux heures après l'ingestion, alors que la patiente se remettait, on n'a plus retrouvé de méthomyl.

Un travailleur chargé d'épandre des pesticides, qui n'avait pas pris la moindre précaution alors qu'il préparait une bouillie à base de méthomyl en poudre pour traiter des légumes, a présenté des symptômes d'intoxication au bout d'une heure avec réduction à 40% de la normale de son activité cholinestérasique sanguine au bout de 12 heures, la récupération à 80% de la normale intervenant 36 heures plus tard. D'autres travailleurs, qui avaient pris les précautions d'usage, n'ont présenté aucun symptôme ou effet sur l'activité de leur cholinestérase érythrocytaire ou plasmatique lors de l'épandage de méthomyl par voie aérienne.

8. Effets sur les organismes non visés au laboratoire et dans leur milieu naturel

Le méthomyl n'a eu aucun effet sur des populations de champignons ou de bactéries terricoles, et en particulier sur leur action nitrifiante ou sur l'activité de la déshydrogénase, lorsqu'il était appliqué aux doses recommandées.

Des études en laboratoire ont permis de fixer à 6,5 mg/litre la concentration sans effets observables sur la croissance des algues.

Le méthomyl est moyennement à fortement toxique pour les poissons, les valeurs de CL_{50} à 96 heures se situant, pour diverses espèces, dans l'intervalle 0,5-2 mg/litre. Une étude à long terme (21 jours) a montré que la CL_{50} pour des alevins de truite exposés à du Lannate 20L (21,5% de méthomyl), était égale à 1,3 mg de méthomyl par litre. Lors d'une étude toxicologique portant sur de

jeunes cyprinidés de l'espèce *Pimephales promelas*, la MATC (concentration maximale acceptable de substance toxique) a été trouvée comprise entre 57 et 177 µg/litre.

Des études de toxicité aiguë portant sur d'autres organismes aquatiques ont montré que *Daphnia magna* était l'espèce la plus sensible au méthomyl, la CL_{50} à 48 heures étant de 0,032 mg/litre. Lors d'une étude de 21 jours au cours de laquelle on a étudié la survie, la croissance et la capacité de reproduction de *Daphnia magna*, on a constaté que la concentration maximale acceptable de substance toxique (MATC) pour le méthomyl était comprise entre 1,6 et 3,5 µg/litre.

Le méthomyl est toxique pour les abeilles, la DL_{50} par contact étant de 1,29 µg/insecte et la DL_{50} par voie orale, de 0,2 µg/insecte.

On a évalué la toxicité aiguë du méthomyl chez plusieurs espèces d'oiseaux, les valeurs caractéristiques de DL_{50} aiguë par voie orale se situant à 10 mg/kg de poids corporel chez les pigeons et à 34 mg/kg de poids corporel chez la caille japonaise. Il est relativement moins toxique lorsqu'il est mêlé à la nourriture, la CL_{50} à 8 jours étant dans ce cas de 1100 mg/kg de méthomyl (mêlé à la nourriture) pour le colin de Virginie et de 2883 mg de méthomyl/kg de nourriture pour le colvert. Lors d'études qui ont duré de 18 à 20 semaines et ont porté sur une génération, on a évalué à 150 mg/kg de méthomyl dans la nourriture, la concentration sans effets nocifs observables pour le colin de Virginie et le colvert.

Aucun effet n'a été observé chez des colins de Virginie qui avaient été exposés à une série de pulvérisations de méthomyl aux doses recommandées. Après un épandage de méthomyl sur une zone forestière et des champs de houblon, aux doses recommandées, on a effectué deux études sur des populations aviaires sauvages. Elles n'ont pas révélé de modification de l'activité des oiseaux et n'ont provoqué aucun effet, en particulier aucun effet létal. Par rapport aux témoins, on a constaté qu'il y avait réduction des dépôts graisseux chez les oiseaux chanteurs des forêts traitées; on estime qu'il s'agit là d'un effet indirect dû à la réduction des populations d'insectes dont se nourrissent ces oiseaux.

9. Evaluation des risques pour la santé humaine et des effets sur l'environnement

Le méthomyl est un carbamate qui inhibe la cholinestérase et dont le mode d'action toxique est bien connu. Il présente une toxicité particulièrement élevée lorsqu'il est absorbé par voie orale ou par inhalation, ainsi que le montrent les études sur l'animal, mais sa toxicité par voie cutanée est faible. Chez l'animal, les signes d'intoxication aiguë sont caractéristiques d'une inhibition de la cholinestérase. Cette intoxication est rapidement réversible, avec une disparition rapide des symptômes et une désinhibition également rapide des cholinestérases sanguine et cérébrale. Cette prompte récupération est due au fait que l'inhibition par le méthomyl de la cholinestérase est rapidement réversible, et d'ailleurs facilitée par la vitesse d'excrétion élevée de ce composé. Ce que l'on sait des intoxications humaines accidentelles ou volontaires montre que la toxicité aiguë du méthomyl est du même ordre chez l'homme que chez l'animal de laboratoire.

Comme l'action du méthomyl est rapidement réversible pendant la période d'administration, il a rarement été possible d'observer des signes d'intoxication aiguë et d'inhibition de la cholinestérase sanguine au cours des études où on l'administrait mêlé à la nourriture. Les observations les plus régulièrement rapportées à l'occasion d'études à long terme consistent, aux doses les plus élevées dans l'alimentation, en une réduction du gain de poids chez les rongeurs et une diminution des paramètres érythrocytaires chez les rongeurs et les chiens. Trois études de longue durée chez des rongeurs n'ont pas permis de mettre en évidence d'activité cancérogène. Le composé ne s'est pas non plus montré génotoxique lors d'épreuves *in vitro* portant sur divers paramètres biotoxicologiques, néanmoins il y a une possibilité d'effets cytogénétiques sur les lymphocytes humains. Une étude chromosomique effectuée *in vivo* sur la moelle osseuse de rats s'est également révélée négative.

Chacune des études à long terme sur l'animal a permis, à partir de la réduction du gain de poids et des paramètres érythrocytaires, d'obtenir une valeur de la dose sans effets nocifs observables. Elle se situait à 5 mg/kg de poids corporel par jour chez le rat, à 8,7 mg/kg de poids corporel par jour chez la souris et à 3 mg/kg de poids corporel par jour chez le chien. Faute d'une différenciation marquée des effets toxiques entre les différentes espèces, il ressort de ces études que la dose sans effets nocifs

observables chez le chien, c'est-à-dire 3 mg/kg de poids corporel par jour, peut être utilisée pour évaluer le risque chez l'homme.

Le méthomyl est faiblement à modérément adsorbé aux particules du sol, et ne s'en désorbe pratiquement pas. Dans le sol, il se décompose en aérobiose (avec une demi-vie d'environ une semaine) environ deux fois plus vite qu'en anaérobiose.

Une fois déposé sur les feuilles de végétaux, le méthomyl est rapidement absorbé à hauteur de 50% de la dose - les 50% restant étant adsorbés - et rien n'indique qu'il y ait transport à l'intérieur de la plante. La concentration du méthomyl absorbé par les cultures vivrières tombe rapidement à environ 5% de sa valeur initiale en l'espace d'une semaine.

Plusieurs invertébrés aquatiques, et en particulier les daphnies, sont très sensibles au méthomyl avec des valeurs de la CL_{50} de l'ordre de 10 à 100 µg/litre.

Les poissons, qu'il s'agisse d'espèces d'eau douce ou d'espèces estuarielles, y sont moins sensibles, puisque les valeurs de la CL_{50} s'étagent entre 0,5 et 7 mg/litre. Etant donné la faible persistance du méthomyl et sa toxicité aiguë relativement faible pour les poissons, le risque encouru par ces derniers est relativement faible.

Aux doses d'emploi recommandées, le méthomyl n'a pas d'effets nocifs sur l'activité microbienne terricole en climat tempéré.

Le méthomyl est classé comme hautement toxique pour les abeilles avec une DL_{50} topique d'environ 0,1 µg/insecte.

Les valeurs de la DL_{50} aiguë par voie orale varient entre 10 et 40 mg/kg de poids corporel chez diverses espèces d'oiseaux. Les valeurs de CL_{50} à cinq jours par voie alimentaire vont de 1100 à 3700 mg/kg de nourriture. Il y a risque d'intoxication aiguë pour les oiseaux, en particulier lorsque le méthomyl est sous forme de granulés; son absorption à partir de nourriture contaminée ne devrait cependant pas être mortelle pour les oiseaux.

La forte toxicité aiguë du méthomyl pour les mammifères de laboratoire permet de conclure qu'il est tout aussi dangereux pour les mammifères sauvages.

10. Conclusion

Compte tenu des aspects qualitatifs et quantitatifs de la toxicité du méthomyl, le groupe de travail a conclu qu'une dose quotidienne de 0,03 mg/kg de poids corporel ne devrait probablement pas causer d'effets nocifs chez l'homme, quel que soit le mode d'exposition.

Resumen

1. Identidad, propiedades físicas y químicas y métodos analíticos

El metomilo es un sólido cristalino blanco con un punto de fusión de 77 °C y una presión de vapor de 0,72 mPa (25 °C). Tiene una solubilidad en agua de 54,7 g/litro y su coeficiente de reparto octanol/agua (K_{ow}) es de 1,24. Es estable en agua estéril a pH 7, pero se descompone a pH más elevado, con una semivida de 30 días a pH 9 y 25 °C.

El procedimiento analítico para la determinación del metomilo en muestras diferentes es la extracción seguida de limpieza y análisis mediante cromatografía líquida de alto rendimiento o cromatografía gas-líquido. En algunos casos, el metomilo se convierte en su derivado oxima o en un derivado fluoróforo (después de la columna) antes de su determinación analítica.

2. Fuentes de exposición humana y ambiental

El metomilo de produce haciendo reaccionar el *S*-metil-*N*-hidroxitioacetimidato (MHTA) en cloruro de metileno con isocianato de metilo gaseoso a 30-50 °C. Es un insecticida de tipo carbamato utilizado en una gran diversidad de cultivos en todo el mundo. Entre los cultivos protegidos figuran frutales, vides, lúpulo, hortalizas, cereales, soja, algodón y plantas ornamentales. En espacios cerrados se utiliza en establos o vaquerías para luchar contra las moscas.

Las formaciones principales son polvos hidrosolubles y líquidos hidromiscibles, que se diluyen en agua para el rociado superficial o aéreo de los cultivos. Las proporciones normales del principio activo son de 0,15-1,0 kg/ha. La exposición humana ocurre principalmente durante la preparación y aplicación de estos productos y por ingestión de residuos que quedan en los alimentos cosechados (véase la sección 5.3.1.4).

3. Transporte, distribución y transformación en el medio ambiente

En estudios de laboratorio se ha observado que el metomilo se adsorbe poco al suelo. Se ha demostrado una adsorción débil a los minerales arcillosos, sobre todo la ilita; la adsorción a la materia

orgánica del suelo es 50 veces mayor, pero sigue siendo relativamente escasa. Prácticamente no hay desorción del residuo adsorbido. Estas características llevan a prever que el metomilo tendrá movilidad en el suelo.

En condiciones medioambientales naturales, su degradación abiótica por hidrólisis o fotólisis es lenta o no se produce.

La degradación aerobia en el suelo es alrededor de dos veces más rápida que la anaerobia. Las semividas notificadas para el metomilo en el suelo varían entre unos días y más de 50. Las condiciones secas retrasan la degradación. En la práctica, la mayor parte de las aplicaciones en el campo deberían dar lugar a una semivida de alrededor de una semana.

En condiciones de campo, el metomilo no sufre lixivi-ación en el suelo a profundidades superiores a 20-30 cm y no contamina las aguas subterráneas.

El ^{14}C-metomilo aplicado a las hojas de las plantas es absorbido, pero no transportado a otras partes de la planta. Se si lo aplica en el sistema radicular, la planta lo absorbe y el componente principal del residuo que queda es el propio metomilo. Los productos volátiles derivados de su descomposición son CO_2 y acetonitrilo. El resto de la actividad se incorpora a los componentes naturales de la planta, tales como lípidos, ácidos del ciclo de Krebs y azúcares. La semivida del metomilo en el follaje de la planta es de unos pocos días.

No se han encontrado indicios de acumulación del metomilo en truchas irisadas expuestas al compuesto durante 28 días en un sistema de flujo continuo.

4. Niveles medioambientales y exposición humana

Los análisis de diversas fuentes de agua tras la aplicación de las dosis recomendadas del compuesto indican que los niveles de metomilo en las aguas subterráneas probablemente serán muy bajos o inferiores al límite de detección (< 0,02 mg/litro).

En los cultivos de productos alimenticios y de otro tipo se observan niveles bajos de residuos de metomilo en el momento de la recolección; su concentración depende de diversos factores, como la cantidad aplicada, el periodo transcurrido desde la última

aplicación y el tipo de cultivo. Los residuos están formados básicamente por metomilo.

Los residuos de metomilo en los productos lácteos no son detectables o son muy bajos. No se observaron residuos detectables de metomilo ni del metabolito MHTA en la leche ni en los tejidos (< 0,02 mg/kg) de vacas lactantes que habían recibido en el pienso cápsulas de metomilo en una concentración equivalente a 80 mg/kg durante 28 días. No se detectó la presencia de metomilo en los huevos ni en los tejidos de gallinas ponedoras a las que se habían administrado cantidades de 1 ó 10 mg/kg en los alimentos durante cuatro semanas.

En los Estados Unidos de América se hicieron análisis de regímenes completos de alimentación y de determinados alimentos; en los estudios de muestreo correspondientes, las concentraciones de metomilo resultaron inferiores al límite de detección o muy bajas. Los niveles de residuos se reducen aún más por efecto de procesos tales como el lavado, pelado y guisado de los alimentos.

En estudios sobre la exposición de quienes regresan a zonas tratadas, en particular en las condiciones del desierto de California, se ha observado que los trabajadores que volvieron a los viñedos cuando los residuos foliares que podían desprenderse se habían reducido a 0,1 $\mu g/cm^2$, sufrieron la mayor exposición en la parte superior del cuerpo y en la cabeza durante el atado de los racimos y en la parte superior del cuerpo y en las manos durante la vendimia. La recogida y el embalado de las uvas de mesa dieron lugar a la exposición más baja. La exposición por inhalación fue mínima.

Tras haberse rociado con metomilo plantas de pepino y tomate, las concentraciones en el aire del invernadero llegaban a 4,7 $\mu g/m^3$ al día siguiente del rociado. Tres y siete días después del rociado, las concentraciones de metomilo en la zona de respiración ascendían a 14,5 y 0,7 $\mu g/m^3$, respectivamente. Los valores del metomilo en el agua de lavarse las manos oscilaban entre 10 y 322 μg por hora de trabajo en un invernadero. Esto indicaba que la vía de exposición cutánea era más importante que la inhalación y que los intervalos previos al regreso al lugar tratado deberían basarse en los datos sobre la exposición cutánea.

5. Cinética y metabolismo en animales de laboratorio

La absorción, el metabolismo y la excreción del metomilo tras la administración oral a ratas es muy rápida, completándose el proceso en unos pocos días. En un plazo de siete días después de la administración a ratas de 5 mg/kg de peso corporal de metomilo radiomarcado, el 54% se excretó en la orina, el 2-3% en las heces y el 34% en el aire expirado (en cinco días). Después de siete días, en los tejidos y en el esqueleto quedaba el 8-9% de la dosis de ^{14}C, que se había incorporado a los constituyentes endógenos. La mayor concentración de radiactividad se detectó en la sangre (equivalente al 2% de la dosis).

Los componentes metabólicos principales en el aire expirado por las ratas eran el anhídrido carbónico y el acetonitrilo, en una proporción de 2:1. El principal metabolito en la orina fue el derivado mercaptúrico del metomilo, que era igual al 17% de la dosis. No se detectó metomilo ni su derivado oxima.

La vía metabólica propuesta comprende el desplazamiento del grupo *S*-metilo por el glutatión, seguido de una transformación enzimática que da lugar al derivado mercaptúrico. Otra vía es la hidrólisis, por la que se produce MHTA, que se descompone rápidamente hasta dar anhídrido carbónico. Otra vía posible es la conversión del *sin*-metomilo (la forma insecticida) en su *anti*-isómero, que sufre reacciones de hidrólisis, recomposición y eliminación hasta dar acetonitrilo. El metomilo se metaboliza de forma semejante en el mono, salvo que el derivado mercaptúrico es un componente secundario en la orina.

La penetración del ^{14}C-metomilo una hora después de haber sido aplicado a ratones por vía cutánea en una solución de acetona se estimó en un 85%. Para entonces, el 3% de la dosis se hallaba presente en la sangre, el 5% en el hígado y el 13% se había excretado. En un plazo de 8 horas la excreción total era del 54,5%.

La descomposición y eliminación rápidas del metomilo en la rata, junto con su falta de acumulación en los tejidos, son comparables a lo observado en rumiantes.

El metomilo sufre una descomposición completa en las vacas y cabras que han recibido una dosis. No se detectaron metomilo ni su derivado oxima en la leche ni en los tejidos de estos animales.

Se puso de manifiesto que el producto se metabolizaba e incorporaba a los componentes naturales de la leche y del hígado.

No se detectó la presencia de nitrosometomilo después de haberse incubado ^{14}C-metomilo con nitrito sódico en un macerado de carne curada, en condiciones que simulaban las del estómago.

6. Efectos en mamíferos de laboratorio y en sistemas de prueba *in vitro*

El metomilo administrado por vía oral tiene una elevada toxicidad aguda, con una DL_{50} oral de 17-45 mg/kg de peso corporal en la rata. También es muy tóxico para la rata por inhalación; en aerosol, la CL_{50} a las 4 horas es de 0,26 mg/litro. La toxicidad cutánea es muy baja; la DL_{50} es de más de 2000 mg/kg de peso corporal en conejos (piel intacta) y > 1000 mg/kg de peso corporal en ratas (piel raspada). Los signos de toxicidad aguda son los que cabe esperar de un inhibidor de la colinesterasa, entre otros salivación profusa, lacrimación, temblor y contracción pupilar. La recuperación de estos efectos fue rápida. En los órganos examinados no se observaron efectos patológicos graves. El metomilo no irrita ni sensibiliza la piel, pero irrita levemente los ojos.

La administración repetida de metomilo con los alimentos durante periodos más largos no produjo aumento de los efectos tóxicos ni acumulación. Las ratas y perros cuya alimentación contenía metomilo en cantidades de hasta 250 mg/kg y 400 mg/kg, respectivamente, durante 13 semanas no mostraron signos de toxicidad ni acusaron mortalidad. Las ratas que recibieron con los alimentos 250 mg/kg mostraron una pequeña disminución en el aumento del peso corporal, niveles de hemoglobina más bajos e hiperplasia eritroidea moderada de la médula ósea. El NOEL en ratas fue de 50 mg/kg en los alimentos (equivalentes a 3,6 mg/kg de peso corporal por día). Los conejos que recibieron aplicaciones cutáneas repetidas de metomilo en dosis de hasta 500 mg/kg de peso corporal por día durante 21 días mostraron hiperactividad y una reducción de la actividad colinesterásica plasmática y cerebral con la dosis más elevada. El NOAEL en este estudio fue de 50 mg/kg de peso corporal por día.

Se realizaron estudios de larga duración en ratas que recibían metomilo en los alimentos en concentraciones de 0, 50, 100 ó 400 mg/kg y en ratones que recibían 0, 50, 75 ó 200 mg/kg. Los

efectos de la dosis más alta en las ratas fueron una disminución del aumento de peso y una reducción de la concentración de hemoglobina y del valor hematócrito. El NOEL fue de 100 mg/kg de alimentos, equivalente a 5 mg/kg de peso corporal por día. En el estudio en ratones, se observó aumento de la tasa de mortalidad y una reducción de la hemoglobina y del número de eritrocitos en los dos niveles de dosis más elevados. El NOEL fue de 50 mg/kg de alimentos, equivalente a 8,7 mg/kg de peso corporal por día. En un estudio de dos años sobre toxicidad en perros (0, 50, 100, 400 ó 1000 mg/kg de alimentos) con la dosis más elevada se detectaron síntomas de toxicidad en algunos animales, junto con anemias de ligeras a moderadas. El NOEL fue de 100 mg/kg de alimentos, equivalentes a 3 mg/kg de peso corporal por día.

En estudios de dos años en ratas y ratones no se encontró ningún indicio de aumento de la incidencia de tumores relacionado con el tratamiento, signo de que el metomilo no es carcinógeno. No fue genotóxico en célula de bacterias o de mamíferos *in vitro* y las pruebas realizadas para determinar la presencia de lesiones primarias del ADN en células de bacterias y de mamíferos *in vitro* dieron resultados negativos; un estudio cromosómico *in vivo* de médula ósea de rata también dio resultados negativos. El potencial citogenético del metomilo en linfocitos humanos *in vitro* se puso de manifiesto mediante un aumento del número de micronúcleos y de aberraciones cromosómicas. El metomilo no produjo efectos embriotóxicos ni teratogénicos en ratas ni en conejos en dosis de hasta 400 mg/kg en los alimentos y de 16 mg/kg de peso corporal por día administrados por sonda, respectivamente; a esos niveles produjo efectos tóxicos en las madres. En un estudio de reproducción de tres generaciones en ratas con dosis de 50 ó 100 mg/kg de alimentos (equivalentes a 5 ó 10 mg/kg de peso corporal por día), el metomilo no tuvo efectos sobre los índices de fecundidad, gestación o lactación y no se produjeron anomalías graves relacionadas con el tratamiento.

No se observó neurotoxicidad retardada después de la administración de una sola dosis o de una serie de dosis de metomilo. En un estudio de cinco meses en el que se suministraron a ratas 800 mg/kg de alimentos se observó una reducción importante de la actividad de la colinesterasa sanguínea sólo en las fases iniciales. En un estudio de 28 días, la administración de esa misma dosis con los alimentos dio lugar a una reducción ligera solamente de la actividad de la colinesterasa cerebral. Esto indica que la inhibición de la actividad de la

colinesterasa por el metomilo es reversible rápidamente en los animales durante los periodos de ingestión. *In vitro*, la actividad de la eritrocito colinesterasa humana fue seis veces más sensible a la acción inhibidora del metomilo que la de la rata, aunque los índices de reactivación espontánea fueron semejantes.

Los resultados obtenidos en estudios realizados con varias especies mostraron que la atropina es el antídoto de eficacia más general contra la intoxicación por metomilo.

7. Efectos en el ser humano

Las notificaciones de intoxicaciones accidentales y suicidas con metomilo proporcionan alguna información sobre los niveles de efectos y la recuperación. Tres de cinco víctimas accidentales de intoxicación por una comida contaminada murieron antes de que transcurrieran tres horas desde la ingestión. Se estimó que las víctimas habían consumido alrededor de 12–15 mg de metomilo/kg de peso corporal. Una mujer de 31 años y su hijo de seis, que murieron a causa de un envenenamiento deliberado, tenían en el hígado concentraciones de metomilo de 15,4 y 56,5 mg/kg, respectivamente. Las dosis estimadas fueron de 55 mg/kg de peso corporal para la madre y de 13 mg/kg de peso corporal para el hijo. Seis horas después de haber ingerido unos 2,25 g de metomilo, la sangre de una mujer contenía 1,6 mg de metomilo/kg. A las 22 horas de la ingestión no se podía detectar la presencia de metomilo y la mujer se estaba recuperando.

Un operario que manipulaba plaguicidas había mezclado, sin tomar precauciones, una formulación de metomilo en polvo para el rociado de hortalizas; antes de una hora manifestó síntomas de intoxicación y después de 12 horas la actividad de colinesterasa sanguínea se había reducido al 40% de la normal; a las 36 horas la recuperación llegaba al 80% de la actividad normal. Otros operarios que habían tomado las precauciones recomendadas no acusaron ningún síntoma ni efectos en la actividad de la colinesterasa eritrocitaria y plasmática durante actividades de aplicación aérea de metomilo.

8. Efectos en organismos no destinatarios en el laboratorio y sobre el terreno

No se observaron efectos en poblaciones de hongos y bacterias del suelo, en particular en su acción nitrificante y en la actividad

de la deshidrogenasa después de haberse aplicado metomilo en las dosis recomendadas.

En estudios de laboratorio se determinó una NOEC de 6,5 mg/litro para el crecimiento de las algas.

El metomilo tiene una toxicidad entre moderada y alta para los peces, con una CL_{50} a las 96 horas de 0,5 a 2 mg/litro para una serie de especies. En un estudio de mayor duración (21 días), utilizando la formulación Lannate 20L (21,5% de metomilo), la CL_{50} para los alevines de trucha fue de 1,3 mg/litro. En un estudio de toxicidad de 28 días durante la primera fase de la vida de piscardos (*Pimaphales promelas*), la máxima concentración intoxicante aceptable (MATC) estimada fue de > 57 y < 117 µg/litro.

En pruebas de toxicidad aguda con otros organismos acuáticos, *Daphnia magna* fue una de las especies más vulnerables al metomilo, con una CL_{50} de 0,032 mg/litro a las 48 horas. En un estudio de 21 días sobre la capacidad de supervivencia, crecimiento y reproducción de *Daphnia magna*, la máxima concentración intoxicante aceptable para el metomilo fue de > 1,6 y < 3,5 µg/litro.

El metomilo es tóxico para las abejas melíferas; se ha notificado una DL_{50} por contacto de 1,29 µg/abeja y una DL_{50} oral de 0,2 µg/abeja.

Se ha evaluado la toxicidad aguda del metomilo en varias especies de aves; los valores característicos de la DL_{50} oral aguda son de 10 mg/kg de peso corporal en palomas y de 34 mg/kg de peso corporal en la codorniz japonesa. El metomilo es relativamente menos tóxicos si se ingiere con los alimentos; en ese caso, la CL_{50} en ocho días es de 1100 mg/kg de metomilo en los alimentos para la codorniz *Colinus virginianus* y de 2883 mg/kg de metomilo en los alimentos para el pato silvestre. En estudios de una generación realizados durante 18 a 20 semanas, la NOEC fue de 150 mg/kg de metomilo en los alimentos para la codorniz *Colinus virginianus* y para el pato silvestre.

No se observaron efectos sobre *Colinus virginianus* tras su exposición a una serie de aplicaciones de metomilo por rociado en las dosis recomendadas. En dos estudios sobre poblaciones de aves silvestres, después de haberse rociado con metomilo tierras

forestales y campos de lúpulo en las dosis recomendadas, no se observó ningún cambio manifiesto en la actividad de las aves ni se produjeron efectos ni mortalidad relacionados con el tratamiento. Los depósitos de grasa de las aves canoras de los bosques tratados se redujeron en comparación con el grupo testigo; se consideró que se trataba de un efecto indirecto de la disminución de los insectos que les sirven de alimento.

9. Evaluación de los riesgos para la salud humana y efectos en el medio ambiente

El metomilo es un inhibidor de la carbamato colinesterasa mediante un mecanismo bien conocido de acción tóxica. En estudios realizados en animales se ha observado una toxicidad aguda particularmente alta por vía oral y respiratoria, pero la toxicidad por vía cutánea es baja. Los signos de toxicidad aguda en animales son los característicos de los inhibidores de la colinesterasa. La reversibilidad de la acción tóxica aguda es rápida; los supervivientes se recuperan con rapidez de los signos tóxicos y de la inhibición de la colinesterasa en la sangre y el cerebro. La pronta remisión de los efectos tóxicos se debe a la rápida reversibilidad de la inhibición de la colinesterasa, reversibilidad favorecida por la eliminación rápida del metomilo del organismo. Los datos sobre intoxicaciones humanas accidentales e intencionales muestran que el nivel de toxicidad aguda del metomilo en el ser humano es semejante al observado en los animales de laboratorio.

Habida cuenta de la reversibilidad rápida de la acción del metomilo durante los periodos de ingestión, en los estudios realizados raramente se observaron síntomas de toxicidad aguda e inhibición de la colinesterasa sanguínea. Los resultados más constantes en los estudios de mayor duración con niveles de alimentación más elevados fueron una reducción del aumento del peso corporal en roedores y una disminución del número de glóbulos rojos en roedores y perros. No se observaron indicios de carcinogenicidad potencial en tres estudios de larga duración realizados en roedores. El compuesto dio resultados negativos en las pruebas de genotoxicidad *in vitro* en las que se investigaron varios puntos finales, en cambio mostró potencial citogenético en linfocitos humanos. El resultado de un estudio cromosómico realizado *in vivo* sobre médula ósea de rata fue negativo.

Se identificaron los NOEL en cada uno de los estudios de larga duración realizados con animales, teniendo en cuenta la reducción del aumento del peso corporal y el número de eritrocitos. Los NOEL resultaron ser de 5 mg/kg de peso corporal por día en ratas, 8,7 mg/kg de peso corporal por día en ratones y 3 mg/kg de peso corporal por día en perros. Como esos estudios no revelaron diferencias acentuadas entre especies en cuanto a los efectos tóxicos, se debería utilizar el NOEL en el perro, que es de 3 mg/kg de peso corporal por día, a efectos de la estimación del riesgo en el ser humano.

La adsorción del metomilo al suelo es de baja a moderada, y prácticamente no hay desorción. La degradación aerobia en el suelo (con una semivida de alrededor de una semana) es aproximadamente dos veces más rápida que la degradación anaerobia.

La aplicación de metomilo a hojas de plantas da lugar a una absorción rápida de casi la mitad de la cantidad aplicada (la otra mitad se adsorbe) y no hay indicios de transporte. La concentración del metomilo absorbido en los cultivos de productos alimenticios disminuye rápidamente hasta alrededor del 5% en una semana.

Varios invertebrados acuáticos, en particular los dáfnidos, son muy sensibles al metomilo, con CL_{50} del orden de 10 a 100 μg/litro.

Los peces, tanto de agua dulce como estuarinos, son menos sensibles, oscilando la CL_{50} entre 0,5 y 7 mg/litro. Dada la escasa persistencia del metomilo y su toxicidad aguda relativamente baja para los peces, se supone que el riesgo es bajo.

En las dosis de aplicación recomendadas, el metomilo no menoscaba la actividad microbiana en suelos templados.

Este producto está clasificado como muy tóxico para las abejas melíferas y su DL_{50} tópica es de aproximadamente 0,1 μg/abeja.

La DL_{50} aguda por vía oral para varias especies de aves oscila entre 10 y 40 mg/kg de peso corporal. Los valores de la CL_{50} en la alimentación (cinco días) varían entre 1100 y 3700 mg/kg de alimentos. El metomilo, sobre todo en forma de gránulos, constituye un riesgo agudo para las aves, pero no se prevé que la

ingestión de alimentos contaminados con metomilo pueda causarles la muerte.

La elevada toxicidad aguda del metomilo para los mamíferos de laboratorio indica que existe un peligro semejante para los mamíferos silvestres.

10. Conclusiones

Teniendo en cuenta las características cualitativas y cuantitativas de la toxicidad del metomilo, el Grupo de Trabajo llegó a la conclusión de que 0,03 mg/kg de peso corporal al día probablemente no causarían efectos adversos en el ser humano por ninguna vía de exposición.

Food additives and contaminants in food, principles for the safety assessment of (No. 70, 1987)
Formaldehyde (No. 89, 1989)
Genetic effects in human populations, guidelines for the study of (No. 46, 1985)
Glyphosate (No. 159, 1994)
Guidance values for human exposure limits (No. 170, 1994)
Heptachlor (No. 38, 1984)
Hexachlorobutadiene (No. 156, 1994)
Alpha- and beta-hexachlorocyclohexanes (No. 123, 1992)
Hexachlorocyclopentadiene (No. 120, 1991)
n-Hexane (No. 122, 1991)
Hydrazine (No. 68, 1987)
Hydrogen sulfide (No. 19, 1981)
Hydroquinone (No. 157, 1994)
Infancy and early childhood, principles for evaluating health risks from chemicals during (No. 59, 1986)
Inorganic lead (No. 165, 1995)
Isobenzan (No. 129, 1991)
Isophorone (No. 174, 1995)
Kelevan (No. 66, 1986)
Lasers and optical radiation (No. 23, 1982)
Lead (No. 3, 1977)[a]
Lead - environmental aspects (No. 85, 1989)
Lindane (No. 124, 1991)
Linear alkylbenzene sulfonates and related compounds (No. 169, 1996)
Magnetic fields (No. 69, 1987)
Man-made mineral fibres (No. 77, 1988)
Manganese (No. 17, 1981)
Mercury (No. 1, 1976)[a]
Mercury - environmental aspects (No. 86, 1989)
Mercury, inorganic (No. 118, 1991)
Methomyl (No. 178, 1996)
2-Methoxyethanol, 2-ethoxyethanol, and their acetates (No. 115, 1990)
Methyl bromide (No. 166, 1995)
Methylene chloride (No. 32, 1984, 1st edition)
Methyl ethyl ketone (No. 143, 1992)
Methyl isobutyl ketone (No. 117, 1990)
Methylmercury (No. 101, 1990)
Methyl parathion (No. 145, 1992)
Mirex (No. 44, 1984)
Morpholine (No. 179, 1996)
Mutagenic and carcinogenic chemicals, guide to short-term tests for detecting (No. 51, 1985)
Mycotoxins (No. 11, 1979)
Mycotoxins, selected: ochratoxins, trichothecenes, ergot (No. 105, 1990)
Nephrotoxicity associated with exposure to chemicals, principles and methods for the assessment of (No. 119, 1991)
Neurotoxicity associated with exposure to chemicals, principles and methods for the assessment of (No. 60, 1986)
Nickel (No. 108, 1991)
Nitrates, nitrites, and *N*-nitroso compounds (No. 5, 1978)[a]
Nitrogen, oxides of (No. 4, 1977)[a]
2-Nitropropane (No. 138, 1992)
Noise (No. 12, 1980)[a]
Organophosphorus insecticides: a general introduction (No. 63, 1986)
Paraquat and diquat (No. 39, 1984)
Pentachlorophenol (No. 71, 1987)
Permethrin (No. 94, 1990)
Pesticide residues in food, principles for the toxicological assessment of (No. 104, 1990)
Petroleum products, selected (No. 20, 1982)
Phenol (No. 161, 1994)
d-Phenothrin (No. 96, 1990)
Phosphine and selected metal phosphides (No. 73, 1988)
Photochemical oxidants (No. 7, 1978)
Platinum (No. 125, 1991)
Polybrominated biphenyls (No. 152, 1994)
Polychlorinated biphenyls and terphenyls (No. 2, 1976, 1st edition)[a]
(No. 140, 1992, 2nd edition)
Polychlorinated dibenzo-*p*-dioxins and dibenzofurans (No. 88, 1989)
Progeny, principles for evaluating health risks associated with exposure to chemicals during pregnancy (No. 30, 1984)
1-Propanol (No. 102, 1990)
2-Propanol (No. 103, 1990)
Propachlor (No. 147, 1993)
Propylene oxide (No. 56, 1985)
Pyrrolizidine alkaloids (No. 80, 1988)
Quintozene (No. 41, 1984)
Quality management for chemical safety testing (No. 141, 1992)

---

[a] Out of print

Radiofrequency and microwaves
(No. 16, 1981)
Radionuclides, selected (No. 25, 1983)
Resmethrins (No. 92, 1989)
Selected synthetic organic fibres
(No. 151, 1993)
Selenium (No. 58, 1986)
Styrene (No. 26, 1983)
Sulfur oxides and suspended particulate
matter (No. 8, 1979)
Tecnazene (No. 42, 1984)
Tetrabromobisphenol A and derivatives
(No. 172, 1995)
Tetrachloroethylene (No. 31, 1984)
Tetradifon (No. 67, 1986)
Tetramethrin (No. 98, 1990)
Thallium (No. 182, 1995)
Thiocarbamate pesticides: a general
introduction (No. 76, 1988)
Tin and organotin compounds (No. 15, 1980)
Titanium (No. 24, 1982)
Toluene (No. 52, 1986)
Toluene diisocyanates (No. 75, 1987)
Toxicity of chemicals (Part 1), principles
and methods for evaluating the (No. 6, 1978)
Toxicokinetic studies, principles of
(No. 57, 1986)
Tributyl phosphate (No. 112, 1991)
Tributyltin compounds (No. 116, 1990)
Trichlorfon (No. 132, 1992)
1,1,1-Trichloroethane (No. 136, 1992)
Trichloroethylene (No. 50, 1985)
Tricresyl phosphate (No. 110, 1990)
Triphenyl phosphate (No. 111, 1991)
Tris- and bis(2,3-dibromopropyl) phosphate
(No. 173, 1995)
Ultrasound (No. 22, 1982)
Ultraviolet radiation
(No. 14, 1979, 1st edition)
(No. 160, 1994, 2nd edition)
Vanadium (No. 81, 1988)
Vinylidene chloride (No. 100, 1990)

To obtain further copies of monographs in this series, please write to the Office of Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland (Fax No. 41-22-7914857)

Price: Sw.fr. 23.–
Price in developing countries: Sw.fr. 16.10

ISBN 92 4 157178 0